# Army Medicine Peer-Reviewed Publications

## October 2012

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## Executive Summary

October 2012-- Journal coverage for October focused primarily on post-traumatic stress disorder, technology, sexual health and suicide. Coverage of PTSD noted sleep, alcohol abuse and aggression's affect on PTSD, new treatment options and a link between certain illnesses and the disorder. Notably, one journal's findings indicate that studying a part of the brain will help diagnose PTSD faster and can potentially reveal a predisposition for developing PTSD. A significant number of journals presented research regarding the use of technology in medical training as well as the link between electronic device use and mental health. Particularly of note given the Army's development of mental and behavioral health applications, was research on the feasibility of using smartphones to track psychotic symptoms. Articles addressing suicide focused on combat exposure, early diagnoses of mental health disorders and the global suicide crisis. Coverage of sexual health focused exclusively on HIV with articles noting research on HIV among deployed Soldiers, the development of home tests and the spread of HIV through sex workers in Asia Pacific. Coverage of military medical issues was spread across journals with Military Medicine, The Lancet and BMC Psychiatry printing a significant number of articles relevant to military medicine.

A considerable number of journals observed during this month addressed the effect of the quality and quantity of sleep, nutrition and fitness on Soldier's physical, mental and emotional health. Given top MEDCOM leaders recent statements underscoring the importance of promoting a full complement of health, medical journals, trade publications and traditional media may delve into enhancing Soldier's sleep, nutrition and exercise habits.

## Medical Journal Coverage

***Nutrition***

### BMC Complementary and Alternative Medicine: Confidence in the efficacy and safety of dietary supplements among United States active duty army personnel

Despite limited evidence supporting the benefits of dietary supplements, Army Soldiers regularly use such supplements. Two-year research including 990 Soldiers at 11 Army bases found that Soldiers are somewhat confident that their dietary supplements are safe and work as advertised. Confidence of dietary supplements increased with rank, diet quality, fitness level and education. Less than half of those surveyed were aware that companies issuing dietary supplements are not required to demonstrate efficacy and one

third surveyed incorrectly believe the FDA effectively regulates pre-market supplements. As the Army focuses on nutrition, fitness and sleep in enhancing behavioral health, expect coverage to focus on dietary supplement and nutrition issues in the military.

***Fractures***

### BMC Emergency Medicine: Identical fracture patterns in combat vehicle blast injuries due to improvised explosive devices; a case series

Researchers assessed four incidents involving IED blasts under and around armored personnel carriers where two Soldiers were injured in each blast. A comparison of their injuries supported existing literature on the prevalence of thoracic vertebral, radial neck, calcaneal and talar fractures. In most instances, Soldiers injured in the blast received similar injuries. In locating and diagnosing fractures in remote theater, it is appropriate for Army medical personnel to pay special attention to areas of the body that do not appear injured but that correspond to injuries more visible in other Soldiers in the incident. This may help locate and treat fractures that are not immediately visible.

### Journal of Brachial Plexus and Peripheral Nerve Injury: Reconstruction of sciatic nerve after traumatic injury in humans - factors influencing outcome as related to neurobiological knowledge from animal research

Surgery trials performed on rats indicate that information gathered from animal experiments can be used in decision making regarding nerve repair and reconstruction data. One can translate data to clinical practice to predict the outcome of human patients, but should be cautious when doing so. Other factors involved in nerve repair, such as cognitive capacity and coping, are difficult to study using rat models. Research on this topic affects ongoing studies regarding the reconstruction and rehabilitation of limbs post-injury.

***PTSD***

### European Journal of Pyschotraymotology: Sleep disturbances and PTSD: a perpetual circle?

In a series of three experiments focused on the relationship between sleep and post-traumatic symptoms, researchers focused on pre-deployment insomnia symptoms, physiological responses from veterans with and without PTSD symptoms, and the affect of prazosin on veterans with PTSD symptoms. Pre-deployment nightmares predicted PTSD symptoms within six months of deployment, but insomnia did not have the same effect. PTSD patients experienced higher levels of ACTH, lower levels of GH secretion. GH secretion together with mid-sleep awakenings predicted delayed recall, which was lower in PTSD. Prazosin was not seen to improve

any metrics. The link between sleep and PTSD helps medical professionals understand symptoms and what to look for when diagnosing PTSD. Also, the insufficient effect of prazosin indicates it should not be used to treat PTSD, but it can be used effectively to treat nightmares.

### PLoS One: Early altered resting-state functional connectivity predicts the severity of post-traumatic stress disorder symptoms in acutely traumatized subjects

In a study of 15 PTSD sufferers, researchers sought to determine the relationship between resting-state functional connectivity and the severity of PTSD symptoms. Using imaging scans, the participants were subjected to testing just two days post-traumatic event and were diagnosed with PTSD between one and six months following the initial trauma. Resting state connectivity with certain areas of the brain (posterior cingulate cortex, bilateral amygdala) can accurately predict the severity of PTSD and may also constitute a predisposition in patients in developing PTSD. The resulting discovery that the relationship between areas of the brain may be a predictor of a predisposition to PTSD can serve as a messaging tool for the Army going forward as a significant discovery in how the brain operates and what may predispose a Soldier to the syndrome.

### National Center for PTSD, Boston Healthcare System: Treatment Improves Symptoms Shared by PTSD and Disordered Eating

Using the unique similarities of the symptoms of PTSD and eating disorders, researchers sought to determine whether cognitive processing therapy (CPT) would help alleviate the shared symptoms: cognitive disturbances, emotion dysregulation, dissociation and impulsivity. The study focused solely on women who had a history of rape or physical assault. The research concluded that the PTSD treatment affected both PTSD and eating disorder symptoms. In a media environment where sexual assault and PTSD are common criticisms, the study offers insight into possible treatments that will impact both PTSD and eating disorders.

### BMC Psychiatry: What are the effects of having an illness or injury whilst deployed on post deployment mental health? A population based record linkage study of UK Army personnel who have served in Iraq or Afghanistan

In a study of UK soldiers who were deployed to Iraq or Afghanistan, research focused on the relationship between illnesses and injury to PTSD. The study found that evacuated personnel with illnesses were more susceptible to PTSD after having been evacuated and that no relationship existed between illness while deployed and alcohol misuse. In addition, injuries sustained from hostile environments were more reliably linked to PTSD than non-hostile ones.

## Military Medicine: Eating Disorders, Post-Traumatic Stress, and Sexual Trauma in Women Veterans

In a study conducted over the life cycle (childhood, military service and lifetime), associations between sexual trauma, eating disorders and PTSD were found to exist in female veterans. The study found that sexual trauma during military service, more than during childhood, resulted in a lifetime of eating disorder(s). The recommendation, then, is to screen women veterans for eating disorders and/or histories of sexual trauma.

## Military Medicine: Postdeployment Alcohol Use, Aggression, and Post-Traumatic Stress Disorder

The study examined both Active Duty and Reserve personnel post-deployment to determine a relationship between high-risk behavior and PTSD checklist cutoff scores. Active Duty personnel displayed a greater likelihood to participate in high-risk behaviors in every outcome observed, while Reserve personnel showed similar behavior but not with regard to alcohol use. The study's conclusion is that Active Duty personnel may be at higher risk for developing problems as a function of the deployment cycle.

***Sexual Health***

## The Lancet: Sex workers, HIV, and the law in Asia Pacific

The article focuses on sex workers in Asia Pacific and the men who serve as the driving force behind Asia's HIV epidemic. Pointing to the criminalization of sex work, the article argues that the lack of openness impedes HIV prevention efforts according to *Sex Work and the Law in Asia and the Pacific*. The article continues to spell out how laws can be used to protect sex workers' rights, which can be an effective tool in preventing HIV. With criminalization, for example, sex workers are subjected to limited social services necessary to treat HIV.

## AIDS Research and Human Retroviruses: Short Communication: Investigation of Incident HIV Infections Among U.S. Army Soldiers Deployed to Afghanistan and Iraq, 2001-2007

Research was conducted after reports surfaced in 2007 that Soldiers were contracting HIV while on deployments. Findings indicate that the HIV-rate in the Army is significantly lower than the U.S. population. Forty-two percent of the Soldiers infected with HIV contracted the virus before deployment, 27 percent contracted it during leave and only 2 percent developed HIV while deployed, despite blood tests excluding Soldiers with HIV from deploying. Research noted high-risk, unprotected exposure during sex with strangers or sex workers. Research on this topic is particularly relevant given the Army's shift in focus to Asia Pacific.

## Cleveland Clinic Journal of Medicine: Home testing for HIV: Hopefully, a step forward

Over-the-counter HIV tests have recently been approved by the FDA and will be available to consumers soon. Advanced testing for HIV prevents symptoms from progressing and limits unknown transmission of the virus. While the tests are specific for HIV, they do miss 7 percent of cases and present some false positives. The availability of cheap, over-the-counter HIV tests may encourage enhanced testing among high-risk service members.

***Substance Abuse***

## Military Medicine: Alcohol Abuse or Dependence in the Military Aviator: Guidance for the Non-Flight Surgeon

The study brought to attention the problematic disconnect that exists between civilian and military caregivers as relates to military aviators and alcohol abuse. In the description, the report delineates between military, civilian, and National Guard and Reserve airmen. Particular focus is placed on the National Guard and Reserve airmen category and how there is no clear line of communication between the civilian and military caregivers. As these caregivers encounter airmen exhibiting dependence on alcohol, a false choice is presented: Protect the airman's career or protect safety. The report suggests that airmen with alcohol issues, both military and civilian, have the potential to rehabilitate both themselves and their careers through distinct paths.

***Suicide***

## Journal of Clinical Psychology: Combat Exposure and Suicide Risk in Two Samples of Military Personnel

Research focused on military personnel and veterans, as the study sought to determine direct or indirect effects of combat operations in Iraq and Afghanistan on suicide risk and PTSD symptom severity. The findings indicate greater combat exposure is directly associated with fearlessness about death and PTSD symptom severity. PTSD and depression symptom severity were strongly linked to suicide risk. The findings of a strong relationship between PTSD, depression, and suicide risk allow the Army to focus messaging on a universal approach to all three issues.

## The Lancet: Depression and the global economic crisis: is there hope?

In an article on the effects of global austerity on the mental health industry, Lancet argues that depression is of global concern, labeling it a global crisis, and points to global austerity as exacerbating the problem by removing access to vital social programs. The

article alleges that research for depressive treatments is inadequate and proposed that depression-related spending could leap from a current $2.5 trillion estimate to well over $6.0 trillion by 2030.

### Military Medicine: Association Between Mental Health Conditions Diagnosed During Initial Eligibility for Military Health Care Benefits and Subsequent Deployment, Attrition, and Death by Suicide Among Active Duty Service Members

In order to determine if there is a link between findings in initial health screenings and eventual suicide among active duty service members, researchers studied newly enlisted Soldiers' medical records in the first six months of their service between 2003 and 2006. Researchers found that early mental health diagnoses were associated with a 69 percent rate of attrition and a 77 percent reduction in the odds of deploying; research on this topic allows leadership to evaluate the cost benefit of accepting Soldiers who may not be able to perform duties. Researchers also found that there was no correlation between early mental health diagnoses and suicide, potentially indicating that undiagnosed mental disorders account for suicide.

***Technology***

### BMC Psychiatry: Computer use and stress, sleep disturbances, and symptoms of depression among young adults -- a prospective cohort study

This study indicates that high and medium computer use is associated with sleep disturbances among men and women aged 20 to 24 while high email and chat use is associated with mental health issues in women. Researchers note that disturbances in sleep cause a wide variety of mental health issues. This study provides useful backup to MEDCOM's focus on improving Soldiers' sleep as a key component in enhancing mental and behavioral health.

### Military Medicine: Use of Portable Sleep Monitors to Diagnose Sleep Apnea During Predeployment Assessment

This study covered the issue of obstructive sleep apnea (OSA) and the feasibility of Portable Sleep Monitor (PMs) use as a tool of diagnosis. With 101 subjects, PMs were successful in determining OSA with high pretest probability. The use of PMs to determine OSA is a more practical solution to diagnosing OSA than utilizing in-laboratory studies. The authors suggest using PMs during predeployment assessments.

## BMC Psychiatry: The feasibility and validity of ambulatory self-report of psychotic symptoms using a smartphone software application

Though a structured personal interview is the best possible treatment for assessing psychosis, self-reporting through the use of a smartphone application avoids some of the limitations of personal interviews including, bias and time accuracy, and is the only possible option for patients in remote areas. Research supports smartphone use as a viable option for assessing psychosis.

## Military Medicine: The Effects of a Human Patient Simulator vs. a CD-ROM on Performance

This study provides unprecedented comparison between training medical personnel to treat combat injuries through a human patient simulator and through use of a CD-ROM. Results indicate that students who trained through the use of a human patient simulator performed better than those who trained with a CD-ROM. Human patient simulators, though more expensive to implement, provide medical personnel with a more realistic situation that lends itself to practicing cognitive skills and applying principles, laws and theory more than the CD-ROM training.

## Military Medicine: Injuries, Changes in Fitness, and Medical Demands in Deployed National Guard Soldiers

Researchers studied 54 Soldiers from the Arizona National Guard who completed pre and post-deployment fitness tests and medical examinations in order to assess the demands on medical personnel. Findings indicate that 80 percent of Soldiers needed medical treatment for injuries or illness during their deployment, and musculoskeletal injury is the most common injury treated. National Guard Soldiers enhanced their body composition, strength and endurance but decreased their aerobic fitness during deployments. Soldiers replace aerobic exercise with resistance training, due to extreme weather in deployments as well as unsafe conditions and less than optimal running surfaces. Those Soldiers who displayed a sharp decrease in aerobic fitness required twice as much medical attention as Solders who maintained aerobic fitness. Enhancing aerobic fitness can decrease the medical demands on personnel during deployments.

### *Traumatic Brain Injury*

## PLoS One: Traumatic Brain Injury-Induced Dysregulation of the Circadian Clock

Because TBI shares similar characteristics and processes with the circadian rhythm, which is responsible for memory formation, injuries sustained from TBI may explain the disruption, or dysregulation, of the circadian clock. Put simply, TBI may cause or result in

a loss of memory or cognitive function. The resulting suggested medication, then, is to include drugs with chronobiotic properties as part of a larger TBI treatment.

### Journal of Neuroinflammation: New perspectives on central and peripheral immune responses to acute traumatic brain injury

As TBI goes underdiagnosed, especially mild cases, it is important to note that long-term consequences such as cognitive, behavioral and immunologic responses can still arise. For example, TBI may disrupt the barrier between the blood and the brain resulting in the infiltration of white blood cells into the brain, which causes inflammation and neurological deterioration and possibly multi-organ damage in the long-term.

### Military Medicine: Relationship Between Mechanism of Injury and Neurocognitive Functioning in OEF/OIF Service Members With Mild Traumatic Brain Injuries

In a study of Soldiers suffering from blast-related and non-blast-related minor TBI (mTBI) sustained in Iraq or Afghanistan, the article focused on the distinguishing characteristics of the blast versus non-blast consequences.

***Warrior Care***

### Military Medicine: Medical Stability Operations—One Approach to Transforming the Department of Defense Military Health System

An 8-step process developed by internationally acclaimed leadership and organizational change expert Dr. John Kotter addresses how Medical Stability Operations will meet DoD standards as U.S. forces will no longer be sized to conduct large-scale operations. This 8-step process includes leadership expressing a sense of urgency regarding changes to Medical Stability Operations and establishing a matrix that will diversify and expand leadership. Leadership should determine actionable goals for changes to Medical Stability Operations, should empower junior employees to get involved and changes should be implemented over the next 12 to 24 months.

### Military Medicine: Mission Essential Fitness: Comparison of Functional Circuit Training to Traditional Army Physical Training for Active Duty Military

This study compared the effectiveness of Mission Essential Fitness (MEF) circuit-style training with current Army Physical Readiness Training and each training method's effects on fitness, physiological and body composition. Results indicate that both methods improved muscular strength and endurance while MEF improved cardiovascular endurance and flexibility. Research on this subject is essential given recent MEDCOM messaging on the importance of physical fitness in maintaining strong physical, emotional and behavioral health.

### Emerging Infectious Disease: Monkey Bites among US Military Members, Afghanistan, 2011

Research into determining the risk to Soldiers in Afghanistan of contracting serious infections from monkey bites studied ten instances of monkey bites among military in Afghanistan, eight of which were Army Soldiers. Eight of the ten instances were received by monkeys kept by Soldiers, Afghan National Security Forces or Afghan civilians as pets. Risk of monkey bites could increase as Soldiers work closer with ANSF and Afghan civilians, and the Army can mitigate this by issuing protocol that discourages Soldiers from approaching monkeys and that provides medical personnel with education on treating bites

***Other***

### Military Medicine: 2003-2009 Marital Functioning Trends Among U.S. Enlisted Soldiers Following Combat Deployments

This study used three primary measures to determine the effect of increased frequency in deployments on marriages: marriage quality, instances of infidelity and intent to separate or divorce. The soldiers studied between 2003 and 2009 reported declining quality in their marriages with incidences of infidelity and intent to separate rising. The study observed, however, that actual marriage dissolution rates did not increase between the six-year timeframe. Recent media coverage has noted the link between relationship issues and PTSD, depression, anxiety and suicide among Soldiers.

### Military Medicine: Interpersonal Conflict and Referrals to Counseling Among Married Soldiers Following Return From Deployment

The study focused on the prevalence of interpersonal conflict among military families following deployment. Higher rates of interpersonal conflict existed among those military spouses who reported health problems, depression, PTSD or alcohol abuse. The study also discovered that 11 percent of those Soldiers who were not currently receiving health services were referred to counseling.

### The Lancet: Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study

The study set out to determine the length of time necessary to conduct resuscitation with in-hospital heart attacks and whether the duration has any impact on survival rates. The study could not establish an optimal time of resuscitation, but increased efforts at extending the duration of resuscitation were seen to improve the high-risk population.

### The Lancet: Duration of in-hospital resuscitation: when to call time?

In continued research related to cardiac arrest, researchers utilized data from 64,339 patients at US hospitals from years 2000 to 2008. To relate the duration of resuscitation to survival rates, researchers found the median resuscitation time for survivors was 12 minutes with 87.6 percent regaining circulation within 30 minutes of attempted resuscitation. The clinicians also found no implications that increased durations may cause severe neurological injury.

### The Lancet: Fire without smoke: targeting smokeless tobacco use

This article covers the dangers of using smokeless tobacco including nicotine addiction, dental disease, mouth cancer, cardiovascular disease and pregnancy complications. It notes that some users are unaware of these dangers and urges health professionals to discuss the risk associated with using smokeless tobacco with their patients.

### The Lancet: Job strain as a measure of exposure to psychological strain

High job demands coupled with a lack of control over these demands leads to stress, which can adversely affect one's mental and physical health, especially in jobs of a physical nature. This article notes that few studies have evaluated the interplay between job demands and job control in causing a stressful work environment. Research on this topic is especially applicable to the military, as Soldiers, especially those on deployments, work in a high-demand, low-control environment.

### Military Medicine: Occupational Effect on the Occurrence of Idiopathic Venous Thromboembolism

Researchers studied the affect of age, body side and occupation within the U.S. Military on blood clots that form within a vein. Results indicate that Soldiers serving in infantry, artillery and combat positions had the highest risk of developing blood clots followed by health care workers. This increased risk may reflect a requirement for prolonged standing. Normal weight protected against blood clots but body size had less of an effect than researchers anticipated.

## Military Medicine: Meningitis Admitted to a Military Hospital: A Retrospective Case Series

Researchers filled the void in information and studies on meningitis and its affect on the U.S. Military population. This study utilized data from 2004 through 2008 and focused on 221 cases of meningitis among service members in all branches of the military. Out of 221 cases, only three had poor outcomes with one death and two who suffered long-term neurologic deficits. Although meningitis is a common diagnosis, serious outcomes are rare in the U.S. Military population.

## Military Medicine: Chinese Scalp Acupuncture Relieves Pain and Restores Function in Complex Regional Pain Syndrome

Complex Regional Pain Syndrome (CRPS) is a potential effect of trauma or surgery that can be difficult to manage as it often occurs alongside nerve damage. Its symptoms include neuropathic pain, allodynia, sudomotor changes and a decreased range of motion. Two Soldiers who failed conservative treatments for CRPS underwent Chinese Scalp Acupuncture twice per week for one to four weeks. These Soldiers improved pain by over 80 percent, enhanced functional movement and normalized sensation. Effects were sustained for a 20 month follow up period. Acupuncture as an alternative pain treatment has been covered in recent media given in-depth reporting on abuse of prescription pain medication.

## Military Medicine: Perceived Stigma and Barriers to Mental Health Care in Marines Attending the Combat Operational Stress Control Program

This study of 553 Marines in the Combat/Operational Stress Control (COSC) briefings and programs found that Marines preferred to solve stress, mental and behavioral health problems on their own. Fear that their peers would view them differently, their unit would stop trusting them and that their statements in therapy session weren't confidential were significant barriers preventing service members from seeking therapy. Particularly significant was the fear that seeking mental health care would negatively affect the service member's career. Younger Marines had more misconceptions about CSRs while college educated Marines displayed embarrassment at seeking help for mental health problems, losing trust and being treated differently by leadership. Findings indicate that removing the stigma will be particularly difficult as mental health diagnosis in some cases are provided to military leadership. Leadership should focus on reinforcing confidentiality in order to remove the stigma.

## Medical Journal Clips

***Nutrition***

# Confidence in the efficacy and safety of dietary supplements among United States active duty army personnel

BMC Complementary and Alternative Medicine
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Abstract

Background

United States Army Soldiers regularly use dietary supplements (DS) to promote general health, enhance muscle strength, and increase energy, but limited scientific evidence supports the use of many DS for these benefits. This study investigated factors associated with Soldiers‟ confidence in the efficacy and safety of DS, and assessed Soldiers‟ knowledge of federal DS regulatory requirements. Methods Between 2006 and 2007, 990 Soldiers were surveyed at 11 Army bases world-wide to assess their confidence in the effectiveness and safety of DS, knowledge of federal DS regulations, demographic characteristics, lifestyle-behaviors and DS use.

Results

A majority of Soldiers were at least somewhat confident that DS work as advertised (67%) and thought they are safe to consume (71%). Confidence in both attributes was higher among regular DS users than non-users. Among users, confidence in both attributes was positively associated with rank, self-rated diet quality and fitness level, education, and having never experienced an apparent DS-related adverse event. Fewer than half of Soldiers knew the government does not require manufacturers to demonstrate efficacy, and almost a third incorrectly believed there are effective pre-market federal safety requirements for DS.

Conclusions

Despite limited scientific evidence supporting the purported benefits and safety of many popular DS, most Soldiers were confident that DS are effective and safe. The positive associations between confidence and DS use should be considered when developing DSrelated interventions or policies. Additionally, education to clarify Soldiers‟ misperceptions about federal DS safety and efficacy regulations is warranted.

Keywords

Consumer beliefs, Military, Government regulation, Dietary supplement health and education act (DSHEA)

## Background

Since the passage of the Dietary Supplements Health and Education Act (DSHEA) in 1994, U.S. sales of dietary supplements (DS) – defined by the legislation as products intended to supplement the diet, including vitamins, minerals, herbs and botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites [1] – have risen dramatically from $8.8 billion [2] to an estimated $28.7 billion for 2010 [3]. There has also been a substantial increase in the proportion of adults, both civilian and military, who regularly use DS – current estimates suggest that 52% of U.S. adults and 53% of military personnel regularly use some form of DS [4,5].

Dietary supplements are commonly consumed by Americans to promote general health, improve energy or memory, and to treat or prevent medical conditions such as osteoporosis or arthritis [6]. However, for a majority of supplements, there is limited evidence to support such benefits. Consumers may also believe that DS are “natural” remedies, and are, therefore, safer to consume than traditional medical treatments, such as drugs [7]. However, U.S. federal regulations do not subject DS to the same stringent safety and efficacy regulations that the Food and Drug Administration (FDA) imposes on prescription and over-the-counter drugs [8].

Although manufacturers are legally responsible for ensuring the safety of DS and for ensuring any product claims are not false or misleading [1], they are not required to provide definitive pre-market substantiation of either safety or efficacy, or to have the product evaluated by an independent scientific regulatory entity. Rather, the onus for determining if or whether a DS is unsafe is on the FDA; for the agency to recall a supplement, it must obtain sufficient evidence that the specific supplement in question is unsafe and poses a “significant or unreasonable risk of illness or injury” [8,9]. Manufacturers must inform the FDA prior to introducing a new dietary ingredient to the market. However this notification is often not accompanied by a safety assessment of the product [10]. Statements and claims suggesting possible benefits of consuming a DS are also minimally regulated. Manufacturers may make “structure-

function claims" on packaging, provided claims do not reference a specific disease or condition, and provided their claims are qualified with the disclaimer, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

Industry data indicate that consumer confidence in the safety, quality and effectiveness of DS has increased over the past decade. In 2001, 74% of American adults surveyed indicated they were somewhat or very confident in the safety, quality and effectiveness of dietary supplements. By 2010, that number had increased to 82% [11,12]. This high level of confidence may be due to consumers‟ misconceptions about the extent of pre-market review and regulatory oversight that a DS must undergo. Many Americans are unaware or misinformed about the FDA‟s role in regulating DS [7,9,13,14], and may assume that DS are subject to the same efficacy and safety testing as OTC drugs [8]. Such beliefs may foster a false sense of security in the efficacy and safety of supplements. In fact, making individuals explicitly aware that the FDA had not approved a particular DS made them more skeptical of the product's safety, although it did not affect participants‟ ratings of product efficacy [15].

This may suggest consumers are willing to rely on their own experiences to form opinions regarding DS efficacy, but are less likely to rely on their own experiences to form opinions regarding DS safety.

While there is an increasing body of literature examining characteristics of supplement users, relatively little is known about the factors that influence consumer confidence in DS. However, regular users of DS are more inclined to believe supplements are effective and safe compared to non-users [2,9,16,17]. The purpose of this study was to assess beliefs about DS efficacy and safety among U.S. Army Active Duty personnel, a population known to have a high frequency of DS use [4], and to investigate whether certain demographic and lifestyle factors of DS users are associated with higher confidence in either attribute. We hypothesized that confidence in DS efficacy and safety would be associated with age, education, and self reported fitness level because similar factors were associated with DS use among military personnel in a previous investigation [4]. Additionally, we evaluated whether knowledge of the government's role in DS regulation influenced users‟ beliefs that DS work and are safe to consume.

## Methods

Sample population The survey sample consisted of 990 respondents from 11 military bases – 9 in the U.S. and 2 overseas – and were collected in 2006-7. Survey sites were selected based on the distribution of the Soldier population and their availability. The eligible population included all active duty U.S Army personnel (a total of 504,422 individuals as of 1 January 2007). Both DS users and nonusers were included in the sample. Survey sites were selected according to the distribution of the soldier population, site availability, and potential to capture a diversity of soldier ranks and job descriptions. Individuals who were on temporary or

transitional status, including individuals absent without leave, incarcerated, or moving between permanent duty stations were excluded. Soldiers enrolled in Basic Combat Training or Advanced Individual Training were also excluded, as DS are prohibited during such training. The study was approved by the Institutional Review Board of the United States Army Research Institute of Environmental Medicine (Natick, MA, U.S.A.).

Survey administration

The data used in this study were obtained from the "Dietary Supplement and Caffeine Intake Survey of US Army Active-Duty Personnel" [4,18]; see Additional file 1 for a copy of the survey. This survey assesses the frequency and reasons for using DS, in addition to demographic and lifestyle information, including questions related to beliefs in the confidence and efficacy of DS. A pilot survey was first conducted with 30 local Army Soldiers to confirm comprehension of study questions and determine time required to complete the survey. Feedback from these volunteers and evaluation of the pilot data indicated volunteers provided reliable and accurate responses to the questions. Following administration of this pilot survey, a contact – typically a dietitian or other health care professional – administered the questionnaire at each study site. The contact arranged with a unit manager or class instructor to distribute the survey at a meeting or class held for another purpose. Typically, when a unit entered the room where the survey was administered, they were seated. A variety of units and classes were approached to ensure representation of all demographic groups. A standardized study briefing was then presented that described the purpose of the survey, which was to assess DS use in the Army.

The briefing also described the contents of the survey and its confidential and voluntary nature (no identifying data were collected), and procedures for completing multipart questions. Volunteers then remained in their seats and completed the survey. The completed surveys were returned to the investigators via mail and were scanned and tabulated with ScanTools Plus with ScanFlex (version 6.301; Scantron Corporation, Eagan, MN, U.S.A.), and SPSS (version 15.0; SPSS Inc, Chicago, IL, U.S.A.). Approximately 80% of Soldiers who attended a study briefing opted to complete the survey. Demographic data could not be collected on non-participants, therefore it was not possible to determine whether participants differed from non-participants in any way. However, as 80% of Soldiers given the opportunity to participate did so, and they represented a diverse sample of the Army, response bias is unlikely to have substantially impacted the findings of this study.

Variables

Two survey questions assessed participants‟ confidence in DS: "How confident are you that your dietary supplements will do as they claim?" and "How confident are you that your dietary supplements are safe to consume?" For each question, participants selected between four response options: "Extremely confident", "Very confident", "Somewhat confident" or "Not at all confident". Two more

questions assessed knowledge of DS regulation: “Does the U.S. Government require that all dietary supplements sold will work as promised?” and “Does the U.S. Government require that all dietary supplements sold are safe for consumption?” For these two questions, participants answered “Yes”, “No”, or “I don't know”.

The survey instrument also assessed demographic and lifestyle factors, including sex, age, racial background, military rank, Special Forces status, deployment status, education, military occupation, marital status, tobacco use, aerobic exercise duration, and strength-training participation. Additional questions evaluated usage patterns and reasons for use of both generic supplements (including vitamins, minerals, combination products, antioxidants, herbals, protein and amino acid supplements, and purported steroid analogs) and specific, brand-name products, chosen for inclusion based on then-current patterns of DS purchases at the Army Air Force Exchange System and General Nutrition Center stores on or near Army installations. Participants also had the option to write-in supplements they used that were not listed in the survey. These data are reported elsewhere [4].

Data analysis

SAS (version 9.2; SAS Institute, Cary, NC, U.S.A.) was used for data analysis. All data were weighted by sex, age, rank, and Special Forces status to represent the overall Army composition as of January 1, 2007. Weights were based on demographic data obtained from the Defense Manpower Data Center (www.dmdc.osd.mil/) and the characteristics of survey respondents.

For the purposes of analysis, Soldiers were classified as DS users if they reported consuming a DS (excluding sports drinks, sports bars or gels, and meal replacements) ≥ 1 time/wk during the six months before the survey; all other respondents were classified as nonusers. Standard errors were estimated using a Taylor series linearization method that incorporated sampling weights using the SAS mean procedures. Responses to the two high-confidence categories (i.e. “Extremely confident” and “Very confident”) were pooled for analysis. Category percentages were derived from the „surveyfrequency‟ procedure in SAS. The „surveylogistic‟ procedure was used to estimate the likelihood of confidence in DS efficacy or safety (odds ratio and 95% confidence interval) among DS users according to the following participant characteristics: age group; sex; racial background; education; rank; tobacco use; self-rated health, eating habits and fitness level; and reported DS-related adverse events. The likelihood of confidence in DS efficacy and safety was also estimated according to participants‟ knowledge of government regulation of DS efficacy and safety. To adjust for multiple comparisons, a Bonferonni adjustment was used for comparisons being made on 26 associations between independent variables and confidence dependent variables. Confidence intervals were calculated with alpha set to 0 .0019 in the model statement of the „surveylogistic‟ procedure. The „surveyfrequency‟ procedure was also used to derive a Wald chi square test of general association between DS user status and the confidence and knowledge variables. All analyses that required sub-setting the data according to DS user status were performed using the domain statement. We tested for statistical interaction between sex and all

predictor variables. However, no interaction term was significant in any model. Thus, all analyses are presented for men and women combined, with the exception of analyses of sex as the independent variable.

## Results

### Sample characteristics

All survey respondents were Active Duty Army personnel.

Table 1 displays the characteristics of the sample and frequency of any DS use by demographic group, weighted to represent the full Army composition. Accordingly, demographic percentages were highest for males (86.8%), white/Caucasians (69.5%), 18-24 year olds (41.0%), and enlisted Soldiers (83.5%). More subjects reported their overall health (88.3%), fitness level (76.6%), and eating habits (63.3%) to be “excellent/good” as opposed to “fair/poor”. Most subjects also reported not having experienced an adverse event (86.0%) attributed to DS use. Over half of all respondents (53.2%) used some form of dietary supplement, as defined by DSHEA, at least once per week during the 6 months prior to the survey. Similar to previously published data [4], the percentages of any DS use was highest among those with older age, a Bachelor‟s degree or higher, and warrant officers and officers.

1 Study sample was weighted by sex, age, rank, and Special Forces status to represent the full Army composition as of January, 2007 2 Any DS included all DS at defined by the DSHEA legislation that were reported used at least once a week or more often over the last six months prior to the survey. Any DS excludes sports drinks, sports bars/gels and meal replacement beverages
In addition, proportionately more former or never smokers (58.1%) used DS compared to current smokers (46.9%), as well as those that rated their overall health and eating habits as excellent/good compared to fair/poor (54.2% vs. 45.2% and 55.7% vs. 49%, respectively). Proportionately more subjects with APFT scores above the median category (61.3%) used DS than those with APFT scores at the median (50.3%) or below (51.8%). The majority of subjects reported not experiencing an adverse event (86.0%)

### Confidence in DS efficacy

Two-thirds (67%) of all respondents were at least somewhat confident that DS work as advertised, and approximately half had high confidence (i.e. selected “Extremely” or “Very confident”) (Figure 1). Confidence in the purported efficacy of DS differed significantly by user status ($p < .001$); 86.5% of users had at least some confidence that DS work as advertised, compared to only 38.3% of non-users. Most non-users (61.7%) were “Not at all confident” that DS work as advertised; however, 13.5% of the respondents who used

DS also endorsed this response option. Among users, beliefs regarding DS efficacy did not significantly differ significantly by age, sex, racial background, education, or rank (Table 2).

Among DS users, self-reported fitness level and eating habits were both significantly associated with beliefs about DS efficacy (Table 2). Those who reported fitness levels as “Excellent/Good” were more than twice as likely to be highly confident in DS efficacy than those who reported fitness levels as “Fair/Poor” (OR = 2.37, 95% CI = 1.01-5.57). Those who reported their eating habits as “Excellent/Good” were nearly two and half times as likely to be extremely/very confident (OR = 2.47, 95% CI = 1.19-5.11) and approximately 50% less likely to be somewhat confident (OR = 0.49, 95% CI = 0.24-0.99) in DS efficacy than those who reported their eating habits as “Fair/Poor”. On the other hand, neither perceived overall health status, nor tobacco use (current vs. former/never) was related to confidence in DS efficacy. Finally, a significant association was observed between self-reported adverse events and confidence, such that participants who believed they had experienced an adverse event due to DS usage were over two times more likely to be somewhat confident in DS efficacy than those who did not experience an adverse event (OR = 2.35, 95% CI = 1.03-5.38), but were less likely to be either extremely/very confident or not at all confident, although these associations were not significant.

Confidence in DS safety

Soldiers had slightly more confidence in DS safety than efficacy; 70.8% of all respondents were at least somewhat confident DS are safe to consume, and of them, 42.2% reported high confidence (Figure 2). Confidence in the safety of DS differed significantly by user status ($p < .001$). Eighty-eight percent of users reported at least some confidence in DS safety, while less than half (45.0%) of non-users reported at least some confidence. Surprisingly, while 55.0% of non-users were “Not at all confident” that DS are safe to consume, 11.7% of users also indicated they had no confidence in DS safety.

Figure 2 Percentage of respondents reporting degree of confidence in DS safety (extremely/very confident, somewhat confident, or not at all confident) for all respondents and according to DS user status. $P < 0.001$ indicates a significant association between DS use status and confidence according to the Wald chi-square test Among users, reported confidence in DS safety did not differ by sex or racial background (Table 3). In general, all older age groups were more likely to be somewhat confident and less likely to be not at all confident in DS safety than 18-24 year olds, but these associations were only significant for 25-29 year olds (somewhat confident; OR = 2.06, 95% CI = 1.16- 3.65) and 30-39 year olds (not at all confident; OR = 0.38, 95% CI = 0.17, 0.84). Both education status and rank were also associated with how participants viewed the safety of their supplements; Participants who had completed a bachelor’s degree or higher and officers were less likely to be not at all confident in DS safety than those with less education (OR = 0.41, 95% CI = 0.19-0.93) or enlisted personnel (OR = 0.30, 95% CI = 0.11-0.83), respectively. Former or individuals who had never

smoked were less likely to be somewhat confident in DS safety than current smokers (OR = 0.61, 95% CI = 0.38-0.96). Interestingly, former or individuals who had never smoked were more likely to be both extremely/very confident and not at all confident, but these associations were not significant.

There were significant relationships between both self-reported fitness-level and eating habits and participants‟ confidence in DS safety. Those who reported their fitness level and eating habits as “excellent/good” were less likely to be somewhat confident in safety than those who reported those factors as “fair/poor” (OR = 0.56, 95% CI = 0.34-0.92 and OR = 0.49, 95% CI = 0.31-0.77, respectively). Those who reported their eating habits as “excellent/good” were also over twice as likely to be extremely/very confident in safety than those who reported their habits as “fair/poor” (OR = 2.18, 95% CI = 1.07-4.43). Conversely, neither self-reported overall health status nor enrollment in the Army Weight Control Program were related to participants‟ beliefs that supplements are safe to consume. Those who reported scoring at or above the median category of Army Physical Fitness Test (APFT) score (≥ 240) were over two times more likely to be extremely/very confident in safety (OR = 2.14, 95% CI = 1.03, 4.46) and less likely to be somewhat and not at all confident in safety (OR = 0.62, 95% CI = 0.39, 0.99 and OR = 0.49, 95% CI = 0.26-0.89, respectively). Users who believed they had experienced one or more adverse events from taking DS were less likely to be extremely/very confident in safety (OR = 0.34, 95% CI = 0.14-0.79) and more likely to be only somewhat confident in safety (OR = 3.33, 95% CI = 1.95-5.7) than those who did not report experiencing an adverse event. Knowledge of government regulation Nearly half of all respondents did not know whether the U.S. government requires DS to work as advertised and 46.4% knew it does not. Only 3.8% of all respondents incorrectly believed the government requires DS to be effective (Figure 3). However, many Soldiers (30.3%) believed the government requires all marketed DS to be safe for consumption (Figure 4).

Figure 3 Percentage of respondents reporting knowledge of government regulation of DS efficacy for all respondents and according to DS user status. Respondents prompted to answer „Yes‟, „No‟, or „Don’t know‟ to the following question, “Does the U.S. Government require that all dietary supplements sold will work as promised?” P < 0.001 indicates a significant association between DS use status and knowledge of government regulation of DS efficacy according to the Wald chi-square test Figure 4 Percentage of respondents reporting knowledge of government regulation of DS safety for all respondents and according to DS user status.

Respondents prompted to answer „Yes‟, „No‟, or „Don’t know‟ to the following question, “Does the U.S. Government require that all dietary supplements sold are safe for consumption?” P < 0.001 indicates a significant association between DS use status and knowledge of government regulation of DS safety according to the Wald chi-square test Knowledge about DS regulation for efficacy and safety differed significantly by user status ($p < .001$; $p < .001$) (Figures 3 and 4). Most users (55.2%) knew the government does not require DS to work as advertised, whereas most non-users (60.4%) did not know whether or not there are federal regulations for DS efficacy. Also, proportionately more users than nonusers believed that the U.S. Government requires DS to be safe for

consumption (38.3% and 21.4%, respectively). Beliefs about federal DS regulation were significantly associated with how confident users were in the efficacy and safety of supplements (Table 4). Users who believed the government does not require all DS sold to be effective were less likely to be extremely/very confident in DS efficacy compared to those who did believe (OR = 0.40, 95% CI = 0.11-0.99). Users who did not know whether the government requires all DS sold to be safe were less likely to be extremely/very confident (OR = 0.43, 95% CI = 0.26-0.71) and more likely to be not at all confident (OR = 6.52, 95% CI = 2.58-16.5) in DS safety than those who did believe the government requires all DS sold to be safe. Those who did not believe the government requires all DS sold to be safe were also more likely to be not at all confident in DS safety than those who did believe.

## Discussion

This study is the first to assess beliefs about DS efficacy and safety among U.S. Army Soldiers and to examine demographic and lifestyle factors are associated with higher confidence in DS efficacy or safety among DS users. Additionally, it is the first to assess whether knowledge of federal DS regulatory requirements affected users‟ perceptions of supplement efficacy or safety. We found most Soldiers were at least somewhat confident DS work as advertised and are safe to consume, that confidence in DS efficacy and safety was higher among users compared to non-users, and that users who had not experienced DSrelated adverse events had higher confidence in both attributes. Most Soldiers had limited or inaccurate knowledge of federal DS regulatory requirements. Furthermore, confidence in DS efficacy and safety was higher among users who believed government regulations require that all marketed supplements work as advertised and are safe to use.

### Confidence in DS efficacy and safety

Confidence in both DS efficacy and safety was substantially greater among regular supplement users, who make up about half the Army population. The positive association between usage and confidence in DS is not surprising, and is consistent with other reports. For example, Blendon et al. [2] showed regular DS users, compared to non-users, were more likely to believe that advertisements about DS are generally true, that DS undergo adequate pre-market testing, and that DS “rarely or never” harm the user. Likewise, individuals who use herbal supplements or OTC weight-loss aids were found to be more likely to perceive such products as effective and/or safe compared to nonusers [16,17]. Marketing research has shown that direct product exposure (e.g. sampling or using a product) results in higher, and more firmly-held beliefs and attitudinal confidence in the product compared to indirect product exposure (e.g. viewing advertising materials) [19], presumably because people generally trust their own judgment, but recognize that advertisements are often biased. Thus, DS users may be more likely to believe DS work and are safe, simply because they have tried the product, even if the product is ineffective. It is also possible that individuals with low confidence in DS are less likely to begin using the product in the first place.

Our findings indicate DS users‟ product confidence was positively related to self-rated diet quality, perceived fitness level, and rank. These associations may be due in part to participants‟ level of optimism and/or self -confidence. Individuals with healthier lifestyles are more likely to have an optimistic cognitive bias compared to those with less healthy behaviors [20], and thus may be predisposed to believe DS are efficacious and safe.

Similarly, Soldier rank correlates positively with self-confidence [21], so officers may be more likely to believe their actions are purposeful and beneficial (e.g. that consuming DS is efficacious and safe) compared to enlisted personnel. Because U.S. Army officers generally have more formal education compared to enlisted personnel, our observation that DS confidence in safety increased with education may be a reflection of respondents‟ rank and, hence, self-confidence. This may explain why our result differs from other studies, which reported lesser-educated individuals more likely to believe DS are effective and/or safe [7,9]. On the whole, these observations suggest that DS users‟ confidence in product efficacy and safety is partly dependent on internal factors – such as self-confidence and optimism. Self-confident individuals may not seek out accurate product knowledge (i.e. from scientific sources) because they trust their ability to evaluate the veracity of product information, regardless of source; and optimistic individuals may not seek out scientific confirmation because they are already inclined to believe the product will work.

Knowledge of DS regulation

Most Soldiers had a limited or inaccurate understanding of the U.S. government's role in regulating DS, which reflects what has been reported in the general American population [2,7,13,14]. Of note, Soldiers were more apt to believe the government requires DS to be safe than to think the government imposes strict efficacy requirements, particularly if they used DS. Twice as many users as non-users incorrectly believed the U.S. government requires DS to be safe. The reasons for this difference are not clear. Confidence may be influenced by the disclaimer statement required on many DS, which states that the FDA has not approved any health or structure-function efficacy claims made on the label, but says nothing about product safety. Consumers may interpret this lack of a safety disclaimer to mean the product is not harmful (see Dodge and Kaufman, 2007 [15]). One limitation of this study is that we did not separately assess participants‟ confidence in each supplement, or for each type of supplement (e.g. protein/amino-acid supplements, vitamins/minerals, etc.), therefore, it is not possible to conclude whether users‟ confidence in DS varies between individual types of supplements. Future research should investigate whether confidence varies by supplement type. Additionally, Soldiers may have misinterpreted the questions about government regulation of DS, since even without pre-market approval requirements for efficacy and safety, there is some limited de facto regulation by the U.S. government in the form of post-market FDA surveillance.

Information on Soldiers‟ level of confidence in DS may be useful when developing educational strategies for Soldiers about DS, as confidence and beliefs can affect how people receive information on a particular topic. In addition, these strategies should also consider that DS users may already engage in health behaviors. For example, self-reported health behaviors, including smoking, overall health, and fitness levels appeared to be related to DS use in this study. Those in the highest APFT score category also reported the highest percentage of DS use. While the majority of subjects have not experienced an adverse event (86.0%), 14% did report experiencing an event, indicating that although adverse events are not widespread, they do occur. Taken together, these data suggest that the behavioral interventions aimed at motivated individuals who use DS in conjunction with health behaviors may best be focused on providing education on evaluating DS efficacy and safety. This may aid individuals in making decisions regarding DS use to optimize effectiveness, while minimizing the risk of experiencing an adverse event. Results of this study indicate that education to clarify Soldiers‟ misperceptions about federal DS safety and efficacy regulations is warranted. Furthermore, because an individual's beliefs regarding the value of a particular action (i.e. use of a particular supplement) may influence his/her his motivation to change that behavior [22], an intervention approach that works in individuals with low confidence will likely not be effective in highly-confident users. In this survey, respondents most frequently cited magazines, friends, and the internet (data not shown) as the source of their dietary supplement information, thus these sources may be a potential target of educational interventions.

Conclusions

This study expands the existing literature on dietary supplements by exploring factors associated with DS users‟ confidence in these products, and is the first to investigate beliefs regarding efficacy and safety of DS in a military population. Although there is limited scientific evidence in support of manufactures‟ claims regarding the benefits and safety of most popular DS, this analysis demonstrated most Soldiers were at least somewhat confident that these products are effective and safe. In general, confidence in both attributes was higher among users compared to non-users, and among users, is positively associated with rank, education, self-perceived diet quality and fitness level, and having experienced no adverse events resulting from DS consumption. The positive associations between confidence and DS use should be considered when developing DS-related interventions or policies. Education to clarify Soldiers‟ misperceptions about federal DS safety and efficacy regulations is warranted. Additionally, future studies should consider surveying a matched group of civilians for comparison to Soldiers.

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***Fractures***

# Identical fracture patterns in combat vehicle blast injuries due to improvised explosive devices; a case series

BMC Emergency Medicine
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10 Oct 2012

Background

In November 2008, a surgical team from The Red Cross Hospital Beverwijk, the Netherlands, went to Afghanistan to attend in the army hospital of Kandahar Air Field (KAF). During the three-month stay, several armored personnel carriers, type MRAP, encountered improvised explosive devices (IEDs). IEDs are homemade explosives that are often used by insurgents and terrorists in the Middle East. In Iraq, in 2005, 10,000 attacks were reported. From June 2003 to January 2008, IEDs caused over 1,500 fatalities. IEDs are similar to mines and are often activated by the victim himself. Often, IEDs incorporate metal fragments and/or animal fecal excrements [1-4]. IEDs contributed to the majority of injuries in casualties in the British Military Field Hospital, Shaibah, Iraq in 2006[5].

Upon the victims' arrival in the hospital, after triage, resuscitation and stabilization, it became clear that the occupants in each vehicle had sustained strikingly similar injuries. In this report we will describe the four cases and the trauma mechanisms.

To comprehend the trauma mechanisms, it is important to be well aware of the different types of blast trauma and their impact.

Blast injuries can be classified into four types. Primary blast injuries (explosive forces) are those caused by the direct effect of overpressure on a person. Secondary blast injuries are injuries caused by the effect of projectile fragments incorporated in the bomb, like nails, rocks or scrap metal. Tertiary blast injuries are caused by the effects from the blast wind, resulting in physical displacement. Also in this group are injuries resulting from collapsing buildings. Most fractures, blunt trauma and tissue contusions are tertiary blast effects [1,2,6]. A variety of injuries are classified in the group of quaternary blast injuries, including burns, psychological trauma, toxic inhalation and exposure to radiation [2,6]. The cases described below are classified in the tertiary injury group.

Furthermore the magnitude of the effects of an explosion on a person is dependent on several factors. Most important is the magnitude of the explosion, the medium through which the pressure wave passes, the distance of a person to the epicenter and, lastly, the environment of the incident (i.e., open air or enclosed space) [2,7,8]

The aim of the article is to establish whether useful adjuncts in the assessment of blast injury patients can be put forward following the assessment of four paired cases of blast injury. Case presentation

Case pair A

An armored vehicle was hit by an IED strike. The two soldiers sitting on the front seat of the vehicle were hemodynamically and respiratory stable. Both men complained of back pain and on physical examination palpation of the lower thoracic vertebrae elicited pain. No abnormal neurologic signs were found on examination. A CT scan revealed unstable fractures, Magerl/AO spine fracture classification type 3.2, burst-split, of the anterior and intermediate columns of the 9th thoracic vertebra in both patients (Figure 1). Presumably, a large blast force from beneath pushed their bodies up in their belts, resulting in this type of burst-split fracture. Although lumbar fractures are seen more frequently in sub-vehicle blast injuries, both fractures concerned Th 9[9,10]. The Abbreviated Injury Score (AIS) was 3[11]. Figure 1 Case pair A, two sagittal reconstructions of CT-scans of two separate thoracic vertebral columns of two passengers of an armored personnel carrier that hit an improvised explosive device (IED). Both showed identical, unstable burst-split fractures of the 9th thoracic vertebra

In Afghanistan, both patients were treated conservatively. Within 48 hours they were transported to Landstuhl, Germany, for additional treatment.

Case pair B

Two soldiers, both board gunners, were sitting behind their weapons (attached to the vehicle) on the right and left sides of the truck, holding their weapon in the same way, both hands positioned on a grip. Axial forces injured both soldiers after their truck hit an IED. ATLS work-up did not reveal any airway, respiratory or circulatory instability. In addition to multiple open wounds of the face and hands, they complained of elbow pain. In both cases, X-rays revealed the same radial neck fracture, AO 21-A2.2, slightly displaced. The fact that the soldiers were holding weapons, which were attached to the vehicle contributed to this kind of injury, otherwise when soldiers were thrown around in the vehicle, one would expect other injuries. The AIS was 2[11]

Case pair C

In this vehicle, also after an IED attack, there was a significant displacement of the base of the truck. Both soldiers sustained a direct blow from beneath directly to the calcaneus. Again, primary assessment did not reveal vital injuries, and the patients were hemodynamically and respiratory stable. On secondary survey, both men complained of heel pain and on physical examination, swelling and discoloration surrounding the heel was seen. Pain was elicited by axial compression. Radiography showed comminuted, displaced fractures of the calcaneus in both patients, type Sanders 4 (Figure 3). Unexpectedly, they did not sustain other injuries, which would have been expected according to a previous report of Ramasamy et. al.concerning 'deck-slap' injuries[12]. The AIS was 3.

Case pair D

Two soldiers, both board gunners were standing behind their weapons on the left and right side of the truck. During an IED strike, the bottom of their vehicle struck their lower legs by a direct blow, caused by the vertical forces of the explosion just below their vehicle. After initial ATLS assessment, both patients were respiratory and hemodynamically stable. During the regular trauma work-up, both patients, although protected by heavy army boots, complained of pain in the ankle joint of the weight bearing leg. Radiographs of the ankles showed an irregular surface of the talus. A CT-scan, showed an unusual flake fracture of the lateral talar wall with 180-degree rotation of the fragments in both patients, type Müller AO/OTA C1 (Figure 4). The AIS was 3[11]. Both soldiers were operated in the US.

Discussion

As described in the background, the distance to the blast center plays an eminent role in the severity and type of injury[6]. In the cases described above, the occupants were approximately at the same distance from the blast center, which could partially explain why the impact of the explosion was similar. Furthermore, in each case, both occupants sustained injuries caused by the same blast injury pattern, namely the tertiary type.

The blast wave, coming from an IED, interacts with the vehicles by coupling energy from the blast field into the vehicle[13]. It is clear that the entire vehicle is being exposed to the same amount of energy. This case series shows that strikingly similar and unusual injuries could occur to patients seated in the same vehicle, hit by an explosion.

In all cases, the involved vehicles were MRAPs (Mine Resistant Ambush Protected), their weight is approximately 20,000 kilogram, equipped with armor and glass protection and specialized v-shaped hull design, which especially is developed to protect vehicles against IEDs.

All patients were male US soldiers. After performing damage control surgery in the army hospital in Kandahar, injured soldiers are transported to their home country or to the Landstuhl Regional Medical Center in Germany, a military hospital operated by the United States Army and the Department of Defence. Based on the described cases, since injuries were found that were unexpected and paired, a thorough secondary and tertiairy survey with special attention for injured bodily areas of the codriver is essential. To improve the trauma work-up, one should be well aware of the trauma mechanism and its consequences.

A literature search on identical orthopedic injuries after blast trauma yielded one report: in 2002 in Karachi, Pakistan, 12 survivors of a suicide bombing of a bus were brought to a private tertiary university hospital. Of these twelve survivors, all had lower limb fractures, including eleven who had fractures of the foot and ankle region and seven who suffered bilateral calcaneal fractures. Remarkable was that five of them had a Gustilo-Anderson grade III A calcaneal fracture (widespread damage of soft tissue, muscle, skin and neurovascular structures, but adequate soft-tissue coverage of the fractured bone [14]). It is important to know that the suicidal motorist hit the bus from the side and below, which implies that the blast wave came from a lower level than the victims[15].

Conclusion

From the striking similarities in the paired trauma cases of blast injuries, we conclude that special attention in the secondary and tertiary survey should be focused on bodily areas that are injured in the co-driver.

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## Reconstruction of sciatic nerve after traumatic injury in humans - factors influencing outcome as related to neurobiological knowledge from animal research.

Journal of Brachial Plexus and Peripheral Nerve Injury
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Abstract

Background

The aim was to evaluate what can be learned from rat models when treating patients suffering from a sciatic nerve injury. Methods Two patients with traumatic sciatic nerve injury are presented with examination of motor and sensory function with a five-year follow-up. Reconstruction of the nerve injury was performed on the second and third day, respectively, after injury using sural nerve grafts taken from the injured leg. The patients were examined during follow-up by electromyography (EMG), MRI and functionalMRI (fMRI) to evaluate nerve reinnervation, cell death in dorsal root ganglia (DRG) and cortical activation; factors that were related to clinical history in the patients.

Results

One patient regained good motor function of the lower leg and foot, confirmed by EMG showing good activation in the leg muscles and some reinnervation in the foot muscles, as well as some sensory function of the sole of the foot. The other patient regained no motor (confirmed by EMG) or sensory function in the leg or foot. Factors most influential on outcome in two cases were type of injury, nerve gap length and particularly type of reconstruction. A difference in follow-up and rehabilitation likely also influence outcome. MRI did not show any differences in DRG size of injured side compared to the uninjured side. fMRI showed normal activation in the primary somatosensory cortex as a response to cutaneous stimulation of the normal foot. However, none of the two patients showed any activation in the primary somatosensory cortex following cutaneous stimulation of the injured foot.

Conclusions

In decision making of nerve repair and reconstruction data from animal experiments can be translated to clinical practice and to predict outcome in patients, although such data should be interpreted with caution and linked to clinical experience. Rat models may be useful to identify and study factors that influence outcome after peripheral nerve repair and reconstruction; procedures that should be done correctly and with a competent team. However, some factors, such as cognitive capacity and coping, known to influence outcome following nerve repair, are difficult to study in animal models. Future research has to find and develop new paths and techniques to study changes in the central nervous system after nerve injury and develop strategies to utilize brain plasticity during the rehabilitation.

Keywords

Sciatic nerve injury, Nerve regeneration, Reconstruction, Outcome, fMRI, Dorsal root ganglia

## Background

Traumatic sciatic nerve injuries are not unusual in the context of war, but they are rare in civilian healthcare compared to peripheral nerve injuries in the upper extremity. The incidence of peripheral nerve injuries in Sweden is 13.9 per 100000 inhabitants and year, out of which only 2% are injuries to the sciatic nerve at hip and thigh level. The consequences of loss of sciatic nerve function are severe and despite improved microsurgical techniques injuries to peripheral nerves hinder the patients, who often are young adults, in activities of daily living and at work and thus bring large costs to society. Therefore, it is of great importance to improve existing treatment strategies and furthermore to develop new treatment strategies based on new knowledge in neurobiology. Most animal research done on peripheral nerve repair and reconstruction use the rat sciatic nerve as a model for injury.

Here, an overview of the literature on factors influencing outcome after nerve repair and reconstruction is presented followed by two cases of traumatic nerve injury that illustrate the factors influencing outcome after sciatic nerve reconstruction in humans. The clinical cases are related and compared to the knowledge gained from neurobiological research using the rat sciatic nerve injury model. The aim of the present case reports and review is to evaluate what can be learned from the rat sciatic nerve injury model when treating humans with such an injury, and furthermore to predict outcome in patients suffering from sciatic nerve injury. Here, we present two patients with traumatic sciatic nerve injury with different outcome of motor and sensory function with a three-year follow-up and related function to present knowledge about neurobiology after sciatic nerve injuries.

## Material and methods

This paper is divided into two parts. The first part is a literature review of factors influencing outcome after reconstructive surgery in peripheral nerves based on experimental and clinical studies. The factors were chosen from key references. A search was conducted in the PubMed database for each factor. The key words “peripheral nerve injury and repair”, combined with each factor or key words for each factor, gave several articles for each factor as presented. The limit “English” was used consistently. In two instances when the search generated a large quantity of articles the limit “review” was added. Articles were then chosen based on relevance to the aim presented above with focus on studies and reviews concerning sciatic nerve injuries and outcomes, such as progress of regeneration and result after reinnervation. Some articles referred to original articles that had been missed in the first database search. These were included as well.

The second part is constituted of a description of two patients treated at the Department of Hand Surgery, Skåne University Hospital in Malmö, Sweden. All experimental data reported and conducted by the authors were performed with approval of the appropriate ethics committee (Lund University; several reference numbers; provided by request). In addition, the ethics committee (humans) approved the follow up procedures (Lund University; reference number on request) and were performed according to the declaration of Helsinki. Both patients gave their consent for the report to be publised.

After injury to a peripheral nerve, several intracellular signaling pathways, initiated at the site of the lesion, convey information of the event to the neuron cell body. As a result of these signals, the cell can either go into regeneration mode or enter a pathway to programmed cell death, i.e. apoptosis. Similar alterations in signal transduction pathways also occur in Schwann cells (SC). Successful nerve regeneration depends on Schwann cell activation and proliferation as well as changes in the neurons themselves. When the axon is divided, Ca2+-ions flood into the cell causing the cell membrane to reseal. The influx of ions also creates an action potential that constitutes the first signal of injury. The normal retrograde transport of signaling molecules, such as nerve growth factor (NGF), from the periphery to the cell body is inhibited and this in itself a signal (i.e. negative signal), which alerts the neuron that an injury has occurred. Growth factors, such as leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF), present at the site of injury, bind to a tyrosine kinase receptor on the nerve cell. Thus, a signaling cascade (i.e. positive signal) is initiated, where phosphorylation and activation of subsequent enzymes end in activation of
transcription factors. The transcription factors extracellular signal-regulated kinase ½ (ERK 1/2), c-Jun N-terminal kinase (JNK), activating transcription factor 2 (ATF2) and signal transducer and activator of transcription 3 (STAT3) are activated at the site of injury and then transported by motor proteins along microtubules to the nucleus where they are imported by means of nuclear localization signals.

At the tip of the regenerating axon a growth cone with fingerlike filopodia and veil-like lamellipodia is formed. The growth cone interacts with the environment through surface integrins [8]. There are both attracting and repulsive signals acting on cytoskeleton elements.

Direction of the growth cone is achieved by polymerization or destruction of actin filaments as well as protrusion of microtubules in the growth cone. The SC, myelinating or non-myelinating, act as a supportive cell to the neuron and has a close contact with the outgrowing axons. When the axon is injured, signaling pathways similar to those in the neuron are present in the SC as well, causing it to shed its myelin and start proliferating. A multitude of genes are up-regulated as well as down-regulated in response to e.g. ERK1/2, which is activated shortly after injury. A time follows where the purpose of the SC is to ensure a favorable milieu for growing axons, including preparing the basal lamina with an encouraging surface for the outgrowing axons. Positive growth factors

are released and the proliferating cells constitute the bands of Büngner, which act as guides for the regenerating axons [13]. When regeneration is complete the SCs take up their former role as a provider of neurotrophins, like NGF and glial cell-derived neurotrophic factor (GDNF). The close one-to-one contact between neuron and glial cell is reinstated [5]. The type of axon will determine whether the SCs produce myelin or not by contact through e.g. the neural cell adhesion molecule (N-CAM) [14].

Cell death

Damage to the axon may lead to death of the neuron, impairing the possibilities for functional recovery [5]. In addition, SCs also go through apoptosis at the site of the lesion and in the distal nerve segment [15]. There are two intracellular pathways leading up to apoptosis; the intrinsic pathway, where proapoptotic enzymes are released from the mitochondria, and the extrinsic pathway, where the cell reacts to activation by receptors binding to cell surface death receptors [8]. In young animals, cell death is more common; probably due to the naturalpart apoptosis takes in neural development [16]. In studies with young animals, enzymes called caspases play a major role for the development of apoptosis. This has not been seen in adult motor and sensory neurons, but in SCs, and in satellite cells surrounding sensory neurons in dorsal root ganglia; thus, caspase 3 may be a reliable marker of apoptosis in such cells [17]. Sensory neurons are more susceptible to proapoptotic signals, which can be illustrated by the loss of dorsal root ganglia (DRG) mass seen in rats following a nerve injury [18]. There are studies in the rat model where magnetic resonance imaging (MRI) is used to evaluate the size of the DRG at the level corresponding to the peripheral nerve injury [18]. This may also be used to illustrate cell death in patients.

Age

Age of the injured individual is one of the most recognized factors determining outcome after reconstruction [19]. Children generally are considered to have a better outcome after peripheral nerve injuries; an advantage that is most notable before the age of 10 with a decline in outcome in the late teens [6,20]. Several possible explanations for this exist. The shorter distance between injury and target is one factor. Another factor is the greater capabilities of the young brain to adjust, i.e. plasticity, to the altered nerve signal pattern from the periphery through the injured nerve induced by misdirected growth of particularly the axons of the sensory neurons [19]. As we will see later, plasticity is an important factor for outcome after nerve repair and reconstruction [21]. Children have a greater learning capacity in general, for example learning languages, and it is believed that this skill complies with learning to cope with a changed sensibility as well [20].

Timing of nerve repair and reconstruction

The optimal time for repair and reconstruction of transected or lacerated nerve trunks is frequently discussed. Out of necessity, repair and reconstruction has often been delayed because of unfavorable wound conditions and the risk for infection. However, repair and reconstruction of closed nerve injuries with no apparent regain of function may also be delayed [2]. New neurobiological data, and also clinical observations, indicate that early nerve repair and reconstruction promotes axonal outgrowth and final recovery in the patient [22]. Neuronal cell death is more frequent after delayed repair, and more pronounced in sensory neurons than in motor neurons [23]. The neurons also loose regenerative potential, which is illustrated by the decreased expression of activating transcription factor 3 (ATF-3), a retrograde signal involved in inducing the genetic growth program, after delayed repair [24]. SCs distally to an injury react rapidly to denervation with de-differentiation and proliferation or apoptosis [8]. While proliferation is necessary to support axonal outgrowth, apoptosis of SCs increase with time; thus, the longer delay the less possibility of neuron regeneration [15,17]. Remaining SCs also loose their ability to react to axonal signals after prolonged denervation [12]. Furthermore, there is a greater number of non-myelinating SCs along the distal segment with delayed nerve repair [24].

Timing in cases with closed injuries is a separate matter, where the difficulty lies in determining which injuries should be explored. Overall, a three months limit is suggested, during which the clinical progress should be monitored by repeated clinical examinations, i.e. active surveillance, and in some specific cases – EMG investigation. If no return of motor function can be seen at three months exploration should be considered. Exploration of a closed nerve injury with insufficient recovery is also an alternative, where the condition of the nerve and the extent of the injury can be tested intraoperative with nerve stimulator to judge the nature of any possible repair or reconstruction procedure. However, in open injuries there is no reason to delay exploration and repair longer than absolutely necessary since the setting for regeneration is as best within the first few days following injury, after which the degree of activation in neurons and Schwann cells rapidly declines .

Type and level of injury

The type and level of a nerve injury influence the result after repair and reconstruction in several ways. There are several types of peripheral nerve injuries ranging from mild acute compression injuries which will resolve without treatment (if compression is relieved), through chronic compression injuries and compression injuries with damage to the axons to transection, laceration or even avulsion of a nerve root from the spinal cord. In the case of transections and lacerations, where the whole nerve structure is divided, regeneration is difficult, if not impossible, unless surgical co-aptation of the nerve ends is performed.

The level of injury is important as related to time until target reinnervation and thus preservation of the target with a possibility to recover its function. A muscle without innervation will start to atrophy. This starts within the first three months after injury [27,28] and the process reaches a critical level after two years. Muscle atrophy is mainly non-reversible if such a critical time point is reached,

and hinders reinnervation [6]. Sciatic nerve injuries at the level of the gluteal muscles have a worse outcome than injuries at the thigh level, probably due to the greater distance to target when the injury site is proximal in the leg [3,30]. There is also a larger amount of neuronal cell death with proximal injuries, i.e. injuries closer to the neuron cell body [5].

Reconstruction technique

Transection or laceration of a nerve trunk will leave the proximal and distal nerve ends separated from each other. In these cases, it is important to establish continuity in the nerve in order for the axons to find their way over the area of scar tissue [25]. Direct repair is preferable, but not always possible, especially since tension in the repair has a negative influence on the result [31]. If direct repair is possible the nerve ends should be prepared by removal of necrotic tissue; then, approximated so that the fascicular pattern matches.

Finally, the nerve ends are kept in position by tissue glue or sutures [32]. In order to bridge the gap in cases where direct repair is not possible a graft is needed. The current standard method is autologous nerve grafting with a dispensable sensory nerve. Multiple segments are placed side by side, without tension (preferably length >10% longer than gap due to shrinkage), to match the width of the nerve [32].

Some experimental data indicate that a motor nerve graft would be preferential in repair of motor nerves, but the supply of redundant motor nerves is limited leaving repair with a sensory nerve as standard [33,34]. In addition, the usefulness of a motor nerve graft, as compared to the gold standard sensory nerve graft, has not been shown in clinical cases. Sacrificing a sensory nerve is not optimal and other alternatives are being investigated. Nerve conduits are synthetic or biological tubes, used instead of autografts, which have been tried and found useful, albeit only for short gaps [25]. Allografts have been used and work relatively well, but the need for immunomodulative treatment limits its use [25,35,36].

However, extracted nerve allografts, i.e. cellular content and myelin extracted, are available [37] and commercially obtainable in some countries. End-to-side repair is a much-studied technique, where the distal end of the transected nerve is sewn on to the side of a healthy nerve [32]. However, the technique is probably only suitable for a limited number of nerve injuries, such as injuries in the brachial plexus [38].

Nerve transfer is a technique where a nerve branch or some nerve fascicles close to the target is cut and sewn onto the distal end of the injured nerve [25]. It is an alternative that may be useful when the site of injury is far from the target and reinnervation is unlikely before muscle atrophy reaches a critical level. A less important nerve close to the target is then used and connected with the distal segment of the injured nerve. The technique may still suffer the problem of sacrificing another nerve [29]. Furthermore, the method

relays on cerebral plasticity in order to execute the new function. However, several favourable techniques have been described, like the Oberlin procedure [39].

Pre-degeneration

An injury to a nerve starts the complex process of degeneration in the distal segment as described above. Based on the fact that this process enhances growth of axons through a graft or the distal segment toward its target organ, the concept of pre-degeneration of nerve grafts was introduced. This means that the graft used for repair of the injured nerve trunk is damaged by crush or transection before use in reconstruction, and through this is already activated. Pre-degeneration has a positive effect on regeneration after nerve reconstruction [40]. The greatest effect is that of shortening delay of onset of axonal outgrowth, which is most evident between 3 and 14 days after the initial injury to the graft [41].

Donor-site morbidity

The nerve most commonly used as a donor for autologous nerve transplantation is the sural nerve; i.e. a sensory nerve of the lower leg. This is due to its length, few branches and the relatively small consequences of its loss [32]. The area innervated by the sural nerve is located on the lateral aspect of the foot and heel. Although most patients are satisfied with donor site result [42], there often remains an area of anesthesia on the foot when further recovery is impossible [43]. Normally, this causes little discomfort. However, it is worth to note that recovery of sensation in this area is slower or less probable in a sciatic nerve injured patient, where the donor-site is ipsilateral to the injury [43].

Type of nerve

The type of nerve injured accounts for differences in the inert regeneration potential between different peripheral nerves [6]. Pure motor nerves have the best regeneration potential. As mentioned above sensory neurons are more sensitive to injury, and many will not survive axonal transection [18]. However, even pure sensory nerves have an advantage in comparison with mixed nerves, which have both sensory and motor components. The different types of axons in mixed nerve trunks are normally organized in fascicles, but when the nerve is reconstructed the axons may find their way through the wrong endoneurial tubes. This gives rise to isdirection, a concept described further below. Different mixed nerves have different outcomes in motor function [6]. In sciatic nerve injuries the gastrocnemius muscle, innervated by the tibial branch of the sciatic nerve, often recovers well, while the anterior tibial muscle, innervated by the peroneal branch of the sciatic nerve and needed to extend the foot, often proves more difficult to restore [30]. One may consider the possibility that the potential of the axons to grow is better in the tibial nerve than in the peroneal nerve, which

may have several causes. There is also a possibility that a coordinated input is needed to activate the elongated anterior tibial muscle [3].

Misdirection

The mechanisms of how the regenerating axon finds its way back to the correct target are under discussion. Some studies indicate that there is preferential targeting, while others claim that axons innervating the wrong target are sorted out [5]. However, although many axons find the correct target, some do not. This affect the functional outcome after nerve repair and reconstruction [44]. Motor axons may end up connecting with other muscle fibers than originally, as can sensory axons after reinnervation supply another skin area than they originally did [45]. In reinnervation of muscle, one axon can innervate a greater number of muscle fibers than before. This leads to bigger motor units, which can be seen as large motor unit action potentials in EMG [46]. There is also an amount of polyinnervation, where one muscle fiber is activated by two or more axons, which may resolve with passing time [47]. In the rat sciatic nerve injury model, misdirection leading to simultaneous activation of antagonistic muscles leads to impaired gait [44]. In adult humans, motor function is less disturbed by misdirection than sensory function. As mentioned above, misdirection of sensory axons give rise to a changed signal pattern from the peripheral nerve to the brain requiring a learning process [20]. There is also a misdirection between axons from sensory and motor neurons, which will contribute to the disturbed function [7].

Changes in the CNS

A peripheral nerve injury and reinnervation result in changes in the central nervous system both at the spinal and cerebral levels [45]. Both in the sensory and in the motor systems in the brain changes arise in two phases, first as a response to denervation and second in response to reinnervation of target organs. In the sensory system, the first phase consists of the removal of input, deafferentation, leading to expansion of the surrounding cortical areas. The first phase is followed by a period of reinnervation of target tissues and renewed sensory input [7].

This sensory input is changed, due to misdirection of the outgrowing nerve, resulting in a changed organization of the primary sensory cortex [48]. In the motor system loss of target muscle leads to loss of activity in the corresponding areas of the motor cortex. This is reversed with reinnervation [49]. The dynamics of the cerebral changes following a peripheral nerve injury can be studied using different neuroimaging techniques, such as functional magnetic resonance imaging (fMRI).

Cognitive brain capacity

Although much variance in result after peripheral nerve repair and reconstruction can be attributed to the above mentioned factors, this does not account for the whole spectrum of patient outcome. Since rehabilitation is a learning process, part of the variance in clinical outcome may lie in the cognitive capacities of the injured individual [7]. It has been shown that certain abilities, such as verbal capacity and visuo-spatial logic ability, relates to a better functional sensibility following nerve repair [19]. Sensory training should be adjusted to the individual capacities and stage in the nerve reinnervation process [7]. Rehabilitation of motor function depends on several factors, such as motivation, misdirection, timing, and loss of muscle mass. The motivation and coping abilities of the patient are important to keep up with the sensory and motor training needed to achieve an acceptable outcome after peripheral nerve injury and repair [32].

## Case reports

### Case 1

A 26-year old man accidentally had a cut from a circular saw in the medial, posterior part of the right thigh during work. Due to vascular damage of the femoral vessels he suffered substantial blood loss and when he was brought to the emergency room he was in shock but awake. The damage to the femoral artery and vein was repaired immediately and circulation of the leg and foot was restored within three hours of injury. On examination the day after surgery it was discovered that the patient had loss of sensory and motor function matching the area of the sciatic nerve below the point of injury. On the third postoperative day the area was explored and the sciatic nerve was found to be transected. After trimming of the nerve ends there was a gap of 3–4 cm. The individual tibial and peroneal groups of fascicles could be identified in the wound and by electrical stimulation of the distal nerve end. The sural nerve of the injured leg was harvested and divided into eight segments, which were then used as grafts, 5 segments for the tibial component and 3 segments for the peroneal component (Figure 1). The grafts were applied with extended knee position and fixed with single 9–0 sutures and tissue glue (Tissel®).

Figure 1 Peroperative photos from case 1. a) Wound of the patient on posterior part of thigh. b) Harvest of sural nerve graft (arrowheads) from the same lower leg. c) Injured sciatic nerve (arrow indicates distal nerve end). d) The injured sciatic nerve ends (arrows) with the long sural nerve graft. e) Eight segments of sural nerve graft attached with single sutures between the proximal (left) and distal (right) nerve ends. f) The sural nerve grafts glued with tissue glue (Tissel®)

The leg was immobilized in semi flexion for four weeks. The initial rehabilitation was without complication. Follow-up was conducted at our department, every three months the first year and then every six months. The patient used an orthosis during daytime for

support and to hold the foot up and physical therapy to counter contractions. Sensory re-education was performed. He later had some tendency towards plantar flexion contracture, especially in the mornings, which was treated with an orthosis during night.

The physical therapy aimed to encourage counter contractions in the leg. Motor function progress was measured according to the British Medical Research Council (MRC) scale showing a continuous improvement of muscle force (Table 2) At final follow up (58 months) he, above the muscle force described in Table 2, also had M4 in toe extensor muscles and even M3+ in toe flexor muscles, although more concentration was required by the patient to activate the latter muscles. Regeneration was followed with Tinel's sign. Sensory function was examined with Semmes-Weinstein monofilament conducted by an independent occupational therapist. At 24 months follow-up he could feel the 4.56 evaluator filament (indicating diminished protective sensation) on the mid lateral part of the sole of the foot.

Apart from that he only had deep pressure sensation in the foot. He had no sensation over the heel. At 40 months follow-up he could feel the 4.31 evaluator filament (diminished light touch) in the mid lateral part of the sole of the foot and under the third and fifth toe.

Under the big toe and the heel he could feel the 6.65 evaluator filament (deep pressure sensation) and in the rest of the sole of the foot he could feel the 4.56 evaluator filament (diminished protective sensation). At 58 months he could feel 3.61 evaluator filament in all toes and in most of the sole of the foot, except at the heel (4.31 evaluator filament). At no point did he have problems with cold sensitivity. He had some problems with allodynia, which was treated with tramadol hydrochloride (Tramadol®) for pain relief. An electromyography (EMG) done at 41 months showed decreased nerve conduction over knee level compared to the un-injured leg. In the majority of the muscles of the lower leg denervation activity was seen, most prominent in the distal muscles. However, in the gastronemius, long peroneal and anterior tibial muscles there were good voluntary activations. A low voltage response from the abductor hallucis muscle on stimulation of the tibial nerve at the ankle indicated that there was some reinnervation of the muscles of the foot.

Case 2

A 16-year old man sustained an open fracture of the left femur after a motorcycle accident. The distal fracture segment perforated the posterior aspect of the thigh, thus lacerating the sciatic nerve proximally of the bifurcation of the peroneal and tibial nerve components, resulting in a gap between the nerve ends of 6–7 cm. The femoral blood vessels were intact. The fracture was treated surgically by insertion of a femur rod. The wound was revisited on the second postoperative day, considered to be sufficiently clean without necrosis to proceed to nerve reconstruction, and the nerve injury was repaired with autologous nerve grafts. The ipsilateral sural nerve was used as a donor for nerve grafting. A two-segment sural nerve graft was used to traverse the gap (maintenance

unknown, probably were sutures used). The wound was infected postoperatively, where bacterial culture showed Bacillus cereus and the patient received treatment with clindamycin (Dalacin®). The wound then healed uneventfully. The leg was not immobilized post operatively. He was fitted with a foot-drop brace. Follow-up was conducted at an orthopedic clinic. He was reexamined with radiography to follow the healing of the femur fracture every six weeks during the first three months and then every six months. After 17 months the femur rod was removed due to pain. He had problems with pain during the first six months, which was treated with pregabalin (Lyrica®) with sufficient effect.

After 20 months there was little progress of nerve regeneration. An EMG was performed that showed denervation activity, fibrillations and positive sharp-waves in all the muscles of the lower leg, below the site of lesion. No voluntary units could be seen. In addition, no reaction in the tibial muscle after stimulation of the peroneal nerve at the knee was seen. Thus, there were no neurophysiologic signs of reinnervation of the lower leg. This related to the result of examination at our department 29 months after repair. At this point there was extensive atrophy of the muscles of the lower leg. Tinel's sign was positive at a point 18 cm proximal to the medial malleolus, but without any detectable subjective or objective signs of sensibility in the lower leg or foot. No function, i.e. no voluntary contraction, in the muscles of the lower leg below the site of the lesion could be seen (Table 3). Different additional surgical procedures, like nerve transfers as palliation in the lower leg, were declined.

MRI investigations

MRI data were acquired using a 3 T MRI system (Siemens Skyra, Erlangen, Germany).

fMRI and brain morphology

Functional data were acquired using a 32 channel head coil. During functional acquisition tactile stimuli of the sole of the right and left foot, respectively, were applied simultaneously with 3 pneumatic pads placed over the distal phalanx of first and second toe and over the distal part of the first metatarsal bone. Tactile stimuli were applied in a block design, alternating between individual stimulation of each foot, separated by a rest condition of no stimuli (e.g. right foot – rest – left foot – rest). All activation/rest block lengths were 17.5 s.

Sensory stimulation was delivered using a pneumatically driven and electronically controlled stimulus system (pulse frequency = 1 Hz, pulse width = 100 ms, pressure = 2.5 bars) [51,52].

For functional imaging, a gradient-echo echoplanar imaging (GE-EPI) pulse sequence was used with scan parameters, TR/TE = 2500/30 ms, voxel size = 2×2×2 mm3, 33 slices and 112 dynamic scans. A high-resolution image volume was also acquired, using an anatomical 3D magnetization prepared rapid acquisition pulse sequence (MP-RAGE), with scan parameters TR/TE = 1900/2.54 ms, voxel size = 1×1×1 mm3 and 176 slices.
Prior to analysis, the functional image data were realigned, slice time corrected, co-registered to the anatomical MP-RAGE volume, and smoothed using a Gaussian kernel with FWHM = 5 mm. Statistical parametric maps were created using the general linear model (GLM). Four specific contrasts were evaluated for both individuals: (1) healthy foot > rest, (2) nerve injured foot > rest, (3) healthy foot > nerve injured foot and (4) nerve injured foot > healthy foot. All preprocessing and statistical analysis was performed using SPM8 [http://www.fil.ion.ucl.ac.uk/spm].

Spinal MR

MR of the lumbar and sacral spine was acquired with the spine coil and a sagital 3D T2 SPACE sequence (Sampling Perfection with Application optimized Contrast using different flip angle Evolution) with voxel size = 0.6x0.6x0.6 mm3, 120 slices, TR/TE = 1500/136 ms, allowing image reconstruction in any plane. The cross sectional area of the dorsal root ganglion was measured on a reconstructed image through the largest portion of the ganglion and perpendicular to the length axis of the spinal nerve. Measurements were performed bilaterally for the fourth and fifth lumbar nerve (L4 and L5 nerve) and the first and second sacral nerve (S1 and S2 nerve).

Results

fMRI and brain morphology

No brain pathology was delineated on morphological images.

Activation maps were thresholded at p = 0.001 (uncorrected for multiple comparisons, corresponding to t = 3.17), and an additional cluster size threshold of 10 was applied. No activation was seen during stimulation of the foot ipsilateral to the sciatic nerve injury (nerve injured foot) while stimulation of the contralateral foot (healthy foot) resulted in activation in the sensory cortex (Figure 2a and b show activation t-maps for the contrast healthy foot > rest for both patients). Figure 2c and d show activation t-maps for the contrast healthy foot > nerve injured foot for both patients showing a significant activation difference between the healthy and the nerve-injured foot.

Figure 2 Activation t-maps, overlaid on the high-resolution MP-RAGE volume (threshold at t = 3.17, corresponding to p = 0.001, cluster size threshold = 10) for the contrast healthy foot > rest for the patients with right (patient 1) (a) and left (patient 2) (b) side sciatic nerve injury, respectively, and for the contrast healthy foot > nerve injured foot for the same two patients (c and d)

Spinal MR

The sciatic nerve originates in the lumbar and sacral spinal cord (L4 to S3) and supplies motor and sensory innervation to the lower extremity (Figure 3). Maximum cross sectional areas of the dorsal root ganglia are given in Table 4. Cross sectional areas did not correlate to side of injury.

Figure 3 Magnetic resonance images (T2 weighed CCI SPACE sequence) of the left S1 spinal nerve at the level of the dorsal root ganglion (arrows). 1. Coronal view, 2. Sagittal view and 3. axial view. All views are reconstructed projections parallel (coronal and sagittal) or perpendicular (axial) to the length axis of the nerve.

Discussion

The two cases presented above had similar sciatic nerve injuries, but different outcome after the nerve reconstruction. The explanation may be found by examining the factors known to influence outcome after peripheral nerve injuries. The gap length has some influence, since a longer gap leads to a worse outcome. This has likely contributed to the poor result for the second case, which had a final gap of 11 cm. On the other hand, and more importantly, the manner of reconstruction differed between the cases as well. Even though they both received sural nerve autografts from the injured leg, the first patient was operated on using an eightnerve segment reconstruction, while the second patient only got a two-segment graft. Due to the size ratio between the nerve and the segment graft, such a difference will most probably have implications on the efficiency of the axonal outgrowth through the graft and thus over the defect. A sufficient diameter of the graft is needed to attract a sufficient number of axons and to direct the axons on their right path [32]. The sciatic nerve is a thick mixed nerve and he individual sural grafts are very thin. The reconstruction performed on the second patient appeared to be insufficient, based both on the lack of reinnervation and on the clinical signs of severely impaired axonal outgrowth with only a Tinel’s sign 18 cm proximal to the medial malleolus. A neuroma forms mainly under conditions that prevent the regenerating axons to reach a target organ, these conditions being scar tissue or lack of guidance over a gap. One should stress that an appropriate number of segments provide the outgrowing axons with growth stimulating factors through a sufficient number of proliferating Schwann cells. No information is available on why not the contralateral nerve as well as the entire sural nerve was utilized in the second case to create a better reconstruction. Most probably, nerve regeneration should have proceeded better if multiple nerve graft segments have bridged the defect in the second case. Interestingly, experimental data

have shown that axonal outgrowth is better in the larger tibial nerve than in the smaller peroneal nerve branch. This indicates that the amount of proliferating Schwann cells in the distal nerve segment contributes to attract outgrowing axons [53]. Thus, in cases where there is a shortage of nerve graft segments, the available segments should be directed to the tibial nerve due to its better regeneration capacity and a palliative tendon transfer could have compensated the lack of peroneal nerve function. Alternatives, such as extracted acellular nerve grafts [54], were not available in our country at the time of the injury and such grafts, although they lack Schwann cells and may be insufficient for the present nerve defect in the second case, could have contributed to axonal outgrowth. In addition, nerve transfers, as an alternative or a palliation procedure, may also be a possibility in the second case [50], but was declined for several reasons (e.g. no suitable nerve transfer in relation to a possible improvement and good outcome at the time when the patient was referred and opinion by the patient).

Other differences between the two cases were the method of follow up and the postoperative care, including the treatment of the limited local infection, given. The first patient was followed by a team used to this type of injuries and examined closely for signs of regeneration, and when such signs were found specific rehabilitation efforts were directed at the muscle or skin area recently reinnervated. A team that focused on the healing of the femur fracture followed the second patient. Subsequently, attention was directed against fracture healing and not towards the status of the regenerating nerve. The result was a delay in diagnosing the lack of regeneration until two years after the injury when a great part of the muscle mass of the lower leg was already lost and little hope of regaining function remained.

If there are sparse signs of regeneration after the reconstruction of the sciatic nerve injury, like no advancement of Tinel´s sign and reinnervation of muscles, one should consider reexploration of the injured area, particularly focusing on the distal coaptation, within an appropriate time perspective, as timing is crucial. Unfortunately, this was not done in the second case. Thus, active surveillance of nerve repairs and reconstructions is essential to follow nerve regeneration after repair or reconstruction procedures and to decide if a nerve injury should be re-explored, particularly if no advancement of Tinel´s sign is observed. The different treatment regimes may also have induced a difference in the support of any coping ability. A meticulous follow-up with constant progress would make the first patient more optimistic and motivated. There is always a risk for a postoperative local infection after a nerve injury with an open wound, with or without fractures, particularly if necrotic tissues are present such as after gunshot wounds [30]. In such cases it is not advisable to perform any nerve reconstruction, but to do a meticulous revision of the wound and later a nerve reconstruction depending on the medical condition of the patient. In both the present cases the condition of the wounds were considered clean enough to perform the nerve reconstruction procedure early. However, in the second case a limited local infection occurred and was successfully treated, but we do not interpret the local infection responsible for the poor outcome. There seems to be a low infection rate after immediate nailing of femoral shaft fractures if the condition of the wound is addressed properly [55].

The two cases also had several things in common which allows an analysis of factors influencing the outcome equally and in a similar fashion. The injuries were rather similar in severity, i.e. laceration of the sciatic nerve with a nerve defect. Such injuries have a negative influence on the outcome [21]. This has been observed clinically and in experimental studies. Age is the factor most commonly accepted to influence outcome (18).

Both patients presented here were adults with an age where the prognosis of a peripheral nerve injury is substantially worse than in children. The patients' age is not in their favor, but equally against both of them.

Figure 4 Schematic drawing of a sciatic nerve at mid-thigh level with the potential factors that influence functional outcome extending from local signal transduction mechanisms in Schwann cells and neurons, secondary changes in the target areas, apoptosis of neurons in e.g. dorsal root ganglia, and reorganization at the cortical and subcortical levels Timing is of great importance due to the changes in both neuron and Schwann cells described above. In the present cases, the injury to the nerve was apparent either with presentation or soon after. Repair and reconstruction was performed within three days. Repair within this timeframe is referred to as delayed primary repair and reconstruction, a strategy generating as good results as can be expected with this kind of injuries [6].

The graft used for reconstruction in both cases was the sural nerve ipsilateral to the injury.

The grafts had been denervated for two and three days, respectively, at a time point where the pre-degeneration was initiated in the ipsilateral sural nerve, i.e. a pre-degenerated nerve graft, which can be expected to promote axonal growth over the transplant [40]. In rat sciatic nerve models it is possible to use pre-degeneration on the sciatic nerve contra-lateral to the planned injury and use this as a graft. In humans, this is not easily arranged and the use of an autograft harvested a few days after injury is likely to be one of few strategies, which benefit from the effects of pre-degeneration.

Misdirection results in loss of hind leg functionality due to the simultaneous activation of opponent muscle groups [44]. This loss of functionality does not appear to be as relevant in humans, as the first patient regained good function in his leg, although he had some difficulties to selectively activate his toe flexor muscles properly at the last follow up, but this did not impaired his function. Locomotion studied in rats is an automated action and has less impact on human behavior. Also, with slower reinnervation rate and longer distances to overcome, muscle function is regained a little at a time with time to rehabilitate function gradually.

A better understanding of the biological mechanisms of peripheral nerve regeneration will hopefully improve the care of patients (Figure 4). Research in the rat model has shown that several factors can influence nerve regeneration and the outcome in patients.

For example, the importance of timing of reconstruction and repair for outcome has been clearly shown in the rat sciatic nerve model. The conclusions from the experimental research have prompted the rapid reoperation and nerve repair in the cases presented here.

However, repair and reconstruction is not all.

Cognitive capacity and coping strategies is an area where more research is needed. In this study, there is some indication to the importance of these factors. It is possible that the use of a rat model has limitations here. Using fMRI, we demonstrated a normal contralateral activation in the S1 following cutaneous stimulation of the uninjured foot. Stimulation of the injured foot did not show any cortical activation in any of the subjects. This could be expected in the subjects lacking sensibility in the foot. However, the other subject had some sensibility in the foot. Even though a subject may perceive the stimulation, it is not certain that such cutaneous stimulation may be captured using fMRI. The hemodynamic response is highly individual and some individuals may have a more subtle response leading to statistics below the threshold of the fMRI analysis.

A strong correlation between DRG volume and the number of sensory neurons have been described [56]. Furthermore, the volume of DRG, quantified by MRI or by morphology, has been shown to correlate closely with the number of sensory neurons after a rat sciatic nerve injury. MR imaging of the human dorsal root ganglia has been previously described [57-59]. Normally, the DRG lie obliquely in the superolateral portion of the lumbar intervertebral foramen; thus, neither standard cross-sectional nor coronal imaging provides a view allowing for a comprehensive analysis of the DRG. Here, we measured the cross sectional area of the DRG on a reconstructed image through the largest portion of the ganglion and perpendicular to the length axis of the spinal nerve. We believe that this produce provides the most correct values. Previous studies on the rat sciatic nerve injury model have described volume reduction in the DRG following sciatic nerve injury [18]. To our knowledge, no previous studies exist that have used MRI to show any reduction in size or volume of DRG following a sciatic nerve injury in humans. Here, we could not show any differences in the size of the DRG following sciatic nerve and reconstruction. This could be due to several reasons. First of all, the effect on the DRG in terms of volume reduction following a sciatic nerve injury is not known in detail. The DRG at levels L4-S3 do not only support the sciatic nerve and volume loss, due to degeneration, might partly be prevented by activated glial cells and endoneurial macrophages that are presented in DRG for various reasons. Individual variability in formation and size of the ganglia at different levels can not been taken into account when studying only two subjects. Furthermore, although patients were examined with high resolution MR, artefacts and partial volume effects cannot be avoided due to still limited image resolution. Another possibility is that there is no volume loss in the DRG that supply the sciatic nerve in humans. In the future, further advanced neuroimaging techniques may be of great importance offering an opportunity to better understand the biology behind to regeneration process following a sciatic nerve injury. These techniques may also offer a possibility to monitor recovery of the nerve function and even the axonal outgrowth following injury and reconstruction.

The comparison between clinical research on patients and the results from studies on animals has the benefit of being translational in the most literal meaning of the word. The truly interesting part of any research conducted in the field of medicine must be the question: How does this affect the patient? However, the method of case reports has its limitations, but can be useful if the numbers of cases are rare and if they may generate new hypotheses. They may also add information and some clinical experience, which should be shared in the medical literature. Another methodological problem is the potential bias in the selection of articles for the background. The structured searched in the Pubmed database is designed to minimize this, but since only one person took part in the selection some bias is likely.

Conclusions

The present paper, based on two cases with different outcome, reviews points that may be raised in decision making of nerve repair and reconstruction where experimental data can be useful to predict outcome in patients. A number of factors influence outcome of repair and reconstruction of nerve injuries, illustrated here in the two patients with injuries of the sciatic nerve, even if the factors behind the poor result in the second case are obvious. The rat sciatic nerve injury model is useful in identifying and studying factors that influence outcome after peripheral nerve repair and reconstruction, although such a model cannot completely mimic the dilemmas in the clinical situation. Results from experimental studies can be translated to clinical practice, although with caution and discernment as well as be related to clinical experience, and used in repair and reconstruction of nerve injuries in humans. However, some factors, such as cognitive capacity and coping, are difficult to study in rat models. Future research has to find and develop new paths and techniques to study the changes in the central nervous system after injury and develop strategies to utilize brain plasticity during rehabilitation.

BACK TO TOP

***PTSD***

## Sleep disturbances and PTSD: a perpetual circle?

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Abstract

Background

Sleep facilitates the consolidation of fear extinction memory. Nightmares and insomnia are hallmark symptoms of posttraumatic stress disorder (PTSD), possibly interfering with fear extinction and compromising recovery. A perpetual circle may develop when sleep disturbances increase the risk for PTSD and vice versa. To date, therapeutic options for alleviating sleep disturbances in PTSD are limited.

Methods

We conducted three studies to examine the relationship between sleep and posttraumatic symptoms: (1) a prospective longitudinal cohort study examining the impact of pre-deployment insomnia symptoms and nightmares on the development of PTSD; (2) a cross-sectional study examining subjective sleep measures, polysomnography, endocrinological parameters, and memory in veterans with PTSD, veterans without PTSD, and healthy controls (HCs); (3) a randomized controlled trial (RCT) (n=14) comparing the effect of prazosin and placebo on sleep disturbances in veterans with PTSD. In addition to these studies, we systematically reviewed the literature on treatment options for sleep disturbances in PTSD.

Results

Pre-deployment nightmares predicted PTSD symptoms at 6 months post-deployment; however, insomnia symptoms did not. Furthermore, in patients with PTSD, a correlation between the apnea index and PTSD severity was observed, while obstructive sleep apnea syndrome was not more prevalent. We observed a significant increase in awakenings during sleep in patients with PTSD, which were positively correlated with adrenocorticotropic hormone (ACTH) levels, negatively correlated with growth hormone (GH) secretion, and the subjective perception of sleep depth. Also, heart rate was significantly increased in PTSD patients. Interestingly, plasma levels of GH during the night were decreased in PTSD. Furthermore, GH secretion and awakenings were independent predictors for delayed recall, which was lower in PTSD. In our RCT, prazosin was not associated with improvement of any subjective and objective sleep parameters. Only a few RCTs have been published. They show promising results for atypical antipsychotics and prazosin, the latter especially on nightmare reduction.

Conclusions

Disturbed sleep due to nightmares increases the risk for PTSD. PTSD in turn leads to increased sleep fragmentation, decreased GH secretion, and frequent nightmares, which may again compromise fear extinction, synaptic plasticity, and recovery. This suggests that disturbed sleep is a precipitating and perpetuating factor in PTSD symptomatology, creating a perpetual circle. This dissertation suggests that activity of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS) is involved in disturbed sleep in patients with PTSD.

Keywords: PTSD, sleep, nightmares, polysomnography, cortisol, growth hormone, memory, noradrenalin

This dissertation focuses on sleep in patients with a combat-related posttraumatic stress disorder (PTSD). Nightmares and insomnia are highly prevalent in patients with PTSD (Neylan et al., 1998; Ohayon & Shapiro, 2000). However, cross-sectional polysomnographic (PSG) studies on objective sleep quality in patients with PTSD leave the researchers in the field puzzled, since these studies showed only mild disturbances in objective sleep quality (Breslau et al., 2004; Hurwitz, Mahowald, Kuskowski, & Engdahl, 1998; Kobayashi, Boarts, & Delahanty, 2007; Pillar, Malhotra, & Lavie, 2000).

Sleep is important for synaptic plasticity and memory formation. Fear extinction memory is a process of “forgetting” the association between a certain neutral trigger and an aversive stimulus. Like learning, in general, fear extinction memory consolidation requires synaptic plasticity. Remarkably, sleep, and presumably rapid eye movement sleep (REMS), enhances the process of fear extinction. Longitudinal studies have reported an association between sleep disturbances in the early aftermath of trauma and the development of PTSD (Kobayashi, Sledjeski, Spoonster, Fallon, & Delahanty, 2008; Koren, Arnon, Lavie, & Klein, 2002; Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). Other studies also found that sleep disturbances before the trauma, as measured retrospectively, predicted PTSD (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; Mellman, David, Kulick-Bell, Hebding, & Nolan, 1995). This indicates that sleep disturbances may be related to the pathophysiology of PTSD, for instance, disruption of fear extinction memory consolidation during sleep.

Sleep may be fragmented by a number of external factors, such as sleep apneas, which lead to frequent short arousals. A high prevalence of obstructive sleep apnea syndrome (OSAS) has been reported in patients with PTSD (Krakow, Germain, et al., 2000; Krakow et al., 2004, 2006). These studies also indicated relief from PTSD when OSAS was successfully treated. When sleep is disturbed by obstructive airway events, followed by a short arousal and thus interrupted sleep, the decreased sleep quality may compromise beneficial processes during sleep and may hypothetically lead to therapy resistance or chronicity in the course of the illness.

In patients with PTSD, activity of the hypothalamic–pituitary–adrenal (HPA) axis and locus coeruleus (LC)/noradrenergic system is altered, which may be responsible for overstimulation of the amygdala and related limbic structures in the brain, as well as dysregulation of the negative feedbacks system that need to dampen stress responsivity (for a review, see Sherin & Nemeroff, 2011). At night, the altered activity of these neurohormones, neurotransmitters, and limbic structures may lead to altered REMS and arousal regulation (Germain, Buysse, & Nofzinger, 2008). The alteration in stress-related biological systems may be related to insomnia and re-experiences of the trauma during REMS, when limbic structures are most active (for a review, see Dang-Vu et al., 2007). The restoration of sleep in patients with PTSD may improve sleep-dependent neuroplasticity and stimulate recovery. However, only few randomized controlled trials (RCTs) have investigated the ways to alleviate sleep disturbances in patients with PTSD. To improve sleep, the profile of sleep disturbances in patients with PTSD and the underlying neurobiological systems require further study. So far, PSG studies have not clarified regulating mechanisms involved in sleep disturbances in patients with PTSD. This warrants alternative methods for the assessment of sleep regulation in patients with PTSD.

Research questions

This dissertation consists of several experimental studies designed to answer the following questions regarding the relationship between sleep and PTSD:

Do insomnia and nightmares pre-deployment predict the development of PTSD symptoms?

Is the prevalence of OSAS increased in patients with PTSD? Are apneas related to nightmares and insomnia complaints, or to PTSD severity?

Are heart rate (HR) during sleep and the nOctoberurnal secretion of melatonin, cortisol, and ACTH altered in PTSD and is this related to decreased objective and subjective sleep quality?

What is the relationship between objective sleep parameters according to polysomnography and subjective sleep quality in patients with PTSD?

Are growth hormone (GH) secretion and memory formation disturbed by PTSD and is this due to decreased objective sleep quality?

What is the effect of prazosin, an α1-adrenoceptor antagonist, on objective and subjective sleep quality in PTSD when compared to a placebo?

Summary of major findings

Chapter 2 shows that nightmares, but not insomnia, are associated with an increased risk of developing PTSD symptoms after military deployment. This has been studied in a sample of 453 military service members who were deployed to Afghanistan.

Screening for sleep disturbances and nightmares pre-deployment may contribute to early identification of those at risk of developing PTSD symptoms.

Chapter 3 shows that disturbed sleep due to obstructive apneas may exert a negative effect on PTSD symptoms as PTSD patients with OSAS have more severe PTSD complaints. Obstructive sleep apnea (OSA) is not more common in patients with PTSD compared to trauma controls (TCs) and HCs.

Chapter 4 shows that sleep is more fragmented and HR is increased in patients with PTSD compared to TCs and HCs. In this study, polysomnographic registrations and 20 min blood samples were obtained simultaneously. Plasma ACTH, cortisol, and melatonin concentrations are not significantly altered in PTSD, while a trend is seen for lower cortisol levels in the first half of the night. ACTH is positively related to the number of awakenings. Furthermore, ACTH is inversely related to the amount of slow wave sleep (SWS). Patients with PTSD exhibit a significantly decreased cortisol:ACTH ratio (CORT: ACTH) upon awakening compared to TCs. TCs demonstrate an increased CORT:ACTH during the night compared to both PTSD patients and HCs, suggesting an increased response of the adrenals upon ACTH stimulation under baseline conditions in veterans without lifetime psychiatric disorders.
Chapter 5 shows that PTSD patients have lower GH levels during the night. Fragmented sleep is inversely related to GH secretion. Noticeably, overnight memory consolidation is inversely related to awakenings. A positive relationship between memory recall and GH secretion has been observed.

Chapter 6 comprises a systematic review, showing that pharmacotherapeutic options for sleep disturbances in PTSD have not been extensively studied with RCTs. So far, best results have been described in small RCTs investigating drugs with α1-antagonistic properties.

Chapter 7 shows that treatment of sleep symptoms in PTSD patients with prazosin (n=6) has no effect on the number of awakenings or other PSG parameters and sleep diary measurements compared with placebo (n=6) in a small RCT. Significantly, more side effects occur after prazosin treatment.

Repercussions of disturbed sleep

Nightmares before military deployment, that is, a period of increased risk of trauma exposure, increase the risk for PTSD symptom development in response to deployment. Furthermore, sleep apnea has been related to higher PTSD scores in PTSD patients. These observations indicate that disturbed sleep may influence PTSD symptomatology. Evidence from previous studies show that sleep promotes generalization of extinction of memory in healthy humans (Pace-Schott et al., 2009; Spoormaker et al., 2010, 2011).

This indicates that disturbed sleep may directly contribute to PTSD development by means of disrupting the beneficial process of sleep with regard to fear extinction. Nightmares predominantly occur during REMS (Nielsen & Levin, 2007), while they may also occur during nonrapid eye movement sleep in PTSD patients (Hefez, Metz, & Lavie, 1987). REMS in particular seems to have an effect on fear extinction (Spoormaker et al., 2010, 2011). The observed relationship between nightmares and the risk of developing PTSD symptoms may suggest that disturbed REMS is a risk factor for PTSD.

Besides, nightmares have been associated with increased noradrenalin levels (Raskind et al., 2007). Furthermore, noradrenergic activity may be involved in PTSD development (Southwick et al., 1999). Thus, alternatively, the development of PTSD and the occurrence of nightmares may be epiphenomena, both induced by increased noradrenalin levels, and may not be causally linked. Our results suggest that nightmares are a trait, making an individual more vulnerable to developing PTSD symptoms. Our study also shows that insomnia symptoms fail to predict PTSD symptoms at 6 months post-deployment when pre-deployment mood and anxiety complaints are taken into account. These results differ from the previous studies in which a positive association between the development of PTSD and insomnia symptoms before or directly after trauma exposure (Bryant et al., 2010; Koren et al., 2002; Mellman, David, et al., 1995) was observed. This may be explained by the fact that these studies did not correct for mood and anxiety complaints. The relationship between insomnia symptoms and mood and anxiety complaints is complex and may be bidirectional: insomnia symptoms may contribute to mood and anxiety complaints and—vice versa—insomnia symptoms may be moderated by mood or anxiety complaints (Abad & Guilleminault, 2005). Therefore, it is possible that mood and anxiety complaints caused by insomnia increase the risk of developing PTSD after trauma and are therefore mediators in the relation between insomnia symptoms and PTSD development. Alternatively, mood and anxiety complaints may be confounding factors, causing both insomnia symptom complaints and PTSD development. In the current design, we could not differentiate whether mood and anxiety complaints are confounding factors or mediators in the relation between insomnia symptoms and PTSD development.

OSAS was not more prevalent in patients with PTSD compared to TCs and HCs, contrary to previous uncontrolled studies that suggested indices between 60 and 90% in PTSD (Krakow, Germain, et al., 2000; Krakow et al., 2004, 2006; Yesavage et al., 2010). In these studies, screening instruments for detecting OSA may have been more sensitive than in our study, especially because some studies defined a cutoff of five events per hour. Another explanation for the high incidence of OSA in some previous studies is that the usage of benzodiazepines was not discontinued before sleep recordings, which increases the occurrence of OSA (Dolly & Block, 1982). In our study, participants with regular benzodiazepine usage were excluded, and participants with habitual benzodiazepine usage were refrained from sleep medication in the sleep laboratory. Finally, our study group consisted of middle-aged veterans, whereas other studies included either female PTSD patients or elderly veterans with PTSD. The incidence of OSA may be different in other populations with PTSD. As none of the previous studies included a control group, it cannot be concluded that the incidence of

OSA is elevated in PTSD. Our study underlines the importance of controlled studies to determine whether OSA is more prevalent in PTSD than in matched controls.

Nonetheless, we did observe a positive correlation between the apnea–hypopnea index per hour and more severe PTSD. Possibly, PSTD is a risk factor for OSAS, leading to a higher incidence of OSAS in severe PTSD. Alternatively, PTSD patients who happen to suffer from OSA as well may experience symptom increases due to disturbed sleep. One uncontrolled study has suggested a positive effect on PTSD symptoms after treating OSAS with continuous positive airway pressure (Krakow, Lowry, et al., 2000). Possibly, when sleep is important for recovery, and is compromised by arousals due to obstructive events, OSAS may intervene with response to treatment. It would be advisable to screen for OSAS in case of snoring and other indicators of OSAS, especially in therapy resistant patients.

In this dissertation, we also report a putative working mechanism for how sleep disturbances may influence daytime complaints. We found that GH levels during the night were decreased in PTSD patients, compared to HCs. Reduced GH secretion correlated with awakenings during the night. A regression analyses with delayed recall as dependent showed that both sleep fragmentation and GH secretion were significant predictors for memory retention of a declarative memory task. This indicated that sleep-dependent memory consolidation is disturbed in PTSD due to decreased nOctoberurnal GH secretion and more interrupted sleep. More research is warranted to confirm these novel findings.

GH receptors are present in the hippocampus (Lai, Emtner, Roos, & Nyberg, 1991). It is suggested that GH stimulates neuroplasticity in the hippocampus (Kim, Grover, Bertolotti, & Green, 2010). A recent functional MRI study in healthy volunteers showed decreased hippocampus activation and decreased performance on a memory task after a night of experimentally induced sleep fragmentation (Van der Werf et al., 2009). Thus, sleep fragmentation can have an effect on hippocampal function. In patients with PTSD, structural and functional changes in the hippocampus also have been reported (Bremner, 2006). Interestingly, insomnia complaints in PTSD are inversely related to volume on the CA3 area of the hippocampus (Neylan et al., 2010). Decreased GH secretion may hypothetically be related to decreased hippocampus activity and possibly also hippocampal volume in PTSD. The effect of GH on neurons of the hippocampus during sleep deprivation has been shown in a recent preclinical study (Kim et al., 2010). This study shows that in the absence of GH during sleep deprivation N-methyl-d-aspartate (NMDA) receptor-mediated synaptic currents decreased in hippocampal neurons. Moreover, NMDA receptor loss was observed, as was a decline in long-term potentiation. These processes normalized when GH injections were administered during sleep deprivation. Reduced GH secretion may possibly be related to decreased hippocampal functioning in patients with PTSD. The relationship between treatment response to a selective serotonin reuptake inhibitor (SSRI) and neurogenesis in the hippocampus was reported in a preclinical study (Santarelli et al., 2003). In combat-related PTSD, a relationship between treatment response and hippocampal volume has also been suggested (Vermetten,

Vythilingam, Southwick, Charney, & Bremner, 2003). Future research should indicate whether GH secretion is related to hippocampus volume or functioning in PTSD. Furthermore, the relationship between hippocampal volume, neurogenesis, and treatment response remains to be elucidated.

Characteristics of sleep disturbances in patients with PTSD

Sleep in PTSD patients was characterized by more awakenings compared to TCs and HCs. Increased awakenings were also reported in earlier studies (Breslau et al., 2004; Habukawa, Uchimura, Maeda, Kotorii, & Maeda, 2007; Mellman, Kulick-Bell, Ashlock, & Nolan, 1995). In agreement with a meta-analysis of PSG studies in PTSD total sleep time (TST) in our study was unchanged, as was REMS (Kobayashi et al., 2007). Our study did not demonstrate reduced SWS, which was decreased according to the meta-analysis on PSG studies in PTSD (Kobayashi et al., 2007).

In our study, cortisol levels tended to be lower during the first half of the night in patients with PTSD. ACTH levels were not elevated, which may have been due to the sample sizes (effect size f=0.42, required total sample 58). Both cortisol and ACTH levels were correlated with SWS, while in a regression analysis only ACTH was an independent predictor for SWS. Interestingly, ACTH levels also correlated positively with the number of awakenings. ACTH secretion is stimulated by CRH activity. The correlation between ACTH and both SWS and awakenings may therefore be indicative for CRH being involved in waking and SWS regulation in PTSD. CRH is known to inhibit SWS and increase awakening during sleep (Steiger, 2007). It was previously observed that CRH is increased in cerebrospinal fluid and plasma in PTSD patients (Baker et al., 1999). Furthermore, in a meta-analysis on PSG studies, SWS was decreased in patients with PTSD. Further explorations of CRH in sleep complaints in PTSD may in time contribute to the development of novel treatment strategies.
We also hypothesized increased activity of the LC in PTSD-related sleep fragmentation. The LC is a nucleus in the pons where noradrenergic neuronal cell bodies are located, which have projections throughout the brain. Also the sympathetic nervous system (SNS) is innervated by the LC. Noradrenergic activity stimulates awakening by stimulating the ascending reticular arousal system (ARAS) and inhibiting sleep-promoting ventrolateral preoptic nucleus (VLPO) activity (Saper, Scammell, & Lu, 2005). Noradrenaline is therefore one of the key players in the so-called “sleep/wake switch,” a system involving the ARAS, VLPO, and related neurotransmitters (Saper et al., 2005). We did indeed find increased HR in PTSD patients in comparison with TCs and HCs, which is in accordance with previous work and indicative for increased sympathetic activity (Muraoka, Carlson, & Chemtob, 1998; Woodward et al., 2009). We did not find any relationships between HR and awakenings in patients with PTSD or in the combined sample. This may have been due to the small sample size; only eight PTSD patients were allowed to enter the analyses after excluding those with cardiovascular medication, which was used by a relative large portion of the PTSD patients (3/13). Recent research has indeed

shown increased cardiovascular risk in patients with PTSD (Boscarino, 2012). Possibly, the elevated SNS activity during the night may increase the risk of developing cardiovascular complications in PTSD.

The involvement of noradrenaline in PTSD-related sleep disturbances was further supported by RCTs that demonstrate a positive effect of prazosin on nightmares and insomnia in PTSD (Germain et al., 2012; Raskind et al., 2003, 2007; Taylor et al., 2008).
In summary, HRs were significantly higher during sleep in PTSD patients, indicating increased SNS activity. Furthermore, we found that awakenings were increased in patients with PTSD. Interestingly, awakenings were positively related to ACTH secretion. In addition, perceived sleep quality was inversely related to the number of awakenings. Therefore, it is advised to calculate the number of awakenings in future PSG studies, as this seems to be a robust alteration in objective sleep quality in PTSD.

Treatment of sleep disturbances in PTSD

Insomnia and nightmares are frequently residual complaints in PTSD after successful psychotherapy with cognitive behavior therapy (Zayfert & De Viva, 2004) or pharmacotherapy with SSRIs (Davidson, Rothbaum, Van der Kolk, Sikes, & Farfel, 2001). In Chapter 5, we systematically reviewed studies that were published before 2006, investigating pharmacotherapeutic options for sleep disturbances in patients with PTSD. Our review shows that even though benzodiazepines are the most widely prescribed sleep medication, their effects on sleep disturbances in PTSD have not been extensively studied by RCTs. Only two small RCTs (n=6, n=22), with short treatment periods of 1 week, have been conducted (Cates, Bishop, Davis, Lowe, & Woolley, 2004; Mellman, Bustamante, David, & Fins, 2002). Several small RCTs have indicated that prazosin is superior to placebo in improving subjective sleep in patients with PTSD (Germain et al., 2012; Raskind et al., 2003, 2007; Taylor et al., 2008). Also, RCTs have shown the efficacy of the atypical antipsychotics olanzapine and risperidone as add-on therapy alongside an SSRI (Rothbaum et al., 2008; Stein, Kline, & Matloff, 2002). Prazosin and quetiapine, another atypical antipsychotic, were similar in their short-term effects (Byers, Allison, Wendel, & Lee, 2010). However, quetiapine more often led to discontinuation due to adverse side effects. RCTs showed that guanfacine, an α2-adrenoceptor agonist, was not effective in treating nightmares and insomnia (Neylan et al., 2006).

Objective measurements of sleep were employed in two studies. One RCT investigating the effect of prazosin estimated REMS and TST with an eye tracker (Taylor et al., 2008). This study suggested increased TST and REMS after prazosin treatment. Another RCT with three groups (prazosin, placebo, and a cognitive behavior therapy) measured polysomnography, the golden standard for measuring sleep architecture (Germain et al., 2012). In this study, no differences over time were seen between groups on all PSG parameters and most subjective sleep measures. Only the number of reported nightmares was reduced in the active treatment groups in comparison with placebo. We also measured polysomnography and sleep questionnaires in a small RCT on the effect of prazosin, as has been described in Chapter 6. Our study was in agreement with the observations from the study by Germain et al.

(2012) that PSG parameters, Pittsburgh sleep quality index scores, and sleep diary measurements did not differ between groups. We also measured the number of awakenings pre- and posttreatment but did not find a significant difference. This may have been due to the intensity of our study.

A meta-analysis including all RCTs on prazosin using polysomnography should be performed to further analyze the effect of prazosin on objective sleep quality in PTSD. However, polysomnography may not be a suitable method for detecting the underlying mechanism of nightmares in PTSD. Alternative methods may further elucidate the suggested effect of blocking α1-adrenoceptor activity on nightmares. For instance, functional MRI with combined EEG during sleep may demonstrate decreased activity of limbic brain structures during (REM) sleep in relation to a reduction in nightmare complaints.

In summary, prazosin and atypical antipsychotics are effective in the treatment of PTSD-related sleep complaints. However, prazosin does not increase the risk of a metabolic syndrome and has therefore a more favorable side effect profile. One RCT showed that sleep-focused behavioral therapy was as effective as prazosin on both insomnia and nightmares. Imaginary rehearsal therapy (IRT) is also effective for those suffering from nightmares, but cannot be applied in those without dream content recall. Prazosin treatment, IRT, and sleep-focused cognitive behavior therapy (CBT) are all effective for treating sleep disturbances (Germain et al., 2012; Krakow et al., 2001). Unfortunately, prazosin is no longer available in the Netherlands. Distribution has been stopped because prazosin was not regularly prescribed to patients suffering from hypertension and benign prostate hypertrophy. Alternatively, quetiapine, or the selective α1-adrenoceptor antagonists doxazosin and alfuzosine, may be useful. However, RCT is warranted to assess the efficacy of doxazosin and alfuzosine in PTSD-related sleep disturbances. Also sleep-focused psychotherapy may not always be available to PTSD patients, as not all psychologists and psychiatrists are familiar with these interventions. The choice of treatment depends on the preference of the patient and availability of therapeutic options.

The HPA-axis and adaptation after trauma exposure

Changes in the functioning of the HPA axis have repeatedly been associated with PTSD (for a review, see de Kloet et al., 2006). Generally, increased responsivity to dexamethasone has been reported. Also, increased CRH levels have been demonstrated in cerebrospinal fluid and plasma (Baker et al., 1999; de Kloet et al., 2008). Results on peripheral cortisol values are inconsistent. Most studies report low or normal cortisol concentrations compared with controls (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012; Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007). A previous study suggests that HPA-axis alterations after traumatic stress are also related to trauma exposure and not merely with PTSD symptoms (de Kloet, Vermetten, Bikker, et al., 2007; de Kloet, Vermetten, Heijnen, et al., 2007). We therefore included two control groups in our study: one group that comprised veterans without lifetime psychiatric disorder and one control group of nondeployed–or otherwise traumatized—individuals. ACTH values in our study did not

differ at night or in the morning between the three groups. Cortisol levels tended to be lower in PTSD during the first half of the night. However, significant group differences in the ratio of CORT:ACTH were demonstrated. The CORT:ACTH ratio reflects the responsiveness of the adrenals upon ACTH stimulation. It appeared to be a sensitive measure for changes in HPA axis activity. It is advisable to test not only plasma cortisol in future research but also, if possible, to measure ACTH levels in order to calculate the ratio of CORT:ACTH.

In our small study, with a limited power to detect significant differences, we were able to demonstrate group differences in CORT:ACTH ratio. First, an increased CORT:ACTH ratio was observed in TCs during the night compared with both PSTD patients and HCs. This alteration in TCs compared with both PTSD patients and HCs was first described by Golier et al. (2007) in Gulf War veterans. Second, in PTSD patients a decreased CORT:ACTH ratio was observed upon awakening. Both observations may be ascribed to the responsiveness of the adrenals upon ACTH stimulation. Hyporesponsive adrenals to ACTH may explain the decreased ratio in PTSD patients. In contrast, in TCs higher responsive adrenals to ACTH may explain the observed difference. We postulate that adaptation to trauma exposure leads to more responsive adrenals to ACTH, while a reduced responsiveness of the adrenals upon ACTH stimulation is seen in those who do not accomplish adaptation. This may implicate insufficient cortisol levels to induce an adequate inhibiting feedback response to HPA-axis activity in PTSD. In contrast, in TCs higher cortisol secretion may induce a more rapid normalization of a stress response, which may be reflected by “resilience” and adaptation.

Noticeably, glucocorticoid receptors (GR) are hyperresponsive in PTSD patients, who demonstrate exaggerated responses to dexamethasone administration (de Kloet, Vermetten, Heijnen et al., 2007; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004; Yehuda, Halligan, Golier, Grossman, & Bierer, 2004). A higher number of GR has also been reported before exposure to potentially traumatic events, in service members who developed PTSD symptoms post-deployment (Van Zuiden et al., 2011). It is unknown whether in patients with PTSD the reduced response of the adrenals to ACTH stimulation and elevated GR number and responsivity may be related. Presumably, low responsiveness of the adrenals to ACTH may imply relatively lower cortisol levels upon stimulation, and, subsequently, an upregulation of GR receptors as a compensatory mechanism. One study also found elevated sensitivity of the GR receptor in TCs compared with HCs (de Kloet, Vermetten, Heijnen, et al., 2007). When cortisol secretion is increased in TCs after ACTH stimulation, and GR receptor enhancement takes place after trauma, the HPA-axis may be even further sensitized for the negative feedback response of cortisol in TCs.

Future research investigating stress and posttraumatic symptoms should focus on the dynamic characteristics of the HPA-axis, for instance, calculating CORT:ACTH ratios. In addition, sensitivity and upregulation of receptors involved in the HPA-axis should be further explored.

Concluding remarks and recommendations

Sleep has been studied with polysomnography in the early days of PTSD research. However, the lack of objective findings in PSG studies urged the need to develop alternatives for measuring sleep in patients with PTSD. This dissertation shows that sleep in patients with PTSD is characterized by frequent awakenings at night, according to polysomnographic registrations. The number of awakenings in patients with PTSD is associated with HPA-axis functioning, subjectively perceived sleep, and, interestingly, GH secretion and memory consolidation. Furthermore, this dissertation supports the idea that disturbed sleep exerts a negative effect on PTSD symptomatology. First, nightmares before military deployment predicted PTSD symptom development, independently early life trauma, mood, and anxiety symptoms. Second, a positive correlation was observed between PTSD severity and the number of sleep apneas, which may indicate an increase in PTSD symptoms when sleep quality is compromised by external factors. Our results suggest that disturbed sleep increases the risk for PTSD. PTSD, in turn, leads to increased sleep fragmentation, decreased GH secretion, and frequent nightmares, which may again compromise fear extinction, synaptic plasticity, and recovery. This suggests that disturbed sleep is a precipitating and perpetuating factor in PTSD symptomatology, possibly creating a perpetual circle. Longitudinal studies are warranted to investigate whether the differences in sleep fragmentation, GH secretion, and increased HR during sleep, found in our cross-sectional studies, are “trait or state” phenomena. In addition, more research is needed to further investigate the effects of sleep disruptions on fear extinction memory consolidation. New approaches are advised, such as combined functional MRI/EEG studies to elucidate brain activation patterns and functional connectivity during sleep. More studies investigating sleep-dependent neuroplasticity and growth factors during sleep are also needed to further explore whether sleep disturbances affect biological underpinnings of psychiatric disease and recovery through the effect of sleep on synaptic plasticity.

BACK TO TOP

## Early altered resting-state functional connectivity predicts the severity of post-traumatic stress disorder symptoms in acutely traumatized subjects

PLoS One
Zhou Y, Wang Z, Qin LD, Wan JQ, Sun YW, Su SS, Ding WN, Xu JR.
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Abstract

The goal of this study was to investigate the relationship between resting-state functional connectivity and the severity of post-traumatic stress disorder (PTSD) symptoms in 15 people who developed PTSD following recent trauma. Fifteen participants who experienced acute traumatic events underwent a 7.3-min resting functional magnetic resonance imaging scan within 2 days post-event. All the patients were diagnosed with PTSD within 1 to 6 months after trauma. Brain areas in which activity was correlated with that of the posterior cingulate cortex (PCC) were assessed. To assess the relationship between the severity of PTSD symptoms and PCC connectivity, contrast images representing areas positively correlated with the PCC were correlated with the subject's Clinician-Administered PTSD Scale scores (CAPS) when they were diagnosed. Furthermore, the PCC, medial prefrontal cortex and bilateral amygdala were selected to assess the correlation of the strength of functional connectivity with the CAPS. Resting state connectivity with the PCC was negatively correlated with CAPS scores in the left superior temporal gyrus and right hippocampus/amygdala. Furthermore, the strength of connectivity between the PCC and bilateral amygdala, and even between the bilateral amygdala could predict the severity of PTSD symptoms later. These results suggest that early altered resting-state functional connectivity of the PCC with the left superior temporal gyrus, right hippocampus and amygdala could predict the severity of the disease and may be a major risk factor that predisposes patients to develop PTSD.

## Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop following exposure to a traumatic event, such as military combat, traffic accidents, rape, assault, or natural disasters. It is a complex syndrome that involves re-experiencing of symptoms (e.g., nightmares and flash-backs), hyperarousal symptoms (e.g., insomnia), numbing symptoms (e.g., restricted affect and anhedonia), and avoidance symptoms (e.g., avoiding trauma-related stimuli), in addition to cognitive impairment, such as poor concentration and difficulty in explicitly recalling aspects of the traumatic event [1]. More than one third of people with PTSD fail to recover, even after many years [2]. Additionally, 50% of PTSD patients have comorbid drug abuse and other mental disorders, and their suicide rate is six times that of normal individuals [3]. Therefore, how to reduce the damage to human health and the large consumption of social rescources caused by PTSD is becoming a scientific cutting-edge issue primarily focused by the government and scientific community. A deeper understanding of the neurobiological basis of PTSD may also explain individual differences in susceptibility to the disorder and aid in the development of more effective treatments.

Over the past decade, neuroimaging techniques have been critical in the process of identifying important brain systems in the pathophysiology of PTSD. Specifically, findings from functional neuroimaging studies indicated abnormalities in amygdale and amygdala-linked circuitry involving the medial prefrontal cortex (mPFC), insula, anterior cingulate cortex (ACC), and hippocampus [4], [5], [6], [7], [8] Studies [5], [6], [7], [8] have shown heightened amygdala responsivity in PTSD during symptomatic states and during the processing of trauma-unrelated affective information. Importantly, amygdala responsivity is positively associated with the

severity of symptoms in PTSD [9], [10], [11], [12], [13]. In contrast, the mPFC responsivity is negatively associated with the severity of PTSD symptoms [9], [14], and the mPFC appears to be hyporesponsive during symptomatic states and the performance of emotional cognitive tasks in PTSD.

Resting-state functional connectivity has been widely used in the study of PTSD [9], [10], [11], [12], [13], [14], [15], [16], because during scanning, the absence of demanding cognitive activity and instructions makes it more straightforward to compare brain activity across groups that may differ in motivation or cognitive abilities. It is unknown whether the structural and functional changes are due to the effect of the traumatic event on neural function, or rather represent underlying risk factors that predate the trauma and predispose individuals to developing PTSD. To partially assess this topic, we aimed to assess the relationship between resting-state functional connectivity and clinical severity of PTSD in patients who developed PTSD following recent trauma.

## Materials and Methods

### Subjects

The current study included 15 car accident victims randomly recruited from the Emergency Department of Renji Hospital. Most of them witnessed actual or threatened death or serious injury to others, and some of them had mild concussive neurotrauma and bruises. In order to guarantee scanning quality, to avoid major head movements during data acquisition, and to eliminate the potential effect of lesions in the brain on the analysis of resting state functional connectivity, we excluded the patients with significant head injury. All subjects underwent baseline evaluation within 2 days (2d). The tests included the Mini-International Neuropsychiatric Interview (MINI) [17], Acute Stress Disorder Structured Interview (ASDI) [18] and functional magnetic resonance imaging (fMRI) scans. Follow-up evaluation for the PTSD diagnosis, based on the Clinician-Administered PTSD Scale (CAPS) [19], was conducted at 1 and 6 months post-accident. All PTSD subjects fulfilled criterion for PTSD as assessed using CAPS, either 1 month or 6 months post-accident. All participants were right-handed.

The exclusion criteria were as follows: (1) younger than 18 or older than 60 years, with an education <9 years; (2) ASDI <3; (3) significant head injury (i.e., abnormalities on conventional MRI, neurological abnormalities during emergency department evaluation, and loss of consciousness longer than several seconds during the accident); (4) a history of neurological disorders; (5) current axis I disorders at the time of the accident, as assessed using the MINI [17], or drug or alcohol abuse/dependence within 6 months prior to the accident; (6) medications (psychotropic drugs within 4 weeks prior to scanning); and (7) contraindications to MRI.
The current study was approved by the Research Ethics Committee of Renji Hospital. All subjects gave their informed written consent. All procedures were in accordance with institutional guidelines.

MRI Acquisition

MRI was performed on a 3T magnetic resonance scanner (GE Signa HDxt 3T, USA). A standard head coil with foam padding was used to restrict head motion. During resting-state fMRI, the subjects were instructed to keep their eyes closed, remain motionless, and not to think of anything in particular. A gradient-echo echo-planar sequence was used to acquire functional images (repetition time [TR] = 2000 ms, echo time [TE] = 30 ms, field of view [FOV] = 230 mm2×230 mm2, matrix = 64×64, thickness = 4 mm, and gap = 0). Each fMRI scan lasted 440 s. Other sequences were also acquired, including: (1) sagittal T1-weighted 3D-magnetization prepared rapid acquisition gradient echo sequences (TR = 9.4 ms, TE = 4.6 ms, flip angle = 15°, slice thickness = 1 mm, gap = 0 mm, FOV = 256 mm×256 mm, matrix = 256×256, and slices = 155); (2) axial T1-weighted fast field echo sequences (TR = 331 ms, TE = 4.6 ms, FOV = 256 mm ×256 mm, slice thickness = 4 mm, gap = 0, slices = 34, and matrix = 512×512); and (3) axial T2-weighted turbo spin-echo sequences (TR = 3013 ms, TE = 80 ms, FOV = 256 mm×256 mm, slice thickness = 4 mm, gap = 0, slices = 34, and matrix = 512×512).

Image Analysis

Brain MR imagings (T1-weighted and T2-weighted images) were evaluated by two experienced neuroradiologists. No gross abnormalities were observed in the participants. Functional MRI preprocessing was carried out using Data Processing Assistant for Resting-State fMRI (DPARSF V 2.0, by YAN Chao-Gan, http://www.restfmri.net), which is based on MRIcroN (by Chris Rorden, http://www.mricro.com), statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), and the Resting-State fMRI Data Analysis Toolkit (REST V1.5 software, by SONG Xiao-Wei et al., http://www.restfmri.net). The first 10 volumes of each functional time series were discarded because of instability of the initial MRI signal and the initial adaptation of participants to the situation. Data from each fMRI scan contained 220 time points, and the remaining 210 images were preprocessed. The images were subsequently corrected for slice timing and realigned to the first image for rigid-body head movement correction. No participant had motion of more than 1 mm with maximum translation in x, y, or z, or 1° of any angular motion throughout the course of scan. The functional images were normalized into standard stereotaxic anatomical Montreal Neurological Institute space. The normalized volumes were resampled to a voxel size of 3 mm×3 mm×3 mm. The echo-planar images were spatially smoothed using an isotropic Gaussian filter of 4 mm full width at half maximum.

Each voxel’s time-series was detrended to correct for lineral drift over time. Nine nuisance covariates (time-series predictors for global signal, white matter, cerebrospinal fluid, and the six movement parameters, including the first derivative, obtained during realignment to account for motion-related effects in blood oxygenated level-dependent) were sequentially regressed from the time-

series [20]. Following this procedure, temporal filtering (0.01 Hz–0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise [21], [22], [23].

The PCC template, which consisted of Brodmann's areas 29, 30, 23, and 31, was selected as the region of interest (ROI) using WFU-Pick Atlas software [24]. The BOLD time series of the voxels within the seed region were averaged to generate the reference time series.

For each subject and seed region, a correlation map was produced by computing the correlation coefficients between the reference time series and the time series from all the other brain voxels. Correlation coefficients were then converted to z values using Fisher's z-transform to improve the normality [22]. The individual z value was entered into a random effect one-sample t-test in a voxel-wise manner to determine brain regions showing significant connectivity to each seed region within PTSD patients under a combined threshold of $P<0.01$ and cluster size n = 486 mm3. This yielded a corrected threshold of $P<0.05$, determined by Monte Carlo simulation with the program AlphaSim in AFNI with the following parameters: full width at half maximum = 4 mm, within the BrainMask in REST. This procedure produced significant functional connectivity z-statistic maps for the PTSD group.

To examine whether the strength of functional connectivity in the PCC varies with the severity of disease in PTSD patients, Pearson's correlative analysis was performed to examine relationships between the z-values and CAPS in PTSD patients at the time that patients were diagnosed using a threshold of $p<0.05$ as corrected by AlphaSim. Left and right amygdala templates were selected as ROIs using WFU-Pick Atlas software [24], acting as separate seed regions. The mPFC was selected as the seed region centered at Montreal Neurological Institute coordinates of −2, 48, and −4 in a 10-mm sphere, as described in a previous study [15]. For each seed region, the BOLD time series of the voxels within the seed region was averaged to generate the reference time series. Using ROI-wise functional connectivity analysis, the correlation coefficients of the functional connectivity in each pair of seed regions were calculated and then converted to z values within correlation coefficients. Pearson's correlative analysis was performed to examine relationships between the z-values and CAPS in PTSD patients at the time of diagnosis using a threshold of $p<0.05$ as corrected by AlphaSim.

## Results

### Subject Characteristics

The mean age of PTSD patients (4 females, 11 males) was 41.52±12.56 years, and the mean duration of education was 12.02±2.56 years. All subjects underwent baseline evaluation within 2 d post-accident. No patient met diagnostic criteria for current axis I

disorders as assessed using the MINI, and the mean ASDI was 15.42±6.01. Follow-up evaluation for PTSD diagnosis was conducted at 1 month and 6 months post-accident. Eleven and 4 patients were diagnosed 1 month and 6 months post-accident, respectively, and the mean time from accident to PTSD diagnosis was 2.33±2.28 months. The mean CAPS when the patients were diagnosed was 44.53±15.76.

Correlation between PCC Connectivity and CAPS

Connectivity with the PCC was negatively correlated with CAPS scores in the left superior temporal gyrus and right hippocampal gyrus/right amygdala (see Table 1 and Fig. 1).

Brain regions where functional connectivity with the PCC correlated with CAPS scores at the time PTSD patients were diagnosed. Brain regions where functional connectivity with the PCC was correlated with CAPS at the time when patients were diagnosed with PTSD.

Correlation of Functional Connectivity within Seed Regions and CAPS

Four regions were selected, including the PCC, mPFC and bilateral amygdala. Correlation analysis of the strength of functional connectivity within each pair of seed regions and CAPS was performed. The strengths of functional connectivity of the PCC-right amygdala ($r = -0.57$, $p = 0.03$), PCC-left amygdala ($r = -0.53$, $p = 0.04$) and right amygdala-left amygdala ($r = -0.54$, $p = 0.04$) were negatively correlated with CAPS scores in the PTSD patients at the time of diagnosis. (See Table 2 and Fig. 2).
Pearson's correlations between the PCC, mPFC, left amygdala, right amygdala and CAPS in PTSD patients.

Correlation between PCC-left amygdala, PCC-right amygdala, left-right amygdala connectivity and CAPS in 15 PTSD patients: (Fig. 2a) PCC-left amygdala connectivity and CAPS, $r = -0.53$, $p = 0.04$; (Fig. 2b) PCC-right ...

Discussion

To the best of our knowledge, this is the first study to examine the relationships between default network connectivity and prospective PTSD symptoms soon after trauma. This study demonstrated that resting state connectivity with the PCC was negatively correlated with CAPS scores in the left superior temporal gyrus and right hippocampus/amygdala. Furthermore, the strength of connectivity between the PCC and bilateral amygdala, and even between the bilateral amygdala could predict the severity of PTSD symptoms later.

These results are partly consistent with previous studies [9], [10], [11], [12], [15], [16], [25]. Structural abnormalities in the superior temporal gyrus have been found in maltreated children and adolescents with PTSD [26]. The superior temporal gyrus has connections with temporolimbic areas, including the hippocampus, amygdala, entorhinal cortex, thalamus, and neocortical association areas in prefrontal and parietal cortices [27]. The superior temporal gyrus is involved in auditory processing, including language, and has also been implicated as a critical structure in social cognition. De Bellis et al. [26] found that superior temporal gyrus volumes were larger in the chronic PTSD patients than in control subjects. They suggested that there might be a compensatory synaptic increase in the superior temporal gyrus related to the increase of the sensitivity to conditioned auditory stimuli during development, or the larger superior temporal gyrus gray matter in the PTSD subjects could be a consequence of a decreased developmentally-related input from the frontal cortex. The hippocampus is essential for the formation of stable declarative memory in humans and spatial memory in rodents, and is the brain functional domain most closely associated with learning, memory, and cognitive function [28]. Dickie et al [9] found that change in the activity of the hippocampus and subgenual anterior cingulate cortex (as a function of emotional memory) was correlated with improvement in PTSD symptoms, suggesting that activity in these areas may be associated with recovery. We found a negative correlation of the connectivity with the PCC in superior temporal gyrus and hippocampus with CAPS, suggesting that early altered resting-state functional connectivity in these areas could predict the severity of the disease and may be a major risk factor that predisposes patients to develop PTSD.

Amygdala activity plays a causal role in the experience of negative effects, such as fear, anxiety, and distress. In healthy brains, amygdala activity is thought to be dampened via top-down inhibition by the mPFC, yielding a reduction in subjective distress. However, in PTSD, a defect in mPFC function impairs inhibition of the amygdala, resulting in abnormal amygdala activity and pathological distress [5], [29]. Therefore, PTSD neuroimaging data support a model of PTSD pathogenesis that proposes two important elements: 1) the emotional distress characterizing PTSD arises from hyperactivity in the amygdala; and 2) amygdala hyperactivity is caused by defective inhibition from a hypoactive mPFC [29], [30]. A previous study [31] suggested that amygdala damage abolishes the development of PTSD among combat veterans, which supports the assertion that amygdala hyperactivity plays a causal role in the pathophysiology of PTSD. Numerous studies, using a variety of tasks and stimuli, have reported significant positive correlations between the severity of PTSD symptoms and amygdala activity [12], [13] and both positive [25] and negative [32], [33], [34] correlations with activity of the mPFC. We found that the strength of connectivity between the PCC and bilateral amygdala was negative correlated with CAPS, which may be caused by hyper-inhibition by the mPFC in the early stage of post-trauma. Early abnormal function of amygdala-linked circuitry may lead to the subsequent onset of illness. Interestingly, we also found a negative correlation of the strength of functional connectivity in right-left amygdala with CAPS. Further research is necessary to explain this phenomenon in detail.

We did not observe any significant differences in PCC connectivity to the mPFC or anterior cingulate cortex in PTSD patients at rest. This is a notable negative finding and requires replication; however, we acknowledge that it could have resulted from the following: (1) a small sample size may have led to false negative results and/or more subtle connectivity abnormalities; and (2) the resting-state task may be insensitive to detecting early and mild PCC-prefrontal and amygdala-mPFC connectivity abnormalities, which may require engagement by an overt task. Koenigs et al. [31] considered that the finding of mPFC hypoactivity in functional imaging studies of PTSD does not necessarily reflect a causal contribution to the disorder. It is possible that the mPFC hypoactivity observed in PTSD develops as a consequence of chronic distress associated with PTSD. Koenigs et al. [31] found that mPFC lesions resulted in decreased susceptibility to PTSD and they proposed that the causal role of mPFC in PTSD may be related to its function in self-insight and self-reflection. Therefore, a loss of self-insight or self-reflection may diminish the core symptoms of the disorder.

The current study has several limitations. First, the sample size was relatively small. Second, the seed-point method as the mode of analysis may have been biased by the particular seed region chosen, focusing on long-distance patterns of connectivity. However, we applied all of the ROIs mentioned in previous studies. Third, we did not obtain the patient's fMRI again when they were diagnosed. Fourth, these connectivity differences could be resolved by other factors unrelated to the traumatic event. Fifth, we excluded the patients with significant head injury (i.e., abnormalities on conventional MRI, neurological abnormalities during emergency department evaluation, and loss of consciousness longer than several seconds during the accident). PTSD can commonly result from concussive injury resulting in loss of consciousness; thus, this criterion for exclusion severely limits generalizability. Follow-up studies should be conducted in the future to verify the present findings.

Conclusions

This paper describes a preliminary study investigating the relationship between resting-state functional connectivity and the severity of post-traumatic stress disorder (PTSD) symptoms in people who developed PTSD following recent trauma. Early altered functional connectivity in the PCC with the left superior temporal gyrus, right hippocampus and amygdala could predict the severity of the disease, and may be a major risk factor that predisposes patients to develop PTSD.

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## Treatment Improves Symptoms Shared by PTSD and Disordered Eating.

National Center for PTSD, VA Boston Healthcare System

Mitchell KS, Wells SY, Mendes A, Resick PA
25 Oct 2012

Abstract

Eating disorders and posttraumatic stress disorder (PTSD) are debilitating conditions that frequently co-occur. Although the two disorders have different clinical presentations, they share associated features, including cognitive disturbances, emotion dysregulation, dissociation, and impulsivity. We hypothesized that reductions in PTSD symptoms following cognitive processing therapy (CPT) and its treatment components (CPT without the written account or the written account only) would be associated with improvements in symptoms common to PTSD and eating disorders. Participants in the current investigation included women with PTSD (N = 65) who reported a history of rape or physical assault, were in a randomized dismantling study of CPT, and completed the Eating Disorder Inventory-2 (EDI-2) at pre- and posttreatment. Latent growth modeling results indicated that decreases in PTSD symptom scores were significantly associated with reductions in the Impulse Regulation, Interoceptive Awareness, Interpersonal Distrust, Ineffectiveness, and Maturity Fears subscales of the EDI-2. Thus, PTSD treatment affected symptoms shared by PTSD and eating disorders. Currently, there are no clear guidelines for treatment of comorbid PTSD and eating disorders. Traditional CPT may impact symptoms common to both, but additional therapy may be needed for specific disordered eating attitudes and behaviors.

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## What are the effects of having an illness or injury whilst deployed on post deployment mental health? A population based record linkage study of UK Army personnel who have served in Iraq or Afghanistan

BMC Psychiatry
Harriet J Forbes, Norman Jones, Charlotte Woodhead, Neil Greenberg, Kate Harrison, Sandra White, Simon Wessely and Nicola T Fear
24 Oct 2012

Abstract (provisional)

Background

The negative impact of sustaining an injury on a military deployment on subsequent mental health is well-documented, however, the relationship between having an illness on a military operation and subsequent mental health is unknown.

Methods

Population based study, linking routinely collected data of attendances at emergency departments in military hospitals in Iraq and Afghanistan [Operational Emergency Department Attendance Register (OpEDAR)], with data on 3896 UK Army personnel who participated in a military health study between 2007 and 2009 and deployed to Iraq or Afghanistan between 2003 to 2009.

Results

In total, 13.8% (531/3896) of participants had an event recorded on OpEDAR during deployment; 2.3% (89/3884) were medically evacuated. As expected, those medically evacuated for an injury were at increased risk of post deployment probable PTSD (odds ratio 4.25, 95% confidence interval 1.81 to 9.99). Less expected was that being medically evacuated for an illness was also associated with a similarly increased risk of probable PTSD (4.43, 1.61 to 12.16) and common mental disorders (2.82, 1.43 to 5.56). There was no association between having an OpEDAR event and alcohol misuse. Having an injury caused by hostile action was associated with increased risk of probable PTSD compared to those with a non-hostile injury (3.88, 1.15 to 13.06).

Conclusions

Personnel sustaining illnesses on deployment are just as, if not more, at risk of having subsequent mental health problems as personnel who have sustained an injury. Monitoring of mental health problems should consider those with illnesses as well as physical injuries.

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## Eating Disorders, Post-Traumatic Stress, and Sexual Trauma in Women Veterans

Military Medicine
Forman-Hoffman, Valerie L.; Mengeling, Michelle; Booth, Brenda M.; Torner, James; Sadler, Anne G.
Oct 2012

Abstract

We examine lifetime eating disorders (EDOs) and associations with post-traumatic stress disorder (PTSD) and sexual trauma during various stages of the life course (childhood, during military service, and lifetime) among women veterans. The sample included 1,004 women aged 20 to 52 years who had enrolled at 2 Midwestern Veterans Affairs Medical Centers or outlying clinics completed a retrospective telephone interview. Over 16% reported a lifetime EDO (4.7% had received a diagnosis, and an additional 11.5% self-reported suffering from an EDO). Associations were found between lifetime EDO, PTSD, and sexual trauma. Relationships maintained significance for both diagnosed and self-reported EDOs as well as lifetime completed rape and attempted sexual assaults. Sexual trauma during military service was more strongly associated with lifetime EDOs than childhood sexual trauma. The significant associations found between EDOs, PTSD, and sexual trauma indicate that EDO screening among women veterans with PTSD or histories of sexual trauma may be warranted.

Introduction

Eating disorders (EDOs) in military and veteran populations have begun to be investigated in recent years. The few estimates of either lifetime or current EDO prevalence have varied across studies, in part because of methodological differences. Striegel-Moore et al1 found that 0.3% of hospitalized veterans had a current EDO diagnosis, whereas another medical record review study of U.S. military service members determined an annual incidence of 0.4% in 20062 among active duty service members. Given that females are approximately 10 times as likely as males to have a current or lifetime EDO,3 studies focused on women service members or veterans have found higher prevalence estimates. Using self-reported information collected via survey Methodology, studies have estimated that 8% of active duty women4 and 5% of U.S. Military Academy female cadets have a lifetime history of EDOs.5 A study by McNulty et al6 conducted on active duty service women found that 1.1% reported anorexia nervosa, 8.1% reported bulimia nervosa, and 62.8% reported eating disorder-not otherwise specified. In addition, approximately one-fifth to one-third of active duty women engage in behaviors that put them at risk for developing an EDO7,8 based on self-reported screening instruments. Service members may be at increased risk for EDOs, given the weight standards requirements of recruits.9–11 EDOs are an important area of investigation in military and veteran populations, given the increasing incidence2 and increased risk of premature mortality, functional impairment, and medical conditions including cardiovascular, renal, and endocrine dysfunction among those suffering from EDOs. In addition, whereas there is an increased risk of comorbidity with other psychiatric disorders,1 the relationship among these requires clarification.

In addition, there appears to be a significant association between traumatic events (as well as potential sequelae of traumatic events like post-traumatic stress disorder [PTSD]) and EDOs. Several studies have found that individuals with a current or lifetime EDO are more likely to report experiences of traumatic events and dissociation.12–15 Specific types of trauma such as childhood maltreatment16 and childhood sexual abuse have been identified as risk factors for EDOs,13,17–25 with about one-half of patients with an EDO also having a history of sexual abuse.18,26 In addition to traumatic events, significant associations have been found between EDO pathology and symptoms of PTSD.27–29 A study by Tagay et al30 found that 10% of patients with anorexia nervosa and 14.1% of patients with bulimia nervosa experienced concurrent PTSD.

The association between traumatic events, PTSD, and EDOs also appears to have a synergistic effect, with the presence of two risk factors increasing the likelihood of the other occurring. For example, traumatic events have been found to increase the risk of psychiatric comorbidity, including PTSD in those with EDOs.13 The presence of synergistic risk factors also appears to increase the risk of other psychopathology. For example, a study by Fullerton et al31 found that female EDO patients who were sexually abused as children suffered more depression than patients who were not sexually abused. Other research has determined an association between recent adult sexual assault and current EDO symptoms, even after controlling for childhood sexual abuse.32 These relationships, however, have not been widely studied.

The associations between EDOs, traumatic events and PTSD found in civilian female samples have not been thoroughly investigated in military and veteran populations. Although one study by Striegel-Moore et al1 found that hospitalized veterans with a medical record diagnosis of an EDO had a significantly elevated risk of co-occurring PTSD, the associations have not been replicated. In an attempt to address this research gap as well as the paucity of evidence examining the association between trauma, PTSD, and EDOs in military and veteran populations, this study has several objectives. First, this study will examine lifetime self-reported and diagnosed EDOs and related attitudes and behaviors in a sample of Veterans Affairs (VA)-enrolled women veterans. Second, this study will examine the association between sexual trauma during various stages of the life course (childhood, during military service, and lifetime), PTSD, and EDOs.

## Methods

## Materials and Methods

### Sample and Sources of Data

This was a cross-sectional study that examined 1,004 women ≤51 years of age who had enrolled at two Midwestern VA Medical Centers or outlying clinics within the 5 years preceding study interviews (July 2005 through August 2008). Women veterans enrolled after June 2005 and before the study completion were periodically identified and added to the cohort. VA enrollment could have been initiated to receive health care, complete a disability claim, enroll in a registry, or in response to veteran outreach.

An introductory letter and consent forms with postage-paid, preaddressed return envelopes were mailed to 2,414 potential subjects providing them with a toll-free number so that they could address any further questions, schedule interviews, or refuse participation. Two weeks following the introductory letter, potential subjects not initiating contact were recruited by telephone. Institutional Review Board-approved mail and phone protocols were continued until contact was made or subjects were deemed unreachable. When address or phone problems occurred, effort was taken to find current contact information using internet white pages, VA's Computerized Patient Record System, and Accurint (a confidential Lexis Nexis research tool).33 Of the 2,414 potential subjects, 707 were unreachable, 30 were ineligible, and 7 were deceased. Sixty-nine percent (1,670/2,414) of the sample were located and invited to participate in the study. One thousand, fifty-five subjects consented to participate, resulting in a response rate of 63%. Women refusing participation were asked why they refused and to answer three questions related to the original purpose of the study (gynecologic health) to allow comparison with participants: (1) “In general would you say your health is: excellent, very good, good, fair, or poor?”; (2) “Have you ever been told you have had an abnormal Pap smear?”; and, (3) “In the last year, approximately how many times have you seen a dOctoberor or health care provider for gynecologic health issues?” No significant differences were found between participants and refusers with regard to average age (38.3 years vs. 37.9 years), self-report of very good or excellent health (43.5% vs. 45.1%), number of gynecologic visits in last year (2.1 vs. 1.7), or ever being told by a provider they had an abnormal Pap test (56.9% vs. 51.2%).

For reasons related to the original study of gynecologic health,34 screening before interview excluded women who were (1) aware of in utero diethylstilbesterol exposure (n = 10), (2) currently receiving treatment with immunosupressants (n = 7), or (3) greater than age 51 years at time of sample selection (n = 3). One woman turned 52 at time of interview, which is the age reported herein. An additional 21 subjects could not be reached by phone and 13 were unable to complete the interview, resulting in 1,004 subjects who completed the interview. The study was approved by the University of Iowa and Iowa City VA Medical Center Institutional Review Boards.

Following return of signed consents and meeting inclusion criteria, participants completed a computer-assisted telephone interview (CATI). The CATI provides a structured interview that standardizes interviews across participants. Participants were asked questions and almost always given the response options (e.g., yes/no, agree/disagree, etc.). The only “open response” items were ones that couldn't be reduced to a small finite set of options (e.g., age), although on many of these, appropriate ranges were programmed into

the interview (e.g., ages 18–60 years). This was done to increase the reliability and validity of the data collected. Skip patterns were also programmed into the tailored interview such that questions that did not apply to a specific participant were not asked. For example, if a woman never experienced a sexual assault, then follow-up questions, such as when and where, were not asked. Every item included response options “Don't know” and “Refuse.” Interviewers did not probe further into responses of “Don't know” or “Refuse.”

The CATI assessed demographics and service-related characteristics, health history including eating and weight-related thoughts and behaviors, as well as reports of ever having had an EDO and reported lifetime mental disorder diagnoses including EDOs, PTSD, depression and substance use (alcohol or drug) disorders (abuse or dependence), smoking, self-reported weight and exercise, and sexual assault experiences (lifetime, during military service, and during childhood). The average interview took 1 hour and 16 minutes in length, and the majority of subjects (89%) completed it in one call. Subjects who completed the interview were reimbursed $30.00 for their participation.

Measures

The primary outcome for this study was a three-level variable regarding ever having an EDO. If a woman responded “yes” to the question, “have you ever been diagnosed with an eating disorder?,” she was coded as having a diagnosed lifetime eating disorder (DX-EDO). Otherwise, if a women responded “yes” to the question, “have you ever suffered from an eating disorder?,” she was coded as having a lifetime EDO. If a woman responded “no” to both EDO survey questions, she was assigned as having no lifetime EDO (NO-EDO), which was used as the reference category in analyses.

The main independent variables of interest included (1) ever diagnosed with PTSD and (2) sexual trauma experiences at any time during lifetime, during military service, and during childhood (less than 18 years old). PTSD was queried with the question “Have you ever been diagnosed with PTSD?” Sexual traumas were queried with multiple questions regarding the type and time period of attempted sexual assaults and completed rapes. Responses to the sexual trauma questions were collapsed into three mutually exclusive categories: completed rape, attempted sexual assault (no reported completed rape), and no sexual trauma (no reported completed rape or attempted sexual assault). Completed rape was assessed using the legal definition adopted by the American Medical Association and the American College of Obstetricians and Gynecologists, and commonly used in sexual violence research (American Medical35 and American College of Obstetricians36). If a respondent answered “yes” to any of the questions assessing completed sexual penetration of the vagina, mouth, or anus using force or threat of harm, she was coded as having a completed rape. Otherwise, if she reported “yes” to the attempted sexual assault question, “has anyone, male or female, using force or threat of harm, ever attempted to sexually assault you? By attempted sexual assault, I mean that an attempt was made but penetration did not

occur," she was coded as having an attempted sexual assault. If the respondent answered "no" to both the completed rape and the attempted sexual assault question, she was coded as having no sexual trauma. Three sexual trauma variables were created using this algorithm, each corresponding to a different time period: (1) lifetime (completed rape, attempted sexual assault, no sexual trauma ever), (2) during military service (completed rape, attempted sexual assault, no sexual trauma during military service), and (3) during childhood before 18 years old (completed rape, attempted sexual assault, no sexual trauma before 18 years old).

Patient demographics included age (grouped into ages 20–34, 35–44, and 45–52), race/ethnicity (white, nonwhite, multi [more than one racial/ethnicity]), education level (high school, some college or technical training, or completed college or graduate training), employment (employed, retired, student, or unemployed), and marital status (married, divorced, or single). Service-related characteristics included service (Active Component [AC] only, Reserve or National Guard (RNG) only, or both AC and RNG), pay grade (officer or enlisted), and service in a military combat area or war zone. Behavioral characteristics included current weight category based on self-reported height and weight (underweight body mass index [BMI] < 19, normal weight BMI 19–25, overweight BMI 25–30, obese BMI 30+), and exercise (none, 1–90 min/wk, more than 90 min/wk). Eating and weight-related thoughts and behaviors included self-reported satisfaction with eating patterns, eating in secret, and agreement with the statement "weight affects how I feel." Lifetime mental disorder diagnoses (self-reported) included depression and substance use (alcohol or drug) disorders (abuse or dependence).

Analyses

Examination of univariate frequencies of all study variables, bivariate crosstabs, and $\chi 2$ analyses were conducted between the three-level lifetime EDO indicator (DX-EDO, EDO, and NO-EDO) and each demographic, service-related, behavioral, sexual trauma, and mental disorder variable of interest, including PTSD. Next, the proportion of the sample who had each individual or combined experiences of a lifetime EDO (either DX-EDO or EDO), lifetime sexual trauma (completed rape or attempted sexual assault), or PTSD diagnosis were calculated to evaluate the extent of overlap of these experiences. Next, both unadjusted and adjusted multinomial regression models were constructed to determine whether each three-level sexual trauma variable and PTSD diagnosis was significantly related to the three-level EDO outcome variable (DX-EDO, EDO, and NO-EDO). The NO-EDO group was used as the reference category; thus, odds ratios (ORs) were reported for the DX-EDO group vs. the NO-EDO group and the EDO group vs. the NO-EDO group in each multinomial regression model. Each adjusted model included age, race/ethnicity, education, employment, marital status, service, served in combat/war zone, weight category, weekly exercise, lifetime depression diagnosis, and lifetime substance use (drug or alcohol) disorder (abuse or dependence) as covariates. The first adjusted model included PTSD diagnosis, the three-level lifetime sexual trauma variable (lifetime completed rape, attempted sexual assault, no sexual trauma [reference group]), and covariates. The second adjusted model included PTSD diagnosis, the three-level sexual trauma during military service

variable (completed rape, attempted sexual assault, no sexual trauma during military service [reference group]), and covariates. The third adjusted model included PTSD diagnosis, the three-level sexual trauma during childhood variable (completed rape, attempted sexual assault, no sexual trauma during childhood [reference]), and covariates. The presence of a significant interaction between each sexual trauma variable (lifetime, military, childhood) and PTSD diagnosis was also evaluated in each adjusted model.

Missing categorical data resulted in the listwise exclusion of less than 1.5% of participants in adjusted analyses. Analyses were conducted at the two-tailed $p < 0.05$ level of significance, performed with SAS 9.2 software.

Results

Female veterans (n = 1,004) enrolled in one of two Iowa VA Medical Centers (Iowa City or Des Moines) ranged in age from 20 to 52 years old at time of interview (Table 1). Most (79.9%) were White, reported completing at least some college or technical training (56.4%), were employed (51.6%) and married (43.9%). A majority served in the AC only (59.6%), whereas 28.1% served on both AC and RNG duties. Approximately 30% reported serving in a military combat area or war zone.

Weight category mirrored that of the general U.S. population, with about 64.8% being overweight or obese. Although 28% reported no weekly exercise, over 40% reported exercising 90 or more min/wk. Slightly over 30% reported receiving a lifetime diagnosis of depression, whereas 34.5% reported receiving a lifetime diagnosis of drug or alcohol abuse or dependence.

Overall, nearly 62% of respondents reported at least one attempted or completed sexual trauma during their lifetime, nearly 51% reported at least one completed rape, and an additional 10.9% reported attempted sexual assault solely. Almost one-third (32.5%) of respondents reported sexual trauma during military service (24.6% completed rape and an additional 7.9% attempted sexual assault). About two in five respondents (41.0%) reported sexual trauma during childhood (31% completed rape and an additional 10.0% attempted sexual assault). In addition, about one in five (24.6%) reported lifetime PTSD diagnosis.

Over 16% of respondents reported a lifetime EDO (4.7% diagnosed and an additional 11.5% self-reported). Most women with a reported lifetime EDO (92%) reported receiving all or some of their medical care at a VA Medical Center during the past 5 years. In addition, less than half of respondents reported satisfaction with their eating patterns, two-thirds reported that weight affects how they feel, and over 10% reported eating in secret (data not shown) presents the proportion of respondents with diagnosed and self-reported lifetime EDOs (DX-EDO and EDO) within each sexual trauma and PTSD category. All of the sexual trauma variables were significantly associated with lifetime EDOs using $\chi 2$ analyses. Women with lifetime PTSD or who reported sexual trauma during military service or lifetime were about twice as likely to have a diagnosed or self-reported lifetime EDO than women without PTSD or

military or lifetime sexual trauma, respectively. Women who reported completed rape during childhood were about three times as likely to report a lifetime DX-EDO as compared to women with no sexual trauma during childhood (8.7% vs. 2.7%). In addition, of the covariates tested in bivariate analyses, respondents with more education and those who reported being divorced were more likely to have had an EDO than respondents with less education and married or single respondents, respectively, as did respondents with lifetime depression diagnoses or alcohol or drug abuse or dependence (data not shown).

Upon examination of the proportion of women with different combinations of lifetime EDO, PTSD, and sexual trauma experiences, 31.6% did not report any of these three experiences, whereas 5.9% reported having all three experiences (Table III). There was substantial overlap between PTSD and sexual trauma (14.7% of the sample) and between EDO and sexual trauma (7.4% of the sample) as well.

Multivariate models adjusted for demographic, service-level, behavioral, and other mental health characteristics of the sample revealed significant associations between PTSD and EDOs as well as sexual trauma and EDOs (Table IV). In each adjusted model examining the association between lifetime PTSD, sexual trauma during various time periods, and lifetime EDOs, those with PTSD were significantly more likely to have lifetime EDO, but not DX-EDO, than those without PTSD. In addition, women with lifetime completed rape or attempted sexual assault were over four times as likely to have lifetime DX-EDO and over twice as likely to have lifetime EDO than women with no lifetime sexual trauma. Similarly, women with completed rape during military service were over twice as likely as women with no sexual trauma to also report lifetime DX-EDO (OR = 2.28, 95% confidence interval [CI] = 1.12–4.64) and nearly twice as likely as women with no sexual trauma to also report a lifetime EDO (OR = 1.84, 95% CI = 1.15–2.95). Although women with an attempted sexual assault during military service (but no completed rape) were over three times as likely as women with no sexual trauma during military service to have lifetime DX-EDO (OR = 3.05, 95% CI = 1.09–8.54); they were not significantly more likely to have lifetime EDO (OR = 1.76, 95% CI = 0.85–3.63). The only significant association between sexual trauma during childhood and lifetime EDOs was women with completed rape during childhood being more likely to have a DX-EDO than women with no sexual trauma during childhood (OR = 3.07, 95% CI = 1.54–6.12). The relationships between attempted sexual assaults during childhood and EDOs and between completed rape during childhood and EDO failed to reach statistical significance. No significant interactions were found between PTSD and sexual trauma variables in any of the models tested.

## Discussion

In the current study, over 16% of the sample of women veterans reported a lifetime EDO, with nearly 5% reporting a lifetime DX-EDO. These estimates fall within the range of prior self-reported survey estimates of EDOs among female military samples. The current study additionally found significant eating and weight-related impairment among women veterans. For example, one in ten

women reported eating in secret, most (2/3) reported that weight affected how they felt, and nearly half were unsatisfied with their eating patterns, which are reflective of other national investigations of weight-related thoughts and behaviors in nationwide samples of women.

Analogous to previous research findings in civilian samples, significant relationships were found between sexual trauma, PTSD, and EDOs in this study of women veterans. Significant associations were found in models adjusting for potential confounders between PTSD and lifetime EDOs as well as sexual trauma throughout the life course (childhood, during military service, lifetime) and lifetime EDOs, with few exceptions. First, PTSD was significantly associated with EDO but not DX-EDO. Second, there was a significant association between both lifetime EDO categories (DX-EDO and EDO) and both types of lifetime sexual trauma (completed rape and attempted sexual assault). Third, completed rape during military service was significantly associated with both lifetime DX-EDO and EDO; yet, attempted sexual assault during military service (with no completed rape during military service) was only significantly associated with DX-EDO and not EDO. Finally, only completed rape, and not attempted sexual assault, during childhood was significantly associated with DX-EDO and not EDO.

Several of the associations may have failed to reach statistical significance given that few reported DX-EDO (n = 47) in this sample, coupled with relatively low sample sizes of those reporting attempted sexual assault without also reporting a completed rape. Our findings, however, fail to support previous findings showing strong links between childhood sexual trauma and EDOs. Most prior studies have focused on more global measures of child sexual trauma rather than separating completed rape from attempted sexual assaults during childhood (e.g., Smolak and Murnen19). It will be important to replicate our finding of only completed childhood rape (and not attempted sexual assault) being significantly associated with diagnosed EDOs in future studies to determine its validity. The current study found a more consistent association between sexual trauma during military service and lifetime EDOs as compared to the relationship between childhood sexual trauma and lifetime EDOs.

Various studies have hypothesized the explanatory mechanism for the relationship between trauma and EDOs. One potential explanation involves the association having a biological basis as evidenced by dexamethasone suppression test results of trauma and EDOs mirroring that found in post-traumatic stress syndromes.39 In fact, weight loss experienced in some individuals with EDOs appears to lead to physiological changes that increase susceptibility to PTSD.40 In addition, hypothalamic pituitary axis dysregulation has been associated with both EDO behaviors like binge eating and traumatic events.41 More psychopathological explanations for the link between traumatic events and EDOs include EDO development as a way to gain a sense of control, “purify” the “damaged self,” and regulate the overwhelming affective state that results from the experience of the trauma,42 possibly as a result of dissociation following the sexual trauma.

The current study is not without limitations. First, only women veterans who were enrolled at two Midwestern U.S. VA Medical Center or outlying clinics and who agreed to participate (response rate = 63%) comprised the sample, thus reducing the generalizability of findings. Given that the sample was not racially or ethnically diverse, the proportion of women reporting lifetime EDOs and significant associations found in the current study may not apply to all veterans, particularly those who are not VA-enrolled. Second, lifetime EDOs were not assessed with standardized diagnostic instruments, decreasing the reliability of the psychiatric assessment. Comparisons of self-reported chronic diseases to administrative database diagnoses in veterans receiving care in VA health care system have revealed that self-reports have high specificity (88%–100%) but low to moderate sensitivity (24%–78%).43 Third, the survey assessed age of first diagnosis but not age at onset of EDOs and PTSD, which could be very disparate ages given the length of time in between onset and diagnosis for these disorders. Thus, the assessment of temporal associations and the direction of causality between EDOs and trauma could not be made, preventing conclusions about whether trauma precedes EDOs or whether EDO development places individuals at higher risk of later onset of trauma. Finally, since the only type of trauma investigated in this article was sexual trauma, which our prior research conducted on this sample of women veterans has identified as the worst type of trauma,44 the current investigation is unable to make conclusions about the associations between EDOs and other types of trauma.

The current study, however, was conducted on a large group of women veterans, increasing the power to detect significant associations and ability to look at a number of different associations while adjusting the analyses for potential confounders. Examining various degrees of sexual trauma (completed rape and attempted sexual assault) over the life course and EDOs (diagnosed and self-reported only) lends validity to the findings. The survey's assessment of a number of different health conditions, demographic variables, and military exposures made the investigation of these important investigations possible. Future studies can capitalize on these findings by investigating these relationships in more generalizable samples such as women veterans from other VA Medical Centers, women veterans who do not seek care from the VA, and men veterans. Also, future studies can build on the results of the current study by using standardized diagnostic tools to assess Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)45 diagnoses of EDOs (including details related to onset and course of illness) as well as query study participants about single vs. multiple sexual and other types of trauma exposures.

Given the recurrent nature of EDOs,46,47 high rate of comorbidity with other psychiatric disorders48,49 and other health concerns,50,51 and high likelihood of transmitting eating disordered behaviors to female children,52 women veterans should be screened and monitored for EDOs accordingly. This is particularly true for women veterans who have or have had PTSD or who have a history of sexual trauma exposure. The high proportion of women veterans who reported sexual trauma in this sample indicates that many women veterans are likely at high risk for having or developing EDOs. Many of these women currently receive all or some of their medical care at a VA Medical Center as indicated by the 92% of the women with a reported lifetime EDO in the current study sample also reporting that they have received all or some of their medical care at a VA Medical Center during the past

5 years. Additional education in the early identification and treatment of EDOs using a multidisciplinary team approach for VA providers may be warranted. Improvements in screening and referral to appropriate providers with the capability to treat EDOs may limit lost productivity and morbidity associated with EDOs and comorbid conditions, ultimately resulting in significant cost savings to the VA health care system.

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## Postdeployment Alcohol Use, Aggression, and Post-Traumatic Stress Disorder

Military Medicine
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Abstract

Current military personnel are at risk of developing serious mental health problems, including chronic stress disorders and substance use disorders, as a result of military deployment. The most frequently studied effect of combat exposure is post-traumatic stress disorder (PTSD). High-risk behaviors, including alcohol use and aggression, have been associated with PTSD, but the optimal cutoff score on the PTSD Checklist (PCL) for determining the risk for these behaviors has not been clearly delineated. Using postdeployment active duty (AD) and Reserve component military personnel, the relation between various cutoff scores on the PCL and engaging in high-risk behaviors was examined. AD personnel, for every outcome examined, showed significantly greater odds for each problem behavior when PCL scores were 30 or higher compared to those with PCL scores in the 17 to 29 range. A similar pattern was shown for Reserve component personnel with respect to several problem behaviors, although not for alcohol use behaviors. The differences in problem behaviors for these two populations may be an indication that deployment experiences and combat exposure affect them differently and suggest that despite lower critical PCL scores, AD personnel may be at higher risk for developing problems as a function of the deployment cycle.

Introduction

The wars in Iraq and Afghanistan are producing a new generation of veterans who are at risk of developing serious mental health problems, including substance use disorders (e.g., alcohol, illicit drugs, prescription drugs) and chronic stress disorders. Based on the most current estimates, about 200,000 American troops are serving in Iraq and Afghanistan.1 Studies have shown that the short-

term rates of psychiatric and substance use disorders among this group are higher than in the civilian population.2–4 Combat duty is associated with increased utilization of mental health services and increased attrition from the military.5–7

The most frequently studied psychological effect of combat exposure is post-traumatic stress disorder (PTSD), a term for the psychological consequences of exposure to stressful events that an individual experiences as traumatic. Clinically, such events involve actual or threatened death, serious physical injury, or a threat to physical and/or psychological integrity.8 It has been estimated that up to 19% of Operation Iraqi Freedom /Operation Enduring Freedom combat veterans develop PTSD within a year of returning home.9 The presence of a PTSD response is influenced by the intensity of the experience, its duration, and individual differences (e.g., coping, social support). For those personnel who exhibit symptoms of PTSD, comorbidity with other psychiatric disorders, including substance use disorders, is common.5

Top levels of military medical commands recently acknowledged that almost all combat veterans experience some degree of combat and operational stress response, including lack of sleep, irritability, isolation, and other responses, including PTSD.10 Indeed, exposure to combat in Iraq and Afghanistan has been linked to high rates of alcohol use on return from deployment, particularly among Soldiers and Marines.6 These higher rates of alcohol use among combat veterans may be due to increased combat and operational stress response in this population and individuals may increase substance use to suppress these symptoms, both as a short-term coping mechanism or as a long-term suppression mechanism.11

A number of additional high-risk behaviors have been associated with PTSD symptomatology. Begic and Jokic-Begic12 found a significantly greater occurrence of aggressive behavior among combat veterans diagnosed with PTSD compared to combat veterans with no PTSD diagnosis. Likewise, others have reported that violent outbursts and aggressive behavior, hostility, and poor anger control are common sequelae of military combat, particularly among those with PTSD.13–15 PTSD has been shown to be predictive of greater risk-taking propensity, as well as increased alcohol use and verbal and physical aggression toward others.16 As well, problematic alcohol use has been reported as a risk factor for aggression in both military and civilian populations.17,18

Epidemiologic studies have shown that the majority of combat veterans do not develop full-blown PTSD, thus, relying solely on a "diagnostic" cutoff score may exclude those with less severe but practically meaningful symptoms for stress responses. These lower cutoff scores may be useful for identifying those who may use substances to control stress reactions or who may engage in aggressive or impulsive behavior as a release for stress. To address this issue, a measure of PTSD symptoms is needed that will allow us to relate risk behaviors to the severity of PTSD symptoms. One such measure widely used in scientific surveys is the PTSD Checklist (PCL). The PCL is a self-report measure of the 17 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition symptoms of PTSD.19 Items are rated on a 5-point scale ranging from 1 (not at all) to 5 (extremely) with a suggested cumulative

cutoff score of 50 as a clinically useful score suggestive of the need for further evaluation for PTSD. More recent studies have indicated that an optimal score for identifying PTSD in various populations may be somewhat lower, ranging from 3020,21 to 44.22 These various studies have not considered the relation to other associated symptoms and do little to aid clinicians who may be working with patients whose characteristics do not match those in the various studies.

With such a wide range of cutoff scores being documented as relevant for the accurate screening for PTSD, the question arises as to whether the various cutoff scores relate to risk for other types of problematic behaviors and how this might be useful to clinicians. Using active duty (AD) and Guard/Reserve personnel, our study examines the relations among various PCL cutoff scores and the self-report of engaging in a number of high-risk behaviors, including alcohol and drug use, physical and verbal aggression, and risk-taking/impulsiveness. Our aim is to provide clearer guidelines for distinguishing among the different cutoff scores and their relation to other behaviors potentially needing clinical intervention.

## Method

### Participants

Participants in this study comprised AD, and Reserve component (RC) military personnel randomly selected to complete a self-report survey as part of two large studies. The Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel (HRB survey) is a population-based study conducted periodically among U.S. military personnel stationed worldwide to assess a variety of health behaviors. The 2005 HRB survey included items to assess alcohol and tobacco use, drug use, mental health, risk taking and impulsive behavior, and deployment among other areas of functioning. The eligible population for the 2005 HRB survey consisted of all U.S. AD military personnel except recruits, service academy students, personnel absent without official leave, and personnel who had a permanent change of station at the time of data collection. Participants were selected to represent men and women in all pay grades of the active forces throughout the world. The final sample consisted of 16,146 military personnel (3,639 Army, 4,627 Navy, 3,356 Marine Corps, and 4,524 Air Force) who completed self-administered questionnaires anonymously for a response rate of 51.8%. Data were weighted to reflect respondents' probabilities of selection and adjusted to account for the potential effects of nonresponse. Additional details on HRB survey Methodology may be found elsewhere.23 Military population statistics provided by the Defense Manpower Data Center were used to poststratify the sample data to represent the target population.

The 2006 RC survey was conducted among U.S. military personnel stationed in all 50 states. The target population included all nonactivated military Reserve and Guard personnel at the time of data collection, April through September 2006. Personnel came

from six RCs—Army Reserve, Army National Guard, Navy Reserve, Marine Corps Reserve, Air Force Reserve, and Air National Guard. The 2006 RC questionnaire was nearly identical to the questionnaire used for the 2005 HRB survey and included questions assessing alcohol and tobacco use, drug use, mental health, risk taking, and impulsive behavior. Data were collected primarily from participants in group settings at military installations; they were obtained by mail for those not attending the sessions. The final RC sample consisted of 15,212 completed surveys (2,268 Army National Guard, 1,467 Army Reserve, 3,104 Navy Reserve, 1,867 Air National Guard, 5,409 Air Force Reserve, and 1,097 Marine Corps Reserve). The overall response rate was 55.3%, and data were weighted to represent all RC personnel. The analysis sample for this study consisted of all AD and RC personnel with PCL scores who had deployed within the past 2 years (n = 14,428; AD = 8,354, RC = 6,074).

Measures

The HRB and RC surveys examined alcohol use and several measures of alcohol-related problems, including possible alcohol dependence, drinking and driving, verbal and physical aggression, impulsiveness, and other risky behaviors. They also included the PTSD Checklist–Civilian version (PCL-C).

PTSD Symptoms

The PCL-C19 is a 17-item self-report assessment corresponding to symptom Criteria B, C, and D for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and is scored by summing individual item responses to obtain a total score. Scores on the PCL-C range from 17 to 85, with higher scores indicating greater symptom severity. The PCL-C has been found to be highly correlated (r = 0.93) with a structured interview for PTSD, has good diagnostic efficiency (>0.70), and robust psychometric properties with a variety of trauma populations.19,24,25 Given the support for various score cutoffs,20–22 four groups were formed from the scores on the PCL (PCL 17–29, PCL 30–43, PCL 44–49, PCL ≥ 50). Although there is a military version of the PCL (PCL-M), the HRB surveys (and other Department of Defense studies) use the civilian version for several reasons. The PCL-M asks respondents to consider symptoms of PTSD specifically related to military experiences,19 whereas the PCL-C evaluates symptoms resulting from any past traumatic event, not only those attributable to military service. Assessment of PTSD symptoms from both military and nonmilitary sources is important when considering the overall mental health and readiness of military personnel.26 Also, the military version misses common causes of deployment or war-related PTSD in women (e.g., sexual assault rather than combat per se), and deployment-related exacerbations of PTSD symptoms if the original inciting trauma is not military related.

Alcohol Use

Alcohol use was assessed with three measures of use over the past 30 days: any alcohol use, heavy alcohol use, and heavy episodic drinking. Heavy drinking was classified as the consumption of five or more drinks per typical drinking occasion at least once per week over the past 30 days. Heavy episodic drinking was defined as consumption of five or more drinks (four for women) on a single occasion at least once in the past 30 days.

Problematic Alcohol Use

This measure used the Alcohol Use Disorders Identification Test (AUDIT27), which was developed by the World Health Organization as a simple method of screening for excessive drinking and of assisting in brief assessment. The AUDIT consists of 10 questions, each scored 0 to 4, which are summed to yield a total score ranging from 0 to 40.

Driving After Drinking

Respondents were asked how often they had driven a car or other motor vehicle within 2 hours of drinking any amount of beer, wine, or liquor. Responses were coded as a dichotomous variable classifying persons into those who did and did not drive after drinking.

Physical Aggression

Respondents were asked two questions about two types of physical aggression—hitting a spouse, live-in fiancé, boyfriend, or girlfriend, and getting into fights and hitting someone other than a family member during the past 12 months. A positive response to either question classified persons into the physical aggression category.

Verbal Aggression

Two questions assessed verbal aggression with a positive response to either question classifying respondents into this category. Questions involved having heated arguments with family or friends or getting into a loud argument in public in the past 12 months.

Risk Taking/Impulsiveness

Personnel were asked a series of nine questions about their tendency to take risks or act impulsively (e.g., “I often act on the spur of the moment without stopping to think,” “I like to test myself every now and then by doing something a little chancy,” and “You might

say I act impulsively"). Responses were based on a four-point Likert score ranging from 0 (Not at All) to 4 (Quite a Lot). Personnel were determined to be risk taking/impulsive if they responded with "Some" or "Quite a Lot" to six of the nine items.

Drug Use

Illicit drug use was measured in terms of the prevalence of nonmedical use of any of nine categories of drugs: (1) marijuana or hashish, (2) cocaine (including crack), (3) hallucinogens/Phencyclidine/lysergide, (4) amphetamines/stimulants, (5) tranquilizers or other depressants, (6) barbiturates/sedatives, (7) heroin or other opiates, (8) analgesics and other narcotics, and (9) inhalants. Nonmedical use was defined as any use of these drugs either without a dOctoberor's prescription or in greater amounts or more often than prescribed, or for any reasons other than as prescribed, such as for the feelings they caused. Responses were coded as a dichotomous variable classifying persons into those who did and those who did not use illicit drugs over the past year depending on whether they reported the use of at least one illicit drug.

Statistical Analyses

Analyses consisted of calculating population prevalence estimates and analysis of variance comparisons. Prevalence data were computed for alcohol use (any alcohol use, heavy alcohol use, heavy episodic drinking) and alcohol-related problems (driving after drinking and AUDIT) for military women and men in both the AD and RC populations. Multiple predictor logistic regression analyses were used to compute odds ratios (ORs) and were adjusted to control for the effects of demographic differences. Demographic variables included age, pay grade, education, family status, and race/ethnicity. All analyses were weighted to reflect the original sampling design, to adjust for unequal selection probabilities, and to adjust for nonresponse bias. SUDAAN software28 was used to take into account the survey's complex sampling design and yield accurate standard errors.

Results

As shown in Table I, in both the AD and RC populations, the majority of personnel were male, white, non-Hispanic, married, had some college education, and were in pay grades E4 to E6. RC personnel were older, with the largest proportion being between 25 and 44 years of age, compared to AD personnel, the largest proportion of whom were between the ages 18 and 34. In both samples, 75% of personnel acknowledged scores between 17 and 29 on the PCL, whereas 9% of RC and 7% of AD personnel had scores in the highest range (i.e., ≥ 50).

Table II reports on alcohol use across the AD and RC populations and the relation of alcohol use to PCL scores. Overall, more than 75% of both populations showed any alcohol use. AD personnel, however, reported significantly higher levels of heavy alcohol use (OR = 1.54, confidence interval [CI] = 1.22–1.94) and heavy episodic drinking (OR = 1.53, CI = 1.20–1.94) than their counterparts in the RC (20% vs. 14%; 48% vs. 38%, respectively). AD personnel also had significantly higher AUDIT scores ($b = 1.99$, $t(1, 77) = 3.86$, $p < 0.001$) compared to RC personnel.

Prevalence rates for alcohol use increased in both populations as PCL scores increased, with the largest proportion of individuals reporting increased alcohol use when PCL scores were at or above 44. Among those with PCL scores in the range of 17 to 29, any alcohol use in the past 30 days was reported by 77% of AD personnel and 74% of RC personnel, while in comparison for those with PCL scores at or above 50, past 30 days alcohol use was reported by 85% and 86%, respectively. For AD personnel, past month heavy episodic drinking was reported by 44% of those with PCL scores between 17 and 29, and by 66% of those with scores at or above 50. For RC personnel, 35% of those with PCL scores in the 17 to 29 range reported heavy episodic drinking, whereas the largest percentage (50%) reported heavy episodic drinking when PCL scores were between 44 and 49.

In both populations, a somewhat lower cutoff score on the PCL was associated with the largest percentage reporting driving after drinking. For both AD and RC personnel, driving after drinking was two to three times higher for those with PCL scores in the 44 to 49 range compared to the reference group of those with PCL scores in the 17 to 29 range. Finally, AUDIT scores were significantly higher in both populations when PCL scores were at or above 44.

Table III presents additional high-risk behaviors with results indicating similar findings to those for alcohol use behaviors. Overall, AD personnel reported significantly higher levels of verbal aggression (OR = 1.27, CI = 1.11–1.44) and impulsivity (OR = 1.35, CI = 1.12–1.63) than RC personnel. For AD personnel, reports of both verbal (72%) and physical (19%) aggression were highest among those with PCL scores at or above 50. Similarly, acknowledgement of risk taking/impulsiveness was highest among AD personnel with the greatest PTSD symptomatology (73%). In contrast, reports of drug use for AD personnel were highest (46%) among those with PCL scores between 44 and 49.

Among RC personnel, verbal aggression (66%) and risk taking/impulsiveness (70%) were highest for those with PCL scores between 44 and 49. Physical aggression (16%) and drug use (31%) were reported most frequently by individuals who had PCL scores at or above 50.

Tables II and III also indicate the results of all pairwise comparisons of each alcohol-related behavior at each level of PCL response grouping. A clear pattern of differences emerged for AD personnel. Each behavior was significantly more likely for response groups

with PCL scores higher than 17 to 29, indicating that PCL scores higher than 29 were associated with enhanced risk. Differences between the upper three categories of PCL response did not show uniform differences. This pattern also held for RC personnel, except for any alcohol use and heavy use. Both of these behaviors were significantly more prevalent only when PCL scores were 50 or higher.

## Discussion

The current study examined associations among PTSD symptom reports, alcohol problems, and high-risk behaviors for AD and RC personnel. To maximize the likelihood of finding PTSD symptoms, participants were subsetted to persons who had been deployed during the past 2 years. The findings revealed a positive association in both AD and RC populations among PCL scores and alcohol use, aggressive behaviors, drug use, and risk taking/impulsiveness. Those with lower PCL scores were more likely to have lower problem behavior scores, and those with higher PCL scores were more likely to have higher problem behavior scores. For example, 20% of AD personnel with PCL scores in the 17 to 29 range engaged in heavy alcohol use compared to 31% of AD personnel with PCL scores 50 or higher. This suggests that personnel with more severe PTSD symptoms are more likely to engage in heavy drinking as noted in prior research on this issue for substance use.11 In addition, for both AD and RC populations, a lower cutoff score was associated with driving after drinking. Although part of the pattern of risk-taking, it is not possible to determine whether this is the result of generally accepted practice in this population or if it is an artifact of the measurement of the behavior since alcohol consumption before driving was not quantified.

The most notable finding of this study is that it was not necessary for personnel to have PTSD symptoms (i.e., PCL scores) in the clinically diagnostic range (50 or higher) to be at higher risk for substance use or other problems. This was especially true for AD personnel who, for every outcome examined, showed significantly greater odds for each problem behavior when PCL scores were 30 or higher compared to those with PCL scores in the 17 to 29 range. However, it is important to note that the risk for associated problems may not simply be the result of deployment experiences per se, but may be related to the length of deployment, number of deployments, or deployment location.

A similar pattern was shown for RC personnel with respect to several problem behaviors, although not for alcohol use behaviors. For RC personnel, only those with PCL scores of 50 or higher had greater odds of reporting any alcohol use, heavy alcohol use, and heavy episodic drinking. These findings suggest that personnel with PCL scores higher than 50 are likely to have additional problems, including increased alcohol use, aggression, and risky or impulsive behaviors. Thus, even for those who do not exhibit strong PTSD symptomatology, screening for other high-risk behaviors should be conducted. Reducing the PTSD criterion score for

recognizing potential stress reactions may lead to the identification of a larger percentage of personnel who need additional care in dealing with combat stress.

The differences in findings of problem behaviors for AD and RC personnel may be an indication that deployment experiences and combat exposure affect AD and RC populations differently and suggest that AD personnel may be at higher risk for developing problems as a result of their combat experiences. At first these results may appear counterintuitive in that AD personnel, as a function their AD status appear to have stronger support systems in place than RC personnel in terms of continuing family and unit programs, and physical and mental health care. However, AD personnel may have greater concerns about stigma issues if they seek needed services to help them cope with their stressors. It is easier for RC personnel, upon return to their civilian jobs, to obtain civilian care that will be covered by insurance than for AD personnel to seek similar care. It may be cost prohibitive for AD persons to go outside the system and pay for their own mental health care needs. Other relevant issues may have led to the differences across these two populations such as the higher frequency of deployment among AD personnel or more frequent relocations from a permanent change of station.

There are limitations to the current study. First, the restricted item content for physical and verbal aggression is a limitation of the study. Evidence from some military studies suggests that direct versus indirect forms of aggression correlate differently with PTSD, whereas other studies have found an increase in intimate partner violence among those with PTSD symptomatology.29,30 There is also evidence among civilian studies suggesting that the hyperarousal symptom cluster in PTSD may lead to reactive aggression and impulsive behavior.31,32 Clearly, research that examines a more detailed assessment of different forms of aggression, an analysis of whether aggression was directed toward a partner or others, and the relations between specific symptom clusters and behavior is warranted.

Second, our data are cross-sectional and do not allow us to make causal inferences. Thus, we are not able to isolate whether a greater number of PTSD symptoms leads to more stress reactions or whether postdeployment personnel may use alcohol and/or other drugs as a way of coping with stress.

Finally, other factors could contribute to the development of behavior problems found to be associated with lower PCL scores. It may be that those without family or social support are more likely to have substance use or aggression regardless of PTSD symptom endorsement. A number of variables beyond the scope of this study (e.g., family support, spirituality, resilience, deployment length, and number of deployments) should be included in future research on the associations between PTSD and problem behaviors to more accurately elucidate this relation.

The current study highlights the need to better understand the relations among PTSD symptoms, alcohol use, and aggression in order to develop interventions aimed at reducing both the health and interpersonal consequences associated with postdeployment functioning. Results suggest that negative behaviors increase as symptomatology increases and point to the potential value of the early treatment of stress symptoms to reduce the likelihood of engaging in high-risk behaviors by military personnel. More importantly, clinicians should be encouraged to consider the likelihood of the presence of problem behaviors even in the absence of a critical value on a PTSD assessment. Military providers have access to postdeployment assessments that can aid in their treatment of personnel and are encouraged to go beyond the critical cutoff scores to develop a full picture of potential treatment issues. A comprehensive assessment including a substance abuse screen, anger management or violence propensity, risk of engaging in impulsive behaviors, in addition to measuring PTSD symptomatology should be used by civilian providers.

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***Sexual Health***

## Sex workers, HIV, and the law in Asia Pacific

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In 2008, Redefining AIDS in Asia, a report presented to UN Secretary General Ban Ki-moon, pointed out that “men who buy sex are the single-most powerful driving force in Asia's HIV epidemics”. However, sex work is criminalised in nearly all countries in Asia Pacific, hampering HIV prevention efforts according to a new UN report—Sex Work and the Law in Asia and the Pacific.

Law can be used to protect and promote the human rights of sex workers. For instance, national HIV laws in Cambodia, Fiji, Laos, Papua New Guinea, the Philippines, and Vietnam prohibit compulsory testing for HIV, respect confidentiality of people who are HIV-positive, and protect them from discrimination. Legal empowerment of sex worker communities has been shown to be an effective

approach in HIV prevention. However, law is often used to criminalise and penalise sex workers, resulting in their exposure to violence and discrimination from society in general, and law enforcement officers and health-care providers in particular. This situation limits access by sex workers to health and social services they need, and increases the risk of HIV for them and their clients.

Although there is some evidence that 100% condom use programmes have had some beneficial HIV prevention outcomes, the report finds that as presently implemented, these programmes harm HIV responses owing to their coercive nature and implicit human rights violations, such as requiring compulsory registration, mandatory health examinations, and monitoring by health authorities. Furthermore, confiscation of condoms and harassment of sex workers by police is a widespread problem in Asia. Alternative condom programming models are needed.

Giving condoms to people who have been long referred to as a “social evil”, culturally and legally, will not curb the HIV epidemic in Asia Pacific. However, giving them legal protection and respecting their rights will help. It is imperative to review and reform the current laws, ensuring that sex workers and sex worker organisations are fully and centrally engaged in improving legal environments to safeguard their human rights.

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## Short Communication: Investigation of Incident HIV Infections Among U.S. Army Soldiers Deployed to Afghanistan and Iraq, 2001-2007.

AIDS Research and Human Retroviruses
Scott PT, Hakre S, Myles O, Sanders-Buell EE, Kijak GH, McCutchan FE, O'Connell RJ, Peel SA, Eggleston JC, Sateren WB, Robb-McGrath M, Mott RL, Tobler SK, Nolan E, Petruccelli BP, Michael NL, Cersovsky SB.
Oct 2012

Abstract

The U.S. Army initiated an investigation in response to observations of a possible increase in HIV incidence among soldiers deployed to combat. Human immunodeficiency virus (HIV)-infected U.S. Army soldiers are not eligible to deploy. Combat presents a health

hazard to HIV-infected soldiers and they pose a threat to the safety of the battlefield blood supply and their contacts. All soldiers are routinely screened for HIV every 2 years and those who deploy are also screened both prior to and after deployment. Seroconversion rates were estimated for all soldiers who deployed to Afghanistan or Iraq in the period 2001–2007 and all active duty soldiers who did not. Seroconverters with an estimated date of infection, based on calculation of the midpoint between the last seronegative and first seropositive test date, that was either before or during deployment were eligible for inclusion. Confidential interviews and medical record reviews were conducted to determine the most likely time, geographic location, and mode of infection. Reposed predeployment samples were tested for HIV ribonucleic acid. The HIV seroconversion rate among all soldiers who deployed was less than the rate among those who did not deploy: 1.04 and 1.42 per 10,000 person-years, respectively. Among 48 cases, most were determined to have been infected in the United States or Germany and prior to deployment (n=20, 42%) or during rest and relaxation leave (n=13, 27%). Seven seronegative acute infections were identified in the predeployment period. Subtype was determined for 40 individuals; all were subtype B infections. All were acquired through sexual contact. These findings can inform development of preventive interventions and refinement of existing screening policy to further reduce HIV-infected deployed soldier person time.

The prevalence of HIV infection in the U.S. Army population remains at approximately 0.02%,1 and is significantly lower than that of the general U.S. population. The epidemic in the Army is similar to that in the U.S. general population; HIV infection disproportionately affects blacks and males and also disproportionately affects certain regions of the country including the South and Northeast.2–4 By regulation, all U.S. soldiers are subject to periodic serologic screening for HIV every 2 years. In addition, soldiers who deploy to combat are also screened both prior to and after returning from deployments. HIV-infected soldiers are excluded from overseas missions.5,6 Requirements for U.S. Army soldiers who deployed to Afghanistan or Iraq from Octoberober 2001 to December 2007 were for serologic screening for HIV infection within 365 days before deployment and within 30 days after the end of deployment. HIV force screening began in 1986 with the purpose of enhancing the safety of blood products obtained in urgent donation settings, such as a battlefield, preventing potentially fatal complications from administration of military-required, live vaccines, and monitoring HIV-infected troops for continuing physical qualification for duty.7

Approximately 5 years ago observations by Army investigators suggested that there may be an increase in HIV incidence among soldiers associated with combat deployments.8–10 On July 14, 2007, the U.S. Army Surgeon General ordered an investigation to describe the location, time, and mode of transmission of HIV infections among U.S. Army soldiers who had deployed to Afghanistan and Iraq after Octoberober 1, 2001.

Soldiers with HIV seroconversions were identified using archived personnel, deployment, and HIV screening surveillance data from the Defense Medical Surveillance System (DMSS).11 The rate of HIV seroconversion among soldiers who deployed to Afghanistan or Iraq was compared to the rate among active duty soldiers who did not deploy to Afghanistan or Iraq at any time during the study

period. The midpoint between the last seronegative and first seropositive test date was estimated to be the date of HIV infection. Soldiers with an HIV-positive test who had deployed to Iraq or Afghanistan at any time during the study period were eligible for inclusion. Those who had a midpoint date either prior to or during deployment were included in this investigation. Soldiers were confirmed as cases after they individually verified their deployment dates.

All confirmed cases were invited to participate in a detailed epidemiologic interview and to permit a review of existing personnel and medical records. Soldiers were reminded of the protections from adverse action and confidentiality of the information obtained as part of epidemiologic interviews required by Army regulation.5 To avoid the potential for favorable reporting, soldiers were not required to participate. Veterans who had separated from the Army were asked to provide informed consent and permission to release existing medical records. A single military infectious disease physician, who conducted interviews at U.S. Military Treatment Facilities, administered a questionnaire that guided the interviews and elicited individual health, social, and military occupational history including medical encounters and potential exposures to HIV.

For each case, archived serum remaining from the last seronegative HIV test performed prior to deployment was obtained from the Department of Defense Serum Repository (DoDSR)11 and subjected to confirmatory HIV serologic testing2,12 and nucleic acid amplification testing (NAAT, Amplicor HIV-1 Monitor v 1.5, Roche). Acute HIV infection (AHI) in an individual was identified by an HIV-seronegative sample that was NAAT positive. Whole blood specimens were collected at the time of epidemiologic interview for genotyping. Nucleic acid was extracted from plasma and serum using the QiAamp Viral RNA mini kit (QIAGEN Inc., Valencia, CA). HIV genotyping and sequence analysis were performed, as previously described, using a multiregion hybridization assay (MHA) for subtype B/non-B (MHAbnb) and partial length sequencing.2,13

The most likely time, geographic location, and mode of acquisition of HIV infection were determined using all available data. A timeline of events in the period of risk prior to HIV infection was generated for each participant and included self-assessment of the most likely time, location, and mode of infection; self-reported behavioral and occupational exposures; medical encounter and laboratory test records; and the dates and locations of all deployments, rest and relaxation (R&R) activities, and military assignments. Cases of probable, acute retroviral syndrome were identified using clinical histories and compatible medical encounter data. Where possible, administrative and medical records data were used to validate participant self-reports.

Approval of this investigation was obtained from the Division of Human Subjects Protections and Institutional Review Board of the Walter Reed Army Institute of Research (WRAIR #1678).

Among the 1,134,001 soldiers who deployed to Afghanistan or Iraq during the study period, 131 seroconverted (1.04/10,000 person years). By comparison, 258 of the 1,816,901 soldiers who did not deploy to Afghanistan or Iraq during the study period seroconverted (1.42/10,000 person-years).

Of the 131 seroconverters who deployed, 67 were not included because their midpoint date did not meet the inclusion criteria or due to misclassification of infection status or history of deployment. Of the 64 who were eligible for inclusion, nine declined participation, one was deceased, and one did not respond. Five others were excluded because the actual deployment dates individually verified by the soldier were different from those obtained from archived surveillance data such that their midpoint date was not prior to or during deployment. Thus, 48 confirmed cases participated. Compared to the overall deploying Army, cases were older, of higher rank, and were more frequently black and unmarried (Table 1).

Characteristics of HIV-Infected Cases (n=48) Compared to All HIV-Uninfected Active Army Personnel Who Deployed in the Period 2001–2007

Of the 48 confirmed cases, 20 (42%) were determined to have been infected before deployment, 13 (27%) during leave for R&R, and one (2%) while deployed. Determination of the most likely time of infection for four of the soldiers could be narrowed to only two time periods because exposure histories spanned more than one period. Five (10%) were determined to have been infected in the period between their deployment end date and postdeployment HIV serologic screening. For five other soldiers, there were insufficient existing data or exposure histories obtained in the interview to narrow the most likely time of infection down to even two periods (Fig. 1).

Numbers of cases with determination of most likely time of infection occurring during particular periods in relation to deployment (n=48). R&R locations: 11 continental United States, 1 South America, 1 unknown. *The most likely time of infection ...

Most were determined to have been infected in the continental United States or Germany. Most (13/20) of the soldiers who were determined to have acquired their HIV-1 infection prior to deployment were infected in the last 6 months prior to departing for Afghanistan or Iraq (Fig. 2). Seven soldiers' predeployment samples were HIV seronegative and NAAT positive. These samples were collected between 290 and 41 days (median 76) prior to deployment. HIV subtype was determined by MHA or partial length sequencing for 40 of 48 participants and all were subtype B. For eight participants, samples were either not available or nontypeable.

Days from determination of most likely time of acquisition of HIV infection to start of deployment for soldiers infected prior to deployment (n=20).

High-risk exposures in the period at risk included unprotected sex with opposite and same sex partners; unprotected sex with strangers and other high-risk partners including commercial sex workers, injection drug users, and persons subsequently identified as HIV-infected; unprotected sex with multiple partners; and unprotected sex after alcohol use. None were emergency blood transfusion donors or recipients. One individual refused to provide a history of exposures.

Twenty-three individuals (48%) had a clinically apparent illness consistent with acute retroviral syndrome (ARS). Five were medically evacuated for evaluation of lymphadenopathy and one for evaluation of a febrile illness. Two soldiers contracted a sexually transmitted infection in addition to HIV during the period between when they were determined to have been infected and the end of their deployment. No participant experienced any vaccine adverse events.

This is the first report of HIV infections among U.S. Army soldiers deployed in support of combat operations. Overall, the rate of new HIV infections among those who deployed did not exceed the rate among nondeploying soldiers and infection while deployed in Afghanistan and Iraq was extremely rare. Single, male, and black soldiers were overrepresented among the soldiers with new HIV infections who deployed. This was not unexpected as these findings are consistent with those in a previous report of the epidemic of HIV in the U.S. Army and Air Force.2 However, these data demonstrate that HIV infection results in short-term morbidity and lost duty time in the combat environment. The realities of the current combat environment support the rationale that served as a basis for implementing force-wide screening policies 25 years ago.7 Deployment and the battlefield present potential exposures to blood-borne pathogens including HIV. In addition to sexual transmission14,15 there is potential contact with the battlefield supply of non-FDA-approved blood products,16,17 occupational combat exposures, and casualty care with infection control measures limited by austere field conditions.18,19 The probability of any transfusion-transmitted (TT) infection in combat settings is relatively low, while the potential impact is high. Underscoring this is a recent report of the first documented case of TT hepatitis C virus infection in a U.S. military recipient of a battlefield transfusion of non-FDA licensed, fresh whole blood,16 as well as a recent report of TT HIV infection in the United States.20

Optimal HIV-related policy development and decision making rely on both knowledge of the current epidemiology and careful consideration of the technical, fiscal, and operational costs associated with each potential strategy. The observed, small number of HIV-infected soldiers in the combat theater of operations suggests that periodic force screening and perideployment screening using serological diagnostic algorithms to identify HIV infection are highly successful and effectively decrease HIV-infected deployed soldier person time. These findings contributed to an interim change in deployment screening policy that shortened the required HIV testing interval from 365 days to 90 prior to deployment in order to increase case finding, referral for clinical care, and exclusion from deployment eligibility. They may also inform further refinement of screening policy and laboratory Methodology.

These data identify potential time period targets for the delivery of preventive interventions. As part of soldier readiness processing, soldiers preparing to deploy receive country-specific threat briefs that include information about potential disease, environmental, and occupational health hazards, and individual countermeasures available to stay healthy. These briefs include specific information and prevention messages about HIV/HIV-related infections. These data also reinforce the need to maintain a highly sensitive, readily adaptable, state-of-the-art capacity to determine HIV infection status when the tempo of military operations is high. Identification of acute HIV infection is a rare event.21 By using an enhanced diagnostic algorithm that included HIV NAAT testing in this investigation that exceeded the sensitivity and time of earliest detection of the routine deployment serology-only screening diagnostic algorithm in place during the study period, we identified seven HIV infections that were RNA positive and serology negative. These results indicated that infection occurred as early as 5–22 days prior to sample collection.22 The finding of acute infection occurring in close proximity to predeployment HIV screening suggests that there may be an association between mobilization for deployment and HIV infection acquisition.

Predeployment HIV testing is one part of the soldier readiness processing and training that occurs prior to deployment. This testing, performed in addition to the periodic HIV testing of the entire force, is conducted only among soldiers preparing to deploy. It is possible then that there is a relationship between incident HIV infection and deployment. There was no control group so additional study is warranted to investigate the possibility that deployment is associated with changes in behavior and exposures associated with HIV infection.

Future study is also warranted of soldiers who had incident HIV infections and deployed but were not compliant with deployment screening interval regulations and were not included in this investigation. A limitation of this study is that the inclusion criteria excluded those who have an estimated date of infection that was after the end of deployment. Due to the variability in compliance with predeployment and postdeployment and periodic HIV screening interval requirements, these inclusion criteria potentially excluded soldiers who may have contributed HIV infected person time while deployed and also eliminated description of the epidemiology of postdeployment incident HIV infection. Additional study of those soldiers with deployment exposure and postdeployment HIV infection is warranted. And on-going surveillance efforts of and reporting requirements for HIV screening compliance should continue. Findings from these studies would inform development and optimal timing for delivery of preventive interventions.

This study supports the utility of perideployment HIV screening. The findings of this investigation can advance the objectives of a force-wide HIV screening program to improve individual and force health, prevent the deployment of HIV-infected soldiers, and protect the safety of the battlefield blood supply.

Acknowledgments

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## Home testing for HIV: Hopefully, a step forward

Cleveland Clinic Journal of Medicine
CHRISTINE E. KOVAL, MD
Oct 2012

Abstract

An over-the-counter at-home test for human immunodeficiency virus (HIV) infection has been approved and will likely be available soon. It is intended to decrease the percentage of HIV-infected people unaware of their infection (estimated at 18% of the 1.2 million people infected in the United States). Since early and continued treatment prevents disease progression and reduces HIV transmission, testing is the first step toward effective care.

Key points

The new test is highly (99.9%) specific for HIV but is not quite as reliable at ruling out infection (93% sensitivity). Therefore, it may miss some cases of HIV, especially during the 90-day window after initial infection.

False-positive test results may occur, especially in people at low risk. A positive result must be confirmed with a laboratory-based third- or fourth-generation blood test.

It is important to continue to assess and counsel patients on how to modify their risk of HIV infection.

Providers are urged to offer HIV testing to all patients ages 13 to 64 at least once, regardless of their risk.

At least once a year, patients at high risk should get one of the more sensitive laboratory blood tests.

People who choose to test themselves at home should seek medical care for verification of the test result and for HIV counseling, and, if the result is confirmed positive, access to HIV care.

In july 2012, the US Food and Drug Administration approved the first over-the-counter test kit for human immunodeficiency virus (HIV) infection, the OraQuick In-Home HIV Test (OraSure Technologies, Bethlehem, PA). This test is a variation of the currently available OraQuick ADVANCE Rapid HIV-1/2 Antibody Test used in clinical settings by trained personnel for rapid detection of HIV. The home HIV test is expected to become available in the fall of 2012 from the company's Web site and at retail drugstores. This will put the power of HIV testing into the hands of anyone able to afford the estimated $60 price and willing to purchase the item online or in stores.

GOAL: TO REDUCE THE NUMBER OF INFECTED PEOPLE WHO ARE UNAWARE

How home testing will change the demographics of HIV testing is not clear, but the intention is to reduce the number of HIV-infected people who are unaware of their infection and to get them in for care. Anthony Fauci, MD, the director of the National Institutes of Allergy and Infectious Diseases, has called the new test a "positive step forward" in bringing the HIV epidemic under control.[1] Recent figures from the US Centers for Disease Control and Prevention (CDC) indicate that, of the 1.2 million HIV-infected people in the United States, up to 220,000 are unaware of their infection.[2,3] Since antiretroviral therapy is now considered beneficial even in the early stages of HIV infection, those who are unaware of their infection are missing an opportunity for the most effective therapies. They may also be unknowingly transmitting the virus, thus perpetuating the HIV epidemic. Awareness of one's HIV infection may lead to behavioral changes that can reduce the risk of transmission. It has also become clear that antiretroviral therapy can dramatically reduce transmission rates, a concept known as "treatment as prevention." [4] Thus, access to care and initiation of antiretroviral therapy have the potential to prevent progression to acquired immunodeficiency syndrome (AIDS) in the individual and to interrupt the spread of the virus in the community.

There are several steps between awareness of HIV infection and full engagement in HIV care that require attention from the health care community.[5] Only a quarter of those with known HIV infection are in care and adherent to antiretroviral therapy, leaving much work to be done on removing barriers to effective treatment.[5] The first step is still to identify those infected. The effort to increase the percentage of HIV-infected individuals who know their HIV status is one of the goals of the National HIV/AIDS Strategy and HealthyPeople2020.[6]

## HOW THE TEST IS USED

The OraQuick In-Home Test consists of the device and reagents, instructional materials, information on interpreting the results, and contact information for the OraQuick Answer Center for information, support, and local medical referral.[7] The overall time needed for testing is 20 to 40 minutes.

To perform the test, an oral fluid specimen is collected by swabbing the upper and lower buccal mucosa along the gum line. Once inserted into the developer solution the swabbed sample is carried onto a membrane strip containing HIV-1/2 antigens.

The device has two windows, one labelled “T” (for test) and the other labelled “C” (for control). If the patient has sufficient antibodies to HIV proteins, the “T” window indicates a positive result if a band is visible. The “C” (control) window displays a band to indicate if the device and reagents are working. If the control window does not show a band, then the kit has not functioned properly and the test result is not reliable.

## SOME PEOPLE MAY STILL NEED HELP

For the test to succeed in informing people of their HIV status, it must be used effectively and the results must be interpretable. Of 5,662 participants in phase III investigational-device studies, 99% were able to use the kit and determine a result.[7] While the test’s simplicity is similar to that of pregnancy test kits, it is possible that some people (at least 1% of those using the kit) may seek guidance from medical practitioners because they are unable to understand the test results.

For a test result to have the desired outcome of leading to HIV care, individuals must act on a positive result. When home test results are positive, the instructions indicate that “you may have HIV” and provide contact information for the OraQuick Answer Center. It is unclear how reliable the counseling, information, and referral process from OraSure will be and if people will use the service. Individuals may access medical care at a variety of levels for further assistance if they have a positive test result. These may include primary care offices, emergency and urgent care settings, health departments, and HIV clinics.

LESS SENSITIVE THAN BLOOD TESTS

To provide additional care, clinicians must understand the performance of the home HIV test. Most importantly, the test result must be confirmed.

The In-Home test is less sensitive than currently available HIV blood tests used in the clinical setting, particularly the HIV-1/2 enzyme immunoassay (EIA) with confirmatory Western blot testing. The In-Home test is less likely to detect HIV infection during the 90-day "window period" when seroconversion is occurring, and so it should not be relied on to rule out HIV during this early period after infection.

The sensitivity and specificity of the OraQuick In-Home HIV test were determined in a phase III trial in 5,662 people (80% at risk of HIV), who were tested concurrently with the "gold standard" blood tests (EIA and Western blot). The sensitivity was 93% (giving a positive result in 106 of 114 patients who had a positive result on blood testing), and the specificity was 99.9% (giving a negative result in 5,384 of 5,385 patients who had a negative result on blood testing).[7]

Therefore, a positive In-Home test result is likely to be truly positive, but a negative result is not as reliably truly negative. False-negative results may occur particularly in the window period early after HIV infection, so the test should not be relied on within 90 days of high-risk behavior. In contrast, with the fourth-generation blood HIV tests, the window period is approximately 16 days.

The predictive value of the test will depend on the population using it and on the patient's pretest probability of disease at the time of testing. In the population tested by OraQuick, the positive predictive value was 99.1% and the negative predictive value was 99.9%.[7] Mathematical modeling has been done to examine the potential outcomes for use in subpopulations at lower risk and at higher risk. As clinicians, we will have to address the potential for both false-positive and false-negative test results. False-positive results may be more likely in low-risk populations and may occur in the setting of cross-reactive antibodies from pregnancy, autoimmune diseases, or previous receipt of an experimental HIV vaccination. False-negative results may occur in the setting of acute HIV infection and in those with severely impaired immunity (eg, from agammaglobulinemia or immunosuppressive drugs) and will be more likely in higher-risk populations, such as men who have sex with men, intravenous drug users, blacks, and Hispanics ages 18 to 35 with multiple sexual partners. A positive In-Home HIV test should be followed up with a blood EIA and confirmed with Western blot in all patients.

WHO WILL USE THIS TEST?

It is unclear who will use this new test. In OraSure's clinical trial, the percentages of people who indicated they would "definitely or probably buy" the test were:
20% of the general population
27% of those ages 18 to 35
49% of blacks ages 18 to 35
47% of homosexual men
43% of people who said they had more than two sexual partners per year
32% who said they use condoms inconsistently.

If this is true, the test may appropriately target several populations that are not currently being tested, either because they lack access to care or because they do not see themselves as being at high risk. Of those with newly diagnosed HIV infection from 2006 to 2009, 40% had had no prior testing, and the groups with the highest percentages of people in this category were black, men with injection drug use as their sole risk factor, those older than 50 years, and those with heterosexual contact as their sole risk factor.[8]

Because of difficulties in identifying some of these groups as "at risk," the current CDC guidelines recommend that HIV testing be offered to all patients ages 13 to 64, regardless of their risk factors.[9]

The home HIV test may fill a gap in testing, extending it to those still not tested in the health care setting or to those who have not sought health care. For the home test to fill that gap, people still have to perceive themselves as at risk and then purchase the test. Through public health strategies and at clinical points of care, we must continue to inform our patients about HIV risk and work to identify new or ongoing risk factors that would prompt additional testing.

MANY QUESTIONS REMAIN

Will those who need testing want to use this test? People will buy the test only if they perceive themselves to be at risk.
Is this test affordable for the target populations? $60 will be unaffordable to some.
Will the directions be followed effectively?
Will home testing reduce opportunities to counsel patients on their HIV risk factors?
Will there be situations in which individuals are socially pressured to take the test?
Can users of the test expect the appropriate amount of privacy? Availability on the Internet and in drug stores is not a guarantee of privacy when purchasing the test, although the result presumably will not be known.

Will those with positive results seek medical care?
Will those with negative results who are still at high risk forgo more sensitive testing and continue to engage in high-risk activities?

Nevertheless, since early and continued treatment prevents disease progression and reduces HIV transmission, testing is the first step toward access to effective HIV care. The home HIV test is a step forward in providing high-quality HIV testing to the wider population.

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***Substance Abuse***

## Alcohol Abuse or Dependence in the Military Aviator: Guidance for the Non-Flight Surgeon

Military Medicine
Franzos, M. Alaric; Franzos, Tracy L.; Woolford, Jeffrey S.; McDonald, William A.
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Abstract

Alcohol is tightly interwoven with the image and culture of aviation. When alcohol is combined with aviation, the result can be fatal to aircrew, passengers, and bystanders. Alcohol has been implicated in 8 to 12% of fatal general aviation accidents. With approximately 10% of the general population estimated to have alcohol abuse or dependence, alcohol issues are similarly common among aviators. Clear and concise guidelines exist to address alcohol disorders in both civilian and military aviation. However, few health care providers outside the aviation community are aware of these guidelines. When an aviator presents with an alcohol disorder, the well-intentioned provider may be reluctant to address the issue because of poor understanding of the occupational implications or a misplaced effort to preserve the aviator's career. However, proper therapy often permits the aviator to continue flying duties without adverse career impact. This review will discuss the implications, guidelines, and prognosis for the alcohol-dependent aviator and provide resources to enable the responsible health care provider to return the pilot to flight status as soon as practicable. Knowledge of these civilian and military guidelines will help close the treatment and communication gaps between aeromedical specialists and other medical professionals.

AEROMEDICAL IMPLICATIONS OF ALCOHOL USE

Ethyl alcohol is a central nervous system depressant that may degrade cognitive and physical performance. Although persistent use of alcohol may lead to chronic degradation of performance, the most significant and well-known impact is that of acute alcohol intoxication. The hallmarks of acute alcohol intoxication are poor coordination, inattention, reduced decision-making capacity and disinhibition, prolonged reaction time, decreased visual acuity, nausea, vomiting, diplopia, vertigo, ataxia, dysarthria, amnesia, respiratory depression, and myocardial conduction abnormalities (e.g., “Holiday Heart”). These effects of alcohol ingestion significantly degrade a pilot's capability to safely perform flying duties.

A landmark 1964 article by Harper and Albers revealed a shocking correlation of alcohol abuse and associated civil aviation mishaps: postmortem studies (n = 158) showed that 35.4% of pilots involved in fatal general aviation accidents were positive for blood or tissue alcohol. However, the results of the study may have overestimated the presence of alcohol, secondary to the inclusion of tissue where ethyl alcohol was formed as a by-product of putrefaction. To mitigate this likely inaccuracy, current alcohol analysis relies on samples less prone to putrefaction, such as vitreous fluid. Nevertheless, this article prompted a review of aviation policies following the authors' conclusion that there was a “great need for medical and human factor studies in civil aircraft accident investigations.”

In a 1973 study, Billings et al monitored the performance of pilots while they flew an instrument landing system (ILS) approach under the influence of alcohol. The test was run using a modified Cessna 172 and a safety pilot. An error was defined as an event where the safety pilot took the controls. The error counts among the eight subject pilots increased significantly with increasing blood alcohol ($p < 0.01$), going from once at 40 mg/dL (0.04%), three times at 80 mg/dL (0.08%), and 16 times at 120 mg/dL (0.12%). This finding reinforces the increased risk from alcohol use in aviation. Studies in simulators of more complex, multiengine aircraft also showed that pilot performance was not only degraded by alcohol consumption but also by symptoms of postintoxication hangover effects.

Both military and civilian policy interventions (see below) and educational programs have helped to reduce the involvement of alcohol in general aviation accidents. Based on data from the Civil Aerospace Medical Institute, incidents with blood alcohol content (BAC) ≥40 mg/dL (0.04%) dropped from over 30% before policy interventions10 to 7.9% between 1989 and 1993,10 to 7.0% between 1994 and 1998,2 and to 5% from 2000 to 2007. Rates in commercial aviation were even lower. Results of the U.S. Federal Aviation Administration (FAA) mandatory alcohol testing program revealed alcohol use violations in 0.03% of commercial flight crews between 1995 and 2005.

GUIDELINES

Typically, recommended medical management is dependent upon the status of the airman, either military or civilian. If the aviator is in the military, Department of Defense (DoD) and service-specific medical regulations are provided to the military Primary Care Manager outlining the requisite course of action to manage the patient's care and to expedite their return to flight status. Although these regulations are well-known among specially trained service-specific flight surgeons (FSs), most military Primary Care Managers are completely unaware of their existence. Similarly, if the pilot participates in civilian flying under U.S. jurisdiction, FAA regulations provide the Aeromedical Examiner (AME) guidance when treating an airman found to exhibit alcohol dependence or abuse. There is a third situation, a hybrid arrangement unique to National Guard and/or Reserve aircrew, which deserves particular attention and requires increased vigilance. These aviators are routinely managed by both civilian and military health care providers, without any formal line of diagnostic communication between them. The risk in this situation is fractional continuity of care, either incidental or deliberate, which could make recognition of alcohol abuse or dependence much more elusive.

Military and civilian physicians may encounter an aviator with alcohol abuse or dependence leading to an apparent dilemma: protect the aviator's career or protect safety-of-flight? This is a false choice. In reality, following clearly delineated aeromedical guidelines can preserve both career and safety. In the case of the military aviator, these guidelines permit return to flight status in 90 days, provided rehabilitative therapeutic goals are met. Military aviators involved in the Personal Reliability Program, those responsible for nuclear weapons employment, require 180 days before return to flight status. In the case of the civilian pilot, federal guidelines permit a return to flight status after 4 to 6 months pending proper therapeutic management. When a case of alcohol abuse or dependence is identified in an aviator, the issue should be referred to the responsible aeromedical specialist, the FS in the military or the AME in the civilian community.

FSs provide specific annual occupational medicine evaluations for military aviators and are trained to balance patient advocacy with safety-of-flight issues. When alcohol abuse/dependence concerns arise, FSs directly advise the commanding officer of the unit according to service-specific instructions (outlined in “Policy Interventions” below and summarized in Table I). U.S. Navy and Marine Corps guidance stems from OPNAV 3710.7U, Manual of the Medical Department Ch 15, and the Aeromedical Reference and Waiver guide. The U.S. Army instructions include AR 40-501, Aeromedical Policy letters, and AR 600-85. The Air Force Waiver Guide, AFI 11-202 Vol 3, and AFI 48-123 provide guidelines for U.S. Air Force personnel. In addition, the Personal Reliability Program (DoD Regulation 5210.42) places supplementary requirements on those personnel responsible for the security of nuclear weapons.

Reserve and Guard components are subject to the instructions of their parent service during duty periods. These tri-service instructions provide clear guidance regarding a spectrum of medical issues, of which alcohol abuse or dependence is one of the most common. Civilian aeromedical examination frequency varies based on age and flying class qualification. In the case of the AME,

there is no communication with the patient's supervisor, but forfeiture of the required flying class physical clearance indirectly accomplishes the same goal.

Aviators are directed to report any changes in their medical status to their FS or AME. However, an aviator may intentionally avoid doing so because of three reasons: a misplaced effort to preserve his career, poor understanding that an acute event is a sign of a chronic disease, or frank denial. Therefore, it is critical that nonaeromedical health care providers ensure that proper referral is made to the aviator's FS or AME when indicated. At a minimum, this can be facilitated by medically “grounding” the aviator, effectively removing them from flight status. Any health care provider can ground an aviator by submission of a grounding notice or simply adding the following statement to medical documentation, “Medically grounded from performing duties involving flight.” (Note: the specific documents for grounding are the NAVMED 5140/2 [U.S. Navy], AF 1042 [U.S. Air Force], and DA Form 4186 [U.S. Army].) This requires the aviator to obtain proper follow-up because only an FS or AME can provide clearance to resume flying duties, thus enabling and ensuring continuity of care. This requires proactive communication by all involved health care providers as electronic medical records in their current form do not ensure proper continuity. Ideally, the health care provider uncovering the potential alcohol issue would communicate directly with the responsible authority: the AME in civilian cases and the FS or commanding officer in military cases.

Disclosure by civilian providers must be balanced between the duty to protect and the Health Insurance Portability and Accountability Act privacy and security rules. Health Insurance Portability and Accountability Act15 and its military equivalent, DoD Health Information Privacy Regulation,16 allow disclosure of protected health information “to prevent or lessen a serious and imminent threat to the health or safety of a person or the public.”

## POLICY INTERVENTIONS

### Federal

The federal regulations regarding preflight alcohol use were established in the Federal Aviation Regulations (CFR 14, FAR Part 121.458—“Misuse of Alcohol”). This regulation stipulates that “no FAA certificate holder [flight crewmember or flight attendant] shall report for duty with a BAC of greater than 40 mg/dL (0.04%).”17 Those with BAC between 0.02 and 0.039 must be removed from safety-sensitive duties until BAC is below 0.02. Furthermore, this regulation requires any certificate holder to prohibit anyone suspected of being under the influence of alcohol from performing safety-sensitive functions. Finally, performance of flight crewmember or flight attendant duties is prohibited within 8 hours of alcohol consumption, although most commercial airlines have company policies that extend this alcohol abstinence period to 12 hours. The Omnibus Transportation Employee Testing Act of

199118 established federal protocols for testing of those involved in safety-sensitive functions for illegal drug or alcohol use. Testing may be required at different phases: pre-employment, random testing, reasonable suspicion, return-to-duty, and postaccident.

Military

No specific BAC is defined within military regulations. Previously, the alcohol abstinence period was 12 hours before takeoff or 12 hours from “bottle to throttle.” Recognizing that flight duties begin earlier than takeoff, the U.S. Navy regulation has changed to prohibit alcohol consumption within 12 hours of flight planning. In addition, all services require aviators and aircrew to be free of hangover effects. Although there is a robust testing program for illegal drugs, the military does not have a testing program for alcohol use. However, if alcohol use is suspected when a military member reports for duty, they may be required to submit to a “fitness for duty exam” including blood alcohol analysis.

REHABILITATION

In both civil and military aviation, the rehabilitation plan is similar (Table I). All programs require the aviator to make an unqualified acknowledgment of the alcohol disorder. After appropriate initial treatment (outpatient or inpatient), the aviator must abstain from alcohol and attend aftercare programs. The aftercare programs consist of documented participation in a recovery program (Alcoholics Anonymous [AA]) and documented meetings with designated professionals as directed. In the military, the designated professionals include psychiatrists/psychologists and the alcohol rehabilitation program coordinator. The rehabilitation program coordinator takes different names and acronyms within the different services (Navy = Drug and Alcohol Program Advisor; Marine Corps = Substance Abuse Control Officer; Air Force = Alcohol and Drug Abuse Prevention and Treatment; Army = Alcohol Drug Abuse Prevention and Control Program).

PROGNOSIS

In aviation, the diagnosis of alcohol abuse or dependence is less damaging than the manner in which it comes to light. Even more stringently than the civilian cases outlined above, military aviators who report for duty in an intoxicated state are typically subject to swift criminal prosecution or nonjudicial punishment. Although medical rehabilitation will be offered, career rehabilitation is much more difficult after reporting drunk for duty. However, career rehabilitation is not only possible but also likely if the alcohol problem is brought to light through intervention, self-referral, or medical evaluation (other than command-directed “Fitness for Duty” or postmishap evaluations). The career impact following an alcohol-related incident (driving under the influence, disorderly conduct, etc.) is less clear. In such cases, a military aviator may be able to return to flying duties but the incident may impact competitiveness

for promotion. In the civilian setting, aviators are required to report alcohol-related incidents to the FAA within 60 days, but are eligible for rehabilitation as supervised by their AME.

In both the civilian and military programs for alcohol rehabilitation, the rates of success are high. In the United States, the FAA funds a substance abuse treatment program called the Human Intervention and Motivation Study. Since 1973, Human Intervention and Motivation Study has treated more than 4,000 pilots for alcohol abuse or dependence with 3 year success rates of 95% and an estimated lifetime abstinence rate of 88% to 90%.

Military regulations do not distinguish between alcohol abuse and alcohol dependence. The same treatment plan is required for both diagnoses to return to flying: alcohol rehabilitation, abstinence, and participation in an aftercare program. Once these conditions are met, the aviator is eligible for an alcohol waiver permitting resumption of flight duties. The U.S. Air Force rate for approval of initial alcohol waivers was 79% from 2003 to 2005.20 Rates are not available for the U.S. Navy or Army. The most common cause for denial of a waiver was failure of the aviator to unconditionally acknowledge the alcohol disorder. Abstinence rates are not tracked among military aviators, but reports of revocation of established alcohol waivers are rare.

For those that acknowledge the disorder and embrace therapy, they will find a robust support structure. Because it is a common disorder, clear aeromedical guidelines are in place and support is available at nearly all military bases and in thousands of communities worldwide. There is a special branch of AA developed to address the specific pressures of aviation. Birds of a Feather (www.boaf.org) is an international organization dedicated to providing support for pilots and flight station crewmembers, whether active or inactive in aviation. With meetings across the world, Birds of a Feather helps aviators deal with a disorder that is not only a threat to their health but also to their career if they fail treatment.

With such strong recovery support and high success rates, aviators with alcohol disorders can achieve career milestones at a rate similar to their peers. This preservation of career progression is accomplished in conjunction with maintenance of a safe flying environment. Therefore, it is critical that all health care providers understand that career progression and safety of flight are parallel goals of screening for and treating alcohol disorders in aviators. These goals can only be achieved, and the therapeutic programs brought to bear, if health care providers initiate direct communication with the commanding officer, the FS, or the AME. Such communications are considered protected in the Military Health System. Though privacy regulations permit disclosure with an imminent threat to safety, civilian providers will have to balance their duty to protect the public with their duty to safeguard protected health information.

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***Suicide***

## Combat Exposure and Suicide Risk in Two Samples of Military Personnel

Journal of Clinical Psychology
Bryan CJ, Hernandez AM, Allison S, Clemans T.
15 Oct 2012

Abstract

Objective:

In light of increased suicidal behaviors among military personnel and veterans since the initiation of combat operations in Afghanistan and Iraq, questions have been raised about the potential causal role of combat. The objective of the current study was to identify any direct or indirect effects of combat exposure on suicide risk through depression symptom severity, posttraumatic stress disorder (PTSD) symptom severity, thwarted belongingness, perceived burdensomeness, and fearlessness about death, consistent with the interpersonal-psychological theory of suicide (Joiner, 2005).

Method:

Structural equation modeling was utilized with two separate samples of deployed military personnel, 1 nonclinical (n = 348; 89.7% male, mean age = 24.50) and 1 clinical (n = 219; 91.8% male, mean age = 27.88), to test the effects of combat exposure on suicide risk.

Results:

Greater combat exposure was directly associated with fearlessness about death and PTSD symptom severity in both samples, but failed to show either a direct or indirect effect on suicide risk. PTSD symptom severity was strongly associated with depression symptom severity, which in turn was related to suicide risk directly (in the nonclinical sample) or indirectly through low belongingness and perceived burdensomeness (in the clinical sample).

Conclusions:

In both samples of deployed active duty military personnel, combat exposure was either unrelated to suicide risk or was too distally related to have a measurable effect. Results do not support the interpersonal-psychological theory's hypothesis that combat exposure should be indirectly related to suicide risk through acquired fearlessness of death.

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## Depression and the global economic crisis: is there hope?

The Lancet
6 Oct 2012

Last week saw Spain become the latest debt-ridden European country to announce a drastic austerity budget, and in a Correspondence letter in today's issue, two researchers sum up what austerity means for science in Spain: “there is no hope”.

Unemployment, poverty, debt, and diminished public services also have direct implications for human health. Depression, and its associates suicide and alcohol-use disorders, are known consequences the world over. It is timely, then, that this year's World Mental Health Day on October 10 focuses on depression as a global crisis.

The hard reality of mental illnesses such as depression must not be lost in controversies over psychiatric classification that have arisen during the revision of the Diagnostic and Statistical Manual of Mental Disorders. In a Comment in this week's issue, Dilip Jeste asks “How can any sensible person believe that mental illnesses, which are disorders of the brain, are any less deserving of treatment than those that affect the lungs or liver?” The Mental Health Parity and Addiction Equity Act passed by the US Government in 2008, and the recent progress of the Mental Health (Discrimination) Bill in the UK, are welcome examples of legislators recognising the seriousness of mental illness.

The utterly devastating nature of depression is clear if one considers that many people with the illness prefer death to life with their symptoms. More than 50% of people who die by suicide will have had a depressive episode at the time of death. “I don't like standing near the edge of a platform when an express train is passing through”, said Winston Churchill. “A second's action would end everything. A few drops of desperation.” Others will self-harm—more than 70% of patients in a UK sample who self-harmed had a

depressive disorder. Many more people with milder forms of depression will not experience such profound despair. But they will nevertheless cease to function as a healthy individual: they may become unable to work, to care for their children, or simply to get through a day without feeling worthless and empty or reckless and angry.

The burden of depression worldwide is huge. Current WHO estimates put unipolar depressive disorders third in the global burden of disease league table. They are expected to overtake lower respiratory infections and diarrhoeal diseases by 2030. However, unlike many large-scale global health issues, depression is readily treatable, and, to an extent, preventable. Diagnosis, which usually takes place in the primary-care setting, requires rigorous history taking and examination to identify any comorbid disorders (typically anxiety, alcohol-use disorders, and chronic illnesses such as cancer and diabetes). Treatment preferably consists of basic psychosocial support combined with antidepressant drugs, short-term psychotherapy (such as cognitive behaviour therapy), or both. Unfortunately, an estimated 50% of patients worldwide still do not receive such treatment.

Prevention of depression is an under-researched area that deserves greater attention. Since the underlying cause of some people's depression will be dysfunctional beliefs and thought processes built up from early learning experiences, some prevention strategies have involved psychoeducational interventions designed to strengthen resilience. Interventions such as school-based problem-solving programmes and behavioural child-rearing strategies for parents have shown modest but real reductions in incident depressive episodes, as have exercise programmes for older people.

Prevention, at all stages of life, forms a prominent part of WHO's draft Global Mental Health Action Plan for 2013—20. Developed in response to a World Health Assembly resolution in May this year, the draft plan is currently out for public consultation until October 19. The other objectives of the plan are strengthened leadership and governance, provision of integrated mental health services in the community, and strengthening of information systems, evidence, and research. A commitment by countries to this plan would be “the best thing to happen to global mental health in the last decade”, according to Shekhar Saxena, Director of WHO's Department of Mental Health and Substance Abuse.

Governments can certainly not afford to ignore the burden of mental disorders. According to World Economic Forum estimates, the global cost of mental illness in terms of lost economic output was US$2·5 trillion in 2010, and could reach $6·0 trillion by 2030. And so we return to the global economic crisis, and the dangerous undertow of austerity. Job losses and tax rises might be inevitable, but governments must not cut back on the social protection systems and mental health services that could aid recovery, economic or otherwise.

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# Association Between Mental Health Conditions Diagnosed During Initial Eligibility for Military Health Care Benefits and Subsequent Deployment, Attrition, and Death by Suicide Among Active Duty Service Members

Military Medicine
Col Robert R. Ireland, USAF MC (Ret.); Amii M. Kress, MPH; Lucinda Z. Frost, PsyD
Oct 2012

Abstract

Objective: To examine incidence of mental health diagnoses during initial service of U.S. active duty military members and identify associations with deployment, attrition, and suicide. Methods: A retrospective cohort of 576,502 service members (SMs) newly enlisted between 2003 and 2006 was identified. Data included medical encounter, deployment and attrition, and suicide. Multivariable logistic regression models examine the association between mental health diagnoses coded within the SMs' first 6 months of eligibility for health care benefits and deployment. Multivariable Cox proportional hazards models quantify the association between mental health diagnoses and attrition and suicide. Results: The cumulative incidence of mental health diagnoses was approximately 9% at 6 months of service. Adjustment, depressive, and anxiety disorders were most common. Those with any mental health diagnosis during initial eligibility had increased risk of early attrition and were 77% less likely to deploy. Early mental health diagnoses were not statistically significantly associated with death by suicide. Conclusion: Mental health diagnoses during initial eligibility are common and associated with reduced odds of deployment and increased risk of early attrition. Policies designed to either retain or discharge SMs with a mental health diagnosis identified during initial training merit close examination in light of these findings.

Introduction

The U.S. military imposes medical accession standards to ensure those newly recruited are fit and able to meet the needs of the military. Accession standards are intended to filter applicants with specific chronic conditions, including mental disorders and those unable to pass physical fitness tests or who are outside of weight standards. Accession medical standards are generally more restrictive than the standards applied after successful completion of basic and initial specialty training. New recruits are required to

be healthy and able to perform their job at the time of induction to help mitigate the risks of premature attrition, untoward health care burden, and loss of duty time to illness and sick leave.

Once the accession requirements have been met and the new recruit is inducted, medical standards for retention may become less stringent than those required for accession. For example, those identified with an episode of a nonsevere mental disorder during their first months of service may be retained if stable with treatment, whereas were the same disorder present at the time of application for service, the accession standards would not have been met. Increased retention became more evident in 2006 owing to a decline in those enlisting in the military concomitant with the increased need for military personnel associated with the conflicts in Iraq and Afghanistan. Also at play was consideration of recoupment of the investment in the inductees recruitment and initial training. In Fiscal Year 1993, the estimated costs of recruiting, screening and training an individual through basic training were approximately $28,800. In 2005, the $28,800 estimate was adjusted to 2004 dollars which converted to $33,372 average cost per enlistee. A subsequent analysis conducted by a University of California Blue Ribbon Commission in 2006 accounting for overhead and technical training estimated that actual costs were 91% more, over a decade, than those costs obtained by using the Government Accountability Office (GAO) methods.

The incidence of mental health disorders during initial eligibility has not previously been studied systematically. There are data on medical separations based on GAO and Service-specific studies. In the late 1990s, 30 to 35% of service members (SMs) separated before completion of the first term of service of approximately 4 years. About 10 to 15% of these individuals were discharged in the first 6 months of duty. The most common reasons for medical discharge were asthma, back pain/orthopedic problems, and psychiatric conditions. Previous data on medical discharges indicate that the rate of medical discharge for psychiatric conditions in 1995 was 65/100,000. The Air Force has been the leader in the Service-specific research. Among Air Force basic trainees, the mental health-related separation rate for calendar year 2001 was approximately 4.2%. Adjustment disorders and depressive disorders were the most common diagnostic categories related to recommendations for early discharge. Air Force trainees recommended for discharge often had a history of depression, expressed a lack of motivation to continue in the military, reported suicidal ideation, and typically had withheld information on their mental health history during Military Entrance Processing Station assessment.

The burden of mental health disorders during initial eligibility is not well documented. There are several studies quantifying the prevalence of mental health disorders among retained SMs. Before the current conflicts, Operations Enduring Freedom and Iraqi Freedom, mental disorders were the leading hospitalization discharge diagnosis among men and the second leading diagnosis category among women. Approximately 6% of active duty personnel received ambulatory care for mental disorders annually, and 13% of active duty hospitalizations were attributed to mental disorders. There is a much richer body of mental health research

focusing on SMs returning from deployment. Unfortunately, these studies are not applicable to this study because the entire cohort is new to the military.

This study was designed to examine and quantify outcomes associated with the retention of those SMs identified as having a mental health disorder diagnosed during their first 6 months health care eligibility. The intent was to examine the findings of associations between those diagnosed with a mental disorder during this time period with deployment, attrition, and death by suicide for implications that may inform policy, especially policy related to retention standards. This study was determined to be exempt from an Institutional Review Board review as determined by the Department of Defense (DoD) Health Affairs' TRICARE Management Activity Exemption Determination Official, September 2008.

## Methods

### Study Cohort

The study population was selected from a census of SMs, aged 17 to 34, who were new accession active duty and activated National Guard or Reserve between Octoberober 1, 2003 and December 31, 2006 (*N* = 900,410). “Newly Eligible” for TRICARE, the Health Maintenance Organization-like health care benefit option in the Military Health System (MHS) is an administrative designation that new recruits are given upon completion of their initial paperwork, usually within the first 48 hours of their arrival at basic training. The first date of TRICARE eligibility was used as a proxy for time of entry into the Service, expediting identification of SMs newly accessed over a period of time and setting initial time boundaries from which to mark any emerging mental health data. Analyses were restricted to newly eligible active duty personnel (*N* = 576,502) because the health care utilization data are considered more robust for those on active status as their on-going care is directly administered through the Military Treatment Facility-delivered benefit program. All demographic data were based on data collected at the date of entry into the cohort. This information included age, gender, marital status, Service, and rank.

### Measures

#### Mental Health Diagnoses

For purposes of these analyses, the SMs' first 6 months benefit coverage under the military health care system was coined the period of “initial eligibility.” The first 2 to 3 months include “boot camp” or basic training and subsequently there may be a continuation of basic training or technical or specialty training, depending on the requirements of the career field. SMs were categorized as having

a mental health diagnosis during initial eligibility if they had a coded mental health diagnosis event recorded in the MHS clinical administrative database or in the network administrative claims database (care received external to the MHS). The International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) mental disorders diagnostic codes were used as this is the diagnostic classification system for health care encounters. Individuals whose only coded mental disorder diagnosis was related to nicotine use (ICD9 code: 305.1) or mental retardation (ICD9 codes: 317-319) were excluded and added to the comparison group for all analyses. There were 172 individuals with a coded diagnosis of mental retardation and 165 (95.9%) of these individuals had another coded mental health diagnosis and were therefore included in the mental health diagnosis group. There were 17,537 individuals with a nicotine use diagnosis. 22% (*n* = 3897) of these were included in the mental health diagnosis group because of a co-occurring mental health diagnosis.

The Behavioral Health Coding Handbook (BHCH), a mental health diagnosis coding taxonomy inclusive of all ICD-9-CM mental diagnoses, was used to sort the individual ICD-9-CM mental disorder diagnoses into broader categories of types of disorders for study analysis and reporting purposes. BHCH groupings correspond, in general, to the diagnostic chapters in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR). The diagnostic codes listed in the DSM-IV-TR are considered to be “legal and valid ICD-9-CM codes” and either one of these coding systems—DSM-IV-R or ICD-9-CM and their subsequent revisions—may be cross-walked with each other and retain internal consistency. The health care claims data were merged with personnel, discharge, deployment, and suicide data.

Outcomes

Deployment data was based on the DoD Contingency Tracking System deployment file, which is used identifying the location of deployed SMs. Early attrition was defined as a tour of duty less than 4 years, the standard length of time for an active duty tour. Time in service was based on cumulative months of health care eligibility. SMs with less than 48 months of eligibility, a proxy for a 4-year tour, were defined as early attrition. Data for the aforementioned outcomes were available through December 31, 2007. Death by suicide was identified using data from the Office of the Armed Forces Medical Examiner. This data was available through December 31, 2008.

Analyses

Descriptive analyses were used to describe the demographic characteristics of the study cohort. Bivariable analyses were used to examine the prevalence of mental health diagnoses at several times (4-weeks, 8-weeks, and 6-months) during initial eligibility. After reviewing the data in conjunction with the a priori research question focusing on the initial eligibility in its entirety, all subsequent

analyses were based on mental health diagnoses through the first 6 months of eligibility. Bivariable analyses, $\chi^2$ tests for categorical variables, and *t*-tests for continuous variables were used to compare the mental health diagnoses by demographic characteristics. Multivariable logistic regression was used to identify demographic characteristics associated with having a mental health diagnosis during initial eligibility.

### Deployment

Multivariable logistic regression was also used to quantify the association between a mental health diagnosis during initial eligibility and subsequent deployment. This model controlled for demographic covariates including gender, rank, Department, age, and marital status at baseline.

### Attrition

The attrition analysis was restricted to a subcohort of active duty SMs newly eligible between Octoberober 31, 2003 and December 31, 2003 in order to have at least 48 months of follow-up. To address the null hypothesis related to early attrition, the cohort of SMs who died by suicide (*N* = 13) or were discharged for personality disorder (*N* = 551) were not included in the "early attrition" group but contributed person time until their date of death by suicide or discharge date when they were administratively censored (time no longer counted to increase accuracy of the person-year denominator in the study group). All other participants were administratively censored on December 31, 2007. The resulting cohort consisted of 39,596 active duty SMs. In order to assess the relationship between mental health diagnosis during initial eligibility and early attrition, a multivariable Cox proportional hazard model was developed. The model controlled for gender, Department, age, and deployment.

### Death by Suicide

A Cox proportional hazards model was used to assess the relationship between mental health diagnosis during initial eligibility and death by suicide. Cohort members who were not identified as a death by suicide case were administratively censored on their last date of eligibility or December 31, 2008. SAS version 9.1.3 and STATA Version 10 were used for analyses.

## Results

### Incidence of Mental Health Diagnoses

The study cohort consisted of 576,502 active duty SMs, aged 17 to 34, with an initial eligibility start date between Octoberober 1, 2003 and December 31, 2006.

The majority were male (84%), between 17 and 24 years of age (88%), single (88%), and enlisted (94%). Approximately 42% were in the Army, 18% in the Air Force, 18% the Marine Corps, and 22% in the Navy.

There were notable demographic differences in cumulative mental health diagnoses at 6 months of service statistically significant at $p < 0.0001$ using $\chi^2$ tests for categorical variables and *t*-tests for continuous variables (age). Diagnoses were more common among women (16%) compared to men (7%), and SMs aged 17 to 24 had a greater incidence compared to those aged 25 to 34, 8.8% and 8.3%, respectively. Enlisted had a greater incidence of mental health diagnoses, 9%, compared to officers, 2%. There were also Department differences in mental health diagnoses. The Army incidence was 11%, Navy 8%, and Air Force and Marine Corps 6%. By year cumulative incidence of mental health diagnoses by Department may reflect a change in application of Army retention standards at the end of 2005, resulting in a 14% rate of mental diagnoses during the first 6 months of service in 2006.

Prevalence of mental health diagnoses was also calculated at the first 4 and 8 weeks of service by year and Department. In the total population, the cumulative incidence of mental health diagnoses increased from 2.6% at 4 weeks to 4.0% at 8 weeks and 7.7% at 6 months. The most notable increase occurred in the Army with incidence of a coded mental diagnosis by 6 months rising from 8.7% in 2003 to 13.8% in 2006. Although year of initial eligibility was statistically significantly associated with mental health diagnoses in the other Services, there was not a notably increasing trend.

Incidence of Mental Health Diagnoses by CBHIG Diagnostic Groups During Initial Eligibility Among Active Duty SMs, Aged 17 to 34, Newly Eligible Between Octoberober 1, 2003 and December 31, 2006

presents the incidence of mental health diagnoses using CBHIG Diagnostic Groups to identify what types of diagnoses were most common. The overall incidence of any mental health diagnosis during the first 6 months was 876 per 10,000. The most common diagnoses groups were Adjustment Disorder, 445/10,000; Depression, 363/10,000; and Anxiety, 205/10,000. SMs frequently had more than one diagnosis. The mean number of unique diagnoses was 1.93 (SD 1.17) with a range from 1 to 11.

Deployment

Approximately 41% of the study cohort was identified as having a deployment: more commonly men, 43%, than women, 26%; and slightly greater among ages 25 to 34, 45%, compared to those aged 17 to 24, 40%. Deployment was more prevalent in the Army,

50%, and Marine Corps, 46%, compared to the Navy, 31%, and Air Force, 26%. Sixteen percent of individuals with a mental health diagnosis during initial eligibility deployed compared to 43% of those without a mental health diagnosis who deployed. The association between a mental health diagnosis during initial eligibility and odds of deployment was examined, controlling for sociodemographics with a multivariable logistic regression model. Those with a mental health diagnosis were 77% less likely to deploy compared to those without a mental health diagnosis, controlling for the covariates listed gender, age, rank, Service, and marital status.

Multivariable Models of the Relationship Between Early Career Mental Health Diagnoses and Subsequent Deployment and Early Attrition Among Active Duty SMs, Aged 17 to 34, Newly Eligible Between Octoberober 1, 2003 and December 31, 2006. These data support the phenomena of the "Healthy Warrior Effect," a result of restrictions on deploying members with unstable mental disorders. Males, individuals aged 25 to 34, those in the Army, Marine Corps, and Navy compared to the Air Force, and enlisted all had increased odds of deployment.

Attrition

The cohort consisted of 39,032 AD SMs, of whom 5,088 (13%) did not complete 48 months of Service. Approximately 84% were male, 87% were aged 17 to 24, 97% enlisted, and 87% single. Approximately 38% were Army, 23% Air Force, 18% Marines, and 21% Navy.

The cohort's overall incidence rate of early attrition was 328/10,000 person-years of follow-up. (Person-years is time at risk in years that all persons contributed to the study.) The hazard of attrition appeared to peak around 3 years of eligibility.

The incidence rate was 529/10,000 person-years of follow-up among those with a mental health diagnosis for break-out by diagnosis category) during initial eligibility and 313/10,000 person-years of follow-up among those without a mental health diagnosis. The incidence rate ratio was 1.69 indicating 69% increased rate of early attrition among those with a mental health diagnosis during initial eligibility compared to those without a mental health diagnosis during initial eligibility, $p < 0.0001$. In both univariable and multivariable models, the hazard ratio for the association between mental health diagnosis during initial eligibility and eligibility of less than 48 months was statistically significant, $p < 0.0001$. Univariable regression indicates that a mental health diagnosis during initial eligibility is associated with close to a 72% increased risk of early attrition (<48 months of eligibility). After controlling for demographic and Service characteristics, mental health diagnosis during initial eligibility is associated with a 19% increased risk of early attrition (<48 months of eligibility) Certain demographic characteristics were also significantly associated with completion of less than 48 months of service. Males are statistically more likely than females, and enlisted SMs are more likely than officers, to serve less than

48 months. Individuals in the Army are four times more likely than the Air Force to have less than 48 months of eligibility. Individuals in the Marine Corp and Navy are statistically significantly less likely than the Air Force to have less than 48 months of eligibility.

Death by Suicide

There were 266 individuals, or 13/100,000 person-years of follow-up among those with initial eligibility between Octoberober 1, 2003 and December 31, 2006 who subsequently died by suicide during the study follow-up through December 31, 2008. The incidence rate of suicide was smaller among individuals with a mental health diagnosis (11.6/100,000 person-years) compared to individuals without a mental health diagnosis (13.6/100,000 person-years); this difference is not statistically significant. In multivariable analyses, there was not an association between mental health diagnoses during initial eligibility and subsequent death by suicide.

Discussion

This study was based upon identifying active duty SMs with mental diagnoses during initial eligibility with the focus on potential issues related to early application of less stringent retention standards before completion of initial military training. Before this study, early career mental health diagnoses were not systematically studied. The proportion of active duty SMs who receive a mental health diagnosis during initial eligibility (8.75%) is concerning and warrants further evaluation to include validation of the diagnoses with medical records. Although early career mental diagnoses were not associated with an increased risk of death by suicide, they were associated with other outcomes of potential significance for policy: a 69% increased rate of attrition and 77% reduced odds of deploying. The impact of findings such as these on manning for combat end strength may merit future cost–benefit analyses to quantify opportunity costs of retaining members with early mental diagnoses, as SM authorizations are fixed by Congress. Specifically, future studies should clarify the overall effects of personnel policies that lower accession or retention standards, or apply retention standards to personnel with less than 6 months of military service.

Mental disorders are a known risk factor for suicide. However, increases in SMs retained with early career mental health diagnoses did not account for increases in military suicides over the same time period. Such might be explained by cohort members being formally diagnosed and their conditions treated, as opposed to those with potentially undiagnosed, untreated disorders, or by the cohort's 77% decreased rate of deployment, a risk factor for suicide. The majority of those diagnosed with most mental diagnoses did complete 48 months of service. Though completion rate was lower than for those not so diagnosed, an argument can be made for the efficacy care in terms of assisting most members with mental diagnoses to complete their tours of duty.

Several limitations should be considered when interpreting the results. First, the study relied on a proxy measure for entry into the military, the start date for TRICARE eligibility. Although this is not an ideal measure, any measurement error associated with this proxy is likely to be both nondifferential and independent (not associated with the exposure, mental health diagnosis, or outcomes) and will therefore not induce a significant bias. Second, the study has all of the limitations of a retrospective cohort study including the use of coded diagnoses from medical claims. These diagnoses were not confirmed with medical record review. Third, the estimates presented are likely an underestimate of the true burden of mental health disorders. This study is based on SMs who sought medical care and were diagnosed with a mental health condition. There are likely many more SMs who do not seek care for such conditions as a result of perceived stigma. Last, the results are not readily generalized to the U.S. population. Although the U.S. military is not representative of the general population, it represents an important segment of the adult working population.

Despite these limitations, this study has numerous strengths and important policy implications. The study was population-based, consisting of a census of active duty SMs who were new to the military between 2003 and 2006. This cohort is diverse with respect to ethnicity, gender, age, and education. The MHS clinical administrative data include all medical claims data (inpatient, outpatient, military, and civilian providers) for these SMs. All SMs also have equal access to comprehensive medical care. The quantification of the study outcome, mental health diagnoses, is considered to be extremely inclusive. This is the first study to be able to provide a population-based estimate of the burden of mental health disorders among new SMs.

This study demonstrated that clinical administrative data can be used to address policy questions in a timely fashion. Hypothesis development began in April 2008, data utilization agreements were completed in August 2008, and IRB protocol was approved as exempt and data extracted in September 2008. Analyses were completed in January 2009. Results were presented to the DoD Accession Standards Working Group in June 2009 and to Pentagon Personnel leadership in September 2009, The results of this study indicate mental health disorders are common in initial eligibility. In the general population, mental disorders are associated with morbidity, disability, reduced quality of life, occupational morbidity (absenteeism, unemployment), and high health care utilization. Previous research in military cohorts has shown that mental health conditions are a significant predictor of disability, medical discharge, early attrition, and increased health care utilization. Among SMs hospitalized with a mental disorder, almost half left military service within 6 months.

These findings provide information that contributes to understanding the potential outcomes of policy that regulates the recruitment and retention of SMs. The results indicate that the long-term implications of implementing less stringent retention standards during initial training warrants careful monitoring by the Military Departments and the DoD. It will be important to evaluate these findings in entirety with findings from follow-on analyses whenever retention polices are changed. The end goal of the information garnered from

such a series of analyses is to assist decision-makers in appraising and reconciling current policy, as needed, to enable sustainment of the operational end strength required for military force readiness.

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***Technology***

## Computer use and stress, sleep disturbances, and symptoms of depression among young adults -- a prospective cohort study

BMC Psychiatry
Sara Thomée, Annika Härenstam and Mats Hagberg
22 Oct 2012

Abstract

Background

We have previously studied prospective associations between computer use and mental health symptoms in a selected young adult population. The purpose of this study was to investigate if high computer use is a prospective risk factor for developing mental health symptoms in a population-based sample of young adults.

Methods

The study group was a cohort of young adults (n = 4163), 20–24 years old, who responded to a questionnaire at baseline and 1-year follow-up. Exposure variables included time spent on computer use (CU) in general, email/chat use, computer gaming, CU without breaks, and CU at night causing lost sleep. Mental health outcomes included perceived stress, sleep disturbances, symptoms of depression, and reduced performance due to stress, depressed mood, or tiredness. Prevalence ratios (PRs) were calculated for prospective associations between exposure variables at baseline and mental health outcomes (new cases) at 1-year follow-up for the men and women separately.

Results

Both high and medium computer use compared to low computer use at baseline were associated with sleep disturbances in the men at follow-up. High email/chat use was negatively associated with perceived stress, but positively associated with reported sleep disturbances for the men. For the women, high email/chat use was (positively) associated with several mental health outcomes, while medium computer gaming was associated

with symptoms of depression, and CU without breaks with most mental health outcomes. CU causing lost sleep was associated with mental health outcomes for both men and women.

Conclusions

Time spent on general computer use was prospectively associated with sleep disturbances and reduced performance for the men. For the women, using the computer without breaks was a risk factor for several mental health outcomes. Some associations were enhanced in interaction with mobile phone use. Using the computer at night and consequently losing sleep was associated with most mental health outcomes for both men and women. Further studies should focus on mechanisms relating information and communication technology (ICT) use to sleep disturbances.

Background

The widespread use of modern information and communication technology (ICT) in work life and private life follows in the wake of rapid advances in technology and popularization of different devices and applications, implying fast changes in exposure profiles in the population over the past few decades. The issue of possible negative effects of exposure to ICT has been raised by various groups. Musculoskeletal symptoms and ergonomics in relation to computer use and different input devices have been examined [1-3], but also, mental health effects have been considered (e.g. [4]). The term techno-stress emerged more than two decades ago, to describe stress reactions in relation to computer use [5]. It was suggested that computer use can lead to psychophysiological stress reactions due to occupational strain, and that these reactions can become conditioned to the computer work environment, leading to symptoms associated with computer use [5,6]. The term ICT stress has been used to describe stress induced by interruptions at work, time pressure, and technical problems in connection with ICT use [7].

In 2010, 91% of the Swedish population (16–74 years old) had access to the Internet at home. Young adults, 20–24 years old, were the most frequent users compared to all other age groups [9]. In a previous prospective cohort study, we found associations between high use of ICT, including chatting, emailing, Internet surfing, the sum of hours spent at the computer and mobile phone per week, and the number of mobile phone calls and text messages (SMSs) per day, and reported mental health symptoms among college and university students aged 19–25 years [10]. The study was followed by a qualitative interview study with 32 high users of ICT who had reported mental health symptoms at 1-year follow-up in the cohort questionnaire [11]. Based on these young adults' own concepts and ideas, a model of possible paths for associations between ICT use and mental symptoms was proposed via consequences of high quantitative computer or mobile phone use, negative qualitative use, and user problems. Consequences of computer use included spending more time than planned at the computer (e.g., working, gaming, or chatting), leading to time pressure, neglect of other activities and personal needs (e.g., breaks, physical activity, social interaction, sleep), exposure to bad ergonomics, and mental overload. Chatting or emailing interrupted other tasks, with difficulties filtering important from unimportant messages, leading to mental overload. Getting stuck in what was perceived as unproductive activities, such as game playing, or "gaming," was another concern, and participants could also relate to having insufficient or dislocated sleep after sitting up late in front of the computer because of getting stuck in tasks, meeting deadlines, chatting, or gaming. In a study among Finnish adolescents [12], intensive computer use among the boys was a

risk for poor perceived health through deteriorated sleeping habits and waking time tiredness. (For the girls, it was intensive mobile phone use that was directly associated with poor perceived health, likewise through deteriorated sleeping habits and waking time tiredness).

There has been a growing number of publications concerning ICT addiction [13]. Internet addiction has been proposed as a specific psychiatric illness [14]; however, this form of problematic Internet use could also be considered to share elements with impulse control disorders and be related to the specific activities done on the Internet (such as gambling) rather than the Internet per se [15,16]. Internet addiction has been associated with sleep disorders and depression among adults [17] and adolescents [18]. Most studies we have found concerning problematic Internet use and mental health have a cross-sectional design, but one exception is a prospective study among Chinese adolescents 13–18 years old [19], where Internet addicts, compared to non-pathological users, had a relative risk of about 2.5 for new cases of depression (using the Zung Depression Scale).
Another focus has been computer gaming. Playing computer games is more common among men and boys than among women or girls (e.g. [12,20,21]). In a longitudinal study among youths, pathological gaming predicted higher levels of depression, anxiety, social phobia, and poor school performance [22]. It seemed to be a long-term exposure, as most (84%) of the youths who were pathological gamers at baseline were still pathological gamers after 2 years.

Furthermore, in our interview study [11], social isolation was a concern. A negative loop was suggested, where people who are already lonely may have a preference for using computers, which in turn could increase their tendency to lack real-life contacts, and lead to an even higher use. This is in line with the findings of Morahan-Martin and Schumacher [23].

Positive effects of computer use were also listed, such as efficiency, access to information, fun and recreation, the ease of keeping up social contacts, and access to social support [11]. We concluded that there seemed to be many factors in different domains that should be taken into consideration in epidemiological studies concerning associations between ICT use and mental symptoms. While we have previously performed a prospective study on computer use in relation to mental health symptoms in a selected university student cohort [10], it is important to examine possible prospective associations between computer use and mental health outcomes in a more general and heterogeneous population of young adults. The present study was performed in a population-based sample of young adults. We have recently performed a study on mobile phone use and mental health outcomes in the same cohort population [24].

Frequent mobile phone use was a prospective risk factor for sleep disturbances in the men, and for symptoms of depression in the men and women.

Aims

The purpose of this study was to investigate if high computer use is a risk factor for developing mental health symptoms in a population sample of young adults. Specific aims included examining associations, if any, between time spent on computer use in general, time spent on communication (emailing or chatting) in leisure, time spent on computer gaming, using the computer without breaks, and getting stuck behind the

computer screen at night and thus losing sleep, on the one hand, and perceived stress, sleep disturbances, and symptoms of depression, on the other. Furthermore, we wanted to explore perceived social support in relation to computer use. As a final goal, we aimed to examine potential interaction between computer and mobile phone use on mental health symptoms.

## Methods

### Study population and data collection

The study population consisted of a cohort of young adults (Figure 1), 20–24 years old (age span corresponding to the United Nations' definition of young adults [25]). A cohort of 10000 men and 10000 women, born between 1983 and 1987, were randomly selected from the general population from a registry held by the Swedish Tax Agency, 50% living in the County of Västra Götaland, and 50% in the rest of Sweden. In Octoberober 2007, a questionnaire [26] containing questions about health, work- and leisure-related exposure factors, demographic factors, and psychosocial factors was sent to the selected young adults by post.

Besides returning the postal questionnaire it was also possible to complete the questionnaire online if desired. As an incentive to respond, a lottery ticket (value approx. 1 Euro) was attached to the cover letter and could be used regardless of participation in the study. Two reminders were sent by post. The response rate at baseline was 36% (n = 7125; 2778 men and 4347 women). Twelve months later, those respondents who had indicated that they would consider participating in future studies (n = 5734) were invited to respond to an identical questionnaire, this time administered via the Web. The data collection process was similar to that at baseline, with the addition of a third reminder offering a paper version of the questionnaire and two cinema tickets for participating. The response rate at follow-up was 73% (Figure 1; n = 4163; 1458 men and 2705 women). The study was approved by the Regional Ethics Review Board in Gothenburg, Sweden (Reg. no. 191–05 and 876–11).

### Exposure variables

Information about computer use was collected from the cohort study questionnaire at baseline, including average time spent daily on general computer use, on emailing or chatting in leisure, and on computer gaming, as well as how often the computer was used for more than 2 hours without breaks, and how often sleep was lost because of getting stuck late at night by the computer. Also, information about mobile phone use (average number of calls and SMSs sent and received per day) was collected from the questionnaire. Response data were categorical, and were further divided into high, medium, and low categories. Exposure variables, questionnaire items, response categories, and categories used in the present study are presented in Table 1.

Frequencies and percentages in exposure variables, including categorizations into low, medium, and high, are presented. Missing values (non-responses to items) are not accounted for, which means that the n varies for the variables Questionnaire items: Computer use (CU): On average, how much time per day have you used on a computer (total use)? Email/chat use: On average, how much time per day have you used on a computer for emailing and chatting (leisure/private use)? Computer gaming: On average, how much time per day have you spent on computer

gaming (e.g., computer games or online games, private/leisure use)? CU without breaks: How often have you used a computer for more than 2 hours without taking a break longer than 10 minutes? CU causing lost sleep: How often have you lost sleep because of sitting late at night at the computer? Mobile phone use: How many mobile phone calls on average have you made and received per day?, and How many SMS messages on average have you sent and received per day? The time span for all items was “over the past 30 days”.

Mental health outcome variables

Information about perceived mental health symptoms was collected from the cohort study questionnaire at baseline and follow-up. The outcome variable current stress was constituted by a validated single-item stress indicator [27], with the responses divided into yes and no.
The variable sleep disturbances was constructed for the study by including the most common sleep disturbances (difficulties falling asleep, fragmented sleep, and premature awakening) into a single item, loosely adapted from the Karolinska Sleep Questionnaire [28], with responses divided into yes and no based on clinical significance (sleep problems several times per week or more). The two depressive items from the Primary Care Evaluation of Mental Disorders (Prime-MD) screening form [29] were included in the questionnaire. It has been proposed that if one of the two items is confirmed at screening to go forward with clinical assessment of mood disorder, a procedure that has been shown to have high sensitivity for major depression diagnosis (86% [29] and 96% [30]), but lower specificity (75% [29] and 57% [30]), in primary care populations. In the youngest age group (<35 years old) in Whooley et al. [30], the sensitivity was 100% and the specificity 59%. In our cohort study group, approximately 50% of the men and almost 65% of the women confirmed at least one of the two depressive items, which indicates that the instrument is probably very sensitive but had low specificity in our study group. Therefore, we constructed two separate outcomes: symptoms of depression (one item) and symptoms of depression (two items), the latter presumably with higher specificity. The variable reduced performance was based on reporting that stress, depressed mood, or tiredness had influenced performance “quite a lot” at work or school over the past 2 weeks. Mental health outcome variables, questionnaire items, response categories, and categories used in the present study are presented in Table 2.

Social support

The variable social support was based on the item: When I have problems in my private life I have access to support and help, constructed for the study as a single item adaptation of the social support scale in the Karasek-Theorell Job Content Questionnaire [31], here relating to private life (rather than work life). Response categories were: a = applies very poorly; b = applies rather poorly; c = applies rather well; d = applies very well. The responses were categorized as low (response categories a–b), medium (response category c), and high (response category d).

Sociodemographic variables

In the multivariate analysis, potentially confounding sociodemographic factors were collected from the baseline questionnaire and adjusted for, including relationship status: single or in a relationship; highest completed educational level: elementary school (basic schooling for 6–16-year-

olds), upper secondary school, or college or university studies; and occupation: working, studying, or other (other included being on long-term sick leave, or on parental or other leave, or being unemployed).

Analysis

Spearman correlation analysis was used to examine associations between the different computer exposure variables, and between the exposure variables and social support. For analysis of dropout between the initial cohort baseline and 1-year follow-up, Wilcoxon's (two-sided) two-sample test was used. The Cox proportional hazard model, using SAS PROCPHREG (SAS Institute, Inc., Cary, NC, USA), with time set to 1, was used to calculate prevalence ratios (PRs) with a 95% confidence interval (CI) for multivariate analysis of prospective associations between exposure variables high, medium, and low (reference level) and mental health outcomes (yes or no). The robust variance option (COVS) was used to produce accurate CIs [32,33].

In all prospective analyses, participants who reported symptoms at baseline were excluded from the analysis of the mental health outcome variable concerned. For example, when analyzing sleep disturbances, subjects with sleep disturbances at baseline were excluded. It is possible that the included subjects had one or more of the other mental health symptoms at baseline; however, these were not accounted for in the analysis of sleep disturbances. Two sets of extra analyses were performed; one, including also those with symptoms at baseline, adding the baseline value of the outcome variable as a confounder, and the other, including only those who reported symptoms at baseline.

All analyses were performed separately for the men and women. The PRs were adjusted for sociodemographic factors including relationship status, educational level, and occupation.

These potential confounders were chosen based on theoretical hypothesis and were added to all analyses if $p \leq 0.10$ in at least some of the analyses. Age was not considered a confounder because of the limited age span of the study group. Missing values (i.e., non-responses to items in the questionnaire) were excluded from the analyses, which means that the n varied in all analyses. PRs with a 95% CI not including 1.00 (before rounding) were considered statistically significant.

Furthermore, some computer exposure variables were analyzed for possible interaction with mobile phone use, by using all nine possible category combinations of the two variables in the analysis. Multivariate analyses were performed to calculate PRs using the Cox procedure, as described earlier, using the "low–low" category combination as reference.

All analyses were performed using the statistical software package SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Exposure, mental health symptoms, and social support in study group at baseline. Almost 40% of the men and 30% of the women were categorized as having high computer use (>4 hours per day) (Table 1). The majority spent less than 1 hour per day on leisure time email/chat use, while about 20% spent 1–2 hours per day, and 10% spent more than 2 hours per day on this activity. The percentage of men who spent >1 hour on computer gaming (medium or high gaming) was more than four times that of women. Lost sleep because of late night computer use (CU causing lost sleep) was more common among men than among women (Table 1). There were moderate positive associations between the exposure variables at baseline (Spearman correlation coefficients, Table 3), with the strongest associations found between computer use (hours per day) and frequency of CU without breaks. There were little if any correlations between computer exposure variables and mobile phone use.

Spearman correlation coefficients for the men (n = 1458) and women (n = 2705) included in the study. All correlations are statistically significant ($p < 0.05$) except where indicated as non-significant (ns) The women reported current stress almost twice as often as the men (29% compared to 16%) at baseline. Twenty-three percent of the men and 34% of the women indicated sleep disturbances. Of the men, 27% reported one and 24% both symptoms of depression, and of the women, 30% reported one and 34% both symptoms of depression. Ten percent of the men and 20% of the women reported reduced performance due to stress, depressed mood, or tiredness. Among participants who were symptom-free at baseline (in terms of the outcome variable concerned), the prevalence of new cases at 1-year follow-up was as follows, for men and women respectively: current stress: 10% and 19%, sleep disturbances: 15% and 20%, symptoms of depression (one item): 24% and 28%, symptoms of depression (two items): 12% and 18%, and reduced performance: 7% and 14%. Sixteen percent of the men and 13% of the women perceived low social support in private life. Forty-one percent of the men and 32% of the women reported medium, and 43% of the men and 56% of the women reported high social support.

Prospective associations between computer exposure at baseline and mental health outcomes (new cases) at 1-year follow-up
Both high and medium computer use compared to low computer use at baseline were associated with sleep disturbances at 1-year follow-up for the men, but not for the women (Table 4). For men, high computer use was also associated with reduced performance (due to stress, depressed mood, or tiredness). High email/chat use was negatively associated with perceived stress for the men, but positively associated with reported sleep disturbances. For the women, both high and medium email/chat use were (positively) associated with stress and sleep disturbances. For the women, high email/chat use was also associated with symptoms of depression (one item) (PR 1.9, 95% CI 1.46–2.52, not presented in the Table).

There were no other statistically significant associations with symptoms of depression (one item).

The only clear association concerning computer gaming and mental health outcomes was for women, where medium gaming was associated with symptoms of depression (two items).

Furthermore, both high and medium CU without breaks were associated with perceived stress, sleep disturbances, and symptoms of depression (two items) for the women. For the men, medium CU without breaks was associated with sleep disturbances. High (and, for women, medium) CU causing lost sleep was associated with stress and sleep disturbances for both the men and the women. Furthermore, high and medium CU

causing lost sleep were associated with reduced performance among the men, while medium (but not high) CU causing lost sleep was associated with symptoms of depression (two items) and reduced performance for the women.

The extra analyses including also participants with symptoms at baseline, and adjusting for baseline health, gave results in the same direction as the results presented above. The PRs were approximately in between the PRs in Table 4 and those that resulted when including only participants with symptoms at baseline (PRs mostly around 1.0).

Interaction effects: computer and mobile phone use

Because computer use and email/chat use were risk factors for sleep disturbances among the men, as mobile phone use had been in a previous study (PR 1.8, CI 1.21–2.69) [24], we tested these two exposure variables in combination with mobile phone use, with sleep disturbances as the outcome. Furthermore, since CU without breaks was a risk factor for symptoms of depression among the women, as mobile phone use had been in the previous study (PR 1.5, CI 1.02–2.24), these were tested in combination, with symptoms of depression (two items) as the outcome.

There seemed to be an interaction between computer use and mobile phone use in relation to sleep disturbances in a near additive fashion for the men, while for the women, only the "high–high" category was a risk exposure (Table 5). Men with high email/chat use in combination with medium or high mobile phone use had an almost tripled risk for sleep disturbances at follow-up, using "low–low" users as reference (Table 5). In the same analysis, for women, only effects of the email/chat use variable could be seen. Finally, there was a tendency towards interaction between CU without breaks and mobile phone use with symptoms of depression (two items) as outcome for the women (Table 6). Caution in interpretation is necessary since in all the combined analyses, the CIs overlapped.

Social support

There were no associations between social support and computer exposure variables at baseline for the men, except for a very low negative association with CU causing lost sleep (−0.10; $p < 0.001$). For the women, there were very low negative associations with all computer variables (between −0.06 and −0.12; $p < 0.05$).

Dropout analysis

The non-respondents at the initial cohort baseline were more often male (a difference of 17 percentage points) and were somewhat younger (an age difference of <0.1 years), more often married (a difference of 1.4 percentage points), and more often foreign-born (8 percentage points difference), compared to the study population invited to participate [26].

Furthermore, the dropout group (n = 2962) from the initial cohort baseline (n = 7125) to 1- year follow-up also had a higher proportion of men, resulting in almost twice as many women as men (65% vs. 35%) in the final study group (n = 4163). The participants in the study group had a

slightly higher educational level and differed in occupation in that they were less often working and more often studying at baseline compared to the dropout group (differences of up to 10 percentage units). The level of computer use and CU without breaks was slightly higher in the study group, while mobile phone use was lower (differences of up to 10 percentage units). The women in the study group were less often single (34% compared to 37%) and reported a slightly higher level of social support (differences of up to 3 percentage units). With the exception of a lower prevalence of sleep disturbances among the men in the study group (23% compared to 27%) the prevalence of mental health symptoms at baseline was about the same among the dropouts and those who remained in the study.

## Discussion

We found prospective associations between aspects of computer use and several mental health outcomes in this population-based sample of young adults. Some of the associations were enhanced in interaction with mobile phone use. A major strength of the study is its longitudinal design, with exposure assessed among symptom-free participants prior to outcome assessment. (Extra analyses, including also participants with symptoms at baseline and adjusting for baseline health, gave results in the same direction as the presented results, although with lower PRs). However, the latency period in our study is fairly long (1 year) and we have no information about the exposure and mental health outcomes in the latency period.

The mental health symptoms are common in the population and may come and go in the latency period. Hence, the time span between measurements may not be optimal for assessing possible effects of the exposure on mental health. For example, it is possible that long-term exposure is needed to develop, say, depression, or that a short-term exposure/short latency period is relevant for perceived stress.

The results were not consistent for all outcomes or for both men and women. For example, for men, hours spent on general computer use was a risk factor; by contrast, for women, it was the intensity of use, i.e., using the computer without breaks. The mental health outcome that seemed most affected for men was sleep disturbances, while for women, a more general pattern occurred.

Effects of computer exposure on perceived current stress at follow-up were mostly seen in parallel with sleep disturbances. This could be expected since the current stress item actually encompasses sleep problems. We have not assessed the relationship between the different mental health outcomes or pursued possible comorbidity within the study. For example, we do not know if other mental health symptoms were present among those participants who were symptom-free in the outcome concerned in the specific analysis. Sleep disturbances can be a first step towards depression (and is a diagnostic criterion for depression, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV)). For example, in one study of young adults [34], sleep disorders was a predictor of major depression onset with an odds ratio of nearly 4. It is possible that those who developed symptoms of depression in our study already had sleep disturbances at baseline.

With regard to inconsistency of results, there was even a negative association between high email/chat use and stress among the men (while the association was positive for the women), implying that men who communicated via the computer more than 2 hours per day had less than half the risk to perceive stress a year later, compared to low users. On the other hand, at the same time, they had an almost double risk for developing

sleep disturbances. There is of course a risk of chance findings when performing multiple tests, as in this study. However, the variables we tested were not chosen at random, and the results are in part supported by a previous study in a university sample of young adults [10], where, e.g., high chat use and high email use (as separate variables) were associated with symptoms of depression in women.

It has been claimed that women, more than men, use the computer for communication purposes [35]. In our study, men and women reported almost the exact same levels of email/chat use exposure. It is possible to develop and maintain large social networks via email, SMS, Facebook, web forums, and other social aspects of ICT. The positive effects of the social aspects of ICT use are often emphasized (e.g., among the subjects participants in [11]). Social support is a well-known factor that both promotes health and buffers negative effects of psychosocial strain [36,37]. Interestingly, there seemed to be little or no association between hours spent emailing or chatting and perceived social support in our study. It should be noted that the study was carried out before Facebook (and other networking services) became a widespread and popularly used application. In future studies, besides including social media use, it should be taken into consideration that social media as well as emails are increasingly accessed via the mobile phone and other portable devices, and developments seem to be towards an ever-increasing accessibility. The email/chat use variable in our study concerned leisure use. Email use in work life can also induce stress. In a study among employees in an engineering company [38], time spent emailing was associated with feeling overloaded, and the overload was independent of the hours worked. While participants spent time on other activities their emails accumulated, and email use also implied interference between work and private life. It was concluded that emailing became a symbol of stress, as it seemed to be experienced as stressful regardless of the amount of work it generated, and even made the participants overlook other aspects of work that contributed to overload [38].

Social isolation is another possible consequence of high computer use, and a negative loop has been suggested [11,23]. Morahan-Martin and Schumacher [23] found support for the position that loneliness leads to increased Internet use, while Caplan [39] concludes that social anxiety (rather than loneliness) explains the preference for online social interaction, because of benefits in comparison to face-to-face communication. Such benefits, according to the author, include having control of self-presentation, phrasing, and the speed of interaction, and therefore feeling safer and more confidence than during interactions “in real life.”

Addiction to the Internet has been suggested as a possible mental health risk factor, but was not assessed in the present study. In a Norwegian cross-sectional adult population sample [17], the prevalence of Internet addiction was 1% and that of at risk users was approximately 5%. Problematic Internet use (addicted and at risk users) was more common among men and younger age groups, and was also associated with self-reported sleeping disorders and depression.

Computer gaming was more common among the men than the women in our study (as in other studies (e.g., [12]). Only a few percent of the women played games more than 2 hours per day, and playing 1–2 hours per day almost doubled the risk of symptoms of depression among the women. This was, however, the only risk category in the analysis of computer gaming. Computer gaming may, on the other hand, be a way of coping with stress. In a study of online game players [40], playing computer games in the workplace was associated with recovery experience. By contrast, playing long hours and at night may have detrimental effects. In a population of Internet game players, habitual gaming at night was related to an increase in depression scores in adolescents (13–17 years) and emerging adults (18–22 years), though not in the group defined as

young adults (23–30 years) [41]. The association with depression was independent of total time spent playing, and gaming at night was not related to sleep problems. However, the study was cross-sectional, which limits interpretation of causality. In a laboratory study [42], computer gaming before going to bed increased sleep latency and heart rate, and decreased subjective sleepiness and rapid eye movement (REM) sleep, compared to controlled conditions. Getting stuck behind the screen and thus losing sleep was reported as a problem in our interview study [11] and was the basis for constructing the variable CU causing lost sleep, which also turned out to be a risk factor for several mental health outcomes including reduced performance, for both men and women. It may be argued that the variable involves circular reasoning, since it encompasses lost sleep as part of the exposure, which at the same time may be considered an outcome.

High ICT use can mirror a hectic lifestyle with high demands (extrinsic as well as intrinsic). It can mirror a lifestyle with lack of recovery, and have potential effects on sleep. Moreover, it is possible that ICT use contributes to a sedentary lifestyle. A sedentary lifestyle can have negative effects on mental health, while physical activity has positive effects on mental health and is acknowledged as a possible complementary treatment for depression and stress-related disorders [43,44]. A review suggests that sedentary behavior, including TV viewing and computer/Internet use, is associated with an increased risk of depression [45]. However, the possible role of physical activity was not assessed in the present study.

Methodological considerations

There are several limitations in the study, which need to be considered, for example the inconsistencies in the results, as discussed above. The study was performed in a populationbased sample of young adults, which is one of its strengths. However, caution must be taken when generalizing the results. The study suffered from a high dropout rate, as is common in questionnaire studies administered in the general population (and probably more so among young adults), resulting in, e.g., women and native-born Swedes being overrepresented in the study group. It is possible that ICT exposure in the study group differs from that of the source population. There is probably a healthy participation selection bias in the cohort, which may be further enhanced when excluding participants with symptoms at baseline before analysis, as the remaining participants might differ from the source population in several aspects including health and resilience. We did adjust for potential confounding by occupation, educational level, and relationship status. However, this was done only at baseline and situations may have changed during the latency period, which will not have been accounted for. Furthermore, we adjusted for potential confounding in all analyses, even though all confounders were not relevant in all analyses. Moreover, geographical confounding may be present because half of the source population was from one region of Sweden and the other half was from the rest of the country. Gender bias was eliminated by separately analyzing men and women.

There are several limitations in using a questionnaire to collect information on exposure and health aspects. Recall bias and recall difficulties are most likely present. Agreement between self-reported and registered exposure clearly was low in one validity study concerning computer use [46] where more than 80% of respondents misclassified their computer use, with almost all respondents overestimating their use. Perhaps in a future study, we would want to use objective exposure assessment via technical registration, rather than self-report.

Some of the mental health outcomes used in the study were not validated (sleep disturbances and reduced performance due to stress, depressed mood or tiredness), including the social support variable, which is a limitation of the study. It is important to point out that the study concerns subjective symptom reports and not actual mental disorders or diagnoses. The prevalence of reported depressive symptoms was alarmingly high in our study group; approximately 50% of the men and almost 65% of the women confirmed at least one of the two depressive items. Following the suggested PRIME-MD procedure [29,30], a predictive power of 33% [30] would imply that about 20% of the study group was clinically depressed. However, the prevalence of depression in a population such as the one included in this study is most likely lower than in primary care populations. For comparison, the 1-month prevalence of depression among Finnish young adults (20–24 years of age) was 9.6% [47].

Suspecting that the instrument would be too sensitive for our population, we chose to adapt the analysis accordingly, expecting that the two-item outcome would have higher specificity than if following the suggested procedure.

The computer use variables based on time spent at the computer in our study did not permit us to evaluate extreme use, since the cutoff for the highest category of general computer use was 4 hours per day, which was the time that almost 40% of the men and 30% of the women spent on the computer. The cutoff for the high category in email/chat use and computer games was 2 hours per day. It is possible that more extreme exposure is more hazardous to health than the tested exposures and having more categories with higher cutoffs may have enabled a dose–response analysis. Perhaps the variables concerning intensity of use (i.e., CU without breaks, and CU causing lost sleep) can reflect a more extreme and, possibly, destructive use, than those concerning mere hours of use. Also, it is important, though difficult, to keep up to date with advances in technology and applications, and to create items that sufficiently capture relevant exposure, especially in longitudinal studies.

Implications

Aspects of ICT use can contain risk factors for mental wellbeing among young adults, and may be markers for (other) mechanisms associated with mental health risks. Consequently, it seems desirable to support healthy use of modern technologies in order to prevent possible destructive uses or effects, since ICT is an ever-increasing part of daily life, at work, at school, and at leisure. Since sleep and recovery are essential for maintained health, further studies could focus on mechanisms relating ICT use to sleep disturbances, to deepen our understanding and develop meaningful and evidence-based intervention programs.

Conclusions

Time spent on general computer use was prospectively associated with sleep disturbances and reduced performance for the men included in this study. For the women, using the computer without breaks was a risk factor for several mental health outcomes. Some associations were enhanced in interaction with mobile phone use. Using the computer at night and thus losing sleep was associated with most mental health outcomes for both men and women. Further studies should focus on mechanisms relating ICT use to sleep disturbances.

BACK TO TOP

# Use of Portable Sleep Monitors to Diagnose Sleep Apnea During Predeployment Assessment

Military Medicine
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Oct 2012

Abstract

Introduction: Portable sleep monitors (PMs) may be more expeditious and convenient than in-laboratory sleep studies in diagnosing obstructive sleep apnea (OSA). We report for the first time the use of PMs in a military population to demonstrate feasibility in predeployment assessments. Methods: A nested, descriptive study was undertaken at 7 military medical facilities as part of a larger clinical trial. Subjects answered two questionnaires to identify OSA symptoms and used an ApneaLink Plus portable monitor to test for OSA. Descriptive statistics were used to characterize the subjects and to report results of PM use. Results: 101 subjects were enrolled, and 77 subjects completed the study. 4.0% of subjects did not tolerate PM use. We found 15 subjects with OSA, with mean age of 31.4 ± 12.8 years, mean body mass index of 33.0 ± 7.4 kg/m2, and mean apnea–hypopnea index of 19.6 ± 13.9 per hour. Subjects with OSA were more likely to have high pretest probability of disease than those without OSA. Conclusion: We demonstrate that PMs are well-tolerated and can successfully identify OSA in those with high pretest probability. We propose a method to implement PM use during predeployment assessments.

## Introduction

Obstructive sleep apnea (OSA) is a significant disorder of breathing that causes collapse of upper airway tissue during sleep.1 OSA has an overall incidence in middle-aged adults of 9% in females and 24% in males.2 The symptoms associated with OSA are snoring, excessive daytime sleepiness (EDS), and fatigue. These have been linked to impaired judgment, decreased work productivity, memory difficulty, and an increased rate of motor vehicle accidents. The potential long-term cardiovascular sequelae of untreated OSA include hypertension, cardiac arrhythmias, acute coronary syndromes, a cor pulmonale.3

OSA among service members represents a particular concern for the Department of Defense because of its impact on military performance, safety, and mission.4,5 Untreated, symptomatic OSA is currently a nondeployable condition, and diagnosing sleep apnea efficiently and accurately is an important task in the predeployment assessment process. The traditional means of diagnosing

OSA includes a consultation to a sleep disorders center, where an overnight, in-laboratory polysomnogram (PSG or sleep study) is performed. The burden upon sleep centers can be tremendous, especially when the need arises to evaluate and process a large group of soldiers for mission readiness. Portable home sleep monitors (PMs) may offer a more expeditious and convenient means of screening for sleep apnea in a qualifying population. Early identification of OSA is crucial because it may affect the decision to deploy a service member.

To our knowledge, there is no data in the literature evaluating use of portable monitors in service members. We are currently undertaking a multi-institutional clinical trial within the military to evaluate the role of adult tonsillectomy in treatment of OSA. This trial involves utilizing a PM to screen a group of service members and dependents, who are scheduled for tonsillectomy, for OSA and to determine the effect of surgery. We are also collecting data on our experience with PM use, tolerability of home monitors, and pretest probability of OSA. We report this latter data here, review current military policy on ambulatory monitors, and suggest an algorithm for PM use.

## Methods

A multi-institutional, prospective clinical trial is being conducted at San Antonio Military Medical Center, Darnell Army Medical Center, Reynolds Army Community Hospital, Bayne-Jones Army Community Hospital, Landstuhl Regional Medical Center, Madigan Army Medical Center, and Tripler Army Medical Center. Subjects are being recruited from young adult patients scheduled to undergo tonsillectomy by the Ear, Nose, and Throat service and then evaluated for OSA before and after surgery using a portable home monitor. This current report is a nested, descriptive study within the larger clinical trial in order to discuss our experience using the portable monitor in military subjects so far. The research protocol was approved by the Institutional Review Board at each medical facility.

An informed consent process was undertaken and documented for each subject. Subjects were recruited from adult patients aged 18 and older who were scheduled to undergo tonsillectomy for chronic, recurrent tonsillitis and who had no prior known diagnosis of OSA. We hypothesized that at least some of these patients would have underlying sleep apnea, which could be diagnosed on portable home monitoring. We also hypothesized that subjects with OSA would have higher pretest probability of disease based on questionnaires. We excluded subjects if they had a prior history of upper airway surgery or significant nasal pathology that impaired nasal breathing. Subjects who consented to the project were given the Epworth Sleepiness Scale (ESS)6 and questions about snoring from the Berlin Questionnaire before scheduled surgery.7 They were then given an ambulatory sleep monitor, the ApneaLink Plus (ResMed Corp, San Diego, California), to use before the planned tonsillectomy. Subjects repeated questionnaires and home

monitor use after surgery to report changes, and these surgical outcome data will be reported elsewhere. Here, we report our experience with PM use, subject characteristics, prevalence of OSA, and implications for pretest probability of disease.

Data collected for this study included patient characteristics, ESS and Berlin scores, and the Apnea–Hypopnea Index (AHI). The AHI was calculated by a board-certified, fellowship-trained sleep physician (William C. Frey or Peter D. O'Connor) by manually reviewing the ApneaLink Plus signal data. Respiratory events were scored using definitions established by the American Academy of Sleep Medicine and hypopneas were scored using the “recommended” definition.8 OSA was defined as an AHI greater than or equal to 5. We defined high pretest probability of disease if a subject had an ESS score of greater than or equal to 8 and a positive Berlin snoring score (Berlin category 1 score greater than or equal to 2). We chose to use the ESS and the snoring section of the Berlin because we felt that EDS and snoring were the symptoms most indicative of OSA, and that these validated surveys would be a systematic way to document symptoms in all of our subjects.

Collected data were then analyzed to describe the success in using the monitors and to describe subject characteristics and PM results. Number counts, means with SD, and proportion calculations were used to describe the data. A $\chi 2$ analysis was used to compare proportions and a Mann–Whitney test was used to compare means. All statistical analyses were performed using Stata version 11.0 software.

## Results

One hundred one subjects undergoing tonsillectomy were enrolled into the study and attempted to use the portable monitor. Four subjects (4.0%) could not tolerate use of the machine and were withdrawn from the study. Twelve subjects (12.0%) used the PM, but the machine did not record sufficient data because the evaluation period was too short. Of these 12 subjects, 9 chose not to repeat the sleep study and so were withdrawn. The other 3 chose to repeat use of the PM and all were successful at obtaining usable data the second time. Eleven subjects were withdrawn because they failed to use the machine at all or their surgery was canceled. Thus, the total number of subjects completing the study was 77 (76.2%).

The demographic characteristics of the patients completing the study are listed in Table I . There were no significant differences between those completing the study and those who were withdrawn. Based on the AHI calculated by the sleep medicine physician, 15 were positive for OSA (range AHI 7.0–56.4 per hour). This equals a prevalence of OSA of 19.5% in our population. Table II lists the characteristics of the subjects based on OSA status. The OSA group contained a larger percentage of males and had a higher mean body mass index (BMI) level. A total of 37 subjects who completed the study had a high pretest probability of disease. Those

with OSA were much more likely to have a high pretest probability than those without OSA. Based on our findings, Figure 1 represents a suggested algorithm for PM use before deployment.

## Discussion

OSA is prevalent among service members and can be as frequent in the military as in civilian counterparts.9 Even younger, nonobese service members can have significant, symptomatic OSA.10 Our study confirmed a high rate of OSA in a population of service members and dependents that have demographic characteristics similar to a group of predeployment soldiers. The literature reports cases of how OSA can impact military missions. Fatigue from sleep apnea caused a shipwreck in one group of loudly snoring conscripts5 and two cases of OSA presented during infantry field exercises as “snoring so loud as to risk betraying the unit's position.”11 As Powers et al4 have stated “The impact [of OSA] on individual readiness for deployment, and the potential degradation of performance in critically important military duties, often results in tremendous expenditures of training resources, time, and expertise to replace the military member with a suitable substitute or release of the individual from active duty.” Untreated, symptomatic OSA of any severity is currently nondeployable, and any service member who uses continuous positive airway pressure (CPAP) therapy may require a waiver to allow deployment. To avoid negative impact upon the mission and unit readiness, it is critical to identify patients with OSA early in the screening process.

An in-laboratory PSG is often quoted as the current accepted gold standard for diagnosis of OSA and for initiation of treatment with CPAP.12 Whether a home monitor is equivalent to a laboratory-based PSG in screening for OSA is debatable in the literature and considerable controversy exists. In this study, we chose to use the ApneaLink Plus ambulatory monitor, which is a type 3 sleep monitor. A standard PSG incorporates the full range of cardiorespiratory and sleep stage recordings with an attendant present, and can diagnose and differentiate between various sleep disorders. A typical type 3 portable monitor includes 4 channels—heart rate, oxygen saturation, respiratory chest movement, and nasal airflow. Type 3 portable devices can differentiate central from OSA and diagnose Cheyne–Stokes respiration, but do not record electroencephalography data and thus cannot calculate sleep stages or respiratory effort-related arousals.13 The major advantage to type 3 devices is self-application of monitor leads without the need for an attendant and comfort of use within an individual's home.

The conflicting opinion about portable versus more comprehensive sleep studies is based in part on whether home monitors are as accurate as PSG. In several studies, AHI outcomes of type 3 home monitors have been shown to compare well to PSG.14–18 Ng et al compared 50 consecutive subjects using the Apnea Link device with a diagnostic in-laboratory study. They documented high sensitivity and specificity (0.977 and 1.0, respectively, at AHI ≥ 10 and 0.969 and 1.0, respectively, at AHI ≥ 20).17 Some reports raise concerns that there can be variability in results, however, especially with mild to moderate OSA.19 Some believe there is a

systematic underestimation of the AHI as well.13 Ghegan et al20 performed a systematic review of portable monitors versus in-lab studies on 11 articles comparing the main outcome of the respiratory distress index (RDI, a surrogate for AHI) between the two. Their meta-analysis did demonstrate that the RDI on home monitors tended to be 10% lower on average than the formal sleep study. A commentary on this article notes that this 10% difference is not a clinically meaningful change.21 In our study, changing the AHI by 10% would not have resulted in any statistical difference in the severity of OSA.

Although the debate continues on the official guidelines on PM use, type 3 monitors are currently an acceptable method of diagnosing OSA. The biggest advantage over formal PSG can be considered rapid results with use. Use of portable monitors may indeed decrease the burden of using a sleep center bed, while providing faster results, convenience for the patient, and possibly better sleep quality.17 Long wait times for in-laboratory PSG result when demand exceeds the capacity of sleep laboratories to provide service for patients suspected of having OSA.22 Wait time for an in-laboratory PSG at San Antonio Military Medical Center was as long as 2 months in 2011. Physicians within Veterans Affairs and military hospitals were informally surveyed and most expressed interest in being able to obtain their own portable sleep studies because of the time and cost involved in standard in-lab PSGs.23

In our study, portable monitor use was tolerated well by the subjects. Only a very low percentage of patients withdrew because of inability to tolerate the PM machine. We did note that 12.0% of subjects did not have enough recorded time to generate an AHI after first use. Most of these subjects report that the monitor fell off during the night. All subjects who had insufficient data who were willing to repeat use of the machine were successful at obtaining a valid AHI the second time. Berry et al24 also report the need to repeat use of a portable monitor one time in cases where not enough data is recorded after the first use. Our rate of insufficient data recording is similar to other studies utilizing portable monitors. In a series of 176 primary care adult patients using the Apnea Link monitor to diagnose OSA, 10.8% of subjects had insufficient data recording after first use.25 Therefore, the PM we used was able to obtain enough data for the large majority of subjects in our study after first use and for all subjects who repeated use of the monitor when it was necessary. The remaining withdrawal rate in this study can be contributed to subject interest in continuing participation in the research project and not to device tolerability or technical problems.

Although our study confirms existing data about PMs, it demonstrates for the first time high success in using these monitors in a military population. A military setting is unique because of the implication for use during predeployment assessments, when rapid diagnosis is crucial to making decisions about whether a service member is healthy enough to deploy. However, military health care does not widely utilize these devices during predeployment assessments, and there is no official military policy regarding their use. In order to adopt a policy, home monitors could be considered when a patient does not have significant medical problems, such as pulmonary disease, neuromuscular disease, or congestive heart failure, or other known sleep conditions, such as central sleep

apnea, periodic limb movement disorder, circadian rhythm disorders, or narcolepsy. For patients with these comorbidities, an in-laboratory PSG should be obtained.26 PMs are reasonable for deploying active duty service members since it is rare for them to have limiting comorbid conditions. Additionally, according to the 2007 Portable Monitoring Task Force of the American Academy of Sleep Medicine, the current use of PMs is for diagnosis of OSA when a patient has symptoms of sleepiness and has a high probability of disease.26 In other words, portable monitors are not used to exclude sleep apnea but rather are useful when the pretest probability of disease is sufficiently high, which reduces false negative results.27 The military therefore would have to adopt a method of screening predeployment service members in order to identify those who have high pretest probability of OSA.

Ayas et al28 determined that an ambulatory monitor is advantageous if a clinician deems that a symptomatic patient has a probability of having OSA of greater than 0.47. However, what constitutes a high pretest probability can be subjective. History taking usually guides identification of patients most at risk for OSA. Snoring, choking, or gasping for air while asleep, witnessed pauses in breathing, un-refreshed sleep, EDS, and impaired concentration all represent symptoms that suggest OSA. Validated questionnaires have sought to objectify these symptoms. For sleepiness, the ESS is one method of calculating severity of EDS. Mulgrew et al27 found the prevalence of moderate to severe OSA (AHI ≥ 15) was 49% among patients with an ESS score of 10 or greater. Another validated survey, the Berlin Survey, has been noted to have a sensitivity of 86%, specificity of 77%, and positive predictive value of 89% for OSA.7 Many authors favor a combination of symptoms and use of questionnaires to determine those most at risk for OSA.29

We chose to use a combined survey approach for determining high pretest probability, utilizing both the ESS and the snoring questions from the Berlin Questionnaire. However, deciding which parameters to use for defining high probability for OSA can be challenging and there are no accepted criteria. One popular method, for instance, uses age, BMI, gender, and snoring to stratify risk of OSA as low, moderate, or high.30 Our questionnaire-based approach to screen for high pretest probability, summarized in Figure 1, does not utilize age, BMI, or gender. However, our population of subjects is young and we found presence of OSA even among nonobese service members. With use of a questionnaire-based method, we found that those with OSA still had a much more statistically significant chance of having a high pretest probability than those subjects without sleep apnea. Therefore, the algorithm proposed in Figure 1 would have been sufficient for diagnosis in 12/15 subjects with OSA, and these subjects would have avoided wait times associated with an in-lab procedure. This could lead to earlier decisions about whether to deploy a service member. It must be noted that after testing, it is essential to have appropriate follow up to either discuss therapy options or to determine if further sleep evaluation is warranted.

We recognize some limitations to this study. First, this is a nested study that is not specifically evaluating predeployment service members. Also, our population of patients with large tonsils may be at increased risk of having OSA. The results may reflect our tonsil population rather than a group of predeployment service members, who may not have similar rates of sleep apnea. Given the

incidence of disease in the general population, however, one would expect to find cases of OSA even among young, otherwise healthy service members with symptoms. Another limitation is that we did not compare our PM data to in-lab data. This prevented us from analyzing our PM results with the current gold standard. A follow-up study could be done looking at what percentage of high-risk patients who tested negative for OSA on a PM would also test negative on an in-lab PSG. This might be impractical to perform in a large group of subjects given the already long wait times associated with sleep center consultations. We also decided on using an ESS score of 8 combined with a positive Berlin result as a surrogate for high pretest probability. We recognize that these criteria are subjective and future studies should be done to look at the best measures for disease in military populations.

Conclusions

The group of subjects we studied in this trial is a good representation of a military population at risk for sleep apnea. We demonstrate that it is feasible to detect a large percentage of patients with OSA, of various military ranks, by using questionnaire-based screening for high pretest probability. PM monitor use was tolerated very well by subjects. PMs were also successful at diagnosing OSA, within a range of AHI that was mild to moderate in severity. This group of patients allowed us to simulate soldiers without previous diagnosis of OSA who could be atrisk, such as would occur during screening in a predeployment medical readiness assessment process. Although home monitors are still not currently the gold standard of care, they may permit earlier decisions to be made about service members before they deploy.

BACK TO TOP

## The feasibility and validity of ambulatory self-report of psychotic symptoms using a smartphone software application

BMC Psychiatry
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Abstract

Background

Semi-structured interview scales for psychosis are the gold standard approach to assessing psychotic and other symptoms. However, such assessments have limitations such as recall bias, averaging, insensitivity to change and variable interrater reliability.

Ambulant, real-time self-report assessment devices may hold advantages over interview measures, but it needs to be shown that the data thus collected are valid, and the collection method is acceptable, feasible and safe. We report on a monitoring system for the assessment of psychosis using smartphone technology. The primary aims were to: i) assess validity through correlations of item responses with those on widely accepted interview assessments of psychosis, and ii) examine compliance to the procedure in individuals with psychosis of varying severity.

Methods

A total of 44 participants (acute or remitted DSM-4 schizophrenia and related disorders, and prodromal) completed 14 branching self-report items concerning key psychotic symptoms on a touch-screen mobile phone when prompted by an alarm at six pseudo-random times, each day, for one week. Face to face PANSS and CDS interviews were conducted before and after the assessment period blind to the ambulant data.

Results

Compliance as defined by completion of at least 33% of all possible data-points over seven days was 82%. In the 36 compliant participants, 5 items (delusions, hallucinations, suspiciousness, anxiety, hopelessness) showed moderate to strong (rho 0.6-0.8) associations with corresponding items from interview rating scales. Four items showed no significant correlation with rating scales: each was an item based on observable behaviour. Ambulant ratings showed excellent test-retest reliability and sensitivity to change.

Conclusions

Ambulatory monitoring of symptoms several times daily using smartphone software applications represents a feasible and valid way of assessing psychotic phenomena for research and clinical management purposes. Further evaluation required over longer assessment periods, in clinical trials and service settings.

Keywords

Mobile-phone, Psychosis, Assessment, Ambulant, Schizophrenia

Background

Schizophrenia is distressing and disabling to the individual [1], with an associated cost in the United Kingdom of around 6.7 billion pounds each year [2]. Clinical outcome is usually poor despite treatment, with 80% relapsing by 5 years after the first episode. The major need is for better treatments. Treatment development is slow in this area, with a high rate of failed clinical trials. Currently, we assess treatments by asking patients to recall symptoms over the last 7-28 days, using widely-used semistructured symptom assessments such as the Positive and Negative Syndrome Scale (PANSS [3]) and Calgary Depression Scale (CDS [4]). This introduces bias and averaging, thus clinical information is lost. In addition, standard rating scales require training of raters to ensure high reliability, often difficult to achieve and maintain in multisite studies. For instance, a decrease in between-rater intraclass correlation from 0.9 (“high”) to 0.7 (“acceptable”) on PANSS full-scale score will reduce the power of a study to show an effect from 90% to 72% [5,6]), increasing the risk of a Type 2 error and a failed trial. An advance is needed in the real-time documentation of psychotic symptoms.

One under-explored possibility is that of patient self-rating of symptoms. There is scepticism as to the validity of self-report measures of psychosis. This view is often motivated by knowledge that cognitive deficits [7] and lack of insight [8] are common in patient populations. However, moderate concordance has often been observed between selfreport measures and clinician based ratings of psychosis, which has been demonstrated in a range of symptom domains. This includes delusions [9], hallucinations [10], and negative symptoms [11]. Self-report measures may be a more time and cost efficient method of assessing psychosis than clinical interviews, as they do not require the presence of a trained assessor. Thus, self-report measures may be the more attractive option for clinical assessment.

Over the past decade Personal Digital Assistants (PDAs) have been adapted for self-report symptom monitoring in individuals with severe mental illness [12]. Studies evaluating PDAs have shown low rates of drop-out in community dwelling individuals with psychotic disorders [13-15]. For example, Granholm and colleagues [13] found that 87% of patients were compliant to PDA based momentary assessment as defined as completing at least four out of 28 data-points. Other studies have observed similarly low rates of drop-out when using more conservative definitions of compliance (eight out of 28 data-points) [15].

PDAs are offline systems and whilst the data is collected in the real world it cannot be assessed until brought into the laboratory/clinic and downloaded. Assessing data in vivo is desirable in that it could help to facilitate earlier and more immediate intervention, which in turn could help to reduce relapse, self-injury and the need for unscheduled acute care.

Automated and personalised feedback could help clinicians to devise and review treatment strategies prior to consultation allowing for more effective care. An appropriately enabled mobile phone may have the advantage that people are accustomed to carrying and recharging it and are often familiar with the technology. Software applications are also easily uploaded to participants‟ own smartphones ensuring that the individual does not have to carry with them an additional device. In a recent Ofcom report in the United Kingdom, 27% of adults and 47% of teenagers currently owned a smartphone [16]. With advances in mobile phone technology PDAs are becoming increasingly obsolescent.

The first objective of this study was to evaluate and validate new mobile phone based selfreport assessment scales for psychosis against the PANSS and the CDS, both widely used retrospective interview assessments of psychotic and related symptoms and considered to be benchmark scales accepted by regulatory authorities in clinical trials. Scales were specifically developed for purpose-built smartphone assessment software (i.e. ClinTouch) in order to monitor psychotic symptoms in real time. The second objective was to assess feasibility and acceptability to patients with serious mental illness, examining levels of compliance and drop-out to the procedure in individuals at different stages of psychosis. We also aimed to examine the internal consistency of the scales and their instability over time.

In order to gauge the feasibility of installing this software onto participants own phones, we assessed the extent to which participants used mobile-phone technology in their everyday lives. In order to assess safety, in that that this approach did not cause distress, we assessed “reactivity” to the method as reported by participants at the end of sampling.

Thus, the study had two main hypotheses. First, that symptom data collected over a smartphone software application would show good correlations with corresponding data collected by conventional, gold standard rating scales. Second, high levels of compliance and low dropout from smartphone based assessment would be possible in individuals at different stages of psychosis (ultra-high risk, acute and remitted). In this study we also predicted that the self-report scales would show high internal consistency (α coefficients), but be sensitive to change, as represented by instability across time-points. No predictions were made as to participant‟s level of phone use in their everyday lives.

## Method

### Participants

In order to fully assess usability and the validity of collected data, we chose three clinical subgroups of patients who represent different severities and stages of the disorder and are commonly the focus for clinical trials. Group one consisted of patients meeting

the criteria for a Diagnostics and Statistical Manual (Fourth Edition; DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, delusional disorder or schizophreniform disorder and were in partial or full remission, as defined by having mild or absent positive symptoms and being on stable antipsychotic medication for at least three months. Group two consisted of acutely psychotic patients with the same diagnoses, but who were within four weeks of starting, restarting or changing their medication because of worsened symptoms or within four weeks of a hospital admission. Group three comprised of individuals who had met criteria for being at ultra-high risk of developing psychosis at some point during the past year ("prodromal") according to the Comprehensive Assessment of At Risk Mental State [17,18] and who were not currently on antipsychotic medication: 50% of these participants still met the CAARMS criteria for the ultra-high risk (UHR) mental state at the time of taking part in the study. Organic and substance induced psychosis were exclusion criteria for all three groups. Full demographic and clinical information is provided in Table 1. Eligible participants were prospectively recruited into the three groups until each group contained 12 subjects who had managed to complete at least 33% of the 42 data entry points possible during the six consecutive days of testing in accordance with momentary assessment studies.

Equipment

The assessment software was developed specifically for touch screen Android mobile phones. Android is an open source operating system developed by Google that runs on a range of phones from different manufacturers such as HTC, Samsung and Sony Ericsson. Android devices are becoming increasingly widespread in the mobile phone market and it is expected to be the most popular mobile operating system by the end of 2011 (http://www.gartner.com/it/page.jsp?id=1622614). For this trial we chose to use the Orange San Francisco device, although the software was developed to work with any compatible Android based phone.

Measures

Semi-structured interviews

The "gold standard" Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale (CDS) assessments were administered to each subject at baseline, and again after completion of the six day data collection period. The PANSS (Kay et al., 1987) is a semi-structured interview where a range of positive (7 items), negative (7 items) and general symptoms (16 items) are rated on a seven point scale (1 = absence; 7 = severe). Its validity and reliability have been demonstrated (Bell et al., 1992; Kay et al., 1987). An experienced researcher (JPC) was blind to mobile assessment scores during the debriefing interview (unblinded once).

Excellent inter-rater reliability was demonstrated with an independent rater rating 12 (5 acute, 3 remitted and 4 UHR) of the audio-recorded PANSS interviews (Spearman‟s correlations, PANSS positive subscale, rho = .91; negative, rho = .82; global, rho = .81; total, rho = .79).

The CDS assesses depression and related manifestations, and contains 9 items scored from absent (1) to severe (4). It has good internal consistency and convergent validity with other measures of depression, and effectively discriminates the presence or absence of co-morbid depression [4,20]. In this study the CDS was used to assess the previous week in order to cover the 7 day time sampling procedure.

Mobile phone assessment questions

The mobile phone assessment items were designed to be equivalent to 12 items of the PANSS and 2 items of the CDS, and are displayed in Additional file 1. The items were selected to give an appropriate range of key positive and mood symptoms. Participants were required to respond on an analogue scale indicating the degree to which they agreed or disagreed with statements relating to their symptoms since the last entry (see Figure 1). This was, therefore, not an experience sampling study, where questions would have related to the present moment in time. Although these reports were retrospective, the time between an event and its recollection was minimal, reducing the effects of memory bias. Retrospective ambulant assessment may better capture infrequent, but nevertheless important, clinical phenomena that would otherwise be missed at the time of entry. For example, assessments at the time of entry may miss perceptual abnormalities in individuals at UHR of psychosis (unpublished observation). The first entry of the day related to the period of time since wakening.

In order to reduce the length of time taken to complete the items, these were divided into two sets, displayed at alternative time-points. Guilt, hopelessness, depression, social withdrawal, conceptual disorganisation, excitement and hallucinations were assessed in set one, whereas anxiety, grandiosity, hostility, somatic concern, guilty ideas of reference, paranoia and delusions were assessed in set two. The allocation of scales to the two sets was based on the need to assess overlapping symptom domains (e.g. paranoia and delusions) at the same timepoint and to keep the number of items balanced. Some of the self-report scales were branched so that the use of certain items was contingent on the participant‟s previous response. The stem and branching questions related to the constructs measured on the PANSS and the CDS items, while being compatible with self-report. Thus, 15 to 30 questions were presented in set one and 11 to 31 questions were presented in set two.

When developing frequently repeated symptom scales it is necessary to keep the number of items to a minimum in order to reduce burden on participants [21]. However, a wide range of delusional beliefs have been reported in patient populations [22] making this problematic.

Therefore, ClinTouch was equipped with a „delusion‟ menu on the admin page, which allowed the researcher to personalise which delusions a participant was currently experiencing based on the initial PANSS interview and reports by clinical staff. The selected delusion then populated the questions that were administered, which were scored for preoccupation, distress and behavioural impact (see Additional file 1). A maximum of two delusions could be entered for each participant. For participants who were experiencing three or more delusions those two associated with the greatest conviction and distress were entered into the ClinTouch software.

The frequency of different delusions were: „I have felt like other people could read my thoughts‟ (**n**=6), „I have felt like my thoughts were being controlled or influenced‟ (**n**=6), „I have felt like I could read other people‟s thoughts‟ (**n**=4), „I have felt like people were not what they seemed‟ (**n**=2), „I have felt like things on the TV, radio or magazines had a special meaning for me‟ (**n**=2) and „I have felt like there was a conspiracy against me‟ (**n**=2).

Two items were included on the mobile phone to assess safety, or “reactivity” to the methodology [23]. These items were „keeping the diary has influenced my thoughts‟ and„keeping the diary has influenced my mood‟. Important to note is that these questions did not measure the direction of the reactivity (i.e. whether it made someone feel better or worse).

Procedure

The study received approval from the North West One National Health Service Research Ethics Committee (ref: 11/H1017/3). The purpose of the briefing session was to obtain written consent, complete the initial PANSS and CDS interviews, and run training in the ClinTouch software (including practise questions). At the end of this session, participant number, group identity (acute, remitted and UHR), alarm volume, and delusion type were also entered onto the device via a password protected admin screen

The assessment procedure started on the morning following the briefing session. The ClinTouch software caused the mobile phone handsets to emit an alarm and vibrate at six pseudo-random times of the day (generated by a random number generator stratified within set epochs of time at least one hour apart) between 9:00 and 21:00 hours. It also triggered a „start questions‟ icon on the touch screen. The participant was given the option to trigger a repeat alarm 5 minutes later if they were occupied (a „snooze function‟). All participants had 15 minutes from the initial alarm within which to complete the questions. A pseudo-random, as opposed to fixed, sampling schedule was thought to be advantageous since it facilitated the assessment of a wide range of situations

and times of the day and prevented individuals from greatly changing their activities in order to account for completing the questions [23]. Forced entry times were also expected to reduce response bias (e.g. only completing the diary when asymptomatic). The researcher telephoned participants once or twice during the week (participant‟s preference) to gauge acceptability, offer encouragement, and remind them to charge the device. Participants were able to access all applications on the mobile phone devices (e.g. games, camera), but at this proof-of-concept stage of the study the devices had no wireless connectivity. Important to note is that the lack of connectivity made no difference to the way that the software operated from a user perspective.
Upon completion of the 7 day momentary assessment procedure the researcher met with the participant to re-administer the PANSS and CDS, and to assess general mobile phone usage outside of the sampling procedure. UHR individuals were also assessed with the CAARMS in order to ascertain whether they currently met this criteria.

Statistics

All analysis was performed in Stata 10.0 [24] and SPSS 15.0 [25]. First, the analogue scales for each mobile-phone assessment item were converted to 7-point Likert scales by the computer software for the purpose of the analysis. Grandiosity item 1 („Compared to the average person, I am: (analogue scale: worse - better)‟) was transformed so that only positive (grandiose) appraisals of oneself contributed to the gradient of the score (i.e. 1-4 coded as 1, 5 coded as 2, 6 coded as 3, 7 coded as 4).
In order to assess the multifaceted nature of the constructs measured by each PANSS scale, there were multiple ambulant assessment items. For example, the Anxiety momentary assessment scale consisted of four items. The mean of these items was then calculated to constitute the individual‟s momentary assessment score for that symptom domain or scale (e.g. the mean of items 1, 2, 3 and 4) at a particular time-point. In some cases, in order to better correlate with the PANSS, symptom scales were supplemented by ratings on other scales. The delusion mean score was calculated from the delusion items, and the mean score of the grandiosity, somatic concern and suspiciousness scales (e.g. item 1 + item 2… + grandiositymean + somatic concernmean + suspiciousnessmean). Reports of grandiosity, somatic concern and suspiciousness all inform the rating of the delusion item on the PANSS interview. The depression scale comprised of the depression items and the mean hopelessness score (i.e. item 1 + item 2… + hopelessnessmean). Feelings of hopelessness are part of the criteria for scoring a 4 or greater on the PANSS depression scale (item g6).

All analyses were performed at a person-level. Therefore, a mean symptom score was calculated for each individual from across all available data-points, resulting in a single score for each participant. Logistic and regression models (Enter method) were carried out to establish interview and demographic predictors of drop-out (completion of ≥33% of all available data-points) and diary entries completed respectively. As the person level mean symptom scores were positively skewed, non-parametric Spearman‟s correlations established the degree to which mean diary scores resembled their corresponding interview subscales.

Cronbach‟s α was used to calculate the reliability across items for each scale. In order to measure the instability of the different constructs, the mean squared successive difference (MSSD) and standard deviation (SD) were calculated from across all available data-points for each individual [26], including data point across days and those which were not sequential due to missing time-points.

The MSSD and SD have been recommended as valid metrics of instability, which are widely used in clinical research [27].

## Results

### Adherence to the methodology

Initial verbal approach to participate was made by a member of the clinical care team and about 50% of those approached declined to take part. Of the 51 patients who agreed to be contacted about the study and had their contact details passed on to the research team, four subsequently declined, two were ineligible and one could no longer be contacted.

Compliance to the methodology was defined as completing at least 33% (14 or more) of all possible (42) entries. In all, 44 participants consented to and entered the study to ensure that 36 met this compliance criterion after 7 days: in other words, 82% of participants met the compliance criterion. Six acute and two remitted patients with psychosis failed to meet this criterion (Mean age: 31.5 (SD; 11.1), all male). Logistic regression analysis was performed to examine whether positive, negative and general subscales on the PANSS (prior to sampling), CDS total score (prior to sampling), or age significantly predicted whether an individual was compliant with the methodology. Positive symptom subscale severity was the only significant predictor (OR = 0.68, p = .033, CI: 0.48 – 0.97). The 8 non-compliant participants are excluded from all analyses subsequently presented in this manuscript.

A high number of entries were completed by the 12 acute (Min = 14, Max = 41, Mean = 28.5, SD = 8.1), 12 remitted (Min = 14, Max = 40, Mean = 29.5, SD = 9.3) and 12 UHR (Min = 21, Max = 38, Mean = 31.1, SD = 6.6) participants who were compliant with the procedure. Thus, on average, the aggregated sample completed 31.1 of all possible data-points (72%). A one-way ANOVA showed these differences to be non-significant across groups (F (2,35) = .312, p = .734). Multiple regression analysis was performed to investigate whether age, gender, PANSS subscales, and CDS total predicted the total number of diary entries completed by each individual. There were no statistically significant predictors.

### Reactivity to the method

Reactivity (changes in thoughts or emotions) to filling in the questions was greatest in the acute group (mean: 3.6 (SD: 2.4)), and greater in the remitted (mean: 2.9 (SD: 1.5)) compared to UHR individuals (mean: 2.4 (SD: 1.7)). A Kruskall-Wallis test showed this difference to be statistically non-significant (x2 = 3.351 (df: 2), p = .187). Regression analysis was used to assess whether positive, negative or general symptoms on the PANSS, or CDS total score, significantly predicted reactivity across all three groups. Only negative symptoms predicted greater reactivity to the method (β =.54, p = .001).

Correlation between momentary assessment and interview subscales

Summary statistics for the mobile-phone assessment items and clinical interviews are provided in Table 2. The standard deviation (SD) score reported in this table represents variability between individuals‟ mean scores (not within individual variability). The CDS item 2, guilty ideas of reference, was only ever endorsed by two participants and was therefore not analysed.

The strength of the associations between the diary and corresponding interview subscales varied considerably (Table 2).

Hopelessness, delusions, anxiety, hallucinations and suspiciousness diary items showed strong Spearman‟s correlations with the corresponding items on the CDS and the PANSS (rho > .60). Moderate and still statistically significant correlations were also observed for grandiosity, depression, guilt, and somatic concern (rho >.35). However, passive and apathetic social withdrawal, hostility, excitement, and cognitive disorganisation were not significantly correlated with their corresponding PANSS subscales.

The internal consistency and instability of the scales

As can be seen in Table 2, the alpha scores for each of momentary assessment scales were high suggesting good internal consistency. The MSSD and SD scores for each momentary assessment scale are displayed in Table 3. A greater score represents greater instability across time. The delusion instability score was only calculated in individuals who triggered the delusion questions at briefing. All momentary assessment scales showed some instability across time. Passive apathetic social withdrawal was the least stable subscale, followed by excitement, conceptual disorganisation and anxiety. Delusions and grandiosity were the most stable self-report scales.

General phone usage of the sample

A series of questions were asked to gauge the feasibility of using the ClinTouch software on participants‟ own phones. Of the sample of 36, 83.3% currently owned a mobile phone, and 44.4% owned a smart phone (30.6% with a touch screen). Phone use included

individuals who were acute (66.7%), remitted (91.7%) and UHR (91.7%). 63.9% of individuals with mobile phones reported that they kept these on them all or most of the time, with an identical number usually or always taking their phones with them when they went out. The sample had owned a mean of 8.3 (SD = 7.0) mobile-phones devices. 86.1% of the current sample reported that they would buy a new phone in the future.

## Discussion

This study attempted to examine the validity and feasibility of a self-report scale for assessing psychotic symptoms on appropriately enabled mobile phones. The results suggest that the methodology is both feasible and acceptable across different stages of psychosis.

Additionally, the data support the validity and reliability of several of the momentary items, suggesting that they pose a useful alternative to traditional symptom assessment.

The number of individuals dropping out of the study was relatively low across remitted and UHR samples, although slightly elevated in acute patients, where a third of individuals were non-compliant. This may explain the finding that positive symptoms significantly predicted non-compliance to the procedure. This supports the notion that momentary assessment is a relatively demanding approach, to which certain more symptomatic and chaotic patients may have difficulty in remaining compliant [21]. Thus, in acute settings it may be beneficial to adapt the momentary assessment procedure (e.g. sampling rate, item number) to individual‟s preferences and needs, or use an alternative method of assessment.

In compliant individuals, the number of assessment occasions was relatively high and similar to past momentary assessment research using PDAs in this population. For example, Swendsen and colleagues [15] observed an identical completion rate of 72% of all data-point completed, whereas Granholm and colleagues [13] found this to be 69%. In our study the number of entries was non-significantly different between the groups, suggesting that although a subgroup of acute patients struggled to complete the minimum number of entries, the majority were just as able to comply with the procedure as those with more attenuated symptoms. It should be noted that although compliance was high in this study rates of refusal to initially take part could not be assessed. Furthermore, socioeconomic status and reading ability were not considered, which may have predicted levels of non-compliance.

Reactivity to the methodology was minimal across the groups, although it was slightly elevated in individuals with greater levels of negative symptoms. This may explain why these symptoms have been found to predict drop-out in experience sampling studies

(unpublished observation). Important to note is that reactivity could not be assessed in individuals who dropped out of this study and did not complete any diary entries. It is possible that greater levels of reactivity may be observed in non-compliant participants.
In line with the hypotheses, correlations with PANSS and CDS subscales were mainly significant, although there was considerable variability. Positive symptom scales (i.e. delusions, hallucinations, grandiosity, somatic concern and suspiciousness) generally showed moderate to strong correlations with their corresponding PANSS scales. Affective symptoms, including hopelessness, anxiety, guilt and depression, also significantly correlated with the interview measures. Therefore, ClinTouch appears to collect data which is comparable to traditionally used, gold standard assessments of psychotic symptoms and mood.

Passive apathetic social withdrawal, excitement, hostility and cognitive disorganisation items showed weak and non-significant correlations with their corresponding interview scores, requiring further consideration. There are several possible reasons for this finding. Most important is that the equivalent PANSS item ratings are based largely on observable behaviour during the interview, often supplemented by the reports of clinical staff and family members. Replicating this in a self-report item is a challenge. This is not to say that either holds a more valid or clinically useful viewpoint, but rather that they assess different constructs. Also, hostility and excitement represent socially undesirable behaviours, which patients may not associate with themselves or may wish to underplay in self-report measures.

Finally, there was a limited range of scores observed on the apathetic social withdrawal and cognitive disorganisation PANSS subscales, which may have attenuated the correlations with the momentary assessment scales.

All of the mobile phone self-report scales showed instability (ie fluctuations) across time as shown by high within subject MSSD and SD scores, suggesting that they were sensitive to subtle shifts in symptomatology. Indeed, the mood scales (i.e. anxiety, depression and guilt) showed equivalent or greater levels of instability than typically employed experience sampling scales [27]. Delusions and grandiosity were the most stable across time potentially suggesting that these reflect relatively fixed and inflexible belief systems.

Passive apathetic social withdrawal showed the greatest instability, perhaps representing changes in the individual‟s inclination to be around others. All of the self-report scales also showed good internal consistency.

The advantages of using technology to monitor mental illness have recently been documented [28,29]. Ambulant monitoring provides detailed information about an individual‟s symptoms across a variety of situations and times of the day. This could generate discussion points for consultation; identify „relapse signatures‟; and highlight momentary symptom triggers. It could also be used to monitor real-time acute phase medication treatment effects in the early stages of intervention [30]. This is important given that most clinical improvement is now known to occur within the first 7-days after receiving antipsychotic treatment [31,32].

Furthermore, mobile assessment techniques can be adapted for use alongside psychosocial intervention [33]. For example, person-tailored interventions could be triggered when an individual‟s symptom score reaches a certain threshold or to facilitate „homework‟ [34]. In research, it will also potentially allow better clinical phenotyping, and stratification for clinical trials.

Perhaps the greatest strengths of ClinTouch are that it offers automatic wireless uploading of clinical information to a central server and can be installed on patients‟ own phones, thus obviating the need to carry a special purpose device. Furthermore, smartphone technology may be more user-friendly and time-efficient than text-based systems [35]. We observed that the majority of this sample currently owned and regularly used mobile phone technology, many of which were smart phones. With advances in technology it is likely that advanced mobile phones will become increasingly affordable and widespread, and this will make it a viable option for clinical assessment within clinical services. Future research will need to evaluate the merits and pitfalls of this approach.
Previous research in the area of telehealth and telecare devises suggests a need for deeper understanding of how ClinTouch is used in practice to identify the factors that facilitate implementation of this device. As the field of new technology in mental health aspires to moves beyond demonstration and towards the embedding of devices such as ClinTouch in everyday clinical practice, there is a need to engage methods and sub-studies that are able to describe the processes, identifying facilitators to context specific and successful implementation of telecare [36]. Qualitative methods are being used to consider the social practices behind the integration and incorporation of the ClinTouch technology. Understanding their interactions with professionals and the synergy or otherwise with clinical expectations will inform its future use.

Conclusions

ClinTouch is a valid form of self-assessment, which could facilitate the real-time monitoring of symptoms in schizophrenia in research and clinical management settings. In addition to overcoming the constraints of rater training and limited reliability, recall bias and averaging, it potentially offers advantages over semi-structured interview administered scales allowing finer-grained analysis over briefer time periods, with potential inclusion of external contingency data, diurnal and short-term variability and adding in of other behavioural data gathered by the same device, such as sleep pattern and activity. Limitations currently include restricted ability to assess negative and behavioural symptoms. Further pilot testing is required to assess whether it can be used to monitor symptoms over a longer period of time or treatment effects.

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## The Effects of a Human Patient Simulator vs. a CD-ROM on Performance

Military Medicine
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Abstract

Objectives: Military health care personnel need to have skills relative to caring for patients on the battlefield. No studies have compared the two teaching strategies of using the human patient simulator (HPS) and a CD-ROM in caring for combat injuries. The objective of this study was to determine if there were statistically significant differences in HPS and CD-ROM educational strategies relative to caring for patients who have trauma. Methods: A pretest/post-test prospective experimental design was used. Anesthesia students were randomly assigned to one of three groups: HPS, CD-ROM, or a control group. A valid and reliable instrument, Combat Performance, was used to evaluate the participant's ability to give care to trauma patients. Results: A repeated analysis of variance and a least significant difference post hoc test were used to analyze the data. The HPS group performed better than the CD-ROM and control groups relative to performance ($p$ = 0.001). There was no difference between the CD-ROM and control group ($p$ = 0.171). Discussion: We speculate that the HPS group performed better than the CD-ROM group because of the realism. Conclusion: In this study, the HPS method of instruction was a more effective method of teaching than the CD-ROM approach.

Introduction

Military nurses, including certified registered nurse anesthetists, are required to have education relative to care of combat injuries before being deployed to Afghanistan or Iraq. These nurses are expected to perform beyond what they usually perform in the hospital setting. Such practice is within the scope of practice for nurse anesthetists, and they may be the most qualified to perform life-saving procedures on patients on the battlefield and during mass casualties. Because of the potential number of casualties and extent of injuries found in trauma related to combat, these nurses need to know how to care for these patients. However, the most effective methods of instruction have not been studied. One method that may be effective is the use of simulation. Simulation is defined as a realistic representation (model) of the dynamics or processes with which the participant interacts with the environment, applies previously learned knowledge into the decision making process, and responds with definitive decisions and actions to deal with a problem or situation. Simulation as a teaching method allows an interactive experience to reflect or parallel patient scenarios.

The simulator is the tool used to produce the interactive clinical scenarios through the use of computer programs. Performance feedback can be provided without concern regarding real-life consequences. Leigh states that simulation is a method of translating

didactic knowledge into a safe learning environment. Further, Jeffries emphasizes that simulation is a teaching strategy that can be used to facilitate making connections between and among concepts through a process that actively engages students in learning. Such a strategy facilitates learning skills and knowledge.

## Framework for Study

The framework for this study was an integration of situated psychology and critical thinking. The basis of situated cognition is that individuals best learn “what to do” and “how to do” in a real world environment, which may be afforded by learning with a high-fidelity simulator such as the human patient simulator (HPS). Situated cognition asserts that critical thinking has to occur within the context of the situation and is an essential component of critical thinking in the care of combat casualties. Critical thinking is the process of seeking information, collecting data, discriminating between relevant and nonrelevant data, analysis of situations, applying standards of care, using logical reasoning, and performing the appropriate skills. Appropriate care of patients of battlefield trauma requires all of these components.

## Operational Definitions

The investigators developed an instrument relative to caring for patients with trauma: Combat performance (CP). For the purposes of this study, performance was operationally defined as a score from 0 to 100% on the CP.

## Background on Simulation

Very little prospective, randomized, experimental research exists on the use of simulation as a teaching method, and no studies have investigated the use of the HPS compared to a CD-ROM relative to caring for combat casualties. In addition, no researchers have investigated the effects of simulation on critical thinking relative to caring for combat casualties. However, a wealth of literature addresses the value of using simulation as a teaching method but fails to use a rigorous research design. For example, McIndoe surveyed participants and found that the majority preferred problem-based simulation to lecture, rounds, or tutorial teaching formats but did not investigate the effectiveness of such an approach. Korndorffer et al found that simulation showed a significant improvement in overall scores from baseline for performing laparoscopic suturing, but they did not compare simulation to any other teaching method. Rauen found that simulation as a method of teaching allows learners to apply theory to practice in an integrated manner. Furthermore, she found that a simulator has the capacity to demonstrate more than a single event or parameter at a time which allows participants to identify relationships essential and common to clinical practice. She found that the evaluation of the

simulation sessions were universally positive. As a result of the use of simulation, students became confident and were able to demonstrate skills learned.

However, Rauen did not compare the simulation approach to any other method or to a control group. One study compared the success rate of endotracheal intubation among paramedic students trained on a HPS group or on human subjects in the operating room. The HPS training was as effective as students who were trained on human subjects. Steadman et al investigated whether full-scale simulation was superior to interactive problem-based learning for teaching medical students acute care assessment and management skills. They used a pretest/post-test design and determined that simulation-based learning was superior to problem-based learning for the acquisition of critical assessment and management skills.

Wayne et al conducted a retrospective study of cardiac arrest team responses and compared them to a simulator-trained group and a control group to determine if simulation would improve the quality of Advanced Cardiac Life Support care provided. They found that simulator-trained residents showed significantly higher adherence to standards vs. traditionally trained students. Gordon surveyed both students and educators about their opinions about simulation as a teaching tool. Both groups thought that the advantage of using the simulator outweighed the disadvantage of the cost of the simulator. Eaves created a 10-bed simulated medical unit as part of a new graduate nurse orientation. The program received outstanding evaluations from the new graduates, the educators, and preceptors in the clinical setting where the new graduates were being oriented. However, the study did not compare the simulation with any other methods. Cioffi investigated the effectiveness of simulation on clinical decision making of midwifery students; however, the study used a post-test design with no mention of score reliability or instrument validity. Results showed that the students who received the simulation strategy collected more clinical information and had higher confidence levels and reached a final decision more quickly than the lecture group. Dieckmann introduced concepts into medical simulation that help to clarify potential problems during simulation and foster its goal-oriented use. Their introduction of these concepts allow for improved matching of simulation realism with desired outcomes. Johnson investigated the effectiveness of using the HPS compared to a CD-ROM group in teaching care of patients exposed to chemical warfare agents for military nurses. He found that there were no significant differences in lower-level cognition between the two approaches, but the HPS was more effective relative to higher-level cognition and critical thinking. Hoadley compared results of two Advanced Cardiovascular Life Support classes on measures of knowledge (content exam) and resuscitation skills (performance exam). Both the control and experimental groups consisted of physicians, nurses, emergency medical technicians, respiratory therapists, and advanced health care providers. The control group used low-fidelity simulation; the experimental group was exposed to enhanced realism via high-fidelity simulation (HFS). HFS group did score higher on both cognitive and behavioral tests, but the difference was not statistically significant. The experimental group stated that learning using HFS was enjoyable and adamantly recommended that Advanced Cardiac Life Support should only be taught using HFS.

Researchers stress that there are limited, rigorously designed pretest/post-test studies of simulation and the need for investigations that compares the approach to other educational methods. Rourke reviewed the literature relative to simulation and found that HFSs are used extensively in nursing education; however, little research justifies their use. Others support the use of simulation but struggle to substantiate their opinions.

## Research Question

The following research question guided the study: Are there statistically significant differences in the HPS and CD-ROM educational strategies compared to a control group relative to the scores on the CP instrument?

## Methods

This study was a prospective, pretest-post-test experimental, mixed (within and between) design and was approved by the Institutional Review Committee (IRB) at Brooke Army Medical Center. Potential participants were given the purpose of the study and were assured that their participation was voluntary. ‘

All individuals who chose to participate in the study were evaluated on the HPS relative to the scores on the CP instrument. After the initial evaluation, participants were randomly assigned to one of three groups: HPS, CD-ROM, or control group. The participants in the HPS and CD-ROM groups were given a briefing that included the content that would be covered and then received instruction as described below. After 1 month, all of the participants then returned and were evaluated using the same instrument and the HPS. Participants in the control group received no instruction but were given the opportunity to complete the HPS or CD-ROM educational teaching strategy after all the data were collected. Two faculty members evaluated all of the participants and were blinded to which group they were assigned. The study was conducted at a military nursing simulation center configured to represent a typical facility located in Iraq or Afghanistan. After all data were collected, individuals were debriefed in terms of their performance.

## Sample

A convenience sample consisting of 60 student nurse anesthetists from the U.S. Army Graduate Program in Anesthesia Nursing completed both the pretest and post-test instruments. One in the HPS, 6 in the CD-ROM, 4 in the control group did not return to complete the post-tests and were excluded from the study. The mean age was 29 and ranged from 24 to 47 years of age. There were 49 participants who completed the study: HPS (*n* = 19), CD-ROM (*n* = 14), and control group (*n* = 16).

Human Patient Simulation

A high-fidelity simulator, the HPS (Medical Education Technologies, Sarasota, Florida), was used as a teaching strategy and was programmed with three patient scenarios: hypovolemic shock, tension pneumothorax, and cardiac tamponade. Each scenario was 30 minutes in length for a total of 90 minutes.

The rationale for using these scenarios was that these are common occurrences on the battlefield. Also, these conditions lend themselves to the use of the HPS that allows participants to identify the problem, intervene, and evaluate care given. The HPS is a computerized, full-body mannequin capable of providing real-time physiological and pharmacological responses to various health conditions and pharmacological interventions. The complete HPS system included the mannequin, computer software, monitors, and gases required to operate the system. A cordless microphone located in the mannequin's head was used to simulate the “patient's voice.” Participants were able to ask the mannequin questions, and the operator was able to respond by transmitting his voice through the mannequin.

The HPS was programmed to manifest signs and symptoms relative to combat casualties that included absent breath sounds, deviated trachea, tachycardia, hemodynamic changes, muffled heart sounds, and diaphoresis. The HPS was attached to a cardiac monitor so that blood pressure, pulse, and cardiac rhythms could be assessed by observing the monitor. In addition, participants were able to auscultate breath and heart sounds and palpate carotid, radial, and femoral pulses. In the hypovolemic scenario, the monitor demonstrated that the patient had hypotension with tachycardia. In this scenario, radial and brachial pulses were absent but carotid pulses were present. HPS provided participants with the ability to assess, make an inference, intervene, and evaluate the intervention. Appropriate physiological responses to pharmacological interventions such as administration of fluids were immediately demonstrated by the HPS. For example, in the hypovolemic model, fluid administration resulted in a decrease in pulse and an increase in blood pressure. After fluid was administered, radial and brachial pulses were palpable. The administration of oxygen resulted in an increased saturation as monitored by pulse oximetry.

Combat Casualty Care CD-ROM

A CD-ROM was developed for this study that allowed participants to view PowerPoint slides that covered the pathophysiology of three types of combat injuries: cardiac tamponade, pneumothorax, and hypovolemic shock, the same three scenarios developed for the HPS. After each set of slides addressing the pathophysiology of the combat injuries, the CD-ROM presented a patient portrayed by an actor who was mouloged to demonstrate the various signs and symptoms. The narrator asked rhetorical questions such as, “What manifestations do you see?” “What other data would you collect?” “What do you want to do now?” Each question was followed

with an actor and monitor demonstrating appropriate data and a nurse administering an appropriate intervention. Once the intervention was complete, questions were asked, “How would you evaluate the effectiveness of your intervention?” followed by the nurse collecting appropriate information from the simulated patient and the monitor. Examples of the parameters displayed were vital signs, auscultation of the chest, breathe sounds, distended jugular veins, heart sounds, chest bruising, bleeding abdominal wound, etc. Interventions included such items as administration of oxygen, intravenous fluids, cardiac and chest decompression, and other treatment modalities needed to stabilize the patient. Each scenario took 30 minutes to complete for a total of 90 minutes. The content presented by both the HPS and CD-ROM methods were the same, but the method was different.

Performance Instrument

Content Validity

After review of the literature, the investigators developed the CP instrument relative to the care of patients with battlefield injuries, specifically tension pneumothorax, cardiac tamponade, and hypovolemic shock. The CP measured the ability to assess, intervene, and evaluate care given to simulated patients using the HPS. The original instrument had 120 criteria. The instrument was given to an expert panel that consisted of six military registered nurses who had been deployed to either Iraq or Afghanistan. Three of the experts had a MSN, two had a PhD, and 1 had a BSN. The panel reviewed the CP for comprehensiveness, appropriateness, and accuracy. The experts individually rated each criterion as very pertinent, pertinent, not pertinent, or not at all pertinent. Items rated as not pertinent were excluded from the instruments leaving 107 criteria, each scored as met or not met. The expert panel had a 100% agreement that all of these items were comprehensive and reflected essential content.

Reliability

Three investigators initially used the instrument to independently evaluate 30 subjects to acquire psychometric data relative to the instrument. These subjects were not part of the study. A Pearson R was used to determine the correlation between the scores given by the investigators and was $r = 0.96$ indicating good interrater reliability. Two weeks after the initial evaluation, the investigators evaluated the same participants using the same instruments. A Pearson R was used to determine the correlation between the two scores, which was $r = 0.94$, indicating that the instrument was stable over time. The two faculty members who evaluated the performance of all participants independently evaluated two participants not involved in the study. A Pearson R was used to determine the correlation between the evaluators, which was $r = 0.90$. After discussion, the same two faculty members evaluated the performance of ten participants. The first rater scored the participants at a mean of 84 ± 7%, and the second rater scored the

participants at 85 ± 6%. A Pearson R was used again to determine the correlation between the two evaluators, which was $r = 0.97$ indicating excellent interrater reliability.

## Results

A multivariate analysis of variance indicated that there were no significant differences in the groups relative to pretest scores, age, number of years experience, or rank ($p > 0.05$), indicating that the groups were equivalent relative to these parameters. A repeated measures analysis of variance and least significant difference post hoc analysis were used to determine if there were significant differences between the groups over time. An $\alpha$ of 0.05 was used for all analyses. The Wilks' $\lambda$ multivariate test indicated that there were significant differences in group means by time ($p < 0.001$). The least significant difference post hoc indicated that the HPS group had significantly higher scores than the CD-ROM and control groups relative to performance ($p < 0.001$). There was no significant difference between the CD-ROM group and control group ($p = 0.171$).

## Discussion

Based on the results of this study, the choice of teaching strategies is the use of HPS. We speculate the reason that participants in the HPS group performed better than the CD-ROM and control groups is that the HPS allowed realism and hands-on experience. In addition, the findings may be related to the fact that teaching strategies using the HPS provide the opportunity for learners to apply principles, concepts, laws, and theory more than the CD-ROM. The HPS allowed participants to use the cognitive skills of evaluation and treatment in a realistic simulated environment. For example, in the tension pneumothorax scenario, participants were able to collect data such as absence of breath sounds and increased resonance on the affected side, cyanosis, deviated trachea, reduced pulse oximetry, etc. After collection of pertinent data, the participants were able to identify appropriate intervention and evaluate the effectiveness. In the tension pneumothorax scenario, evaluation of the effectiveness of needle decompression and chest tube placement was possible by observing changes in vital signs, normal breath sounds, trachea in midline, normal pulse oximetry, etc. Such skills represent critical thinking skills of assessment, intervention, and evaluation. Perhaps, the reason that the CD-ROM was no more effective than the control may be that the approach did not lend itself to assessment, intervention, and evaluation. These processes were covered in the CD-ROM but may have lacked the realism provided by the HPS. The use of the HPS is an effective method of translating didactic knowledge into a safe learning environment and can be used to facilitate making connections between and among concepts through a process that actively engages students in learning. Although the participants in the HP group stated that the approach was excellent and provided realistic scenarios, the cost of the HP is approximately $240,000. In addition, it takes between one and two individuals to run the system and teach using this modality. The approach is costly but has demonstrated superior performance which may translate into better patient care.

This was the first study that compared the effectiveness of HPS and CD-ROM teaching strategies in care of trauma patients in terms of performance using nurse anesthesia students. A limitation of the study may be that the performance on the HP does not translate into actual clinical practice. Future studies should be implemented investigating other types of content, with different participants, and the effectiveness of such an approach with real patients.

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## Injuries, Changes in Fitness, and Medical Demands in Deployed National Guard Soldiers

Military Medicine
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Oct 2012

Abstract

Purpose: To characterize noncombat injury/illness, determine changes in physical fitness, and evaluate the influence of these changes on medical resource utilization by National Guard (NG) Soldiers. Methods: Fifty-four Soldiers from the Arizona NG completed pre- and postdeployment fitness testing. Additionally, individual deployment medical records were inventoried. Results: The majority of noncombat-related medical visits (41%) were musculoskeletal in nature, followed by miscellaneous (33%) and respiratory (13%). Soldiers experienced significant decreases in percent fat mass (−11.1%, $p < 0.001$) and $VO_2$ peak (−10.8%, $p < 0.001$). There were significant increases in push-ups (16.4%, $p < 0.001$), sit-ups (11.0%, $p = 0.001$), bench-press (10.2%, $p < 0.001$), and back squat (14.2%, $p < 0.001$) measures. $VO_2$ peak was inversely correlated to medical resource utilization ($r = -0.45$ to $-0.28$, $p \leq 0.05$). The tertile of Soldiers experiencing the sharpest declines in $VO_2$ peak had significantly more medical visits over the course of the deployment than the other two tertiles (8.0 vs. 2.6 vs. 3.1 medical visits/Soldier, $p \leq 0.05$). Conclusion: The predominate noncombat medical issue was musculoskeletal injury. NG Soldiers improved their body composition, strength, and endurance but experienced significant declines in aerobic fitness while deployed. These data document the association between declining aerobic fitness and increased utilization of medical resources.

Introduction

Since the beginning of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), more than 2 million Soldiers have deployed to Iraq and Afghanistan. As of April 2012, more than 650,000 of these deployed Soldiers had been activated from the Air National Guard and the Army National Guard (ANG). It has previously been shown that noncombat-related injury and illness accounts for the most significant portion of the deployed medical assets' responsibilities. Specifically, noncombat musculoskeletal (MSK) injuries comprised the largest percentage of these responsibilities. Noncombat injury/illness accounts for 72 to 91% of the all the medical evacuations that occurred during OIF and OEF, 2004–2007, and MSK issues were the leading cause of these noncombat medical evacuations. The total number of evacuations because of MSK disorders exceeded the number of evacuations related to combat during the evaluated period. More recent data covering the entire period (2003–2011) of operations in Iraq show that combat injuries only accounted for 18% of the medical evacuations whereas MSK injury resulted in 30%. Most of the previous reports typically characterize utilization of medical resources in all Soldiers without delineation between the active duty and ANG components. Currently, there are very little data assessing deployment related injury and illness occurring specifically in the ANG. Only one previous study comparing the medical utilization between active duty and ANG Soldiers showed that the ANG Soldiers were more likely to seek care while deployed.

Soldiers' physical fitness and body composition may influence these noncombat injuries and illness. It has previously been shown that Soldiers who maintained a lower aerobic capacity were more likely to become injured. In a limited body of literature examining only active duty Soldiers, it was demonstrated that fitness levels and body composition can deteriorate over the course of deployments. Recently, predeployment fitness and body composition were assessed in the deployed ANG Soldiers and found to be similar to the active duty Soldiers. Changes in fitness levels and body composition over the full course of deployment have not been reported in ANG Soldiers. Because of the different environments that exist for day-to-day training between the ANG and an active duty unit, it is certainly conceivable that these ANG Soldiers' physical conditions would respond differently during the deployment than that of the previously measured active duty Soldiers. Before deployment, ANG Soldiers are expected to maintain the standards of physical fitness on an individual basis, possibly performing unit physical fitness training when they meet on the assigned one weekend per month. Active duty Soldiers typically spend 1 to 1½ hours on 4 days per week performing physical fitness training as a unit.

In an effort to evaluate physical changes associated with high-stress environments, research has been conducted in both operational theaters and training. The training scenarios were created to simulate the stressful experiences that Soldiers encounter over periods of days to weeks. Decreases in fitness and job performance were detected in these highly stressful environments. The most recent publications evaluating physical fitness in deployed Soldiers demonstrated declines in maximal cardiorespiratory function and increases in fat mass. The published results for changes in strength and power associated with deployment are conflicting.

Explaining these changes in the deployed environment is difficult because every Soldier may have a different deployed experience. Most deployed Soldiers have significant autonomy in terms of their physical fitness training. This autonomy is largely attributable to the unit's operations tempo and the individual Soldier's duty requirements. Typically, a deployed Soldier has been expected to take responsibility for his or her own fitness training while deployed.

Physical fitness in military personnel or recruits has been correlated to occupational injury. These previous investigations demonstrated that increased levels of aerobic fitness, strength, endurance, and flexibility reduced the risk of MSK injury. Additionally, some of the research indicated that higher levels of activity and cardiorespiratory fitness reduced the prevalence of illness. Currently, no published reports have been found that have evaluated the relationship of physical fitness and injury/illness in military service members who are performing their duties while deployed. Because of the long duration of the current military deployments and the significant burden of noncombat-related injury and illness during deployment, the effects of fitness levels on medical resource utilization during a deployment should be considered.

The goals of this research were to characterize noncombat injury and illness among ANG Soldiers and to determine if ANG Soldiers experience changes in physical fitness similar to active duty Soldiers during the course of the deployment. Additionally, if changes in fitness occur in ANG Soldiers, the influence of these physical fitness changes on medical resource utilization would be evaluated.

Methods

The study was approved by the institutional review board at Arizona State University, as well as by the Arizona National Guard State Surgeon's Office. All Soldiers were cleared for deployment by the Arizona National Guard upon completing the medical screening conducted during the Soldier Readiness Program. Volunteers read and signed an informed consent before participation. No incentives for participation were offered. All volunteers were screened using the American College of Sports Medicine (ACSM) and American Heart Health/Fitness Facility Preparticipation Screening Questionnaire before the initial testing. Subjects also signed a Health Insurance Portability and Accountability Act release form to allow the investigator to review deployment medical records. Consistent with the ACSM risk stratification for maximal testing, male Soldiers older than 45 years and female Soldiers older than 55 years, or anyone having severe physical limitations that would prevent successful completion of testing or uncontrolled chronic disease (i.e., hypertension, diabetes, sleep apnea, asthma) were not eligible for this investigation. Males and females of all races were eligible for this study.

Fifty-four Soldiers (Male = 47, Female = 7) completed both pre- and postdeployment testing. Soldiers deployed for less than 10 months or greater than 15 months were not included. At the time of enrollment, the mean (±SD) age was 27(±7.0) years, height was

174.2(±7.4) cm, and weight was 82.9(±15.8) kg. The majority of study participants were recruited from three separate units, including the 363rd Explosive Ordinance Detachment, 1404th Transportation Company, and 855th Military Police. Multiple occupations were represented within each unit.

It was not the intention of this study to intervene or change physical fitness training of the Soldiers while deployed. Existing autonomy was maintained. Soldiers enrolled in this study were encouraged to conduct themselves while deployed in accordance with their respective unit requirements. The study was designed to assess the effects of deployment on ANG Soldiers' physical performance without an additional intervention.

Pre- and postdeployment physical fitness testing included the measurement of body composition, muscular strength, muscular endurance, peak power, cardiorespiratory fitness, and joint flexibility. Assessments were selected that were deemed valid and reliable for use in a population of Soldiers and could be conducted without interfering with Soldier training and duties. All data collection was conducted using standard methods. Predeployment testing was performed within 30 days of deployment. Postdeployment testing was conducted within the first 10 days of a Soldier's return to the United States.

A detailed description of the testing methods has been previously published. In brief, body composition (percent fat mass and fat free mass) was measured using air displacement plethysmography (Bod Pod; COSMED, Concord, California). Strength was determined using a 1-repetition maximal (RM) bench press and back squat in accordance with the guidelines set forth by the National Strength and Conditioning Association and the ACSM. Muscular endurance was assessed by completion of a push-up (PU) and sit-up (SU) test in accordance with the U.S. Army Physical Fitness Test protocol. A Wingate anaerobic power test was used to assess lower extremity power. Flexibility was assessed using three different tests: sit-and-reach (SNR) for lower extremity flexibility, shoulder elevation test, and trunk extension test.[2] Soldiers' cardiorespiratory fitness ($VO_2$ peak) was estimated with indirect calorimetry while completing an incremental treadmill test. Criteria for adequate testing included the following: RER > 1.00 and heart rate ± 10 beats per minute of age-predicted maximum heart rate.

Upon return to the United States, each Soldier's deployment medical record was screened and noncombat injury and illness related visits were retrospectively inventoried. Any mandatory visits for medical screenings or immunizations were not counted during the inventory. Both hard copies and electronic medical records were evaluated by the primary investigator within the medical facilities of the ANG in an attempt to account for all deployed medical visits. It is understood that some of the medical visits documented on paper may have been lost during the deployment. Numbers of visits for each subject were tabulated by medical category on a spreadsheet. Medical visits were categorized to correspond with those that have been previously reported in the literature. The

numbers of visits were then compared to the various physical fitness outcome measures to determine the relationships between the fitness variables and medical resource utilization.

Differences between pre- and postdeployment measures were statistically evaluated using paired *t*-tests. Spearman Rho correlations were conducted to evaluate for significant relationships between physical fitness variables and the appropriate medical condition/diagnosis. For correlations, the MSK categories were condensed into three regions: the "cervical, thoracic, and lumbar" categories were collapsed into one category titled "back"; the "shoulder, elbow, and wrist/hand" categories were collapsed into one category titled "upper extremity"; and the "hip, knee, and ankle/foot" categories were collapsed into one category titled "lower extremity." Variables that were significantly correlated were further evaluated by separating subjects into tertiles (T1, T2, T3) based on the percentage of change in the assessed fitness variable (T1 = least improved, T3 = most improved). Tertile groups were analyzed via analysis of variance to assess differences in medical resource utilization. Significant resource utilization-by-tertile interactions were further assessed by Scheffe post hoc tests if significance was attained.

## Results

### Characterization of Noncombat Injury and Illness

During this 10- to 15-month deployment period, there were 252 medical visits tabulated among the 54 ANG Soldiers. This equates to a mean of 4.7 medical visits per Soldier over the course of the deployment for the entire cohort. However, 20% of the Soldiers had 0 medical visits during the same period. MSK issues accounted for the largest percentage of all medical visits inventoried.

More than half of all the Soldiers (55.6%) sought care at least 1 time for a MSK complaint. Respiratory complaints resulted in the second most single cause for a medical visit. Forty-one percent (*n* = 22) of Soldiers sought care for respiratory illness at least 1 time. Only 22% (*n* = 12), sought care for gastrointestinal issues. Of the MSK visits, 36% were related to the lower extremity, 22% upper extremity, 17% back, and 25% were physical therapy visits.

Pre- to Postdeployment Physical Fitness Changes Significant changes were detected between pre- to postdeployment measures in all assessed variables except for peak power and two of the flexibility components (SNR or shoulder elevation. There were 17 smokers in this cohort. However, there were no significant differences in the percentage of change to fitness levels between smokers and nonsmokers or between genders.

### Correlations

There were no significant correlations detected between the different medical conditions/diagnosis and predeployment scores, postdeployment scores, or change in fitness scores among measures of relative strength, muscular endurance, or peak power. Significant negative correlations were detected between change in fat mass and gastrointestinal visits, indicating that a greater decline in fat mass during deployment was also associated with a higher number of gastrointestinal visits. SNR scores at postdeployment and the percentage of change in SNR were both negatively correlated to the number of lower extremity visits. This would indicate that Soldiers with greater hamstring and low back flexibility at postdeployment had a lower number of visits related to the lower extremity, whereas greater declines in SNR were associated with a higher number of lower extremity visits. The percentage change in the shoulder elevation score also maintained a negative correlation to upper extremity visits.

Cardiorespiratory fitness was the single measure that was most related to medical visits. It was correlated to three of the inventoried medical categories and maintained the strongest relationships. A negative change in the Soldiers $VO_2$ peak was significantly correlated to a higher number of back and behavioral health visits while nearly reaching significance for total visits ($r = -0.27$, $p = 0.058$). The postdeployment $VO_2$ peak scores were negatively correlated to behavioral health and total number of visits demonstrates the mean percentage of change in body fat, SNR, and shoulder elevation by perspective tertile. The mean differences between tertiles in $VO_2$ peak.

Body Composition

Although T1 demonstrated an increase in the mean percent of fat mass, T2 and T3 both had reductions. Soldiers experiencing the greatest improvement (T3) in their percent body fat (−25.6%) also had a higher number of visits related to gastrointestinal complaints (0.1 vs. 0.1 vs. 0.6 gastrointestinal visits/Soldier).

Flexibility

Both the T1 and T2 tertiles experienced declines in SNR score, whereas T3 did demonstrate an improvement. Soldiers in T1 and T2 also demonstrated a higher number of lower extremity visits compared to T3 (0.8 vs. 0.9 vs. 0.4 lower extremity visits/Soldier). Only half as many lower extremity medical visits occurred in the tertile of Soldiers who demonstrated a mean improvement in hamstring flexibility.

When comparing the number of upper extremity visits/Soldier, it is seen that the T1 has a higher mean of upper extremity visits when compared to the T2 and T3 (0.8 vs. 0.2 vs. 0.3 upper extremity visits/Soldier). This indicates that Soldiers experiencing the greatest declines in their shoulder elevation scores also had the highest number of visits related to the upper extremity.

Aerobic Fitness

Only T3 demonstrated a mean improvement in percentage of change in $VO_2$ peak. Demonstrates the change in aerobic fitness by tertile. T1, those who showed the greatest declines in $VO_2$ peak, had the highest number of back-related medical visits (0.75 vs. 0.24 vs. 0.00 back visits/Soldier) and all of the behavioral health visits occurred in Soldiers within T1 (0.13 vs. 0.00 vs. 0.00 behavioral health visits/Soldier). Greater declines in cardiorespiratory function were associated with higher medical resource utilization as well (8.0 vs. 3.1 vs. 2.6 total visits/Soldier). The Soldiers who had the greatest decline in $VO_2$ peak (T1) had more than twice as many total visits when compared to the other two tertiles.

Discussion

Injury and Illness

The findings of this study are consistent with previous findings that indicate that MSK medical issues in deployed ANG Soldiers make the highest percentage of responsibilities for medical resources. According to Cohen et al, MSK injuries accounted for 22 to 28% of all medical evacuations. Zouris et al reported that the injury and MSK categories accounted for 40.4 to 46.5% of all noncombat injuries and illness in the Army for OIF I and II. Similarly, MSK visits accounted for 41% of all the inventoried visits in this cohort. Fifty-seven percent of these ANG Soldiers reported for at least 1 MSK visit. Sanders et al reported that only 35% of the Soldiers deployed to OIF/OEF during 2003–2004 sought care for a MSK injury. This finding suggests that these ANG Soldiers were more likely to seek care for MSK reasons than previously reported active duty populations.

It appears that these ANG Soldiers suffered from fewer gastrointestinal issues when compared to previous published reports. Sanders et al reported that 40% of Soldiers serving in Iraq and Afghanistan in 2003–2004 sought medical care for only diarrhea. Gastrointestinal visits only accounted for 5% of all medical visits in this cohort and only 22.2% of the ANG Soldiers sought care for gastrointestinal causes. This included gastroesophageal reflux, vomiting, diarrhea, etc. This decline in reported cases of gastrointestinal distress may be a function of a more established combat theater. Sanders et al reported on cases occurring in 2003–2004. From 2003 until the recent troop draw down, improvements to Soldier living conditions have continually been made. Ideally, this has resulted in more hygienic living and a decline in gastrointestinal complaints.

It would appear that respiratory illness was more prevalent in these ANG Soldiers as compared to active duty Soldier previously reported on. Respiratory complaints accounted for 13% of all medical visits in this study. Zouris et al reported that respiratory issues only accounted for 2.9 to 4.6% all noncombat injury and illness in Army Soldiers during OIF I and II. Sanders et al reported that only 17% of Soldiers sought care for respiratory infection while deployed, but 41% of these ANG Soldiers sought care for a respiratory cause. Smoking rates offer no explanation for the apparent higher rates of respiratory visits in these ANG Soldiers. Although Sanders et al reported that 39% of the active duty Soldiers smoked at least 0.5 packs per day, only 32% of the ANG Soldiers in this study reported smoking. These seemingly similar smoking rates do not help explain why a higher percentage of these ANG Soldiers sought care for respiratory infection. Smoking intensity was not analyzed during this study and may have offered some insight to this question. Similar to MSK visits, the ANG Soldiers may have sought care for respiratory illness more frequently because of an increased availability and accessibility of medical resources during the deployment.

Relationship to Physical Fitness

Declines in physical fitness levels were demonstrated by the significant decrease in aerobic fitness and trunk extension. However, this group of Soldiers improved their fitness in a number of different areas including relative strength (bench press and back squat) and muscular endurance (PUs and SUs), and they reduced their percentage of fat mass. At this time, it can only be hypothesized as to why aerobic fitness declined while strength and endurance improved. Perhaps, these results indicate that these ANG Soldiers performed resistance training in lieu of aerobic training while deployed. Possible reasons for this include Soldiers' preference for “strength type” training as opposed to “aerobic type” training, amount or type of resources that are available to the Soldiers while deployed, or they were in an environment that is not conducive to aerobic training. Extreme weather, suboptimal running surfaces, or unsafe conditions could have deterred Soldiers from performing aerobic training outside while deployed. If Soldiers were required to train indoors, then perhaps there were a greater amount of resistance training equipment and opportunities available as compared to the numbers of aerobic training treadmills or bikes.

Most of the findings in this study indicate that moderate and plausible relationships exist between Soldiers' declining fitness and their increased utilization of medical resources. Although the correlations are significant, it is understood that they only account for 8 to 20% of the variance among the respective medical visits. Declines in body fat percentages may be influenced by gastrointestinal issues, but there a number of other components of health (changes in activity levels or caloric intake) that may offer a better explanation. Further research assessing predeployment vs. deployment activity levels and dietary intake is needed.

The negative correlations between SNR scores vs. lower extremity visits and shoulder elevation scores vs. upper extremity complaints are significant, but they too only offer explanation to a small percentage of the variance for the respective medical visits. These examples do demonstrate how components of physical fitness may influence medical resource utilization. In both cases, it is certainly possible that an injury of the respective extremity resulted in a decline in flexibility which simply exacerbated the problem. However, in the case of the SNR, there has been prospective research in occupational environments that demonstrated a link between a low SNR score and a higher prevalence of occupational injury. Craig et al reported that decreased SNR scores maintained an odds ratio of 3.56 (95% Confidence Interval = 2.31–5.17, $p = 0.046$). Similarly, the relationship between declining aerobic fitness and increased number of back visits ($r = -0.31$, $p = 0.03$) is consistent with previous findings in firefighters, which showed much higher rates of back injury in the individuals with the lowest level of fitness.

Although this population of ANG Soldiers demonstrated improvements in relative strength as a whole, no relationships between strength at pre- or postdeployment or change in strength and any of the inventoried medical variables were detected. It appears that cardiorespiratory fitness maintains a more important role when evaluating the overall utilization of medical resources. This was particularly apparent when these ANG Soldiers were organized into tertiles based on their percentage of change in cardiorespiratory fitness over the course of the deployment. The tertile of Soldiers experiencing the most severe declines in cardiorespiratory fitness (−27.5%) demonstrated more than a 150% increase in total medical visits (8.0 vs. 3.1 vs. 2.6 total visits) when compared to the other two tertiles. Soldiers in the middle tertile, who experienced a mean decline in cardiorespiratory fitness of only 12%, had a similar number of total medical visits to those Soldiers who improved their cardiorespiratory fitness. These data could indicate that there may be a threshold for declines in cardiorespiratory fitness. Once declines in cardiorespiratory fitness have been exceeded, the number of total medical visits increases significantly. Although we cannot truly establish cause and effect in this situation, these findings are consistent with previous studies that have shown that lower levels of aerobic fitness are related to higher levels of injury and illness. If cardiorespiratory fitness declines were minimized during deployment, there may have been fewer medical encounters among the Soldiers in T1.

Interestingly, all behavioral health visits occurred in T1. Previous research has demonstrated an increase in depressive symptoms associated with declines in cardiorespiratory fitness. It has also been described that higher levels of physical fitness can help attenuate the affects of stress because of sustained operations. Aerobic training while deployed may not only be beneficial for physical health but may also benefit one's mental health. However, it is also possible that depressive symptoms led to a reduction in aerobic training, hence a decline in measured cardiorespiratory fitness.

It would appear that the Soldiers in this study may have been performing resistance training at the expense of their aerobic training as demonstrated by the significant declines in cardiorespiratory fitness while demonstrating improvements in strength and

endurance. Seeing that strength was not correlated to the medical variables, military leadership may be advised to guide their Soldiers in performing a balance of resistance training and aerobic activity. This relatively young and fit sample of ANG Soldiers has demonstrated that it may be advantageous to adjust training protocols during the deployment when possible, in an effort to maintain cardiorespiratory fitness. Additional research using a large sample of ANG Soldiers with numerous occupations would likely be beneficial in validating the current findings. However, based on these current findings, it can be theorized that a decline in medical resource utilization could be realized if Soldiers trained to improve or at least minimize declines to their level of aerobic fitness during deployments.

In summary, of the 54 ANG Soldiers, 80% required medical attention for noncombat-related injury or illness during deployment. The majority of these noncombat injury/illness visits (41%) were MSK in nature, followed by miscellaneous (33%) and respiratory (13%). Although aerobic fitness declined, these ANG Soldiers improved their strength, muscular endurance, and body composition. The utilization of medical resources was inversely proportionate to aerobic fitness. Those ANG Soldiers who demonstrated the sharpest declines in their aerobic fitness required more than twice the amount of medical attention. There was no relationship between strength or muscular endurance and medical resource utilization. These ANG Soldiers were similar to previously studied active duty Soldiers in terms of noncombat injury/illness and some of the changes in fitness. In conclusion, results from this study suggest that if military leaders were able to ensure that their Soldiers maintained their predeployment level of aerobic fitness, then overall medical resource utilization could be significantly decreased.

BACK TO TOP

***Traumatic Brain Injury***

## Traumatic Brain Injury-Induced Dysregulation of the Circadian Clock

PLoS One
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Abstract

Circadian rhythm disturbances are frequently reported in patients recovering from traumatic brain injury (TBI). Since circadian clock output is mediated by some of the same molecular signaling cascades that regulate memory formation (cAMP/MAPK/CREB), cognitive problems reported

by TBI survivors may be related to injury-induced dysregulation of the circadian clock. In laboratory animals, aberrant circadian rhythms in the hippocampus have been linked to cognitive and memory dysfunction. Here, we addressed the hypothesis that circadian rhythm disruption after TBI is mediated by changes in expression of clock genes in the suprachiasmatic nuclei (SCN) and hippocampus. After fluid-percussion TBI or sham surgery, male Sprague-Dawley rats were euthanized at 4 h intervals, over a 48 h period for tissue collection. Expression of circadian clock genes was measured using quantitative real-time PCR in the SCN and hippocampus obtained by laser capture and manual microdissection respectively. Immunofluorescence and Western blot analysis were used to correlate TBI-induced changes in circadian gene expression with changes in protein expression. In separate groups of rats, locomotor activity was monitored for 48 h. TBI altered circadian gene expression patterns in both the SCN and the hippocampus. Dysregulated expression of key circadian clock genes, such as Bmal1 and Cry1, was detected, suggesting perturbation of transcriptional-translational feedback loops that are central to circadian timing. In fact, disruption of circadian locomotor activity rhythms in injured animals occurred concurrently. These results provide an explanation for how TBI causes disruption of circadian rhythms as well as a rationale for the consideration of drugs with chronobiotic properties as part of a treatment strategy for TBI.

## Introduction

In humans, circadian disturbances have been linked to many physiological and psychological consequences such as cancer, diabetes, metabolic disorders, hypertension, depression, bipolar disorder, and learning and memory dysfunction [1], [2]. Disruption of circadian rhythms may also contribute to several of the pathophysiological consequences of traumatic brain injury (TBI). Reports of circadian dysregulation in TBI patients include altered homeostatic mechanisms such as regulation of blood pressure, heart rate, body temperature [3], and hormone cycles [4], as well as the sleep-wake cycle [5], [6]. Moreover, circadian disturbances can inhibit neurogenesis, which is a critical component of recovery after TBI [7].

It is well established that patients recovering from TBI are prone to sleep-wake cycle disturbances, which suggests dysregulation of the central timing mechanism that regulates sleep [8]–[10]. The suprachiasmatic nuclei (SCN), located in the anterior hypothalamus, are the anatomical location of the endogenous master clock that controls circadian rhythms. The SCN communicate with peripheral “clocks” to regulate homeostasis and other cyclic physiological patterns (see Golombek & Rosenstein, 2010 for review) [11]. The internal circadian rhythm generated by the SCN is controlled by a cycle of gene expression changes in SCN pacemaker neurons that entrain physiological functions and behavior to external stimuli for proper adaptation to daily temporal cycles in the environment. Signals from the SCN are communicated throughout the brain and the body to various peripheral clocks. One of the important recipients of circadian signaling in the brain is the hippocampus, which is vital for cognitive functions such as learning and memory and is particularly vulnerable to TBI [12], [13].

Circadian clock genes are expressed in many brain regions outside the SCN, including the hippocampus [14], and circadian rhythms have long been known to regulate hippocampal function [15]. There is strong evidence that the endogenous circadian clock modulates long-term potentiation (LTP) – an electrophysiological indication of synaptic plasticity – in the hippocampus [16]. In fact, an operational circadian system appears to be crucial for hippocampal-dependent learning to function properly [17]. For example, in rats, chronic phase shifting of the light-dark cycle impaired both acquisition and retention of platform location in a hippocampal-dependent water maze task [18]. Thus, we speculated that injury-induced alterations in circadian clock genes might contribute to learning and memory dysfunction often reported in human TBI patients [19]. The

association between circadian dysfunction and learning and memory problems may be the result of disrupting sensitive time-dependent neural circuitry and/or may be mediated by molecular substrates such as the cyclic-adenosine monophosphate (cAMP)/mitogen-activated protein kinase (MAPK)/cAMP response element binding protein (CREB) signal transduction pathways that are common between the SCN and the hippocampus and many other cells and tissues [20], [21].

In the SCN, protein products of the circadian locomotor output cycles kaput (Clock) gene and the brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)-like (Bmal1) gene heterodimerize in the nucleus and induce target genes including Period (isomers Per1 and Per2) and Cryptochrome (isomers Cry1 and Cry2), that encode proteins, which in turn, heterodimerize in the cytoplasm, translocate to the nucleus and inhibit CLOCK:BMAL1-mediated transcription [22]. This transcriptional-translational feedback loop functions in an autoregulatory (activation/repression) cyclic fashion. For example, SCN rhythms can be regulated by MAPK activity through decreasing basal Bmal1 expression levels and thereby decrease firing rhythms [23], [24]. This is a process in common with time-of-day expression and persistence of hippocampal-dependent memory, which depends on functioning SCN [25]. These aforementioned processes signify conservation of cAMP/MAPK/CREB-dependent mechanisms between anatomical locations that underlie neuronal plasticity mechanisms for learning and memory.

Thus, using naïve rats and rats subjected to moderate fluid-percussion TBI and sham-injury, we addressed the hypothesis that TBI disrupts the cyclic pattern of circadian clock and clock-associated gene expression in the SCN as well as in the hippocampus (which is particularly vulnerable to injury). We also investigated whether TBI altered the expression of injury-associated genes (such as brain-derived neurotrophic factor [BDNF]) in these two brain areas. Specific brain areas were isolated by laser capture microdissection (LCM) or manual microdissection, and gene expression was quantified by real-time PCR. Confirmation of changes in gene expression was assessed using analysis of protein products of selected genes of interest. Since daily rhythms of rodent locomotor activity are well known to be controlled by the master pacemaker in the SCN, we measured locomotor activity as a functional outcome [26]. This is the first investigation of the effects of TBI on circadian clock gene expression in the SCN and the hippocampus.

## Materials and Methods

### Animals

Adult male Sprague-Dawley rats (350 g–400 g) from vendor Charles Rivers (Portland, Maine) were housed 2 per cage with food and water ad libitum in a vivarium with these constant conditions: light cycle (6[ratio]00–18[ratio]00) temperature (21°C–23°C), and humidity (40%–50%). All animal experiments were approved by the Institutional Animal Care and Use Committee of the University of Texas Medical Branch, Galveston, Texas and conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (8th edition, National Research Council).

### Surgical Preparation and Lateral Fluid-Percussion TBI

To standardize the time of injury, moderate lateral fluid percussion TBI or sham injury was performed at the same time (12[ratio]00) each day. Male Sprague-Dawley rats weighing 350 g to 400 g were anesthetized with 4% isoflurane, intubated, and mechanically ventilated (NEMI Scientific; New England Medical Instruments, Medway, MA) with 1.5% to 2.0% isoflurane in oxygen:air (70[ratio]30). Rectal and temporalis muscle temperatures were monitored using a Physitemp Thermalert Model TH-8 (Physitemp Instruments, Inc., Clifton, NJ), and rectal temperature maintained at 37°C throughout the procedure, using a thermostatically controlled water blanket (Gaymar Industries, Inc., Orchard Park, NY). Rats were prepared for lateral fluid-percussion TBI according to the procedure developed and characterized by McIntosh, et al. (1989) [27]–[29]. Fluid-percussion TBI is a well-established model of closed-head injury that reproduces aspects of human TBI, including cerebrovascular [30] and pathophysiological, neurological and behavioral responses [31]. Rats were placed in a stereotaxic head holder, a midline incision was made in the scalp, and the fascia was removed to expose the skull. Using a Michele trephine, a parasagittal craniotomy was performed 3 mm to the right of the sagittal suture, midway between the bregma and lambda sutures. The bone chip was removed exposing the intact dura. A modified 20-gauge needle hub was secured in the craniotomy site, and cemented in place with hygienic dental acrylic. Once the acrylic was solidified, isoflurane was discontinued and preparation was made for the delivery of the fluid pulse. The trauma device was connected to the rat by a tube that terminated with a male adapter that connected to the modified needle hub. The device consists of a Plexiglas cylinder (60 cm long and 4.5 cm in diameter) filled with isotonic saline connected to a hollow metal cylinder housing a pressure transducer (Statham PA856-100; Data Instruments, Acton, MA, USA) and closed by a Plexiglas piston mounted on O-rings. After the return of a withdrawal reflex to a paw pinch the rats were subjected to a moderate (2.0 atm) pressure pulse. The pulse was delivered by a 4.8 kg steel pendulum striking the piston after being dropped from the appropriate height (determined by prior optimization using an oscilloscope to record the pressure). After TBI or sham injury (no pressure pulse delivered), rats were disconnected from the device and righting reflex was assessed every 60 seconds until a normal response was observed. Rats were then placed on 2% isoflurane, and wound sites were infused with bupivacaine and sutured. Isoflurane was discontinued and rats were extubated and allowed to recover in a warm humidified chamber.

Experimental Design

Experiment 1: Circadian clock gene expression in the rat SCN and hippocampus after TBI

After fluid-percussion TBI or sham surgery, rats were euthanized at 4 h intervals, over a 48 h period (n = 6 rats per experimental group/time point). Injured and sham-injured rats were anesthetized with isoflurane for surgical procedures. Since anesthetics perturb circadian rhythms and can impair cognition in postoperative patients [32], [33], tissue was collected at 4 h intervals over a 24 h period from naïve rats to assess the effects of anesthetics. The ipsilateral hippocampus was removed and placed in RNAlater (Ambion, now Life Technologies, Grand Island, NY) and stored at 4°C; the remaining brain was fresh frozen on dry ice for LCM and stored at −80°C.

For total RNA Isolation from the hippocampus, each hippocampus was homogenized in 1 ml of UltraSpec (Biotecx, Houston, TX) and total RNA was isolated using the manufacturer's protocols. RNA samples in 15 µl to 20 µl of nuclease-free water were DNase treated using the Turbo-DNase kit (Ambion) at 37°C for 30 min. Total RNA was quantified on a Nano-drop spectrophotometer (Thermo-scientific, Wilmington, DE).

LCM of suprachiasmatic nuclei was performed using 10 µm coronal sections cut on a cryostat and mounted on uncoated, pre-cleaned, superfrost glass slides (Fisher Scientific, Pittsburgh, PA). When the SCN region of the brain was reached (located above the optic chiasm), every section was collected through the optic chiasm. The frozen sections were thawed at room temperature for 30 seconds and fixed in 75% ETOH for 1 min. After fixation, the slides were briefly rinsed in RNase-free water (1 min), stained with 1% cresyl violet (1 min), rinsed in RNase-free water, dehydrated in 95% ethanol, 100% ethanol and cleared in xylene. The sections were then air-dried for 10 to 15 min in a fume hood. All solutions were prepared with RNase-free water, and the cresyl violet was sterile filtered with a 0.22 µM filter. Each section was viewed under the microscope to confirm the presence of the SCN. LCM was performed using a PixCell IIe laser capture microscope with an infrared diode laser (Life Technologies). Both lobes of the SCN were captured on the thermoplastic film of a CapSure macro LCM cap (Life Technologies). The smallest laser spot size (7.5 µm) was used with a power setting of 75 mW to 100 mW and pulse duration of 0.85 ms to 1.5 ms, for optimum capture of the cells. The CapSure caps that contained the SCN neurons were transferred to 0.5 ml tubes filled with lysis buffer solution from the RNAqueous-Micro kit (Ambion). Samples were vortexed to insure cell lysis and stored at −80°C until RNA isolation.

Total RNA was isolated from the LCM SCN neurons using the RNAqueous-Micro kit (Ambion) according to the manufacturer's protocols. Total RNA was eluted in 20 µl of nuclease-free water and DNase1 treated at 37°C for 20 min to remove trace amounts of genomic DNA.
The total RNA from the SCN neurons was linearly amplified using the Message Amp II aRNA kit (Ambion) according to the manufacturer's protocol. The amplified RNA was quantified on a Nanodrop spectrophotometer (Thermoscientific).

Total hippocampal RNA (500 ng) and SCN RNA (80 ng) was reverse transcribed as previously described [34]. The reactions were incubated for 10 min at 25°C, then 30 min at 48°C, and 5 min at 95°C in a thermocycler (TechGene), centrifuged and then stored at −20°C until use. Quantitative real-time PCR was performed on a MX3000P multiplex PCR system (Stratagene, La Jolla, CA) with Taqman reagents (Applied Biosystems, now Life Technologies, Grand Island, NY) as previously described [34]. The level of each gene was normalized to GAPDH and analyzed by the MXPro software (Stratagene). Values were expressed in quantities relative to the calibrator. Relative quantification can be used to determine fold increases and decreases in gene expression compared with a certain sample or "calibrator." The calibrator was run on each PCR plate through the entire experiment. For these experiments, whole rat brain RNA was used as the calibrator. Probe and primer sequences of clock genes, clock-associated genes and injury-induced genes are shown in Table S1.

Experiment 2: Confirmation of circadian clock gene expression changes in the hippocampus by protein analysis

To confirm that gene expression data correlated with changes in protein levels, a time point was chosen where the expression of the circadian clock gene was different in tissue from injured rats compared with that of naïve or sham-injured rats. For these experiments, rats were subjected to moderate fluid-percussion TBI or sham injury as described above. In addition, naïve rats were included and all tissue was collected at the same time-point post injury, or time of day in the case of the naïve rats.

For immunohistochemical analysis, rats were perfused with 4% paraformaldehyde and sacrificed 20 h after TBI at 08[ratio]00. Naïve rats were also sacrificed at 08[ratio]00. Each brain was dissected and post-fixed in paraformaldehyde, rinsed in PBS, embedded in 30% sucrose and stored

at 4°C until sectioned. Brains were embedded in Tissue-Tek O.C.T. (Sakura, Hayward, CA) for sectioning. Coronal sections (10 µm) of the hippocampus were mounted on pre-cleaned, plus slides (VWR, West Chester, PA). Immunofluorescence localization was performed as follows: sections were hydrated in PBS at room temperature and blocked in 5% normal goat serum/0.3% Triton X-100 in PBS. Slides were then incubated with a primary antibody diluted in 1.5% normal goat serum/0.3% Triton X-100 in PBS overnight at 4°C. Sections were washed in PBS and incubated in an ALEXA-conjugated antibody diluted in 1.5% normal goat serum/0.3% Triton X-100 in PBS at room temperature in the dark. Then, sections were washed in PBS, rinsed in dH20, mounted in hard set-DAPI (Vecta-Shield, Vector laboratories, Inc. Burlingame, CA) and cover slipped. All antibodies were purchased from Santa Cruz Biotechnology Inc. (Per2 # H-90, Cry1 # H-84) except for Bmal1 (catalog # Ab3443, Abcam, Cambridge, MA). Mean fluorescence intensity levels were calculated for each image and corrected for the background using ImageJ software (NIH).

For Western blot analysis, rats were subjected to moderate TBI or sham injury as described above. Naïve rats were also included. Rats were sacrificed 20 h after moderate TBI or sham injury at 08[ratio]00 and 32 h after injury at 20[ratio]00 h. Hippocampi were dissected and frozen on dry ice. Tissue was homogenized in an ice-cold buffer containing 2% sodium dodecyl sulphate (SDS), protease cocktail inhibitor (Sigma-Aldrich), 1 mM phenylmethylsulphonyl fluoride (PMSF), 1 mM dithiothreitol (DTT), 5 mM ethylenediaminetetraacetic acid (EDTA) in 50 mM Tris-HCl, pH 7.4, incubated on ice for 5 min and then centrifuged at 14,000 g for 10 min at 4°C. Protein concentrations were determined by means of the bicinchoninic acid (BCA) assay (Thermo Scientific, Rockford IL) using a Nano-drop spectrophotometer (Thermo Scientific, Rockford IL) according to the manufacturer's instructions. Proteins (40 µg) were separated on an SDS-PAGE 8% to 16% gel and transferred to 0.2 µm PVDF membranes. Blots were blocked using a blocking solution (BS: 5% non-fat dry milk in TBS containing 0.1% Tween 20 (TBS-T), then incubated with a mouse anti-Period 2 antibody (catalog # 611138, BD Biosciences, San Jose, CA) diluted 1[ratio]1000 in BS at 4°C overnight. Blots were then incubated with an anti-mouse HRP conjugated secondary antibody (catalog # 7076, Cell Signaling, Danvers, MA) diluted 1[ratio]3000 in BS for 1 h at room temperature. The blots were washed in TBS-T, followed by incubation for 5 min in enhanced chemiluminescent solution (ECL plus, GE Healthcare), and exposed onto X-ray films for varying lengths of time (5 sec to 1 min). To normalize the expression of Period 2, the blots were re-incubated with a mouse anti-GAPDH antibody (catalog # ab8245, Abcam, Cambridge, MA) diluted 1[ratio]10,000 in BS. Blots were incubated with an anti-mouse HRP-conjugated secondary antibody (catalog # 7076, Cell Signaling, Danvers, MA) diluted 1[ratio]3000 in BS. The intensities of the bands were quantified using UN-SCAN-IT software (Silk Scientific Corporation, Orem, UT) and PER2 protein expression was normalized to the expression of the housekeeping gene GAPDH (n = 3).

Experiment 3: Circadian locomotor activity after TBI

Rats were either naïve or received a sham injury or moderate TBI as described above (n = 6). Surgical procedures were performed at 12[ratio]00 each day; 2 h after recovery from anesthesia, rats were placed in the activity-monitoring home cages with food and water ad libitum. Locomotor behavior was monitored after injury using the Cage Rack Photobeam System with Flex-Field software (San Diego Instruments, San Diego, CA), which quantifies rat locomotor activity using a 4 × 8 photo-beam configuration. Beams were set 5 cm above the cage floor to track horizontal activity. The number of beam breaks were counted and categorized as either peripheral or central activity. Data was collected in 30 min bins over a 48 h period.

Statistical Analysis

Each circadian clock gene was analyzed for expression in the hippocampus and SCN separately. Data analyses were conducted using analysis of variance (ANOVA) for a two-factor experiment. The two factors were treatment group (naïve-day1, sham-day1, sham-day2, TBI-day1, TBI-day2) and time of day (16[ratio]00, 20[ratio]00, 24[ratio]00, 04[ratio]00, 08[ratio]00, and 12[ratio]00). Main effects and interactions were assessed at the $\alpha = 0.05$ level of significance. Multiple comparisons were conducted using a t statistic with the standard error computed from the residual mean square in the ANOVA. Since more than 100 comparisons were tested, the 0.0005 level was used for comparison-wise error rate. Statistical computations were carried out using PROC GLM in SAS®, Release 9.1 [35].

For immunohistochemistry data, fold changes between the mean fluorescence intensities were measured and calculated, using ImageJ software, in sections from TBI and naïve rat brains, and analyzed using the one sample T-test.

Western blot data were analyzed for PER 2 protein at each time point using ANOVA for a single-factor experiment, i.e injury group (naïve, sham and TBI). The injury group was assessed at the $\alpha = 0.05$ level of significance. Multiple comparisons were conducted using Fisher's least significant difference procedure with Bonferroni adjustment for the number of comparisons. Statistical computations were carried out using PROC GLM in SAS®, Release 9.1 [35].

Our locomotor activity experiment is a two-factor experiment with repeated measures. The two factors are treatment group (naïve, sham, TBI) and time (48 h and 5 periods). Data analysis was conducted using the SAS® system, Release 9.1 [35]. Main effects and interactions were assessed at the $\alpha = 0.05$ level of significance. Multiple comparisons were conducted using Fisher's least significant difference procedure with the Bonferroni adjustment for the number of comparisons.

Results

TBI Effects on the Expression of Circadian Clock Genes in the SCN and Hippocampus

We first confirmed, by quantitative, real-time PCR analysis, previous reports showing that several circadian-related genes such as Bmal1, Clock, Cry1, and Period 1, 2 and 3 (Per1, Per2, Per3) and Timeless (Tim), are present in the SCN and the hippocampus of naïve rats and are expressed in an oscillating manner (Figure S1A). Moreover, in addition to the circadian-related genes, we found that injury-induced genes in the hippocampus, including BDNF, heat-shock protein 70 (Hsp70) and glutathione peroxidase-1 (Gpx-1), were expressed in an oscillating manner in naïve rats (Figure S1B).

We found that TBI disrupted the expression of several of the circadian genes that were expressed in an oscillating manner. In neurons of the SCN, obtained by LCM (Figure 1A, upper left panel), a significant increase in the expression of Cry1 was detected at 08[ratio]00 (20 h post injury) on

day 1 (TBI vs. naïve and sham at the same time point; $p<0.05$, as well as between TBI on day 1 vs. TBI on day 2 at the same time point; $p<0.05$). Bmal1 expression was significantly increased on day 2 at 08[ratio]00 h (44 h post injury; TBI vs. naïve and sham at the same time point; $p<0.05$) (Figure 1A).

TBI alters cyclic expression of circadian clock genes measured in rat suprachiasmatic nuclei (SCN; A) and hippocampus (HC; B) using quantitative real-time PCR (qPCR).

In whole tissue samples of the hippocampus, expression of four clock-related genes was altered by TBI (Figure 1B). A significant reduction was observed in the expression of Cry1 at 08[ratio]00 (20 h post injury) on day 1 (TBI vs. sham at the same time point; $p<0.05$), and at 08[ratio]00 on day 2 (44 h post injury; TBI vs. sham at the same time point; $p<0.05$).

Expression of Bmal1 was significantly reduced in the hippocampus at 08[ratio]00 on day 2 (44 h post injury) in TBI vs. sham at the same time point ($p<0.05$). Per2 expression in the hippocampus was also significantly reduced at 20[ratio]00 (4 h post injury) on day 1 (TBI vs. naïve and sham at the same time point; $p<0.05$) and at 20[ratio]00 (32 h post injury) on day 2 (TBI vs. naïve at the same time point; $p<0.05$). Finally, expression of Tim was significantly reduced at 20[ratio]00 (8 h post injury) on day 1 in TBI vs. naïve and sham at the same time point ($p<0.05$), and at 08[ratio]00 h (20 h post injury) in TBI vs. naïve, and at 20[ratio]00 (32 h post injury) in TBI vs. sham at the same time point ($p<0.05$; Figure 1B, lower panel). Two other genes associated with circadian function, the transcriptional repressor, Rev-erb alpha (also known as nuclear receptor subfamily 1, group D, member 1; Nr1d1), and the transcriptional co-activator, peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), also showed diurnal rhythms of expression in the hippocampus of naïve rats, but the expression of Nr1d1 and PGC-1α was not altered by TBI (data not shown).

TBI Disrupts Diurnal Expression of BDNF

To determine whether disruption of circadian gene expression patterns in the SCN impacted clock-regulated genes in the hippocampus, we measured mRNA levels of BDNF, Hsp70 and Gpx-1 in hippocampal tissue from injured, sham-injured and naïve rats over a 24 h period. Expression of BDNF at 08[ratio]00 (20 h after injury) was significantly reduced in the TBI group compared with the naïve group ($p<0.05$; Figure 2A, upper panel). Although not statistically significant, BDNF mRNA levels showed a tendency to be increased in the sham-injured group compared with the naïve group at 04[ratio]00 h (16 h after injury). Large variability in Hsp70 and Gpx-1 data prevented these results from reaching significance (Figure 2B, C).

Injury-associated genes in the hippocampus that also demonstrate diurnal variations in mRNA levels.

Protein Expression Confirmation of Q-PCR Results

Immunofluorescence and Western blot analysis were used to correlate the results of the circadian gene expression studies with protein expression. Based on the q-PCR results, three genes of interest (Bmal1, Cry1 and Per2) were selected and hippocampal tissue was tested using immunofluorescence techniques for sensitivity to detect the protein product of each gene. We were able to detect PER2, CRY1 and BMAL1 in the dentate gyrus (DG) and PER2 and CRY1 in the cornu ammonis (CA; Figure S2). However, we found that PER2 and BMAL1 protein expression did not correlate with mRNA expression at the time points in which gene expression differences were detected. Differences in expression of CRY1 were apparent. Thus, we compared hippocampal tissue from injured rats with that of naïve rats at one time point 08[ratio]00 (20 h after injury). CRY1 protein expression in hippocampal pyramidal neurons was reduced after injury compared with the naïve brain (Figure 3) and this result correlated with changes in Cry1 gene expression at the same time point (20 hours) after TBI (Figure 1B). Using immunofluorescence, no other correlations between mRNA levels and protein levels were detected. This is most likely due to variability in a time lag between mRNA and protein expression. However, using Western blot analysis, we did observe a correlation between gene and protein expression of PER2 at 08[ratio]00 (20 h post injury) and 20[ratio]00 (32 h post injury; Figure S3).

Immunofluorescence detection of Cryptochrome1 (CRY1) protein expression in hippocampal neurons from naïve rats (A–C) and injured rats (D–F).

TBI Effects on Diurnal Rhythms of Locomotor Activity

In separate groups of rats, locomotor activity was monitored for 48 h after TBI or sham injury, or the equivalent time period for naïve rats. This was averaged over 30 min intervals to demonstrate a diurnal pattern of activity (Figure 4). Activity profiles were constructed by dividing the 48 h time course into 5 periods based on the light/dark cycle and the mean activity was calculated for each period (Figure 4, inset). Dark phase increases in activity were significantly reduced during Period 2 (the first dark phase measured) for both TBI and sham-injured groups compared with naïve rats ($p<0.05$). By Period 4 (the second dark phase), the sham group had returned to the same level as naïve However, the TBI group continued to show significantly reduced activity compared with both naïve and sham ($p<0.05$). Patterns of behavioral activity in the TBI and sham groups correlated with and mirrored the patterns of Cry1 and Bmal1 gene expression in the hippocampus (compare Figures 1 and and4)4) and like the gene expression data, were not phase-shifted.

Time-course of locomotor activity in rats, measured over a 48 h period, following surgery.

Discussion

This is the first demonstration that TBI alters circadian clock gene expression in the SCN and the hippocampus. TBI enhanced expression of Cry1 mRNA at 20 h after injury and Bmal1 mRNA at 44 h after injury in the SCN while reducing expression of these two genes in the hippocampus (Cry1 mRNA expression is reduced at both 20 h and 44 h after injury and Bmal1 mRNA expression is reduced at 44 h after injury). This is consistent with the concept of a feedback loop regulating oscillatory gene expression between the SCN and the hippocampus. These injury-induced alterations in expression of Cry1 and Bmal1 in both the SCN and hippocampus imply that TBI disrupts the timing of the central master

clock. This is the first report that shows TBI disrupts the oscillatory expression pattern of several circadian clock and clock-associated genes in the SCN and the hippocampus, and for some genes (e.g., Cry1 and Per2), these changes in patterns of mRNA expression correlate with changes in levels of protein expression and patterns of locomotor activity. Consistent with previous reports, our results showing diurnal patterns of expression of circadian clock-and clock-associated genes as well as injury-associated genes in the hippocampus [36] and SCN [37] are substantiated by the presence of protein products for these clock-genes in the hippocampus (CRY1, PER2 and BMAL1 in the dentate gyrus, and CRY1 and PER2 in the cornu ammonis).

Our primary finding that the expression patterns of key central-regulator genes, Bmal1 and Cry1 are altered by TBI in both the SCN and the hippocampus suggests that the communication between these two brain areas may be disrupted or dysregulated due to injury. Since the hippocampus mediates learning, memory and cognition, and diurnal regulation by the SCN is essential for proper hippocampal function, disruption of the oscillatory gene expression patterns in these two brain areas seems likely to play a role in the long-term cognitive effects of TBI.

The changes in gene expression observed here in genes with diurnal expression patterns are not phase-shifted; it is the magnitude of expression of clock genes that has increased or decreased compared with naïve and sham-injured animals at specific time points (this is true for the locomotor activity changes as well). Most of these differences occurred at 08[ratio]00 or 20[ratio]00 – at times when normal peak expression would occur. These points in time each coincided with 2 h after a change in phase (dark to light at 06[ratio]00 and light to dark at 18[ratio]00), so it seems that the internal system of entrainment is awry and either not able to mount the appropriate response or over-responsive to the daily phase changes. Because the oscillatory expression of Cry1 and Bmal1 are essential for the core autoregulatory transcriptional-translational feedback loops that compose the mammalian clock [38], [39], these disruptive effects of TBI on expression of these genes in the SCN and hippocampus support the hypothesis that circadian rhythms are important in learning and memory and disruption of these rhythms may have debilitating consequences for hippocampal function [40]–[42]. Our data provide evidence for a plausible molecular mechanism for circadian clock dysfunction and memory problems associated with TBI.

The circadian clock is intimately involved in cellular functions [43]; disruption of circadian rhythms in all organisms is associated with reduced fitness and increased vulnerability to disease [2], [44]. Circadian oscillations in hippocampal MAPK and cAMP activity suggest that the persistence of long-term memories may depend on reactivation of the cAMP/MAPK/CREB transcriptional pathway in the hippocampus during the circadian cycle [20]. Phase-shifting has been shown to disrupt circadian oscillations in MAPK and cAMP signaling pathways, which play critical roles in hippocampal-dependent memory [23]. The pattern of oscillations of the injury-associated genes BDNF and Hsp70 seemed phase-shifted in the sham-injured group. Although we did not directly test for phase-shifting, it would be expected due to effects of general anesthesia (isoflurane) [45]. However, in the injured rats, the expression of BDNF, and to a lesser extent, Hsp70, appeared to be reduced at 08[ratio]00, which is consistent with the results for the clock-related genes, suggesting that the effects of injury have a temporal aspect. Expression of Gpx1 appeared to be damped at 08[ratio]00 to 12[ratio]00 in both the sham and TBI groups, again pointing to the effects of anesthesia [45].

Given the disruptive effects of TBI on endogenous circadian gene expression, we note with interest that TBI patients who commonly suffer from disorders of the sleep-wake cycle and depression often receive interventions using such compounds as melatonin (an endogenous

neuroendocrine hormone) and fluoxetine (a selective serotonin reuptake inhibitor [SSRI], antidepressant), that, in addition to their primary therapeutic effects, also manifest chronobiotic properties [46], [47]. Although the antidepressant effects of fluoxetine are primarily associated with promotion of synaptic plasticity and neurogenesis [48], [49], it is conceivable that these may also be attributable to its chronobiotic effects, i.e. fluoxetine has been shown to phase advance the circadian clock in the SCN [50].

Both melatonin and lithium (a mood-stabilizer), reduce neurodegeneration in animal models of TBI; these effects have been attributed, at least in part, to antioxidant properties [51]. However, effects on circadian function may also play a role. Endogenous melatonin secretion can be disrupted in TBI patients. Patients with severe brain trauma exhibited clearly disrupted patterns of melatonin secretion, whereas those with less severe trauma showed relatively intact diurnal rhythms [52], suggesting that exogenous supplementation with melatonin may improve circadian clock function and potentially improve outcome after injury. Melatonin has been shown to contribute to improvement of hippocampal-dependent cognition in immature rats after brain injury [51] and, positively modulate memory processing [53]. Lithium also influences the circadian clock and enhances hippocampal neurogenesis [54]. Lithium acts via inhibition of glycogen synthase kinase-3β which phosphorylates and stabilizes Nr1d1, which we found to be expressed in the hippocampus [55]–[57]. Thus, melatonin and lithium may contribute to recovery from brain injury through multiple mechanisms that sometimes overlap to re-establish circadian function and to provide neuroprotection through anti-oxidant effects [58].

The dearth of clinically effective therapy for TBI patients makes the prospect of a novel therapeutic strategy to re-establish normal circadian rhythms worth investigating. Another potential compound for re-setting the master clock is rosiglitazone, a peroxisome proliferator-activated receptor-γ (PPARγ) agonist currently in use to regulate blood sugar in type II diabetic patients. It has been shown to be neuroprotective in brain injury [59]. Rosiglitazone directly effects expression of Bmal1 in blood vessels, and is important in regulating circadian rhythms in blood pressure and heart rate [60]. Considering that Bmal1 is a key component of the molecular circadian clock, rosiglitazone is another compound that could potentially be used to re-set circadian rhythms.

DNA damage from TBI can result in apoptotic and necrotic cell death. Aberrant cell cycle activation after TBI is known to cause cell death. Cellular circadian clocks are functionally linked to the cell cycle. Thus, DNA damage can alter the circadian clock within cells [61], [62]. Dysfunctional circadian rhythms could thereby enhance TBI-induced neurodegeneration by contributing to DNA damage and increasing expression of genes involved in oxidative stress and inflammation. Furthermore, nucleotide excision repair activity, up-regulated after TBI in the mammalian brain, is highest in the afternoon and evening hours [63], further indicating that functional outcome after TBI has a temporal component that could be manipulated therapeutically.

The disruption of circadian rhythms after TBI may influence the physiological response to therapeutic interventions; dysregulation of diurnal patterns of expression of genes involved in drug absorption, distribution, metabolism and excretion has been associated with lack of efficacy in clinical trials. Basically, drugs can have different effects when given at different times of the day [64]. In TBI patients, dysregulation of circadian rhythms may be a confounding factor in assessing the timing of, or response to treatment.

Here, we present a plausible molecular mechanism for the disruption or disturbance of circadian rhythms after TBI. However, since we did not examine clock gene expression or behavior beyond the first 48 h after injury, our studies merely suggest a conceivable mechanism for disturbed circadian rhythms but do not constitute proof. The coincidence of locomotor changes with changes in clock gene expression is suggestive but not definitive and requires further study that is beyond the scope of this initial investigation.

Understanding the molecular mechanisms of dysregulated circadian rhythms after TBI provides insight into other neurological and mental disorders such as Alzheimer's disease and depression for which TBI is a risk factor [65]–[68]. Disturbed circadian rhythms are thought to contribute to the pathophysiology of these disorders. Thus, we speculate that pharmacotherapies with beneficial chronobiotic effects that may be used to treat TBI patients may also prove efficacious in mitigating circadian rhythm disturbances in Alzheimer's and depressed patients.

Supporting Information

Diurnal variations in expression of clock and clock-associated genes in the hippocampus of naïve rats. A: circadian clock and clock-associated genes: B: injury-associated genes with oscillating expression patterns. mRNA levels were determined using quantitative real-time PCR (qPCR). Tissue was collected at 4 h intervals starting at 16[ratio]00 for a 24 h period. Data are presented as mean+SEM (n = 6 rats/time point).

Immunofluorescence detection of three circadian clock gene products in hippocampal tissue taken from naïve rats at 08[ratio]00. CRY1 and PER2 protein are detectable in the dentate gyrus (DG) and pyramidal cells of the hippocampal CA1-3 regions (CA). BMAL1 is only detectable in the DG. The antibodies used are as follows: rabbit anti-CRY1 (1[ratio]50 dilution); rabbit anti-PER2 (1[ratio]50 dilution); rabbit anti-BMAL1 (1[ratio]250 dilution). All antibodies were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA). Nuclei are stained blue with DAPI. Magnification is 10×.

Western blot analysis. Period 2 (PER2) protein expression in rat hippocampus at 08[ratio]00 (20 h post-injury) and 20[ratio]00 (32 h post-injury) demonstrates changes in relative protein expression levels after injury. Data did not reach statistical significance but does correspond with qPCR data at the same time points. Rats received moderate fluid-percussion traumatic brain injury (TBI) or sham injury at 12[ratio]00 or were naïve. Data was averaged for each group (n = 3), normalized to GAPDH and quantified using UN SCAN it software (Silk Scientific).

BACK TO TOP

## New perspectives on central and peripheral immune responses to acute traumatic brain injury.

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Abstract

Traumatic injury to the brain (TBI) results in a complex set of responses involving various symptoms and long-term consequences. TBI of any form can cause cognitive, behavioral and immunologic changes in later life, which underscores the problem of underdiagnosis of mild TBI that can cause long-term neurological deficits. TBI disrupts the blood–brain barrier (BBB) leading to infiltration of immune cells into the brain and subsequent inflammation and neurodegeneration. TBI-induced peripheral immune responses can also result in multiorgan damage. Despite worldwide research efforts, the methods of diagnosis, monitoring and treatment for TBI are still relatively ineffective. In this review, we delve into the mechanism of how TBI induced central and peripheral immune responses affect the disease outcome and discuss recent developments in the continuing effort to combat the consequences of TBI and new ways to enhance repair of the damaged brain.

Keywords

Traumatic brain injury, blood–brain barrier, neuroinflammation, cytokines, chemokines, stem cells

## Introduction

Traumatic brain injury (TBI) is a complex process involving a broad spectrum of symptoms and long-term consequences including disabilities. It is a serious health problem in the United States and around the world. Recent data show that approximately 1.7 million people sustain a TBI annually [1,2] including U.S. soldiers involved in combat operations and public safety personnel surviving terrorist attacks. An estimated 150 to 300,000 military personnel from Operation Iraqi Freedom and Operation Enduring Freedom suffered from TBI [3-5]. It contributes to 30% of all injury-related deaths and costs about $60 billion annually. TBI of any form, mild to severe, can cause intellectual and cognitive deficits, mood and behavioral changes both short- and long-term [6-9]. In the long term, these can cause potentially permanent changes and may lead to posttraumatic stress disorder (PTSD) in the general population as well as those in the military.

Besides psychological symptoms, immune suppression from TBI and subsequent infections are important consequences [10].

Although TBI can range from mild to severe, most TBI is mild and characterized by brief changes in mental status and cognitive ability [11]. Although the consequences of mild TBI are not readily appreciated, it can still cause infrastructural damage to the brain and secondary axonal injury [12] and shows symptoms like cognitive or intellectual deficits and behavioral and personality changes

even six months after injury [10]. In most patients suffering from mild brain injury, the symptoms disappear within six months but many others suffer in a variety of way that may be underappreciated and treated inadequately or improperly. Even under asymptomatic conditions, unhealed neurodegeneration may cause a spectrum of diseases with huge cost to society [10].

Once the brain suffers mechanical insult, the injury process evolves over time and includes (a) primary injury caused by direct or indirect contusion resulting in shearing or stretching of brain tissue, subdural hematoma and cerebral ischemia (b) secondary injury characterized by diffuse axonal injury and inflammatory reactions, and (c) regeneration. The secondary, that is, the nonmechanical injury phase, is progressive and lasts from hours to days [13,14], significantly contributing to neurological disabilities [15]. Injury to the cerebral vasculature breaks the blood– brain barrier (BBB), allows entry of immune cells and stimulates inflammatory reactions. The molecular events result in apoptosis, inflammation, altered plasticity and neuronal regeneration.

The complex nature of acute and chronic inflammatory reactions may aggravate the pathologic outcome or promote the repair process [16,17]. Also, multiorgan damage in trauma patients can lead to elevated circulatory levels of inflammatory cytokines that may contribute to the post-TBI pathogenesis of the brain [18] and cause multiple organ dysfunction syndrome (MODS) and death [19]. In this review we discuss the mechanism of interaction between the systemic immune response and the brain after TBI and current novel treatment approaches to combat TBI-induced damage (Figure 1).

Figure 1 Possible mechanism and the interactions between brain and systemic immunity after traumatic brain injury (TBI). Blood–brain barrier (BBB) disruption allows peripheral immune cell infiltration into the brain. Interaction between brain and peripheral immune organs can cause either hyperinflammation or immune suppression. Anti-inflammatory cytokines may eventually lead to neuronal recovery

Response of the central nervous system to TBI: neuroinflammation and pathobiology of the CNS The BBB protects the brain and maintains the homeostasis. Following TBI, a massive release of excitatory amino acid neurotransmitters, particularly glutamate, takes place [20,21]. These molecules interact with neurons and astrocytes and cause increased Ca2+, Na+, and K+ fluxes through overstimulation of glutamate receptors. As a consequence, catabolic processes are activated resulting in BBB breakdown [17]. The kinin system, excitotoxicity, activation of the innate immune system leading to neutrophil recruitment, mitochondrial alterations and microglial activation lead to generation of reactive oxygen species (ROS) which in turn trigger downstream pathways and cause oxidative damage, modifications in tight junctions and matrix metalloproteinase (MMP) activation. Thus ROS play an important role in mediating TBI-induced changes in BBB permeability [22]. ROS have also been implicated in fungal toxin T-2-mediated alteration in

BBB permeability [23]. Recent animal studies have shown that BBB breakdown involves transcriptional changes in the neurovascular network and eventual neurodegeneration [24].

The leaky BBB allows the passage of inflammatory molecules and cells into and out of the injured brain initiating a cascade of responses in the brain and other organs. The most important events contributing toward the pathology of TBI are reactive astrogliosis, microglial activation, infiltration of immune cells in the CNS and neurodegeneration. Both the primary and secondary mechanisms of TBI cause neurodegeneration and contribute to post-traumatic neurological deficits [25,26]. One of the major pathological outcomes of these mechanisms is diffuse axonal injury (DAI), the main clinical feature of human TBI, leading to diffuse degeneration of cerebral white matter [27,28]. In a rodent model of diffuse TBI, Cernak et al. [26] have shown hypertension, brain edema, increased permeability of BBB, DAI and apoptosis of the cerebral cells following a high velocity impact. Alder et al. have characterized the pathological and behavioral changes in a lateral fluid percussion model (LFPI) of TBI in mice [29]. The process of TBI-induced neuronal cell death has multiple, overlapping and distinct molecular mechanisms [30]. Following TBI, neuronal cell death can be induced by caspase-dependent or –independent pathways [31], by cell cycle activation in which mature neuronal cells reenter the cell cycle and then die [32] or by autophagy [33]. In the caspase-dependent pathways, caspase 3 appears to play the major role in causing TBI-induced apoptosis, although caspase 6 and 7 have also been acknowledged as proapoptotic molecules [34]. The caspase-independent pathway is more complex and involves mitochondrial proapoptotic molecules including apoptosis-inducing factor (AIF) [35] and its regulators like PARP-1 [36,37], cyclophilin [38,39] and heat shock protein-70 (HSP-70) [40]. These mechanisms probably work together in stress-induced neuronal cell death and, therefore, inhibition of only one pathway may not be sufficient to protect neurons after TBI [41] (Table 1).

Role of neurocytokines and neurochemokines in the central response to TBI

In the 1980s, scientists observed that the brain, endocrine system and immune system function together to maintain homeostasis in health and prevent disease [55]. After Spangelo and coworkers identified cytokines and their role in inflammation and immunity [56], brain researchers began to study the actions of cytokines in the CNS. In 1992, Ban et al. [57] found that interleukin-1β (IL-1β) was synthesized in the brain under pathological conditions while others showed that peripherally synthesized cytokines were transported to the brain via the bloodstream or cerebrospinal fluid (CSF) and secreted into the brain parenchyma during breakdown of the BBB [58], thus linking the brain and immune system [59]. The chemokines are the chemotactic cytokines that play an important role in leukocytes migration [60]. Their role in signaling in the CNS was reported by investigators in the late 1990s [61-63]. Under inflammatory or neurodegenerative conditions in the CNS, chemokine molecules are synthesized by activated microglia or astrocytes which take part in the defense of the CNS by recruiting monocytes to the injury site [64-67]. Under normal physiological conditions the tight junctions of the BBB prevent infiltration of circulating leukocytes into the brain parenchyma [16,68]. Pathological conditions

like infections, mechanical trauma or toxicity may disrupt the BBB and allow immune cells to enter the brain parenchyma in response to chemokine signaling from resident immune cells.

In addition to macrophages and glial cells, neurons have also been found to express chemokines and chemokine receptors in the brain under physiological and pathological conditions [2,62,69,70]. Fractalkine (CX3CL1) was the first chemokine seen to be constitutively expressed by the neuronal cells of the CNS [66]. Later, other chemokines like CXCL14/BRAK; [71,72], CCL20 [45], CCL21 [47], CXCL12/SDF-1 and CCL2/MCP-1, were found in neuronal cells under various pathological conditions including TBI. Helmy et al. [43] have reviewed the temporal profile of 42 cytokines after TBI in human patients. Upregulation of CCL20 has been observed in human subjects one day after severe TBI [43]. Furthermore, a recent study identified CCL20 as a dual-acting chemokine with the potential for inhibiting immune reactions and more importantly in attracting inflammatory effectors and activators [44]. Studies in our laboratory showed cerebral as well as systemic expression of CCL20 after mild TBI in rats [45]. Recently, Biber and co-workers [46,47,73] showed that damaged neurons produce CCL21, which assumes a neuromodulatory function. In a spinal cord injury model, Zhao et al. [74] have shown that CCL21 expressed by the damaged neurons used the CXCR3 receptor instead of the usual CCR7 receptor to activate the local microglial cells [75-77] and initiate inflammatory reactions. These neurochemokines can also be involved in nonimmune-related functions like neuromodulation or neurotransmission, which could be important in TBI. As Rostene and colleagues have pointed out, this could be the complex communication network between the neurons and the cells in its microenvironment that informs them about the damage [2].

In addition to chemokines, various cytokines have also been reported to be expressed following TBI, including TNF-α associated with activated microglia and astrocytes that may initiate the inflammatory process [78]. IL-6 in the injured brain has been associated with reactive astrogliosis, neuronal injury, and infiltration of peripheral cells [78-81]. TGF-β expression in the astrocytes and microglia after injury has been implicated in the pathology and dysfunction of the CNS and IL-1, IL-6, IL-8, IL-10, granulocyte colony-stimulating factor, TNF-α, FAS ligand and monocyte chemo-attractant protein 1 [18,82-84] are thought to account for the progressive injury. In a rat fluid percussion injury model a biphasic production of TGF-β, mainly of TGF-β 2, was detected in the ipsilateral cortex, with a first peak at 30 minutes and a second peak at 48 hours after the lesion. This response was accompanied by transient production of TNF-α and IL- 6 occurring between five and eighteen hours after trauma. From this temporal pattern, Rimaniol et al. suggested an alternative pro- and anti-inflammatory role of TGF-β in the regulation of the brain cytokine network providing an endogenous mechanism for the control of the inflammatory reaction in traumatic brain injury [85].

Activation of resident immune cells of the CNS following TBI

Microglial activation is integral to the response of the brain and spinal cord to injury [86]. A number of factors including pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, nitric oxide, prostaglandins, and superoxide and other reactive oxygen species are released by microglia and modulate secondary injury as well as recovery after injury. Microglial activation is regulated in part by poly(ADP-ribose) polymerase-1 (PARP-1)[87].

Using a PARP-knockout mouse model of TBI, Whalen et al. [54] showed improved motor and cognitive functions after TBI and thereby indicated a detrimental role of PARP in the pathogenesis of TBI. In 2006, Bernardo and colleagues [88] observed that inhibition of microglial activation by peroxisome proliferator-activated receptor (PPAR)-gamma and its synthetic agonists by expression of surface antigens, synthesis of nitric oxide, prostaglandins, inflammatory cytokines and chemokines by TBI-induced brain inflammation could be controlled [88]. Perivascular macrophages are reactive cells that produce IL-1β and TNFα after CNS injury. In the perivascular endothelium these cytokines induce the expression of adhesion molecules and promote leukocyte infiltration [89].

Response of the peripheral immune system to TBI: systemic immune activation and suppression after TBI

Multi-organ damage following TBI can lead to increased numbers of infiltrating inflammatory cells and levels of cytokines in the brain. Because of the compromised BBB, these cells and molecules gain access to the brain and aggravate the pathogenesis of TBI [18]. In spite of the importance of systemic inflammation and circulating inflammatory molecules in TBI, only limited investigations have been performed in this area. In a study on rats, Whalen et al. [54] observed systemic neutrophilia together with increased BBB permeability when granulocytecolony stimulating factor (GCSF) was administered prior to cortical contusion injury (CCI). In another study Utagawa et al. demonstrated that systemically administered IL-1β markedly influenced the histopathological and behavioral outcome following fluid percussion injury. The leaking of pro-inflammatory molecules like cytokines, arachidonic acid metabolites, proteins of the contact-phase and coagulation systems, complement factors and acute-phase proteins, as well as hormonal mediators [90] through the compromised BBB into the circulation may generate a systemic immune response syndrome (SIRS) [90,91] characterized by hyper-inflammation or may release anti-inflammatory molecules targeting IL-1β, IL-6 or TNFα resulting in compensatory anti-inflammatory response syndrome (CARS) to block development of SIRS [19].

The production of inflammatory mediators is regulated by the negative feedback provided by the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) efferent limbs in CARS [19]; but in TBI, an imbalance between these two can lead to immunological dysfunction like organ damage or susceptibility to infections [91]. Stress-mediated release of cortisol and catecholamines can enhance the immune suppression. Direct infection through a skull fracture in TBI or from the transmigration of enteric bacteria after a closed head injury may cause infection, pneumonia and sepsis which can be life threatening in TBI or

immunecompromised patients [10]. Griffin [10] has also pointed out that immune suppression after TBI causes retardation of healing in the brain infrastructure. In a 2001 human study, severe immune suppression was observed following severe TBI. Eighteen to seventy-two hours after head trauma, the numbers of circulating T-cells, T-helper cells, T-suppressor [92,93] and NK cells were reduced while the B-lymphocyte count remained normal [92]. There was also an increase in CD4+/CD45+ T cells [10,93]. The immune regulatory functions within the CNS following TBI, for example, microglia and astrocyte activation lead to antigen presentation to T-cells that alters their cytokine response and this may contribute to TBI pathology. On the other hand, the ability of these neuroantigen-reactive T cells to specifically infiltrate the CNS can be used to deliver molecules to augment a recovery response in degenerating CNS tissues [94].

Response of peripheral immune organs to TBI.

Despite ongoing research, the effect of TBI on other organs is largely unknown. In one study Mirzayan et al. [95] evaluated the histopathological changes in lung and liver. Following a single TBI event, they observed migration of immunocompetent cells to peripheral organs leading to various degrees of organ dysfunction. The spleen is a reservoir of peripheral macrophages and other immune cells in the body, and it is now well known that splenic signaling contributes to injury of various tissues after ischemic insult. For example, splenectomy prior to insult protects both the liver [96] and brain [84] from ischemic damage. They have also observed a reduction in spleen size following ischemic insult 84]. Li et al. [97] showed that splenectomy immediately after severe TBI induced by weight drop in rats decreased pro-inflammatory cytokine production, mortality rate and improved cognitive function. It was observed by Das et al. [45] that splenectomy immediately after the induction of mild TBI by lateral fluid percussion in rats attenuated eurodegeneration and CCL20 chemokine expression in the brain. Although the mechanism of spleen-brain interaction is not clear, it as found by Lee et al. [98] that the spleen participates in cerebral inflammation following intracerebral hemorrhage in a stroke model, as splenectomy reduced cerebral edema and inflammatory cell counts (probably by increased circulating catecholamines) [99]. Stewart and McKenzie [100] suggested that sympathetic stimulation can cause the release of immune cells from the spleen and subsequent infiltration into brain tissues. Regardless of the neural mechanism, removal of the spleen  mmediately after the insult would remove the largest pool of immune cells, which should decrease infiltration and consequent neuroinflammation. The thymus is the major source of maturing T-cells in the body.

Although a great deal of investigation has been done to elucidate the relationship between brain trauma and the immune system, very little has been done to explore the function of the thymus after TBI. In a study of LFPI in rats, Das et al. found elevated CCL20 expression in the thymus following TBI [45]. Further investigation is needed to identify the specific function of thymus after TBI in adult rats. In a model of polytrauma combined with shock, Guan et al. observed apoptosis in the thymus, spleen, lung, liver and intestine which could cause the early organ injury and late organ failure seen in polytrauma patients [101]. In an effort to elucidate the

hepatic response to acute brain injury, Campbell et al. [102] observed that clodronate-mediated Kupffer cell (KC) depletion reduced neutrophil- and ED-1-positive macrophage infiltration in IL-1β- injected brain or contusion-injured spinal cord by 70% and 50% respectively. Suppression of KC proliferation may, therefore, reduce secondary injury. Previously this group had pointed out that hepatic cytokines or chemokines produced as a result of acute injury may inhibit neutrophil recruitment to the CNS. [102-105]. In recent studies, decreased liver weight and protein content, altered energy metabolism [106] and p450 dysfunction [107] have been observed following TBI.

Cytokines and chemokines secreted peripherally control TBI

Following TBI, the signaling pathways are activated, inflammatory cells are mobilized and there is enhanced secretion of multiple inflammatory mediators like cytokines, chemokines and damage-associated molecular patterns (DAMPs). DAMPs in turn reactivate the inflammatory mediators and aggravate the damage [108]. The exact role of cytokines in brain trauma is not fully known, although experimental evidences suggest that cytokines play a major role in the body's response to TBI. The major cytokines produced after TBI include tumor necrosis factor– alpha (TNF-α), IL-1β, IL-2, IL-6, IL-8, [91,109], IL-4 [110] and IL-18 [111]. Free radical nitric oxide (NO) is produced by the enzyme inducible NO synthase (iNOS) [112], which is an important inflammatory mediator after trauma in mice [113]. Among peripherally secreted chemokines in response to TBI the role of CCL20 has recently been described. This unique chemokine interacts specifically with the CC chemokine receptor 6 (CCR6) and induces chemotaxis of dendritic cells, T cells and B cells [114]. These cells are residents of the spleen and have the potential to promote neuroinflammation. CCL20 is expressed in inflamed epithelial cells [115] and in the synovial tissues of rheumatoid arthritis patients [116,117]. It has also been shown to be upregulated under normothermic conditions in a rat middle cerebral artery occlusion (MCAO) model [118]. Upregulation of CCL20 along with other cytokines has been observed in human subjects one day after severe traumatic brain injury [43]. Furthermore, CCL20 has been identified as a dual-acting chemokine with the potential for inhibiting immune reactions and more importantly in attracting inflammatory effectors and activators [44]. In a recent study using the LFPI rat model of TBI, Das et al. showed the expression of CCL20 mRNA and protein in spleen and thymus 24 hours after TBI, which is 24 hours before its expression in the brain. Since the thymus is the major source of mature circulating T cells, CCL20 expression in the thymus in adult rats as observed in this study seems significant [45] and should be further investigated.

Is TBI associated with other neurodegenerative disorders?

There is increasing evidence showing that TBI is associated with neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotropic lateral sclerosis (ALS) [119,120]. Epidemiological data indicates a single TBI event may triggeror accelerate the onset of Alzheimer's disease (AD) in later life [121-124]. On the other hand, repetitive

mild TBI has been associated with progressive neurodegeneration [125]. Since, Rudelli et al. [126] reported a case of classic AD pathology in a 38 year old severe head trauma patient, both tau pathologies and Aβ plaques were identified in survivors of single TBI [121,123] Subsequently, cases of AD-like pathology including neurofibrillary tangles and Aβ deposition [124,127-130] were reported in head trauma victims, including boxers, irrespective of age [131].

Although the Aβ plaques in AD and TBI are morphologically different, both contain primarily β1- 42 with some occurrence of Aβ1-40 in TBI [129,130,132]. Aβ1-42 has also been observed in the CSF of severe TBI patients and is thought to be directly related to the increased level of cerebral Aβ [133] and neuronal amyloidogenic amyloid precursor protein (APP) levels after TBI [134]. Although results of animal studies on TBI induced AD pathologies are conflicting, it has been observed that post TBI activation of microglia and proinflammatory cytokine release exacerbates the AD like pathologies [135] in rats and is involved in APP processing that leads to generation of Aβ plaques [136,137].

In contrast to AD, studies attempting to correlate TBI and MS, another neurodegenerative, demyelinating disease of the CNS, are limited. Goldacre and colleagues [138] and Kurland [139] found no evidence of association between TBI and the development of MS. However, risk analysis using Taiwan's National Health Insurance Research Database, indicated higher risk of incidence of MS in patients with a history of TBI compared to non TBI control group [140]. Parkinson's disease (PD) is a neurodegenerative disorder, which affects the dopaminergic neurons of the substantia nigra. PD-associated mitochondrial dysfunction and pathology was observed after mild to moderate TBI and trichloroethylene (TCE) exposure in rats [141]. Also, TBI was reported to cause the nigrostriatal dopaminergic neurodegeneration in a rat model of LFPI suggesting that TBI is a risk factor of PD development [142]. Thus, although TBI appears to be associated with the development of some neurodegenerative diseases, conflicting data exist and detailed human and animal studies are necessary in this field. The most studied association between TBI and AD appears to suggest that TBI activation of immune mechanisms and proinflammatory cytokine activation of microglia contribute to neurodegenerative processes.

Therapeutic approaches for TBI

A number of drugs for TBI have been tested in clinical trials but none has shown much promise. Most of the approaches to TBI therapy aim at treating the secondary neurodegeneration as a single component. Recently, a therapeutic regimen using multifunctional drugs has been proposed and tested in experimental neurotrauma models. The therapeutic agents included hormones like thyrotropin releasing hormone (TRH) and progesterone, heat shock proteins, neurotrophic factors, erythropoietin, statin drugs and antibiotics [143,144], substance P antagonists, cyclosporine, and magnesium salts among others [145].

Anti-inflammatories for TBI

The inflammation following TBI causes tissue damage correlating with the secondary injury phase. Recently much attention has been drawn to the potential therapeutic benefits of inhibiting reactive oxygen species (ROS), reactive nitrogen species (RNS), and several types of tissuedigesting enzymes (matrix metalloproteinases), prostanoids, leukotrienes, and proinflammatory/inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α).

Inhibition of TNF-α with cannabinoids like pentoxifylline and dexanabinol, and use of corticosteroids or NSAIDs like ibuprofen or minocycline to reduce inflammation in the brain have shown promise in animals but failed in clinical trials [146]. Corticosteroids are a family of anti-inflammatory drugs that are widely used in autoimmune and allergic conditions and to reduce tumor-induced cerebral edema; but they failed to show any benefit in human trials of TBI involving adults and children [147]. Reduction of oligodendrocyte death and axonal degeneration by minocycline, a tetracycline derivative was observed in a spinal cord injury model [42]. Cederberg et al. [148] suggested that timing is crucial in inflammatory intervention, as IL-1, IL-6, and TNF-α may also play an anti-inflammatory role in a later stage of TBI-induced brain inflammation. Also, the PPAR-gamma agonist 15d-prostaglandin J(2) was shown to control brain inflammation by inhibiting microglial activation after TBI.

Gene therapy for TBI

Gene therapy is a promising approach for the treatment of several diseases and conditions including TBI. With the advent of improved experimental techniques like microarrays for gene expression analysis, new targets are emerging for the treatment of diseases, drug development,immunotherapeutics and gene therapy. Colak et al. have identified several gene networks potentially involved in TBI that includes the C1ql2, Cbnl, Sdc1, Bdnf, MMP9, and Cd47 genes [149]. Redell et al. observed changes in hippocampal miRNA expression corresponding to the pathophysiological changes following injury and identified these as potential targets for gene therapy [150]. Degeorge and coworkers demonstrated that administration of viral-mediated glial cell-line derived neurotrophic factor (AdGDNF) one week prior to cortical contusion injury in rats resulted in neuroprotection but not functional recovery [151]. Attempts have been made to target mRNA translational regulation to combat neurodegeneration. Aberrant RNA oxidation, RNA degradation, altered RNA splicing and ribosomal changes – all leading to mRNA translational abnormalities have been described by many authors in different neurodegenerative conditions [152,153]. The mRNA translational regulation is affected by small non-coding microRNAs. The miRNA-argonaute complex suppresses the translation of target mRNA and each miRNA can regulate the translation of hundreds of mRNA targets and control the expression of many genes. Under cellular stress, a subset of microRNAs increases while expression of other miRNAs is decreased [154]. High throughput sequencing has shown that the human brain expresses over 1000 miRNAs, the functions of only approximately 500 of which have been determined [155]. MiRNAs have

been implicated in various neurodegenerative conditions including TBI. Using microarray analysis, Redell and coworkers observed changes in the hippocampal expression levels of 444 miRNAs at 3 and 24 hours after controlled cortical impact injury in rats. In this study, 50 miRNAs were overexpressed including targets for proteins known to be initiated after injury [150]. Lei et al. also observed up- and down-regulation of rat cerebral miRNA up to 72 hours after TBI [156] while Liu et al. reported altered miRNA profiles after traumatic spinal cord injury in mice [157]. The potential exists for using miRNAs and small interfering RNAs (siRNAs) as therapeutic agents, but much work needs to be done before they will become a regular part of the physician's tool kit. The si/miRNAs can be various transfection agents including liposomes, polyethylenimine (PEI), chitosan nanoparticles or by electroporation. Apart from the potential disadvantage of off-target effects, RNA knockdown can be useful in treating TBI.

Transplantation-based approaches for treating TBI

In the past two decades, restorative therapeutic approaches focusing on repair or replacement of damaged or dead cells following TBI have gained importance [158]. Cellular transplantation is the method of choice because the brain itself has a limited capacity for self-repair. Early experiments with transplantation of fetal neural tissues with or without nerve growth factor (NGF) were effective [159], but raised issues of practicality and ethics. NT2N cells showed promise in graft survival [160,161]. It was found that ex vivo NGF gene therapy improved cognitive deficits following CCI in rodents [162,163]. Both rodent and human embryonic stem cells have shown encouraging results in survival, integration and attenuation of post-traumatic sequellae. Stem cells have the ability to self-renew and differentiate depending on specific cues.

Neural stem cells in particular can divide unlimitedly and differentiate into neurons or glial cells. It was observed that E14.5 mouse embryonic stem cells transplanted with or without a fibronectin scaffold following CCI improved behavioral symptoms [164]. Xenotransplanted human neural stem cells have been found to survive in injured rodent brains and to express astrocytic and neuronal antigens [165,166]. They migrated to the hippocampus, corpus callosum and ipsilateral sub-ependymal zone [167] and decreased the number of degenerating neurons [168]. Bone marrow-derived stem cells (BMSCs), either hematopoietic or mesenchymal, are advantageous in that they can be harvested from the same animal and thereby avoid the problems of cell availability and immune rejection. These cells have successfully been transplanted into injured rats by different routes where they express neural and glial cell markers (35, 36) and migrate to the subventricular zone, hippocampus and pericontusional areas [169] indicating neurogenesis and improved neurobehavioral outcome [170]. Ma et al. [171] transplanted neural stem cells (NSCs) modified to encode brain derived neurotrophic factor (BDNF) in rats after TBI and found significant improvement in graft survival, neurogenesis and behavioral outcome. In another study in Wistar rats, functional improvement and colonization of BMSCs were observed after TBI and the recovery was found to be facilitated by granulocyte colony stimulating factor (G-CSF) [172]. Human fetal

neural stem cells (hfNPCs) transplanted after CCI in SD rats increased angiogenesis and reduced astrogliosis [173]. As a long term effect they observed functional improvement, reduced lesion volume and increased neuronal survival surrounding the lesion [173].

The potential of therapeutic transplantation of immortalized progenitor cell lines after TBI, has also been tested by various authors. HiB5 cells derived from embryonic rat hippocampus [174,175], MHP36, the fibroblast growth factor 2 (FGF-2)-responsive Maudsley hippocampal cell line clone 36 [176] and C17.2, which is a clonal multipotent progenitor cell from murine cerebellum [177], have been tested for their efficacy in improving repair of the contusion site, migration, neurogenesis and neurobehavioral outcome. Hunang et al. [178] reviewed successful preclinical studies and clinical trials of cell-based therapeutics for different neurodegenerative conditions including TBI. They mentioned the use of restorative transplantation involving fetal/embryonic brain and spinal cord tissue, stem cells including embryonic, neural, hematopoietic, adipose-derived adult stem/precursor cells, skin-derived precursor and induced pluripotent stem cells, glial cells (Schwann cells, oligodendrocyte, olfactory ensheathing cells, astrocytes, microglia, tanycytes), neuronal cells (various phenotypic neurons and Purkinje cells), mesenchymal stromal cells originating from bone marrow, umbilical cord, and umbilical cord blood, epithelial cells derived from the layer of retina and amnion, menstrual blood-derived stem cells, Sertoli cells, and active macrophages. Functional recovery and angiogenesis were observed following transplantation of endothelial progenitor cells derived from adipose tissues in the injured rat brain [179] showing promise. Some of these approaches have also gone to clinical trials for SCI/TBI [180,181], and the clinical and scientific communities are paying more attention to the restorative treatment options for TBI.

## Conclusion

Traumatic brain injury is a complex process evoking systemic immune responses as well as direct local responses in the brain tissues. The primary or direct damage disrupts the BBB and injures the neurons. This initiates a cascade of inflammatory reactions including chemokine production and activation of resident immune cells. The leakage of the inflammatory molecules through the compromised BBB attracts peripheral immune cells to the site of injury. The effect of TBI is not restricted to the brain; it can cause multi-organ damage and evoke systemic immune response including cytokine and chemokine production. This facilitates the recruitment of immune cells to the site of injury and progression of the inflammatory reaction and subsequent repair processes. In spite of the socioeconomic burden of TBI and worldwide research efforts, an effective treatment is still not available. Translational regulation of mRNA by si/mi RNA shows promise as a safe and specific treatment to combat neurodegeneration. Transplantation-based therapies also have the potential to repair and restore brain structure and function but continued in-depth investigations are needed before they become successful therapeutics.

## Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MD has researched and prepared the manuscript; SM and SSM have made critical suggestions on the content and reviewed the manuscript. All authors have read and approved the final manuscript.

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## Relationship Between Mechanism of Injury and Neurocognitive Functioning in OEF/OIF Service Members With Mild Traumatic Brain Injuries

Military Medicine
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Abstract

Military personnel deployed to combat theaters in Iraq and Afghanistan are at risk of sustaining mild traumatic brain injuries (mTBI) from causes such as improvised explosive devices, motor vehicle accidents, and falls. Despite the high incidence of mTBI in deployed personnel, questions remain about the effects of blast-related vs. non-blast-related mTBI on acute and long-term sequelae. This investigation is a retrospective review of service members who presented for evaluation of suspected mTBI and underwent neurocognitive screening evaluation. mTBI diagnosis was made by semistructured clinical interview. Only individuals in whom mechanism of injury could be determined (blast vs. non-blast) were included. Sixty individuals were included in the final sample: 32 with blast mTBI and 28 with non-blast mTBI. There were no differences between the blast-related and non-blast-related mTBI groups on age, time since injury, combat stress symptoms, or headache. Analysis of variance showed no significant between-group

differences on any of the neurocognitive performance domains. Although speculation remains that the effects of primary blast exposure are unique, the results of this study are consistent with prior research suggesting that blast-related mTBI does not differ from other mechanisms of injury with respect to cognitive sequelae in the postacute phase.

## Introduction

Military service members deployed to Iraq and Afghanistan are at risk of sustaining a mild traumatic brain injury (mTBI) from improvised explosive devices, blunt force trauma, motor vehicle accidents, and falls. An increasing proportion of these injuries are blast-related. It has been argued1 that blast exposure may be associated with distinct neuropathological changes compared to non-blast head injuries because of the unique mechanism of blast pressure waves and potentially compounding effects of that with penetrating trauma from projecting fragments, being thrown against other objects from the explosion, and injuries due to burns, asphyxia, and toxin exposure. Consistent with this notion, some studies have suggested a link between blast exposure and increased headaches2 and vestibular dysfunction.3 However, at this time, the research evidence for specific blast effects on the central nervous system (i.e., nonimpact, blast-induced mTBI) remains highly limited.4
Questions also remain about the neurocognitive effects of blast-related injuries vs. other injury mechanisms for TBI. Recent investigations have found no differences with respect to cognitive sequelae between blast-related injury and mTBI from other injury mechanisms in the acute5 or chronic phase.6 The purpose of the present study was to further examine this issue by comparing the neuropsychological performance of blast vs. non-blast mTBI patients in a clinical sample of individuals referred for assessment in postacute or chronic phase of care.

## Methods

### Participants and Procedures

Participants were identified from consecutive admissions of Operation Enduring Freedom/Operation Iraqi Freedom military service members referred to the TBI Clinic at Brooke Army Medical Center (BAMC) for neuropsychological testing between January 2008 and January 2010. This archival study was approved by the BAMC Institutional Review Board. One hundred and twenty service members were referred for neurocognitive screening and served as the sample pool for the current investigation. Diagnosis of TBI was made through semi-structured clinical interview and record review by a physiatrist, nurse practitioner, or physician assistant. The Department of Defense utilizes an electronic medical record system (Armed Forces Health Longitudinal Technology Application, or AHLTA) with built-in templates which guide the provider with specific questions and prompts which the clinician can use to elaborate if necessary. The specific AHLTA template developed for mTBI was used to structure these interviews. Consistent with the American

Congress of Rehabilitation Medicine criteria,7 mTBI (also referred to as concussion) was operationally defined as one or more of the following: loss of consciousness (LOC) less than 30 minutes; loss of memory for events immediately before (retrograde amnesia) or after the injury event (post-traumatic amnesia [PTA] < 24 hours); any alteration in mental state at the time of the injury (dazed, disoriented, confused); presence of focal neurological deficits; or a Glasgow Coma Scale (GCS) score ≥13. Moderate TBI was defined as GCS score between 9 and 12, LOC greater than 30 minutes but less than 24 hours, and/or duration of PTA >24 hours but <7 days. Consistent with current Department of Defense guidance,8 individuals with positive neuroimaging findings who otherwise met criteria for mTBI were classified as moderate TBI. Demographic and injury data were also collected as part of the archival design of the current study.

Thirteen participants were excluded because they did not meet criteria for mTBI. An additional 14 service members were excluded because they had major body burns (n = 3), traumatic amputations (n = 10), or both (n = 1) affecting administration of the neurocognitive measures. Twenty-nine participants were excluded because they fell below empirically derived cut scores for suboptimal effort on psychometric testing (see “Measures” for additional details). Four service members were excluded because they were missing variables on key measures of interest. Participants were not excluded based on a comorbid psychiatric disorder or a history of psychiatric diagnosis.

The final sample consisted of 60 individuals, all of whom were at least 18 years of age, spoke English fluently, and had sustained an injury while on active duty military service. The study population was divided into two subgroups on the basis of etiology of the interview-confirmed mTBI diagnosis: blast (n = 32) and non-blast (n = 28). If blast was one of multiple mechanisms of injury, the participant was assigned to the blast group. Study participants were assessed approximately 6 months postinjury. Statistical analysis was completed using PASW software Version 18.0 (PASW, Chicago, Illinois).

## Measures

### Cognitive Functioning

After being determined medically stable, patients were administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)9,10 as a neurocognitive screening instrument as part of their initial work-up in the TBI Clinic. The RBANS was administered as a stand-alone instrument and was not used in combination with a larger battery of neuropsychological tests. The RBANS is a widely used measure of cognitive functioning and provides five domain index scores (i.e., immediate memory, visuospatial/constructional, language, attention, and delayed memory) and a combined total index score. The RBANS has been validated to assess cognitive functioning among a variety of populations including TBI.11 An effort index (EI) was

calculated for the RBANS based on the work of Silverberg et al12 using digit span and memory recognition raw scores. Individuals with an EI greater than zero (i.e., if list recognition < 18 or digit span < 8) were excluded from analysis secondary to unreliable test results.

Headache Intensity

The Headache Impact Test (HIT-6) is a brief, six-item questionnaire measuring headache severity and its impact on daily functioning. It was developed using item response theory to provide a brief measure of headache-related disability.13 Given the finding of increased headache in blast-injured individuals in a prior investigation,2 a specific measure of headache intensity was included in the study.

Post-Traumatic Stress

The Post-Traumatic Checklist-Military version (PCL-M)14 is a self-rated interval-level rating scale used to screen for post-traumatic stress disorder (PTSD). The PCL-M consists of 17 items, each designed to capture one of three distinct clusters of symptoms representing the B, C, or D diagnostic criteria described for PTSD in the "Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision."15 These three clusters are labeled re-experiencing ("B" items, 1–5), avoidance or numbing ("C" items, 6–12), and hyperarousal ("D" items, 13–17). The frequency of occurrence of each symptom for the past month is marked using a 1 (not at all) to 5 (extremely) Likert-scale scoring. Scores are derived by summing the weighted frequencies for all items marked and can range from 17 to 85. The PCL-M has been validated for use in samples of military veterans and active duty populations.

Results

Blast-related (n = 32) and non-blast-related (n = 28) mTBI groups were compared on demographic variables and injury characteristics (Table I). There were no differences between groups on age, time since injury, HIT-6 scores, or PCL-M scores. Blast vs. non-blast groups did differ on gender, with the sample including only 6 females, all in the non-blast group. However, males did not differ from females on any neuropsychological measure.

The RBANS scores are interval data with a normative mean of 100 and a standard deviation of 15. A series of six analyses of variance showed no significant blast-related vs. non-blast-related mTBI group differences on the RBANS total performance score or any of the five subscales, even without a correction for multiple comparisons. Analyses were rerun using age, time since injury, HIT-

6 scores, and PCL-M scores as covariates. Although PCL-M was a significant covariate, no blast-related group differences were found on any RBANS score.

## Discussion

The current study examined the neuropsychological performance of military service members who sustained a mTBI of blast vs. non-blast etiology an average of 6 months postinjury. Results revealed no differences between blast and non-blast TBI groups on RBANS total score or any of the five RBANS cognitive domain scores (i.e., immediate memory, visuospatial/constructional, language, attention, and delayed memory). Overall, results do not provide any evidence that TBI with blast etiology differs from other TBI mechanisms, at least with respect to cognitive sequelae in the postacute timeframe. A handful of previous investigations have examined cognitive sequelae of blast vs. non-blast injuries and the current findings are consistent with these studies. Belanger et al[6] found no differences in cognitive performance between blast and non-blast groups an average of 2 years postinjury and Luethcke et al[5] found similar results when examining blast and non-blast groups within 72 hours of injury. Although speculation remains that the effects of primary blast exposure are unique, current study results, in combination with previous findings, suggest that blast and non-blast TBI have similar cognitive presentations over time, beginning from the more acute injury stages and continuing over the course of several years.

In addition to neurocognitive outcomes, a few investigations have examined the association between blast mechanism and increased vestibular dysfunction and psychiatric disturbances. Wilk et al[2] found that blast mechanism was significantly associated with increased headaches at 3 and 6 months postdeployment compared with a non-blast injury mechanism, and Belanger et al[6] found that individuals with a blast injury tended to endorse greater PTSD symptoms in the chronic postinjury stage than individuals with a non-blast mechanism of injury. These authors speculated that these findings may be attributable to unique contextual features of blast injury (i.e., proximity to high decibel explosions which could be associated with eardrum rupture and tinnitus, the presence of particularly distressing events following blasts such as vulnerability to attack by snipers and witnessing injury of others that are less prevalent in non-blast injuries) and not necessarily reflecting brain dysfunction from mTBI. Notably, in our sample, blast mechanism was not associated with increased headaches or PTSD symptoms.

This investigation had some unique strengths. The study examined cognitive differences associated with TBI mechanism of injury at a time point not previously explored (an average of 6 months postinjury), which yielded similar results to past studies that examined groups in the acute phase as well as several years postinjury. Additionally, we utilized a clinical sample and therefore potentially averted some of the issues associated with the evaluation of individuals seeking disability. Further, we included only subjects who passed an embedded effort measure.

Given the retrospective nature of the study, there were also however several limitations. First, the sample size was relatively small. Although this could be considered a threat to statistical power, it should be noted that assuming a moderate effect size for the measures included and an $\alpha$ of 0.05, the study was sufficiently powered at a level of ≥0.80.[18] Additionally, there may have been some degree of selection bias as a minority of patients seen in the TBI clinic (i.e., 16%) underwent neuropsychological screening. Such a bias may offer an explanation for the equal number of blast vs. non-blast injuries seen in this sample relative to the Wilk et al[2] study. Additionally, study participants were categorized as blast-injured if any element of their concussive experience resulted from blast exposure, and thus some participants in the blast-injured group may have sustained additional non-blast injuries. Such a classification could potentially confound results and future research may wish to examine those affected by only primary blast injury. Next, the principal dependent variable in this study was a brief cognitive screening tool (RBANS), rather than a more comprehensive neuropsychological evaluation. Future investigations should aim to replicate and expand the scope of the current findings. Future research should also seek to include symptom validity tests that possess greater sensitivity as the RBANS EI has been shown to lack sensitivity relative to stand-alone measures of effort.

Finally, the designation of injury mechanism was in large part based on patient self-report. Although recent efforts across the service branches have improved the medical documentation of combat related mTBI/concussion, historically there has been limited information other than patient self-report available to clinicians during postacute or chronic TBI assessments. Consequently, this clinical and empirical limitation is common in this type of evaluation but could nevertheless have impacted group designation. With the expected improvement of theater medical documentation, this limitation may resolve as research of this nature continues. In addition, it is possible that a blast mechanism of injury may have resulted in greater medical comorbidities. This study did not have variables that examined medical comorbidities and whether one group received more medical treatment before the evaluations conducted in this study. However, none of the subjects in the study received cognitive rehabilitation services in our clinic before completing neurocognitive evaluation. Therefore, potential treatment differences between groups are unlikely to have eliminated group differences in cognitive functioning.

Despite these limitations and the concurrent need for replication and expansion, the current findings are still considered of importance given the relative dearth of research in this area. Considering the high numbers of deployed soldiers experiencing blast-related concussions while serving in recent military conflicts, the current study supports previous research suggesting that mechanism of injury may not be a variable of significance with regards to neurocognitive outcome or treatment planning.

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***Warrior Care***

## Medical Stability Operations—One Approach to Transforming the Department of Defense Military Health System

Military Medicine
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The Department of Defense Instruction (DoDI) 6000.16 entitled Military Health Support for Stability Operations was published in 2010 and established policy that Medical Stability Operations (MSOs) would be a core military mission. The instruction set out to institutionalize how the Military Health Support (MHS) would effectively support MSOs and assist in bridging the gap with other actors operating in the same space. What is less clear is the current status of the MHS in accomplishing the responsibilities outlined in the DoDI. Even more concerning is how these efforts will support the “new” strategic guidance for the DoD published in January 2012 that states U.S. forces will no longer be sized to conduct large-scale, prolonged stability operations. In the absence of a publicly available DoDI 6000.16 implementation strategy, this article proposes the use of an organizational transformation process developed by internationally acclaimed leadership and organizational change expert Dr. John Kotter. The eight-step process is used as a framework to explore ways to effectively transform the DoD in meeting the intent of the MSOs DoDI. The past decade has transformed how service members think about MSOs. Now is the time to transform the MHS with urgency to institutionalize these thoughts.

As ill-trained and equipped service members returned from their early assignments in support of Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF), a sense of urgency was felt to institutionalize the lessons observed in what became known as Stability Operations. The Office of the Secretary of Defense published a revolutionary Department of Defense Directive (DoDD) in 2005 entitled Military Support for Stability, Security, Transition, and Reconstruction Operations. The DoDD 3000.05 signed by the

Deputy Secretary of Defense established policy that stability operations were now a core mission for DoD and given priority comparable to combat operations. Many responsibilities were clearly outlined and appropriate action initiated by the highest levels of leadership throughout the Services for implementation. These actions facilitated the training and equipping of service members to meet the existing and projected future stability operation requirements.

During this time, the Office of the Secretary of Defense for Health Affairs embarked on an effort to define the role of Military Health Support (MHS) for stability operations. Missions, tasks, and activities employed during previous and ongoing stability operations including military-to-military and military-to-civilian peacetime (e.g., Southern Philippines), conflict (e.g., Afghanistan), and postconflict (e.g., Bosnia-Herzegovina) missions; humanitarian assistance (e.g., hospital ship missions); disaster response (e.g., Pakistan earthquake); and medical capacity building efforts were assessed. The Department of Defense Instruction (DoDI) 6000.16 entitled Military Health Support for Stability Operations was finally published in 2010 and established policy that Medical Stability Operations (MSOs) would be a core military mission. MSOs were defined as “tasks assigned to establish, reconstitute, and maintain health sector capacity and capability for the indigenous population when indigenous, foreign, or U.S. civilian professionals cannot do so.”

The DoDI signed by the Under Secretary of Defense for Personnel and Readiness echoed policy articulated in the DoDD 3000.05 by stating MSOs shall be given priority comparable to combat operations. The DoDI further mandated this policy would “be explicitly addressed and integrated across all MHS activities.” Mandating the MHS be prepared to work closely with other government, nongovernmental, and private sector organizations was welcomed by many returning from the battlefield. Quite frankly, these were tasks already being conducted by military medical personnel in support of OEF and OIF. The new instruction set out to institutionalize how the MHS would effectively support MSOs and assist in bridging the gap with other actors operating in what is referred to as the MSOs space.

What is less clear is the MHS status in accomplishing the responsibilities outlined in the DoDI 6000.16. Even more concerning is how these efforts will support the “new” strategic guidance for the DoD released in January 2012. This new guidance mentions the term stability on 11 occasions. It states U.S. forces will be ready to conduct limited stability operations if required but asserts in italics, “U.S. forces will no longer be sized to conduct large-scale, prolonged stability operations.” Reassuring all those who have and continue to serve in stability operations throughout the world, the guidance clearly highlights divesting capabilities to conduct any mission would be unwise, which brings us back to how the MHS is transforming itself to meet the responsibilities of MSOs that will remain an instrument for future engagement. In the absence of a publicly available DoDI 6000.16 implementation strategy, the remainder of this article will use an organizational transformation model developed by Dr. John Kotter to propose one approach.

Kotter is an internationally recognized expert in leadership and organization change behavior. He developed many of his concepts while researching Fortune 500 companies as a professor of Leadership in the Harvard Business School. Kotter published 18 books (12 best sellers) and his Harvard Business Review articles have sold more reprints than any other expert in the field during the same period. In his seminal article “Leading Change, Why Transformation Efforts Fail,” Kotter (1995) proclaims two general lessons from his analysis of successful organizational change: (1) transformation is a process composed of a series of phases that takes considerable time to achieve and (2) critical mistakes within or between any of these phases can have catastrophic impact on the change process. To facilitate successful business transformation, Kotter developed a sequential eight-step process for leaders to employ. The steps and their associated actions and pitfalls are listed. The eight-step process will be used as a framework to explore ways to transform the DoD in meeting the intent of the MSOs DoDI.

Step 1. First, leaders within the MHS must generate a sense of urgency for implementing the DoDI. This urgency must transcend the medical community and be promulgated by the military line leadership. As proposed, it is certainly much easier said than done. However, Kotter contends without a high urgency rate (approximately 75% of management convinced business as usual is unacceptable) serious problems could ensue later in the transformation process. A key element to facilitate this sense of urgency is to contend the status quo poses more problems than moving forward in a new direction. This could be achieved by quantifying the costs associated with current ad hoc MSO activities conducted by the different Services and Combatant Commands. Another option is to quantify the results of current MSO projects to see what impact the MHS is achieving. Objectively identifying inputs and outputs associated with current MSO activities should highlight areas of duplication, poor results, no results, and potentially negative press. If the results are poor, convincing the DoD of embracing the DoDI and moving forward in a unified effort to achieve the specified MSO requirements should be easier. Gaining efficiencies and effectiveness in a time of proposed budget cuts within the DoD should assist the MHS leadership in communicating the sense of urgency and gaining the support of both military medical and line personnel.

Step 2. The second step is to form a powerful guiding leadership coalition that grows over time. Kotter emphasizes both the organizational leader and another 5 to 50 leaders and managers are necessary to implement successful transformation. Diversity from within and outside of the organization is key, based on the assumption the current system is not working. In the context of military MSOs, having the Assistant Secretary of Defense for Health Affairs as the organizational leader with support from the Senior Military Medical Advisory Council (SMMAC) is critical.

The SMMAC is composed of all Service Surgeon Generals, the Joint Staff Surgeon, and other Health Affairs Deputy Assistant Secretaries of Defense. Expanding the military leadership coalition to include Combatant and Functional Command Surgeons as they are tasked with developing strategic plans for MSO implementation is essential. Integrating representation outside the MHS including the Deputy Administrator for U.S. Agency for International Development, the Under Secretary of State for Democracy and

Global Affairs, and the President of InterAction may not fit the normal military business model. However, their participation and input could provide expert guidance, lend credibility to the process, and yield positive results beyond DoD to include the interagency and nongovernmental communities. As the MHS budget tightens, collaboration between the military services, interagency, and broader global health community will be essential to conducting meaningful and sustainable MSOs.

Step 3. Creating a clear vision that explains the direction the organization needs to move is the third step in the transformation process. The DoDI 6000.16 outlines the policy and responsibilities for implementing MSOs; however, a convincing vision of where the effort is leading is somewhat lacking. Injecting ideas such as moving away from low or unmeasured return on investment MSO activities (e.g., Medical Civic Action Programs) and toward true capacity building efforts (e.g., laboratory and surveillance activities) could shed some light. Without this vision, MHS managers will continue to keep the present system of ad hoc medical engagement activities operating and minimize the additional effort necessary to change their organizations. The leadership coalition must develop the MSO vision so that those serving in and out of uniform readily understand it. Ensuring military medical personnel comprehend and take the necessary action to achieve the vision is only half the crusade. Equally important is the ability of other actors in the MSO space to understand the DoD vision and how it may impact their organizations.

Step 4. To facilitate this effort, Kotter incorporates communicating the vision as the fourth step in the model. He observed through research that transformation is impossible without the willingness of a majority of employees to assist and potentially make short-term scarifies to achieve the change. Mobilizing these individuals requires persistent, diverse, and targeted methods to communicate the vision. Without this level and intensity of credible communication, Kotter uses a phrase routinely quoted by military personnel—"the hearts and minds of the troops are never captured." A marketing campaign similar to the one now employed by the MHS addressing military health care reform is essential. Although some may argue the comparison does not match in scale, the current international perception of military MSO activities and host nation beneficiaries deserve nothing less. This marketing campaign could include public discourse about the MSO transformation process. Venues such as the U.S. Institute for Peace, InterAction, and think tanks such as the Brookings Institute, Center for Strategic and International Studies, and Kaiser Family Foundation located in Washington, DC would be ideal locations for the Assistant Secretary of Defense for Health Affairs, Deputy Administrator for U.S. Agency for International Development, and other key members of the leadership coalition to discuss the effort. Linking the MSO transformation effort to the new DoD strategic guidance as well as the National Security Strategy is important. Highlighting where MSOs could support U.S. foreign policy via global health diplomacy and the international communities global health efforts should engender confidence and acceptance by the broader community. Leveraging these external organizations to facilitate the dialogue and communicate the MSO vision beyond the military medical sector through their social media networks would be a wise investment.

Step 5. The fifth step in transforming organizations is to empower others to act on the vision. Encouraging a large number of employees to try new approaches and cultivate new ideas within the parameters of the vision occurs in this phase. Empowering action by removing perceived and actual obstacles such as antiquated organizational structures will embolden employees and lend further credibility to the leadership's commitment for success. A lack of funding to implement the DoDI 6000.16 may be perceived as an obstacle although the potential savings in streamlining existing expenditures on disparate MSOs activities and programs could be leveraged. Lessons should be learned from the implementation of the DoDD 3000.05. Although not solely tied to the Stability Operations Directive, new funding authorities such as Section 1206 of the National Defense Authorization Act for fiscal year (FY) 2006 provided the authority and resources for the Secretary of Defense to train and equip foreign military forces to conduct counterterrorism and stability operations. From FY 2006 to 2011, total allocations were $1.57 billion, which supported programs in 40 countries. Significant efforts made by the Secretary to provide the means for the DoD to implement the Stability Operations Directive clearly empowered the entire department to act on the vision.

Furthermore, there are existing systems in place within the MHS that could facilitate the cultivation of new ideas and turn them into actionable items for the leadership coalition. The DoD Civil Military Medicine Working Group (CMMWG) is composed of joint and interagency personnel that led the DoD Initial Capabilities Document to identify existing shortfalls in conducting MSOs. The Medical Stability Operations Working Group replaced the CMMWG in 2010 and supported the formulation of the Document Change Request outlining how the MHS should adapt to meet future MSO requirements. Leveraging these existing groups of diverse experts in tandem with other internal MHS bodies such as the MHS Metrics Standardization Board to bring new ideas from the field to the leadership should rapidly turn them into standard operating procedures. Current business practices suggest these bodies should report to the MHS Force Health Protection Council led by the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness (DASD FHP&R). However, with the urgency applied to this transformation effort, they should report directly to the MSO leadership coalition (to which the DASD FHP&R is a member) who in turn could update the Military Health System Executive Review Advisory Body that was historically chaired by the Under Secretary of Defense for Personnel and Readiness
Although it is unclear whether this advisory body remains active, policy exists outlining their role and function. Reinvigorating existing structures in a timely manner empowering the MHS to act on the MSO vision will build resolve within their employees and the organization writ large.

Step 6. To transform an organization and achieve the vision takes time. Kotter acknowledges without short-term wins in 12 to 24 months, employees may not be willing to continue on the long journey. He builds in the need to systematically plan and create short-term wins as the sixth step in the transformation model. His experience with successful transformation found managers using techniques such as process evaluation to obtain and disseminate performance improvement data. Additionally, successful organizations publicly rewarded individuals and teams for their innovating contributions throughout the organizational transformation

process. Within the MHS, few resources are dedicated to monitoring and evaluating MSO activities and many within and outside of DoD criticize this shortfall. Hiring experts to fill the void would be ideal. However, as an interim solution, reaching into the existing pool of quantitative and qualitative experts tracking fixed facility MHS data could be a viable alternative. Providing small teams of experts to each of the Services and Combatant Command Surgeon's Offices to develop relevant, reliable, and timely MSO metrics and data should not only support the tracking of short-term wins, but also revolutionize how impact is captured. This information will be vital to the transformation effort and assist the leadership coalition in communicating the successes with personnel in and out of the DoD, to include our elected officials and taxpayers.

Step 7. Assuming performance improvements will be achieved in the near term (possibly 2 years), caution must be exercised in declaring victory. Early gains remain fragile unless the transformation becomes part of the organization's culture. One could argue the MHS experienced this first hand after the DoDI on MSOs was published in 2010. A substantial effort and sense of urgency went into writing, staffing, and publishing the instruction. However, the actual implementation process seems to be unclear and sense of urgency waning. In step 7, Kotter highlights the need to consolidate improvements and produce more change to mitigate this risk. He suggests leaders use the credibility gained from the short-term wins to take on larger challenges that include the systems and structures impeding the transformation vision. Promoting, hiring, and developing change agents at critical junctures and organizations is important to produce more change in support of the vision. Replicating the example set by the Health Affairs International Health Division in creating space for temporary interagency liaisons (e.g., Department of State) to work through, by, and with military medical personnel to address MSOs and other issues could inspire this phase. Conversely, permanently assigning military medical personnel to commensurate interagency and international partner organizations to facilitate the MSO transformation could pay substantial dividends in bridging perceived and actual rifts between these organizations.

Step 8. The final stage in the Kotter model is to institutionalize new approaches. He rightly states until the new behavior becomes part of the social norm and shared values, they remain vulnerable to collapse, should the sense of urgency and pressure fade. Publicizing how the new knowledge, attitudes, beliefs, and behaviors improved performance and ensuring the incoming generation of senior management exemplifies the new vision will enable success toward this goal. Military medicine personnel returning from OEF and OIF as well as other stability operation missions throughout the world such as the Asian Tsunami and Haiti earthquake responses understand the value and inherent challenges with MSOs. Many have taken it upon themselves to institutionalize these lessons observed and learned in their individual organizations. Expanding their noble efforts from the bottom up to the Service and MHS level through the use of resources listed in step 5 will aid in promulgating and institutionalizing MSOs throughout the DoD. Building a medical profession, not a simple additional skill identifier or temporary appointment (e.g., Air Force International Health Specialist), specifically trained and placed in key joint leadership positions to successfully enable MSOs will ensure this transformation effort remains institutionalized beyond the ebb and flow of political administrations.

Kotter recognizes successful transformation efforts can be messy and full of surprises. The MHS should expect nothing less in their MSO transformation effort. It will take time, years to be sure. There will be challenges. Setbacks will occur. However, using a clear and straightforward change process such as the one described here can assuage these negative impacts and set the course for short- and long-term success in achieving the new vision. Key individual and committee leadership at all levels as outlined will be critical. Employing the same sense of urgency currently underway to transform the rising health care costs in the DoD will be necessary—this process will directly support the broader efforts. The past decade has transformed how service members think about MSOs. Now is the time to transform the MHS to ensure deployed service members will no longer have to figure out MSOs on their own.

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## Mission Essential Fitness: Comparison of Functional Circuit Training to Traditional Army Physical Training for Active Duty Military

Military Medicine
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Abstract

Appropriate and effective physical fitness training is imperative for soldier survival and mission success. The purpose of this study was to determine the effects of Mission Essential Fitness (MEF) circuit-style training program compared to standard Army Physical Readiness Training (APRT) on fitness, physiological, and body composition changes. Active duty Army personnel were randomly assigned to two groups (MEF = 34 or APRT = 33) for 8 weeks of training (15 sessions each). The MEF program included functional movements focused on strength, power, speed, and agility. Fifteen exercises were performed continuously for 60 to 90 seconds for 45 minutes. Baseline and post-test measures included the Army physical fitness test, physiological indicators, body composition, and additional fitness indicators. One-way analysis of covariance models indicated that MEF participants significantly increased their push-ups ($p = 0.033$), bench press ($p = 0.001$), and flexibility ($p = 0.003$) and significantly decreased their 2-mile run ($p = 0.003$) and step test heart rate ($p = 0.004$) compared to participants doing APRT. Both groups maintained body composition ($p > 0.05$) and reported no injuries. The MEF training program safely improved muscular strength and endurance, cardiovascular endurance, and flexibility, supporting functional fitness circuit-style exercise training for military personnel.

Introduction

It is widely known that soldiers require a certain level of overall or complete fitness to meet the physical demands of war. Jumping, crawling, rolling, stopping, starting, bounding, climbing, pushing, sprinting from cover to cover, carrying heavy loads long distances, and still being able to complete the mission at hand represent a short list of the required tasks placed upon a soldier. Key measurable fitness components include endurance, mobility, strength, and flexibility. Throughout Army basic training and their Army careers, soldiers are told that they are first soldiers and that their military occupation specialty comes second. Thus, all soldiers must be capable of completing basic infantry tasks. Today, soldiers of the U.S. Military are deemed “Tactical Athletes” or individuals that require high levels of strength, speed, power, and agility because of potential engagement in combat. Deciding on the most appropriate physical training program is imperative for soldier survival and mission success.

To date, most training research conducted by the military emphasizes combat readiness and overall performance improvements on the Army Physical Fitness Test (APFT), which tests aerobic and muscular endurance. The Army Physical Readiness Training (APRT) program is conducted 5 days per week with a focus on mobility, strength, and endurance. The APRT program consists of a warm-up, 50 minutes of exercise, and a cooldown. The exercise portion consists of aerobic and resistance training, a combination that commonly is used by the Army and shows improved fitness and performance on the APFT. However, some have argued that the APFT test does not adequately test combat preparedness (i.e., it does not contain mobility, strength, or anaerobic fitness components and focuses too much on endurance) and the APRT program is not sufficient for combat preparation. Accordingly, the Functional Movement Screen testing endurance, mobility, strength, and flexibility have been implemented for some military populations.

Other training methods combining aerobic and resistance exercises have demonstrated similar improvements in fitness as the APRT program. For example, a 12-week study compared a circuit resistance training program (i.e., 25-minute sessions for 3 days per week of weight machine exercises interspersed with stationary cycling in 60 s intervals) to a standard aerobic exercise program (i.e., 60-minute running sessions for 4–5 days per week) with Air Force personnel and found significant improvements on the Army Physical Fitness Test (APFT) with less training volume, as well as improvements in abdominal circumference for the circuit training group only. Eight weeks of weight-based training (i.e., 60–80 minute sessions for 5 days per week including weight training exercises, 3.2-km runs, sprinting, agility training, and weighted hikes) were compared to the APRT program for Army personnel and resulted in similar improvements on a series of fitness tests.

More recently, circuit-style programs emphasizing functional fitness exercises (i.e., training that familiarizes the body with its operational environment) performed at high intensity have begun to gain popularity among military populations. However, in a meeting with professionals from the American College of Sports Medicine, the Department of Defense expressed reservations about programs characterized by high-intensity repetitions and short rest periods between sets because of increased risk of muscle strains, ligament tears, stress fractures, and the threat of rhabdomyolysis. Stated strengths of these programs included their ability to motivate, excite, and meet unmet training needs in military personnel, as well as their ability to better address skills related to combat readiness. It was deemed important that effective implementation of such programs would need to minimize injury risk and should be monitored closely for signs of overtraining as well as effectiveness.

A newer, mission-specific comprehensive strength and conditioning program called Mission Essential Fitness (MEF) was created to specifically address perceived weaknesses of the existing APRT program (e.g., insufficient for combat preparation) by focusing on movements in multiple planes using a variety of speeds in a circuit training format. MEF is designed to be integrated, progressive, periodized, and focused on increasing core stability. Functional exercises are utilized to mimic movements experienced in combat situations. The purpose of this study was to compare the MEF training program to a standard APRT program. We hypothesized that soldiers randomly assigned to the MEF training would show greater overall physical preparedness through improvements on APFT, physiological and other fitness measures when compared to APRT while maintaining body composition and minimizing injuries.

## Methods

### Participants

Following standard chain-of-command protocol, approval was obtained to conduct and evaluate the MEF training program compared with the APRT program. Active duty Army personnel were invited to participate in the study through contacts with the Army chain-of-command. Rank and years of service were used to randomly assign participants to the MEF intervention group (*n* = 34) or the APRT group (*n* = 33). All participants were currently active in regular physical training.

MEF participants were 82.4% (*n* = 28) male, average age was 27.29 ± 5.68 years, and average years of service were 5.52 ± 4.9. Participants in the APRT group were 84.8% (*n* = 28) male, 27.88 ± 5.38 years of age, and averaged 6.92 ± 5.39 years of service. Institutional review board approval was received to publish study results.

### Measures

Each of the following measures was completed before the initiation (baseline) and at the end of the participants' respective 8-week training programs (post-test). Testing was done during the same time of day for both groups. Participants were asked to maintain adequate hydration throughout the testing as water was provided on-site.

### Army Physical Fitness Test

Push-ups were tested using the Army standards; men and women began with hands shoulder width apart and elbows and body straight. Participants were required to lower themselves until their upper arms were parallel to the ground and complete as many push-ups as possible in 1 minute, pausing only in the up position to rest.

Sit-ups also were tested using the Army range of motion standards; men and women began lying on their backs with their knees bent 90°. While a partner secured their ankles, participants interlocked their fingers behind their head and raised up until the base of their neck was above the base of their spine. They completed as many sit-ups as possible in 1 minute, pausing only in the up position to rest.

One-and-a-half mile and 2-mile run times and maximal heart rate were tested simultaneously on a flat paved road running route. Participants were split up into groups of 10 and outfitted with racing numbers and heart rate monitors. Five testers monitored the run with two at the start/finish line and two testers at the 1.5-mile mark. Run times were recorded using an Ultrak gl10-10 lane timer. Heart rates were monitored using Polar F-11 heart rate monitors. Run times and heart rates were recorded for each participant at the 1.5- and 2-mile markers.

### Physiological Indicators and Body Composition

Physiological measures included resting heart rate, blood pressure, and height. Resting heart rate and blood pressure were taken using a machine after participants had rested for 10 minutes. Height was measured using a wall-mounted FMS grid. These tests, along with body weight, were entered into the Polar Body Age System. Body weight, body composition, and metabolic rate were estimated using a Tanita segmental body composition analyzer/scale (model BC418), a single-frequency device with 8 polar electrodes (Tanita, Japan). This model has shown acceptable validity in comparison to dual-energy X-ray absorptiometry for men ($r$ = 0.54–0.78, $p$ < 0.05–0.001) and women ($r$ = 0.37–0.91, $p$ < 0.05–0.001). Height and weight were used to calculate body mass index (BMI).

### Field Fitness Indicators

The Kasch 3-minute step test (i.e., a submaximal measure of cardiorespiratory fitness) using a 12-inch box and heart rate monitors was conducted where each participant stepped 24 cycles (up-up-down-down) per minute (to a metronome setting of 96) for 3 minutes. Immediately after the 3 minutes of stepping, the participant sat down. Heart rate was taken 60 s after completion of stepping. The Kasch test has been established as a valid submaximal test of $VO_2$ max in males and females aged 7 to 57 ($r$ = 0.95) as well as in women aged 28 to 35 ($r$ = 0.824).

To assess strength, one rep max bench press was tested after instructing the participants on proper form and technique for flat bench press. Participants completed 10 repetitions with a light to moderate load followed by an additional heavier warm-up set of 3 to 5 repetitions. Weight was added in increments until muscular failure was obtained after one successful lift. A 2-minute rest period was given between each lifting attempt. This test is the standard for determining isotonic strength and has shown significant test–retest reliability ($r$ > 0.90).

Mobility components that were tested included flexibility, power, and agility as detailed below.

Flexibility was tested using a flex-tester sit and reach box. Participants sat shoeless with feet six inches apart, toes pointed upward, and heels flat against the flex-tester. The participants kept their hands adjacent to each other and maintained contact with the box during the reach, pushing the guide as far as possible without bending their knees. The best of three trials were recorded to the nearest 0.25 inch (or 1cm). The sit and reach test has been found to be a good predictor of hamstring flexibility with high reliability ($r$ = 0.96–0.98) and validity ($r$ = 0.24–0.53, $p$ < 0.05) for females and males.

To assess power, standing vertical jump was measured using a wall-mounted vertical jump tester. Participants began each test with both feet flat on the floor and reaching as high as possible, marked their reach with a magnet. The participant then lowered themselves to jump without a preparatory or stutter step. A counter movement was performed during the jump, with the arm reaching up and placing an additional marker on the wall. The score was the vertical difference between the two magnets. The best of three trials was recorded to the nearest 0.5 inch. This test has shown acceptable validity in comparison to peak and average power measured by force plates ($r$ = 0.88 and $r$ = 0.73, respectively) as well as high reliability (Cronbach's $\alpha \geq 0.962$).

Standing broad jump was tested to also assess power using a starting line and additional marks every three feet. Participants stood with toes just behind the starting line and jumped as far forward as possible. The participants were required to land on both feet for the jump to be scored. A marker was placed at the back edge of the athletes' rearmost heel, and the yard stick was used to

determine the distance from the starting line to the mark. The best of three trials was recorded to the nearest 0.5 inch. This test has shown good reliability (ICC = 0.97) and validity for peak power ($r = 0.334$, $p < 0.01$) and mean power ($r = 0.499$, $p < 0.01$).

Agility was tested using the pro-agility test, which is a highly utilized test with a standardized protocol and norms for comparing results. Three parallel lines five yards apart were marked with tape. Participants straddled the centermost of the three lines using a three-point stance. On the tester's call, the participant sprinted five yards to the line on the left, then changed direction and sprinted 10 yards to the line on the right, then again changed direction and sprinted five yards back to the center line. Foot contact was required at all lines. The better of two trials was recorded to the nearest 0.01 s.

Aerobic capacity was calculated using 1.5-mile run times with the following formula: relative $VO_2 = 3.5 + 483/(\text{time to run 1.5 miles in minutes})$.

### Intervention

The MEF training program consisted of multiple exercises that focused on strength, power, speed, and agility and was designed to train the body in various planes of movement and at different speeds. This was accomplished by using exercises that allowed the joints to be flexed, extended, and/or rotated. Movement speed was manipulated by adding resistance to the exercise such as barbells, dumbbells, resistance bands, medicine balls, sleds, tires, and body weight. All exercises involved multiple joints (e.g., Olympic lifts, squats, bench press, and pull-ups). Exercises were set up in a circuit fashion, including Olympic weight lifting movements, plyometrics, lower body movements (e.g., weighted walking lunges), upper body movements (e.g., band bicep curls), and core exercises (e.g., plank with feet elevated on a medicine ball). In total, 15 different exercises were performed for 60 to 90 s each, with little to no rest in between each station, for a total of 45 minutes. Participants attended fifteen separate MEF sessions during the 8 weeks, averaging 2 sessions per week.

The APRT program followed published guidelines and focused on a combination of mobility, strength, and endurance exercises. APRT participants attended fifteen one-hour sessions during the 8 weeks, averaging 2 sessions per week.

### Statistical Analyses

All data were double-entered and standard data cleaning and verification procedures employed. Statistical analyses were conducted with PASW Statistics 18. Independent samples *t*-tests were used to compare groups on baseline characteristics. Analysis of covariance was used to evaluate between-group changes in study outcomes with the baseline testing value as the covariate and

group as the constant. Paired samples *t*-tests were used to evaluate within-group changes in body composition. The value for statistical significance was set at $p < 0.05$.

## Results

Random assignment to training groups resulted in statistically equivalent groups on all baseline measures. Characteristics of each training group at baseline, including demographics, body composition, physiological indicators, APFT, and other fitness indicators are shown in displays change scores across all measured fitness variables for both groups. On the APFT measures, the MEF intervention group significantly increased their push-ups by an average of 4.2 ± 5.4 compared to 1.3 ± 5.9 additional push-ups for the APRT group ($p = 0.033$). The MEF group also significantly decreased their 2-mile run times (−89.91 ± 70.23 seconds) as compared to the APFT group (−15.33 ± 69.16 s; $p = 0.003$). The MEF group did show a significant decrease in heart rate of −17.0 ± 15.0 on the step test compared to a −9.0 ± 16.1 for the APRT group ($p = 0.004$). The MEF group improved significantly over the APRT group in bench press strength (13.2 ± 12.1 versus 2.7 ± 11.5 pounds; $p = 0.001$) and flexibility (0.6 ± 1.3 versus −0.5 ± 1.5 inches; $p = 0.003$). Changes in body composition measures and physiological indicators were not statistically significant for either group ($p > 0.05$).

## Discussion

We compared a novel and comprehensive fitness training program, MEF, with standard APRT. Results indicated that MEF participants significantly improved their push-ups, 2-mile run times, step test heart rate, bench press strength, and flexibility as compared to participants engaging in APRT. Thus, MEF positively impacted the comprehensive fitness domains, i.e., strength, power, both cardiorespiratory and muscle endurance, flexibility, and mobility, recently outlined as being important part of “Total Force Fitness.” It is notable that the MEF program produced these measurable improvements after a relatively low dose of training (i.e., 2 sessions per week), which may have helped prevent injuries and overtraining. Previous studies used 3 to 6 training sessions per week. No significant differences were found between groups for changes in blood pressure, or resting heart rate. Neither group experienced significant changes in body composition nor reported any injuries.

This study provides evidence that the MEF training program results in greater fitness gains than the APRT program, differing from previous research that found similar improvements between APRT and a weight-based training program. The MEF program successfully used functional exercises in multiple planes (i.e., sagittal, lateral, and rotary exercises) addressing combat readiness to increase fitness, with no reported injuries or signs of overtraining. Combat situations may require soldiers to move laterally in and out of enclosed areas or vehicles with weighted packs and unstable surfaces, requiring muscles, tendons, and ligament strength for controlled acceleration and deceleration. The absence of injuries during the MEF program suggests that progressive and scaled

workouts are safe when incorporating weight lifting and technical lifts into a circuit-type routine that they address important fitness domains relevant to combat readiness.

The current APFT emphasizes muscular and aerobic endurance with the use of push-ups, sit-ups, and the 2-mile run. However, the U.S. military now recognizes that there are other important fitness domains that deserve attention and that are critical to mission completion and combat readiness. The APRT program currently trains soldiers in a limited number of fitness domains, whereas the MEF program is designed to address all physical fitness domains recognized by "Total Force Fitness." The broad stimuli provided by the MEF program resulted in multiple training adaptations and fitness improvements in muscular and aerobic endurance, strength, and flexibility. In fact, the MEF may better prepare soldiers for the new APFT that also includes tests (e.g., 60-m progressive shuttle runs, rower exercise, standing long jump, push-ups, and a 1.5-mile run) of domains beyond those in the traditional APFT that may better prepare warriors of the demands of modern warfare.

Our study had several important strengths including the participation of active duty Army personnel, demonstrating feasibility of real-world implementation during physical training sessions, and the fact that the MEF demonstrated measurable early phase improvements in a sample of young and healthy soldiers. In addition, we assessed a broad range of fitness domains as recommended by "Total Force Fitness." Finally, the MEF program itself is a novel approach to circuit training that optimizes functional training to prepare soldiers for real-world conditions and improved combat readiness. Our primary limitation for this study was equipment availability for broad assessment of multiple physical fitness domains. For example, it would have been ideal if the oxygen volume testing could have been done using the Bruce treadmill protocol to determine actual $VO_2$ max rather than relative $VO_2$. Additional strength testing also could have been conducted that more closely matched the MEF training protocol to include movements such as the deadlift and shoulder press. Tracking nutrition intake could have provided more information regarding body composition. However, budgetary and practical factors limited our access to additional measures. Future studies should include these additional measures to ensure comprehensive physical fitness assessment. As well, future studies could be powered to examine gender differences as well as effects for soldiers with limited mobility.

## CONCLUSIONS

In conclusion, the results of this study demonstrate that MEF improves muscular strength, endurance, cardiovascular endurance, strength, and flexibility while maintaining body composition and minimizing injuries. These outcomes support the utility of circuit-style functional fitness training for military personnel. Future research could examine whether MEF training leads to better combat specific preparedness for military personnel.

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## Monkey Bites among US Military Members, Afghanistan, 2011

Emerging Infectious Diseases
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Oct 2012

Abstract

Bites from Macaca mulatta monkeys, native to Afghanistan, can cause serious infections. To determine risk for US military members in Afghanistan, we reviewed records for September–December 2011. Among 126 animal bites and exposures, 10 were monkey bites. Command emphasis is vital for preventing monkey bites; provider training and bite reporting promote postexposure treatment.

Military members deployed to Afghanistan face many risks; among these are bites from Macaca mulatta monkeys and possible subsequent infections. In August 2011, a 24-year-old US Army soldier died of a rabies infection contracted while in eastern Afghanistan. This tragedy highlights the threat that animal bites pose to deployed military members.

During 2001–2010, a total of 643 animal bites among deployed US military members were reported (1). Dogs were implicated in 50% of these bites, but several other animals pose risk as well. Prominent among these is the nonhuman primate M. mulatta (rhesus macaque), native to and commonly kept as a pet in Afghanistan (2) (Figure). Risks from M. mulatta monkey bites include physical trauma and/or infection with B-virus (Macacine herpesvirus 1), oral bacteria (including Clostridium tetani), and rabies virus. Although not well characterized in Afghanistan, the risk for exposure to M. mulatta monkeys has been described (3) for researchers (4), tourism workers (5), and US pet owners (6). We examined this risk for US military members deployed to eastern Afghanistan. The work presented herein was reviewed and deemed exempt from internal review board oversight by the Joint Combat Casualty Research Team, the human subjects review board responsible for oversight of human subjects research affecting US military members in Afghanistan.

### The Study

Information about all reported animal bites and exposures affecting US military and coalition personnel is collected by preventive medicine officers assigned to Combined Joint Task Force–1 in eastern Afghanistan. We evaluated these records to identify and describe monkey bites and high-risk exposures among US military members serving in eastern Afghanistan during September–

December 2011. For this study, eastern Afghanistan refers to North Atlantic Treaty Organization Regional Command East, which covers ≈43,000 square miles (110,000 km2). The US military population in eastern Afghanistan during the study period was ≈23,500 persons. Case information obtained included patient age, sex, rank, branch of military service, animal exposures, and treatment details.

We evaluated the cases for the 5 parameters that comprise appropriate initial treatment according to the literature. The parameters are wound care (appropriate cleansing of the wound) (7), antiviral medications for B-virus (valacyclovir) (8), antimicrobial drugs for oral bacteria (amoxicillin/clavulanic acid or clindamycin plus sulfamethoxazole/trimethoprim) (3), verification of up-to-date tetanus vaccination status or vaccine administration in accordance with Advisory Committee on Immunization Practices guidelines (9), and rabies postexposure prophylaxis (PEP). US military policy advised that rabies PEP should adhere to World Health Organization guidelines (10), which recommend giving human rabies immunoglobulin plus 5 doses of rabies vaccine. In accordance with the same policy, adherence to Advisory Committee on Immunization Practices guidelines for rabies PEP with human rabies immunoglobulin plus 4 doses of rabies vaccine was also acceptable (11).

When appropriate initial treatment was not administered, subsequent follow-up was conducted to ensure that patients received required treatment. Appropriate treatment was accomplished by contacting and coordinating with the responsible provider, the patients, and their commanders.

During the study period, we identified 126 cases of animal bites or serious exposures (involving animal neural tissue or saliva affecting the mucosal surfaces or open wounds of the patient). Among these cases, 10 were cases of monkey bites.

Among the 10 military members who had been bitten by monkeys, age range was 22–44 years (Table); most (7) were <30 years of age, and 8 were male. All were junior enlisted or noncommissioned officers; 8 were members of the Army, and 2 were members of the Air Force (Table).

In terms of treatment, 6 received appropriate wound care and washing, 5 received appropriate B-virus prophylaxis, and 8 received appropriate antimicrobial drugs (Table). In terms of prophylaxis, only 4 were evaluated for tetanus status, and 8 received appropriate rabies PEP. Beyond the initial trauma and follow-up visits for rabies PEP, no visits for any illness possibly associated with the bite or exposure were recorded.

All cases involved different monkeys, 8 of which were kept as pets. Of these 8 pet monkeys, 4 belonged to Afghan National Security Forces (ANSF), 3 belonged to Afghan civilians, and 1 belonged to US military members. For the other 2, no ownership data were

available; they could have been wild or pets. One monkey was euthanized and sent to US Army Veterinary Laboratory Europe for testing; brain samples were negative for rabies and B-virus.

Conclusions

Our identification of 126 reported bites or exposures over just 4 months suggests that the 643 animal bites reported for all deployed US military members for the past decade greatly underestimate the true number of animal bites in this population. The number of bites and exposures identified in this study might represent more accurate reporting because of increased attention to animal bites after the US soldier died in August 2011. It is possible that before that time, only more severe bites and exposures were reported but that after that time, more lower-risk exposures might have been reported.

The risk for monkey bites in other populations has been described. The 10 monkey bites reported in this study demonstrate that US and coalition military members in Afghanistan are also at risk for the trauma and the B-virus, bacterial, tetanus, and rabies infections that can result from monkey bites and exposures. The demographics of the population bitten (Army, age <30 years, and male) is representative of the underlying population at risk.

Most monkey-bite patients received appropriate care. This care is laudable, considering the recognized difficulties in treating monkey bites (12). Some patients, however, did not receive appropriate medical treatment initially. Because treatment of monkey bites is not a standard part of US medical education, inadequate treatment could reflect insufficient training and lack of familiarity among US-trained health care providers. It is imperative that before providers are deployed to Afghanistan, they receive proper instruction on the care of animal bites and exposures. Appropriate reporting of any animal bite to military preventive medicine personnel is crucial because it permits oversight of care and timely correction of deficiencies.

Most (7/10) monkeys involved were pets owned by ANSF or Afghan civilians. As the mission in Afghanistan shifts from combat to ANSF mentoring and reconstruction, US and coalition troops will come into increasingly close contact with ANSF and Afghan civilians. Accordingly, the likelihood of deployed US military members being exposed to monkeys in Afghanistan will probably increase. However, although risk for contact with monkeys might increase, an increase in bites is not inevitable. Explicit orders prohibit deployed US military members from adopting local mascots and from interacting with animals or pets owned by ANSF or Afghan civilians. To mitigate the risk for animal bites, it is crucial that commanders enforce these regulations (13).

The risk of being bitten by a monkey could increase as US forces work more closely with ANSF and Afghan civilians. Bites could be prevented by appropriate emphasis from command and enforcement of existing policies prohibiting pet adoption and animal contact.

Treatment of patients who are bitten could be improved by further training of military health care providers on appropriate treatment for animal bites, including monkey bites.

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***Other***

## 2003-2009 Marital Functioning Trends Among U.S. Enlisted Soldiers Following Combat Deployments

Military Medicine
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Oct 2012

Abstract

Objective: This study examined 2003–2009 trends in three marital functioning indicators: marital quality, infidelity, and separation/divorce intent, and in marital dissolution rates among U.S. soldiers. Methods: Marital functioning trends were examined with cross-sectional postdeployment sample data collected under the Land Combat Study from married, male, enlisted soldiers who had deployed to Iraq or Afghanistan (n = 5,928). Marital dissolution rates were examined with population data (n = 1,895,571). The relationships between time (measured by year) and all study variables were analyzed with $\chi 2$ tests of association, analysis of variance, and logistic regression analyses adjusting for combat exposure, mental and physical health, and demographic variables.

Results: Marital quality has declined, and reports of past-year infidelity and separation/divorce intent have increased between 2003 and 2009. However, no increases were observed in marital dissolution rates. Conclusions: The results indicate that more proximal indicators of marital functioning such as decreased marital quality, infidelity, and separation/divorce intent may better illustrate the strain that increased deployment tempo exerts on marital relationships. The findings provide a better understanding of how Army marriages have been affected by the wars, and suggest that further inquiry is needed on military marriages.

Introduction

Based on research findings that have demonstrated an increase in the divorce rates of service members who have deployed to prior conflicts such as the Vietnam War,1 there has been an expectation that the wars in Iraq (Operation Iraqi Freedom [OIF]) and Afghanistan (Operation Enduring Freedom [OEF]) would take a similar toll on marriages of service members. However, the most recent data on service members' marital dissolution trends (Fiscal Year [FY] 1996–FY 2005) indicate that any elevation in dissolution rates cannot be attributed to OIF/OEF deployments.2 The increased rates between FY 2001 and FY 2005 did not exceed FY 1996 rates despite increased deployment separations during this period.2

Nevertheless, marital dissolution may be a lagging indicator of the relationship difficulties caused by the demands of deployment.3 It has been contended that more proximal indicators of marital functioning such as decreased marital quality may better illustrate the strain that increased deployment tempo exerts on marital relationships.3,4 However, no studies were found that have examined whether marital functioning among military couples has worsened over time. Such information would be vital for understanding whether a problem truly exists. Further, such data can be critical for informing policy with regard to whether resources need to be targeted toward marital enhancement programs, and can also pinpoint areas for clinical intervention.

The term "marital quality" describes how well a marriage functions and includes concepts such as marital satisfaction and marital happiness.5 Although poor marital quality does not always lead to marital dissolution, it has been consistently found to be a risk factor for divorce.6 Poor marital functioning also has implications for well-being.7 Among civilians, marital functioning has been found to be associated directly or indirectly with physical health8 and has been prospectively linked to alcohol use disorders.9 It has also been linked cross-sectionally and prospectively to psychiatric disorders,10,11 and prospectively to poor psychological health.12

Among U.S. service members, deployments have both been associated with no changes in13 and decrements in marital satisfaction14; neither study assessed mental health problems or combat exposure. Nonetheless, studies have found associations between combat exposure, mental health problems such as post-traumatic stress disorder (PTSD), and poor marital quality.15–17

However, combat exposure may not directly affect marital quality; its effect may be an indirect one through PTSD and depression symptoms18 or through antisocial behavior.1

Two other proximal indicators of marital strain are infidelity and separation/divorce proneness or intent. Divorce intent can be considered a proxy for marital dissatisfaction.19 Studies have also linked infidelity with marital quality,20 with divorce proneness as well as divorce,21 and to depression and anxiety.22 We have not found any studies that have examined these two indicators in service members.

The current study has two main aims. First, it examines 2003–2009 trends in three self-reported marital functioning indicators to investigate whether the percentage of soldiers reporting high marital quality has declined and whether reports of infidelity and separation/divorce intent have increased over the course of simultaneous combat operations in Iraq and Afghanistan. The association of time with the three marital functioning indicators is also examined with adjustments for combat exposure, somatic symptoms, alcohol misuse, depression, PTSD, and demographic variables. Second, building upon Karney and Crown's study,2 we examine whether these marital functioning trends are reflected in soldier divorce rates between 2003 and 2009.

## Data and Methods

### Participants

As part of a larger study on service member health and well-being (the Land Combat Study), confidential cross-sectional data were collected from 19,227 Active Component U.S. soldiers from brigade combat teams between 2003 and 2009, 3 to 6 months after they returned from deployments to Iraq or Afghanistan. No data are reported for 2005 because the units surveyed in that year were primarily from the Reserve Component. Soldiers were recruited by coordinating with unit commanders who made soldiers available for large group recruitment briefings in which they could voluntarily elect to participate. There were 34,884 soldiers available for the data collections, so the response rate is 55% (19, 227/34,884), which is comparable to Land Combat Study response rates reported elsewhere.23–25 Soldiers unable to attend the recruitment sessions had other work-related duties, were on leave, ill, in training, or were on temporary duty elsewhere. After a description of the study, informed consent was obtained under a protocol approved by the institutional review board of the Walter Reed Army Institute of Research. Missing data ranged from 2% to 3% for the outcomes and from <1% to 2% for the covariates. We selected the married, male, enlisted soldiers who had deployed to Afghanistan and Iraq for our analyses (n = 5,928). Other groups such as females and officers had too few soldiers for meaningful analyses.

Additional data were obtained from the Defense Manpower Data Center (DMDC) in order to report Army divorce rates stratified by rank for FY 2003–2009 (n = 1,895,571). Divorce rates were calculated as a change in status from married at the beginning of a fiscal year to divorced at the end of a fiscal year.

## Measures

### Marital Functioning Indicators

Marital quality was assessed with three items from the 6-item scale Quality of Marriage Index26; the individual items can also be used as single-item predictors.26 The three items were “I have a good marriage,” “My relationship with my spouse is very stable,” and “I really feel like part of a team with my spouse.” The items’ response options ranged from 1 (strongly disagree) to 5 (strongly agree). We used the stringent criterion that only soldiers who indicated that they agreed or strongly agreed to all three items were coded as having high marital quality (24%–37% across 2003–2009). These soldiers were compared to those who disagreed or who gave a neutral response to one or more items. Examining marital quality as a categorical instead of as a dimensional variable is supported by recent research that has shown that there is a small subset of couples who are qualitatively and quantitatively different.

This discordant subset represents between 20% and 31% of couples,27,28 which is consistent with our data.

Soldiers were asked to indicate “no,” “yes,” or “unsure” to whether infidelity had been a problem in their marriages in the past year. Those who responded that yes were coded as reporting past-year infidelity and the other responses were combined into a no/unsure category. One yes/no item measured intent to separate or divorce by the soldier or spouse.

### Combat Exposure

Twenty items from the Combat Experiences Scale, which have been used in similar research,29 were used to measure combat exposure resulting in a total number of combat experiences ranging from 0 to 20. Participants were asked whether or not they had the experience during their latest deployment.

### Mental Health Problems

Major depression was measured with the 9-item Patient Health Questionnaire, a well-validated clinical scale used in primary care30 and military survey research.29 To meet screening criteria for major depression, soldiers needed to report 5 or more symptoms and

indicate little interest or pleasure in doing things as well as feeling down, depressed, or hopeless more than half the days of the past month. PTSD was measured using the 17-item PTSD checklist,31 a validated scale in civilian31 and military32,33 settings. To meet screening criteria, soldiers needed a score of at least 50 (17–85) and had to endorse at least 1 re-experiencing symptom, 3 avoidance or numbing symptoms, and 2 hyperarousal symptoms at a moderate or higher level.29

Alcohol Misuse

Soldiers were asked two questions about their past month alcohol use using a modified Two-Item Conjoint Screen for Alcohol (TICS)34: “have you felt you wanted or needed to cut down on your drinking?” and “have you used alcohol more than you meant to?” The modified TICS is a validated measure widely used in postdeployment screening.35,36 A “yes” endorsement for either item was considered a positive screen.24,37

Somatic Symptoms

Twelve items from the Patient Health Questionnaire-15 were used to assess somatic symptoms. Respondents were asked how much they had been bothered by each symptom in the past 4 weeks using a 3-point scale (0 = “not bothered,” 1 = “bothered a little,” and 2 = “bothered a lot”)38; The items were summed (0–36).

Demographic Measures

Demographic measures included age, rank, education, and years married. Age was a categorical variable with these groupings: 18 to 24 years, 25 to 29 years, 30 to 39 years, and ≥40 years. Rank is a binary variable with junior enlisted (E1–E4), and noncommissioned officers (NCOs; E5–E9) in distinct groups. Education is a categorical variable with ≤GED/high school (HS) diploma; some college or other; and ≥bachelor's. Age and education were dichotomized for the logistic regression analyses. Years married is a continuous variable.

Analyses

This section describes the analyses that were conducted with the sample data from the Land Combat Study; the population-based trend data on divorces are reported as provided by DMDC. Descriptive statistics were used to describe the variables used in the study. The bivariate relationships between time and all study variables were analyzed with $\chi 2$ tests of association and analysis of variance as appropriate. Trends in the marital outcomes are graphically displayed for all enlisted male soldiers, and for junior

enlisted, and NCO subgroups. Sample-adjusted trend lines were calculated with logistic regressions with modal (age [18–24], rank [junior enlisted], education [HS or less], depression [not meeting criteria], PTSD [not meeting criteria], and alcohol misuse [not meeting criteria]) or mean (years married [4.58], somatic symptoms [5.45], combat exposure [9.55]) values entered in the model. Multivariate logistic regression models were used to determine whether there were significant associations between time and the marital functioning outcomes adjusting for combat exposure, mental health, alcohol misuse and physical health, age, rank, and years married. In these models, time was entered as a categorical variable with 2003 as the referent year. The significance of the overall trends in the outcomes was assessed by the Wald test for time entered without an omitted category.

## Results

Table I displays the demographic characteristics of the sample across the 7-year period. Across all years, around two-thirds of the sample was between 18 and 29 years old. NCOs constituted over 50% of the sample except in 2008. The modal educational level reported across years was GED/HS diploma. The mean number of years married was between 4 and 5 years. The $\chi 2$ tests showed significant associations between time and the demographic variables, and between time and mental health problems ($p < 0.01$). Analysis of variances showed that there were significant mean differences in combat exposure and somatic symptoms (but not years married) across time. Tukey's post hoc tests show that the mean combat exposure in 2003 was significantly lower than the mean combat exposure in the other years, but the 2003 mean somatic symptoms was only significantly lower than the mean somatic symptoms of 2004 and 2007.

Also displayed in Table I are the number and percentage of soldiers who screened positive for depression, PTSD, and alcohol misuse, and the means for combat exposure and somatic symptoms. No clear pattern was observed across the years for depression or alcohol misuse. Rates for PTSD rose between 2003 and 2007 but began to decline in 2008. Depression and alcohol misuse rates were lowest in 2009, and the rate for PTSD was lowest in 2003; both alcohol misuse and PTSD rates were higher than those for depression. The mean level of combat exposure was highest in 2006 ( = 11.46, SD = 4.21) and lowest in 2003 ( = 4.17, SD = 6.17). Mean somatic symptoms were lowest in 2009 ( = 4.79, SD = 4.16) and highest in 2007 ( = 6.14, SD = 4.64).

## Marital Functioning Trends

Soldiers who indicated agreement or strong agreement to all 3 marital quality items from the Quality of Marriage Index (Norton, 1983) were coded as having high marital quality, which is shown on the y-axis. The sample-adjusted statistical trend lines were calculated with logistic regression with modal or mean values of study variables (age, rank, education, depression, PTSD, alcohol misuse, number of years married, somatic symptoms, and combat exposure) entered into the model.

Soldiers who indicated that infidelity had been a problem in their marriages in the past year were coded as reporting past-year infidelity. Sample-adjusted statistical trend lines were calculated with logistic regressions with modal or mean values of study variables (age, rank, education, depression, PTSD, alcohol misuse, years married, somatic symptoms, and combat exposure) entered into the model.

Soldiers who indicated yes to their own or their spouse's intent to separate or divorce were coded as positive for separation or divorce intent. Sample-adjusted statistical trend lines were calculated with logistic regressions with modal or mean values of study variables (age, rank, education, depression, PTSD, alcohol misuse, years married, somatic symptoms, and combat exposure) entered into the model display the overall percentage of soldiers who reported high marital quality, past-year infidelity, and intent to separate/divorce as well as percentages by rank (junior enlisted soldiers and NCOs). Generally, there was downward trend in the percentage of soldiers reporting high marital quality from a high of around 70% in 2003 to a low of around 57% in 2009 (Fig. 1), which is consistent with in-theater (Iraq) findings that showed that marital quality declined from 79% in 2003 to a low of 58% in 2009 among junior enlisted soldiers.39 The rates for both junior enlisted soldiers and NCOs generally followed the overall trend; however, junior enlisted soldiers reported lower marital quality than NCOs in every year. Figure 1 also displays the sample-adjusted statistical trend line (described in the Methods). This line illustrates that there was a statistically significant 14% decline between 2003 and 2009.

The rates of soldiers reporting that infidelity has been a problem in their marriages during the past year increased between 2003 and 2008, but the rate declined in 2009 (Fig. 2). The rates for junior enlisted soldiers were higher than the rates for NCOs. The statistical trend line, with the sample adjusted as previously described, shows that infidelity significantly increased by 8% between 2003 and 2009.

There was an inconsistent pattern in the rates for soldiers reporting separation/divorce intent (Fig. 3). The rate was lowest (10%) in 2003 and highest (17%) in 2007, but declined in 2009 to 14%. Consistent with previous findings, junior enlisted soldiers had higher rates of separation/divorce intent than NCOs. The sample-adjusted statistical trend line for this outcome shows that reports of intent to separate or divorce significantly increased by 4% between 2003 and 2009.

Karney and Crown's data showed that the FY 1996–FY 2005 marriage dissolution rates for all enlisted male soldiers hovered between 2% and 3%.2 The DMDC data we obtained (Fig. 4) show that the divorce rates for these soldiers remained largely unchanged between FY 2006 and FY 2009 as well. The rates for junior enlisted male soldiers and for male NCOs (the groups for which we report marital functioning trends) were no different than the overall rates for enlisted male soldiers.

Although we do not report marital functioning trends for officers or females, we have divorce rates for these groups (Fig. 4). The rates for officer males did not substantially change, except that the FY 2009 rate of 3% was about 1% higher than the previous 3 years. Between FY 2005 and FY 2007, the rates for female officers remained under 5% but increased from about 5.5% in FY 2008 to 8.7% in FY 2009; the highest rate reported for that group since FY 1996. The rates for enlisted females between FY 2005 and FY 2009 gradually rose from 8.2% to 9.7%; the highest rate reported since FY 1996.

Table II presents the results of four multivariate logistic regression models, which examined the relationship between time and marital quality, adjusting for the health indicators, combat exposure, and demographic variables. Model A demonstrated that compared to 2003, the odds of having low marital quality for every subsequent year was statistically significant and that relationship held in the subsequent models. The test for overall trend indicates that high marital quality generally decreased over time ($p < 0.000$). The relationship between time and marital quality largely remained the same in each of the subsequent models (B–D) that incorporated the covariates. In the final model (D), somatic symptoms, meeting screening criteria for alcohol misuse, depression, and PTSD decreased the odds of having high marital quality. Interestingly, combat exposure was unrelated to marital quality. Soldiers who have education at the HS diploma/GED level or less were less likely to have high marital quality.

Displayed in Table III is the relationship between time and infidelity, which is also explored with a series of multivariate logistic regression models adjusting for the same covariates as in the previous models. Model A shows that compared to 2003, soldiers in 2007–2009 had greater likelihoods of reporting infidelity. In the subsequent models, only soldiers in 2008 and 2009 report greater likelihoods of infidelity. The test for overall trend indicated that past-year soldier or spouse infidelity increased over time ($p < 0.000$). Of the covariates (Model D), somatic symptoms, and screening positive for alcohol misuse, and depression significantly increased the likelihood of infidelity. Younger, junior enlisted, and soldiers who were married longer were more likely to report past-year infidelity. In neither Models C nor D was there a significant association between combat exposure and infidelity.

Table IV displays, with a similar series of multivariate regression models, the relationship between time and separation/divorce intent adjusting for health indicators, combat exposure, and demographic variables. Models A to D showed that soldiers in years 2004 through 2009 had significantly greater odds of reporting separation/divorce intent compared to soldiers in 2003. The overall trend for this outcome over time was significant ($p < 0.001$. Of the physical and mental health covariates, meeting criteria for alcohol misuse, depression, and PTSD increased the odds of separation/divorce intent. Junior enlisted ranked soldiers also had a greater likelihood of separation/divorce intent in the final model. As with the infidelity, combat exposure was not significantly associated.

Discussion

This study examined a 7-year trend in marital quality, infidelity, and separation/divorce intent in enlisted, married, male soldiers who had deployed to Afghanistan or Iraq. Overall, we found that the rates of marital quality decreased over time, whereas the rates of infidelity and separation/divorce intent increased over time. The trend that we identified in separation/divorce intent is of particular concern because it shows a small increase in the proportion of male enlisted marriages that may be nearing dissolution/divorce. These trends remained significant after we adjusted for covariates such as combat exposure, mental health disorders, and physical health symptoms.

Although marital problems have been found to increase the likelihood of divorce,6,21 we have found no study that has shown that marital problems such as decreased marital quality or infidelity inevitably lead to divorce. It has been noted that married individuals often stay in poorly functioning marriages.6 Even if poor marital functioning always leads to divorce, it may be difficult to determine the temporal tipping point at which individuals decide to terminate their marriages. Additionally, Army marriages may be relatively resilient given the instrumental support services offered by the Army.3 Consequently, we do not know whether the marital functioning trends that we have identified will presage increased marital dissolution rates beyond FY 2009. However, the prudent approach would be to exert efforts and resources in the near term to bolster existing marriage interventions and implement marriage enrichment programs among military couples to forestall any dissolution. Instead of being reactive to the possible looming increase in marital dissolutions, the Army can make proactive preventive measures to strengthen soldiers' marriages. Healthy marriages are known to directly contribute to better performance and retention of service members,2 outcomes that contribute to optimal functioning of the military as a whole.

Poor marital functioning in its own right is a significant concern because of its association with psychological and physical morbidity.8,12 Soldiers who have returned from the wars may have mental health problems which could adversely affect marital functioning.15 Children have also been found to be negatively affected by the poor marital functioning of their parents40; thus, our concern about declines in marital functioning extends beyond the dyad. Mental health clinicians who provide services to military families should therefore be cognizant that soldiers or other family members who present for treatment for mental health problems may also be affected by poorly functioning marriages, and that this can also be a target for intervention.

Meeting screening criteria for PTSD was associated with poorer marital quality, and depression was associated with all three outcomes. Alcohol misuse, which is a correlate of mental health problems such as PTSD24 was also associated with poorer marital quality and greater likelihoods of both infidelity and separation/divorce intent. Taken together, these findings suggest that the marriages that may be most at risk across time are those of the soldiers who have been most harmed by their combat exposure.

However, no association was found between combat exposure and infidelity and divorce intent, which is consistent with findings that combat exposure indirectly affects marital functioning through mental health problems.1,18

This study also showed that our findings of decreased marital functioning have yet to be supported by Army divorce rates. We did not find any substantial increases in the enlisted male soldiers' divorce rates from FY 2003–FY 2009. Although we were unable to examine marital functioning trends among either male and female officers, or enlisted female soldiers, the divorce rates for both groups of females suggest that their marriages tend to dissolve more so than that of their male counterparts.

The DMDC data are limited in a few ways, which constrains our ability to determine precisely how OEF and OIF deployments have affected divorce rates. First, the divorce rates for soldiers with deployment experience to Iraq, Afghanistan, or elsewhere could not be disaggregated, so we could not determine whether the rates among soldiers with OEF or OIF deployments differed appreciably from those deployed to other locations and from never-deployed soldiers. Second, we could not examine whether divorce rates varied based on combat exposure levels among soldiers with OEF and OIF deployment experience. Third, we also could not examine divorce rates among soldiers who screened positive for mental health problems. Lastly, the DMDC data do not allow for the examination of divorce rates among soldiers who have left the Army, so it is unknown whether such marriages followed the trends presented or differed substantially.

Additional limitations of this study include the cross-sectional nature of the sample data. Ideally, researchers would follow a cohort of soldiers and spouses before, during, and after deployments, but such a study would be logistically difficult and labor-intensive. As such, our findings, which are based on data that is representative of soldiers in combat arms units,23 provide vital information on the strain that combat deployments place on military marriages. Further, although marital quality has been found to decline over time in couples,41 we did not follow a cohort of soldiers longitudinally, so our data appear to reflect global declines in high marital quality. Also, we had insufficient numbers of soldiers with multiple deployments in every study year to explore the link between such a measure of cumulative burden and marital functioning. In addition, the insufficient numbers of soldiers did not permit us to compare rates of marital functioning between deployed soldiers and soldiers who had never deployed, which precludes us from making definitive statements about the association between combat deployments and marital functioning. Because of the unavailability of civilian data, we also were not able to compare the trends reported here to civilian ones to examine whether this was solely a military phenomenon.

The question about infidelity asked whether it "has been a problem" in the past year differs slightly from other research where respondents were asked if infidelity had occurred42 or their number of sexual partners (infidelity was operationalized as having more than 1 partner).43 However, we expect that the wording of our question likely undercounts the prevalence of infidelity because one

could have had extramarital sex, but believe that it was not a problem. Further, between 7% and 11% of the soldiers across time responded that they were unsure if it was a problem, and it is not unreasonable to assume that in some of these cases, infidelity had occurred. Lastly, although we are aware that interrelationships between variables such as mental health, infidelity, and marital quality are complex in couples generally and more so in military couples, it was beyond the scope of this study to explore such relationships in depth.

CONCLUSIONS

Our main focus in this study was an examination of the trends in three marital functioning indicators since the commencement of the Afghanistan and Iraq wars. We found that marital quality declined, and reports of past-year infidelity and separation/divorce intent have increased. Overall, the relationship between time and the outcomes appears to persist after controlling for combat exposure, mental and physical health, alcohol misuse, and demographic variables. The results of this study provide a better understanding of how Army marriages have been affected by the wars and suggest that further inquiry is needed on military marriages.

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## Interpersonal Conflict and Referrals to Counseling Among Married Soldiers Following Return From Deployment

Military Medicine
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Abstract

Deployment represents a significant potential strain on military families. The impact of postdeployment stresses may be increased if family coping resources are diminished by returning service members' physical injuries, mental health issues, or substance abuse. This article examines the health and mental health correlates of self-reported concerns regarding interpersonal conflict among married soldiers following return from deployment and the likelihood that soldiers acknowledging such concerns are referred to counseling services. Among 20,166 married Army soldiers completing Post-Deployment Health Reassessments, 18% reported having experienced serious interpersonal conflict with their spouse, family members, close friends, or coworkers. Results indicate that interpersonal conflict was more common among those who reported health problems, depression, post-traumatic stress disorder, and alcohol abuse. Among soldiers reporting interpersonal conflict and not already receiving services, 11% were referred to service. Findings support the need to communicate with soldiers and their spouses about the availability of services following return from deployment and to continue efforts to reduce stigma associated with seeking treatment.

## Background

Deployment represents significant strain on military families.1–3 Our understanding of the impacts of deployment on spouses and children has expanded substantially in recent years as unprecedented proportions of service members with families have experienced deployment to Operation Enduring Freedom (OEF) in Afghanistan and Operation Iraqi Freedom (OIF).4 Although many military families identify positive aspects of deployment,5 emerging research suggests that a significant proportion experience substantial challenges during and after deployment.6 These impacts include marital7,8 and family stress,9 family violence,10–12 and adjustment difficulties for both parents13,14 and children.15–17

Family stress theory suggests that reactions to deployment will be mediated by families' interpretation of the event (e.g., whether deployment is seen as a meaningful challenge within a military career or a catastrophic event) as well as their coping resources.18 These resources may be diminished by returning service members' physical injuries or “invisible wounds” such as mental health issues and substance abuse.7,19–21 Any of these may affect marital and family functioning.

Physical health affects both marital quality and child distress. Negative changes in a spouse's health have been associated with both increasing divorce proneness and declining marital happiness, resulting from reduced marital interactions and the spouse's moods and behaviors.22 Among spouses of combat-wounded service members, more than two-thirds reported child distress, the severity of which was unrelated to the service members' injury.16 Consistent with family stress theory, spouses who saw the deployment and postdeployment period as particularly difficult were most likely to report child distress.

Similarly, mental health issues have been found to have adverse effects on marital functioning. Early studies of Vietnam veteran populations found that families of male veterans with post-traumatic stress disorder (PTSD) reported more extensive marital and family adjustment compared to veterans without PTSD.12,23 More recent studies with OIF/OEF veterans have also found mental health issues such as PTSD, depression, anxiety, and dissociation to be related to lower rates of marital and relationship satisfaction, intimacy, effective parenting, and greater family reintegration issues.14,24–26

Alcohol abuse has also been linked to marital functioning among military personnel. For example, binge drinking is more likely to occur among military personnel who are younger, report marital problems, and have recent combat experience.27 This association is further supported in findings from veterans participating in alcohol treatment groups, with those who abstained from heavy alcohol use 1 year following treatment reporting higher marital functioning compared with relapsed drinkers.28 The relationship between alcohol abuse and marital functioning remains a complex one, however, because of the often intertwined contributing versus consequential nature of these issues.

The military screens for health and mental health impacts of deployment using the Post-Deployment Health Reassessment (PDHRA), a surveillance screening instrument administered 3 to 6 months following return from deployment.29 Although marital stress is not directly measured by the PDHRA, the instrument includes a measure of persistent concern regarding serious interpersonal conflicts, endorsed by 14% of active duty soldiers.20 Reported interpersonal conflict concerns have been found to predict co-occurring intimate partner violence among previously deployed soldiers involved in child maltreatment incidents (manuscript under review). However, no research currently describes the relationship between interpersonal conflict concerns and health and mental health issues that may increase family stress.

Services to reduce the impacts of deployment-related health and mental health issues can support adaptation and reduce family impacts.30 The PDHRA provides an opportunity to identify service members who may benefit from referral for further evaluation and treatment.31 However, rates of referral for active duty service members are low, at less than 1% for those reporting alcohol abuse and less than 15% for those reporting mental health issues.20,32 The rates at which service members reporting interpersonal conflict concerns are referred to counseling is unknown.

This article therefore examines correlates of self-reported concerns regarding interpersonal conflict, and referrals to services, among married soldiers following return from OEF/OIF deployments. Specifically, we examine these research questions: (1) What soldier characteristics are associated with concerns regarding interpersonal conflict? (2) Among soldiers reporting interpersonal conflict concerns, what characteristics predict referral to counseling services? Better understanding of these issues can improve response to soldiers who may be at risk for family stress and suggest strategies by which use of existing services may be promoted.

## Methods

### Data and Procedures

Data from this study were drawn from PDHRAs completed by Army soldiers. Data were de-identified by the Armed Forces Health Surveillance Center before being shared with the authors. All study procedures were approved by human subjects review panels at the authors' organization.

### Study Population

Analyses for this study are based on all PDHRAs completed between February and December 2008 by Army soldiers who were identified as married, totaling 20,166 records. Soldiers were predominantly male (92%) and White (64%). Half (49%) were aged 25 to 34, and 20% were younger than 25. Most were in lower pay grades: 29% were junior enlisted personnel (pay grades E1–E4), 38% were noncommissioned officers (NCOs) (pay grades E5–E6), 14% were senior NCOs (pay grade E7–E9), and 20% were officers (pay grade O1–O10 or W1–W5). Most (57%) reported one OEF/OIF deployment, 30% reported two deployments, and 13% reported three or more.

### Measures

In addition to soldier (age, gender, race/ethnicity, and marital status) and military characteristics (pay grade), the PDHRA includes items assessing health changes and the following behavioral health issues: alcohol abuse, PTSD, and depression. These measures have well-established psychometric properties.33,34–37 Additionally, soldiers were asked about interpersonal conflict concerns and whether they would like assistance on any issues, as described below. Health care providers reviewing soldiers' responses add referral recommendations to the PDHRA record.

#### Health

Soldiers rated their health since returning from deployment as much better than, somewhat better than, about the same as, somewhat worse than, or much worse than before deployment.

#### Alcohol Abuse

The current version of the PDHRA includes two items measuring alcohol use risk during the previous month. The two-item Conjoint Screen for Alcohol34 asks respondents whether they "used alcohol more than you meant to" or "felt that you wanted to or needed to cut down on your drinking." An affirmative response to either question indicates alcohol abuse risk. The three-item consumption subscale is taken from the Alcohol Use Disorders Identification Test (AUDIT).38 Questions include: "How often do you have a drink containing alcohol?" "How many drinks containing alcohol do you have on a typical day when you are drinking?" "How often do you have six or more drinks on one occasion?" Scores for each item range from 0 to 4; summed scores of 4 or higher for men and 3 or higher for women indicate alcohol abuse risk.

Mental Health Risk

Two items were used to assess mental health risk during the previous month. The two-item Patient Health Questionnaire36 assesses depression. Items ask soldiers how frequently they had "little interest or pleasure in doing things" or felt "down, depressed, or hopeless." Responses indicating ever experiencing either problem during the past month indicate risk for depression.

The four-item Primary Care PTSD screen39 asks soldiers whether they had any experience that was so "frightening, horrible, or upsetting that you had nightmares or thoughts when you did not want to; tried hard not to think about it or went out of your way to avoid situations that remind you of it; were constantly on guard, watchful or easily startled; and felt numb, detached from others, activities, or surroundings" in the past month. Responding in the affirmative to at least two Primary Care PTSD screen items indicates mental health risk.

Interpersonal Conflict Concerns

Soldiers were asked whether, since returning from deployment, they had experienced "serious conflicts with your spouse, family members, close friends, or at work that continue to cause you worry or concern." Responses were categorized as positive if soldiers responded "yes" rather than "no" or "unsure."

Interest in Assistance

Four items offered soldiers the opportunity to request appointments, information, or assistance. These questions addressed the following topics: health concerns; stress, emotional, or alcohol concerns; family or relationship concerns; and visits with a chaplain or community support counselor.

## Referral to Services

In addition to numerous options for medical care, providers can recommend referral to family services, chaplain services, and Military OneSource.

## Analysis Strategy

Analyses first examined relationships between reported interpersonal conflict and soldier characteristics, including demographic and military characteristics, health changes, alcohol use risk, and mental health risk. A logistic regression model was created to explore the impact of all characteristics when considered together and then reduced to include only significant variables, using a backward elimination process.

Similar steps were used to examine referrals to services for those soldiers who reported having experienced interpersonal conflict concerns. Although the PDHRA does not specify the basis for referrals, we included those that would likely address interpersonal conflict, i.e., chaplain services, family services, or Military OneSource. Because ongoing treatment might preclude an additional referral, soldiers were excluded from this analysis if health care providers noted that they were already in care for mental health issues (depression, PTSD, or suicide risk), anger or aggression, or social or family conflict. A logistic regression model was used to identify variables that independently predicted referral and then reduced to include only significant variables, as above.

Odds ratios (ORs) were calculated to describe the association between interpersonal conflict and soldier characteristics. An OR greater than 1 indicates an increased likelihood of interpersonal conflict and less than 1 indicates a reduced likelihood of interpersonal conflict. A significance level of 0.05 was used for all analyses. We used SAS Version 9.2 for all analyses.

# Results

## Characteristics Associated With Interpersonal Conflict Concerns

Assessing the first research question regarding predictors of interpersonal conflict concerns, we found that these concerns were reported by 3,691 (18%) of the 20,166 married soldiers completing PDHRAs (Table I). After controlling for other variables, race/ethnicity and pay grade were significantly associated with interpersonal conflict concerns in the reduced model. Both Black and Hispanic soldiers were more likely to report interpersonal conflict concerns than White soldiers (OR = 1.34 and 1.35, respectively).

Junior enlisted soldiers were most likely to report interpersonal conflict concerns (OR = 0.84, 0.70, and 0.62 for NCOs, senior NCOs, and officers, respectively).

In addition, all health and behavioral measures were significantly associated with self-reported interpersonal conflict. These included soldiers whose health status was worse than before deployment (OR = 1.51), those reporting two or more indicators of PTSD (OR = 2.85), and those reporting at least one indicator of depression (OR = 5.92). Both measures of alcohol abuse remained independently associated with interpersonal conflict: concern over alcohol abuse (OR = 2.13) and self-reported alcohol consumption (OR = 1.2).

Referral to Counseling Services for Soldiers With Interpersonal Conflict Concerns

To address the second research question of predictors of referral to counseling for soldiers with interpersonal conflict concerns, we examined provider referrals to counseling services. Among soldiers reporting interpersonal conflict, 825 (22%) were already receiving services for mental health issues, anger, or social or family conflict and were excluded from analysis. Of the remaining 2,866 married soldiers with interpersonal conflict concerns, 309 (11%) were referred to one or more of the following services: chaplain services (1%), family support and community services (2%), or Military OneSource (9%). After controlling for all variables, only soldiers' interest in receiving assistance with a family or relationship concern was found to be associated with referral (OR = 2.28). However, even among soldiers expressing such interest, only 124 (17%) were referred to counseling.

Discussion

This study extends prior research in several ways. It provides early insights into the extent and likely correlates of concerns regarding interpersonal conflict among soldiers returning from deployment. Unlike research relying upon clinical samples or surveys drawn from populations, these data represent all soldiers returning from OEF/OIF deployments over a period of nearly 1 year. By focusing on interpersonal conflict among married soldiers, we identify those most likely to be at risk of marital and family stress as they reintegrate following return from deployment.

Nearly one in five married soldiers (18%) acknowledged persistent concerns regarding serious interpersonal conflicts since their return from deployment. Notably, male and female soldiers were equally likely to report interpersonal conflict concerns. Given that female soldiers currently represent an unprecedented proportion of the military10 and are deployed in closer proximity to combat operations than ever before,12,40 these data suggest the need for careful attention to their postdeployment experiences. Increased levels of interpersonal conflict concerns among lower pay grade and non-White soldiers suggest the potential value of additional supports for younger soldiers with less-established marriages, as well as consideration of culturally appropriate supports.

These data also show strong relationships between interpersonal conflict concerns and negative health changes, depression, PTSD, and alcohol abuse, all of which have been associated with marital and family stress.14,24–26 These associations, which have also been established with respect to intimate partner violence,12,14,41,42 underscore the necessity of directing at-risk soldiers to counseling resources in hopes of mitigating conflict and preventing more serious problems.

Unfortunately, these data indicate that referrals to these resources are not occurring within the context of the PDHRA process. Among soldiers reporting serious interpersonal conflict, only 11% were referred to the most commonly used resources for such problems, with the only predictor of referral being soldiers' interest in receiving assistance. Even among these soldiers, only 17% were documented as having been referred. These referral rates are comparable to those previously reported for substance abuse and mental health issues following PDHRA screening.20,32 Previous research has suggested that both provider referral and soldiers' disclosure may be influenced by concerns regarding stigma associated with these conditions and with treatment.19,43,44 However, if interpersonal conflict concerns are less prone to stigma than substance abuse and mental health issues, this PDHRA item would represent a potential low-threshold opportunity for linking soldiers with needed treatment.

Several limitations should be noted when considering these findings. First, the PDHRA item addressing interpersonal conflict concerns refers to issues with a soldier's spouse, family members, close friends, or coworkers and is thus not specific to marital conflict. However, marital conflict is a reasonable consideration when married soldiers raise concerns regarding interpersonal conflict. Second, these data represent all soldiers returning from deployment rather than only those with combat exposure, which may influence behavioral health outcomes. Third, data on traumatic brain injury, not available for these analyses, may influence interpersonal conflict. Fourth, reasons for referral are not documented, and the absence of referral may be based on provider assessment or lack of resources rather than representing insufficient response to soldiers' concerns. Finally, soldiers' PDHRA reports of behavioral health issues may underestimate their actual incidence because of concerns about career repercussions, as suggested by recent research that has documented soldiers' concern regarding stigma and behavioral health treatment.

These findings underscore the urgency of ongoing attention to the impact of soldiers' deployment experiences on marriage and intimate relationships. Such efforts include programs such as Battlemind and Families OverComing Under Stress, which are intended to support reintegration to family and resiliency.45,46 The findings suggest that providers reviewing PDHRAs be encouraged to inquire about family relationships, particularly when items related to behavioral health have been endorsed, and to encourage soldiers to take advantage of available resources. Finally, current efforts to reduce stigma associated with mental health and substance abuse treatment are essential to encouraging utilization of services. Future research exploring the relationship between

interpersonal conflict and other behavioral health issues and subsequent intimate partner violence could inform strategies to identify those at risk and link them to services.

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## Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study

The Lancet
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Summary

Background

During in-hospital cardiac arrests, how long resuscitation attempts should be continued before termination of efforts is unknown. We investigated whether duration of resuscitation attempts varies between hospitals and whether patients at hospitals that attempt resuscitation for longer have higher survival rates than do those at hospitals with shorter durations of resuscitation efforts.

Methods

Between 2000 and 2008, we identified 64 339 patients with cardiac arrests at 435 US hospitals within the Get With The Guidelines—Resuscitation registry. For each hospital, we calculated the median duration of resuscitation before termination of efforts in non-survivors as a measure of the hospital's overall tendency for longer attempts. We used multilevel regression models to assess the association between the length of resuscitation attempts and risk-adjusted survival. Our primary endpoints were immediate survival with return of spontaneous circulation during cardiac arrest and survival to hospital discharge.

Findings

31 198 of 64 339 (48·5%) patients achieved return of spontaneous circulation and 9912 (15·4%) survived to discharge. For patients achieving return of spontaneous circulation, the median duration of resuscitation was 12 min (IQR 6—21) compared with 20 min (14—30) for non-survivors. Compared with patients at hospitals in the quartile with the shortest median resuscitation attempts in non-survivors (16 min [IQR 15—17]), those at hospitals in the quartile with the longest attempts (25 min [25—28]) had a higher likelihood of return of spontaneous circulation (adjusted risk ratio 1·12, 95% CI 1·06—1·18; p<0·0001) and survival to discharge (1·12, 1·02—1·23; 0·021).

Interpretation

Duration of resuscitation attempts varies between hospitals. Although we cannot define an optimum duration for resuscitation attempts on the basis of these observational data, our findings suggest that efforts to systematically increase the duration of resuscitation could improve survival in this high-risk population.

Funding

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## Duration of in-hospital resuscitation: when to call time?

The Lancet
Jerry P Nolan, Jasmeet Soar
27 Oct 2012

Cardiopulmonary resuscitation guidelines are fairly standardised and didactic but recommendations on when to terminate in-hospital resuscitation attempts are less precise, which often means that resuscitation teams have to make subjective decisions. Validated clinical decision strategies for stopping in-hospital resuscitation exist, but are derived from guidelines no longer in use and thus are rarely used in clinical practice.

In The Lancet, Zachary Goldberger and colleagues have used the American Heart Association's Get with the Guidelines—Resuscitation registry (globally, the largest in-hospital cardiac arrest registry) to assess the duration of resuscitation before termination of efforts in non-survivors as an indicator of the overall tendency of a hospital to attempt resuscitation for longer. They analysed data from 64 339 patients with cardiac arrests at 435 US hospitals between 2000 and 2008. Cardiac arrests that lasted less than 2 min were excluded. In the whole study population, the median resuscitation duration was 17 min (IQR 10—26); 31 198 patients (48·5%) achieved return of spontaneous circulation (ie, restoration of a pulse for at least 20 min) and 9912 (15·4%) survived to hospital discharge. Of the 48·5% of patients who achieved return of spontaneous circulation, circulation returned within 10 min in 44·8% and within 30 min in 87·6%. The median resuscitation time was 12 min (IQR 6—21) in patients achieving return of spontaneous circulation and 20 min (14—30) in non-survivors.

Hospitals were classified into quartiles on the basis of the median duration of resuscitation in non-survivors: 16, 19, 22, and 25 min were the median resuscitation durations for the first to fourth quartiles, respectively. Patients at hospitals in the quartile with a median resuscitation duration of 25 min (ie, the longest quartile in non-survivors) were significantly more likely to achieve return of spontaneous circulation (adjusted risk ratio 1·12, 95% CI 1·06—1·18; p<0·0001) and survive to discharge (1·12, 1·02—1·23; 0·021) than were those at hospitals in the quartile with a median duration of 16 min (ie, the shortest quartile in non-survivors). The difference was greatest in cardiac arrests in which the initial rhythm was asystole or pulseless electrical activity. The proportion of patients surviving to discharge with a favourable neurological status (ie, a cerebral performance category score of 1 or 2) did not differ significantly across all quartiles (p=0·858).

730 (8·4%) of the 8724 patients surviving to hospital discharge who had neurological assessments did not achieve return of spontaneous circulation until after 30 min or more of resuscitation attempts; this was broadly the case for all initial cardiac arrest rhythms. A small study5 of 330 in-hospital resuscitation attempts in Taiwan had similar findings; five of the 58 people who survived to discharge achieved return of spontaneous circulation after 30 min of resuscitation.

To our knowledge, Goldberger and coworkers' study is the first time that analysis of duration of resuscitation attempts in non-survivors has been used to assess a hospital's tendency for longer or shorter duration of resuscitation efforts and to relate this tendency to survival. The study's strength is its use of a large database that includes and adjusts for many of the known variables that affect outcome after cardiac arrest, including pre-existing patients' factors, treatment interventions, and time and location of the cardiac arrest.

Retrospective analyses of databases, such as that done by Goldberger and colleagues, have several limitations. The investigators have reported an association between median duration of resuscitation attempts in non-survivors and outcome in all patients, but it is

possible that unmeasured confounders account for this finding. Variation between hospitals in duration of resuscitation attempts and outcome could be associated with process (eg, the presence of a rapid response system or the seniority and experience of the resuscitation team), cultural, and behavioural differences that a registry might not detect. Duration of resuscitation attempts could be a surrogate for the delivery of higher quality resuscitation—chest compression fraction (ie, the proportion of time spent delivering chest compressions during resuscitation attempts), depth, and rate are all associated with survival in out-of-hospital cardiac arrest. Longer resuscitation attempts might reflect the ability of a hospital's resuscitation team to identify and treat potentially reversible causes of cardiac arrest (eg, echocardiography to detect and treat pericardial tamponade) or to allow time for interventions to work. Hospitals that offer a comprehensive package of care after cardiac arrest (including the use of therapeutic hypothermia and percutaneous coronary intervention), which improves survival, might have a more aggressive approach to resuscitation than do hospitals that do not offer such comprehensive strategies. Infrequent implementation of so-called do-not-attempt resuscitation decisions could lead to shorter median resuscitation durations because the resuscitation team might tend to stop earlier in cases that are clearly futile. Only further observational data from other national audits—such as the UK National Cardiac Arrest Audit—will help to confirm and explain these findings because randomised trials are not ethically feasible.

Monitoring could provide information about the chances of successful return of spontaneous circulation. Promising technologies include waveform capnography to measure exhaled carbon dioxide and cerebral oximetry with near-infrared spectroscopy. Alternatively, interventions such as extracorporeal life support can be used to increase the window for successful resuscitation.

What are the implications for clinical practice? Goldberger and colleagues' study reassures clinicians that prolonged resuscitation attempts do not seem to result in a substantial increase in severe neurological injury in survivors. To improve outcomes, all hospitals should audit their cardiac arrests and benchmark outcomes as part of a quality improvement programme. Duration of resuscitation attempts should be established on a case-by-case basis and take into account other known determinants of survival. Prolonged resuscitation efforts can result in high-quality survival. If the cause of cardiac arrest is potentially reversible, it might be worthwhile to try for a little longer.

JPN is editor-in-chief of Resuscitation (honorarium received). JS is an editor of Resuscitation (honorarium received).

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## Fire without smoke: targeting smokeless tobacco use

The Lancet

6 Oct 2012

All health professionals are aware of the health dangers of tobacco smoking but gaps in their knowledge exist when it comes to smokeless tobacco. New guidance from the UK's National Institute for Health and Clinical Excellence (NICE), released last week, aims to fill this void.

The guidance focuses on interventions that help people of south Asian origin—the main users of smokeless tobacco—to quit. It covers a variety of smokeless tobacco products used in England such as the powdered misiri India tobacco, paan, and betel quid. South Asian women, older age groups, individuals from lower socioeconomic groups, and people of Bangladeshi origin are more likely to use smokeless tobacco. Several health problems can arise from use, including nicotine addiction, mouth and oro pharyngeal cancer, dental disease, cardiovascular disease, and problems in pregnancy and after childbirth (eg, fetal anaemia and stillbirth). However, there is low awareness of these health risks among health professionals and the public alike.
The guidance states that a brief intervention from health professionals can help users quit. Such interventions can include simple opportunistic advice, an assessment of a person's commitment to quit, pharmacotherapy or behavioural support, self-help material, or referral to more intensive support.

Additionally, it recommends that health professionals receive training so they can recognise the signs of smokeless tobacco use, record use in patients' notes, and explain the associated health risks using local names for smokeless tobacco products. Changing attitudes to smokeless tobacco, mistakenly seen as safe by many people, will be difficult, especially where cultural and language barriers exist, and health-seeking behaviour is low. The NICE guidance is a valuable aid to improve cessation services for a neglected health problem in an often-underserved population. Its implementation should be coupled with culturally appropriate, targeted prevention programmes in areas of the UK with large south Asian populations. Smokeless tobacco use needs to be viewed in the same way as tobacco smoking—as a habit damaging to health that requires intervention.

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## Job strain as a measure of exposure to psychological strain

The Lancet
Bo Netterstrøm
14 Oct 2012

Although work contributes to material wellbeing and might be beneficial to health, strain caused by qualitative or quantitative elements of an individual's work can be harmful to a person's physical or mental health. Karasek and colleagues' 1981 job-strain model was a breakthrough in the epidemiology of work-related psychosocial factors and diseases. The model suggested that high job demands plus low individual control over those demands would contribute an essential part of the psychological load that might lead to stress and, therefore, an increased risk of development of cardiovascular and mental diseases, particularly in industrial work environments. The model was noteworthy in its ability to predict potential risks—eg, the prevalence of antidepressant drug use and sickness absence in the Finnish working population.

In The Lancet, Mika Kivimäki and colleagues report findings from their collaborative meta-analysis of individual participant data from 197 473 European men and women without pre-existing coronary heart disease. 30 214 participants (about 15%) reported job strain. The investigators measured exposure to job strain (high demands and low control) on the basis of just one baseline assessment (done between 1985 and 2006), noting an association between job strain and coronary heart disease across age groups, sexes, socioeconomic strata, and regions, and after adjustments for socioeconomic status, and lifestyle and conventional risk factors. The sex-adjusted and age-adjusted hazard ratio for job strain versus no job strain (all other combinations of demands and control) was 1·23 (95% 1·10—1·37). The investigators used data from both unpublished (1·16, 1·02—1·32) and published (1·43, 1·15—1·77) studies to minimise publication bias; however some bias still seems to be present, but with no material effect on the conclusions. Furthermore, the study sought to reduce bias owing to reverse causation by exclusion of disease events that occurred in the first 3 years (1·31, 1·15—1·48) and 5 years (1·30, 1·13—1·50) of follow-up.

The article's appendix provides data for alternative measures of job strain in four categories: low strain (low demands and high control), passive (low demands and low control), active (high demands and high control), and high strain (high demands and low control). Only a few studies have reported the possible synergistic effect of high demands and low control.2, The hazard ratios were 0·93 (95% CI 0·89—0·98) for high control and 1·02 (0·96—1·08) for high demands. With the combination of high control and low demands as comparator, the hazard ratios were 1·12 (0·99—1·27) for low demands and low control, 1·06 (0·94—1·19) for high demands and high control, and 1·28 (1·11—1·48) for high demands and low control. These findings support Karasek's idea that harmful psychological load often results from a combination of high demands and low job control, rather than from either of these factors alone.

Karasek's method of measuring exposure in the psychosocial work environment does not distinguish between quantitative, cognitive, and emotional demands. Whereas quantitative and emotional demands might be a burden for workers, cognitive demands could be a stimulating challenge in many jobs. Furthermore, high work pace is not necessarily a stressor if sufficient time is allowed, and

difficult tasks might be a challenge rather than being excessively strenuous if achieved successfully; hence, different types of work will have different strain profiles.

The formulation of the job-strain model is best suited to industrial work. Societal developments have also contributed to the limitations of the job-strain model: in developed countries, the diminished industrial setting of working environments will reduce the prevalence of this type of exposure. The control dimension in particular seems to be of reduced importance because variation in the use of skills and degree of freedom, which are the major components of control, is less in most developed countries. Other models, such as the effort-reward imbalance model, and exposures such as job insecurity and factors related to social capital and emotions, are likely to be of major importance in the future. The present economic crisis will almost certainly increase this importance.

Job strain is a measure of only part of a psychosocially damaging work environment, which implies that prevention of workplace stress could reduce incidence of coronary heart disease to a greater extent than stated in the authors' interpretation of the calculated population-attributable risk for job strain. However, the job-strain model will remain a useful method to assess part of the psychosocial strain in workplaces, especially in the developing world. Few of the published studies with the job-strain model as an exposure measure have analysed the interaction between demand and control. Because these two dimensions might work in synergy, the statistical association between the outcome and the two dimensions should be reported separately (as in Kivimäki and colleagues' appendix) and together to clarify this possibility.

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## Occupational Effect on the Occurrence of Idiopathic Venous Thromboembolism

Military Medicine
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Abstract

Few studies have explored the effects of various occupations on venous thromboembolism occurrence. We examined idiopathic venous thromboembolism (IVTE) occurrence by occupation, body size, and age in the U.S. military. To capture idiopathic cases, exclusion criteria included recognized venous thromboembolism risk factors. Each case was matched to three controls on branch of service, sex, rank/grade, race, and education level. Body mass index, age, and occupation were analyzed with $\chi^2$ and logistic

regression. Of 2,167 cases, most were male (87%), white (69%), enlisted (78%), averaging 36 years old. IVTE odds increased with age ($p < 0.001$). Every occupation showed greater odds than pilots/aircrew ($p < 0.001$), especially infantry/artillery/combat arms, which showed twice the odds, followed by health care workers. Normal weight was protective, especially in pilots/aircrew (OR 0.52, $p = 0.03$) and repair/engineering (OR 0.72, $p < 0.001$). Our analysis found a lower risk of IVTE among pilots and aircrew compared to other military occupations. Body size had less impact than expected in aircraft and vehicle operators. Greater odds in health care workers and infantry/artillery/combat arms than in pilots/aircrew and armor/motor transport occupational groups may reflect prolonged standing. Limitations include potential miscoding of health records and potential misclassification. Future IVTE research should explore job functions and worker characteristics.

## Introduction

Military deployment-related conditions present risk factors associated with venous thromboembolism (VTE); however, few studies have been done on the incidence of VTE in active duty military personnel[1] or on the comparative health effects of various military occupations. Military personnel are medically screened before entrance into the service, which likely accounts for the lower incidence of VTE compared to the general population. This screening process may also play a role in the high proportion of VTE cases in the military in which no underlying causative factor is detected during their postevent diagnostic evaluation. In fact, idiopathic venous thromboemolism (IVTE) rates in the military have been estimated to approach 50% of all VTE cases. This is significant because over the last 10 years, incidence rates of VTE have dramatically increased in the total active duty military population. In the active component of the military (not including the National Guard and Reserves), the increasing prevalence of IVTE is thought to be the result of both increased incidence and decreased attrition. The military population provides a unique opportunity to better understand the epidemiology of IVTE in a screened occupational group, with the potential for the development of improved prevention strategies Previous studies support an increased risk of VTE associated with certain occupations and activities. In the military, previous analysis suggests an increased risk of IVTE with selected Department of Defense (DoD) occupational categories to include: Communications/Electronics/Intelligence, Combat Arms/Engineering/Seamanship/Aircrew, and Health care.

This study was designed to further explore the linkages between occupation and IVTE incidence in the military. We examined the occurrence of IVTE between occupational categories and explored the influences of body size (as measured by body mass index [BMI]) and age.

## Methods

Data for this analysis were supplied by the Defense Medical Surveillance System (DMSS) database, maintained by the Armed Forces Health Surveillance Center (AFHSC). The surveillance cohort was composed of all active component personnel from January 1, 1999 through December 31, 2008. Analysis was conducted using Stata v.11.1 (StataCorp LP, College Station, Texas) and SAS version 9 (SAS Institute, Cary, North Carolina).

An incident case was defined as the first of either (1) an inpatient encounter with a discharge diagnosis of deep vein thrombosis (DVT) or pulmonary embolism (PE) in any diagnostic position or (2) two or more outpatient encounters within 90 days with a diagnosis of DVT or PE in any diagnostic position (based on International Classification of Diseases, 9th edition, Clinical Modification [ICD-9-CM] codes: 415.0, 451.11, 451.19, 451.89, 453.41, 453.8).

The dataset was restricted to idiopathic cases of VTE. Our exclusion criteria included a history of VTE risk factors commonly cited in the medical literature (based on ICD-9-CM diagnostic codes or Current Procedural Terminology codes): long haul air travel ≥4 hours within the past month (return from deployment within 30 days used as proxy); inpatient surgical procedure within the past 3 months; malignancy detected or treated within the past 3 months; fracture of lower extremity or pelvis; crush injury of lower limb; embolism secondary to trauma; central venous instrumentation; myocardial infarction; stroke; burns; chronic obstructive pulmonary disease chronic; venous injury; venous compression; obesity; embolic complication of pregnancy and peurperium; oral contraceptive use; hormone replacement therapy; and hypercoagulable blood disorder. Since many deployment-related exposures are risk factors for VTE, we restricted our analysis only to cases that were not diagnosed during deployment to Iraq (Operation Iraqi Freedom [OIF]) or Afghanistan (Operation Enduring Freedom [OEF]). To produce a database composed only of incident cases, patients were excluded if they had a prior history of DVT or PE.

Each identified case was matched to three controls randomly selected from military personnel within the active component from January 1, 1999 through December 31, 2008 with the following characteristics: branch of service, sex, rank/grade, race, and education level. Unmatched variables for analysis were BMI (as measured at accession), age (at end of surveillance period), and DoD occupational classification (data from the Defense Manpower Data Center). Occupational classifications were combined into the following categories based on the occupational knowledge of the authors and staff of the Armed Forces Health Surveillance Center, of likely common exposures: pilot/aircrew, armor/motor transport, health care, infantry/artillery/combat arms, communications/intelligence, repair/engineering, and other (all specialties not falling within another category). Pilots and aircrew were subject to the same restriction as other occupational groups using “Return from deployment within 30 days” as the proxy for long-distance air travel.

As a known risk factor for multiple health problems, a medical diagnosis of obesity was exclusionary criteria; however, BMI was utilized as an indirect measure of body habitus in order to explore the relationship between size and IVTE occurrence. Accession into the military is the period at which BMI data are most consistently recorded and entered into a database suitable for DMSS analysis.

Potential overweight or obese cases identified through BMI calculation alone, in the absence of ICD-9 diagnosis, were presumed to have large body habitus but few comorbidities associated with and perhaps prompting a physician's diagnosis of obesity.

A multiple imputation algorithm was used to generate BMI values for the 50% of the sample with no BMI data. This approach estimates the distribution of the missing values based on observed data. Imputed values to replace the missing values are drawn repeatedly from this distribution, yielding a range of imputed values for each missing value. The variation among these imputed values reflects the uncertainty inherent in the imputation process. Age, military occupation, case/control status, sex, service, and rank/pay grade were used as variables in the imputation model. Because BMI was the only variable for which missing data needed to be imputed, the monotone regression method in the SAS MI procedure (SAS Institute) sufficed. Ten imputed datasets were created, each analysis was run separately on the ten datasets, and the results of the analyses were combined using the methods described by Rubin[7] as implemented in the SAS MIANALYZE procedure.

The distribution of IVTE cases in our study population was calculated for each variable. $\chi^2$ tests and conditional logistic regression were performed to investigate the relationships between categories of each independent variable and IVTE occurrence, taking into account the matching between cases and controls. All tests were conducted at the 95% significance level.

Results

Data were obtained for 2,167 IVTE cases and 6,501 matched controls. Demographic Table of IVTE Cases Compared to Controls Among U.S. Military Active Component Service Members by Outpatient or Inpatient Diagnosis Location, 1999–2008 provides the distribution of IVTE cases among variables.

Subjects were primarily male (87%), white (69%), and enlisted (78%), with an average age of 36 years (range, 18–65 years). There was a significant difference ($p < 0.001$) between IVTE cases and controls by age. Cases tended to be in older age categories, whereas controls tended to be younger. The difference between cases and controls by military occupation was also significant ($p < 0.001$).

Half of the BMI data in our sample was missing. The cases had 1.9% more missing data than controls. There was a pattern of increasing data loss with increasing age; 10.4% of BMI data were missing among those 30 years old and younger, 45.5% was missing among 31- to 40-year-olds, and 93.7% was missing among those 41 years and older. A similar pattern was observed within the enlisted population, ranging from 4.5% to 58.9%, respectively, among junior enlisted (E1–E4) and senior enlisted (E5–E9). Rates of missing BMI data in the officer population ranged from 68.9% and 73.3% among junior commissioned officers (O1–O4) and junior warrant officers (W1–W2), respectively, to 91.7% and 98.1% among senior warrant officers (W3–W5) and senior commissioned officers (O5–O9), respectively. Differences were also observed in levels of educational attainment, with the most BMI data missing among those having a postgraduate degree (89.3%), and by occupation, with the greatest percentage of BMI missing among pilots and aircrew (76.5%).

Compared to those ≤30 years of age, the 31 to 40 age group showed an 85% greater odds, whereas the ≥41 age group showed a 256% greater odds. Every occupational category showed greater odds of IVTE when compared to pilots/aircrew ($p < 0.001$). The greatest difference was observed for the infantry/artillery/combat arms with more than twice the odds. Differences by BMI were significant as well ($p < 0.001$). Odds of IVTE occurrence increased ($p < 0.001$) by 33% in those who were overweight at accession into the military, and by almost 70% in those who were obese at accession, compared to those who were normal weight when they entered the military.

This effect is greatest among pilots and aircrew (odds ratio [OR] 0.52, $p = 0.03$), and to a lesser extent the repair/engineering (OR 0.72, $p < 0.001$) and communications/intelligence (OR 0.80, $p < 0.05$) occupational groups. Although the OR increases with weight for all occupational categories, they are only significantly higher for the overweight and above category for infantry/artillery/combat arms (OR 1.39 and 1.88, respectively, $p < 0.05$) and the obese category of “Other” occupations (OR 1.76, $p < 0.05$).
Health care workers had the smallest increase in IVTE odds between overweight and obese among the various occupational groups, and the smallest increase between normal weight and obese. However, this occupational category also experienced the least protective effect from normal weight, although the result was not statistically significant.

## Discussion

Our analysis found a lower risk of IVTE among pilots and aircrew when compared to other military occupations. Previous studies also suggested a lower risk of VTE among pilots. Other published articles suggest greater risk of VTE among occupational groups that are subject to prolonged immobility and cramped working conditions. This was not fully borne out by these findings as normal weight and overweight armor and motor transport personnel had lower risks of IVTE than almost every other occupation, despite having duties that may involve long periods of time in relatively cramped vehicle cabins. However, the lack of statistical significance when

comparing armor/motor transport BMI categories to other occupations' prevents drawing definite conclusions from these findings. Similarly, when comparing health care worker BMI categories to other occupations, a lack of statistical significance complicates making inferences.

We also observed greater IVTE odds among older age groups and heavier BMI categories, which corresponds with other analyses of VTE that did not differentiate between idiopathic and non-idiopathic VTE. The increases we found in IVTE odds among pilots and aircrew with increasing BMI may reflect greater space restrictions on larger sized people although these increases were smaller than those seen in any other occupational category. Some other studies suggest a greater incidence of VTE in larger passengers sitting in what are typically smaller and more cramped economy class seats ("economy class" or "coach class" syndrome). A similar reason may be attributed to increases observed for personnel in the armor/motor transport category. However, this does not explain the same pattern observed for other occupational categories.

As early as the 1970s, some research suggested a higher IVTE incidence among health care workers compared to the general population, perhaps because of prolonged standing or greater recognition and reporting of signs and symptoms associated with VTE. This possible connection to prolonged standing may be reflected in the odds increases observed in infantry and artillery occupations with increasing BMI that were greater than armor and motor transport crew members whose occupations may involve less prolonged standing, even though it is unlikely there is any difference in VTE recognition and reporting between these two occupational groups. If there was a difference in care-seeking behavior among health care workers because of greater recognition of signs and symptoms, or among armor/motor transport workers perhaps because of targeted education, one would expect those occupations to report significantly greater incidence of VTE, creating biased results. To determine if this occurred, one would need the capability to broadly test members of each occupational group for VTE.
Height and weight data used to calculate BMI was measured at accession. A limitation of our study is the assumption that there was not a considerable change in weight between accession and the time of the IVTE event. The military uses a modified BMI calculation, as well as supplemental body-fat measurement and other criteria to determine the fitness level of service members and their subsequent enrollment into weight-control programs. Thus, by excluding those with a medical diagnosis of obesity, most service members with overweight-associated comorbidities (versus large body habitus alone) were likely excluded from the analysis.

Soldiers may have a BMI greater than normal weight but still meet body-fat measurement standards. In addition, ICD-9 diagnosis in the medical record is variable depending on the individual physician. This cannot be controlled or adjusted for in the analysis and may have biased our results.

The lack of BMI data for 50% of the sample is a potentially serious limitation of the study. Because of the nature of the DMSS database and the multiple sources from which it collects information (various electronic records, collecting differing data points at differing times according to evolving service-specific policies), there has not yet been a practical way to uniformly fill all data fields for service members and civilians in its records. Information such as height and weight are drawn from a variety of sources. Changes have been implemented over time by the U.S. Army Medical Command and other military agencies to improve BMI collection, and we expect this data to become more robust in the future. We chose to use accession as the most consistent point at which such data are measured across the services. Multiple imputation allows for analysis of the complete data set, possibly reducing selection bias. However, multiple imputation assumes that the data are missing at random; that is, the likelihood that BMI data are missing depends on the observed data (the variables used in the imputation model) and not on the unobserved BMI values. If, for example, subjects with higher BMI values are less likely to have their BMI recorded, our results might be biased, resulting in a lower measured effect of BMI on IVTE occurrence.

Limitations to this study also include reliance on electronic medical records and ICD-9 coding for VTE diagnoses and the identification of risk factors. Coding of these records may be unreliable over time. Matching ensured comparability between cases and controls, but because of matching to cases our control sample may not be representative of the general military population. Furthermore, the U.S. military is primarily composed of a screened population of young, relatively healthy adults. This selectivity may limit generalizations of our findings to the U.S. civilian workforce populations. However, there are analogous subpopulations among civilian occupations such as police and security officers, firefighters, and other professions that have pre-employment physical requirements and health screening.

Misclassification may have occurred from defining our exclusion criteria. Return from OIF/OEF deployment was used as a proxy for the risk factor of long-distance air travel. This, however, does not account for the totality of long-distance travel undertaken by military service members. Also, there are multiple inherited and acquired hypercoagulability blood syndromes that are risk factors for VTE, including protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden disorder, prothrombin G-A20210 gene variant, increased factor XI, increased factor VIII, and hyperhomocystinemia. Of these conditions, only two can be documented with specific ICD-9-CM codes: increased factor XI and increased factor VIII.

During our study design, we chose not to restrict selection of controls only to those with outpatient or hospitalized status. This ensured that we would have a sufficient population from which to draw matching controls. However, future studies may incorporate just such a restriction. This would allow comparison between cases and controls that are and are not outpatients or hospitalized, possibly revealing differences in etiological factors that may be more common to those seeking medical care.

Strengths of our study include the robust size of our database and our ability to classify the occupations of study subjects. Our study population also preferentially uses a unified health care system, currently known as TRICARE, which feeds into DMSS. This increases confidence that VTE events (for case selection) and/or risk factors (for exclusionary criteria) were accounted for.

## CONCLUSION

The authors believe that this analysis contributes to current understanding of occupational risk factors for the development of IVTE by demonstrating that workplace space restrictions and mobility limited by body size differences may be less important than previously thought in certain occupations such as aircraft and motor vehicle operators. Still, incorporation of design and engineering elements to accommodate larger body sizes, or consistent restrictions on body size and maintenance of normal BMI, may help to decrease IVTE among these occupational groups. More importantly, increasing BMI even in the absence of other risk factors appears to independently increase the odds of IVTE occurrence. This finding supports current trends among employers and health plans to incentivize fitness among employees as a way to decrease health care costs.

This study suggests that decreasing BMI may help to lower the incidence of IVTE within the military. Efforts to improve BMI and other risk factors associated with VTE would serve to improve the overall health and fitness of military service members. Certain potential IVTE risk factors such as prolonged standing are inherent within many military occupations and activities. However, supervisors may reduce work activities, when possible, that increase the risks of IVTE. Recognition of increased risk in certain occupational groups may also result in heightened awareness and surveillance of VTE signs and symptoms within those groups. Early recognition and treatment of VTE will improve the long-term health status of workers with VTE and decrease overall health care expenditures within a resource-constrained environment, as the military experiences a growing proportion of service members with VTE.

Further research is still needed to determine why workers in certain occupations present with more IVTE than others. Analysis of worker health and fitness, job functions, and activities between occupations with greater and lesser IVTE incidence may help discern this. Analysis of like cohorts between civilian and military occupational groups may also reveal differences in etiological factors for military or civilian-specific exposures in otherwise similar occupational fields. Future studies may also incorporate genetic testing and review of medical records to determine whether hypercoagulable disorders are normally distributed among differing occupational groups, and how BMI may affect hypercoagulable states. Questionnaires and/or interviews could also be utilized to ascertain care-seeking behavior and medical awareness between occupational groups and to determine if differences may affect reporting behavior of symptoms leading to IVTE diagnosis.

BACK TO TOP

# Meningitis Admitted to a Military Hospital: A Retrospective Case Series

Military Medicine
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Oct 2012

Abstract

Meningitis is a common admission diagnosis. No case series or descriptive studies on meningitis have recently been published. Additionally, no recent data exist on meningitis in the U.S. Military Health System. We reviewed charts of adult patients admitted to Naval Medical Center San Diego between January 2004 and December 2008 with an admission diagnosis of meningitis. Charts were excluded if they did not meet our case definition of meningitis, if missing data, or if meningitis was nosocomial or iatrogenic. We reviewed results of cerebrospinal fluid cultures during this period. We compared rates and characteristics, and outcomes of bacterial and aseptic meningitis. Two hundred twenty-one cases met our criteria. Of these, 208 were aseptic. Cerebrospinal fluid polymerase chain reaction testing was positive for enteroviruses and herpes simplex viruses in 42 (20.2%) and 17 (8.2%) cases, respectively. Of culture/polymerase chain reaction/serologically positive cases, the pathogens were Neisseria meningitidis (3), Streptococcus pneumoniae (3), viridans streptococci (2), Cryptococcus neoformans (2), Coccidioides immitis (2), and Mycobacterium tuberculosis (1). Three patients had poor outcomes: one died from S. pneumoniae and two had long-term neurologic deficits. Meningitis is a common admission diagnosis, but serious virulent pathogens are uncommon and adverse outcomes are rare.

## Introduction

Meningitis is a clinical syndrome characterized by inflammation of the meninges. It manifests with headache, nuchal rigidity, and photophobia and with cerebrospinal fluid (CSF) pleocytosis.

The annual incidence of aseptic meningitis is approximately 75,000 cases per year in the United States and results in approximately 26,000 to 42,000 hospitalizations each year. In 1995, the reported annual incidence rate for the five most common bacterial pathogens of acute meningitis was 2.4 cases per 100,000 patients. A Dutch study found the incidence in the Netherlands to be 2.6 cases per 100,000 patient-years from October 1998 to April 2002. The most recent data from the Centers for Disease Control and Prevention suggest that the rate of meningococcal meningitis is approximately 0.17 cases per 100,000 and pneumococcal meningitis

is approximately 0.84 cases per 100,000 patient years in the United States, which is much less than that reported in the mid-1990s. This declining incidence may be in part attributable to introduction of conjugated pneumococcal vaccines (PCV7) in 2000 although decline in meningococcal meningitis could not be attributed to meningococcal vaccines. This has been attributed to the timing of administration of vaccine and ages of recipients. A new conjugated pneumococcal vaccine (PCV13) was introduced in 2010 which provides immunity against an additional six serotypes. Newer pneumococcal vaccines have been used widely in pediatric patients; this fact has been suggested to produce herd immunity in nonvaccinated patients.

The Haemophilus influenzae type B vaccine was introduced in 1988. The most recent case series of acute bacterial meningitis collected data from 1985 to 1996. This case series has a relatively low incidence of H. influenzae meningitis but higher Listeria monocytogenes compared to previous studies. This change in incidence is most certainly attributable to the H. influenzae type B vaccine. The conjugated Neisseria meningitidis and Streptococcus pneumoniae vaccines were introduced after this period. The impact of these vaccines on the relative rates of meningitis has not been described recently.

Aseptic meningitis because of nonbacterial causes (such as enteroviruses, herpes simplex virus-2 [HSV-2], or drugs) has a low rate of morbidity or mortality and treatment is supportive in nature. In contrast, bacterial meningitis still carries a high rate of mortality and long-term neurologic deficits even with best treatment. Noninfectious, drug-related causes of aseptic meningitis have also been described, most commonly with ibuprofen but also with trimethoprim–sulfamethoxazole, both of which are common medications prescribed to beneficiaries of the Military Health System in the United States. The purpose of this study is to characterize the etiology of meningitis presenting to our institution in the era of newer conjugated pneumococcal and meningococcal vaccines.

## Methods

Naval Medical Center San Diego (NMCSD) is a tertiary care academic medical center in Southern California which serves a beneficiary population of 243,000 (191,000 adults, age 18 years or older). This population is comprised of active duty military personnel, their dependent spouses and children, and military retirees and their dependents. It is a referral center for the Pacific Rim and is the primary center of care for active and retired military personnel with human immunodeficiency virus (HIV) infection west of the Mississippi River. These populations are very likely to have received all recommended vaccines given their status as either active duty (required) or near universal access to care.

A retrospective chart review was conducted of all adult patients (age 18 years or older) admitted to NMCSD with an admission or discharge diagnosis of acute meningitis (International Classification of Diseases, 9th Revision, Clinical Modification Diagnosis Codes: 320.7, 320.9, 321.8, 322.1, 322.0, 322.2, 322.9, 047.0, 047.1, 047.8, 047.9, 094.2) between January 2004 and December 2008.

Exclusion criteria included a clinical syndrome not consistent with meningitis; discharge diagnosis was other than meningitis; CSF white blood cell (WBC) count was <10 cells/mm3; and no pathogen was determined based on CSF culture, PCR, or serology; and there was incomplete data, such as lack of clinical history or CSF data. Cases of meningitis related to a neurosurgical procedure or acquired nosocomially were also excluded. Readmissions for uncontrolled pain or chronic meningitis were also excluded. Cases were excluded only if agreed upon by both authors. In addition, we queried our electronic laboratory data system to obtain the results of all positive CSF bacterial cultures during this same time period to ensure that no cases of microbiologically defined bacterial meningitis were missed.

We defined a case of bacterial meningitis as a patient presenting with at least one clinical symptom or sign of meningitis (headache, stiff neck, photophobia, or fever) and CSF WBC ≥ 10 cells/mm3, and positive identification of a bacteria known to cause meningitis on CSF culture. We defined a case of aseptic meningitis as a patient presenting with clinical findings (at least one of the following: headache, stiff neck, photophobia, or fever) and CSF WBC ≥ 10 cells/mm3, in which neither Gram stain, culture, nor other standard methods revealed a bacterial, fungal, or mycobacterial cause.

We collected basic demographic data to include age, sex, and race, as well as military health care beneficiary status (active duty, retired, or dependent). We also collected data, such as body mass index (BMI), vital signs on presentation, Systemic Inflammatory Response Syndrome (SIRS) criteria, CSF profile (protein, glucose, WBC count, red blood cell count, culture, PCR, and special studies), HIV status (if known), length of stay, and outcome (good, impaired, or death). A good outcome was defined as no deficits or symptoms from the time of discharge out to 6 months if data available. “Impaired” was defined as continued symptoms, to include headache or any deficits during this same time period. Death was defined as death before discharge. SIRS is a nonspecific inflammatory response to an insult. Three percent of cases of SIRS in one large series were attributed to meningitis.

Statistical analysis was performed to compare characteristics of bacterial and aseptic cases of meningitis by way of analysis of variance for continuous variables and Fisher's exact test for categorical variables. StatCrunch Online was used for the statistical analysis. This study was reviewed and approved by the NMCSD Institutional Review Board.

Results

A total of 391 charts were identified by the inclusion criteria, of which 221 unique cases met our definitions for sufficient data and evaluability. These cases represented approximately 1.5% of admissions to our Internal Medicine service during this period. Of these, 208 (93.7%) were not attributable to bacterial, fungal, or mycobacterial pathogens and were classified as aseptic.

Demographics, to include race, sex, military beneficiary status, and BMI, were similar between patients with bacterial pathogens and aseptic cases.

Age was statistically different between the two groups, with patients with bacterial pathogens being significantly older by 17 years. The median age for bacterial and aseptic cases was 46 years (26.25–74) and 29 years (22–39) (p-value 0.001), respectively. SIRS criteria were treated as categorical variables and were not statistically different between the groups. Median length of stay was statistically different between the groups, with cases of bacterial meningitis being admitted for 9.5 days compared to 4 days for aseptic cases (p-value < 0.0001).

For cases of bacterial meningitis, the pathogens isolated from CSF culture were N. meningitidis (3), S. pneumoniae (3), and viridans streptococci (2). Three patients had poor outcomes because of bacterial meningitis: one death in an elderly female from S. pneumoniae and two deaths in patients with long-term neurologic deficits, one in a middle age diabetic male from S. pneumoniae and one in an elderly male with dementia from viridans streptococci. Of the three cases of meningitis from N. meningitidis, only one was in a military recruit. This was the second illness of meningitis from N. meningitidis in this patient, and he was subsequently diagnosed with terminal complement deficiency (C7).

Other virulent pathogens isolated were Cryptococcus neoformans (2, CSF culture), Coccidioides immitis (2, CSF serology), and Mycobacterium tuberculosis (1, CSF culture).

There were nine cases of meningitis in HIV-positive patients representing 4.1% patients in this series. The pathogens isolated in this group included Cryptococcus neoformans (2), enterovirus (2), and no pathogen in six patients. One patient had two pathogens isolated during the same episode having Cryptococcus grow on CSF culture and had a positive enterovirus PCR. One patient had temporal lobe enhancement on magnetic resonance imaging, suggestive of HSV meningoencephalitis, but had negative HSV PCR testing. One patient required a ventriculoperitoneal shunt because of hydrocephalus from cryptococcal meningitis; the other eight HIV-infected patients had good outcomes in our series.

Of the aseptic cases, CSF PCR testing was positive for enterovirus and HSV in 42 (20.2%) and 17 (8.2%) patients, respectively. There were six cases with adverse outcomes; five cases were identified as impaired and one death (cancer was primary cause of death). Adverse outcomes were variable from chronic headache to severe aphasia with memory impairment and executive function decrement. Of the six aseptic cases with adverse outcomes, only one had a pathogen isolated (positive CSF HSV PCR). This patient had chronic headaches after having aseptic meningitis.

The median CSF WBC for bacterial and aseptic cases was 516.5 cells/mm3 and 36 cells/mm3, respectively. Neutrophils were predominant in bacterial cases (median 88%), whereas lymphocytes were predominant in aseptic cases (median 80.5%). The median CSF protein was elevated in bacterial meningitis (425.5 mg/dL); however, it was normal in aseptic cases (55.5 mg/dL). Aseptic cases tended to have normal CSF:serum glucose ratios (median 0.55), whereas all bacterial cases had low ratios (median 0.03).

## Discussion

Admission to acute care hospitals for the diagnosis of acute meningitis remains common, even as cases of bacterial meningitis appear to have decreased over the last 20 years. New techniques for diagnosing aseptic meningitis, to include CSF PCR for enterovirus and HSV, help to exclude bacterial meningitis, but microbiologic diagnoses are obtained only in a minority of cases. Antibiotic resistance was not identified in our study, as all N. meningitidis, S. pneumoniae, and viridans streptococci isolates were sensitive to ceftriaxone, which is the first-line treatment for bacterial meningitis. Given the relatively benign prognosis for many cases of aseptic meningitis, making the diagnosis of aseptic meningitis on initial presentation may help to reduce hospitalizations and unnecessary empiric antibiotic use. The creation of a clinical decision rule to help exclude the diagnosis of bacterial meningitis could help reduce the number of inpatient patient days. Two clinical decision rules have been developed over the last 10 years for use in the pediatric population, which have 100% sensitivity for the purpose of excluding the diagnosis of bacterial meningitis, the Bacterial Meningitis Score, and Meningitest. Historically, clinical decision rules for adults have been aimed at identifying bacterial meningitis rather than excluding bacterial meningitis, which we deem to not be as helpful, given the motivation to hospitalize and start empiric antibiotics in patients presenting with signs and symptoms consistent with meningitis.

Reviewing our data set, a hypothetical plan to clinically exclude the need for admission can be created. We propose the following schema for excluding harmful/septic meningitis: (all criteria must be met) (1) immunocompetent, (2) normal mental status, (3) normal neurologic exam, (4) CSF WBC less than 40 cells/mm3, (5) CSF protein less than or equal to the upper limit of normal (60 mg/dL at NMCSD), (6) CSF:serum Glucose ratio greater than 0.31, (7) negative CSF Gram stain. In our series, patients were admitted for a total of 893 bed-days over this 5-year period or a mean length of stay of 4.04 days per case. This rule would have reduced the number of admissions by 76 patients and 263 total days of hospitalization in our series. All of these patients had good outcomes. Of course, such a schema would require prospective study and validation, ideally in a multicenter study, to account for different patient populations and to capture a larger number of bacterial cases.

Limitations of our study include the low number of cases of bacterial meningitis, low number of HIV-infected patients, retrospective analysis, and single institution design. The population studied includes active duty service members, their families, and retirees.

Overall, this is a relatively educated and healthy population with high access to care, and this may limit the applicability of our results to other groups. These results may, however, be quite applicable to some populations (such as college students) who have traditionally been considered an at-risk population. The beneficiary or enrolled population served by NMCSD is approximately 250,000 persons (191,000 adults). We calculate crude incidences of both meningococcal and pneumococcal meningitis of 0.31 cases per 100,000 adult patients per year. The rate for meningococcal meningitis is similar to recently reported rates, whereas it is substantially lower for pneumococcal meningitis. Although we do not have serotype data to confirm, it seems plausible that our below-expected rates of pneumococcal disease are related to high rates of vaccination of our beneficiaries or their contacts. Additionally, our location in the southwestern United States exposes our population to the endemic fungus Coccidioides immitis, which would not be expected in other regions of the United States. Conversely, we did not identify any vector-borne pathogens, such as Borrelia burgdorferi and West Nile virus, which would be more common in their respective endemic areas.

In summary, this retrospective review of meningitis cases in a tertiary military hospital suggests that the rates of serious bacterial causes of meningitis are declining. Diagnosis of aseptic meningitis is improving, and with careful application of clinical and lab criteria, admissions and antibiotic use for this condition could be reduced without undue morbidity and mortality.

BACK TO TOP

## Chinese Scalp Acupuncture Relieves Pain and Restores Function in Complex Regional Pain Syndrome

Military Medicine
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Oct 2012

Abstract

Complex Regional Pain Syndrome (CRPS) can result from trauma or after surgery. It is often difficult to manage effectively. If not recognized early, it can result in significant debilitation. Symptoms attributed to CRPS include neuropathic pain, allodynia, sudomotor changes, and decreased range of motion. It can occur with (Type II) or without (Type I) nerve injury. A number of soldiers sustaining extremity injuries during combat have manifested these symptoms. Two subjects were diagnosed with CRPS after sustaining upper extremity injuries during military operations. After failing conservative treatment, Chinese Scalp Acupuncture (CSA) was used once to

twice a week for 1 to 4 weeks. CSA resulted in improvement in the pain visual analog scale or numeric rating scale by over 80% in two soldiers with upper extremity CRPS. Additionally, decreased sensory changes and improved function were noted on exam and therapy assessments. Notably, the pain reduction, functional improvement, and normalization of sensation have been fully maintained between treatments. The treatment response had been sustained at 20-month follow-up with no recurrence. CSA provided lasting pain reduction, and improved function and sensation in this group of combatants with upper extremity CRPS.

## Introduction

Complex Regional Pain Syndrome (CRPS) can result from trauma or after surgery and can cause severe dysfunction and extreme debilitation. Symptoms include neuropathic pain, allodynia, sudomotor changes, and decreased range of motion (ROM). It can occur with (CRPS Type II) or without (CRPS Type I) nerve injury.1 Recalcitrant to conventional treatment, it is often very difficult to manage. Standard treatment includes medications and conservative treatment.1 Pain is typically managed with tricyclic antidepressants, anticonvulsant medications, desensitization, and aggressive physical therapy to maintain ROM. Sympathetic ganglion blocks are used as a diagnostic tool and may improve symptoms for the duration of the block. Finally, if these modalities fail, spinal cord stimulation has held some promise for treatment. However, because of the risk and cost of this invasive procedure, it should be reserved for only the most severe cases. A number of deployed soldiers sustaining upper extremity injuries have developed CRPS. We present a case series of two patients selected out of a group of fourteen consecutive patients that were successfully treated for CRPS or severe scar allodynia with Chinese Scalp Acupuncture (CSA). The fourteen patients were presented in a poster at the 2009 American Academy of Pain Medicine Annual Meeting.

CSA is a neuroanatomic acupuncture approach. The treatment is based on the pain location. Patients with allodynia or hyperesthesia are treated by inserting needles into the scalp in the area overlying the portion of the sensory homunculus that correlates with the painful area. In addition, needles may be inserted into the foot-motor sensory area.

Needles may need to be inserted bilaterally. Once inserted, the needles are rotated, back and forth, approximately a quarter turn between the distal joints of the thumb and forefinger at a frequency of at least 200 times per minute for 1 to 3 minutes. This is repeated approximately every 10 minutes for a total of 20 to 30 minutes. Ideally, treatment should be repeated two to three times weekly for 3 to 4 weeks.

## Methods

Two soldiers were diagnosed with CRPS after sustaining upper extremity injuries. After failing aggressive medication management and occupational therapy, CSA was utilized once to twice weekly for 1 to 4 weeks using Seirin Type L, 40 mm × 0.25 acupuncture needles (SEIRIN-America, Weymouth, Massachusetts). Pain was evaluated using the visual analog scale (VAS) or numeric rating scale (NRS)

CASES

Patient No. 1

A 31-year-old Army male suffered a gunshot wound in Iraq resulting in a right shoulder open fracture. After multiple debridements, he underwent a hemiarthroplasty. After 6 months of little change with conservative therapy and multiple medications, the hemiarthroplasty was removed and an arthrodesis was performed. Six months later, he had a right shoulder revision with no relief of his pain or increase in function. He was then evaluated in the Physical Medicine service. His presentation was significant for right arm and thorax color changes, temperature changes, and severe allodynia. He was diagnosed with CRPS of the right arm and thorax. He was treated with CSA in the middle 2/5ths of the left sensory treatment area. Immediately post-treatment, he had an 80% to 90% improvement in the arm and shoulder allodynia. In addition, he had improved elbow and wrist ROM with very little pain. Three days later, he was treated again resulting in complete resolution of the allodynia. Twenty months after the scalp acupuncture treatment, the CRPS symptoms had not recurred.

Patient No. 2

In early 2007, an 18-year-old active duty male tripped and fell onto his outstretched left hand in Iraq. He immediately complained of the thumb dislocating when he fell. Radiographs demonstrated a fracture at the base of the first proximal phalanx. The next day he had an open reduction and internal fixation. Over the following 6 months, he complained of pain and extensor pollicis longus tendon (EPL) subluxation. As a result, he had an EPL stabilization approximately 9 months after his initial injury. Six weeks after surgery, he was diagnosed with CRPS by his orthopedic surgeon. During the next 8 months, he went through conservative treatment with multiple anticonvulsant medications, fluidotherapy, and desensitization with no improvement.

He was seen by the Physical Medicine service about 10 months after the EPL stabilization. Examination revealed that the affected area included the hand and the distal two-thirds of the left arm. The arm had developed hyperesthesia, allodynia, and a mottled appearance. He held his hand in a claw position with noticeable intrinsic atrophy. The left hand was colder than the right hand. After evaluation, he received CSA in the middle 2/5th of the sensory treatment area bilaterally. During this treatment, he experienced

resolution of allodynia over the ulnar two fingers and hand and there was visible improvement in the color and temperature of the limb, as well as improved strength and finger ROM. Two days later, he was treated again with a 15% to 20% reduction in allodynia of the radial half of the hand. The third treatment, 3 days later, using only a right-sided needle, relieved his allodynia completely except over the surgical scar. One week later, the same treatment completely relieved the pain, color, and temperature changes. The only remaining pain was the orthopedic pain associated with his original injury. Sixteen months after his last treatment, he had no recurrence of the CRPS symptoms.

## Discussion

Acupuncture was first introduced into the conscience of the United States in 1972 by James Reston when, serving as a New York Times correspondent during President Nixon's trip to China, he reported on his postoperative pain relief with traditional Chinese acupuncture after an emergency appendectomy. In 1997, the National Institutes of Health published a consensus statement delineating its efficacy in several conditions, including chemotherapy nausea and, possibly, back pain. As noted in the consensus statement, low-level anecdotal evidence, such as this case series, and poorly designed research protocols supportive of acupuncture's efficacy in internal medicine, neurologic, pain, and other disorders is abundant. Acupuncture, despite the NIH support, has not gained widespread acceptance as a treatment modality in the United States. High-level evidence-based support, as is the case with many other pain treatment modalities, has remained difficult to achieve. When one evaluates the different systems of acupuncture, it becomes difficult to assess what is, and what is not, an acupuncture point. The mere placement of a needle in the body has a physiologic effect. In addition, pain is a subjective experience with a somatic and affective component. Therefore, it can be difficult to assess the efficacy of any pain treatment. Delving deeply into the challenges facing those attempting to create high level evidence for acupuncture is well beyond the scope of this manuscript. The preceding discussion serves as an introduction to this complex issue.

CSA, developed by Dr. Jiao Shunfa, is an acupuncture technique combining traditional needling methods with knowledge of the neuroanatomy. Very little is known about the mechanism of action of CSA. In the Chinese medical literature it is cited, primarily, for the treatment of stroke. A Medline and Google Scholar search did not return any publications in which CSA was used to treat CRPS. One can hypothesize that it, through an unknown mechanism, affects the central component of CRPS. However, even the existence of this “central pain” in CRPS is debated and poorly understood. Although the mechanism of action is unknown and may be difficult to fathom, the results in these cases show that there is a new, low cost, low-risk method that warrants consideration when treating CRPS.

## CONCLUSION

CSA resulted in improvement in the pain VAS or NRS by more than 80% in two soldiers with upper extremity CRPS Pretreatment and Post-treatment Pain Scores. Additionally, decreased sensory changes and improved extremity function were noted on physical exam and therapy assessments. Notably, the pain reduction, functional improvement, and sensory normalization were fully maintained between treatments. To date, the treatment response has been sustained for as much as 20 months with no return of allodynia or decrement in function. This is a small case series that shows promise. Prospective randomized trials should be conducted to evaluate for the placebo effect and to evaluate the efficacy of this treatment.

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## Perceived Stigma and Barriers to Mental Health Care in Marines Attending the Combat Operational Stress Control Program

Military Medicine
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Abstract

The Department of Defense is aggressively addressing combat stress reactions (CSRs) through comprehensive Combat/Operational Stress Control (COSC) briefings/programs and referral resources for the prevention, identification, and treatment of stress reactions. The purpose of this study was to develop and administer a survey to assess perceptions of CSRs and barriers to care which affect help-seeking behavior in Marines attending the COSC program. A sample of 553 U.S. Marine Corps Officers and Enlisted personnel from Air (44%), Logistics (38%), and Infantry (18%) communities were recruited for the survey. The results suggested that misconceptions and stigma about CSRs still persist in Marines. The findings reinforced the need to facilitate treatment utilization by focusing on mental health-related stigma as well as organizational barriers.

Introduction

The recent wars in Iraq and Afghanistan are the most sustained U.S. combat operations since the Vietnam War. Consequently, the number of veterans at risk for mental health problems which are commonly associated with sustained combat operations has continued to rise. A recent longitudinal study suggested that more than 40% of Iraq and Afghanistan veterans who sought treatment from a Veterans Administration hospital suffer from a mental disorder (e.g., post-traumatic stress disorder, depression, and anxiety) or a related behavioral problem (e.g., alcohol abuse). Similarly, another study reported that 35% of Army and Marine veterans accessed military mental health services within 1 year of returning home.

Early identification and treatment for mental illness is particularly important because once chronic post-traumatic adaptation difficulties develop, they tend to persist across the life span. These adaptation difficulties can be resistant to treatments that are otherwise shown to be effective in cases of early diagnosis.

However, early identification and treatment of mental illness is a particular challenge within the military. A previous study has shown that only 23 to 40% of Soldiers and Marines with symptoms of mental illness sought mental health care. Stigma-related beliefs about mental illness and mental health treatment as well as institutional factors have been identified as barriers to health care.

Stigma-Related Beliefs

Stigma is generally categorized as public and self-stigma. Public stigma relates to beliefs held by the general public about the attributes of those with mental illness that can consequently lead to prejudice and discrimination. Therefore, individuals who need treatment may decide against it to avoid these negative consequences. Self-stigma, on the other hand, reflects an individual's internalization of the cultural beliefs about mental illness which leads to feelings of shame and inadequacy, and consequently treatment seeking may be avoided. Although public and self-stigma can be teased apart, they often interact with each other to influence help-seeking behavior.

The development of stigma about mental health problems within the military culture is a systematic issue which is deeply rooted in the military traditions. Many of the attitudes and beliefs that prepare warriors for battle may prevent them from seeking help. Attitudes such as toughness, mission centeredness, and self- and group-based sufficiency are instilled in service members to ensure combat readiness. This training system contributes to the notion that help seeking is a sign of weakness and that strong, self-reliant individuals can prevent problem or injury. Thus, the value placed on strength creates the risk of stigma for any situation in which weakness is perceived.

Hoge and colleagues found that many soldiers and Marines believe that receiving mental health services would cause them to be seen as weak (65%), be treated differently by unit leaders (63%), lose confidence of their peers (59%), or be blamed for their problems (50%), or that their careers would be harmed. Among soldiers and Marines with mental health issues surveyed, only 38 to 45% reported an interest in receiving services.

Negative attitudes about treatment can inversely predict treatment seeking. Moreover, perceptions that asking for help is an admission of failure or weakness also have shown to predict decisions to seek mental health treatment over time. Additionally, treatment-seeking decisions are also affected by perceptions of responsibility for the mental health problem. Service member who believe that individuals with psychiatric problems are responsible for their disorder are less likely to seek care for themselves when they need it.

Interestingly, studies have demonstrated that those individuals reporting highest levels of mental health symptoms have the greatest concerns related to stigma In other words, individuals who might benefit most from receiving mental health care are the ones most affected by stigma and the ones least likely to seek treatment. Thus, stigma about mental health problems is not only a barrier to initiate care, it may also be a barrier to continue care.

Institutional Factors

Perceived organization support and the perception that the organization is committed to the welfare of its employees have been shown to be related to help-seeking behavior. Officer leadership and unit cohesion have also been shown to be associated with lower levels of stigma and perceived barriers to care.

Additionally, the location of the mental health clinics has been identified as a potential barrier to care. Mental health specialty clinics can contribute to stigmatization just by having separate facilities, entrances, and medical records. This problem may be further compounded by the military environment where Marines live and work together, and consequently lack proper privacy when using a mental health clinic on a base or a post. Moreover, a high proportion of soldiers with mental health problems express concerns about such issues as difficulty with scheduling an appointment, getting time off for treatment, and the cost of mental health care.

Overview

The primary consequence of treatment barriers is that many individuals live with, and are negatively affected by, treatable forms of psychopathology. Both institutional and stigma-related factors are modifiable, and the link between these barriers and treatment-seeking decisions highlights the importance of identifying mechanisms that can reduce such concerns.

In recent years, the Department of Defense (DoD) has made considerable efforts to anticipate and address the mental health needs of military personnel. The DoD has pursued a comprehensive approach to combat stress prevention as well as early detection and treatment by offering predeployment combat stress briefings, more comprehensive screening for combat stress reactions (CSRs), and providing mental health treatment services in combat setting (e.g., “forward psychiatry” including Operational Stress Control and Readiness [OSCAR] program). Additionally, in order to facilitate treatment, the DoD has taken measures to overcome barriers to care by providing mental health services in primary care clinics (as opposed to specialty care services for mental health). These efforts are likely to enhance awareness and treatment of mental health issues, establish standardized mental health services as routine (increased screening), improve accessibility through walk-in treatment (i.e., no appointment necessary), and increase patient trust and reduce social stigma of mental illness.

Additionally, the U.S. Marine Corps (USMC) has incorporated the Combat and Operational Stress Control (COSC) program in 2005 to address combat operational stress and encourage service members and their families to seek the help when required. The three main objectives of the program are prevention, identification, and treatment of stress problems in order to create and preserve a ready force as well as to promote the long-term health and well-being of service members and their families.

The current study is the first effort to collect systematic data directly from the USMC personnel who are the target group for the COSC program. The main objective of this explorative study was to identify malleable factors such as attitude towards CSRs and the barriers which affect help-seeking behavior. This study was designed to gather data that can be applied to enhance combat stress briefings to improve help-seeking behavior by targeting the specific concerns. The results of this study can be used as a baseline to track changes in perceptions of CSRs, barriers to care, and treatment utilization, which could help inform future development of the program.

## METHOD

### Participants

The sample consisted of 553 Marines from Marine Corps University at Quantico, Virginia (57.2%), Marine Corps Air Station at Miramar (13.1%), Barstow Logistics Base (10.5%), and March Air Force Base (19.2%). The participants were drawn from all 3 communities: Infantry (18%), Logistics (38%), and Air (44%).

## Measures

The questionnaire was specifically designed to assess common perceptions of CSRs and barriers to help-seeking behavior and treatment utilization. In addition to these measures, the questionnaire included questions about the presence of current stress and emotional problems as well as background information such as demographics and military experience. The instrument was a face-valid measure, which was developed by interviewing military subject matter experts on combat stress, post-traumatic stress disorder, and the COSC programs (i.e., psychiatrists, psychologists, physicians, chaplains, and corpsmen) and by modifying previous scales.

### Common Perceptions of CSRs and Barriers to Care

The common perceptions of CSRs and barriers to care scales consisted of 16 and 18 items, respectively, and was measured on a 5-point Likert-type scale (1 = “Strongly Disagree” to 5 = “Strongly Agree”). These scales were modified from the scales used in a previous study. The scale stem for common perceptions of CSRs asked respondents to: “Rate your degree of agreement with the following views on combat stress reactions.” Examples of common perceptions of CSRs that individuals could indorse included: “CSRs are short-term reactions in most people,” “CSRs are treatable;” and “CSRs result from inexperience with combat settings.” The scale stem for barriers to care asked respondents to: “Rate how each of the following beliefs might affect your decision to receive mental health services if you ever had a problem.” Examples of barriers to care items included: “I want to solve the problem on my own,” “It could harm my career;” and “I don't know where to get help.”

### Emotional Stress

Two items were used to measure the presence and the extent of postdeployment emotional stress on a 4-point scale (1 = “Not at all” to 4 = “A lot”). The scale stem for the presence of emotional stress asked respondents: “Is your most recent deployment still causing you overall emotional stress?” The scale stem for the presence of emotional stress asked respondents: “During the past 12 months how much did your strong emotions resulting from deployment interfere with your ability to perform your military job?”

### Treatment Utilization

A single item was used to assess treatment utilization rates for stress or emotional problem since returning from deployment. The responses were classified as “I never wanted help,” “I needed or wanted help but did not seek help,” “I wanted and sought help but have not received any help so far;” and “I wanted and received help.”

## Procedure

Participating units were selected to ensure variability by including all three communities (i.e., Infantry, Logistics, and Air). Initially, command leadership at participating units made announcements about the survey before their scheduled briefing. Marines in the class rooms were free to choose to participate in the survey or to leave the room at the end of their scheduled briefings. Approximately 99% of the Marines chose to participate in each of the classes. The questionnaire was administered in group settings. In accordance with an Institutional Review Board, participants were asked to fill out an anonymous questionnaire that took approximately 15 to 25 minutes to complete.

## Results

### Analyses

Analyses included $\chi^2$ comparisons of response patterns of the sample based on gender (male vs. female), age (<25 years vs. >25 years), education (an associate degree or higher vs. no college degree), combat experience (any vs. none) and unit (Infantry, Air, and Logistics). Additionally, $\chi^2$ analyses were performed to evaluate the relationship between the most common perceptions and the common barriers to care with help-seeking behavior (needed but did not ask for help; *N* = 49 vs. need and sought help; N = 46). Marines with scores of >3 (agreement or strong agreement) were classified as having agreement with the perceptions of CSRs and the barriers to care and were compared with Marines with scores of <3 (disagreement or strong disagreement). Alpha was set at 0.05 for all comparisons.

### Demographics

A majority of the Marines were men (92%) with an average age of 28 (SD = 5.2). Most of the participants had some college or a college degree (73%), and the most common paygrades were E4-E6 (49.1%). The majority of the participants were active duty (81.6%) and married (57.2%). The mean years of military service was 7.7 (SD = 4.4) years. More than half (57.2%) of the Marines had been deployed at least once, out of which 33.8% had been deployed once and 23.4% had been deployed more than once.

## Combat Experience and Combat Stress

Scores on combat exposure revealed that the most common combat exposures included seeing destroyed homes or villages (27.4%); receiving incoming artillery, rocket, or mortar fire (25.6%); and feeling that they could be killed at any time (20.1%). When asked if their most recent deployment was still causing stress, 43.5% of the Marines agreed or strongly agreed that their recent deployment was stressful, and 34.1% reported that their most recent deployment was still causing stress. About one-third (31.2%) reported having some emotional interference (ranging from "a little" to "a lot") in their job performance.

The mean score of combat stress and emotional interference did not differ significantly across the 3 communities. Moreover, surprisingly, the mean scores of the degree of emotional interference also did not differ significantly according to the number of deployments. Time since deployment, on the other hand, was significantly correlated to reported emotional interference ($F$ (6, 456) = 7.77, $p < 0.05$, partial eta-squared = 0.093). Particularly, emotional interference reported within a month of returning from deployment was significantly higher than that reported after 4 months and beyond. Additionally, although time since deployment affected emotional interference, it did not affect perceived stress after deployment.

## Common Perceptions of CSRs

The most common perception of CSRs was that CSRs are treatable (70.5%), normal (68.2%), can be individually managed (57.4%), and harmful to career (46.7%). In addition, some Marines believed that CSRs are short-term reactions (32.5 %), result from inexperience with combat (30.2%), can improve without treatment over time (29%), and are preventable with training (27.4%). Women were less likely to attribute CSRs to poor leadership, $\chi^2$ (1) = 3.88, $p < 0.05$, but were more likely to believe that CSRs are a form of brain injury, $\chi^2$ (1) = 10.97, $p = 0.001$. Marines in the Infantry unit were less likely to think of CSRs as permanent disability, $\chi^2$ (2) = 14.69, $p = 0.001$, and that CSRs can result in termination of career, $\chi^2$ (2) = 6.83, $p < 0.05$, whereas Marines in the Logistics unit were more likely to think of CSRs as self-serving, $\chi^2$ (2) = 12.06, $p < 0.01$. Marines with combat experience were less likely to think of CSR as brain injury, $\chi^2$ (1) = 5.56, $p < 0.05$ and that it should be managed by the unit, $\chi^2$ (1) = 5.53, $p < 0.05$.

Additionally, Marines with a college degree were less likely to think that CSRs represent permanent disability, $\chi^2$ (1) = 20.82, $p < 0.001$, that it should be unit-managed, $\chi^2$ (1) = 4.44, $p < 0.05$, and that it results from inexperience, $\chi^2$ (1) = 9.35, $p < 0.01$. College educated Marines were also more likely to think of CSRs as treatable, $\chi^2$ (1) = 8.75, $p < 0.01$, and less likely to think of CSRs as brain injury, $\chi^2$ (1) = 8.25, $p < 0.01$ and as self-serving, $\chi^2$ (1) = 4.46, $p < 0.05$. Younger Marines, on the other hand, were more likely to think of CSRs as permanent disability, $\chi^2$ (1) = 9.35, $p = 0.001$, as a form of brain injury, $\chi^2$ (1) = 7.88, $p < 0.01$, and that it should be managed by the unit, $\chi^2$ (1) = 5.21, $p < 0.05$.

Barriers to Help-seeking Behavior

The most common belief that reportedly affected their decision to utilize resources for mental health was their desire to solve their own problem (64.5%). They also reported a fear of their command losing trust in them (49.8%), being treated differently (45%), lack of confidentiality (37%) and a fear of negative effect on their career (36.5%). However, lack of awareness of resources for help (9.4%), belief that the treatment is not effective (8.1%), and discouragement from leadership to seek help (7.7%) were the least common beliefs that reportedly affect their decision to seek out mental health support.

Women were more likely to be concerned about supervisors' discouragement of using mental health services, $\chi^2$ (1) = 4.01, $p < 0.05$. Younger Marines, on the other hand, were more likely to prefer alternative treatment, $\chi^2$ (1) = 6.72, $p = 0.01$, be unsure about the available resources for help, $\chi^2$ (1) = 5.78, $p < 0.05$, and worry about transportation, $\chi^2$ (1) = 5.56, $p < 0.05$ and cost of treatment, $\chi^2$ (1) = 4.29, $p < 0.05$. Additionally, Marines with a college degree were more likely to be embarrassed about mental health problems, $\chi^2$ (1) = 11.70, $p = 0.001$, worry about their units losing confidence in them, $\chi^2$ (1) = 11.05, $p = 0.001$, and leadership treating them differently, $\chi^2$ (1) = 13.59, $p < 0.001$, but were less likely to be concerned about transportation, $\chi^2$ (1) = 7.47, $p < 0.01$ and cost of treatment, $\chi^2$ (1) = 6.45, $p < 0.05$. Interestingly, Marines with and without combat experience did not differ significantly in their perceptions of barriers to care.

Treatment Utilization

A majority (79.9%) of Marines reported that they never needed or asked for help. However, 10.4% reported that they wanted but did not ask for help, 2.3% stated that they sought but did not receive help, and 7.4% of the Marines reported that they wanted and received help.

Help-seeking behavior was not significantly related to any of the common perceptions such as CSRs are treatable, $\chi^2$ (1) = 0.38, $p > 0.05$, normal, $\chi^2$ (1) = 1.84, $p > 0.05$, can be individually managed, $\chi^2$ (1) = 0.21, $p > 0.05$, harmful to career, $\chi^2$ (1) = 1.00, $p > 0.05$, short-term reactions, $\chi^2$ (1) = 0.94, $p > 0.05$, result from inexperience, $\chi^2$ (1) = 1.61, $p > 0.05$, improve over time, $\chi^2$ (1) = 0.70, $p > 0.05$, and preventable with training, $\chi^2$ (1) = 2.28, $p > 0.05$.

Similarly, help-seeking behavior was not significantly related to any of the common barriers to care such as desire to solve own problem, $\chi^2$ (1) = 0.013, $p > 0.05$, fear of command losing trust, $\chi^2$ (1) = 2.25, $p > 0.05$, being treated differently, $\chi^2$ (1) = 1.84, $p > 0.05$, and fear of lack of confidentiality, $\chi^2$ (1) = 0.94, $p > 0.05$.

Discussion

The present study recruited Marine officers and enlisted personnel to evaluate common perceptions of CSRs, barriers to seeking help, and treatment utilization. The results of this survey provided data that can be used as a baseline to track changes of perception over time in service members in the COSC program. These data can also be used to modify combat stress briefings to target the specific concerns and improve help-seeking behavior.

The findings of the survey revealed that the most common perception of the CSRs is that these are treatable, normal, and short-term reactions. Additionally, the most common beliefs that affect mental health decisions included a preference to solve their own problem, fear of being treated differently, fear of their unit losing trust in them, fear of nonconfidentiality, and fear of harming career. Some of the perceptions of CSRs and barriers to care differed based on gender, age, and education. Notably, younger Marines seem to have more misconceptions of CSRs (e.g., permanent disability, form of brain injury), and are more likely to be unsure about the available resources, and worry about cost and transportation related to treatment. College educated Marines, on the other hand, were more likely to be embarrassed about mental health problems and worry about losing the trust of their unit and being treated differently by the leadership.

The results of this study showed that combat stress and the degree of emotional interference did not differ significantly across the three communities. As expected, time since deployment was negatively correlated to reported emotional interference. However, inconsistent with a previous study, the number of deployments was not significantly related to the Marines' perception of CSRs. Similarly, emotional interference did not differ significantly according to the number of deployments. Incidentally, the majority (76.6%) of our sample had none or one deployment experience, and a relatively smaller proportion had 2 or more deployment experiences (23.4%). Thus, a smaller proportion of the sample with 2 or more deployment may have undermined the association between the number of deployments and perceptions of CSRs as well as the degree of emotional interference.

Inconsistent with the previous studies, the results of the current study did not find a relationship between stigma and barriers to care with help-seeking behavior. Incidentally, the majority of the Marines in the sample (79.9%) reported that they never needed or asked for help. Thus, the small proportion of the Marines who actually needed help may have diluted the association between negative attitude and help-seeking behavior.

Overall, the findings of the study reinforce the need to implement policies and programs to promote leadership support and confidentiality. The Marines should be properly advised about the consequences of seeking help for mental health. They should also

be advised regarding confidentiality of personal health information in the military. For many military members, it is often difficult to separate stigma from legitimate concerns regarding real potential consequences of help seeking. Confidentiality regarding mental health treatment is a major concern for many military men and women. Moreover, mental health diagnoses are listed on fitness-for-duty profiles, which may then render service members ineligible for certain career tracks. Consequently, issues of stigma may be more difficult to target for current military members compared to military veterans who have separated from military service which should be taken into consideration when applying stigma intervention.

Further emphasis should be placed on the importance of early identification and treatment to help minimize chronic and post-traumatic adaptation difficulties later on. As noted earlier, early identification and intervention can be particularly effective in treating CSR symptoms. Previous studies have explored effective strategies to encourage help-seeking behavior. For instance, a brief cognitive behavioral intervention, focused on modifying beliefs about mental health treatment, has been shown to be effective in increasing treatment-seeking behavior in a small sample of National Guard soldier during transition after deployment.

A limitation of the current study includes potential selection bias since the survey participants were not randomly selected but were identified via convenience sample. Additionally, all of the measures used in the present study were based on self-report and were assessed at a single point in time. Although the high participation rate provides moderate confidence in our findings, the results of the study should be generalized to the larger Marine population with caution. Another limitation of the survey is that it did not include the current mental health status of the participants, and the majority of the sample reported that they never wanted or needed help for mental health issues.

Strengths of this study, on the other hand, included a focus on multiple barrier domains and perceptions of CSRs in a contemporary cohort involved in the COSC program. Future studies in the area should gather data from a larger, randomly selected population and include mental health diagnoses and prior experiences with mental health treatment in order to reliably evaluate differences in sigma perceptions across multiple groups.

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