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Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?

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IS COMBAT EXPOSURE PREDICTIVE OF HIGHER PREOPERATIVE STRESS IN MILITARY MEMBERS?

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Abstract

Since September 11, 2001, the United States has been engaged in large-scale combat operations exposing numerous military service members to stressful, traumatic, and threatening environments. As a result, many of these individuals have experienced significant psychological problems, such as anxiety, depression, and posttraumatic stress disorder (PTSD), as well as physiological alterations, such as cardiovascular changes and neuroendocrine disturbances. The preoperative experience may be perceived as stressful, often increasing in magnitude as the patient progresses through the preoperative period. Military anesthesia providers frequently provide anesthetic care to military members with a history of combat exposure. Anecdotally, it is not uncommon for this patient population to require a more "heavy-handed" anesthetic regimen, potentially resulting in increased side effects or prolonged recovery.

An enormous gap exists in knowledge related to the preoperative stress response, especially in military members with a history of combat exposure. Therefore, the purpose of this study was to determine predictive relationships between the number of combat experiences and the preoperative stress response in U.S. military personnel on the day of surgery. This prospective, descriptive study was conducted at Naval Hospital Camp Pendleton, enrolling active duty men and women undergoing elective surgery. One to 14 days prior to surgery, anxiety, depression, and PTSD symptoms were assessed. In addition, participants reporting a prior military deployment having received combat-related pay completed a U.S. Army-developed combat exposure scale. On the day of surgery, the preoperative psychological and physiological stress response was measured using the Visual Analogue Scale for Stress, Multiple Affect Adjective Checklist-Revised,

and salivary alpha-amylase. This may be the first investigation to determine predictive relationships between varying degrees of combat exposure and the preoperative stress response in military personnel on the day of surgery.

Dedication

I dedicate this dissertation to my wife, Michelle, for being extremely supportive and understanding throughout my time in school, and to my beautiful children, Mariana, Nick, and Jack, you bring such joy to my life. I also dedicate this dissertation to my mother and father who taught me the value of education. I love you all!

Preface

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I would also like to thank the TriService Nursing Research Program for providing grant funding for this project, as well as the supportive staff at the University of San Diego. Without their support this project would have never been completed.

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Chapter 1: INTRODUCTION AND SIGNIFICANCE

Statement of the Problem

The preoperative experience is a particulary unique phenomenon and may be perceived as extremely stressful. Increased stress often results in hyperarousal states amplifying psychological symptoms and magnifying physiological alterations. Current research suggests patients exhibiting higher degrees of stress in the preoperative setting experience significantly more adverse perioperative phenomena, such as increased heart rate, anesthetic requirement, and postoperative anxiety and pain (Carr, Brockbank, Allen, & Strike, 2006; Demirtas et al., 2005; Hong, Jee, & Luthardt, 2005; McIntosh & Adams, 2011).

Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF) over the last decade have exposed numerous U.S. military service members to stressful, traumatic, and threatening environments (McGhee et al., 2009; Nayback, 2009). As a result, many of these individuals have experienced significant psychological problems, such as acute stress syndrome, posttraumatic stress disorder (PTSD), depression, and risk for dysfunctional socialization (Phillips, Leardmann, Gumbs, & Smith, 2010). Physiological alterations have also occurred, such as significant bodily injury, cardiovascular changes, and neuroendocrine disturbances (Hoge et al., 2004; Nayback, 2009). Alarmingly, patients with exposure to high stress environments, such as combat operations, appear especially prone to hyperarousal states exhibited by increased anxiety, irritability, and being easily started when confronted by stressors (Liberzon, Abelson, Flagel, Raz, & Young, 1999).

Military anesthesia providers frequently encounter and provide anesthetic care to military personnel with a history of combat exposure. Consequently, many perianesthesia clinicians express angst and frustration in how best to manage combat veterans perioperatively when, for example, a Marine communicates a history of aggressive or violent "wake up" following surgery. Anecdotally, it is not uncommon for this particular patient population to require a more "heavy-handed" anesthetic regimen during the perioperative period simply to ensure an adequate state of anesthesia. Additionally, anesthesia providers are resorting to various anesthetic techniques and numerous medications in a desperate attempt to better manage this seemingly heightened perioperative stress response. Not only can this result in increased side effects and potential for prolonged recovery, patients may continue to suffer psychological and physiological alterations during future perioperative visits.

Ten years has passed since the inception of operations OEF/OIF and only one investigation has explored potential factors associated with perioperative phenomena in a military population. A recent study found that combat-exposed veterans experiencing anxiety, depression, and PTSD-symptomatology days prior to surgery exhibited a greater incidence of emergence delirium following surgery (McGuire, 2012). Despite the significance of this finding, no study to date has explored predictive relationships between various degrees of combat exposure and the preoperative stress response in active duty military members on the day of surgery. Therefore, the purpose of this study is to determine predictive relationships between combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health disorders (i.e., anxiety, depression, and PTSD).

Specific Aims

The specific aims of this proposal are to:

Aim 1. Determine the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of more negative emotions at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Multiple Affect Adjective Checklist-Revised.

Hypothesis 2. In U.S. military personnel, a greater number of combat experiences will be predictive of higher degrees of stress at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the visual analogue scale for stress.

Aim 2. Determine the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of higher salivary alpha-amylase values measured at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room.

Research Questions

The research questions this study will answer are:

Research question 1. What are the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF?

Research question 2. What are the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF?

Chapter 2: REVIEW OF THE LITERATURE

Theoretical Framework

For the purposes of this study, stress is a state in which an individual's capacity to maintain the physiologic balance necessary for survival is threatened or perceived to be in danger (Chrousos, 2009; McEwen & Wingfield, 2010). Within this model, the human stress response is considered a multidimensional, interactive process possessing several elements: (a) stressor events (psychosocial; e.g., anticipation of anesthesia and surgery; or biogenic; e.g., cold holding area or operating room); (b) cognitive appraisal and affective integration; (c) neurological triggering mechanisms (e.g., locus coeruleus); (d) the stress response; (e) target-organ activation, (f) and coping behavior. Figure 1 describes the conceptual framework for this model.

Within the context of this study, the *preoperative stress response* will be the phrase used to describe the response or reaction patients exhibit when encountering preoperative stressors (e.g., anticipation of anesthesia or surgery). Cognitive appraisal is how one interprets a stressor and affective integration refers to the blending and coloring of felt emotion into the cognitive interpretation; hence, the combination of these two concepts represents how stressors are perceived (Everly & Lating, 2002). The process is individualized and potentially affected by personality, status or social-role behaviors, genetic vulnerability, past exposure (e.g., prior anesthesia or surgical experiences), timing of events, and/or a history of exposure to traumatic stressors (e.g., combat exposure; Charmandari, Tsigos, & Chrousos, 2005). The acute stress response activates the

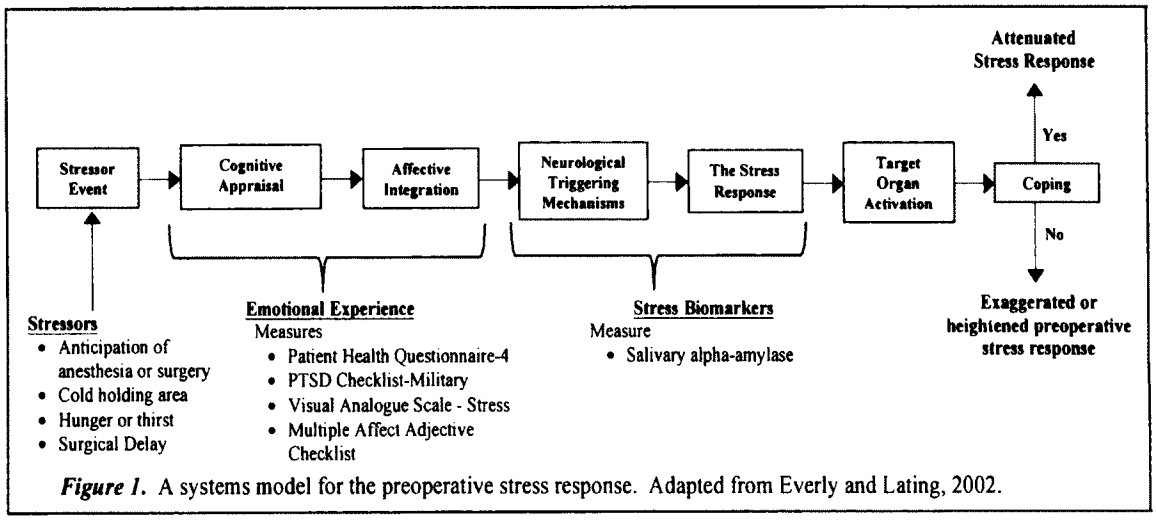


Figure 1. A systems model for the preoperative stress response. Adapted from Everly and Lating, 2002.

sympathetic nervous system (SNS) and triggers the hypothalamic-pituitary-adrenal axis (HPA-axis; Charmandari et al., 2005).

Principal Literature Review

Stress and stressors. Stress is a state in which an individual's capacity to maintain a physiological balance necessary for survival is threatened or perceived to be in danger (Chrousos, 2009; McEwen & Wingfield, 2010). Chrousos (2009) described stressors as external or internal factors that challenge the human body to preserve a state of equilibrium, commonly referred to as homeostasis. Stressors can be classified as psychosocial or biogenic (Everly & Lating, 2002). Psychosocial stressors are those experiences or threats which the individual perceives as real, imagined, anticipated, or recalled; hence one's cognitive assessment of a stressor may or may not manifest in a stress response (Everly & Lating, 2002). Biogenic stressors do not require the individual to appraise an event as threatening or stressful; rather, the biogenic stimulus may activate the stress response by way of a chemical (e.g., caffeine or nicotine) or physical (e.g., trauma or hemorrhage) stressor (Everly & Lating, 2002; Pego, Sousa, Almeida, & Sousa, 2010).

Components of the stress response. Components integral to the human stress response are located centrally and peripherally (Charmandari et al., 2005). Central components include the corticotropin-releasing hormone (CRH) and arginine vasopressin neurons of the paraventricular nucleus located in the hypothalamus, as well as CRH-secreting neurons located in the medulla (Chrousos, 2007). Further, norepinephrine (NE) producing bodies located in the locus ceruleus (LC), medulla, and pons, collectively referred to as the NE/LC system, also contribute significantly to the human stress response (Charmandari et al., 2005; Chrousos, 2007). Peripherally, the human stress response is composed of the HPA-axis, sympathetic-adrenal-medullary axis, and parasympathetic nervous system (Charmandari et al., 2005; Papadimitriou & Priftis, 2009).

Acute stress response. When an individual perceives a stressor as potentially threatening or harmful psychological and physiological alterations may ensue (McEwen, 2008; Schneiderman, Ironson, & Siegel, 2005). Behavioral manifestations of a stress response can include increased arousal and alertness, anxiety, fear, depression, and dysphoria (Chrousos, 2007; Pego et al., 2010). The neurological (i.e., NE/LC system) response to a stressor occurs swiftly, altering many organs and their function, resulting in increased heart rate, blood pressure, and respiratory rate and release of catecholamines from the adrenal glands (Charmandari et al., 2005). Endocrine alterations result from hypothalamic secretion of CRH, subsequently stimulating for the release of adrenocorticotropic hormone from the anterior pituitary gland and subsequent release of cortisol from the adrenal cortex (Bonfiglio et al., 2011; Papadimitriou & Priftis, 2009; Schneiderman et al., 2005). Cortisol has widespread effects upon the body's metabolism

by altering the management of proteins, fats, and carbohydrates, to provide a ready-made source of energy to support the human stress response (Desborough, 2000; Papadimitriou & Priftis, 2009; Schneiderman et al., 2005).

Chronic stress response. The acute stress response is typically short-lived or a brief occurrence associated with minimal risk in otherwise healthy individuals (Chrousos, 2007; Schneiderman et al., 2005). However, if a stress response becomes hyperdynamic and/or chronic, particularly in patients with pre-existing disease, a state of exhaustion may ensue, ultimately exacerbating disease and increasing morbidity (Goldstein, 2010). For example, persistent SNS activity may lead to significant increases in blood pressure, which left untreated may result in thickening and damage to vasculature (Schneiderman et al., 2005). Likewise, prolonged cortisol production due to chronic stress may have profound systemic implications, such as negative nitrogen imbalance resulting from protein catabolism or hyperglycemia because of insulin resistance, lipolysis, and increased gluconeogenesis in the liver (Charmandari et al., 2005; Chrousos, 2007; Desborough, 2000). Other physiological alterations can include water and sodium retention, depressed SNS responsiveness, and immunosuppression (Charmandari et al., 2005; Desborough, 2000; Page, 2005).

Preoperative stress. Preoperative stress might begin days or weeks prior to surgery due to requisite testing or evaluation by anesthesia and surgery staff to ensure adequate perioperative preparation. Potential stressors experienced on the day of surgery can include unfamiliar surgical facilities, confusing procedures and regimens, or preoperative encounters that may be perceived as rushed and apathetic (Pritchard, 2009). In addition, patients find themselves in preoperative settings that are often cold, secluded

from family, harshly lit, and filled with unfamiliar sounds, thus contributing to a sense of vulnerability or loss of independence (Grieve, 2002; Wagner, Byrne, & Kolcaba, 2006). Patients may also experience prolonged wait times, perhaps allowing them to reflect further on the surgery or anesthesia and potentially exacerbating an already stressful situation (Mitchell, 2011).

Anxiety is a well-founded affective manifestation of preoperative stress in the adult population undergoing elective surgery. Anxiety is reportedly the most prevalent stress-engendered emotion in this population with an overall incidence ranging from 54% to 98% (McIntosh & Adams, 2011; Sun, Hsu, Chia, Chen, & Shaw, 2008). This affective state may manifest as restlessness, worry, apprehension, nervousness, or other sympathetically-driven symptomatology, such as increased heart rate, blood pressure, and so on (Pego et al., 2010; Pritchard, 2009). Some research attempts to quantify the magnitude or degree of anxiety since individuals with higher degrees of preoperative stress may experience hyperarousal states, amplifying psychological symptoms and magnifying physiological alterations (Spence, McBeain, Guzman, Roucek, & Maye, 2011). For example, Carr et al. (2006) found over 40% of participants scheduled to undergo various gynecological procedures experienced "high" anxiety during their preoperative clinic visit prior to surgery, and 67% reported high anxiety immediately before entering the operating room. Wong, Chan, and Chair (2010) measured baseline anxiety in male and female subjects with orthopedic fractures requiring surgery and found all participants experienced high degrees of baseline preoperative anxiety. Other studies enrolling men and women scheduled to undergo various types and complexities of surgery reported moderate anxiety in 30% of the subjects, and rates of high and severe

anxiety were 25% and 23%, respectively (Kindler, Harms, Amsler, Ihde-Scholl, & Scheidegger, 2000).

Fear is another emotion associated with preoperative stress. Fitzgerald and Elder (2008) conducted a study in a military medical facility investigating the effects of perioperative education upon fear and found 70% of the study population reported preoperative fear. Kindler et al. (2000) reported patients feared surgery significantly more than anesthesia; however, a phenomenological investigation of patients' perioperative experiences indicated that fear of anesthesia predominated (Costa, 2001). Other research has suggested patients fear general anesthesia significantly more than procedures requiring local anesthesia with sedation (Mitchell, 2011). When asked to rank anesthesia-related fear, subjects indicated death as their primary fear, followed by pain, intraoperative awareness, nausea and vomiting, and the provider's capacity to provide adequate care (Fitzgerald & Elder, 2008). One recent investigation measured positive and negative preoperative affective emotions in a general surgical population and found positive affect scores decreased and correlated significantly with a rise in a SNS biomarker called salivary alpha-amylase (SAA), a biomarker directly linked to increased autonomic activity. This finding suggests patients who experience more negative emotions in the preoperative period may have a greater SNS response (Spence et al., 2011).

Risk factors for preoperative stress. Some research has identified factors that may be predictive of an increased risk for preoperative stress. One study found women experienced significantly higher degrees of preoperative anxiety than men (Aalouane, Rammouz, Tahiri-Alaoui, Elrhazi, & Boujraf, 2011). Another study corroborated the

prevalence of increased anxiety in female subjects and noted that anxiety occurred earlier in the preoperative phase for women than for men (Mitchell, 2011). Additional studies suggest higher degrees of anxiety may be associated with younger age, negative experiences with anesthesia, no prior anesthetic experience, or inability to adequately describe the medical procedure (Kindler et al., 2000; Kiyohara et al., 2004; Sun et al., 2008).

Type of surgery has also been hypothesized as a potential risk factor for increased preoperative stress. Aalouance et al. (2011) enrolled patients scheduled for elective gynecological, general, and oncological procedures and found the oncological sample experienced significantly higher degrees of anxiety than the other two groups. However, an observational study investigating perioperative knowledge found the diagnosis of cancer did not significantly correlate with higher degrees of anxiety when compared with non-cancer patients (Kiyohara et al., 2004). Findings related to complexity of surgery and preoperative stress appear to be mixed as well. Carr et al. (2006) found subjects scheduled to undergo major surgery reported significantly greater degrees of anxiety than subjects having minor surgery; however, another study indicated subjects undergoing intermediate surgery exhibited substantially more preoperative anxiety than those scheduled for minor or major surgeries (McIntosh & Adams, 2011).

Preoperative stress and perioperative outcomes. Researchers have explored the impact of preoperative stress on other aspects of the perioperative experience as well. Gras et al. (2010) investigated the effect of heart rate and preoperative anxiety on intraoperative anesthetic requirements in a gynecological population and found higher state anxiety resulted in an elevated heart rate and higher anesthetic dosages required to

achieve adequate induction of anesthesia. In addition, methodologically similar studies (all female, gynecological) not only corroborated this increased anesthetic requirement during the induction phase, but also found intraoperative anesthetic dosages were greater among subjects with high preoperative anxiety than those with lower levels of anxiety (Hong et al., 2005). However, one study enrolling both men and women scheduled for minor surgery was unable to validate this increased anesthetic requirement in highly anxious patients. The authors attributed this finding to a potential inability of the tool to accurately measure preoperative anxiety (Morley, Papageorgiou, Marinaki, Cooper, & Lewis, 2008).

The effect of preoperative stress upon symptoms and emotions experienced during the postoperative period has also been described. Research has indicated significant correlation of preoperative anxiety with depression and postoperative anxiety (Caumo et al., 2001; McIntosh & Adams, 2011). Pain is another postoperative sequela reportedly linked to preoperative stress. The incidence and severity of pain immediately following surgery has been strongly correlated not only to high levels of preoperative state anxiety, but to individual coping styles as well (Carr et al., 2006; Kain, Sevarino, Alexander, Pincus, & Mayes, 2000). One study investigated the possibility of preoperative anxiety as a risk factor for postoperative nausea and vomiting (PONV) and found subjects exhibiting higher levels of preoperative anxiety experienced a higher incidence of PONV (Van den Bosch, Moons, Bonsel, & Kalkman, 2005).

Physiological measurements of preoperative stress. Physiological markers used to assess stress during the preoperative period range from common measurements (e.g., vital signs) to more invasive or complex biomarkers (e.g., cortisol; Gras et al.,

2010; Leardi et al., 2007; Wetsch et al., 2009). These various physiological measures can generally be categorized as cardiovascular, neuroendocrine, and endocrine (Everly & Lating, 2002). The cardiovascular markers typically encompass heart rate, respiratory rate, and blood pressure. Despite the scarcity of significant correlations between cardiovascular markers and the preoperative stress response, some appreciable insight has been gained and may have very real clinical implications (Oshima et al., 2001). For example, Demirtas et al. (2005) investigated heart rate variations in young patients during a 24-hour period prior to plastic surgery. The average heart rate over this 24-hour period was approximately 76 (±7) beats per minute; however, as patients progressed through the preoperative period the mean heart rate increased to 99 (±11) beats per minute immediately prior to anesthesia induction (Demirtas et al., 2005).

Researchers have also explored neuroendocrine and endocrine biomarkers, often in studies attempting to investigate the effects of preoperative pharmacological or non-pharmacological interventions. The neuroendocrine hormones most often reported in the literature are norepinephrine and epinephrine, typically measured in serum or urine with appreciable correlations to preoperative stress (Duggan et al., 2002; Hahm et al., 2002).

Cortisol is the most commonly reported endocrine biomarker, with some studies reporting significant decreases in cortisol levels following preoperative stress reduction interventions as compared to placebos (Duggan et al., 2002; Leardi et al., 2007). Neuroendocrine and endocrine biomarkers serving as preoperative stress surrogates, however, have many potential methodological limitations that are difficult to manage, such as diurnal cortisol patterns or the effect of adrenergic medications upon SAA secretion (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). Additional

physiological measurements found in the literature include serum potassium, SAA, lymphocyte counts, Bispectral Index, skin conductance, and heart rate variability (Demirtas et al., 2005; Hahm et al., 2002; Leardi et al., 2007; Morley et al., 2008; Spence et al., 2011; Wetsch et al., 2009).

Psychological measures of preoperative stress. There have been numerous psychometric instruments used to study the preoperative stress response. The most popular instrument considered by some to be the "gold standard" is the State-Trait Anxiety Inventory (STAI; Kindler et al., 2000). The STAI is a self-administered tool including both state and trait scales, each containing 20 questions with a weighted response of one to four and a total score ranging from 20 to 80. Depending upon the literature cited, persons scoring greater than or equal to 45 are considered highly anxious (Carr et al., 2006). One criticism of the STAI is the time required to complete this instrument, reported at six to ten minutes (Wetsch et al., 2009).

The visual analogue scale (VAS), also known as the vertical visual analogue scale, is frequently used to measure preoperative stress and anxiety (Gonzales et al., 2010; Spence et al., 2011). The VAS commonly consists of a 100 mm horizontal line with word descriptors at the ends of the continuum, such as "no anxiety" and "very high anxiety" (Williamson & Hoggart, 2005). Patients are instructed to mark a line along this continuum that best depicts their feeling at that particular moment. An inherent methodological issue in using the VAS is the potential for central tendency bias. Essentially, this phenomenon results when patients become less willing or uncomfortable selecting a point that truly represents their feelings; rather, they choose a conservative

point versus an extreme (Polit & Beck, 2012). However, benefits of employing the VAS include simplicity, ease of use, and minimal time for completion.

The Amsterdam Preoperative Anxiety and Information Scale (APAIS) is a six item self-report tool measuring anxiety relative to anesthesia and surgery, as well as the patient's desire for information (Boker, Brownell, & Donen, 2002). Respondents use a five-item Likert-type scale to denote their level of agreement with each of six statements (1= not at all to 5= extremely), four pertaining to anesthesia and surgery-related anxiety and two measuring patient information needs. The APAIS can be completed in less than two minutes and the anxiety portion of the APAIS was found to correlate strongly with the STAI-state scale (Moerman, van Dam, Muller, & Oosting, 1996).

Some psychometric instruments reported in the literature have incorporated measures of affect other than anxiety. These instruments include the Hospital Anxiety and Depression Scale (HADS), the Multiple Affect Adjective Checklist (MAACL), and the MAACL-R (revised) (McIntosh & Adams, 2011; Spence et al., 2011). The HADS instrument has proven to be a reliable and valid instrument in both clinical practice and research. The tool consists of 14 questions, seven related to anxiety (HAD-A) and seven addressing depression (HAD-D; Bjelland, Dahl, Haug, & Neckelmann, 2002). An individual's response to each question is scored on a four-point Likert-type scale (0-3) and the instrument takes less than 10 minutes to complete (McIntosh & Adams, 2011).

The MAACL and MAACL-R have both been shown to be reliable and valid measures of preoperative state and trait affect (Lubin & Zuckerman, 1999). The MAACL-R is a revised version of the MAACL and currently consists of two positive affect scales (positive affect and sensation seeking) and an improved capacity to measure

negative affective emotions (anxiety, depression, and hostility; Lubin & Zuckerman, 1999). The MAACL-R contains a list of 132 adjectives from which patients select words that most accurately describe how they currently feel (state) or how they generally feel (trait). The estimated time to complete the MAACL-R is less than three minutes (Lubin & Zuckerman, 1999).

Preoperative stress and military personnel. Increased OEF/OIF operations over the last decade have exposed numerous U.S. military service members to stressful, traumatic, and threatening environments (McGhee et al., 2009; Nayback, 2009). As a result, many of these individuals have experienced significant psychological problems, such as acute stress syndrome, anxiety, depression, PTSD, and risk for dysfunctional socialization (Phillips et al., 2010). Physiological alterations have also occurred, such as significant bodily injury, cardiovascular changes, and neuroendocrine disturbances (Hoge et al., 2004; Nayback, 2009). Alarmingly, patients with exposure to high stress environments, such as combat operations, appear especially prone to hyperarousal states exhibited by increased anxiety, irritability, and being easily startled when confronted with stressors (Liberzon et al., 1999).

Military anesthesia providers frequently encounter and provide anesthetic care to military members with a history of combat exposure. Anecdotally, it is not uncommon for this particular patient population to require a more "heavy-handed" anesthetic regimen during the perioperative period simply to ensure an adequate state of anesthesia, or for an anesthetist to administer medications with known sedative properties convinced they will ablate or diminish patient responsiveness upon emergence from anesthesia. Not only can this result in increased side effects and potential for prolonged recovery, these

patients may continue to suffer psychological and physiological alterations during future perioperative visits.

Military perianesthesia nurses also struggle with how best to manage veterans perioperatively when, for example, a patient communicates a history of aggressive or violent "wake up" following surgery. Unfortunately, military nurses are resorting to interventions thought to be beneficial in mitigating perioperative stress, such as medications (e.g., midazolam) or non-pharmacological interventions (e.g., quiet postoperative suite), rather than scientific evidence guiding the treatment of highly stressed patients.

Summary

The preoperative period is fraught with stressors, often increasing in magnitude as the patient progresses through the preoperative period. Current research suggests patients exhibiting higher degrees of stress in the preoperative setting experience significantly more adverse perioperative phenomena. U.S. military members deployed in support of combat operations, especially personnel encountering direct firefights or enemy engagements, are at risk for experiencing a heightened preoperative stress response. Although unsubstantiated in research, anecdotal accounts by military anesthesia providers and perianesthesia nursing staff have described this particular population as clinically challenging, appearing more anxious preoperatively and necessitating greater quantities of anesthetic medications intraoperatively. These combat veterans may also be agitated, restless, and confused when emerging from anesthesia (McGuire, 2012).

Only one investigation known to this author has researched military members in the perioperative setting with a history of a deployment to OEF/OIF; however, the

participants in this study were predominately combatants that had either fired a weapon or been fired upon during their deployment (McGuire, 2012). In addition, McGuire (2012) only measured subjective anxiety, depression, and PTSD symptomatology at one time point; i.e., days prior to surgery. Despite this study's significant and noteworthy findings, generalizability to the military population was limited since the study failed to capture other dimensions of combat exposure known to exist in a combat environment. Furthermore, measures of anxiety or depression days prior to surgery may have been significantly less than those emotions experienced on the day of surgery.

Given the paucity of research demonstrated in the review above, an enormous gap exists in knowledge related to the preoperative stress response in active duty military members with varying degrees of combat exposure. More specifically, no study to date has investigated relationships between the number of combat experiences and the psychological and physiological preoperative stress response in a military population. Scientifically investigating predictive relationships between combat experiences and the preoperative stress response in military personnel could potentially validate anecdotal reports by military perianesthesia clinicians, as well as provide preliminary findings supporting future interventional studies.

Chapter 3: METHODOLOGY

Specific Aims

The specific aims of this proposal are to:

Aim 1. Determine the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of more negative emotions at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Multiple Affect Adjective Checklist-Revised.

Hypothesis 2. In U.S. military personnel, a greater number of combat experiences will be predictive of higher degrees of stress at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the visual analogue scale for stress.

Aim 2. Determine the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of higher salivary alpha-amylase values measured at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room.

Research Questions

The research questions this study will answer are:

Research question 1. What are the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF?

Research question 2. What are the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF?

Research Design and Setting

A prospective, descriptive study will be conducted to investigate predictive relationships between varying degrees of combat experience and the preoperative psychological and physiological stress response in military personnel scheduled for elective surgery. The proposed study site is Naval Hospital Camp Pendleton (NHCP). Study approval will be obtained from the department heads of the Same Day Surgery Unit (SDSU) and Anesthesia Department, Directorate of Surgical Services, Commanding Officer of the military medical facility, and the facility's Institutional Review Board. A convenience sample of 120 ASA I-II active duty military members presenting for elective general, gynecological (non-obstetric), orthopedic, otolaryngological (ENT), or podiatric surgery requiring anesthesia services and meeting the inclusion/exclusion criteria will be recruited. Following enrollment (1 to 14 days prior to the day of surgery), all subjects will complete the Demographic and Deployment History questionnaires, Patient Health Questionniare-4 (PHQ-4), and Posttraumatic Stress Disorder Checklist-Military (PCL-M). In order to determine the effect combat exposure has upon the preoperative stress

response, subjects reporting a prior deployment where they have received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits (i.e., combat-exposed group) will also complete the Walter Reed Army Institute of Research Combat Exposure Scale (WRAIR-CES).

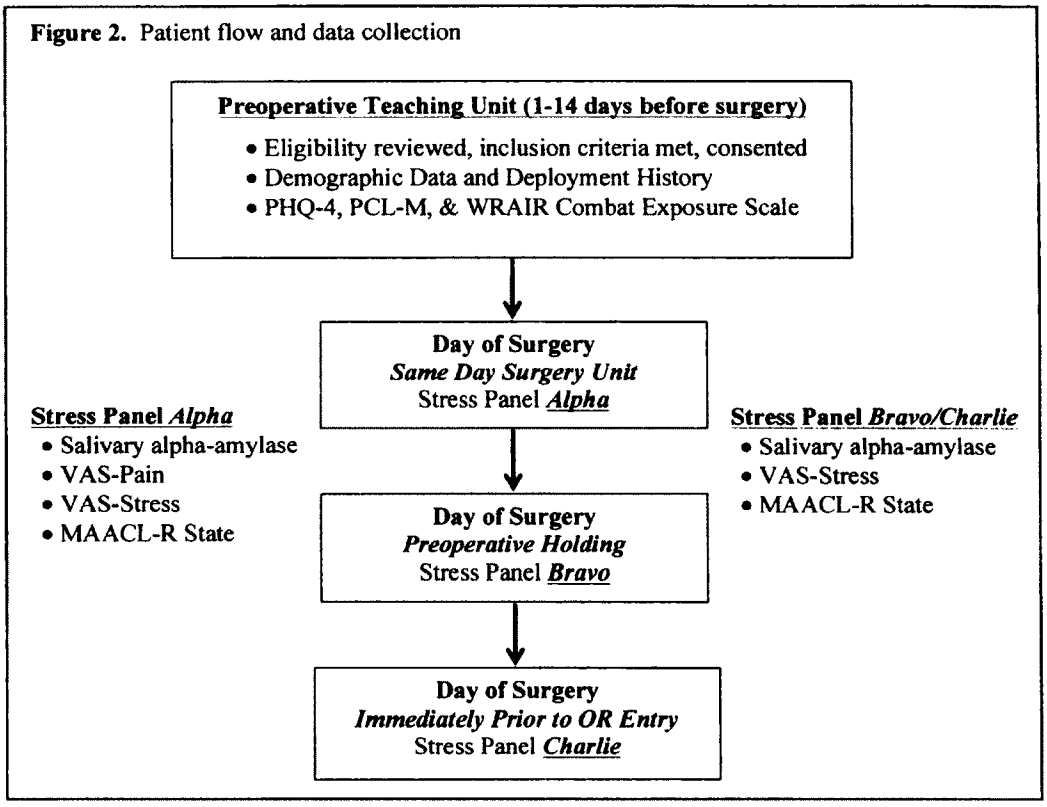
Following admission to the SDSU on the day of surgery, the first SAA sample will be obtained while study subjects complete the verbal analogue scale for pain (VAS-P) and stress (VAS-S) and the MAACL-R. Upon arrival to the preoperative holding area subjects will submit a second SAA sample while completing a second VAS-S and MAACL-R. Immediately prior to receiving anxiolytics and/or transfer to the operating room, subjects will submit a third SAA sample and complete the MAACL-R and VAS-S. See Figure 2 for patient flow and data collection.

Sample Population

The inclusion criteria for this study are: (a) active duty military men or women; (b) age 18-45; (c) ASA category I or II; (d) undergoing elective, non-cancer surgery requiring anesthesia services (e.g., general anesthesia, monitored anesthesia care, regional anesthesia) for general, gynecological (non-obstetric), orthopedic, ENT, or podiatric surgery; (e) able to read and understand the consent form; and (f) consent to participate in the study. The exclusion criteria for this study are: (a) medications known to interfere with SAA (e.g., beta-blockers, albuterol); (b) metabolic disorders (e.g., diabetes, thyroid disorders); and (3) autoimmune disorders (e.g., Sjogren's syndrome).

No study known to this author has utilized the proposed measures and methodology outlined in this proposal. Accordingly, a sample calculation was performed using a moderate effect size ($R^2 = .13$) with a power of .80 and $\alpha = .05$ for 10 predictor

variables. Therefore, a sample of 120 subjects are needed to detect a population R^2 of .13 with 10 predictors, with a 5% chance of a Type I error and a 20% chance of a Type II error (Polit & Beck, 2012).



Data Collection Instruments and Measures

See Table 1 below for proposed study instruments and measures.

Walter reed army institute of research combat exposure scale. The WRAIR-CES consists of 27 dichotomized questions measuring an individual's exposure to combat-related events, particularly personnel participating in OEF/OIF operations. Unlike other combat exposure scales, this instrument evaluates various dimensions of combat exposure, such as combat fighting, threat to oneself, injury, or atrocity. Hoge et al. (2004) used the WRAIR-CES to assess combat experiences in U.S. infantrymen deployed to Iraq and Afghanistan and found greater degrees of combat exposure were

significantly correlated with higher incidences of PTSD. Another study screened for alcohol misuse in U.S. soldiers following a deployment to Iraq and found subjects reporting more combat experiences on the WRAIR-CES exhibited significantly greater reports of alcohol misuse (Wilk et al., 2010). As a result, the WRAIR-CES has become the U.S. Army's primary instrument for measuring a service member's exposure to combat, particularly combat experienced in OEF/OIF (Hoge et al., 2004; Wilk et al., 2010). In addition, the WRAIR-CES has been shown to be a reliable measure of combat experiences with a reported Cronbach's alpha of 0.85 (Hoge et al., 2008). For the purposes of this study, combat exposure is defined as any individual receiving imminent danger pay, hardship duty pay, or combat zone tax exclusion during a military deployment (Millennium Cohort Study, 2012). Combat exposure will be measured using the 27-item WRAIR-CES with scoring ranging from 0 to 27 (Wilk et al., 2010). This instrument is available free of charge.

Posttraumatic stress disorder checklist–military. PTSD symptomatology will be assessed using the PCL-M, a commonly used instrument assessing PTSD symptomatology in the military population (McDonald & Calhoun, 2010). This self-report measure is comprised of 17 items as outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), which asks respondents to relate their military experiences to "how bothered" they are by symptoms listed on the PCL-M over the previous month (Bliese et al., 2008; Weathers, 1993). Scoring consists of a rating scale of 1 = not at all to 5 = extremely, with a possible range of 17-85 (Weathers, 1993). Although the PCL-M is an effective instrument in gauging the likelihood for

Table 1. ***Reliability and Validity for Study Instruments***

Combat Exposure	Walter Reed Army Institute of Research Combat Exposure Scale (Wilk et al.,	Comprised of 27 dichotomized questions measuring combat exposure; commonly used by the U.S. Army to measure combat exposure	Cronbach's alpha = .85 (Hoge et al., 2008)
Anxiety	Patient Health Questionnaire-4 (Kroenke et al., 2009)	Four questions derived from the two core criteria for depression and anxiety; Likert-type scale (0=not at all to 3=nearly every day); cutoff score 3 or > on each subscale is highly sensitive for depression or anxiety disorders	Internal reliability for both subscales is high (> .81; Kroenke et al., 2009)
Depression			
PTSD	Posttraumatic Stress Disorder Checklist-Military	Uses 17 questions to measure PTSD symptomatology; Likert-type rating scale (1=not at all to 5=extremely); scoring range 17-85; recommended cutoff score of 50 or greater to maximize specificity (Hoge et al., 2004)	Internal consistency > .90; strongly correlated with the Clinician-Administered PTSD Scale (Keen et al., 2008)
Dysphoria	Multiple Affect Adjective Checklist-Revised (state version; Lubin & Zuckerman, 1999)	132 adjectives measuring affect along five domains (positive affect, sensation seeking, anxiety, depression, and hostility) or higher order affect (dysphoria = sum of anxiety, depression, and hostility)	Reliability (alpha) on state version in Air Force recruits on all domains and dysphoria was strong (r = .77-.91; Lubin & Zuckerman, 1999)
Pain	Visual Analogue Scale	Commonly used to measure various phenomena; consists of a 100 mm horizontal line with word descriptors at both ends	Consistently very high reliability (r > .90) and excellent sensitivity (Boker et al., 2002; Lara-Munoz et al., 2004; Williamson & Hoggart, 2005)
Stress			
Sympathetic Nervous System Activity	Salivary alpha-amylase	Noninvasive, indirect measure of sympathetic nervous system activity; saliva sample collected over 3 minutes via oral swab and analyzed by Salimetrics, LLC	Highly correlates with other stress biomarkers (r = .53 - .81; Chatterton et al., 1996; Kang, 2010)

PTSD, it is not a diagnostic tool, primarily since it doesn't include all diagnostic criteria outlined in the DSM-IV (Keen, Kutter, Niles, & Krinsley, 2008). However, the most common method for scoring the PCL-M, particularly in military-based research, is the use of a higher cutoff value of 50 or greater, thus maximizing the specificity for combat-related PTSD symptomatology (Bliese et al., 2008; Hoge et al., 2004). The internal consistency of this instrument is > .90 and correlates highly with other questionnaires, such as the Mississippi Scale for Combat Related PTSD (r = 0.85 and .93; Keen et al., 2008; McDonald & Calhoun, 2010). Additionally, the PCL-M strongly correlates with the Clinician-Administered PTSD Scale, currently considered the gold standard for PTSD diagnosis (r = 0.79, n = 114, p < 0.001; Keen et al., 2008). Permission to use this instrument has been granted by the National Center for PTSD.

Patient health questionnaire-4. The PHQ-4 is a self-report measure providing a rapid, yet reliable assessment of likelihood for depression and anxiety-related disorders (Kroenke, Spitzer, Williams, & Lowe, 2009). The PHQ-4 consists of depression (PHQ-2) and generalized anxiety (GAD-2) subscales, both of which contain the two core criteria for depressive and generalized anxiety disorders outlined in the DSM-IV (Arroll et al., 2010; Kroenke et al., 2009). Respondents are asked to indicate how "bothered" they are by each question using a 4-item Likert-type scale to denote their level of agreement with each of the four statements (0 = not at all to 3 = nearly every day). Internal reliability of the PHQ-4 and its subscales are high (all > 0.81), and construct validity of both subscales is reportedly excellent (Kroenke et al., 2009). Recommendations for potential caseness for either a depressive or anxiety disorder for each subscale is a cutoff score of three or greater, resulting in a sensitivity and specificity

of 93% and 89% for the PHQ-2 and 86% and 83% for the GAD-2 (Corson, Gerrity, & Dobscha, 2004; Kroenke et al., 2009). For the purposes of this study, trait measures of depression and/or anxiety will be measured using the PHQ-4 and caseness for either disorder will require a subscale score of three or greater. This instrument is available free of charge from Pfizer, Inc.

Multiple affect adjective checklist-revised. The MAACL-R is a versatile psychological instrument comprised of several affective domains found to be particularly useful in measuring a variety of mental health disorders, as well as basic research on personality and emotion. The MAACL-R consists of two positive affect subscales (positive affect and sensation seeking) and three negative affect subscales (anxiety, depression, and hostility). In addition, an overall dysphoria (sum of negative affect subscales) or well-being (sum of positive affect subscales) score may be calculated. Scoring is ultimately derived from a one-page list of 132-adjectives from which patients select words that most accurately describe how they currently feel (state) or how they generally feel (trait). The MAACL-R's state version has a high internal (alpha) reliability, low test-retest reliability, and has been found to be suitable for investigations that hypothesize changes in affect relative to stressful experiences. The estimated time to complete the MAACL-R is less than three minutes (Lubin & Zuckerman, 1999).

The MAACL-R was specifically chosen for its unique ability to evaluate more than just one preoperative emotion, such as anxiety. For example, a combat veteran undergoing reconstructive surgery following a blast injury to his lower extremity may not experience anxiety preoperatively; rather, he might feel more depressed or angry because of his current situation. Hence, this situational depression or anger may significantly

magnify his preoperative stress response. If state anxiety were the only preoperative emotion measured, then understanding the preoperative stress response, especially in combatants, would be limited or explained by only one affective emotion (e.g., anxiety).

For the purposes of this study, the dysphoria composite score (i.e., sum of the anxiety, depression, and hostility scores) will be used to measure the state negative affective emotions experienced throughout the preoperative period on the day of surgery. The MAACL-R is readily available for purchase through the Educational and Industrial Testing Service, San Diego, CA (Lubin & Zuckerman, 1999).

Visual analogue scale. The VAS has been commonly used to measure various phenomena, such as preoperative pain, stress, or anxiety (Gonzales et al., 2010; Kang, 2010; Lara-Munoz, De Leon, Feinstein, Puente, & Wells, 2004; Spence et al., 2011). The VAS commonly consists of a 100 mm horizontal line with word descriptors at the ends of the continuum, such as "no stress" and "very high stress." Subjects are asked to make a mark along this continuum that best describes their subjective feeling or perception about a particular construct at a particular moment in time, such as "how stressed do you feel right now" (Williamson & Hoggart, 2005). Literature has consistently demonstrated the VAS to have a very high reliability ($r > .90$) and excellent sensitivity across a variety of settings and populations (Boker et al., 2002; Lara-Munoz et al., 2004; Williamson & Hoggart, 2005). Benefits of employing the VAS include simplicity, ease of use, and minimal time for completion. For this study, the VAS will be used to measure subjective pain and stress on the day of surgery.

Salivary alpha-amylase. Amylase is a digestive enzyme that hydrolyzes the alpha-1,4 bonds of large polysaccharides (e.g., starch and glycogen), yielding simpler

carbohydrates such as glucose and maltose (Kang, 2010; Nater et al., 2005). SAA is one of many proteins synthesized and secreted by acinar cells found in major and minor salivary glands, although SAA appears to be predominantly produced by the parotid glands (Rohleder & Nater, 2009; Rohleder, Wolf, Maldonado, & Kirschbaum, 2006). Production and secretion of saliva is autonomically regulated, such that sympathetically-activated salivary glands produce more protein-based saliva (e.g., SAA); whereas, parasympathetically-activated salivary glands produce more water-based saliva (Bosch, Veerman, de Geus, & Proctor, 2011; Humphrey & Williamson, 2001; Rohleder & Nater, 2009). During periods of psychological or physiological stress, such as extremes in temperature, exercise, or academic testing, increased SNS activity results in the secretion of SAA, and for this reason it has become a favorable surrogate for SNS activity (Klein, Bennett, Whetzel, Granger, & Ritter, 2010; Nater et al., 2006; Nater et al., 2005; Takai et al., 2004). Likewise, the production and secretion of SAA following a stressor is almost instantaneous, particularly suitable in settings with multiple stressors like the preoperative environment (Takai et al., 2004). Unlike serum biomarkers requiring venipuncture, SAA sampling is a noninvasive procedure using an absorbent oral swab; thus, less likely to contribute to an already stressful experience or negatively influence an individual's desire to participate in a study out of fear of needles or pain (Kang, 2010).

One recent investigation measured positive and negative preoperative affective emotions in a general surgical population and found positive affect scores decreased and correlated significantly with a rise in SAA, suggesting patients experiencing more negative emotions may exhibit greater degrees of physiological stress (Spence et al., 2011). In addition, SAA has been shown to have moderate to strong correlations (r =

0.53-0.81) with other well-established biomarkers (e.g., heart rate, blood pressure norepinephrine; Chatterton, Vogelsong, Lu, Ellman, & Hudgens, 1996; Kang, 2010). Taken together, this supports the use of SAA as a valid and reliable surrogate for SNS activity and responsiveness to stressors encountered in the preoperative setting. However, more studies are needed to determine SAA's utility as a marker of the preoperative physiological stress response.

Salimetrics oral swab. A total of three saliva samples per subject will be collected using the Salimetrics Oral Swab, which is made of a non-toxic, inert synthetic polymer shaped into a 30 x 10 mm cylinder. Oral swabs have been used extensively in research to evaluate SAA (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004).

Subjects will be directed to place the swab between the upper cheek and gum next to the second molar where the duct of the parotid gland is located for three minutes (Salimetrics, 2011a). Following salivary sampling, the oral swab will be placed in a Salimetric Swab Storage Tube, secured, and labeled with the subject identification number, date, and time. Samples will be placed in a cooler until transport to NHCP's laboratory where they will remain in a freezer at a temperature of -20° C until data collection is completed. All supplies (i.e., oral swabs and storage tubes) will be obtained from Salimetrics, LLC (State College, PA).

SAA assay description. All saliva samples will be shipped to Salimetrics, LLC (State College, PA) for analysis; however, no personal information will be sent and all samples will be destroyed after completion of the study. Salimetrics, LLC's method for assay utilizes chromagenic substrate, 2-chloro-p-nitrophenol, linked to maltotriose. The enzymatic action of SAA on this substrate yields 2-chloro-p-nitrophenol, which can be

spectrophotometrically measured at 405 nm using a standard laboratory plate reader. Saliva samples (10 μL) are diluted 1:200 in assay diluent and well mixed. Eight microliters of diluted sample or control are then pipetted into individual wells of a 96-well microtiter plate. Chromagenic substrate solution (2-chloro-p-nitrophenol, linked to maltotriose) is preheated (37°C) and 320 μL is added to each well and the plate is rotated at 500-600 RPM at 37 °C for three minutes. Optical density (read at 405 nm) is determined exactly at the one-minute mark and again at the three-minute mark. The amount of SAA activity present in the sample is directly proportional to the increase (over a 2 min period) in absorbance at 405 nm (Salimetrics, 2011b). Calibration is standardized using the millimolar absorptivity of 2-chloro-p-nitrophenol. In addition, Salimetrics, LLC is a Clinical Laboratory Improvement Amendments certified testing facility (Salimetrics, 2011b). Salimetrics, LLC will provide results in an Excel spreadsheet to LCDR Bopp.

Data Collection Procedures

Day of enrollment. Patients arriving to the Preoperative Teaching Unit (PTU) for preoperative screening scheduled for elective surgery will be approached and provided information about the study. All risks, benefits, and alternatives to the research study will be explained in detail and all questions will be answered. If subjects agree to participate in the study, then informed consent will be obtained. Once a patient has consented to participate, he or she will be assigned a subject number. All data collected, either hard copy or computer-based, will be identified by that subject number.

Subjects will be provided privacy during enrollment by directing them to the educational office located on the PTU. Following enrollment, all study subjects will be

asked to complete the Demographic and Deployment History questionnaires, PHQ-4, and PCL-M. In addition, subjects reporting a prior deployment where they have received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits will be asked to complete the WRAIR-CES.

Throughout the interpretative process of psychological screening on the day of enrollment, the possibility exists that one or more of the individual results will indicate a higher probability of clinically significant anxiety, depression, or PTSD symptomatology. In such a case, the subject will be contacted by phone to reveal the questionnaires scores and its association with the probability of a later diagnosis of depression, anxiety, or PTSD. At this time, the subject will be reminded of their complete voluntary option to request a mental health consult at either the NHCP Deployment Health Center or Department of Mental Health. Upon request, LCDR Bopp will arrange a consultation through Dr. Daniel Wright, Division Officer of Mental Health as appropriate. Dr. Wright is serving as the combat stress expert for this proposed study and agrees to the above method of consultation. Potential "caseness" for anxiety or depression on either subscale of the PHQ-4 is a cutoff score of three or greater. An interpreted test result of 50 or greater on the PCL-M will be considered a "higher likelihood" of a later diagnosis of PTSD. In all of these cases, the subject will be encouraged to seek the care of a mental health provider as described above, but it WILL NOT be required.

Day of surgery. Following admission to the SDSU on the day of surgery, the investigator will ask subjects to collect the first SAA sample by placing one oral swab between the gum and cheek next to the second upper molar for three minutes. At the same time, patients will be asked to complete the VAS-P, VAS-S, and MAACL-R. After

arriving to the preoperative holding area, subjects will be placed on a gurney and met by the investigator. Subjects will then be asked to submit a second SAA sample while completing the VAS-S and MAACL-R. The anesthesia provider and nursing staff will then interview and start the intravenous line. The final data collection point will occur immediately prior to subjects entering the operating room, but prior to administration of any anxiolytics or opioids. Data collected at this point will include a third SAA sample, VAS-S, and MAACL-R. All swabs will be placed in Salimetric Swab Storage Tubes and placed in a cooler until transport to the laboratory department at NHCP for storage at a temperature -20° C as recommended by Salimetrics, LLC.

Data Analysis

Statistical analysis will be accomplished using the Statistical Package for the Social Sciences software. Descriptive statistics (e.g., means and standard deviations for continuous variables, frequencies and percentages for categorical variables) will be computed for each variable as appropriate. Both non-parametric and parametric techniques will be employed in the data analyses where appropriate. Statistical significance will be set at a $p \leq .05$.

Aim 1. Determine the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *more negative emotions* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the MAACL-R.

The MAACL-R dysphoria score will be used to measure negative emotions at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of more negative emotions. The alternative hypothesis is a greater number of combat experiences will be predictive of more negative emotions. To determine predictive relationships between the independent variable (number of combat experiences) and the dependent variable (mean dysphoria values), a multiple linear regression analysis will be conducted using the predictor variables: (a) number of combat experiences (WRAIR-CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). A separate multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak dysphoria value preoperatively. The peak dysphoria value will consist of the subject's highest dysphoria score among the three time points on the day of surgery. To analyze changes in dysphoria over time, a repeated measures ANOVA or Friedman Test will be used where appropriate.

Hypothesis 2. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher degrees of stress* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the VAS-S.

The VAS-S will be used to measure subjective stress at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of higher degrees of stress. The alternative hypothesis is a greater number of combat experiences will be

predictive of higher degrees of stress. To determine predictive relationships between the independent variable (number of combat experiences) and the dependent variable (VAS-S values), a multiple linear regression analysis will be conducted using the predictor variables: (a) number of combat experiences (WRAIR-CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). A separate multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak stress value preoperatively. Peak stress will consist of the subject's highest stress value among the three time points on the day of surgery. To analyze changes in negative emotions over time as measured by the VAS-S, repeated measures ANOVA or Friedman Test will be used where appropriate.

Aim 2. Determine the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher SAA* values measured at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room.

Since SAA data is typically positively skewed, a logarithmic transformation of the data will be performed prior to analysis. Areas under the curve (see Table 2) with respect to ground (AUC_G) and with respect to increase from baseline (AUC_{Inc}) will be calculated for SAA (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003; Spence et al., 2011). Additionally, any values found to be below the baseline value (i.e., value

measured on SDSU) will be computed using the AUC above the baseline minus the area above the curve below the baseline (AUC_{AB}; Fekedulegn et al., 2007).

The AUC_G and AUC_{Inc} will be used to measure total SAA output and sensitivity, respectively, from SDSU to immediately prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of higher AUC_G and/or AUC_{Inc} in SAA values. The alternative hypothesis is a greater number of combat experiences will be predictive of higher AUC_G and/or AUC_{Inc} in SAA values. To determine predictive relationships between the independent variable (number of combat experiences) and the dependent variables (AUC_G and AUC_{Inc} SAA values), separate multiple linear regression analyses will be conducted using the predictor variables: (a) number of combat experiences (WRAIR-CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). Additionally, a multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak SAA value preoperatively. Peak SAA levels will consist of the subject's highest SAA value among the three time points on the day of surgery. To analyze changes in SAA values over time, repeated measures ANOVA or Friedman Test will be used where appropriate.

AUC_G = sample 1 + sample 2 + ((sample 3 – sample 1)/2)
AUC_{Inc} = (sample 2 + sample 3)/2 – sample 1
AUC_{AB} = $AUC_G - AUC_B$
AUC_B = sample 1 x ((time point 2 – Time point 1) + (time point 3 – time point 2))

Strengths and Limitations

One notable strength of this proposed study is it will be the first investigation to determine the predictive relationship between varying degrees of combat exposure and the preoperative psychological and physiological stress response in military personnel on the day of surgery. Scientifically demonstrating a heightened stress response in active duty military members throughout the preoperative period will finally corroborate anecdotal experiences described by numerous military perianesthesia professionals. Additionally, it will provide the evidence necessary to support future interventional studies designed to mitigate or diminish the pre- and/or perioperative stress response.

A limitation of this study is the likelihood of enrolling predominately U.S. Marines, especially since this study will be conducted in a military hospital located on a Marine Corps training base; thus, potentially limiting the generalizability to personnel in other branches of the service. Another limitation are potential factors that might influence SAA secretion, such as diurnal rhythm, smoking, eating, etc. However, some factors affecting SAA secretion will be minimized since patients will be asked to refrain from the consumption of food or drink on the day of surgery; i.e., nothing by mouth after midnight. Further, investigators will provide subjects with written and verbal instructions not to participate in any physical exercise, consume alcohol, or smoke on the day of surgery.

References

Aalouane, R., Rammouz, I., Tahiri-Alaoui, D., Elrhazi, K., & Boujraf, S. (2011). Determining factors of anxiety in patients at the preoperative stage. *Neurosciences, 16*(2), 146-149.

Arroll, B., Goodyear-Smith, F., Crengle, S., Gunn, J., Kerse, N., Fishman, T., . . . Hatcher, S. (2010). Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Annals of Family Medicine, 8*(4), 348-353. doi: 10.1370/afm.1139

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of Psychosomatic Research, 52*(2), 69-77.

Bliese, P. D., Wright, K. M., Adler, A. B., Cabrera, O., Castro, C. A., & Hoge, C. W. (2008). Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. *Journal of Consulting and Clinical Psychology, 76*(2), 272-281. doi: 10.1037/0022-006X.76.2.272

Boker, A., Brownell, L., & Donen, N. (2002). The Amsterdam preoperative anxiety and information scale provides a simple and reliable measure of preoperative anxiety. *Canadian Journal of Anaesthesia, 49*(8), 792-798. doi: 10.1007/BF03017410

Bonfiglio, J. J., Inda, C., Refojo, D., Holsboer, F., Arzt, E., & Silberstein, S. (2011). The corticotropin-releasing hormone network and the hypothalamic-pituitary-adrenal axis: Molecular and cellular mechanisms involved. *Neuroendocrinology, 94*, 12-20. doi: 10.1159/000328226

Bosch, J. A., Veerman, E. C., de Geus, E. J., & Proctor, G. B. (2011). Alpha-amylase as a reliable and convenient measure of sympathetic activity: Don't start salivating just yet! *Psychoneuroendocrinology, 36*(4), 449-453. doi: 10.1016/j.psyneuen.2010.12.019

Carr, E., Brockbank, K., Allen, S., & Strike, P. (2006). Patterns and frequency of anxiety in women undergoing gynaecological surgery. *Journal of Clinical Nursing, 15*(3), 341-352. doi: 10.1111/j.1365-2702.2006.01285.x

Caumo, W., Schmidt, A. P., Schneider, C. N., Bergmann, J., Iwamoto, C. W., Adamatti, L. C., . . . Ferreira, M. B. (2001). Risk factors for postoperative anxiety in adults. *Anaesthesia, 56*(8), 720-728.

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology, 67*, 259-284. doi: 10.1146/annurev.physiol.67.040403.120816

Chatterton, R. T., Jr., Vogelsong, K. M., Lu, Y. C., Ellman, A. B., & Hudgens, G. A. (1996). Salivary alpha-amylase as a measure of endogenous adrenergic activity. *Clinical Physiology, 16*(4), 433-448.

Chrousos, G. P. (2007). Organization and integration of the endocrine system. *Sleep Medicine Clinics, 2*(2), 125-145. doi: 10.1016/j.jsmc.2007.04.004

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews. Endocrinology, 5*(7), 374-381. doi: 10.1038/nrendo.2009.106

Corson, K., Gerrity, M. S., & Dobscha, S. K. (2004). Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item. *The American Journal of Managed Care, 10*, 839-845.

Costa, M. J. (2001). The lived perioperative experience of ambulatory surgery patients. *Association of PeriOperative Registered Nurses Journal, 74*(6), 874-881.

Demirtas, Y., Ayhan, S., Tulmac, M., Findikcioglu, F., Ozkose, Z., Yalcin, R., & Atabay, K. (2005). Hemodynamic effects of perioperative stressor events during rhinoplasty. *Plastic and Reconstructive Surgery, 115*(2), 620-626.

Desborough, J. P. (2000). The stress response to trauma and surgery. *British Journal of Anaesthesia, 85*, 109-117.

Duggan, M., Dowd, N., O'Mara, D., Harmon, D., Tormey, W., & Cunningham, A. J. (2002). Benzodiazepine premedication may attenuate the stress response in daycase anesthesia: A pilot study. *Canadian Journal of Anaesthesia, 49*(9), 932-935. doi: 10.1007/BF03016877

Everly, G. S., & Lating, J. M. (2002). *A clinical guide to the treatment of the human stress response* (2nd ed.). New York, NY: Kluwer Academic/Plenum Publishers.

Fekedulegn, D. B., Andrew, M. E., Burchfiel, C. M., Violanti, J. M., Hartley, T. A., Charles, L. E., & Miller, D. B. (2007). Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosomatic Medicine, 69*(7), 651-659. doi: 10.1097/PSY.0b013e31814c405c

Fitzgerald, B. M., & Elder, J. (2008). Will a 1-page informational handout decrease patients' most common fears of anesthesia and surgery? *Journal of Surgical Education, 65*(5), 359-363. doi: 10.1016/j.jsurg.2008.07.013

Goldstein, D. S. (2010). Adrenal responses to stress. *Cellular and Molecular Neurobiology, 30*(8), 1433-1440. doi: 10.1007/s10571-010-9606-9

Gonzales, E. A., Ledesma, R. J., McAllister, D. J., Perry, S. M., Dyer, C. A., & Maye, J. P. (2010). Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: A randomized, single-blind study. *American Association of Nurse Anesthetists Journal, 78*(3), 181-188.

Gras, S., Servin, F., Bedairia, E., Montravers, P., Desmonts, J. M., Longrois, D., & Guglielminotti, J. (2010). The effect of preoperative heart rate and anxiety on the propofol dose required for loss of consciousness. *Anesthesia and Analgesia, 110*, 89-93. doi: 10.1213/ANE.0b013e3181c5bd11

Grieve, R. J. (2002). Day surgery preoperative anxiety reduction and coping strategies. *British Journal of Nursing, 11*(10), 670-678.

Hahm, T. S., Cho, H. S., Lee, K. H., Chung, I. S., Kim, J. A., & Kim, M. H. (2002). Clonidine premedication prevents preoperative hypokalemia. *Journal of Clinical Anesthesia, 14*, 6-9.

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *The New England Journal of Medicine, 35*, 13-22. doi: 10.1056/NEJMoa040603

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *The New England Journal of Medicine, 358*(5), 453-463. doi: 10.1056/NEJMoa072972

Hong, J. Y., Jee, Y. S., & Luthardt, F. W. (2005). Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. *Journal of Clinical Anesthesia, 17*(7), 549-553. doi: 10.1016/j.jclinane.2005.01.008

Humphrey, S. P., & Williamson, R. T. (2001). A review of saliva: Normal composition, flow, and function. *The Journal of Prosthetic Dentistry, 85*(2), 162-169. doi: 10.1067/mpr.2001.113778

Kain, Z. N., Sevarino, F., Alexander, G. M., Pincus, S., & Mayes, L. C. (2000). Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. *Journal of Psychosomatic Research, 49*(6), 417-422.

Kang, Y. (2010). Psychological stress-induced changes in salivary alpha-amylase and adrenergic activity. *Nursing & Health Sciences, 12*(4), 477-484. doi: 10.1111/j.1442-2018.2010.00562.x

Keen, S. M., Kutter, C. J., Niles, B. L., & Krinsley, K. E. (2008). Psychometric properties of PTSD checklist in sample of male veterans. *Journal of Rehabilitation Research and Development, 45*(3), 465-474.

Kindler, C. H., Harms, C., Amsler, F., Ihde-Scholl, T., & Scheidegger, D. (2000). The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesthesia and Analgesia, 90*(3), 706-712.

Kiyohara, L. Y., Kayano, L. K., Oliveira, L. M., Yamamoto, M. U., Inagaki, M. M., Ogawa, N. Y., . . . Vieira, J. E. (2004). Surgery information reduces anxiety in the pre-operative period. *Revista do Hospital das Clinicas, 59*(2), 51-56.

Klein, L. C., Bennett, J. M., Whetzel, C. A., Granger, D. A., & Ritter, F. E. (2010). Caffeine and stress alter salivary alpha-amylase activity in young men. *Human Psychopharmacology, 25*(5), 359-367. doi: 10.1002/hup.1126

Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2009). An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics, 50*(6), 613-621. doi: 10.1176/appi.psy.50.6.613

Lara-Munoz, C., De Leon, S. P., Feinstein, A. R., Puente, A., & Wells, C. K. (2004). Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli. *Archives of Medical Research, 35*, 43-48. doi: 10.1016/j.arcmed.2003.07.007

Leardi, S., Pietroletti, R., Angeloni, G., Necozione, S., Ranalletta, G., & Del Gusto, B. (2007). Randomized clinical trial examining the effect of music therapy in stress response to day surgery. *The British Journal of Surgery, 94*(8), 943-947. doi: 10.1002/bjs.5914

Levine, A., Zagoory-Sharon, O., Feldman, R., Lewis, J. G., & Weller, A. (2007). Measuring cortisol in human psychobiological studies. *Physiology & Behavior, 90*, 43-53. doi: 10.1016/j.physbeh.2006.08.025

Liberzon, I., Abelson, J. L., Flagel, S. B., Raz, J., & Young, E. A. (1999). Neuroendocrine and psychophysiologic responses in PTSD: A symptom provocation study. *Neuropsychopharmacology, 21*, 40-50. doi: 10.1016/S0893-133X(98)00128-6

Lubin, B., & Zuckerman, M. (1999). *Manual for the multiple affect adjective checklist-revised.* San Diego, CA: Educational and Industrial Testing Service.

McDonald, S. D., & Calhoun, P. S. (2010). The diagnostic accuracy of the PTSD checklist: A critical review. *Clinical Psychology Review, 30*(8), 976-987. doi: 10.1016/j.cpr.2010.06.012

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology, 583*, 174-185. doi: 10.1016/j.ejphar.2007.11.071

McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior, 57*(2), 105-111. doi: 10.1016/j.yhbeh.2009.09.011

McGhee, L. L., Maani, C. V., Garza, T. H., DeSocio, P. A., Gaylord, K. M., & Black, I. H. (2009). The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. *The Journal of Trauma, 66*, S186-190. doi: 10.1097/TA.0b013e31819ce2f0

McGuire, J. M. (2012). The incidence of and risk factors for emergence delirium in U.S. military combat veterans. *Journal of Perianesthesia Nursing, 27*(4), 236-45.

McIntosh, S., & Adams, J. (2011). Anxiety and quality of recovery in day surgery: A questionnaire study using Hospital Anxiety and Depression Scale and Quality of Recovery Score. *International Journal of Nursing Practice, 17*, 85-92. doi: 10.1111/j.1440-172X.2010.01910.x

Millennium Cohort Study. (2012). Millennium Cohort Study Survey. Retrieved from http://www.millenniumcohort.org

Mitchell, M. (2011). Influence of gender and anaesthesia type on day surgery anxiety. *Journal of Advanced Nursing, 68*(5), 1014-1025. doi: 10.1111/j.1365-2648.2011.05801.x

Moerman, N., van Dam, F. S., Muller, M. J., & Oosting, H. (1996). The Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Anesthesia and Analgesia, 82*(3), 445-451.

Morley, A. P., Papageorgiou, C. H., Marinaki, A. M., Cooper, D. J., & Lewis, C. M. (2008). The effect of pre-operative anxiety on induction of anaesthesia with propofol. *Anaesthesia, 63*(5), 467-473. doi: 10.1111/j.1365-2044.2007.05402.x

Nater, U. M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M. M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity: Associations with adrenergic activity. *Psychoneuroendocrinology, 31*, 49-58. doi: 10.1016/j.psyneuen.2005.05.010

Nater, U. M., Rohleder, N., Gaab, J., Berger, S., Jud, A., Kirschbaum, C., & Ehlert, U. (2005). Human salivary alpha-amylase reactivity in a psychosocial stress paradigm. *International Journal of Psychophysiology, 55*(3), 333-342. doi: 10.1016/j.ijpsycho.2004.09.009

Nayback, A. M. (2009). Posttraumatic stress: A concept analysis. *Archives of Psychiatric Nursing, 23*(3), 210-219. doi: 10.1016/j.apnu.2008.06.001

Oshima, T., Kasuya, Y., Terazawa, E., Nagase, K., Saitoh, Y., & Dohi, S. (2001). The anxiolytic effects of the 5-hydroxytryptamine-1A agonist tandospirone before otolaryngologic surgery. *Anesthesia and Analgesia, 93*(5), 1214-1216.

Page, G. G. (2005). Surgery-induced immunosuppression and postoperative pain management. *American Association of Critical-Care Nurses Clinical Issues, 16*(3), 302-309.

Papadimitriou, A., & Priftis, K. N. (2009). Regulation of the hypothalamic-pituitary-adrenal axis. *Neuroimmunomodulation, 16*(5), 265-271. doi: 10.1159/000216184

Pego, J. M., Sousa, J. C., Almeida, O. F., & Sousa, N. (2010). Stress and the neuroendocrinology of anxiety disorders. *Current Topics in Behavioral Neurosciences, 2*, 97-117.

Phillips, C. J., Leardmann, C. A., Gumbs, G. R., & Smith, B. (2010). Risk factors for posttraumatic stress disorder among deployed US male marines. *BioMed Central Psychiatry, 10*, 52. doi: 10.1186/1471-244X-10-52

Polit, D. F., & Beck, C. T. (2012). *Nursing research: Generating and assessing evidence for nursing practice* (9th ed.). Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Pritchard, M. J. (2009). Managing anxiety in the elective surgical patient. *British Journal of Nursing, 18*(7), 416-419.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916-931.

Rohleder, N., & Nater, U. M. (2009). Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology, 34*(4), 469-485. doi: 10.1016/j.psyneuen.2008.12.004

Rohleder, N., Wolf, J. M., Maldonado, E. F., & Kirschbaum, C. (2006). The psychosocial stress-induced increase in salivary alpha-amylase is independent of saliva flow rate. *Psychophysiology, 43*(6), 645-652. doi: 10.1111/j.1469-8986.2006.00457.x

Salimetrics, LLC. (2011a). Saliva Collection and Handling Advice. (2nd Ed.). State College, PA: Salimetrics, LLC.

Salimetrics, L. (2011b). Salivary alpha-amylase assay kit. State College, PA: Salimetrics, LLC.

Schneiderman, N., Ironson, G., & Siegel, S. D. (2005). Stress and health: Psychological, behavioral, and biological determinants. *Annual Review of Clinical Psychology, 1*, 607-628. doi: 10.1146/annurev.clinpsy.1.102803.144141

Spence, D., McBeain, J., Guzman, J., Roucek, E., & Maye, J. (2011). A pilot investigation evaluating physiological and psychological stress measurements in patients presenting for elective surgical procedures. *Journal of Healthcare, Science and the Humanities, 1*(2), 39-53.

Sun, G. C., Hsu, M. C., Chia, Y. Y., Chen, P. Y., & Shaw, F. Z. (2008). Effects of age and gender on intravenous midazolam premedication: A randomized double-blind study. *British Journal of Anaesthesia, 101*(5), 632-639. doi: 10.1093/bja/aen251

Takai, N., Yamaguchi, M., Aragaki, T., Eto, K., Uchihashi, K., & Nishikawa, Y. (2004). Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults. *Archives of Oral Biology, 49*(12), 963-968. doi: 10.1016/j.archoralbio.2004.06.007

Van den Bosch, J. E., Moons, K. G., Bonsel, G. J., & Kalkman, C. J. (2005). Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? *Anesthesia and Analgesia, 100*(5), 1525-1532. doi: 10.1213/01.ANE.0000149325.20542.D4

Wagner, D., Byrne, M., & Kolcaba, K. (2006). Effects of comfort warming on preoperative patients. *Association of PeriOperative Registered Nurses Journal, 84*(3), 427-448.

Weathers, F. W., Litz, B.T., Herman, D.S., Huska, J.A., & Keane, T.M. (1993). *The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility.* Paper presented at the Annual Meeting of International Society for Traumatic Stress Studies, San Antonio, TX.

Wetsch, W. A., Pircher, I., Lederer, W., Kinzl, J. F., Traweger, C., Heinz-Erian, P., & Benzer, A. (2009). Preoperative stress and anxiety in day-care patients and inpatients undergoing fast-track surgery. *British Journal of Anaesthesia, 103*(2), 199-205. doi: 10.1093/bja/aep136

Wilk, J. E., Bliese, P. D., Kim, P. Y., Thomas, J. L., McGurk, D., & Hoge, C. W. (2010). Relationship of combat experiences to alcohol misuse among U.S. soldiers returning from the Iraq war. *Drug and Alcohol Dependence, 108*, 115-121. doi: 10.1016/j.drugalcdep.2009.12.003

Williamson, A., & Hoggart, B. (2005). Pain: A review of three commonly used pain rating scales. *Journal of Clinical Nursing, 14*(7), 798-804. doi: 10.1111/j.1365-2702.2005.01121.x

Wong, E. H., Chan, S. W., & Chair, S. Y. (2010). Effectiveness of an educational intervention on levels of pain, anxiety, and self-efficacy for patients with musculoskeletal trauma. *Journal of Advanced Nursing, 66*(5), 1120-1131. doi: 10.1111/j.1365-2648.2010.05273.x

Chapter 4: MANUSCRIPTS

Manuscript I

UNIVERSITY OF SAN DIEGO

Hahn School of Nursing and Health Science

A Preoperative Stress Inquiry and a Vulnerable US Military Population

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Abstract

The preoperative setting is fraught with many stressors often increasing in magnitude as patients progress through the perioperative environment. Individuals exposed to traumatic or threatening environments, such as U.S. military personnel involved in combat operations, may be at increased risk of developing altered mental and physical health conditions. Collectively, this may result in a hyperarousal state significantly amplifying psychological symptoms and magnifying physiological alterations. The purposes of this article are to (a) describe stress-related concepts and preoperative stress, (b) discuss potential risk factors for preoperative stress in the adult surgical population, (c) present various psychological and physiological measures of preoperative stress, (d) explore preoperative stress interventions, and (e) discuss potential implications for future preoperative stress research in high-stressed populations.

Keywords: stress response, preoperative stress, military, anesthesia

The preoperative experience is a unique phenomenon and may be perceived by patients as extremely stressful. Preoperative stress might begin days or weeks prior to surgery due to requisite testing or evaluation by anesthesia and surgery staff to ensure adequate perioperative preparation. Potential stressors experienced on the day of surgery can include unfamiliar surgical facilities, confusing procedures and regimens, or preoperative encounters that may be perceived as rushed and uncaring.[1] Patients find themselves in preoperative settings that are often cold, secluded from family, harshly lit, and filled with unfamiliar sounds, thus contributing to a sense of vulnerability or loss of independence.[2,3] Patients may also experience prolonged wait times, perhaps allowing them to reflect further on the surgery or anesthesia and potentially exacerbating an already stressful situation.[4] Research suggests patients exhibiting higher degrees of stress in the preoperative setting experience significantly more adverse perioperative outcomes, such as increased heart rate, greater anesthetic requirement, and postoperative anxiety and pain.[5-8]

U.S. military members deployed since 2001 to Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF), particularly personnel involved in direct firefights or enemy engagements, are a population at risk for experiencing a heightened preoperative stress response. A recent investigation found combat veterans reporting increased preoperative anxiety, depression, and posttraumatic stress disorder symptoms experienced significantly greater degrees of emergence delirium following surgery.[9] Anecdotal accounts by military anesthesia providers and perianesthesia nursing staff describe this particular population as clinically challenging, often appearing overly anxious preoperatively and typically necessitating greater quantities of anesthetic

medications intraoperatively. Postoperatively, military clinicians report combat veterans as being exceptionally more aggressive, agitated, and confused when emerging from anesthesia.

The purposes of this article are to (a) describe stress-related concepts and preoperative stress, (b) discuss potential risk factors for preoperative stress in the adult surgical population, (c) present various psychological and physiological measures of preoperative stress, (d) explore preoperative stress interventions, and (e) discuss potential implications for future preoperative stress research in high-stressed populations, such as U.S. combat veterans.

Stress and Stressors

Stress is a state in which a human's capacity to maintain the physiologic balance necessary for survival is threatened or perceived to be in danger.[10,11] Chrousos[10] described stressors as external or internal factors that challenge the human body to preserve a state of equilibrium, commonly referred to as homeostasis. Stressors can be classified as psychosocial or biogenic.[12] Psychosocial stressors are those experiences or threats which the individual perceives as real, imagined, anticipated, or recalled; hence one's cognitive assessment of a stressor may or may not manifest in a stress response.[12] Biogenic stressors do not require the individual to appraise an event as threatening or stressful; rather, the biogenic stimulus may activate the stress response by way of a chemical (e.g., caffeine or nicotine) or physical (e.g., trauma or hemorrhage) stressor.[12,13]

When an individual perceives a stressor as potentially threatening or harmful, psychological and physiological alterations may develop.[14,15] Behavioral manifestations of a stress response can include increased arousal and alertness, anxiety, fear, depression,

and dysphoria.[13,16] The neurological response to a stressor occurs swiftly, altering many organs and their function, resulting in effects such as increased heart rate, blood pressure, and respiratory rate and release of catecholamines from the adrenal glands.[17] Activation of the endocrine system (e.g., increased cortisol secretion) results in widespread effects upon the body's metabolism in an effort to provide a ready-made source of energy to support the human stress response.[15,18]

Preoperative Stress

Anxiety is a well-founded emotional manifestation of preoperative stress in the adult population undergoing elective surgery. Anxiety is reportedly the most prevalent stress-engendered emotion in this population with an overall incidence ranging from 54% to 98%.[7,19] This affective state may manifest as restlessness, worry, apprehension, nervousness, or other sympathetically driven symptoms, such as increased heart rate, blood pressure, and so on.[1,13] Some research strives to quantify the magnitude or degree of anxiety since individuals with higher degrees of preoperative stress may experience hyperarousal states, amplifying psychological symptoms and magnifying physiological alterations.[20] For example, Carr[8] found over 40% of participants scheduled to undergo various gynecological procedures experienced "high" anxiety during their preoperative clinic visit prior to surgery, and 67% reported high anxiety immediately before entering the operating room. Wong[21] measured baseline anxiety in male and female subjects with orthopedic fractures requiring surgery and found all participants experienced high degrees of baseline preoperative anxiety. Studies enrolling men and women scheduled to undergo different types of surgery with varying degrees of complexity found

approximately 30% of patients experienced moderate anxiety, and rates of high and severe anxiety were 25% and 23%, respectively.[7,22]

Fear is another emotion associated with preoperative stress. Fitzgerald[23] conducted a study in a military medical facility investigating the effects of perioperative education upon fear and found 70% of the study population reported preoperative fear. Kindler[22] reported patients feared surgery significantly more than anesthesia; however, a phenomenological investigation of patients' perioperative experiences indicated that fear of anesthesia predominated.[24] Other research has suggested patients fear general anesthesia significantly more than procedures requiring local anesthesia with sedation.[4] When asked to rank anesthesia-related fear, subjects indicated death as their primary fear, followed by pain, intraoperative awareness, nausea and vomiting, and the provider's capacity to provide adequate care.[23]

Spence[20] investigated the preoperative stress response in a general surgical population using an instrument designed to assess positive and negative affective emotions and a physiological biomarker (i.e., salivary alpha-amylase) to measure the reactivity of the sympathetic nervous system (SNS). As patients progressed through the preoperative period investigators found positive affect scores decreased and correlated significantly with a rise in salivary alpha-amylase. This finding suggests patients who experience more negative emotions in the preoperative period may have a greater SNS response.[20]

Risk Factors for Preoperative Stress

Perioperative stress research has sought to identify risk factors that may be predictive of an increased risk for preoperative stress. Aalouane[25] found women

experienced significantly higher degrees of preoperative anxiety than men. Mitchell[4] corroborated the prevalence of increased anxiety in female subjects and found that anxiety occurred earlier in the preoperative phase for women than for men. Additional studies suggest higher degrees of anxiety may be associated with younger age, negative experiences with anesthesia, no prior anesthetic experience, or inability to adequately describe the medical procedure.[19,22,26]

Type of surgery has also been hypothesized as a potential risk factor for increased preoperative stress. Aalouane[25] enrolled patients scheduled for elective gynecological, general, and oncological procedures and found that oncological patients experienced significantly higher degrees of anxiety than the other two groups. An observational study investigating perioperative knowledge found the diagnosis of cancer did not significantly correlate with higher degrees of anxiety when compared with non-cancer patients.[26]

The complexity or invasiveness of a surgical procedure as a potential contributing factor to increased stress appears to be mixed as well. Carr[8] found subjects scheduled to undergo major surgery reported significantly greater degrees of anxiety than subjects having minor surgery; however, another study indicated subjects undergoing intermediate surgery exhibited substantially more preoperative anxiety than those scheduled for minor or major surgeries.[7]

Preoperative Stress and Perioperative Outcomes

Researchers have also explored the impact of preoperative stress on other aspects of the perioperative experience. Gras[27] investigated the effect of heart rate and preoperative anxiety on intraoperative anesthetic requirements in a gynecological population and found subjects reporting greater degrees of anxiety resulted in increased

heart rate and higher anesthetic dosages required to achieve adequate induction of anesthesia. A similar study enrolling women undergoing gynecological procedures not only corroborated this increased anesthetic requirement during the induction phase, but also found intraoperative anesthetic dosages were greater among subjects with high preoperative anxiety.[6] Morley[28] found men and women scheduled for minor surgery and reporting higher degrees of anxiety preoperatively did not exhibit an increased intraoperative anesthetic requirement; however, the authors attributed this finding to a potential inability of the tool to accurately measure preoperative anxiety.

The effect of preoperative stress upon symptoms and emotions experienced during the postoperative period has also been described. Research has indicated significant correlation of preoperative anxiety with depression and postoperative anxiety.[7,29] Pain is another postoperative sequela reportedly linked to preoperative stress. The incidence and severity of pain immediately following surgery has been strongly correlated not only to high levels of preoperative state anxiety, but to individual coping styles as well.[8,30] Van den Bosch[31] explored the possibility of preoperative anxiety as a risk factor for postoperative nausea and vomiting (PONV) and found subjects exhibiting higher levels of preoperative anxiety experienced a higher incidence of PONV.

Preoperative Stress in Combat Veterans

More than 1.6 million U.S. service members have participated in combat operations throughout Iraq and Afghanistan since September 11, 2001, which has exposed numerous military personnel to stressful, traumatic, and threatening environments.[32,33,34] As a result, many of these individuals have experienced significant psychological problems, such as acute stress syndrome, posttraumatic stress disorder

(PTSD), anxiety, depression, and risk for dysfunctional socialization.[35,35] Physiological alterations have also occurred, such as significant bodily injury, cardiovascular changes, and neuroendocrine disturbances.[34,36] Patients with exposure to high stress environments, such as combat operations, appear especially prone to hyperarousal states exhibited by increased anxiety, irritability, and being easily startled when confronting stressors.[37]

The preoperative period is fraught with stressors, often increasing in magnitude as the patient progresses through the preoperative period, which may result in a hyperarousal state possibly amplifying both psychological symptoms (e.g., anxiety, fear, hostility) and physiological alterations (e.g., tachycardia, hypertension, metabolic changes). High-stressed patients, like combat veterans, may be more difficult to anesthetize, have greater perioperative fluctuations in hemodynamics, experience increased pain, and may be at increased risk for postoperative morbidity. Anecdotally, it's become increasingly ordinary for military perianesthesia providers to characterize OEF/OIF veterans as clinically different, that is to say many clinicians describe this population as appearing overly anxious or unusually sensitive preoperatively, or exhibiting exaggerated or more extreme behaviors when emerging from a state of general anesthesia.

Regardless of a military or civilian setting, a heightened stress response can be extremely challenging and potentially problematic since these patients may be at increased risk for perioperative morbidity. For example, an overly anxious and agitated patient requiring greater anesthetic dosages to maintain an adequate state of anesthesia may experience untoward, medication-related side effects. Likewise, a high-stressed patient could suffer an unintended intraoperative awareness event because the anesthesia

provider unknowingly underestimated the patient's increased anesthetic requirement to attain a sufficient state of amnesia. Some of these psychological and physiological differences commonly reported by military perianesthesia providers about U.S. veterans may be nonexistent within the civilian's perioperative experience(s); however, every U.S. military member will ultimately be discharged or retire from military service and may opt to seek his or her medical treatment exclusively in the civilian medical community.

Physiological Measurements of Preoperative Stress

Physiological markers used to assess stress during the preoperative period range from common measurements (e.g., vital signs) to more invasive or complex biomarkers (e.g., cortisol).[27,38,39] These various physiological measures can generally be categorized as cardiovascular, neuroendocrine, and endocrine.[12] The cardiovascular markers typically encompass heart rate, respiratory rate, and blood pressure. Despite the scarcity of significant correlations between cardiovascular markers and the preoperative stress response, some understanding has been gained and may have valuable clinical implications.[40] For example, Demirtas[5] investigated heart rate variations in young patients during a 24-hour period prior to plastic surgery. The average heart rate over this 24-hour period was approximately 76 (±7) beats per minute; however, as patients progressed through the preoperative period the mean heart rate increased to 99 (±11) beats per minute immediately prior to anesthesia induction.[5]

Researchers have also explored neuroendocrine and endocrine biomarkers, often in studies attempting to investigate the effects of preoperative pharmacological or non-pharmacological interventions. The neuroendocrine hormones mostly reported in the literature are norepinephrine and epinephrine, which are typically obtained from a blood

(i.e., serum) or urine specimen, and have been found to significantly correlate with preoperative stress.[41,42] Cortisol is the most commonly reported endocrine biomarker, with some studies reporting significant decreases in cortisol levels following preoperative stress reduction interventions as compared to placebos.[38,41] Despite the potential value of using physiological markers to measure the stress response, neuroendocrine and endocrine biomarkers have many inherent methodological limitations that are difficult to manage, such as diurnal cortisol patterns or the effect adrenergic medications have upon salivary alpha-amylase secretion.[43] Additional physiological measurements found in the literature include serum potassium, salivary alpha-amylase, lymphocyte counts, Bispectral Index, skin conductance, and heart rate variability.[5,20,28,38,39,42]

Psychological Measures of Preoperative Stress

There have been numerous psychometric instruments used to study the preoperative stress response. The most popular instrument considered by some to be the "gold standard" is the State-Trait Anxiety Inventory (STAI).[22] The STAI is a self-administered tool including both state and trait scales, each containing twenty questions with a weighted response of one to four and a total score ranging from 20 to 80. Depending upon the literature cited, persons scoring greater than or equal to 45 are considered highly anxious.[8] One criticism of the STAI is the time required to complete this instrument (i.e., reported at six to ten minutes), primarily since the availability of time during the preoperative period is often limited.[39]

The visual analogue scale (VAS), also known as the vertical visual analogue scale, is frequently used to measure preoperative stress and anxiety.[20,44] The VAS commonly consists of a 100 mm horizontal line with word descriptors at the ends of the

continuum, such as "no anxiety" and "very high anxiety."[45] Patients are instructed to mark a line along this continuum that best depicts their feeling at that particular moment. An inherent methodological issue in using the VAS is the potential for central tendency bias. This phenomenon results when patients become less willing or uncomfortable selecting a point that truly represents their feelings; rather, they choose a conservative point versus an extreme.[46] Benefits of employing the VAS include simplicity, ease of use, and minimal time for completion.

The Amsterdam Preoperative Anxiety and Information Scale (APAIS) is a six item self-report tool measuring anxiety relative to anesthesia and surgery, as well as the patient's desire for information.[47] Respondents use a five-item Likert-type scale to denote their level of agreement with each of six statements (1= not at all to 5= extremely), four pertaining to anesthesia and surgery-related anxiety and two measuring patient information needs. The APAIS can be completed in less than two minutes and the anxiety portion of the APAIS was found to correlate strongly with the STAI-state scale.[48]

Some psychometric instruments reported in the literature have incorporated measures of affect other than anxiety. These instruments include the Hospital Anxiety and Depression Scale (HADS), the Multiple Affect Adjective Checklist (MAACL), and the MAACL-R (revised).[7,20] The HADS instrument has proven to be a reliable and valid instrument in both clinical practice and research. The tool consists of 14 questions, seven related to anxiety (HAD-A) and seven addressing depression (HAD-D).[49] An individual's response to each question is scored on a four-point Likert-type scale (0-3) and the instrument takes less than 10 minutes to complete.[7]

The MAACL and MAACL-R have both been shown to be reliable and valid measures of preoperative state and trait affect.[50] The MAACL-R is a revised version of the MAACL and currently consists of two positive affect scales (positive affect and sensation seeking) and an improved capacity to measure negative affective emotions (anxiety, depression, and hostility).[50] The MAACL-R contains a list of 132 adjectives from which patients select words that most accurately describe how they currently feel (state) or how they generally feel (trait). The estimated time to complete the MAACL-R is less than three minutes.[50]

Preoperative Stress Interventions

Interventions intended to mitigate stress during the preoperative phase are numerous and vary from pharmacological agents (e.g., benzodiazepines) to non-pharmacological remedies (e.g., education or hypnosis).[19,51] The primary goal of preoperative medications are to provide anxiolysis, sedation, and amnesia; however, these drugs may not be well tolerated or pose risks in some patient populations.[19,52,53] As a result, non-pharmacological interventions have been implemented in an attempt to not only replicate the effects of medications, but also foster a patient's sense of empowerment over their own health and improve perioperative satisfaction.[52,54]

Midazolam is one particular benzodiazepine regularly administered preoperatively and has consistently been shown to markedly decrease anxiety, preoperative dysphoria, and postoperative distress and pain.[30,55] Research suggests that higher dosages of benzodiazepines are no more efficacious than lower dosages in treating preoperative stress and anxiety; however, higher dosages appear to significantly increase patient respiratory rate and may cause greater sedation in the elderly.[19,39] Another

benzodiazepine cited in the literature, diazepam, was found to significantly diminish the preoperative stress response in patients undergoing outpatient surgery.[41]

Other categories of medications suggested to diminish preoperative stress are alpha-adrenergic medications (e.g., clonidine) and beta-adrenergic antagonists (e.g., timolol).[56,57] Carabine[56] compared the sedative and anxiolytic effects of temazepam 20 mg, clonidine 0.2 mg, and timolol 10 mg in a randomized sample of subjects scheduled for minor orthopedic procedures and found no significant difference between the three drugs' anxiolytic effects. The researchers also reported no appreciable decrease in the intraoperative anesthetic requirements among the groups.[56] Paris[57] randomized subjects scheduled for elective ear, nose, and throat surgery to receive either clonidine 0.15 mg or midazolam 7.5 mg preoperatively and found anxiety was not significantly different between the two groups. However, the clonidine group did exhibit a reduction in overall anesthetic requirement.[57]

Medications known not to negatively alter respiratory or psychomotor function have also been explored in an attempt to reduce preoperative stress.[40] An example is Tandospirone, a selective serotonin receptor agonist traditionally used to treat depression and anxiety disorders, which has been shown to be just as efficacious at reducing preoperative anxiety as diazepam and clonidine.[40,58] Medications historically used to treat epilepsy and neuropathic pain, gabapentin and pregabalin, have been hypothesized to modify excitatory neurotransmitters potentially contributing to preoperative stress. White[59] evaluated the anxiolytic effect of three dosages of pregabalin (75 mg, 150 mg, and 300 mg) administered approximately 60 to 90 minutes prior to the induction of anesthesia and found no particular dose of pregabalin was effective in reducing

preoperative anxiety. Gonano[60] administered pregabalin 300 mg preoperatively to patients scheduled for orthopedic knee surgery and found a 40% reduction in pre-induction anxiety.

Two studies investigated the efficacy of gabapentin in reducing preoperative stress. Clarke[53] administered gabapentin 600 mg preoperatively to patients undergoing hip arthroplasty and found no significant difference in preoperative anxiety when compared to placebo. Tirault[61] randomized subjects undergoing elective gastrointestinal (including endoscopic procedures), gynecologic, orthopedic, spinal, and ear, nose, and throat surgery to receive gabapentin 1200 mg, hydroxyzine 75mg (antihistamine), or a placebo approximately two hours preoperatively. Baseline anxiety measures between groups were not significantly different; however, immediately prior to the induction of anesthesia subjects in the gabapentin group reported a significantly greater decrease in anxiety when compared to the hydroxyzine or placebo group.[61]

Unconventional medications reported in the literature hypothesized to diminish the preoperative stress response include melatonin and Passiflora incarnate. Acil[55] compared the effects of melatonin, an endogenous hormone instrumental in sleep and circadian rhythm, to midazolam and found melatonin possessed significant sedative properties, as well as dramatically decreasing preoperative and postoperative anxiety. Similarly, the herbal medication Passiflora incarnate, a flowering plant traditionally considered an anxiolytic, was compared to placebo in men and women undergoing hernia repair and subject's exhibited a significant decrease in preoperative anxiety.[62]

A non-pharmacological intervention commonly reported in the literature and utilized preoperatively is patient education. Educational modalities can include video,

literature, computers, one-on-one education by a medical professional, or a combination of these approaches.[54,63,64] Preoperative education may include general instructions about a patient's perianesthesia experience or can be more specific in nature.[23,63] Educational interventions have been found to significantly reduce preoperative fear and anxiety by as much as 50% in some patients.[65] Additionally, preoperative education has been associated with improved postoperative outcomes, such as decreased anxiety and pain.[21]

More recently researchers have begun investigating non-educational interventions as potential alternatives to pharmacological agents.[66] A particularly common modality reported in the literature is music. Regardless of the patient's choice or whether the patient listens for a specified time pre- or perioperatively, studies consistently reveal significant reductions in patient-reported anxiety.[66,67] The application of acu*pressure* at extra point one (i.e., between the eyebrows at the root of the nose) for 10 minutes was found to significantly reduce preoperative anxiety in one outpatient setting; however, 30 minutes following treatment patient anxiety returned to baseline scores.[68] Acu*puncture*, on the other hand, has been shown to significantly decrease patient anxiety throughout the preoperative period.[69,70] In addition, guided-imagery and hypnosis have been shown to be beneficial in reducing anxiety.[44,71] In fact, Saadat[51] found subjects undergoing hypnosis preoperatively reported a 56% decrease in anxiety when compared to their baseline anxiety scores, and another study conducted by Schnur[72] noted that subjects felt less distress preoperatively following hypnosis. One other novel modality, forced-air warming, has been explored in its ability to diminish preoperative anxiety; however, study findings have been inconsistent.[3,73]

Preoperative Stress, Combat Veterans, and Future Implications

Military anesthesia providers frequently encounter and provide anesthetic care to military members with a history of combat exposure. Anecdotally, it is not uncommon for this patient population to require a more "heavy-handed" anesthetic regimen during the perioperative period simply to ensure an adequate state of anesthesia, or for an anesthetist to administer medications with known sedative properties convinced they will ablate or diminish patient responsiveness upon emergence from anesthesia. Not only can this result in increased side effects and potential for prolonged recovery, these patients may continue to suffer psychological and physiological alterations during future perioperative visits.

Despite the numerous preoperative stress measurements and interventions reported in the perioperative stress literature, no professional practice guideline or consensus has been established to assist or direct the medical management of high-stressed patients pre- or perioperatively. Consequently, military perianesthesia nurses struggle with how best to manage combat veterans when, for example, a patient communicates a history of aggressive or violent "wake up" following surgery. Additionally, perianesthesia professionals are resorting to interventions believed to be beneficial in mitigating perioperative stress, such as medications (e.g., midazolam) or non-pharmacological interventions (e.g., quiet postoperative suite), rather than implementing interventions shown to diminish the stress response in high-stressed military personnel.

Since the inception of OEF/OIF, only one study has investigated this apparent heightened perioperative stress response in combat veterans. McGuire[9] conducted a study

to identify preoperative risk factors associated with greater emergence delirium in military personnel deployed to OEF/OIF combat operations, and found subjects reporting increased anxiety, depression, and PTSD symptomology days prior to surgery experienced a greater incidence of emergence delirium following surgery. Although significant, nearly 90% of study subjects were predominately individuals that had either fired a weapon or been fired upon during their deployment, thus limiting generalizability to "non-warfighting" military members (e.g., nurses, paramedics, linguists, motor-transport personnel, etc.)[9]

Given the paucity of research already discussed, an enormous gap exists in knowledge related to the preoperative stress response in high-stressed patients, specifically individuals exposed to threatening and stressful environments, such as combat operations. Scientifically comparing the preoperative stress response in combatants to non-combatants can potentially validate a presumed heightened stress response described by military perianesthesia professionals, as well as further the understanding of the stress response in high-stressed individuals. In addition, such preliminary findings would potentially support future interventional studies designed to decrease the perioperative stress response in high-stressed patients, such as combat veterans.

Conclusion

Preoperative stress has been associated with many significant psychological and physiological alterations that may complicate the management of high-stressed patients and potentially increase perioperative morbidity. Reviewing preoperative stress literature allows medical professionals to be more aware of potential risk factors indicative of

increased preoperative stress, enables clinicians to become acquainted with various instruments to better measure preoperative stress, and may prompt readers to investigate potential interventions intended to diminish pre- or perioperative stress. The corollary is little is known about the perioperative stress response in high-stressed patients, particularly U.S. military personnel deployed to combat environments. Further, no consensus or practice guideline presently exists to clinically direct an anesthetist or perioperative nurse in the management of patients prone to experiencing increased perioperative stress.

As military veterans tranistion back to "civilian life" nonmilitary perianesthesia providers will begin to encounter these unique and vulnerable patients, and may also experience similar clinical dilemmas described by military perianesthesia clinicians. It's critical perioperative stress research continue to be explored so clinicians can better understand how stressors influence an individual's stress response, as well as identify effective interventions to mitigate the perioperative stress response. Additionally, the formulation of a professional practice guideline for high-stressed patients, much like the evidenced-based clinical guideline for PONV, could potentially improve patient outcomes and decrease perioperative morbidity.[74] Until further research is conducted, military and nonmilitary perianesthesia providers will continue to struggle in their efforts to better care for high-stressed patients.

References

1. Pritchard MJ. Managing anxiety in the elective surgical patient. *Br J Nurs.* 2009;18:416-419.
2. Grieve RJ. Day surgery preoperative anxiety reduction and coping strategies. *Br J Nurs.* 2002;11:670-678.
3. Wagner D, Byrne M, Kolcaba K. Effects of comfort warming on preoperative patients. *AORN J.* 2006;84:427-448.
4. Mitchell M. Influence of gender and anaesthesia type on day surgery anxiety. *J Adv Nurs.* 2012;68:1014-1025.
5. Demirtas Y, Ayhan S, Tulmac M, et al. Hemodynamic effects of perioperative stressor events during rhinoplasty. *Plast Reconstr Surg.* 2005;115:620-626.
6. Hong JY, Jee YS, Luthardt FW. Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. *J Clin Anesth.* 2005;17:549-553.
7. McIntosh S, Adams J. Anxiety and quality of recovery in day surgery: A questionnaire study using Hospital Anxiety and Depression Scale and Quality of Recovery Score. *Int J Nurs Pract.* 2011;17:85-92.
8. Carr E, Brockbank K, Allen S, Strike P. Patterns and frequency of anxiety in women undergoing gynaecological surgery. *J Clin Nurs.* 2006;15:341-352.
9. McGuire JM. The incidence of and risk factors for emergence delirium in U.S. military combat veterans. *J Perianesth Nurs.* 2012;27:236-245.
10. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol.* 2009;5:374-381.

11. McEwen BS, Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. *Horm Behav.* 2010;57:105-111.

12. Everly GS, Lating JM. *A Clinical Guide to the Treatment of the Human Stress Response*. 2nd ed. New York, NY: Kluwer Academic/Plenum Publishers; 2002.

13. Pego JM, Sousa JC, Almeida OF, Sousa N. Stress and the neuroendocrinology of anxiety disorders. *Curr Top Behav Neurosci.* 2010;2:97-117.

14. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol.* 2008;583:174-185.

15. Schneiderman N, Ironson G, Siegel SD. Stress and health: Psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol.* 2005;1:607-628.

16. Chrousos GP. Organization and integration of the endocrine system. *Sleep Med Clin.* 2007;2:125-145.

17. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol.* 2005;67:259-284.

18. Papadimitriou A, Priftis KN. Regulation of the hypothalamic-pituitary-adrenal axis. *Neuroimmunomodulation.* 2009;16:265-271.

19. Sun GC, Hsu MC, Chia YY, Chen PY, Shaw FZ. Effects of age and gender on intravenous midazolam premedication: A randomized double-blind study. *Br J Anaesth.* 2008;101:632-639.

20. Spence D, McBeain J, Guzman J, Roucek E, Maye J. A pilot investigation evaluating physiological and psychological stress measurements in patients

presenting for elective surgical procedures. *Journal of Healthcare, Science and the Humanities.* 2011;1:39-53.

21. Wong EM, Chan SW, Chair SY. Effectiveness of an educational intervention on levels of pain, anxiety and self-efficacy for patients with musculoskeletal trauma. *J Adv Nurs.* 2010;66:1120-1131.

22. Kindler CH, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesth Analg.* 2000;90:706-712.

23. Fitzgerald BM, Elder J. Will a 1-page informational handout decrease patients' most common fears of anesthesia and surgery? *J Surg Educ.* 2008;65:359-363.

24. Costa MJ. The lived perioperative experience of ambulatory surgery patients. *AORN J.* 2001;74:874-881.

25. Aalouane R, Rammouz I, Tahiri-Alaoui D, Elrhazi K, Boujraf S. Determining factors of anxiety in patients at the preoperative stage. *Neurosciences (Riyadh).* 2011;16:146-149.

26. Kiyohara LY, Kayano LK, Oliveira LM, et al. Surgery information reduces anxiety in the pre-operative period. *Rev Hosp Clin Fac Med Sao Paulo.* 2004;59:51-56.

27. Gras S, Servin F, Bedairia E, et al. The effect of preoperative heart rate and anxiety on the propofol dose required for loss of consciousness. *Anesth Analg.* 2010;110:89-93.

28. Morley AP, Papageorgiou CH, Marinaki AM, Cooper DJ, Lewis CM. The effect of pre-operative anxiety on induction of anaesthesia with propofol. *Anaesthesia.* 2008;63:467-473.

29. Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for postoperative anxiety in adults. *Anaesthesia.* 2001;56:720-728.

30. Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. *J Psychosom Res.* 2000;49:417-422.

31. Van den Bosch JE, Moons KG, Bonsel GJ, Kalkman CJ. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? *Anesth Analg.* 2005;100:1525-1532.

32. Finley EP. *Fields of Combat: Understanding PTSD Among Veterans of Iraq and Afghanistan.* Ithaca, NY: ILR Press; 2011.

33. McGhee LL, Maani CV, Garza TH, DeSocio PA, Gaylord KM, Black IH. The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. *J Trauma.* 2009;66:S186-190.

34. Nayback AM. Posttraumatic stress: A concept analysis. *Arch Psychiatr Nurs.* 2009;23:210-219.

35. Phillips CJ, Leardmann CA, Gumbs GR, Smith B. Risk factors for posttraumatic stress disorder among deployed US male marines. *BMC Psychiatry.* 2010;10:52-62.

36. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. *US Army Med Dep J.* 2008:7-17.

37. Liberzon I, Abelson JL, Flagel SB, Raz J, Young EA. Neuroendocrine and psychophysiologic responses in PTSD: A symptom provocation study. *Neuropsychopharmacology.* 1999;21:40-50.

38. Leardi S, Pietroletti R, Angeloni G, Necozione S, Ranalletta G, Del Gusto B. Randomized clinical trial examining the effect of music therapy in stress response to day surgery. *Br J Surg.* 2007;94:943-947.

39. Wetsch WA, Pircher I, Lederer W, et al. Preoperative stress and anxiety in day-care patients and inpatients undergoing fast-track surgery. *Br J Anaesth.* 2009;103:199-205.

40. Oshima T, Kasuya Y, Terazawa E, Nagase K, Saitoh Y, Dohi S. The anxiolytic effects of the 5-hydroxytryptamine-1A agonist tandospirone before otolaryngologic surgery. *Anesth Analg.* 2001;93:1214-1216.

41. Duggan M, Dowd N, O'Mara D, Harmon D, Tormey W, Cunningham AJ. Benzodiazepine premedication may attenuate the stress response in daycase anesthesia: A pilot study. *Can J Anaesth.* 2002;49:932-935.

42. Hahm TS, Cho HS, Lee KH, Chung IS, Kim JA, Kim MH. Clonidine premedication prevents preoperative hypokalemia. *J Clin Anesth.* 2002;14:6-9.

43. Levine A, Zagoory-Sharon O, Feldman R, Lewis JG, Weller A. Measuring cortisol in human psychobiological studies. *Physiol Behav.* 2007;90:43-53.

44. Gonzales EA, Ledesma RJ, McAllister DJ, Perry SM, Dyer CA, Maye JP. Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: A randomized, single-blind study. *AANA J.* 2010;78:181-188.

45. Williamson A, Hoggart B. Pain: A review of three commonly used pain rating scales. *J Clin Nurs.* 2005;14:798-804.

46. Polit DF, Beck CT. *Nursing Research: Generating and Assessing Evidence for Nursing Practice.* 9th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

47. Boker A, Brownell L, Donen N. The Amsterdam preoperative anxiety and information scale provides a simple and reliable measure of preoperative anxiety. *Can J Anaesth.* 2002;49:792-798.

48. Moerman N, van Dam FS, Muller MJ, Oosting H. The Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Anesth Analg.* 1996;82:445-451.

49. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52:69-77.

50. Lubin B, Zuckerman M. *Manual for the Multiple Affect Adjective Checklist-Revised.* San Diego, CA: EdITS; 1999.

51. Saadat H, Drummond-Lewis J, Maranets I, et al. Hypnosis reduces preoperative anxiety in adult patients. *Anesth Analg.* 2006;102:1394-1396.

52. Bauer KP, Dom PM, Ramirez AM, O'Flaherty JE. Preoperative intravenous midazolam: Benefits beyond anxiolysis. *J Clin Anesth.* 2004;16:177-183.

53. Clarke H, Kay J, Orser BA, Gollish J, Mitsakakis N, Katz J. Gabapentin does not reduce preoperative anxiety when given prior to total hip arthroplasty. *Pain Med.* 2010;11:966-971.

54. Stergiopoulou A, Birbas K, Katostaras T, Mantas J. The effect of interactive multimedia on preoperative knowledge and postoperative recovery of patients undergoing laparoscopic cholecystectomy. *Methods Inf Med.* 2007;46:406-409.

55. Acil M, Basgul E, Celiker V, Karagoz AH, Demir B, Aypar U. Perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. *Eur J Anaesthesiol.* 2004;21:553-557.

56. Carabine UA, Milligan KR, Moore JA. Adrenergic modulation of preoperative anxiety: A comparison of temazepam, clonidine, and timolol. *Anesth Analg.* 1991;73:633-637.

57. Paris A, Kaufmann M, Tonner PH, et al. Effects of clonidine and midazolam premedication on bispectral index and recovery after elective surgery. *Eur J Anaesthesiol.* 2009;26:603-610.

58. Iizawa A, Oshima T, Kasuya Y, Dohi S. Oral tandospirone and clonidine provide similar relief of preoperative anxiety. *Can J Anaesth.* 2004;51:668-671.

59. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: A dose-ranging study. *Anesth Analg.* 2009;108:1140-1145.

60. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. *J Psychopharmacol.* 2011;25:249-253.

61. Tirault M, Foucan L, Debaene B, et al. Gabapentin premedication: Assessment of preoperative anxiolysis and postoperative patient satisfaction. *Acta Anaesthesiol Belg.* 2010;61:203-209.

62. Movafegh A, Alizadeh R, Hajimohamadi F, Esfehani F, Nejatfar M. Preoperative oral Passiflora incarnata reduces anxiety in ambulatory surgery patients: A double-blind, placebo-controlled study. *Anesth Analg.* 2008;106:1728-1732.

63. Ayral X, Gicquere C, Duhalde A, Boucheny D, Dougados M. Effects of video information on preoperative anxiety level and tolerability of joint lavage in knee osteoarthritis. *Arthritis Rheum.* 2002;47:380-382.

64. Hering K, Harvan J, Dangelo M, Jasinski D. The use of a computer website prior to scheduled surgery (a pilot study): Impact on patient information, acquisition, anxiety level, and overall satisfaction with anesthesia care. *AANA J.* 2005;73:29-33.

65. Jlala HA, French JL, Foxall GL, Hardman JG, Bedforth NM. Effect of preoperative multimedia information on perioperative anxiety in patients undergoing procedures under regional anaesthesia. *Br J Anaesth.* 2010;104:369-374.

66. Cooke M, Chaboyer W, Schluter P, Hiratos M. The effect of music on preoperative anxiety in day surgery. *J Adv Nurs.* 2005;52:47-55.

67. Haun M, Mainous RO, Looney SW. Effect of music on anxiety of women awaiting breast biopsy. *Behav Med.* 2001;27:127-132.

68. Agarwal A, Ranjan R, Dhiraaj S, Lakra A, Kumar M, Singh U. Acupressure for prevention of pre-operative anxiety: A prospective, randomised, placebo controlled study. *Anaesthesia.* 2005;60:978-981.

69. Gioia L, Cabrini L, Gemma M, et al. Sedative effect of acupuncture during cataract surgery: Prospective randomized double-blind study. *J Cataract Refract Surg.* 2006;32:1951-1954.

70. Wang SM, Peloquin C, Kain ZN. The use of auricular acupuncture to reduce preoperative anxiety. *Anesth Analg.* 2001;93:1178-1180.

71. Ghoneim MM, Block RI, Sarasin DS, Davis CS, Marchman JN. Tape-recorded hypnosis instructions as adjuvant in the care of patients scheduled for third molar surgery. *Anesth Analg.* 2000;90:64-68.

72. Schnur JB, Bovbjerg DH, David D, et al. Hypnosis decreases presurgical distress in excisional breast biopsy patients. *Anesth Analg.* 2008;106:440-444.

73. Wen RJ, Leslie K, Rajendra P. Pre-operative forced-air warming as a method of anxiolysis. *Anaesthesia.* 2009;64:1077-1080.

74. ASPAN. ASPAN'S evidence-based clinical practice guideline for the prevention and/or management of PONV/PDNV. *J Perianesth Nurs.* 2006;21:230-250.

Chapter 4: MANUSCRIPTS

Manuscript II

UNIVERSITY OF SAN DIEGO

Hahn School of Nursing and Health Science

Tri-Service Nursing Research Program Graduate Award HT9404-12-1-TS16 (N12-P16)

Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?

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Abstract

This is a nonexperimental, prospective study investigating the preoperative psychological and physiological stress response in military personnel with varying degrees of combat exposure. The preoperative environment is met with many stressors, often increasing in magnitude as a patient progresses through the preoperative setting. Combat exposure has been associated with various mental and physical disorders, often increasing in magnitude when encountering stressful situations like elective surgery. Perianesthesia professionals anecdotally report anesthetic difficulty when managing this unique patient population, particularly during the induction and emergence phases of anesthesia. No study to date has scientifically corroborated a heightened preoperative stress response in military personnel with exposure to combat operations on the day of surgery. This nonexperimental, prospective study is designed to investigate the preoperative stress response in military members with varying degrees of combat exposure independent of mental health disorders. To address this gap in the science, this study will determine predictive relationships between the number of combat experiences and the preoperative stress response on the day of surgery in military personnel independent of anxiety, depression, and posttraumatic stress disorder. Preoperative psychological and physiological measures of stress will be taken on the day of surgery at three time points throughout the preoperative period; i.e., upon arrival to the Same Day Surgery Unit (time point 1), Preoperative Holding area (time point 2), and immediately prior to OR entry (time point 3). In addition, measures of combat exposure and mental health disorders will be obtained one to fourteen days prior to the day of surgery when subjects undergo preoperative screening in the Preoperative Teaching Unit. Not only

could this proposed study validate the presumption of a heightened preoperative stress response in military personnel, but it would also provide the evidence supporting interventional studies designed to diminish perioperative stress in military members with a history of combat exposure.

This proposed study responds to the Tri-Service Nursing Research Program's research priority of Nursing Competencies and Practice. More specifically, this proposal contributes to improving patient outcomes by researching the preoperative stress response in U.S. military members with a history of combat exposure, thus providing the preliminary evidence necessary for future interventional studies to improve perioperative experiences and patient outcomes. Ten years has passed since the inception of Operations Enduring and Iraqi Freedom, and only one study has investigated potential factors contributing to heightened or exacerbated behaviors many combat veterans exhibit perioperatively. Regrettably, many military perianesthesia professionals consider these phenomena essentially ordinary and never-ending. Further, many clinicians express angst and frustration in how best to manage combat veteran patients perioperatively when, for example, a Marine communicates a history of aggressive or violent "wake up" following surgery. Unfortunately, providers are resorting to anecdotal interventions believed to be beneficial in mitigating perioperative stress, such as medications (e.g., midazolam) or non-pharmacological interventions (e.g., quiet postoperative suite), rather than scientific evidence guiding the treatment of highly stressed patients. There is a significant gap in knowledge related to this unique patient population presenting to the preoperative setting. Scientifically investigating the preoperative stress response in U.S. military personnel with a history of combat experience could corroborate a presumed heightened

preoperative stress response described by military perianesthesia clinicians, as well as provide evidence supporting future interventional studies.

Research Plan

Introduction

The preoperative experience is a particularly unique phenomenon and may be perceived as extremely stressful. Current research suggests patients exhibiting higher degrees of stress in the preoperative setting experience significantly more adverse perioperative phenomena.[1-4] Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF) have exposed numerous U.S. military service members to stressful, traumatic, and threatening environments.[5,6] As a result, many of these individuals have experienced significant psychological problems, such as anxiety, depression, and posttraumatic stress disorder (PTSD).[7]

Military anesthesia providers frequently provide anesthetic care to military personnel with a history of combat exposure. Anecdotally, it is not uncommon for this patient population to require a more "heavy-handed" anesthetic regimen perioperatively, often resulting in increased side effects and prolonged recovery. A recent study found combat veterans reporting anxiety and PTSD symptomatology preoperatively exhibited a greater incidence of emergence delirium following surgery.[8] However, no study to date has researched the preoperative stress response in military personnel with varying degrees of combat exposure on the day of surgery. Therefore, the **purpose** of this study is to determine the predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military

personnel on the day of surgery independent of mental health disorders (i.e., anxiety, depression, and PTSD).

This study responds to TSNRP's research priority of Nursing Competencies and Practice, specifically patient outcomes, by researching the preoperative stress response in active duty military members with a history of combat experience. Many clinicians express angst and frustration in how best to manage military personnel following deployments to combat environments like OEF/OIF. Often clinicians resort to pharmacological and non-pharmacological interventions believed to be beneficial in mitigating perioperative stress since there is limited scientific evidence guiding the treatment of highly stressed patients. There is a significant gap in knowledge related to the preoperative stress response in U.S. military personnel, especially those with exposure to combat operations. Thus, this study would provide new data specifically investigating the preoperative stress response in U.S. military personnel with a history of combat experience, as well as help to confirm a presumed preoperative stress response described by perianesthesia professionals.

Specific Aims and Study Hypotheses

Aim 1. Determine the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *more negative emotions* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Multiple Affect Adjective Checklist-Revised.

Hypothesis 2. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher degrees of stress* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Visual Analogue Scale for stress.

Aim 2. Determine the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher salivary alpha-amylase* values measured at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room.

Background and Significance

The background and significance will discuss: (a) Stress and Stressors, (b) Components of the Stress Response, (c) Acute Stress Response, (d) Chronic Stress Response, (e) Preoperative Stress Measurements, and (f) Preoperative Stress and Military Personnel.

Stress and stressors. Stress is a state in which an individual's capacity to maintain a physiological balance necessary for survival is threatened or perceived to be in danger.[9,10] Chrousos[10] described stressors as external or internal factors that challenge the human body to preserve a state of equilibrium, commonly referred to as homeostasis. Stressors can be classified as psychosocial or biogenic.[11] Psychosocial stressors are those experiences or threats which the individual perceives as real, imagined, anticipated, or recalled; hence one's cognitive assessment of a stressor may or may not manifest in a stress response. Biogenic stressors do not require the individual to appraise an event as

threatening or stressful; rather, the biogenic stimulus may activate the stress response by way of a chemical (e.g., caffeine or nicotine) or physical (e.g., trauma or hemorrhage) stressor.[11]

Components of the stress response. Components integral to the human stress response are located centrally and peripherally.[12] Central components include the corticotropin-releasing hormone and arginine vasopressin neurons of the paraventricular nucleus located in the hypothalamus, as well as corticotropin-secreting neurons located in the medulla.[13] Further, norepinephrine (NE) producing bodies located in the locus ceruleus (LC), medulla, and pons, collectively referred to as the NE/LC system, also contribute significantly to the human stress response.[12,13] Peripherally, the human stress response is composed of the hypothalamic-pituitary-adrenal axis, sympathetic-adrenal-medullary axis, and parasympathetic nervous system.[12,14]

Acute stress response. When an individual perceives a stressor as potentially threatening or harmful psychological and physiological alterations may ensue.[15,16] Behavioral manifestations of a stress response can include increased arousal and alertness, anxiety, fear, depression, and dysphoria.[13,17] The neurological (NE/LC) response to a stressor occurs rapidly, altering many organs and their function, resulting in increased heart rate, blood pressure, and respiratory rate and release of catecholamines from the adrenal glands.[12] Endocrine alterations result from hypothalamic paraventricular secretion of corticotropin-releasing hormone, subsequently stimulating for the release of adrenocorticotropic hormone from the anterior pituitary gland and subsequent release of cortisol from the adrenal cortex, thus activation of the hypothalamic-pituitary-adrenal axis.[14,16,18] Cortisol has widespread effects upon the body's metabolism by altering the

management of proteins, fats, and carbohydrates, to provide a ready-made source of energy to support the human stress response.[14,16,19]

Chronic stress response. The acute stress response is typically short-lived or a brief occurrence associated with minimal risk in otherwise healthy individuals.[13,16] However, if a stress response becomes hyperdynamic and/or chronic, particularly in patients with pre-existing disease, a state of exhaustion may ensue, ultimately exacerbating disease and increasing morbidity.[20] For example, persistent sympathetic nervous system activity may lead to significant increases in blood pressure, which left untreated may result in thickening and damage to vasculature.[16] Likewise, prolonged cortisol production due to chronic stress may have profound systemic implications, such as negative nitrogen imbalance resulting from protein catabolism or hyperglycemia because of insulin resistance, lipolysis, and increased gluconeogenesis in the liver.[12,13,19] Other physiological alterations can include water and sodium retention, depressed sympathetic nervous system responsiveness, and immunosuppression.[12,19,21]

Preoperative stress measurements. Preoperative stress might begin days or weeks prior to surgery due to requisite testing or evaluation by anesthesia and surgery staff to ensure adequate perioperative preparation. Potential stressors experienced on the day of surgery can include unfamiliar surgical facilities, confusing procedures and regimens, or preoperative encounters that may be perceived as rushed and apathetic.[22] In addition, patients find themselves in preoperative settings that are often cold, secluded from family, harshly lit, and filled with unfamiliar sounds, thus contributing to a sense of vulnerability or loss of independence.[23,24] Patients may also experience prolonged wait

times, perhaps allowing them to reflect further on the surgery or anesthesia and potentially exacerbating an already stressful situation.[25]

Anxiety is a well-founded affective manifestation of preoperative stress in the adult population undergoing elective surgery. Anxiety is reportedly the most prevalent stress-engendered emotion in this population with an overall incidence ranging from 54% to 98%.[3,26] This affective state may manifest as restlessness, worry, apprehension, nervousness, or other sympathetically driven symptomatology, such as increased heart rate, blood pressure, and so on.[17,22] Some investigators have attempted to quantify the magnitude or degree of anxiety since individuals with higher degrees of preoperative stress may experience hyperarousal states, thus amplifying psychological symptoms and magnifying physiological alterations.[27] For example, Carr[4] found over 40% of participants scheduled to undergo various gynecological procedures experienced "high" anxiety during their preoperative clinic visit prior to surgery, and 67% reported high anxiety immediately before entering the operating room. Wong[28] measured baseline anxiety in male and female subjects with orthopedic fractures requiring surgery and found all participants experienced high degrees of baseline preoperative anxiety. Other studies enrolling men and women scheduled to undergo various types and complexities of surgery reported moderate anxiety in 30% of the subjects, and rates of high and severe anxiety were 25% and 23%, respectively.[29]

Fear is another emotion associated with preoperative stress. Fitzgerald[30] conducted a study in a military medical facility investigating the effects of perioperative education upon fear and found 70% of the study population reported preoperative fear. Kindler[29] reported patients feared surgery significantly more than anesthesia; however, a

phenomenological investigation of patients' perioperative experiences indicated that fear of anesthesia predominated.[31] Other research has suggested patients fear general anesthesia significantly more than procedures requiring local anesthesia with sedation.[25] When asked to rank anesthesia-related fear, subjects indicated death as their primary fear, followed by pain, intraoperative awareness, nausea and vomiting, and the provider's capacity to provide adequate care.[30] One recent investigation measured positive and negative preoperative affective emotions in a general surgical population and found positive affect scores decreased and correlated significantly with a rise in a sympathetic nervous system biomarker called salivary alpha-amylase, a biomarker directly linked to increased autonomic activity. This finding suggests patients who experience more negative emotions in the preoperative period may have a greater sympathetic response.[27]

Researchers have explored the impact of preoperative stress on other aspects of the perioperative experience as well. Gras[32] investigated the effect of heart rate and preoperative anxiety on intraoperative anesthetic requirements in a gynecological population and found higher state anxiety resulted in an elevated heart rate and higher anesthetic dosages required to achieve adequate induction of anesthesia. In addition, methodologically similar studies (all female, gynecological) not only corroborated this increased anesthetic requirement during the induction phase, but also found intraoperative anesthetic dosages were greater among subjects with high preoperative anxiety than those with lower levels of anxiety.[2] However, one study enrolling both men and women scheduled for minor surgery was unable to validate this increased anesthetic requirement in highly anxious patients. The authors attributed this finding to a potential inability of the tool to accurately measure preoperative anxiety.[33]

The effect of preoperative stress upon symptoms and emotions experienced during the postoperative period has also been described. Research has indicated significant correlation of preoperative anxiety with depression and postoperative anxiety.[3,34] Pain is another postoperative sequela reportedly linked to preoperative stress. The incidence and severity of pain immediately following surgery has been strongly correlated not only to high levels of preoperative state anxiety, but to individual coping styles as well.[4,35] However, one study investigated the possibility of preoperative anxiety as a risk factor for postoperative nausea and vomiting and found subjects exhibiting higher levels of preoperative anxiety experienced a higher incidence of postoperative nausea and vomiting.[36]

Preoperative stress and military personnel. Increased OEF/OIF operations over the last decade have exposed numerous U.S. military service members to stressful, traumatic, and threatening environments.[5,6] As a result, many of these individuals have experienced significant psychological problems, such as acute stress syndrome, anxiety, depression, PTSD, and risk for dysfunctional socialization.[7,37] Physiological alterations have also occurred, such as significant bodily injury, cardiovascular changes, and neuroendocrine disturbances.[5,7] Alarmingly, patients with exposure to high stress environments, such as combat operations, appear especially prone to hyperarousal states exhibited by increased anxiety, irritability, and being easily startled when confronted with stressors.[38]

The preoperative period is fraught with stressors, often increasing in magnitude as the patient progresses through the preoperative period. Collectively, this may result in a hyperarousal state possibly amplifying both psychological symptoms (e.g., anxiety, fear,

hostility) and physiological alterations (e.g., tachycardia, hypertension, metabolic changes). Further, military members with a history of combat exposure may be more difficult to anesthetize, have greater perioperative fluctuations in hemodynamics, experience increased pain, and be at increased risk for postoperative morbidity. Only one investigation has explored military members in the perioperative setting with a history of a deployment to OEF/OIF; however, this study sought to predict potential risk factors for emergence delirium in active duty personnel reportedly having fired a weapon or been fired upon during combat operations.[8] Given the paucity of research demonstrated in the review above, an enormous gap exists in knowledge related to the preoperative stress response in active duty military members with varying degrees of combat exposure. More specifically, no study to date has investigated predictive relationships between various degrees of combat exposure and the preoperative stress response in active duty military personnel on the day of surgery independent of anxiety, depression, and PTSD.

Theoretical Framework

For the purposes of this study stress is defined as a state in which an individual's capacity to maintain the physiologic balance necessary for survival is threatened or perceived to be in danger.[9,10] The conceptual framework used to describe the preoperative stress response, as well as for research purposes, is the systems model of the human stress response adapted from Everly and Lating.[11] Within this model the human stress response is considered a multidimensional, interactive process possessing several elements: (a) stressor events (psychosocial; e.g., anticipation of anesthesia and surgery; or biogenic; e.g., cold operating room), (b) cognitive appraisal and affective integration, (c)

neurological triggering mechanisms (e.g., locus coeruleus), (d) the stress response, (e) target-organ activation, (f) and coping behavior.

Within the context of this study, the *preoperative stress response* will be the phrase used to describe the response or reaction patient's exhibit when encountering preoperative stressors (e.g., anticipation of anesthesia or surgery). Cognitive appraisal is how one interprets a stressor and affective integration refers to the blending and coloring of felt emotion into the cognitive interpretation; hence, the combination of these two concepts represents how stressors are perceived.[11] The process is individualized and potentially affected by personality, status or social-role behaviors, genetic vulnerability, past exposure (e.g., prior anesthesia or surgical experiences), timing of events, and/or history of exposure to traumatic stressors (e.g., combat exposure).[12] The acute stress response activates the sympathetic nervous system and ultimately triggers the hypothalamic-pituitary-adrenal axis.[12] Figure 1 describes the conceptual framework for this model.

Preliminary Studies

This proposal is based on previous work by investigators and mentors associated with this proposed study. The first study was conducted by Navy Registered Nurse Anesthetist Students, which was mentored by CDR Dennis Spence, NC, USN, CRNA, PhD, Clinical Research Director, Navy Nurse Corps Nurse Anesthesia Program, Uniformed Services University of the Health Sciences. The second study was completed by CDR Jason McGuire, NC, USN, CRNA, PhD, for his dissertation research.

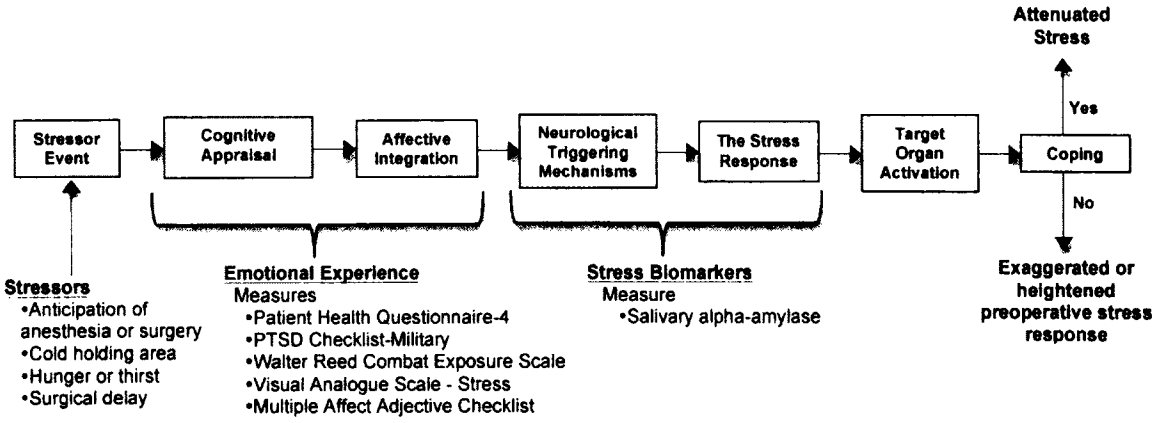

***Figure 1.* A systems model for the preoperative stress response. Adapted from Everly and Lating, 2002.**

Spence[27] conducted a descriptive, correlational pilot investigation measuring the preoperative psychological and physiological stress response in 29 male patients presenting for elective, general surgery. Subjective, self-report measures of negative and positive affect (i.e., Multiple Adjective Affect Checklist-Revised), as well as stress (i.e., Visual Analogue Scale-Stress) were measured along with the physiological biomarker salivary alpha-amylase at three specific time points during the preoperative period. Investigators found a significant negative correlation between positive affective scores on the Multiple Affect Adjective Checklist-Revised and salivary alpha-amylase (r = -.384, P = .04), suggesting patients who experience more negative emotions in the preoperative period may have a greater sympathetic nervous system response.

Recently, McGuire and Burkard[8] conducted an observational, descriptive study to determine the incidence of emergence delirium following surgery in 130 OEF/OIF veterans, as well as explore relationships between mental health disorders and emergence delirium. Investigators measured anxiety, depression, and PTSD symptomatology in study subjects 1-14 days prior to the day of surgery and assessed for emergence delirium

using the Pediatric Anesthesia Emergence Delirium tool on the day of surgery. The investigators found state and trait measures of anxiety were significantly associated with an increase in emergence delirium when controlling for depression and PTSD symptomatology ($F(2,127)=14.738$, $p<.001$, $R^2=.188$).

Although Spence[27] demonstrated the usefulness of using psychological and physiological measures of stress in research, the investigators did not account for any combat-related factors, nor did they examine mental health disorders (e.g., PTSD symptoms or trait depression). In addition, Spence[27] enrolled a small sample of subjects since this was the first investigation to utilize the Multiple Affect Adjective Checklist-Revised questionnaire and salivary alpha-amylase in the same study. In the study conducted by McGuire and Burkard,[8] subjects were predominately combatants (88%), thus limiting the generalizability of the findings since many service members deployed to OEF/OIF are categorically noncombatant military personnel. Also, investigator's operationalized combat exposure as having fired a weapon or taken enemy fire during combat. However, this approach only accounts for two of the multiple dimensions of combat exposure a veteran might experience. Finally, the investigation conducted by McGuire and Burkard[8] measured anxiety, depression, and PTSD symptomatology at only one time point (i.e., 1-14 days prior to the day of surgery).

These two studies led the Principal Investigator of this proposal to ask if similar methodology used by Spence[27] in a comparable population studied by McGuire and Burkard[8] could be used to explore the preoperative stress response in military personnel following a deployment to OEF/OIF. Scientifically demonstrating a heightened stress response in active duty military members throughout the preoperative period will provide

the evidence necessary to support future interventional studies designed to mitigate or diminish the pre- and/or perioperative stress response. As discussed in the background and significance, no study to date has researched the preoperative stress response in military personnel with varying degrees of combat exposure on the day of surgery. **Therefore, this proposed study would be the first investigation to research predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health morbidity (i.e., anxiety, depression, and PTSD).**

Methods

Research Design

A nonexperimental, prospective study will be conducted to investigate the preoperative psychological and physiological stress response in military members with varying degrees of combat exposure presenting for elective general, gynecological, orthopedic, otolaryngological (ENT), or podiatric surgery. The study will be conducted at Naval Hospital Camp Pendleton, Camp Pendleton, California. Study approval will be obtained from the Department Heads of the Same Day Surgery Unit and Anesthesia Department, Directorate of Surgical Services, Commanding Officer of Naval Hospital Camp Pendleton, and the facility's Institutional Review Board. A purposive sample of 120 ASA I-II active duty military members previously deployed to OEF/OIF scheduled for elective, non-cancer general, gynecological, orthopedic, ENT, or podiatric surgery meeting the inclusion/exclusion criteria will be recruited. Following enrollment (1 to 14 days prior to the day of surgery), subjects will complete: (a) Demographic and Military

History questionnaires, (b) Walter Reed Army Institute of Research Combat Exposure Scale, (c) Physical Health Questionnaire-4 (trait anxiety and depression), and (d) Posttraumatic Stress Disorder Checklist-Military questionnaire. Following admission to the Same Day Surgical Unit on the day of surgery, a salivary alpha-amylase sample will be obtained while study subjects complete the Multiple Affect Adjective Checklist-Revised (state) questionnaire, verbal analogue scale for stress, two open-ended questions, and a one-time measure assessing pain using the verbal analogue scale for pain. Upon arrival to the preoperative holding area subjects will submit a second salivary alpha-amylase sample while completing a second Multiple Affect Adjective Checklist-Revised (state) questionnaire, verbal analogue scale for stress, and two open-ended questions. Immediately prior to receiving anxiolytics and/or transfer to the operating suite, subjects will submit a third salivary alpha-amylase sample, complete the Multiple Affect Adjective Checklist-Revised (state) questionnaire, verbal analogue scale for stress, and two open-ended questions. See Figure 2 for patient flow and data collection.

Inclusion and Exclusion Criteria

The inclusion criteria for this study are: (a) active duty military men or women; (b) ages 18-45; (c) ASA category I or II; (d) undergoing elective, non-cancer surgery requiring anesthesia services (e.g., general anesthesia, monitored anesthesia care, regional anesthesia) for general, gynecological, orthopedic, ENT, or podiatric surgery; (e) able to read and understand the consent form; and (f) consent to participate in the study.

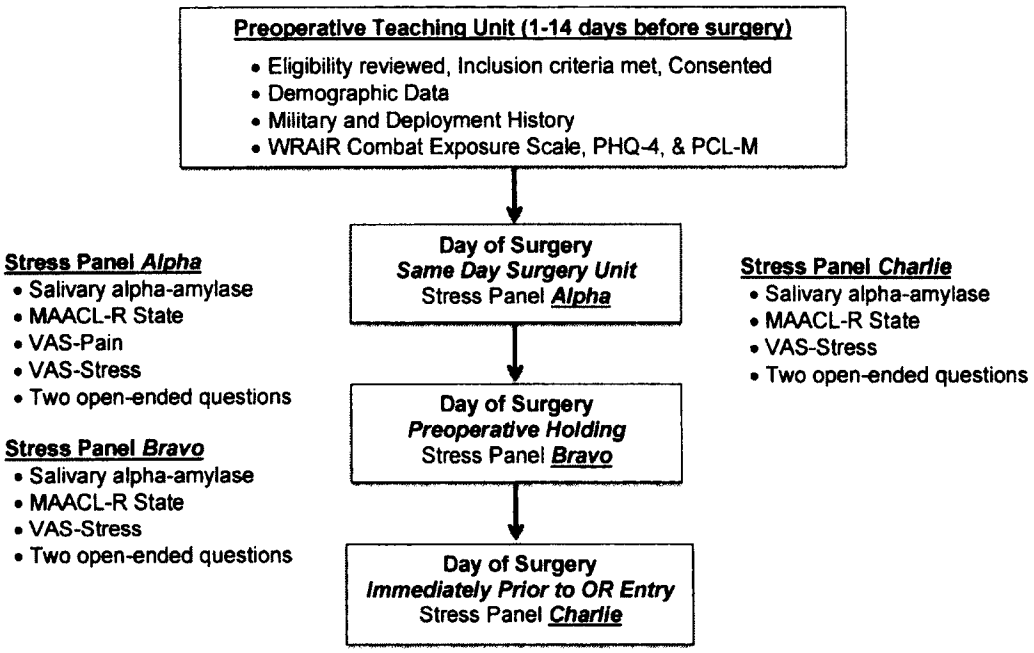

Figure 2. **Patient flow and data collection.**

The exclusion criteria for this study are: (a) medications known to interfere with salivary alpha-amylase (e.g., beta-blockers); (b) metabolic disorders (e.g., diabetes, thyroid disorders); and (3) autoimmune disorders (e.g., Sjogren's syndrome).

... 67struments

(See Table 1 below for proposed study instruments)

Walter reed army institute of research combat exposure scale. The Walter Reed Army Institute of Research Combat Exposure Scale (WRAIR CES) consists of 27 dichotomized questions measuring an individual's exposure to combat-related events, particularly personnel participating in OEF/OIF operations. Unlike other combat exposure scales, this instrument evaluates various dimensions of combat exposure, such as combat fighting, threat to oneself, injury, or atrocity. Hoge[7] used the WRAIR CES to assess combat experiences in U.S. infantrymen deployed to Iraq and Afghanistan and found greater degrees of combat exposure were significantly correlated with higher

incidences of PTSD.[7] Another study screened for alcohol misuse in U.S. soldiers following a deployment to Iraq and found subjects reporting more combat experiences on the WRAIR CES exhibited significantly greater reports of alcohol misuse.[39] Consequently, the WRAIR CES has become the U.S. Army's primary instrument for measuring a service member's exposure to combat, especially combat experienced in OEF/OIF.[7,39] In addition, the WRAIR CES has been shown to be a reliable measure of combat exposure with a reported Cronbach's alpha of 0.85.[40] Therefore, for the purposes of this study an individual's exposure to combat following a deployment to OEF/OIF will be measured using the 27-item WRAIR CES with a score ranging from 0 to 27.[39] This instrument is available free of charge.

Posttraumatic stress disorder checklist – military. PTSD symptomatology will be assessed using the Posttraumatic Stress Disorder Checklist (PCL-M), a commonly used instrument assessing PTSD symptomatology in the military population.[41] This self-report measure is comprised of 17 items as outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, which asks respondents to relate their military experiences to "how bothered" they are by symptoms listed on the PCL-M over the previous month.[42,43] Scoring consists of a rating scale of 1 = not at all to 5 = extremely, with a possible range of 17-85.[43] Although the PCL-M is an effective instrument in gauging the likelihood for PTSD, it is not a diagnostic tool, primarily since it doesn't include all diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders.[44] However, the most common method for scoring the PCL-M, particularly in military-based research, is the use of a higher cutoff value of 50 or greater, thus maximizing the specificity for combat-related PTSD symptomatology.[7,42] The internal

consistency of this instrument is > .90 and highly correlates with other questionnaires, such as the Mississippi Scale for Combat Related PTSD (r = 0.85 and .93).[41,44] Additionally, the PCL-M strongly correlates with the Clinician-Administered PTSD Scale, currently considered the gold standard for PTSD diagnosis, (r = 0.79, n = 114, p < 0.001).[44] The estimated time for completion of this tool is reportedly 5-10 minutes, and permission has been received from the National Center for PTSD, publisher of the instrument.

Patient health questionnaire-4. The Patient Health Questionnaire-4 (PHQ-4) is a self-report measure providing a rapid, yet reliable assessment of likelihood for depression and anxiety-related disorders.[45] The PHQ-4 consists of depression (PHQ-2) and generalized anxiety (GAD-2) subscales, both of which contain the two core criteria for depressive and generalized anxiety disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[45,46] Respondents are asked to indicate how "bothered" they are by each question using a 4-item Likert-type scale to denote their level of agreement with each of the four statements (0 = not at all to 3 = nearly every day). The researcher has the option to report a composite score indicating overall symptom burden; i.e., combined scoring of all four questions (range 0-12), and/or score each subscale separately; i.e., providing depression and anxiety scores individually (range 0-6). Internal reliability of the PHQ-4 and its subscales are high (all > 0.81), and construct validity of both subscales is reportedly excellent.[45] Recommendations for potential caseness for either a depressive or anxiety disorder for each subscale is a cutoff score of three or greater, resulting in a sensitivity and specificity of 93% and 89% for the PHQ-2 and 86%

Table 1. ***Reliability and Validity for Study Instruments***

Combat Exposure	Walter Reed Army Institute of Research Combat Exposure Scale (Wilk et al.,	Comprised of 27 dichotomized questions measuring combat exposure; commonly used by the U.S. Army to measure combat exposure	Cronbach's alpha = .85 (Hoge et al., 2008)
Anxiety	Patient Health Questionnaire-4 (Kroenke et al., 2009)	Four questions derived from the two core criteria for depression and anxiety; Likert-type scale (0=not at all to 3=nearly every day); cutoff score 3 or > on each subscale is highly sensitive for depression or anxiety disorders	Internal reliability for both subscales is high (> .81; Kroenke et al., 2009)
Depression			
PTSD	Posttraumatic Stress Disorder Checklist-Military	Uses 17 questions to measure PTSD symptomatology; Likert-type rating scale (1=not at all to 5=extremely); scoring range 17-85; recommended cutoff score of 50 or greater to maximize specificity (Hoge et al., 2004)	Internal consistency > .90; strongly correlated with the Clinician-Administered PTSD Scale (Keen et al., 2008)
Dysphoria	Multiple Affect Adjective Checklist-Revised (state version; Lubin & Zuckerman, 1999)	132 adjectives measuring affect along five domains (positive affect, sensation seeking, anxiety, depression, and hostility) or higher order affect (dysphoria = sum of anxiety, depression, and hostility)	Reliability (alpha) on state version in Air Force recruits on all domains and dysphoria was strong (r = .77-.91; Lubin & Zuckerman, 1999)
Pain	Visual Analogue Scale	Commonly used to measure various phenomena; consists of a 100 mm horizontal line with word descriptors at both ends	Consistently very high reliability (r > .90) and excellent sensitivity (Boker et al., 2002; Lara-Munoz et al., 2004; Williamson & Hoggart, 2005)
Stress			
Sympathetic Nervous System Activity	Salivary alpha-amylase	Noninvasive, indirect measure of sympathetic nervous system activity; saliva sample collected over 3 minutes via oral swab and analyzed by Salimetrics, LLC	Highly correlates with other stress biomarkers (r = .53 - .81; Chatterton et al., 1996; Kang, 2010)

and 83% for the GAD-2.[45,47] For the purposes of this study, trait measures of depression and anxiety will require a subscale score of three or greater, respectively. Lastly, no

reported completion time for the PHQ-4 was located in the literature; however, the original nine-item depression questionnaire (i.e., PHQ-9) can be completed in less than five minutes. This instrument is available free of charge from Pfizer, Inc.

Multiple affect adjective checklist-revised. The Multiple Affect Adjective Checklist-Revised (MAACL-R) is a versatile psychological instrument comprised of several affective domains found to be particularly useful in measuring a variety of mental health disorders, as well as basic research on personality and emotion. The MAACL-R consists of two positive affect subscales (positive affect and sensation seeking) and three negative affect subscales (anxiety, depression, and hostility). In addition, an overall dysphoria (sum of negative affect subscales) or well-being (sum of positive affect subscales) score may be calculated. Scoring is ultimately derived from a one-page list of 132-adjectives from which patients select words that most accurately describe how they currently feel (state) or how they generally feel (trait). The MAACL-R's state version has a high internal (alpha) reliability, low test-retest reliability, and has been found to be particularly suitable for investigations that hypothesize changes in affect relative to stressful experiences. The estimated time to complete the MAACL-R is less than three minutes.[48]

The MAACL-R was specifically chosen for its unique ability to evaluate more than just one preoperative emotion, such as anxiety. For example, a combat veteran undergoing reconstructive surgery following a blast injury to his lower extremity may not experience anxiety preoperatively; rather, he might feel more depressed or angry because of his current situation. Hence, this situational depression or anger may significantly magnify his preoperative stress response. If state anxiety was the only preoperative

emotion measured, then understanding the preoperative stress response, especially in combatants, would be limited or explained by only one affective emotion (e.g., anxiety).

For the purposes of this study, the Dysphoria composite score (i.e., sum of the anxiety, depression, and hostility scores) will be used to measure the state negative affective emotions experienced throughout the preoperative period on the day of surgery. The MAACL-R is readily available for purchase through the Educational and Industrial Testing Service, San Diego, CA.[48]

Visual analogue scale. The visual analogue scale (VAS), also known as the vertical visual analogue scale, has been commonly used to measure various phenomena, such as preoperative pain, stress, or anxiety.[27,50,53,54] The VAS commonly consists of a 100 mm horizontal line with word descriptors at the ends of the continuum, such as "no stress" and "very high stress." Subjects are asked to make a mark along this continuum that best describes their subjective feeling or perception about a particular construct at a particular moment in time, such as "how stressed do you feel right now."[49] Literature has consistently demonstrated the VAS to have a very high reliability ($r > .90$) and excellent sensitivity across a variety of settings and populations.[49-51] Benefits of employing the VAS include simplicity, ease of use, and minimal time for completion. For this study, the VAS will be used to measure subjective pain and stress on the day of surgery (Appendix V & VI).

Salivary alpha-amylase. Amylase is a digestive enzyme that hydrolyzes the alpha-1,4 bonds of large polysaccharides (e.g., starch and glycogen), yielding simpler carbohydrates such as glucose and maltose.[53,55] Salivary alpha-amylase is one of many proteins synthesized and secreted by acinar cells found in major and minor salivary

glands, although salivary alpha-amylase appears to be predominantly produced by the parotid glands.[56,57] Production and secretion of saliva is autonomically regulated, such that sympathetically-activated salivary glands produce more protein-based saliva (e.g., salivary alpha-amylase); whereas, parasympathetically-activated salivary glands produce more water-based saliva.[57-59] During periods of psychological or physiological stress, such as extremes in temperature, exercise, or academic testing, increased sympathetic activity results in the secretion of salivary alpha-amylase, and for this reason it has become a favorable surrogate for sympathetic nervous system activity.[55,60-62] Likewise, the production and secretion of salivary alpha-amylase following a stressor is almost instantaneous, particularly suitable in settings with multiple stressors like the preoperative environment.[60] Unlike serum biomarkers requiring venipuncture, salivary alpha-amylase sampling is a noninvasive procedure using an absorbent oral swab; thus, less likely to contribute to an already stressful experience or negatively influence an individual's desire to participate in a study out of fear of needles or pain.[53]

One recent investigation measured positive and negative preoperative affective emotions in a general surgical population and found positive affect scores decreased and correlated significantly with a rise in salivary alpha-amylase, suggesting patients experiencing more negative emotions may exhibit greater degrees of physiological stress.[27] In addition, salivary alpha-amylase has been shown to have moderate to strong correlations (r = 0.53-0.81) with other well-established biomarkers (e.g., heart rate, blood pressure, norepinephrine).[52,53] Altogether, this supports the use of salivary alpha-amylase as a valid and reliable surrogate for sympathetic nervous system activity and

responsiveness to stressors encountered in the preoperative setting. However, more studies are needed to determine salivary alpha-amylase's utility as a marker of the preoperative physiological stress response.

Salimetrics, LLC oral swab. A total of three saliva samples per subject (3 x 120 subjects = 360) will be collected using the Salimetrics Oral Swab, which is made of a non-toxic, inert synthetic polymer shaped into a 30 x 10 mm cylinder. Oral swabs have been used extensively in research to evaluate salivary alpha-amylase.[63] Subjects will be directed to place the swab between the upper cheek and gum next to the second molar where the duct of the parotid gland is located for three minutes.[64] Following salivary sampling, the oral swab will be placed in a Salimetric Swab Storage Tube, secured, and labeled with the subject identification number, date, and time. Samples will be placed in storage trays in a cooler with ice until transport to Naval Hospital Camp Pendleton's laboratory (approximately 3 minute walk) where they will remain in a freezer at a temperature of -20° C until data collection is completed. See Appendix VII for the support letter from Naval Hospital Camp Pendleton's Laboratory Department. All supplies (i.e., oral swabs and storage tubes) will be obtained from Salimetrics, LLC (State College, PA).

Salivary alpha-amylase assay description. All saliva samples will be shipped to Salimetrics, LLC (State College, PA) on dry ice for analysis. No personal information will be sent and all samples will be destroyed after completion of the study. Salimetrics, LLC's method for assay utilizes chromagenic substrate, 2-chloro-p-nitrophenol, linked to maltotriose. The enzymatic action of salivary alpha-amylase on this substrate yields 2-chloro-p-nitrophenol, which can be spectrophotometrically measured at 405 nm using a

standard laboratory plate reader. Saliva samples (10 μL) are diluted 1:200 in assay diluent and well mixed. Eight microliters of diluted sample or control are then pipetted into individual wells of a 96-well microtiter plate. Chromagenic substrate solution (2-chloro-p-nitrophenol, linked to maltotriose) is preheated (37°C) and 320 μL is added to each well and the plate is rotated at 500-600 RPM at 37 °C for three minutes. Optical density (read at 405 nm) is determined exactly at the one-minute mark and again at the three-minute mark. The amount of salivary alpha-amylase activity present in the sample is directly proportional to the increase (over a 2 min period) in absorbance at 405 nm.[65] Calibration is standardized using the millimolar absorptivity of 2-chloro-p-nitrophenol. In addition, Salimetrics, LLC is a Clinical Laboratory Improvement Amendments certified testing facility.[65] Salimetrics, LLC will provide results in an Excel spreadsheet to LCDR Eric J. Bopp.

Data Collection Procedures

Preoperative screening. Patients arriving to the Preoperative Teaching Unit for preoperative screening scheduled for elective general, gynecological, orthopedic, ENT, or podiatric surgery will be approached and provided information about the study by the investigators. All risks, benefits, and alternatives to the research study will be explained in detail and all questions will be answered. If subjects agree to participate in the study, then informed consent will be obtained. Once a patient has consented to participate, the subject will be assigned a subject number. All data collected, either hard copy or computer based, will be identified by that subject number. A single master subject list with the subject's name, contact information, and subject number will be maintained by the study investigator in a locked file cabinet in a locked office on the Same Day Surgery

Unit at Naval Hospital Camp Pendleton. All subsequent data collected will be locked in the office of LCDR Robert Krejci, Department Head, Same Day Surgery Unit at Naval Hospital Camp Pendleton, or if maintained on a computer will be password protected with the password known only to the investigators.

Subjects will be provided privacy during enrollment by directing them to the educational office located on the Preoperative Teaching Unit. On the day of enrollment subjects will be asked to complete the following questionnaires: (a) Demographic and Military History questionnaires, (b) Patient Health Questionnaire-4, (c) Posttraumatic Stress Disorder Checklist-Military, and (d) Walter Reed Army Institute of Research Combat Exposure Scale.

Day of surgery. Following admission to the Same Day Surgery Unit on the day of surgery, the investigator will ask subjects to collect a salivary alpha-amylase sample by placing one oral swab between the gum and cheek next to the second upper molar for 3 minutes. At the same time, patients will be asked to complete the following questionnaires: (a) Visual Analogue Scale for pain and stress, (b) Multiple Affect Adjective Checklist-Revised (state) questionnaire and two open-ended questions.

After arriving to the preoperative holding area, subjects will be placed on a gurney and met by the investigator. Subjects will then be asked to submit a second salivary alpha-amylase sample and then asked to complete the visual analogue scale for stress, Multiple Affect Adjective Checklist-Revised (state) questionnaire, and two open-ended questions.

Immediately prior to transport into the operating suite and prior to receiving any sedative medications, study subjects will be asked to submit a third salivary alpha-

amylase sample and complete the visual analogue scale for stress, Multiple Affect Adjective Checklist-Revised (state) questionnaire, and two open-ended questions. All swabs will be placed in Salimetric Swab Storage Tubes and placed in a cooler until transport to the laboratory department at Naval Hospital Camp Pendleton for storage at -20° C as recommended by Salimetrics, LLC.

Samples size and data analysis. Statistical analysis will be accomplished using the Statistical Package for the Social Sciences software. Descriptive statistics (e.g., means and standard deviations for continuous variables, frequencies and percentages for categorical variables) will be computed for each variable as appropriate. Both non-parametric and parametric techniques will be employed in the data analyses where appropriate. Statistical significance will be set at a $p \leq .05$.

Aim 1. Determine the predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *more negative emotions* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Multiple Affect Adjective Checklist-Revised.

The Multiple Affect Adjective Checklist-Revised dysphoria score will be used to measure negative emotions at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of more negative emotions. The alternative hypothesis is a greater number of combat experiences will be predictive of more negative emotions.

To determine predictive relationships between the independent variable number of combat experiences and the dependent variable negative preoperative emotions (i.e., mean dysphoria values), a multiple linear regression analysis will be conducted using the predictor variables: (a) number of combat experiences (WRAIR CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). A separate multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak dysphoria value preoperatively. The peak dysphoria value will consist of the subject's highest dysphoria score among the three time points on the day of surgery. To analyze changes in dysphoria over time, a repeated measures ANOVA or Friedman Test will be used where appropriate.

Hypothesis 2. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher degrees of stress* at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room as measured by the Visual Analogue Scale for stress.

The Visual Analogue for stress (VAS-Stress) will be used to measure subjective stress at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of higher degrees of stress. The alternative hypothesis is a greater number of combat experiences will be predictive of higher degrees of stress. To determine predictive relationships between the independent variable number of combat experiences and the dependent variable stress (i.e., mean stress values), a multiple linear regression analysis will be conducted using the predictor variables: (a) number of combat

experiences (WRAIR CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). A separate multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak stress value preoperatively. Peak stress will consist of the subject's highest stress value among the three time points on the day of surgery. To analyze changes in negative emotions over time as measured by the VAS-Stress, a repeated measures ANOVA or Friedman Test will be used where appropriate.

Aim 2. Determine the predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel with a deployment to OEF/OIF.

Hypothesis 1. In U.S. military personnel, a greater number of combat experiences will be predictive of *higher salivary alpha-amylase* values measured at baseline, upon arrival to preoperative holding, and just prior to transfer to the operating room.

Since salivary alpha-amylase data is typically positively skewed, a logarithmic transformation of the data will be performed prior to analysis.[64] Areas under the curve (see Table 2) with respect to ground (AUC_G) and with respect to increase from baseline (AUC_{Inc}) will be calculated for salivary alpha-amylase.[27,66] Additionally, any values found to be below the baseline value (i.e., measures on the Same Day Surgery Unit) will be computed using the AUC above the baseline minus the area above the curve below the baseline (AUC_{AB}).[67]

The AUC_G and AUC_{Inc} will be used to measure total salivary alpha-amylase output and sensitivity, respectively, from the Same Day Surgery Unit to immediately

prior to transfer to the operating room. The null hypothesis is a greater number of combat experiences will not be predictive of higher AUC_G and/or AUC_{Inc} in salivary alpha-amylase values. The null hypothesis is a greater number of combat experiences will be predictive of higher AUC_G and/or AUC_{Inc} in salivary alpha-amylase values. To determine predictive relationships between the independent variable number of combat experiences and the dependent variables AUC_G and AUC_{Inc} values for salivary alpha-amylase, separate multiple linear regression analyses will be conducted using the predictor variables: (a) number of combat experiences (WRAIR CES), (b) trait anxiety and depression (PHQ-4), and (c) PTSD symptomatology (PCL-M). Additionally, a multiple linear regression analysis will be conducted to explore which of the predictor variables (i.e., combat experiences, trait anxiety and depression, and PTSD symptomatology) best predicts the participant's peak salivary alpha-amylase value preoperatively. Peak salivary alpha-amylase levels will consist of the subject's highest salivary alpha-amylase value among the three time points on the day of surgery. To analyze changes in salivary alpha-amylase values over time, repeated measures ANOVA or Friedman Test will be used where appropriate.

AUC_G = sample 1 + sample 2 + ((sample 3 – sample 1)/2)
AUC_{Inc} = (sample 2 + sample 3)/2 – sample 1
AUC_{AB} = AUC_G – AUC_B
AUC_B = sample 1 x ((time point 2 – Time point 1) + (time point 3 – time point 2))

No study known to this author has utilized the proposed measures and methodology outlined in this proposal. Accordingly, a sample calculation was performed using a moderate effect size ($R^2 = .13$) with a power of .80 and $\alpha = .05$ for 10 predictor

variables. Therefore, a sample of 120 subjects is needed to detect a population R^2 of .13 with 10 predictors with a 5% chance of a Type I error and a 20% chance of a Type II error.[68]

Limitations

A limitation of this study is the likelihood of enrolling predominately U.S. Marines, especially since this study will be conducted at a Naval Hospital on a Marine Corps training base; hence, potentially limiting the generalizability to other branches of the military. However, this particular facility provides access to the population most likely exposed to combat operations supporting OEF/OIF. Additional limitations include potential factors that might affect salivary alpha-amylase secretion, such as diurnal rhythm, smoking, eating, etc. Fortunately, many factors affecting salivary alpha-amylase secretion will be minimized since patients are required not to consume any food or drink on the day of surgery; i.e., nothing by mouth after midnight. Further, investigators will provide study subjects with written and verbal instructions not to participate in any physical exercise, consume alcohol, or smoke on the day of surgery. Additionally, the principal investigator will collaborate with the operating room scheduling officer to ensure study subjects are scheduled for early morning surgery, thus minimizing the degree of diurnal pattern influence upon salivary alpha-amylase secretion.

Protection of Human Subjects

Recruitment: One hundred and twenty active duty military members with a deployment history to either OEF or OIF scheduled for elective general, gynecological, orthopedic, ENT, or podiatric surgery will be invited to participate in the proposed study. Eligibility for enrollment will be determined by the study's inclusion and exclusion

criteria. Study description, rationale, benefits, risks, medical treatment protocol, and right to withdraw will be included in the discussion and all questions will be answered. Any patient who is unable to verbalize understanding of the study protocol will be excluded. The primary investigator will conduct the informed consent process. Subjects will not be monetarily compensated for their involvement. Participation in the investigation is voluntary and subjects may withdraw at any time. Subjects will be assigned a unique subject identification number that will be used with all data collected, including salivary samples. In keeping with the Health Insurance Portability and Accountability Protection Act, the investigators will make every effort to maintain the confidentiality of protected health information we obtain from study subjects. Study informed consent documents, data collection tools, and any patient information will be stored in a locked file cabinet in a locked office on the Same Day Surgery Unit at Naval Hospital Camp Pendleton. Furthermore, electronic data files will be password protected and restricted to the principal investigator. A master subject list will be maintained by LCDR Bopp in a separate locked cabinet from the informed consents in a locked office on the Same Day Surgery Unit at Naval Hospital Camp Pendleton.

Risks: This study is considered to be of minimal risk to subjects. No experimental procedures are being performed and all data collected will be de-identified. The results of this study will in no way be used to modify the anesthetic plan or deviate from the standard of care. All data and saliva samples will be de-identified and only investigators associated with this study will have access to the data. Further, the California Bill of Rights will be strictly followed as outlined in the subject consent:

California Experimental Subject's Bill of Rights:

(a) Be informed of the nature and purpose of the experiment.

(b) Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

(c) Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

(d) Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

(e) Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

(f) Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

(g) Be given an opportunity to ask any questions concerning the experiment or the procedures involved.

(h) Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

(i) Be given a copy of the signed and dated written consent form as provided for by Section 24173 or 24178.

(j) Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

Inclusion of Women and Children

Women and minorities are included in this investigation.

Inclusion of Children: N/A

Vertebrate Animals: N/A

Consortium/Contractual Arrangements

A Collaborative Research and Development Agreement between the University of San Diego and the Naval Medical Center San Diego is currently being drafted. No fees are associated with the drafting of this document.

Dissemination Plan

The University of San Diego's Doctor of Philosophy in Nursing program requires the Principal Investigator of this proposal to complete, at minimum, one manuscript resulting from this study prior to being eligible for graduation. A publication will be prepared upon completion of the data analysis with target journals to be determined by the team associated with this grant proposal (e.g., American Association of Nurse Anesthetists (AANA) Journal or Journal of PeriAnesthesia Nursing). Also, any publication resulting from this proposal will be submitted to a Public Affairs Officer prior to submission to a peer-reviewed journal. Additionally, a podium or poster presentation will be presented at a professional meeting or symposium (e.g., AANA's Annual Meeting).

References

1. Demirtas Y, Ayhan S, Tulmac M, et al. Hemodynamic effects of perioperative stressor events during rhinoplasty. *Plast Reconstr Surg.* 2005;115:620-626. PMCID 15692374

2. Hong JY, Jee YS, Luthardt FW. Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. *J Clin Anesth.* 2005;17:549-553. PMCID 16297756

3. McIntosh S, Adams J. Anxiety and quality of recovery in day surgery: A questionnaire study using Hospital Anxiety and Depression Scale and Quality of Recovery Score. *Int J Nurs Pract.* 2011;17:85-92. PMCID 21251158

4. Carr E, Brockbank K, Allen S, Strike P. Patterns and frequency of anxiety in women undergoing gynaecological surgery. *J Clin Nurs.* 2006;15:341-352. PMCID 16466484

5. Nayback AM. Posttraumatic stress: A concept analysis. *Arch Psychiatr Nurs.* 2009;23:210-219. PMCID 19446776

6. McGhee LL, Maani CV, Garza TH, DeSocio PA, Gaylord KM, Black IH. The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. *J Trauma.* 2009;66:S186-190. PMCID 19359964

7. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med.* 2004;351:13-22. PMCID 15229303

8. McGuire JM, Burkard, J. The Incidence of and risk factor for emergence delirium in U.S. military combat veterans. *University of San Diego.* 2011.

9. McEwen BS, Wingfield JC. What is in a name? Integrating homeostasis, allostasis and stress. *Horm Behav.* 2010;57:105-111. PMCID 19786032

10. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol.* 2009;5:374-381. PMCID 19488073

11. Everly GS, Lating JM. *A Clinical Guide to the Treatment of the Human Stress Response*. 2nd ed. New York, NY: Kluwer Academic/Plenum Publishers; 2002.

12. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol.* 2005;67:259-284. PMCID 15709959

13. Chrousos GP. Organization and Integration of the Endocrine System. *Sleep Med Clin.* 2007;2:125-145. PMCID 18516219

14. Papadimitriou A, Priftis KN. Regulation of the hypothalamic-pituitary-adrenal axis. *Neuroimmunomodulation.* 2009;16:265-271. PMCID 19571587

15. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol.* 2008;583:174-185. PMCID 18282566

16. Schneiderman N, Ironson G, Siegel SD. Stress and health: Psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol.* 2005;1:607-628. PMCID 17716101

17. Pego JM, Sousa JC, Almeida OF, Sousa N. Stress and the neuroendocrinology of anxiety disorders. *Curr Top Behav Neurosci.* 2010;2:97-117. PMCID 21309108

18. Bonfiglio JJ, Inda C, Refojo D, Holsboer F, Arzt E, Silberstein S. The corticotropin-releasing hormone network and the hypothalamic-pituitary-adrenal

axis: Molecular and cellular mechanisms involved. *Neuroendocrinology.* 2011;94:12-20. PMCID 21576930

19. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth.* 2000;85:109-117. PMCID 10927999

20. Goldstein DS. Adrenal responses to stress. *Cell Mol Neurobiol.* 2010;30:1433-1440. PMCID 21061156

21. Page GG. Surgery-induced immunosuppression and postoperative pain management. *AACN Clin Issues.* 2005;16:302-309. PMCID 16082233

22. Pritchard MJ. Managing anxiety in the elective surgical patient. *Br J Nurs.* 2009;18:416-419. PMCID 19373185

23. Grieve RJ. Day surgery preoperative anxiety reduction and coping strategies. *Br J Nurs.* 2002;11:670-678. PMCID 12048453

24. Wagner D, Byrne M, Kolcaba K. Effects of comfort warming on preoperative patients. *AORN J.* 2006;84:427-448. PMCID 17004666

25. Mitchell M. Influence of gender and anaesthesia type on day surgery anxiety. *J Adv Nurs.* 2012;68:1014-1025. PMCID 21806671

26. Sun GC, Hsu MC, Chia YY, Chen PY, Shaw FZ. Effects of age and gender on intravenous midazolam premedication: A randomized double-blind study. *Br J Anaesth.* 2008;101:632-639. PMCID 18772216

27. Spence D, McBeain J, Guzman J, Roucek E, Maye J. A pilot investigation evaluating physiological and psychological stress measurements in patients presenting for elective surgical procedures *Journal of Healthcare, Science and the Humanities.* 2011;1:39-53.

28. Wong EM, Chan SW, Chair SY. Effectiveness of an educational intervention on levels of pain, anxiety and self-efficacy for patients with musculoskeletal trauma. *J Adv Nurs.* 2010;66:1120-1131. PMCID 20337801

29. Kindler CH, Harms C, Amsler F, Ihde-Scholl T, Scheidegger D. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesth Analg.* 2000;90:706-712. PMCID 10702461

30. Fitzgerald BM, Elder J. Will a 1-page informational handout decrease patients' most common fears of anesthesia and surgery? *J Surg Educ.* 2008;65:359-363. PMCID 18809166

31. Costa MJ. The lived perioperative experience of ambulatory surgery patients. *AORN J.* 2001;74:874-881. PMCID 11795060

32. Gras S, Servin F, Bedairia E, et al. The effect of preoperative heart rate and anxiety on the propofol dose required for loss of consciousness. *Anesth Analg.* 2010;110:89-93. PMCID 19910628

33. Morley AP, Papageorgiou CH, Marinaki AM, Cooper DJ, Lewis CM. The effect of pre-operative anxiety on induction of anaesthesia with propofol. *Anaesthesia.* 2008;63:467-473. PMCID 18412643

34. Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for postoperative anxiety in adults. *Anaesthesia.* 2001;56:720-728. PMCID 11493233

35. Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. *J Psychosom Res.* 2000;49:417-422. PMCID 11182434

36. Van den Bosch JE, Moons KG, Bonsel GJ, Kalkman CJ. Does measurement of preoperative anxiety have added value for predicting postoperative nausea and vomiting? *Anesth Analg.* 2005;100:1525-1532. PMCID 15845719

37. Phillips CJ, Leardmann CA, Gumbs GR, Smith B. Risk factors for posttraumatic stress disorder among deployed US male marines. *BMC Psychiatry.* 2010;10:52. PMCID 20579379

38. Liberzon I, Abelson JL, Flagel SB, Raz J, Young EA. Neuroendocrine and psychophysiologic responses in PTSD: A symptom provocation study. *Neuropsychopharmacology.* 1999;21:40-50. PMCID 10379518

39. Wilk JE, Bliese PD, Kim PY, Thomas JL, McGurk D, Hoge CW. Relationship of combat experiences to alcohol misuse among U.S. soldiers returning from the Iraq war. *Drug Alcohol Depend.* 2010;108:115-121. PMCID 20060237

40. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med.* 2008;358:453-463. PMCID 18234750

41. McDonald SD, Calhoun PS. The diagnostic accuracy of the PTSD checklist: A critical review. *Clin Psychol Rev.* 2010;30:976-987. PMCID 20705376

42. Bliese PD, Wright KM, Adler AB, Cabrera O, Castro CA, Hoge CW. Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. *J Consult Clin Psychol.* 2008;76:272-281. PMCID 18377123

43. Weathers FW, Litz, B.T., Herman, D.S., Huska, J.A., & Keane, T.M. The PTSD checklist (PCL): Reliability, validity, and diagnostic utility. *Annual Meeting of International Society for Traumatic Stress Studies.* 1993; San Antonio, TX.

44. Keen SM, Kutter CJ, Niles BL, Krinsley KE. Psychometric properties of PTSD checklist in sample of male veterans. *J Rehabil Res Dev.* 2008;45:465-474. PMCID 18629754

45. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics.* 2009;50:613-621. PMCID 19996233

46. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med.* 2010;8:348-353. PMCID 20644190

47. Corson K, Gerrity MS, Dobscha SK. Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item. *Am J Manag Care.* 2004;10:839-845. PMCID 15609737

48. Lubin B, Zuckerman M. *Manual for the multiple affect adjective checklist-revised.* San Diego, CA: EdITS; 1999.

49. Williamson A, Hoggart B. Pain: A review of three commonly used pain rating scales. *J Clin Nurs.* 2005;14:798-804. PMCID 16000093

50. Lara-Munoz C, De Leon SP, Feinstein AR, Puente A, Wells CK. Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli. *Arch Med Res.* 2004;35:43-48. PMCID 15036799

51. Boker A, Brownell L, Donen N. The Amsterdam preoperative anxiety and information scale provides a simple and reliable measure of preoperative anxiety. *Can J Anaesth.* 2002;49:792-798. PMCID 12374706

52. Chatterton RT, Jr., Vogelsong KM, Lu YC, Ellman AB, Hudgens GA. Salivary alpha-amylase as a measure of endogenous adrenergic activity. *Clin Physiol.* 1996;16:433-448. PMCID 8842578

53. Kang Y. Psychological stress-induced changes in salivary alpha-amylase and adrenergic activity. *Nurs Health Sci.* 2010;12:477-484. PMCID 21210927

54. Gonzales EA, Ledesma RJ, McAllister DJ, Perry SM, Dyer CA, Maye JP. Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: A randomized, single-blind study. *AANA J.* 2010;78:181-188. PMCID 20572403

55. Nater UM, Rohleder N, Gaab J, et al. Human salivary alpha-amylase reactivity in a psychosocial stress paradigm. *Int J Psychophysiol.* 2005;55:333-342. PMCID 15708646

56. Rohleder N, Wolf JM, Maldonado EF, Kirschbaum C. The psychosocial stress-induced increase in salivary alpha-amylase is independent of saliva flow rate. *Psychophysiology.* 2006;43:645-652. PMCID 17076822

57. Rohleder N, Nater UM. Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology.* 2009;34:469-485. PMCID 19155141

58. Bosch JA, Veerman EC, de Geus EJ, Proctor GB. Alpha-amylase as a reliable and convenient measure of sympathetic activity: Don't start salivating just yet! *Psychoneuroendocrinology.* 2011;36:449-453. PMCID 21295411

59. Humphrey SP, Williamson RT. A review of saliva: Normal composition, flow, and function. *J Prosthet Dent.* 2001;85:162-169. PMCID 11208206

60. Takai N, Yamaguchi M, Aragaki T, Eto K, Uchihashi K, Nishikawa Y. Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults. *Arch Oral Biol.* 2004;49:963-968. PMCID 15485637

61. Nater UM, La Marca R, Florin L, et al. Stress-induced changes in human salivary alpha-amylase activity: Associations with adrenergic activity. *Psychoneuroendocrinology.* 2006;31:49-58. PMCID 16002223

62. Klein LC, Bennett JM, Whetzel CA, Granger DA, Ritter FE. Caffeine and stress alter salivary alpha-amylase activity in young men. *Hum Psychopharmacol.* 2010;25:359-367. PMCID 20589924

63. Rohleder N, Nater UM, Wolf JM, Ehlert U, Kirschbaum C. Psychosocial stress-induced activation of salivary alpha-amylase: An indicator of sympathetic activity? *Ann N Y Acad Sci.* 2004;1032:258-263. PMCID 15677423

64. Salimetrics, LLC. Saliva Collection and Handling Advice. 2nd ed. State College, PA; 2011.

65. Salimetrics, LLC. Salivary alpha-amylase assay kit. State College, PA; 2011.

66. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone

concentration versus time-dependent change. *Psychoneuroendocrinology.* 2003;28:916-931. PMCID 12892658

67. Fekedulegn DB, Andrew ME, Burchfiel CM, et al. Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosom Med.* 2007;69:651-659. PMCID 17766693

68. Polit DF, Beck CT. *Nursing Research: Generating and Assessing Evidence for Nursing Practice*. 9th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

Chapter 4: MANUSCRIPTS

Manuscript III

UNIVERSITY OF SAN DIEGO

Hahn School of Nursing and Health Science

Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?

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Abstract

Since September 11, 2001, the United States has been engaged in large-scale combat operations exposing numerous military service members to stressful, traumatic, and threatening environments. As a result, many of these individuals have experienced significant psychological problems, such as anxiety, depression, and posttraumatic stress disorder (PTSD), as well as physiological alterations, such as cardiovascular changes and neuroendocrine disturbances. The preoperative experience may be perceived as stressful, often increasing in magnitude as the patient progresses through the preoperative period. Military anesthesia providers frequently provide anesthetic care to military members with a history of combat exposure. Anecdotally, it is not uncommon for this patient population to require a more "heavy-handed" anesthetic regimen, potentially resulting in increased side effects or prolonged recovery.

An enormous gap exists in knowledge related to the preoperative stress response, especially military members with a history of combat exposure. Therefore, the purpose of this study was to determine predictive relationships between the number of combat experiences and the preoperative stress response in U.S. military personnel on the day of surgery. This prospective, descriptive study was conducted at Naval Hospital Camp Pendleton, enrolling active duty men and women undergoing elective surgery. One to 14 days prior to surgery, anxiety, depression, and PTSD symptoms were assessed. In addition, participants reporting a prior military deployment having received combat-related pay completed a U.S. Army-developed combat exposure scale. On the day of surgery, the preoperative psychological and physiological stress response was measured using the Visual Analogue Scale for Stress, Multiple Affect Adjective Checklist-Revised,

and salivary alpha-amylase. This may be the first investigation to determine predictive relationships between varying degrees of combat exposure and the preoperative stress response in military personnel on the day of surgery.

Keywords: preoperative stress, stress response, military, anesthesia

Introduction

More than 2.5 million U.S. military service personnel have participated in combat operations throughout Afghanistan and Iraq since September 11, 2001, resulting in over 51,000 American troops physically wounded and more than 118,000 clinically diagnosed with PTSD (Congressional Research Service, 2014; Veterans for Common Sense, 2012). The fierce and harsh conditions experienced by military personnel on the battlefield have led to numerous service members experiencing significant psychological problems, such as fear, anxiety, depression, irritability, or being easily startled when confronted by minor or nonthreatening stressors (Liberzon, Abelson, Flagel, Raz, & Young, 1999). In addition, many combat veterans have suffered physiological alterations, such as cardiovascular and metabolic disturbances (Hoge et al., 2008; Nayback, 2009).

The preoperative period is a particularly unique environment and can be perceived as extremely stressful, having the potential to increase psychological symptoms and magnify physiological alterations. Current research suggests patients presenting to the preoperative environment with higher degrees of stress experience significantly more adverse perioperative outcomes, such as increased heart rates, greater anesthetic requirements, postoperative anxiety and pain (Caumo et al., 2001; Carr, Brockbank, Allen, & Strike, 2006; Demirtas et al., 2005; Hong, Jee, & Luthardt, 2005; McIntosh & Adams, 2011). Anecdotal reports by military anesthesia providers characterize combat

veterans as appearing more agitated and anxious preoperatively, often times requiring greater amounts of anesthetic medications to ensure an adequate depth of anesthesia is achieved. In addition, it's not uncommon for these patients to emerge from anesthesia extremely agitated and difficult to manage postoperatively.

To date, only one study has researched perioperative phenomena in a combat veteran population, which found individuals having fired a weapon in combat preoperative trait and state anxiety significantly predicted postoperative emergence delirium in combat veterans (McGuire, 2012). However, no study to date has investigated the preoperative psychological and physiological stress response in U.S. military service members with varying degrees of combat exposure.

McGuire (2012) conducted an observational, descriptive study to determine the incidence of emergence delirium following surgery in military members having fired a weapon in combat. Measures of anxiety, depression, and PTSD symptomatology were taken 1-14 days prior to the day of surgery and emergence delirium following surgery was assessed using the Pediatric Anesthesia Emergence Delirium tool on the day of surgery. This study found state and trait measures of anxiety were significantly associated with an increase in emergence delirium when controlling for depression and PTSD symptomatology ($F(2,127)=14.738$, $p<.001$, $R^2=.188$) (McGuire, 2012). Despite the significance of this study, no study to date has researched the preoperative psychological or physiological stress response in military personnel with varying degrees of combat exposure on the day of surgery. Therefore, this proposed study would be the first investigation to research predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health morbidity (i.e., anxiety, depression, and PTSD).

Purpose

Given the paucity of research demonstrated in the review above, an enormous gap exists in knowledge related to the preoperative stress response in active duty military members with varying degrees of combat exposure. More specifically, no study to date has investigated predictive relationships between various degrees of combat exposure and the preoperative stress response in active duty personnel on the day of surgery. As such, this study scientifically explored the preoperative stress response in U.S. military personnel with varying degrees of combat experience, in addition to contributing to the body of knowledge supporting future interventional studies designed to mitigate perioperative stress and improve patient outcomes. Therefore, the purpose of this study was to determine predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health disorders (i.e., anxiety, depression, and PTSD). More specifically, this study was designed to: a) determine predictive relationships between combat experiences and the preoperative *psychological* stress response in U.S. military personnel, and b) determine predictive relationships between combat experiences and the preoperative *physiological* stress response in U.S. military personnel. Study hypotheses were: a) a greater number of combat experiences will be predictive of *more negative emotions* preoperatively as measured by the Multiple Affect Adjective Checklist-Revised (MAACL-R) on the day of surgery, b) a greater number of combat experiences will be predictive of *higher degrees of stress* preoperatively as measured by the visual analogue scale (VAS) for stress, and c) a greater

number of combat experiences will be predictive of *higher salivary alpha-amylase* (SAA) preoperatively on the day of surgery.

Methods

Study Design

This was a prospective, descriptive study was designed to explore the predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military with out and without a history of combat exposure.

Study site and subjects. A sample of 120 healthy active duty men and women scheduled for elective surgery at a military hospital in southern California were invited to participate in this study. Inclusion criteria for this study included: (a) active duty military men or women; (b) ages 18-45; (c) ASA category I or II; (d) scheduled for elective, non-cancer related surgery requiring anesthesia services (e.g., general anesthesia, monitored anesthesia care, regional anesthesia); (e) able to read and understand the consent form; and (f) consent to participate in the study. The exclusion criteria included: (a) medications known to interfere with salivary alpha-amylase (e.g., beta-blockers); (b) metabolic disorders (e.g., diabetes, thyroid disorders); and (3) autoimmune disorders (e.g., Sjogren's syndrome).

Patients arriving to the Preoperative Teaching Unit (PTU) for preoperative screening days prior to surgery were approached and provided information about the study. If subjects agreed to participate in the study, then informed consent was obtained. Following enrollment, all study subjects were asked to complete demographic and

deployment history questionnaires, Patient Health Questionnaire-4 (PHQ-4), and Posttraumatic Stress Disorder Checklist-Military (PCL-M). In addition, subjects reporting a prior deployment where they had received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits were asked to complete the Walter Reed Army Institute of Research Combat Exposure Scale (WRAIR-CES).

Following admission to the Same Day Surgery Unit (SDSU) on the day of surgery, subjects were asked to submit a saliva sample to obtain a salivary alpha-amylase (SAA) sample by placing an oral swab between the right upper gum and cheek area next to the second upper molar for 3 minutes. At the same time, patients were asked to complete the visual analogue scale for pain (VAS-P), VAS-stress, and the Multiple Affect Adjective Checklist-Revised (MAACL-R). After arriving to the preoperative holding area, subjects were placed on a gurney and met by an a study investigator. Subjects were then asked to submit a second SAA sample while completing the VAS-S and MAACL-R. The anesthesia provider and operating room nurse then interviewed the subject and established intravenous access. Final data collection occurred immediately prior to subjects entering the operating room, but prior to administration of any anxiolytics or opioids. Data collected at this particular time included a third SAA sample, VAS-S, and MAACL-R. All saliva soaked swabs were placed in a cooler until transport to the hospital's laboratory department for storage at -20° C as recommended by Salimetrics, LLC.

Study measures. A brief self-administered questionnaire was given to subjects to obtain demographics information which included: age, race, ethnicity, education, marital status, branch of service, occupation, length of service, deployment history, current

medications, and medical/surgical history. The investigator created the demographic questionnaire, thus reliability and validity was not established for this instrument.

Patient health questionnaire-4. This is a self-report measure providing a rapid, yet reliable assessment of likelihood for depression and anxiety-related disorders (Kroenke, Spitzer, Williams, & Lowe, 2009). The PHQ-4 consists of depression (PHQ-2) and generalized anxiety (GAD-2) subscales, both of which contain the two core criteria for depressive and generalized anxiety disorders outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; Arroll et al., 2010; Kroenke et al., 2009). Respondents are asked to indicate how "bothered" they are by each question using a 4-item Likert-type scale to denote their level of agreement (0 = not at all to 3 = nearly every day). The researcher has the option to report a composite score indicating overall symptom burden; i.e., combined scoring of all four questions (range 0-12), and/or score each subscale separately; i.e., providing depression and anxiety scores individually (range 0-6). Internal reliability of the PHQ-4 and its subscales are high (all > 0.81), and construct validity of both subscales is reportedly excellent (Kroenke et al., 2009). Recommendations for potential caseness for either a depressive or anxiety disorder for each subscale is a cutoff score of three or greater, resulting in a sensitivity and specificity of 93% and 89% for the PHQ-2 and 86% and 83% for the GAD-2 (Corson, Gerrity, & Dobscha, 2004; Kroenke et al., 2009). This instrument is available free of charge from Pfizer, Inc.

Posttraumatic stress disorder checklist–military. PTSD symptomatology was assessed using the PCL-M, a commonly used instrument assessing PTSD symptomatology in the military population (McDonald & Calhoun, 2010). This self-

report measure is comprised of 17 items as outlined in the DSM-IV, which asks respondents to relate their military experiences to "how bothered" they are by symptoms listed on the PCL-M over the previous month (Bliese et al., 2008; Weathers et al., 1993). Scoring consists of a rating scale of 1 = not at all to 5 = extremely, with a possible range of 17-85 (Weathers et al., 1993). The most common method for scoring the PCL-M, particularly in military-based research, is the use of a higher cutoff value of 50 or greater, thus maximizing the specificity for combat-related PTSD symptomatology (Bliese et al., 2008; Hoge et al., 2004). Additionally, the PCL-M strongly correlates with the Clinician-Administered PTSD Scale, currently considered the gold standard for PTSD diagnosis, ($r = 0.79$, $n = 114$, $p < 0.001$; (Keen, Kutter, Niles, & Krinsley, 2008). Permission to use this instrument has been granted by the National Center for PTSD.

Walter reed army institute of research combat exposure scale. The WRAIR-CES consists of 27 dichotomized questions measuring an individual's exposure to combat-related events, particularly personnel participating in OEF/OIF operations. Unlike other combat exposure scales, this instrument evaluates various dimensions of combat exposure, such as combat fighting, threat to oneself, injury, or atrocity. Hoge et al. (2004) used the WRAIR-CES to assess combat experiences in U.S. infantrymen deployed to Iraq and Afghanistan and found greater degrees of combat exposure were significantly correlated with higher incidences of PTSD. The WRAIR-CES has become the U.S. Army's primary instrument for measuring a service member's exposure to combat, particularly combat experienced in OEF/OIF (Hoge et al., 2004; Wilk et al., 2010). In addition, the WRAIR-CES has been shown to be a reliable measure of combat exposure with a reported Cronbach's alpha of 0.85 (Hoge, McGurk, et al., 2008). For the purposes

of this study, combat exposure was defined as any individual receiving imminent danger pay, hardship duty pay, or combat zone tax exclusion during a military deployment (Millennium Cohort Study, 2012). Combat exposure was measured using the 27-item WRAIR-CES with scoring ranging from 0 to 27 (Wilk et al., 2010). This instrument is available free of charge.

Visual analogue scale. The VAS has been commonly used to measure various phenomena, such as preoperative pain, stress, or anxiety (Gonzales et al., 2010; Kang, 2010; Lara-Munoz, De Leon, Feinstein, Puente, & Wells, 2004; Spence, McBeain, Guzman, Roucek, & Maye, 2011). The VAS commonly consists of a 100 mm horizontal line with word descriptors at the ends of the continuum, such as "no stress" and "very high stress." Subjects are asked to make a mark along this continuum that best describes their subjective feeling or perception about a particular construct at a particular moment in time, such as "how stressed do you feel right now" (Williamson & Hoggart, 2005). Literature has consistently demonstrated the VAS to have a very high reliability ($r > .90$) and excellent sensitivity across a variety of settings and populations (Boker, Brownell, & Donen, 2002; Lara-Munoz et al., 2004; Williamson & Hoggart, 2005). For this study, the VAS was used to measure subjective pain and stress on the day of surgery.

Multiple affect adjective checklist-revised. MAACL-R is a versatile psychological instrument comprised of several affective domains found to be particularly useful in measuring a variety of mental health disorders, as well as basic research on personality and emotion. The MAACL-R consists of two positive affect subscales (positive affect and sensation seeking) and three negative affect subscales (anxiety, depression, and hostility). In addition, an overall dysphoria (sum of negative affect

subscales) or well-being (sum of positive affect subscales) score may be calculated. Scoring is ultimately derived from a one-page list of 132-adjectives from which patients select words that most accurately describe how they currently feel (state) or how they generally feel (trait). The MAACL-R's state version has a high internal (alpha) reliability, low test-retest reliability, and has been found to be suitable for investigations that hypothesize changes in affect relative to stressful experiences (Lubin & Zuckerman, 1999).

For the purposes of this study, the dysphoria composite score (i.e., sum of the anxiety, depression, and hostility scores) was used to measure the negative emotions experienced throughout the preoperative period on the day of surgery. The MAACL-R was purchased through EdITS, San Diego, CA (Lubin & Zuckerman, 1999).

Salivary alpha-amylase. Amylase is a digestive enzyme that hydrolyzes the alpha-1,4 bonds of large polysaccharides (e.g., starch and glycogen), yielding simpler carbohydrates such as glucose and maltose (Kang, 2010; Nater et al., 2005). SAA is one of many proteins synthesized and secreted by acinar cells found in major and minor salivary glands, although SAA appears to be predominantly produced by the parotid glands (Rohleder & Nater, 2009; Rohleder, Wolf, Maldonado, & Kirschbaum, 2006). Production and secretion of saliva is autonomically regulated, such that sympathetically-activated salivary glands produce more protein-based saliva (e.g., SAA); whereas, parasympathetically-activated salivary glands produce more water-based saliva (Bosch, Veerman, de Geus, & Proctor, 2011; Humphrey & Williamson, 2001; Rohleder & Nater, 2009). During periods of psychological or physiological stress, such as extremes in temperature, exercise, or academic testing, increased sympathetic activity results in the

secretion of SAA, and for this reason it has become a favorable surrogate for sympathetic nervous system activity (Klein, Bennett, Whetzel, Granger, & Ritter, 2010; Nater et al., 2006; Nater et al., 2005; Takai et al., 2004). Likewise, the production and secretion of SAA following a stressor is almost instantaneous, particularly suitable in settings with multiple stressors like the preoperative environment (Takai et al., 2004). Unlike serum biomarkers requiring venipuncture, SAA sampling is a noninvasive procedure using an absorbent oral swab; thus, less likely to contribute to an already stressful experience or negatively influence an individual's desire to participate in a study out of fear of needles or pain (Kang, 2010).

One recent investigation measured positive and negative preoperative affective emotions in a general surgical population and found positive affect scores decreased and correlated significantly with a rise in SAA, suggesting patients experiencing more negative emotions may exhibit greater degrees of physiological stress (Spence et al., 2011). In addition, SAA has been shown to have moderate to strong correlations (r = 0.53-0.81) with other well-established biomarkers (e.g., heart rate, blood pressure norepinephrine; Chatterton, Vogelsong, Lu, Ellman, & Hudgens, 1996; Kang, 2010). Taken together, this supports the use of SAA as a valid and reliable surrogate for sympathetic nervous system activity and responsiveness to stressors encountered in the preoperative setting.

Salimetrics oral swab. Saliva samples were collected using the Salimetrics Oral Swab, which is made of a non-toxic, inert synthetic polymer shaped into a 30 x 10 mm cylinder. Oral swabs have been used extensively in research to evaluate SAA (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004). Subjects were directed to place the swab

between the upper cheek and gum next to the second molar where the duct of the parotid gland is located for three minutes (Salimetrics, 2011). Following salivary sampling, the oral swab was placed in a Salimetric Swab Storage Tube (Figure 3), secured, and labeled with the subject identification number, date, and time. Samples were placed in a cooler until transport to NHCP's laboratory where they were maintained in a freezer at a temperature of -20° C until data collection was completed. All supplies (i.e., oral swabs and storage tubes) were obtained from Salimetrics, LLC (State College, PA).

Sample size. No study known to this author has utilized the proposed measures and methodology prior to conducting this study. Accordingly, a sample calculation was performed using a moderate effect size ($R^2 = .13$) with a power of .80 and $\alpha = .05$ for 10 predictor variables. As a result, a sample of 120 subjects was needed to detect a population R^2 of .13 with 10 predictors with a 5% chance of a Type I error and a 20% chance of a Type II error (Polit & Beck, 2012).

Statistical methods. The Statistical Package for the Social Sciences (SPSS version 21.0) was used to analyze data. Descriptive statistics were conducted to summarize the demographics and examine measures of central tendency. To explore relationships between study groups (i.e., combat exposure group (CE) vs. no combat exposure (NCE) group), categorical variables were analyzed using a Fisher's Exact Test, Likelihood Ratio, and Pearson's chi-square where appropriate, and for continuous variables independent sample *t* tests were conducted.

Outcome variables used to measure negative emotions on the day of surgery were obtained using MAACL-R dysphoria values. The MAACL-R was scored and returned to the study investigator by EdITS, and then raw scores were converted to t-scores using a

mean score of 50 with a standard deviation of 10 (Lubin & Zuckerman, 1999). Two outcome variables using MAACL-R dysphoria t-scores was computed: MAACL-R mean dysphoria value (i.e., overall mean value computed using all three time points) and MAACL-R peak dysphoria value (i.e., subject's highest dysphoria score among the three time points). To explore relationships between MAACL-R mean dysphoria values and predictor variables, a standard multiple regression was conducted; and to determine the best predictor variable of the MAACL-R peak dysphoria value, a backward multiple regression was conducted.

Subjective stress on the day of surgery was measured using the VAS-stress and two outcomes variables for hypothesis testing were computed: VAS-stress mean value (i.e., overall mean computed using all three time points), and VAS-stress peak value (i.e., subject's highest dysphoria score among the three time points). To explore relationships between VAS-stress mean values and predictor variables, a standard multiple regression was conducted; and to determine the best predictor variable of the VAS-stress peak value, a backward multiple regression was conducted.

The physiological stress response on the day of surgery was assessed using SAA. Following SAA assay for alpha-amylase by Salimetrics, LLC, logarithmic transformations were completed to correct for inherently skewed data. For hypothesis testing, SAA area under the curve with respect to ground (SAA AUC_G), SAA mean increase values, and SAA peak values were calculated (see Table 4.2). To explore relationships between SAA AUC_G and SAA mean increase values, standard multiple regressions were conducted; and to determine the best predictor variable of SAA peak values, a backward multiple regression was conducted.

To analyze changes over time for MAACL-R dysphoria, VAS-stress, and SAA values, repeated measures ANOVA or Friedman's Test were used where appropriate. Lastly, all analyses with a p value of less than .05 were considered statistically significant.

Results

Subject participation included two days of data collection to examine the preoperative psychological and physiological stress response on the day of surgery. Baseline demographics, military background, and trait measures of anxiety, depression, and PTSD were collected on the day of enrollment, typically occurring 1 to 14 days prior to surgery. Study subjects were either classified into the combat exposure (CE) group or no combat exposure (NCE) group based upon whether the subject reported any prior military deployment having received "special combat-related pay;" i.e., subjects having received special combat-related pay were categorized as CE. Special pay also served as the trigger for CE subjects to complete the WRAIR-CES. On the day of surgery, psychological and physiological measures of stress were collected at three time points (TP): (a) Same Day Surgical Unit (TP-1), (b) Preoperative Holding Area (TP-2), and (c) immediately prior to OR entry (TP-3).

Sample. A total of 120 active duty military personnel scheduled for elective, non-cancer related surgery at Naval Hospital Camp Pendleton volunteered to participate in the study. Following informed consent, 120 subjects completed descriptive and psychometric measures on the day of enrollment; however, 119 subjects participated in data collection on the day of surgery. The subject who didn't participate in data collection on the day of

surgery voluntarily withdrew stating, "I really don't want to be in the study." As a result, this patient's data was not included in the data analysis.

Other missing data was due to study measures not being obtained at various time points on the day of surgery, as well as some SAA samples lacking adequate amounts of saliva required for assay. Specifically, one subject was escorted to the PHA prior to meeting with the study investigator while still on the SDSU, resulting in TP-1 measures not being collected. Two additional subjects were interviewed by operating team staff before meeting with the study investigator, ultimately resulting in TP-2 measures being missed on both subjects. Also, Salimetrics, LLC reported a total of eight saliva samples were not assayed because the sample quantity was not inadequate. Lastly, no adverse events occurred throughout the study period.

Baseline demographics. Study subjects were predominately young, Caucasian men serving in the U.S. Marine Corps with an infantry-related background. Slightly more than half (54.6%) of the subjects were either married or in a committed relationship and all had an education level at or greater than a high school diploma. Participants had on average seven of years of military service with 64% of subjects reporting a deployment to an area with combat-related operations (i.e., receiving special combat-related pay). The CE group (n=76) predominately reported deployments to either Afghanistan or Iraq, and had on average seven combat-related experiences when measured using the WRAIR-CES. The NCE group (n=43) included one subject reporting a military deployment; however, this subject denied receiving any special combat-related pay. All study subjects were relatively healthy with no significant medical history, and none were taking medications known to confound SAA (see Table 4.1).

Group comparisons for age and years of military service were conducted using independent sample t-tests and indicated the CE group to be approximately six years older than the NCE group ((CE (M = 29.33, SD = 6.54 years) versus (NCE (M = 23.65, SD = 3.41 years); t (117) = -6.23, $p < .001$)), with an average of six more years of military service, (CE (M = 9.05, SD = 6.21 years) versus NCE (M = 3.33, SD = 3.32 years; t (117) = -6.56, $p < .001$). Group comparisons were conducted for each categorical variable using nonparametric statistics for the following variables: branch of service, military job, ethnicity, highest level of education, marital status, tobacco use, type of surgery, mental health disorders, ASA status, and anesthesia plan for surgery. Of all categorical variables measured on the day of enrollment, only marital status demonstrated a significant statistical difference between CE and NCE groups; i.e., more subjects in the CE group were married or in a committed relationship, χ^2 (3, N = 119) = 20.65, $p < .001$ (see Table 4.1).

Day of Enrollment

Psychological stress measures. A subjective measure of day-to-day stress using the VAS-stress was assessed in both study groups with a slightly lower mean value reported in the NCE group, although not statistically different compared to the CE group, CE (M = 48.87, SD = 18.16) versus NCE (M =47.49, SD = 19.18), t (117) = -.39, p = .697. Trait anxiety and trait depression were measured on the day of enrollment using the PHQ-4 questionnaire. The PHQ-4 mean values displayed lower symptom burden than was expected and was not statistically different between the two study groups, CE (M = 2.78, SD = 2.71) versus NCE (M = 2.65, SD = 2.81), t (117) = -.24, p = .812. CE and NCE group mean values on the PHQ-4's two subscales (GAD-2 and PHQ-2) were also

compared for group differences (see Figure 4.1), but no significant differences were identified, t (117) = -.11, p = .910; t (117) = -.23, p = .823, respectfully (see Table 4.2).

Cutoff values for each subscale of the PHQ-4 were also used to dichotomize the two scales into "high trait anxiety" (i.e., GAD-2 score of 3 or greater) and "high trait depression" (i.e., PHQ-2 score of 3 or greater). This resulted in approximately 16% (n = 12) of the CE group and 25.6% (n = 11) of the NCE group exhibiting high trait anxiety, and approximately 22% (n = 17) of the CE group and 26% (n = 12) of the NCE group reporting high trait depression. Group comparisons using a chi-square test for independence on both subscales indicated no significant associations between high trait anxiety, high trait depression, and study group assignment (χ^2 (1, N = 119) = 1.12, p = .290), χ^2 (1, N = 119) = 1.12, p = .650, respectively) (see Table 4.2).

An independent samples t-test comparing group PCL-M mean values indicated CE subjects reported significantly more PTSD-related symptoms compared to the NCE group, M = 29.89, SD = 12.23 versus M = 24.91, SD = 9.73, t (117) = -2.293, $p < .05$, respectfully. A cutoff value of 50 or greater on the PCL-M was used to dichotomize this variable into high PTSD symptoms (PCL-M score of 50 or greater) or low PTSD symptoms (PCL-M of 49 or less). This assignment resulted in 8, or 11%, of CE subjects and 1 NCE individual being identified as exhibiting high PTSD symptomatology; however, there were no statistically significant difference between the two study groups, Fisher's exact test, p = .15 (see Table 4.2). Interestingly, of the study subjects with PCL-M scores 50 or greater (n=9), 44% had a prior diagnosis of PTSD, 33% had a prior diagnosis of depression, and over half the subjects had deployed four more or times to an environment conducting combat operations (e.g., Iraq, Afghanistan, etc.) (see Table 4.2).

Day of Surgery

Psychological measures of stress. The MAACL-R dysphoria values at each time point for the entire study sample (N=119) were below 44, indicating minimal emotional distress; although, it should be noted four subjects experienced moderate emotional distress (i.e., MAACL-R dysphoria t-score > 65). MAACL-R dysphoriavalues in the two study groups were higher at TP-2 than TP-1, although mean values in both groups decreased when reassessed at TP-3 (Figure 4.2). Independent samples t-tests comparing group MAACL-R dysphoria values at each time point were conducted; however, no statistically significant differences were identified. MAACL-R mean dysphoria values (CE (M = 43.38, SD = 5.80) and NCE (M = 42.22, SD = 5.74)) and dysphoria peak values (CE (M = 46.11, SD = 6.16), NCE (M = 46.40, SD = 7.43)) were very similar between groups, although not statistically significant, t (117) = -.144, p = .886 and t (117) = .209, p = .834, respectfully (see Table 4.2).

The VAS-stress mean values progressively increased in both groups as subjects progressed from TP-1 to TP-3, and the NCE group reported slightly more subjective stress; however, this did not result in statistical significance (see Table 3 and Figure 4.3). Although VAS-stress mean and peak values were greater in the NCE group, no significant differences were identified when conducting independent sample t tests (VAS-stress mean value: t (117) = .67, p = .510; VAS-stress peak value: t (117) = .87, p = .388) (see Table 4.2).

Physiological stress measures. The physiological stress response on the day of surgery was assessed using SAA. Following SAA assay for alpha-amylase by Salimetrics, LLC, logarithmic transformations were completed to correct for inherently

skewed data. For hypothesis testing, SAA area under the curve with respect to ground (SAA AUC_G), SAA mean increase values, and SAA peak values were calculated (see Table 4.2). It should be noted the "SAA mean increase value" label will be used from this point forward to represent the previously used "SAA AUC with respect to increase from baseline" (SAA AUC_{INC}) label, thus ensuring consistency with literature most relevant to the SAA variables used in this study. More importantly, no changes in the proposed calculations were made or altered relative to outcome variables.

Mean SAA values were slightly lower in the CE group across all three time points compared to the NCE group, although independent sample t tests displayed no significant differences between the groups (see Figure 4.4). SAA AUC_G was also slightly lower in the CE group (M = 2.13, SD = 1.28) when compared to the NCE group (M = 2.45, SD = 1.08); however, no significant differences were identified, t (106) = 1.33, p = .187. In addition, the SAA mean increase value was slightly higher in the CE group (M = 0.08, SD = 0.46) compared to the NCE group (M = 0.05, SD = 0.40); however, it too displayed no statistically significant difference between groups, t (106) = -.30, p = .766 (see Table 4.2).

Psychological Stress Response Analysis

MAACL-R mean dysphoria value analysis. It was hypothesized that a greater number of combat experiences would be predictive of more negative emotions (i.e., dysphoria). To explore this hypothesis, a visual inspection of the scatterplots for relations among the predictor variables (i.e., WRAIR-CES, PHQ-4, and PCL-M) and criterion variable (i.e., MAACL-R mean dysphoria values) were completed and indicated all relations was linear. Zero-order correlations were obtained to statistically examine these

linear relations. Correlations between the criterion variable and the predictor variables were all statistically significant and displayed small to moderate relationships (see Table 4.3).

Subsequently, a standard multiple regression analysis was conducted to determine the relationships between the independent variables PHQ-4, PCL-M, and WRAIR-CES and the outcome variable MAACL-R mean dysphoria values with all study subjects included in the regression model. Examination of collinearity statistics suggested collinearity was not a problem (all tolerance > .2). The regression results indicate the overall model significantly predicts MAACL-R mean dysphoria values, $R^2 = .161$, adjusted $R^2 = .139$, $F(3, 115) = 7.356$, $p < .05$. A summary of partial regression coefficients are presented in Table 4.4 and indicate the predictor variable PHQ-4 significantly contributed to the model, $B = .714$, $p < .05$, 95% CI = .212 – 1.216.

A subgroup analysis (i.e., CE group and NCE group) using separate standard multiple regression analyses was conducted to explore the relationships between PHQ-4, PCL-M, and WRAIR-CES and MAACL-R mean dysphoria values. Examination of collinearity statistics for both group suggested collinearity was not a problem (all tolerance > .2). In the NCE group, measures of trait anxiety, trait depression, and PTSD symptomatology did not result in a significant amount of variance in MAACL-R mean dysphoria values, $R^2 = .097$, adjusted $R^2 = .052$, $F(3, 40) = 2.141$, $p = .131$. In the CE group, predictor variables explained approximately 21% of the variance in MAACL-R mean dysphoria values, $R^2 = .213$, adjusted $R^2 = .180$, $F(3, 72) = 6.488$, $p < .001$. Additionally, the partial regression coefficient relating trait anxiety and depression (i.e.,

PHQ-4) to mean dysphoria was statistically significant, $B = .760$, $p < .05$, 95% CI = .044 – 1.475 (see Table 4.4).

An additional standard linear regression analysis was conducted on each group to examine the predictive value of higher degrees of anxiety, depression, PTSD (i.e., using cutoff values on PHQ-4 and PCL-M measures). Therefore, predictor variables PHQ-4 and PCL-M were removed and replaced with the dichotomized variables high trait anxiety, high trait depression, and high PTSD symptomatology. Correlations between the criterion variable and predictor variables were all statistically significant and displayed small to moderate relationships (see Table 4.3).

In NCE subjects, the model did not account for a significant amount of variance in MAACL-R mean dysphoria values, $R^2 = .166$, adjusted $R^2 = .102$, $F(3, 39) = 2.586$, $p = .067$. However, CE group regression results indicate this model significantly predicts mean dysphoria values, $R^2 = .230$, adjusted $R^2 = .187$, $F(4, 71) = 5.302$, $p < .001$. Summaries of regression coefficients are presented in Table 4.5 and indicate two (i.e., WRAIR-CES and PHQ-2 high) of four predictor variables significantly contributed to the model. Based on these results, prior combat exposure and higher degrees of depressive symptoms are better predictors of more negative emotions on the day of surgery.

To examine the unique contribution of combat exposure in the prediction of MAACL-R mean dysphoria values, a hierarchical multiple regression analysis was performed on the CE group. In step one, MAACL-R mean dysphoria was the dependent variable and high trait anxiety, high trait depression, and high PTSD symptomatology were entered as predictor variables, which accounted for 17.5% of the variance in MAACL-R mean dysphoria values, $R^2 = .175$, adjusted $R^2 = .141$, $F(3,72) = 5.102$, $p <$

.05. After entry of WRAIR-CES in step two, the total variance explained by the model was 23%, R^2 = .230, adjusted R^2 = .187, $F(4,71) = 5.302$, $p < .001$. On that account, combat exposure explains an additional 5.5% of the variance in MAACL-R mean dysphoria values after controlling for high trait anxiety, high trait depression, and high PTSD symptoms, R^2 change = .055, $F(1, 71) = 5.043$, $p < .05$ (see Table 4.6).

MAACL-R peak dysphoria value analysis. An analysis using MAACL-R peak dysphoria values was proposed to explore which of the independent variables (i.e., WRAIR-CES, PHQ-4, and/or PCL-M) best predicted a participant's MAACL-R peak dysphoria value. Therefore, a stepwise regression analysis using backward deletion was conducted with all subjects (N=119) included in the model. A visual inspection of the scatterplots for relations among the dependent and predictor variables was completed and indicated all relations were linear. Zero-order correlations were obtained to examine these linear relationships, and correlations between the dependent and predictor variables were all moderate and statistically significant (see Table 4.3).

The proposed model was statistically significant, R^2 = .174, adjusted R^2 = .153, $F(3, 115) = 8.099$, $p < .001$. Additionally, the partial regression coefficient relating PHQ-4 to MAACL-R peak dysphoria values was statistically significant, $B = .995$, $p < .05$, 95% CI = .369 – 1.621. After criterion for backward regression was met (probability of F-to-remove $\geq .01$), the second model removed PCL-M as a predictor and retained PHQ-4 and WRAIR-CES, which explained approximately 17% of the variance in MAACL-R peak dysphoria values, R^2 = .174, adjusted R^2 = .160, $F(2, 115) = 12.255$, $p < .001$. Of the two predictor variables in this model, only PHQ-4 was statistically significant, $B = .996$, $p < .001$, 95% CI = .543 – 1.449 (see Table 4.7). Lastly, a third model removed WRAIR-

CES as a predictor and indicated the final model to be significant, $R^2 = .174$, adjusted $R^2 = .155$, $F(1, 117) = 22.631$, $p < .001$. Trait anxiety and depression account for 17.4% of the variance in peak dysphoria, and the partial regression coefficient relating PHQ-4 to peak dysphoria was significant, $B = 1.064$, $p < .001$, 95% CI = .621 – 1.507 (see Table 4.7).

MAACL-R dysphoria changes over time analysis. To analyze changes over time (i.e., TP-1 to TP3) in MAACL-R dysphoria, a Friedman's test was performed on both study groups. For both groups, a Friedman's test indicated there was no statistically significant difference across the three time points, CE group: X^3 (2, $n = 42$) = .867, p = .648) and NCE group: X^3 (2, $n = 74$) = 2.223, $p = .329$) (Table 4.8).

VAS-stress mean value analysis. It was hypothesized that a greater number of combat experiences would be predictive of higher degrees of subjective stress on the day of surgery. To explore this hypothesis, a standard multiple regression analysis was used using the VAS-stress mean value as the dependent variable and WRAIR-CES, PHQ-4, and PCL-M as the predictor variables. A visual inspection of the scatterplots for relations among independent and dependent variables was completed and indicated all relations were linear. Zero-order correlations were obtained to statistically examine these linear relations and indicated the correlation between the PHQ-4 and VAS-stress mean value was statistically significant, but small, $r(117) = .258$, $p < .05$. Subjects with higher scores on the PHQ-4 reported more subjective stress on the day of surgery. However, correlations between VAS-stress mean values and predictor variables WRAIR-CES and PCL-M were not statistically significant, $r(74) = .045$, $p = .702$ and $r(117) = .121$, p =

.189, respectively (see Table 4.3). An examination of collinearity statistics suggested collinearity was not a problem for either group analysis (all tolerance value s > 2).

With all subjects included in the analysis, the model significantly predicts preoperative subjective stress, R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.125$, $p < .05$. This model accounted for approximately 7% of the variance in VAS-stress mean values. A summary of regression coefficients are presented in Table 4.9 and PHQ-4 was the only predictor variable significantly contributing to the model, $B = 2.304$, $p < .05$, 95% CI = .580 – 1.028. Upon subgroup analysis, the NCE group results indicate the model did not predict VAS-stress mean values, R^2 = .084, adjusted R^2 = .038, $F(2, 40) = 1.830$, p = .174. Likewise, results in the CE group were also not significant, R^2 = .085, adjusted R^2 = .047, $F(3, 72) = 2.239$, p = .091. Regression coefficients for both group models indicated none of the predictor variables significantly contributed to either model (see Table 4.9).

VAS-stress peak value analysis. A backward regression analysis was conducted to explore which of the independent variables best predicted the VAS-stress peak value. As a result, VAS-stress peak values were entered into the regression model as the dependent variable and WRAIR-CES, PHQ-4, and PCL-M were entered as predictor variables. Inspection of the scatterplots for relations among independent and dependent variables indicated all relations were linear. The only significant correlation found between variables was VAS–stress peak values and PHQ-4, which was small, $r(117)$ = .252, $p < .05$ (see Table 4.3).

All subjects were included in the analysis and the overall model was statistically significant, R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.108$, $p < .05$. The partial regression coefficient relating PHQ-4 to VAS-stress peak values was statistically

significant, $B = 2.674$, $p < .05$, 95% CI = .677 – 4.670. After criterion for backward regression was met (probability of F-to-remove $\geq .01$), the second model removed WRAIR-CES as a predictor variable and retained PHQ-4 and PCL-M, thus explaining 7.2% of the variance in VAS-stress peak values, $R^2 = .072$, adjusted $R^2 = .056$, $F(2, 116) = 4.522$, $p < .05$. In this model, the partial regression coefficient relating PHQ-4 to VAS-stress peak values was statistically significant, $B = .2.737$, $p < .05$, 95% CI = .758 – 4.716 (see Table 4.7). A third model removed PCL-M as a predictor and indicated the final model to be significant, $R^2 = .064$, adjusted $R^2 = .056$, $F(1, 117) = 7.965$, $p < .01$. In this model, PCL-M accounted for 6.4% of the variance in VAS-stress peak values (see Table 4.10).

VAS-stress changes over time analysis. A one-way repeated measures ANOVA was conducted on both groups to compare VAS-stress values over time (i.e., TP-1 – TP-3). In the NCE group, there was not a significant effect for VAS-stress over time, Wilk's Lambda = .935, $F(2, 40) = 1.384$, $p = .262$, multivariate partial eta squared = .065. Likewise, there was not a significant effect for VAS-stress over time in the CE group, Wilk's Lambda = .942, $F(2, 72) = 2.223$, $p = .116$, multivariate partial eta squared = .058 (see Table 4.11).

Physiological Stress Response Analysis

SAA AUC_G and mean increase. It was hypothesized that a greater number of combat experiences would be predictive of higher SAA as measured by SAA AUC_G and SAA mean increase values. In order to test this hypothesis using SAA AUC_G, a standard multiple regression analysis was conducted using SAA AUC_G as the dependent variable and WRAIR-CES, PHQ-4, and PCL-M as predictor variables. Scatterplots for relations

among variables displayed negative, linear relationships, and zero-order correlations between the predictor and dependent variables were small and not significant (see Table 4.3). Examination of collinearity statistics suggested that collinearity was not a problem (all tolerance value s > 2).

When including all subjects in the analysis, the model was not significantly predictive of SAA AUC_G, $R^2 = .059$, adjusted $R^2 = .031$, $F(1, 104) = 2.160$, $p = .097$. Subgroup analysis indicated the NCE group results did not account for a significant amount of variance in SAA AUC_G, $R^2 = .056$, adjusted $R^2 = .006$, $F(2, 38) = 1.128$, $p = .334$. Likewise, results from the CE group analysis was not significantly predictive of SAA AUC_G, $R^2 = .050$, adjusted $R^2 = .005$, $F(3, 63) = 1.107$, $p = .353$. A summary table of the partial regression coefficients for each model is presented in Table 4.12.

Next, SAA mean increase value was entered into the model as the criterion variable and WRAIR-CES, PHQ-4, and PCL-M were entered as predictor variables. Collinearity statistics were assessed in both groups indicating collinearity was not a problem (all tolerance > .2). Scatterplots were assessed for relations among the proposed variables and each displayed a linear relationship; however, correlations between the variables indicated small relationships that were not significant (Table 4.3). The model including all subjects did not result in a significant amount of variance in SAA mean increase values, $R^2 = .022$, $F(3, 104) = .773$, $p = .512$. When conducting subgroup analysis, the overall model for NCE group indicated no significant predictive relationships in SAA mean increase values, $R^2 = .008$, $F(2, 38) = .159$, $p = .854$. The regression analysis in the CE group also did not account for any significant variance in SAA mean increase values, $R^2 = .054$, $F(3, 63) = 1.201$, $p = .317$. Partial correlation

coefficients relating the predictor variables to SAA mean increase values in all models are provided in Table 4.13.

SAA peak value analysis. A stepwise regression using backward deletion was conducted to explore which independent variables best predict a participant's SAA peak value. Thus, SAA peak value was entered into the model as the dependent variable and WRAIR-CES, PHQ-4 and PCL-M were entered as predictor variables. A visual inspection of the scatterplots for relations among combat experiences, trait anxiety and depression, PTSD symptomatology, and SAA peak values indicated all relations were linear. Correlations were obtained to statistically examine these linear relations, and WRAIR-CES was the only variable to significantly correlate with SAA peak values, although it was a weak, inverse relationship, $r(74) = -.213$, $p < .05$ (see Table 4.3). This relationship suggests individuals reporting more combat experience will exhibit lower SAA peak values; individuals with less combat experience will exhibit higher SAA peak values.

This first analysis included all study subjects and the overall model significantly predicting SAA peak values, $R^2 = .084$, adjusted $R^2 = .060$, $F(3, 115) = 3.502$, $p < .05$. The partial regression coefficient relating WRAIR-CES to SAA peak values was statistically significant, $B = -.026$, $p < .05$, 95% CI = -.046 – -.007. Individuals reporting more combat exposure exhibited lower SAA peak values and individuals reporting less combat exposure exhibited higher SAA peak values. After criterion for backward regression was met (probability of F-to-remove $\geq .01$), the second model removed the PCL-M as a predictor and retained PHQ-4 and WRAIR-CES, which accounted for 7.7% of the variance in VAS-stress peak values, $R^2 = .077$, adjusted $R^2 = .061$, $F(2, 116) =$

4.808, $p < .05$. Of the two predictors variables, WRAIR-CES significantly contributed to the model, $B = -.023$, $p < .05$, 95% CI = -.041 – -.005. A third model removed PHQ-4 as a predictor and retained WRAIR-CES, $R^2 = .064$, adjusted $R^2 = .056$, $F(1, 117) = 7.978$, $p < .01$. In the final model, WRAIR-CES accounted for 6.4% of the variance in SAA stress peak values. Partial correlation coefficients relating the predictor variables to SAA peak values for all models are provided in Table 4.14.

SAA changes over time analysis. To determine changes in SAA values over time for both study groups, a Friedman's test was performed since assumptions for repeated measures ANOVA were not met. For both groups, the Friedman's test indicated no statistically significant difference in SAA values across the three time points, NCE: X^3 (2, n=41) = 4.439, $p = .109$), CE: X^3 (2, n=67) = 4.299, $p = .117$) (Table 4.15).

Discussion

The first aim of this study was to determine predictive relationships between combat exposure and the preoperative psychological stress response in military personnel on the day of surgery. One of the variables used to measure preoperative psychological stress was MAACL-R dysphoria values. When all study subjects were included in an analysis exploring predictive relationships between dysphoria and combat exposure, trait measures of anxiety and depression, PTSD symptoms, and combat exposure accounted for approximately 16% of the variance in MAACL-R mean dysphoria values. Subgroup was conducted as well, and the CE group model indicated 21% of the variability in dysphoria values was explained for by the predictor variables. What's noteworthy, however, is the only variable significantly contributing to the regression model in both models was the PHQ-4, i.e., trait anxiety and depression. Interestingly, another type of

statistical analysis in this study indicated the PHQ-4 was the best predictive variable for subject's peak dysphoria values. Taken together, these findings may suggest trait measures of anxiety and depression might be better predictors of increased psychological stress on the day of surgery. However, this is the first study known to this author to measure trait emotions of anxiety, depression, and PTSD symptomatology days prior to surgery and operationalize negative emotions on the day of surgery using MAACL-R dysphoria values. Despite this, a significant amount of variability in negative emotions remains unaccounted for, which is not surprising considering the vast amounts of stressors an individual encounters perioperatively.

Much of the perioperative literature describes preoperative stress as manifesting in varying degrees of anxiety, but other emotions such as fear, hostility or even depression may be experienced preoperatively (Caumo et al., 2001; Fitzgerald, B. M., & Elder, J., 2008; Kindler, Harms, Amsler, Ihde-Scholl, & Scheidegger, 2000; Lubin & Zuckerman, 1999). The results from this study suggest that trait anxiety was not particularly predictive of preoperative negative emotions (i.e., dysphoria) on the day of surgery; rather, higher degrees of trait depression were most predictive. Moreover, subgroup analysis of the CE group indicated the most predictive variables of preoperative dysphoria were trait depression and combat exposure when controlling for high trait anxiety, depression, and PTSD and combat exposure. In addition, combat exposure was found to contribute an additional 5.5% above and beyond the variability in preoperative dysphoria when controlling for the trait measures anxiety, depression, and PTSD. This finding corroborates many of the anecdotal reports by military anesthesia providers suggesting combat exposure contributes to a heightened or exacerbated preoperative

stress response. Furthermore, this may be the first study to suggest a predictive relationship between trait depressive symptoms and increased preoperative dysphoria in military personnel, especially in service members reporting a history of combat exposure.

Preoperative psychological stress was also measured using the VAS-stress to gauge an individual's subjective stress on the day of surgery. When all subjects were included in the analysis, study results indicated trait anxiety and depression, PTSD symptomatology, and combat exposure explained approximately 7% of the variability in VAS-stress values; however, the only predictor variable significantly contributing to the model was trait anxiety and depression (i.e., PHQ-4). A subsequent analysis utilized VAS-stress peak values to assess preoperative subjective stress and indicated the best predictor variable was again the PHQ-4, although only 7.5% of subjective stress peak values were accounted for by trait anxiety and depression. Notwithstanding the small R^2 values, there appears to be a trend emerging in this study when considering the entire study sample, that being trait measures of anxiety and depression, or depression alone, are relatively sensitive at predicting negative emotions on the day of surgery. Moreover, when exploring this same trend in the CE group, combat exposure also appeared to significantly predict increased psychological stress in combat veterans.

McGuire (2012) reported the incidence of emergence delirium in military combatants was best predicted by preoperative trait and state anxiety. However, throughout his analysis, McGuire (2012) found the least predictive independent variable foretelling emergence delirium was PTSD, i.e., when controlling for anxiety, depression, and PTSD. Interestingly, when the same independent variables were used to predict MAACL-R peak dysphoria values in this study, PTSD was also the first variable to be

removed from the regression model, and the most predictive variable was the PHQ-4. This same dynamic was replicated when entering the outcome variable SAA peak values into a prediction model; i.e., the PTSD variable was the least predictive among the independent variables. Although outcome variables between these two studies are fundamentally different, both studies used almost identical tools to assess anxiety, depression, and PTSD days prior to surgery, in addition to using similar predictive statistical modeling. When taken together they contradict the commonly held assumption that PTSD foretells increased preoperative stress or risk for emergence delirium. For example, two recent publications discussed anecdotal accounts by anesthetists describing PTSD as one of the primary factors contributing to increased emergence delirium, which is the same assumption previously held by this author (Lovestrand Phipps, & Lovestrand, 2013; Wilson & Pokorny, 2012). What McGuire (2012) and this study highlight is how perioperative phenomena, such as emergence delirium or preoperative stress, is multifactorial and should not be attributed to one contributing factor, such as PTSD.

Another study aim was to explore the physiological stress response using a noninvasive surrogate of the sympathetic nervous system, in this case SAA. Each of the statistical models exploring SAA total output, as well as mean increase values, were not found to be statistically significant. Interestingly, mean SAA values in the NCE group were slightly higher at each time point as compared to the CE group, and although not statistically significant, this was an unexpected finding. One explanation are individuals with prior combat exposure or a history of mental illness may not be as physiologically "ramped up," or be less responsive sympathetically when encountering stressful situations (Rohleder & Nater, 2009). This may be best represented by the results from the

SAA peak value analysis. These results indicated that although 6% of the variability in SAA peak values was explained by the predictor variable combat exposure (WRAIR-CES), this was a negative relationship; suggesting that individuals with more of combat experience produced less SAA and individuals with less combat experience produced more SAA.

Limitations

This study has several limitations, the first being it was conducted at a military hospital located on a Marine Corps installation, resulting in most study subjects being male and serving in the Marine Corps. A broader spectrum of patients from other U.S. military services, as well as more females, are needed to validate this study's findings. Additionally, a larger sample of subjects is necessary to ensure generalizability. Another limitation was this study did not control for thermal comfort, which may contribute to increased preoperative stress for several reasons. Spence et al. (2011) found male subjects reporting feeling cold on the day surgery exhibited a greater SAA response. In addition, other research suggests extremes in temperature may significantly affect SAA responsiveness (Chatterton et al., 1996).

Methodologically, it was very difficult to control for the diurnal pattern known to exist with SAA. The investigator attempted to coordinate the study subject's surgical time on the day of surgery as the first procedure in the morning; however, this proved to be quite difficult since many surgeons weren't available or had request cases for early start times, such as diabetic or pediatric patients. Also, there was significant time variability in data collection, i.e., some patients progressed through the preoperative on

schedule (< two hours), whereas, other patients waited sometimes six or more hours, thus making it difficult to account for the diurnal influence on SAA.

Conclusion

This may be the first study to investigate the preoperative psychological and physiological stress response in a military population with varying degrees of combat exposure. Little is known about how combat experience affects an individual's perception and/or reaction to stressors encountered perioperatively. This study contributes to perioperative stress literature by suggesting trait measures of anxiety and depression may be better predictors of increased negative emotions on the day of surgery, especially higher degrees of trait depressive symptoms. Likewise, this is the second study to indicate PTSD symptomatology as being the least predictive factor of increased perioperative stress when considering other trait measures, such as anxiety and depression. Much of the perioperative stress literature describes preoperative stress as anxiety, and little is known about how various emotions, such as trait anxiety and depression, contributes or relates to emotions experienced on the day of surgery. This study corroborates what many military perianesthesia clinicians have witnessed clinically, that being combat exposure significantly contributes to more preoperative psychological stress in military personnel. However, additional research is needed to further validate the findings in this study, as well as other studies to explore intraoperative and postoperative outcomes in order to better understand the perioperative stress in military members.

Table 4.1

Baseline Demographics

Variable *M (SD)* or N (%)	Total Sample N=119	Combat Exposure N = 76 (64%)	No Combat Exposure N = 43 (36%)	*P* value (CE vs. No CE)
Age (years)	27.28 (6.23)	29.33 (6.54)	23.65 (3.41)	**.000***
Gender				
Female	8 (6.7%)	2 (2.6%)	6 (14%)	**.025¶**
Male	111 (93.3%)	74 (97.4)	37 (86%)	
Ethnicity				
Native American	3 (2.5%)	-	3 (7%)	
Asian	4 (3.4%)	2 (2.6%)	2 (4.7%)	
Caucasian	78 (65.5%)	52 (68.4%)	26 (60.5%)	.080§
Latino	23 (19.3%)	13 (17.1%)	10 (23.3%)	
African American	9 (7.6%)	7 (9.2%)	2 (4.7%)	
Other	2 (1.7)	2 (2.6%)	-	
Highest Level of Education				
High School or equivalent	49 (41.2%)	28 (36.8%)	21 (48.8%)	
Some college, no degree	47 (39.5%)	33 (43.4%)	14 (32.6%)	
Two-year college degree	5 (4.2%)	4 (5.3%)	1 (2.3%)	.575§
Four-year college degree	14 (11.8%)	8 (10.5%)	6 (14%)	
Masters, doctorate, or professional degree	4 (3.4%)	3 (3.9%)	1 (2.3%)	
Marital Status				
Single, never married	46 (38.7%)	18 (23.7%)	28 (65.1%)	
Married or in a committed relationship	65 (54.6%)	51 (67.1%)	14 (32.6%)	**.000§**
Divorced	7 (5.9%)	6 (7.9%)	1 (2.3%)	
Separated	1 (.8%)	1 (1.3%)	-	
Mental Health Disorder(s)				
None	107 (89.9%)	65 (85.5%)	42 (97.7%)	
Anxiety	2 (1.7%)	2 (2.6%)	-	.158§
Depression	1 (.8%)	1 (1.3%)	-	
PTSD	7 (5.9%)	6 (7.9%)	1 (2.3%)	
PTSD & Depression	2 (1.7%)	2 (2.6%)	-	

**t* test; ¶Fisher's Exact Test; §Likelihood ratio

Table 4.1 continued

Baseline Demographics

Variable	Total Sample	Combat Exposure	No Combat Exposure	*P* value (CE vs. No CE)
ASA Status				
ASA I	65 (54.6%)	36 (47.4%)	29 (67.4%)	.055[±]
ASA II	54 (45.4%)	40 (52.6%)	14 (32.6%)	
Type of surgery				
General surgery	22 (18.5%)	13 (17.1%)	9 (20.9%)	
Orthopaedic	60 (50.4%)	39 (51.3%)	21 (48.8%)	
ENT	24 (20.2%)	16 (21.1%)	8 (18.6%)	.701[§]
Podiatry	4 (3.4%)	2 (2.6%)	2 (4.7%)	
Urology	4 (3.4%)	3 (3.9%)	1 (2.3%)	
OMFS	2 (1.7%)	2 (2.6%)	-	
Ophthalmology	3 (2.5%)	1 (1.3%)	2 (4.7%)	
Years in Service	6.98 (6.00)	9.05 (6.21)	3.33 (3.32)	**.000***
Branch of Service				
Marine Corps	105 (88.2%)	70 (92.1%)	35 (81.4%)	.130[§]
Navy	13 (10.9%)	6 (7.9%)	7 (16.3%)	
Army	1 (.8%)	-	1 (2.3%)	
Military Job				
Infantry	26 (21.8%)	20 (26.3%)	6 (14%)	
Armored infantry	4 (3.4%)	4 (5.3%)	-	
Artillery	6 (5%)	5 (6.6%)	1 (2.3%)	
Aviation	6 (5%)	3 (3.9%)	3 (7%)	
Motor Transport	7 (5.9%)	6 (7.9%)	1 (2.3%)	.135[§]
Mechanic	8 (6.7%)	4 (5.3%)	4 (9.3%)	
Supply	12 (10.1%)	8 (10.5%)	4 (9.3%)	
EOD	4 (3.4%)	3 (3.9%)	1 (2.3%)	
Medical	12 (10.1%)	5 (6.6%)	7 (16.3%)	
Communication	14 (11.8%)	6 (7.9%)	8 (18.6%)	
Other	20 (16.8%)	12 (15.8%)	8 (18.6%)	

[±]Pearson chi-square; [§]Likelihood ratio; **t* test;

Table 4.2

Psychological and Physiological Measures

Variable *M (SD)* or N (%)	Total Sample N=119	Combat Exposure N = 76 (64%)	No Combat Exposure N = 43 (36%)	*P* value (CE vs. No CE)
VAS-stress over last 6 months	48.37 (18.47)	48.87 (18.16)	47.49 (19.18)	.697*
GAD-2 score	1.16 (1.46)	1.17 (1.44)	1.14 (1.51)	.910*
PHQ-2 score	1.58 (1.63)	1.61 (1.52)	1.53 (1.83)	.823*
PHQ-4 total score	2.73 (2.74)	2.78 (2.71)	2.65 (2.81)	.812*
High GAD-2 Score				
Score < 3	96 (80.7%)	64 (84.2%)	32 (74.4%)	.290±
Score 3 or greater	23 (19.3%)	12 (15.8%)	11 (25.6%)	
High PHQ-2 Score				
Score < 3	90 (75.6%)	59 (77.6%)	31 (72.1%)	.650 ±
Score 3 or greater	29 (24.4%)	17 (22.4%)	12 (27.9%)	
PCL-M total score	28.09 (11.60)	29.89 (12.23)	24.91 (9.73)	**.024***
High PCL-M Score				
Score < 50	110 (92.4%)	68 (89.5%)	42 (97.7%)	.154¶
Score 50 or greater	9 (7.6%)	8 (10.5%)	1 (2.3%)	
WRAIR-CES total score	-	7.11 (5.80)	-	
MAACL-R dysphoria – TP-1	43.06 (6.22)	43.00 (5.96)	43.16 (6.73)	.892*
MAACL-R dysphoria – TP-2	43.69 (6.94)	43.80 (6.57)	43.50 (7.64)	.824*
MAACL-R dysphoria – TP-3	43.23 (6.52)	43.36 (6.88)	43.00 (5.90)	.776*
MAACL-R mean dysphoria	43.32 (5.76)	43.38 (5.80)	43.22 (5.74)	.886*
MAACL-R peak dysphoria	46.21 (7.23)	46.11 (6.16)	46.40 (7.43)	.834*
VAS-stress – TP-1	33.31 (19.89)	32.64 (19.22)	34.49 (21.18)	.629*
VAS-stress – TP-2	34.20 (20.54)	32.87 (19.37)	36.57 (22.52)	.352*
VAS-stress – TP-3	36.09 (20.98)	35.70 (20.10)	36.79 (22.68)	.786*
VAS-Stress Mean Value	34.70 (18.82)	33.84 (18.07)	36.22 (20.21)	.510*
VAS-Stress Peak Value	42.18 (21.79)	40.88 (20.68)	44.49 (23.70)	.388*

**t* test; ±Pearson chi-square; ¶Fisher's Exact Test

Table 4.2 continued

Psychological and Physiological Measures

Variable	Total Sample	Combat Exposure	No Combat Exposure	*P* value (CE vs. No CE)
SAA – TP-1	1.06 (.62)	1.01 (.622)	1.15 (.60)	.209*
SAA – TP-2	1.09 (.78)	1.01 (.82)	1.23 (.71)	.150*
SAA – TP-3	1.06 (.75)	1.01 (.83)	1.16 (.58)	.308*
SAA AUC_G	2.25 (1.21)	2.13 (1.28)	2.45 (1.08)	.187*
SAA mean increase value	.07 (.43)	0.08 (.46)	0.05 (.40)	.766*
SAA peak value	1.37 (.58)	1.30 (.61)	1.49 (.49)	.081*

**t* test

Table 4.3

Predictor and Criterion Variable Correlations

Pearson *r*	WRAIR-CES	PHQ-4	PCL-M	High trait anxiety	High trait depression	High PTSD symptoms
WRAIR-CES	1	.332*	.439**	.324*	.209	.396**
PHQ-4	.332*	1	.701**	-	-	-
PCL-M	.439**	.701**	1	-	-	-
MAACL-R mean dysphoria value	.328*	.376**	.305**	.205*	.394**	.200*
MAACL-R peak dysphoria value	.331*	.403**	.313**	-	-	-
VAS-stress mean value	.702	.258*	.121	-	-	-
VAS-stress peak value	.038	.252*	.111	-	-	-
SAA AUC_G	-.200*	-.174	-.143	-	-	-
SAA mean increase	-.109	.120	.058	-	-	-
SAA peak value	-.231*	-.167	-.121	-	-	-

*$p < .05$; **$p < .001$

Table 4.4

Standard Regression – MAACL-R Mean Dysphoria

Variable	*B*	*SE B*	*β*	*p* Value	CI
All Subjects					
PHQ-4	.714	.254	.339	.006	.212 – 1.216
PCL-M	.004	.064	.008	.952	-.123 – .131
WRAIR-CES	.141	.095	.141	.140	-.047 – .328
Overall R^2 = .161, adjusted R^2 = .139, F (3, 115) = 7.356, p < .001					
NCE Group					
PHQ-4	.586	.377	.287	.128	-.175 – 1.347
PCL-M	.023	.109	.039	.836	-.197 – .242
Overall R^2 = .097, adjusted R^2 = .052, F (3, 40) = 2.141, p = .131					
CE Group					
PHQ-4	.760	.359	.355	.038	.044 – 1.475
PCL-M	-.008	.084	-.016	.928	-.174 – .159
WRAIR-CES	.218	.117	.217	.066	-.015 – .450
Overall R^2 = .213, adjusted R^2 = .180, F (3, 72) = 6.488, p < .001					

Table 4.5

Standard Regression – MAACL-R Mean Dysphoria and Cutoff Predictors

Variable	*B*	*SE B*	*β*	*p* Value	CI
NCE Group					
High GAD-2	-1.834	2.138	-.141	.396	-6.159 – 2.490
High PHQ-2	5.520	2.016	.437	.009	1.443 – 9.597
High PCL-M	5.479	5.829	.146	.353	-6.312 – 17.269
Overall R^2 = .166, adjusted R^2 = .102, F(3, 39) = 2.586, p = .067					
CE Group					
WRAIR-CES	.256	.114	.256	.028	.029 – .483
High GAD-2	.431	2.605	.027	.869	-4.764 – 5.625
High PHQ-2	4.834	1.862	.349	.011	1.120 – 8.548
High PCL-M	-.437	2.740	-.023	.874	-5.900 – 5.027
Overall R^2 = .230, adjusted R^2 = .187, F(4, 71) = 5.302, p < .001					

Table 4.6

Hierarchical Regression – MAACL-R Mean Dysphoria in CE Group

	B	*SE B*	*β*	*p* Value	CI
Step 1					
High GAD-2	.845	2.670	.053	.752	-4.478 – 6.169
High PHQ-2	4.847	1.914	.350	.014	1.032 – 8.663
High PCL-M	1.123	2.724	.060	.681	-4.307 – 6.553
Overall $R^2 = .175$, adjusted $R^2 = .114$, $F(3, 72) = 5.102$, $p < .05$					
Step 2					
High GAD-2	.431	2.605	.027	.869	-4.764 – 5.625
High PHQ-2	4.834	1.862	.349	.011	1.120 – 8.548
High PCL-M	-.437	2.740	-.023	.874	-5.900 – 5.027
WRAIR-CES	.256	.114	.256	.028	.029 – .483
Overall $R^2 = .230$, adjusted $R^2 = .187$, $F(4,71) = 5.302$, $p < .001$					

Table 4.7

Backward Regression – MAACL-R Peak Dysphoria in All Subjects

	B	*SE B*	*β*	*p* Value	CI
Model 1					
PHQ-4	.995	.316	.376	.002	.369 – 1.621
PCL-M	.001	.080	.001	.995	-.158 – .159
WRAIR-CES	.143	.118	.114	.228	-.091 – .377
Model 2					
PHQ-4	.996	.229	.377	.000	.543 – 1.449
WRAIR-CES	.143	.109	.114	.190	-.072 – .359
Model 3					
PHQ-4	1.064	.224	.403	.000	.621 – 1.507

Table 4.8

Friedman's Test – MAACL-R Dysphoria

		Percentiles		
	n	25th	50th (*Md*)	75th
NCE Group				
TP-1	42	37.00	41.00	47.00
TP-2	42	37.00	40.00	49.25
TP-3	42	37.00	40.50	47.00
CE Group				
TP-1	74	37.00	40.00	47.00
TP-2	74	40.00	44.00	47.00
TP-3	74	37.00	40.00	47.00

Table 4.9

Standard Regression – VAS-Stress Mean Value

Variable	*B*	*SE B*	*β*	*p* Value	CI
All Subjects					
PHQ-4	2.304	.870	.335	.009	.580 – 4.028
PCL-M	-.154	.220	-.095	.485	-.591 – .282
WRAIR-CES	-.144	.325	-.044	.659	-.788 – .500
Overall R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.125$, $p < .05$					
NCE Group					
PHQ-4	2.545	1.336	.354	.064	-.155 – 5.245
PCL-M	-.481	.386	-.232	.220	-1.260 – .299
Overall R^2 = .084, adjusted R^2 = .038, $F(2, 40) = 1.830$, $p = .174$					
CE Group					
PHQ-4	1.941	1.204	.291	.111	-.460 – 4.342
PCL-M	.030	.280	.021	.914	-.528 – .589
WRAIR-CES	-.191	.391	-.061	.627	-.970 – .589
Overall R^2 = .085, adjusted R^2 = .047, $F(3, 72) = 2.239$, $p = .091$					

Table 4.10

Backward Regression – VAS-Stress with All Subjects

	B	*SE B*	*β*	*p* Value	CI
Model 1					
PHQ-4	2.674	1.008	.336	.009	.677 – 4.670
PCL-M	-.189	.255	-.100	.461	-.694 – .317
WRAIR-CES	-.217	.376	-.057	.565	-962 – .529
Overall R^2 = .075, adjusted R^2 = .051, $F(3, 115) = 3.108$, $p < .05$					
Model 2					
PHQ-4	2.737	.999	.344	.007	.758 – 4.716
PCL-M	-.244	.236	-.130	.302	-.711 – .222
Overall R^2 = .072, adjusted R^2 = .056, $F(2, 116) = 4.522$, $p < .05$					
Model 3					
PHQ-4	2.010	.712	.252	.006	.600 – 3.421
Overall R^2 = .064, adjusted R^2 = .056, $F(1, 117) = 7.965$, $p < .01$					

Table 4.11
RM-ANOVA - VAS-Stress

	n	*M*	*SD*
NCE Group			
TP-1	42	33.05	19.18
TP-2	42	36.57	22.52
TP-3	42	36.55	22.90
CE Group			
TP-1	74	33.30	19.12
TP-2	74	32.92	19.50
TP-3	74	35.43	20.00

Table 4.12

Standard Regression – SAA AUC_G

	B	*SE B*	*β*	*p* Value	CI
All Subjects					
PHQ-4	-.094	.093	-.199	.315	-.280 – .092
PCL-M	.016	.022	.153	.462	-.027 – .059
WRAIR-CES	-.041	.030	-.187	.176	-.102 – .019.
Overall R^2 = .059, adjusted R^2 = .031, $F(1, 104) = 2.160$, $p = .097$					
NCE Group					
PHQ-4	-.061	.075	-.157	.422	-.212 – .090
PCL-M	-.012	.022	-.108	.580	-.056 – .032
Overall R^2 = .056, adjusted R^2 = .006, $F(2, 38) = 1.128$, $p = .334$					
CE Group					
PHQ-4	-.094	.093	-.199	.315	-.280 – .092
PCL-M	.016	.022	.153	.462	-.027 – .059
WRAIR-CES	-.041	.030	-.187	.176	-.102 – .019.
Overall R^2 = .050, adjusted R^2 = .005, $F(3, 63) = 1.107$, $p = .353$					

Table 4.13

Standard Regression – SAA Mean Increase

	B	*SE B*	*β*	*p* Value	CI
All Subjects					
PHQ-4	.023	.022	.145	.291	-.020 – .066
PCL-M	.000	.006	-.008	.956	-.011 – .011
WRAIR-CES	-.006	.008	-.085	.430	-.023 – .010
Overall R^2 = .022, $F(3, 104) = .773$, $p = .512$					
NCE Group					
PHQ-4	.004	.028	.030	.879	-.053 – .061
PCL-M	.003	.008	.070	.726	-.014 – .019
Overall R^2 = .008, $F(2, 38) = .159$, $p = .854$					
CE Group					
PHQ-4	.049	.033	.291	.143	-.017 – .115
PCL-M	-.005	.008	-.122	.555	-.020 – .011
WRAIR-CES	-.012	.011	-.152	.269	-.033 – .009
Overall R^2 = .054, $F(3, 63) = 1.201$, $p = .317$					

Table 4.14

Backward Regression – SAA Peak Values

	B	*SE B*	*β*	*P* value	CI
Model 1					
PHQ-4	-.042	.027	-.198	.119	-.094 – .011
PCL-M	.006	.007	.128	.345	-.007 – .020
WRAIR-CES	-.026	.010	-.262	.009	-.046 – -.007
Overall R^2 = .084, adjusted R^2 = .060, $F(3, 115) = 3.502$, $p < .05$					
Model 2					
PHQ-4	-.024	.019	-.116	.209	-.063 – .014
WRAIR-CES	-.023	.009	-.227	.015	-.041 – -.005
Overall R^2 = .077, adjusted R^2 = .061, $F(2, 116) = 4.808$, $p < .05$					
Model 3					
WRAIR-CES	-.025	.009	-.253	.006	-.043 – -.008
Overall R^2 = .064, adjusted R^2 = .056, $F(1, 117) = 7.978$, $p < .01$					

Table 4.15

Friedman's Test – SAA values

		Percentiles		
	n	25th	50th (*Md*)	75th
NCE Group				
TP-1	41	.73	1.31	1.55
TP-2	41	.89	1.36	1.74
TP-3	41	.85	1.25	1.56
CE Group				
TP-1	67	.56	.97	1.51
TP-2	67	.66	1.17	1.60
TP-3	67	.66	1.19	1.54

Figure 4.1 Trait Measures of Anxiety and Depression (PHQ-4)

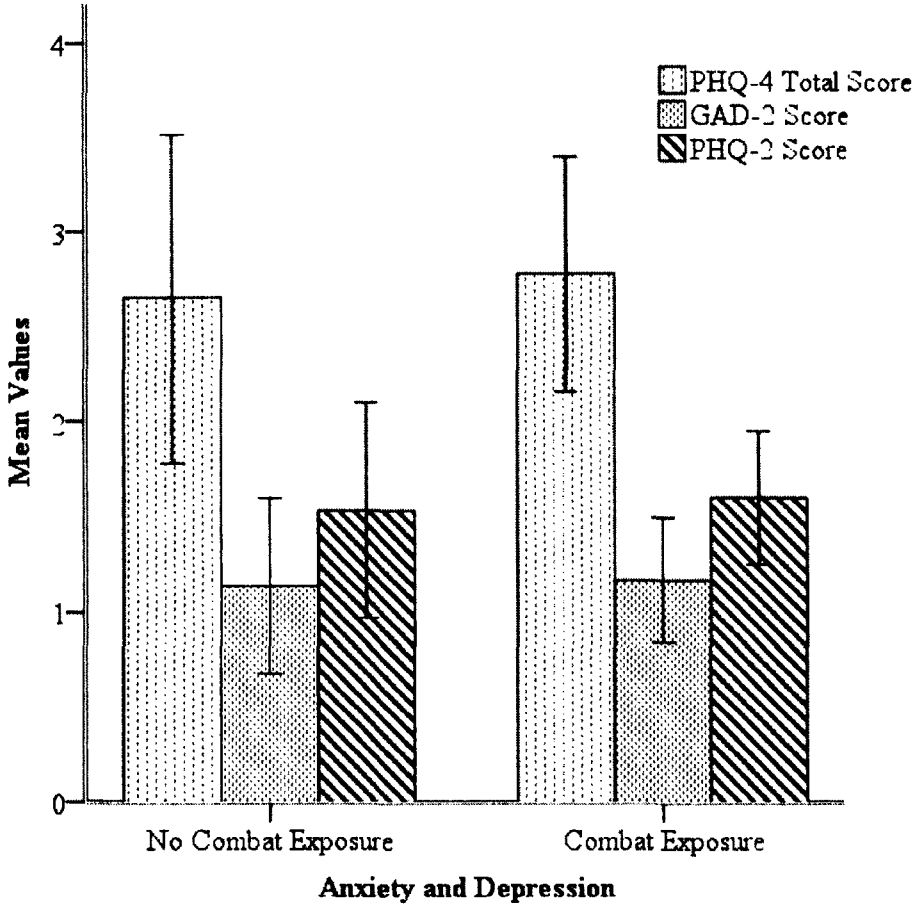


Figure 4.2. MAACL-R Dysphoria Mean Values at TP-1, TP-2, and TP-3

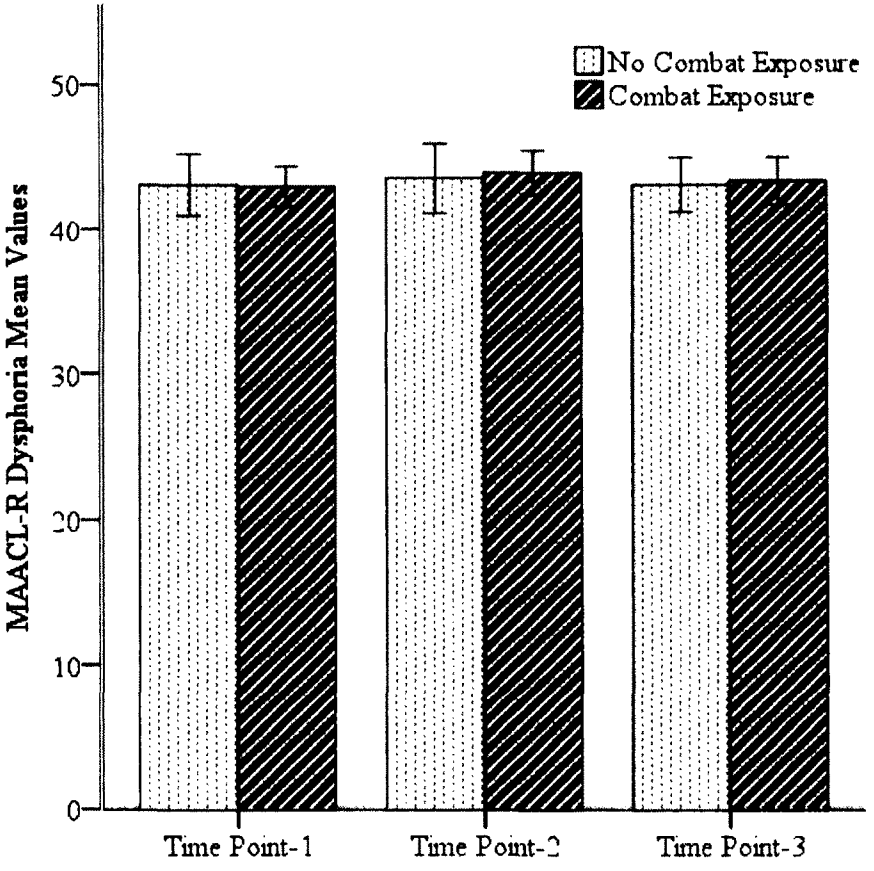


Figure 4.3. VAS-Stress Mean Values at TP-1, TP-2, and TP-3

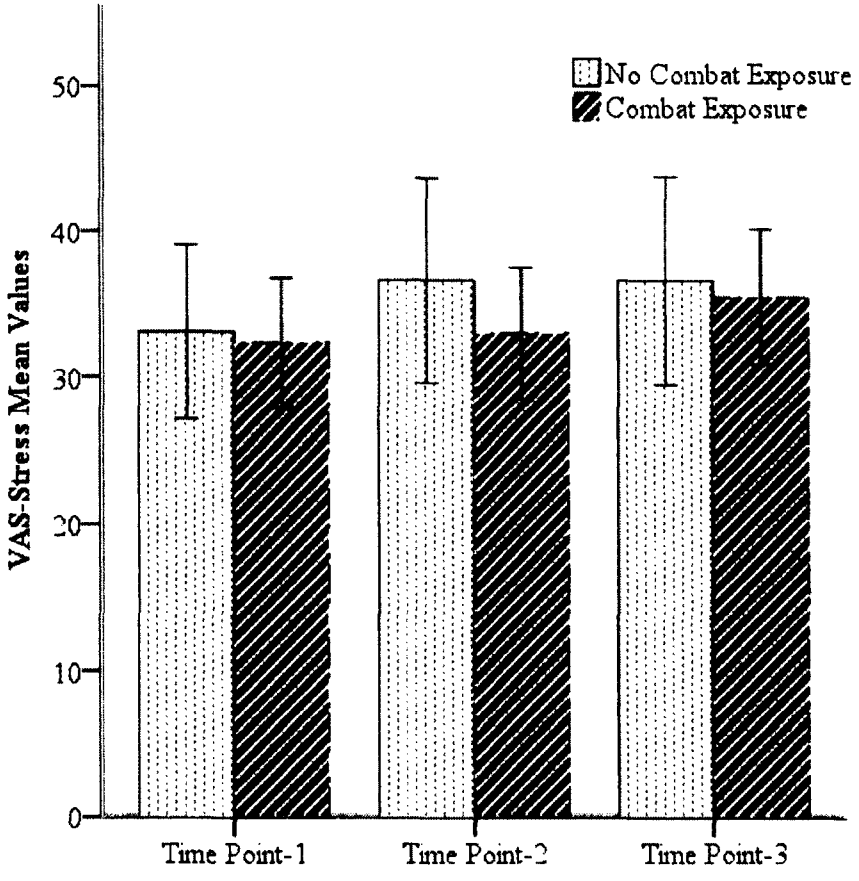
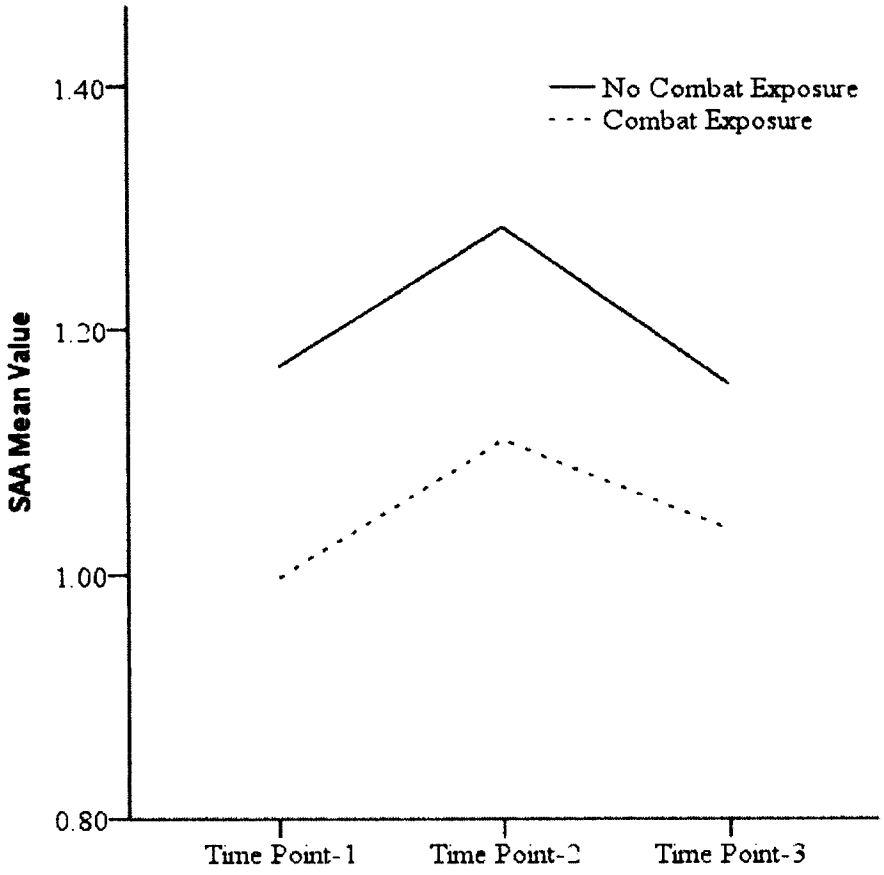


Figure 4.4. SAA Mean Values at TP-1, TP-2, and TP-3



References

Arroll, B., Goodyear-Smith, F., Crengle, S., Gunn, J., Kerse, N., Fishman, T., . . . Hatcher, S. (2010). Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Annals of Family Medicine, 8*(4), 348-353. doi: 10.1370/afm.1139

Bliese, P. D., Wright, K. M., Adler, A. B., Cabrera, O., Castro, C. A., & Hoge, C. W. (2008). Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. *Journal of Consulting and Clinical Psychology, 76*(2), 272-281. doi: 10.1037/0022-006X.76.2.272

Boker, A., Brownell, L., & Donen, N. (2002). The Amsterdam preoperative anxiety and information scale provides a simple and reliable measure of preoperative anxiety. *Canadian Journal of Anaesthesia: Journal Canadien d'Anesthesie, 49*(8), 792-798. doi: 10.1007/BF03017410

Bosch, J. A., Veerman, E. C., de Geus, E. J., & Proctor, G. B. (2011). Alpha-amylase as a reliable and convenient measure of sympathetic activity: Don't start salivating just yet! *Psychoneuroendocrinology, 36*(4), 449-453. doi: 10.1016/j.psyneuen.2010.12.019

Carr, E., Brockbank, K., Allen, S., & Strike, P. (2006). Patterns and frequency of anxiety in women undergoing gynaecological surgery. *Journal of Clinical Nursing, 15*(3), 341-352. doi: 10.1111/j.1365-2702.2006.01285.x

Caumo, W., Schmidt, A. P., Schneider, C. N., Bergmann, J., Iwamoto, C. W., Adamatti, L. C., . . . Ferreira, M. B. (2001). Risk factors for postoperative anxiety in adults. *Anaesthesia, 56*(8), 720-728.

Chatterton, R. T., Jr., Vogelsong, K. M., Lu, Y. C., Ellman, A. B., & Hudgens, G. A. (1996). Salivary alpha-amylase as a measure of endogenous adrenergic activity. *Clinical Physiology, 16*(4), 433-448.

Corson, K., Gerrity, M. S., & Dobscha, S. K. (2004). Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item. *The American Journal of Managed Care, 10*, 839-845.

Demirtas, Y., Ayhan, S., Tulmac, M., Findikcioglu, F., Ozkose, Z., Yalcin, R., & Atabay, K. (2005). Hemodynamic effects of perioperative stressor events during rhinoplasty. *Plastic and Reconstructive Surgery. 115*(2), 620-626.

Fitzgerald, B. M., & Elder, J. (2008). Will a 1-page informational handout decrease patients' most common fears of anesthesia and surgery? *Journal of Surgical Education, 65*(5), 359-363. doi: 10.1016/j.jsurg.2008.07.013

Gonzales, E. A., Ledesma, R. J., McAllister, D. J., Perry, S. M., Dyer, C. A., & Maye, J. P. (2010). Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: a randomized, single-blind study. *Journal of the American Association of Nurse Anesthetists, 78*(3), 181-188.

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *The New England Journal of Medicine, 351*(1), 13-22. doi: 10.1056/NEJMoa040603

Hoge, C. W., Castro, C. A., Messer, S. C., McGurk, D., Cotting, D. I., & Koffman, R. L. (2008). Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. *U.S. Army Medical Department journal*, 7-17.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *The New England Journal of Medicine, 358*(5), 453-463. doi: 10.1056/NEJMoa072972

Hong, J. Y., Jee, Y. S., & Luthardt, F. W. (2005). Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. *Journal of Clinical Anesthesia, 17*(7), 549-553. doi: 10.1016/j.jclinane.2005.01.008

Humphrey, S. P., & Williamson, R. T. (2001). A review of saliva: normal composition, flow, and function. *The Journal of Prosthetic Dentistry, 85*(2), 162-169. doi: 10.1067/mpr.2001.113778

Kang, Y. (2010). Psychological stress-induced changes in salivary alpha-amylase and adrenergic activity. *Nursing & Health Sciences, 12*(4), 477-484. doi: 10.1111/j.1442-2018.2010.00562.x

Keen, S. M., Kutter, C. J., Niles, B. L., & Krinsley, K. E. (2008). Psychometric properties of PTSD checklist in sample of male veterans. *Journal of Rehabilitation Research and Development, 45*(3), 465-474.

Kindler, C. H., Harms, C., Amsler, F., Ihde-Scholl, T., & Scheidegger, D. (2000). The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesthesia and Analgesia, 90*(3), 706-712.

Klein, L. C., Bennett, J. M., Whetzel, C. A., Granger, D. A., & Ritter, F. E. (2010). Caffeine and stress alter salivary alpha-amylase activity in young men. *Human Psychopharmacology, 25*(5), 359-367. doi: 10.1002/hup.1126

Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2009). An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics, 50*(6), 613-621. doi: 10.1176/appi.psy.50.6.613

Lara-Munoz, C., De Leon, S. P., Feinstein, A. R., Puente, A., & Wells, C. K. (2004). Comparison of three rating scales for measuring subjective phenomena in clinical research. I. Use of experimentally controlled auditory stimuli. *Archives of Medical Research, 35*(1), 43-48. doi: 10.1016/j.arcmed.2003.07.007

Liberzon, I., Abelson, J. L., Flagel, S. B., Raz, J., & Young, E. A. (1999). Neuroendocrine and psychophysiologic responses in PTSD: A symptom provocation study. *Neuropsychopharmacology, 21*(1), 40-50. doi: 10.1016/S0893-133X(98)00128-6

Lovestrand, D., Phipps, S., & Lovestrand, S. (2013). Posttraumatic stress disorder and anesthesia emergence. *Journal of the American Association of Nurse Anesthetists, 81*(3), 199-203.

Lubin, B., & Zuckerman, M. (1999). *Manual for the multiple affect adjective checklist-revised.* San Diego, CA: Educational and Industrial Testing Service.

McDonald, S. D., & Calhoun, P. S. (2010). The diagnostic accuracy of the PTSD checklist: a critical review. *Clinical Psychology Review, 30*(8), 976-987. doi: 10.1016/j.cpr.2010.06.012

McGuire, J.M. (2012). The incidence of and risk factors for emergence delirium in U.S. military combat veterans. *Journal of Perianesthesia Nursing. 27*, 236-245. doi:10.1016/j.jopan.2012.04.004

McIntosh, S., & Adams, J. (2011). Anxiety and quality of recovery in day surgery: A questionnaire study using Hospital Anxiety and Depression Scale and Quality of Recovery Score. *International Journal of Nursing Practice, 17*(1), 85-92. doi: 10.1111/j.1440-172X.2010.01910.x

Nater, U. M., La Marca, R., Florin, L., Moses, A., Langhans, W., Koller, M. M., & Ehlert, U. (2006). Stress-induced changes in human salivary alpha-amylase activity -- associations with adrenergic activity. *Psychoneuroendocrinology, 31*(1), 49-58. doi: 10.1016/j.psyneuen.2005.05.010

Nater, U. M., Rohleder, N., Gaab, J., Berger, S., Jud, A., Kirschbaum, C., & Ehlert, U. (2005). Human salivary alpha-amylase reactivity in a psychosocial stress paradigm. *International Journal of Psychophysiology, 55*(3), 333-342. doi: 10.1016/j.ijpsycho.2004.09.009

Nayback, A. M. (2009). Posttraumatic stress: a concept analysis. *Archives of Psychiatric Nursing, 23*(3), 210-219. doi: 10.1016/j.apnu.2008.06.001

Polit, D. F., & Beck, C. T. (2012). *Nursing research: Generating and assessing evidence for nursing practice* (9th ed.). Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Rohleder, N., & Nater, U. M. (2009). Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology, 34*(4), 469-485. doi: 10.1016/j.psyneuen.2008.12.004

Rohleder, N., Nater, U. M., Wolf, J. M., Ehlert, U., & Kirschbaum, C. (2004). Psychosocial stress-induced activation of salivary alpha-amylase: an indicator of sympathetic activity? *Annals of the New York Academy of Sciences, 1032*, 258-263. doi: 10.1196/annals.1314.033

Rohleder, N., Wolf, J. M., Maldonado, E. F., & Kirschbaum, C. (2006). The psychosocial stress-induced increase in salivary alpha-amylase is independent of saliva flow rate. *Psychophysiology, 43*(6), 645-652. doi: 10.1111/j.1469-8986.2006.00457.x

Salimetrics, L. (2011b). Salivary alpha-amylase assay kit. State College, PA: Salimetrics, LLC.

Spence, D., McBeain, J., Guzman, J., Roucek, E., & Maye, J. (2011). A pilot investigation evaluating physiological and psychological stress measurements in patients presenting for elective surgical procedures. *Journal of Healthcare, Science and the Humanities, 1*(2), 39-53.

Takai, N., Yamaguchi, M., Aragaki, T., Eto, K., Uchihashi, K., & Nishikawa, Y. (2004). Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults. *Archives of Oral Biology, 49*(12), 963-968. doi: 10.1016/j.archoralbio.2004.06.007

Weathers, F. W., Litz, B.T., Herman, D.S., Huska, J.A., & Keane, T.M. (1993). *The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility*. Paper presented at the Annual Meeting of International Society for Traumatic Stress Studies, San Antonio, TX.

Wilk, J. E., Bliese, P. D., Kim, P. Y., Thomas, J. L., McGurk, D., & Hoge, C. W. (2010). Relationship of combat experiences to alcohol misuse among U.S. soldiers

returning from the Iraq war. *Drug and Alcohol Dependence, 108*, 115-121. doi: 10.1016/j.drugalcdep.2009.12.003

Williamson, A., & Hoggart, B. (2005). Pain: A review of three commonly used pain rating scales. *Journal of Clinical Nursing, 14*(7), 798-804. doi: 10.1111/j.1365-2702.2005.01121.x

Wilson, J. T., & Pokorny. (2012). Experiences of military CRNAs with service personnel who are emerging from general anesthesia. *Journal of the American Association of Nurse Anesthetists, 80*(4), 260-265.

Appendix A

DEMOGRAPHIC DATA

Collect the following information from the patient and medical record after informed consent is obtained.

Today's Date _____ **Time** _____

Date of Birth _____/_____/_____
Mo Day Year

Gender ☐ Male ☐ Female

Branch of service ☐ Marine Corps ☐ Navy ☐ Army ☐ Air Force

Date you entered military service _____/_____/_____
Mo Day Year

Race/Ethnic Identity (Check the <u>one</u> that you identify with most)

- ☐ American Indian/Native American
- ☐ Asian
- ☐ White/Caucasian
- ☐ Hispanic/Latino
- ☐ Black/African American
- ☐ Pacific Islander
- ☐ Other

The highest level of education you completed

- ☐ Less than high school completion
- ☐ High school degree/GED/or equivalent
- ☐ Some college, no degree
- ☐ Two-year college degree (A.A., A.S.)
- ☐ Four-year college degree (B.A., B.S.)
- ☐ Masters, doctorate or professional degree

Marital status

- ☐ Single, Never Married
- ☐ Married or in a committed relationship
- ☐ Divorced
- ☐ Separated
- ☐ Widowed

Do you <u>currently</u> smoke or use smokeless tobacco on a daily basis, less than daily, or not at all?

☐ Daily ☐ Less than daily ☐ Not at all

On an <u>average day</u>, how many 8-12 oz. beverages containing caffeine do you drink (such as coffee, tea, soda)?

☐ None
☐ 1-2 per day
☐ 3-5 per day
☐ 6-10 per day
☐ 11 or more per day

In a <u>typical week,</u> how many drinks do you have? ☐☐☐ drinks

In a <u>typical week,</u> how many drinks of each type of alcoholic beverage do you have?

☐☐☐ beer(s) ☐☐☐ wine ☐☐☐ liquor

Are you currently taking any of the following supplements (check all that apply)?

☐ Strength/body building supplements (e.g., amino acids, weight gain products, creatine)

☐ Energy supplements (e.g., energy drinks, pills, or energy enhancing herbs)

☐ Weight loss supplements (e.g., Hydroxycut)

Are you taking any *prescription* medications?

☐ Yes ☐ No

If yes, please list all medications

_____

_____

Are you taking any *over-the-counter* medications (including herbals)?

☐ Yes ☐ No

If yes, please list all medications

_____

_____

Questions below to be completed by the Study Investigator

Past Medical History

_____

_____

_____

Past Surgical History

_____

_____

_____

Planned Surgical Procedure

_____

_____

_____

ASA Status

☐ I ☐ II

Planned anesthesia (e.g., going to sleep, twilight, sedation, etc.)

☐ General Anesthesia
☐ Monitored Anesthesia Care (MAC)
☐ Spinal
☐ Epidural
☐ Peripheral Nerve Block

Appendix B
DEPLOYMENT HISTORY

1. **Have you ever deployed?**
   □ Yes □ No
   *If no, stop here!

Country Codes				**Sea Codes**	
01	Afghanistan	11	Pakistan	21	Adriatic Sea
02	Bahrain	12	Philippines	22	Arabian Sea
03	Bosnia or Herzegovina	13	Qatar	23	Gulf of Aden
04	Croatia	14	Saudi Arabia	24	Gulf of Oman
05	Iraq	15	Serbia (includes Kosovo)	25	Persian Gulf
06	Kuwait	16	Tajikistan	26	Red Sea
07	Krygyzstan	17	Turkey	27	Other sea area: _____ please specify
08	Macedonia	18	United Arab Emirates		
09	Montenegro	19	Uzebekistan		
10	Oman	20	Other county: _____ please specify		

2. **During any deployment have you ever received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits?**
   □ Yes □ No
   *If no, stop here!

3. **Use the country and sea codes (01-27) assigned to the locations below to indicate(s) where you received imminent danger pay, hardship duty pay, or combat zone tax exclusion benefits. Please list the most recent first.**

	Location	**Date Arrived** Month / Year		**Date Departed** Month / Year	
a.		/ 2 0	TO	/ 2 0	
b.		/ 2 0	TO	/ 2 0	
c.		/ 2 0	TO	/ 2 0	
d.		/ 2 0	TO	/ 2 0	
e.		/ 2 0	TO	/ 2 0	

Appendix C

PHQ-4				
Instructions: Over the last 2 weeks, how often have you been bothered by the following problems? Circle one of the numbers to the right to indicate how much you have been bothered.	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure idoing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer, Inc. No permission is required to reproduce, translate, display, or distribute.

Appendix D

PCL-M

Instructions: Below is a list of problems and complaints that veterans sometimes have in response to stressful military experiences. Please read each one carefully, then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

1. Repeated, disturbing *memories, thoughts, or images* of a stressful military experience?	1	2	3	4	5
2. Repeated, disturbing *dreams* of a stressful military experience?	1	2	3	4	5
3. Suddenly *acting or feeling* as if a stressful military experience *were happening again* (as if you were reliving it)?	1	2	3	4	5
4. Feeling *very upset* when *something reminded you* of a stressful military experience?	1	2	3	4	5
5. Having *physical reactions* (e.g., heart pounding, trouble breathing, sweating) when *something reminded you* of a stressful military experience?	1	2	3	4	5
6. Avoiding *thinking about or talking about* a stressful military experience or avoiding *having feelings* related to it?	1	2	3	4	5
7. Avoiding *activities or situations* because *they reminded you* of a stressful military experience?	1	2	3	4	5
8. Trouble *remembering important parts* of a stressful military experience?	1	2	3	4	5
9. *Loss of interest* in activities that you used to enjoy?	1	2	3	4	5
10. Feeling *distant or cut off* from other people?	1	2	3	4	5
11. Feeling *emotionally numb* or being unable to have loving feelings for those close to you?	1	2	3	4	5
12. Feeling as if your *future* somehow will be *cut short*?	1	2	3	4	5
13. Trouble *falling or staying asleep*?	1	2	3	4	5
14. Feeling *irritable* or having *angry outbursts*?	1	2	3	4	5
15. Having *difficulty concentrating*?	1	2	3	4	5
16. Being "*superalert*" or watchful or on guard?	1	2	3	4	5
17. Feeling *jumpy* or easily startled?	1	2	3	4	5

PCL-M for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane National Center for PTSD - Behavioral Science Division

Appendix E

WALTER REED ARMY INSTITUTE OF RESEARCH COMBAT EXPOSURE SCALE

The statements below are about your combat experiences during deployment. Please circle "yes" if the statement is true or "no" if the statement is false.

	Response	
1. Receiving small arms fire	YES	NO
2. Disarming civilians	YES	NO
3. Shooting or directing fire at the enemy	YES	NO
4. Calling in fire on the enemy	YES	NO
5. Engaging in hand-to-hand combat	YES	NO
6. Clearing/searching homes or buildings	YES	NO
7. Clearing/searching caves or bunkers	YES	NO
8. Being directly responsible for death of an enemy combatant	YES	NO
9. Being directly responsible for death of a non-combatant	YES	NO
10. Being directly responsible for death of U.S. or ally personnel	YES	NO
11. IED/booby trap exploded near you	YES	NO
12. Working in areas that were mined	YES	NO
13. Participated in demining operations	YES	NO
14. Being in threatening situations where you were unable to respond because of rules of engagement	YES	NO
15. Being wounded/injured	YES	NO
16. Had a close call, dud landed near you	YES	NO
17. Had a close call, was shot or hit but protective gear saved you	YES	NO
18. Had a buddy shot or hit who was near you	YES	NO
19. Seeing dead bodies or human remains	YES	NO
20. Handling or uncovering human remains	YES	NO
21. Witnessing an accident which resulted in serious injury or death	YES	NO
22. Seeing dead or seriously injured Americans	YES	NO
23. Having a member of your own unit become a casualty	YES	NO
24. Witnessing violence within the local population or between ethnic groups	YES	NO
25. Witnessing brutality/mistreatment toward non-combatants	YES	NO
26. Provided aid to the wounded	YES	NO
27. Saved the life of a Soldier or civilian	YES	NO

Adapted from Wilk et al., 2010

Appendix F

Same Day Surgery Unit

Date: _____ **Time:** _____

Visual Analog Scale for *Pain*

How severe is your *pain* at this moment in time? Please place a single vertical (|) mark on the line below to indicate your current *pain* level.

No pain _____ **Very severe pain**

Appendix G

Same Day Surgery Unit

Date: _____ **Time:** _____

Visual Analog Scale for *Stress*

1. The scale below indicates how *stressful* an event might be. Please place a single vertical (|) mark on the line below to indicate how stressed you currently feel.

No stress **Extremely stressed**

_____

2. Have you ingested any caffeine and/or nicotine in the last 4 hours (check all that apply)?

☐ Caffeine ☐ Nicotine ☐ Neither

3. Describe what you have been doing during the last 30 minutes?

_____

_____

_____

_____

_____

4. Describe any sources of stress or stressful feelings you are currently experiencing.

_____

_____

_____

Preoperative Holding

Date: _____ **Time:** _____

Visual Analog Scale for *Stress*

1. The scale below indicates how *stressful* an event might be. Please place a single vertical (|) mark on the line below to indicate how stressed you currently feel.

No stress **Extremely stressed**

_____

2. Describe what you have been doing during the last 30 minutes?

_____
_____
_____
_____
_____
_____

3. Describe any sources of stress or stressful feelings you are currently experiencing.

_____
_____
_____
_____
_____
_____

Prior to OR Entry

Date: _____ **Time:** _____

Visual Analog Scale for *Stress*

1. The scale below indicates how *stressful* an event might be. Please place a single vertical (|) mark on the line below to indicate how stressed you currently feel.

No stress _____ **Extremely stressed**

2. Describe what you have been doing during the last 30 minutes?

_____

_____

_____

_____

_____

3. Describe any sources of stress or stressful feelings you are currently experiencing.

_____

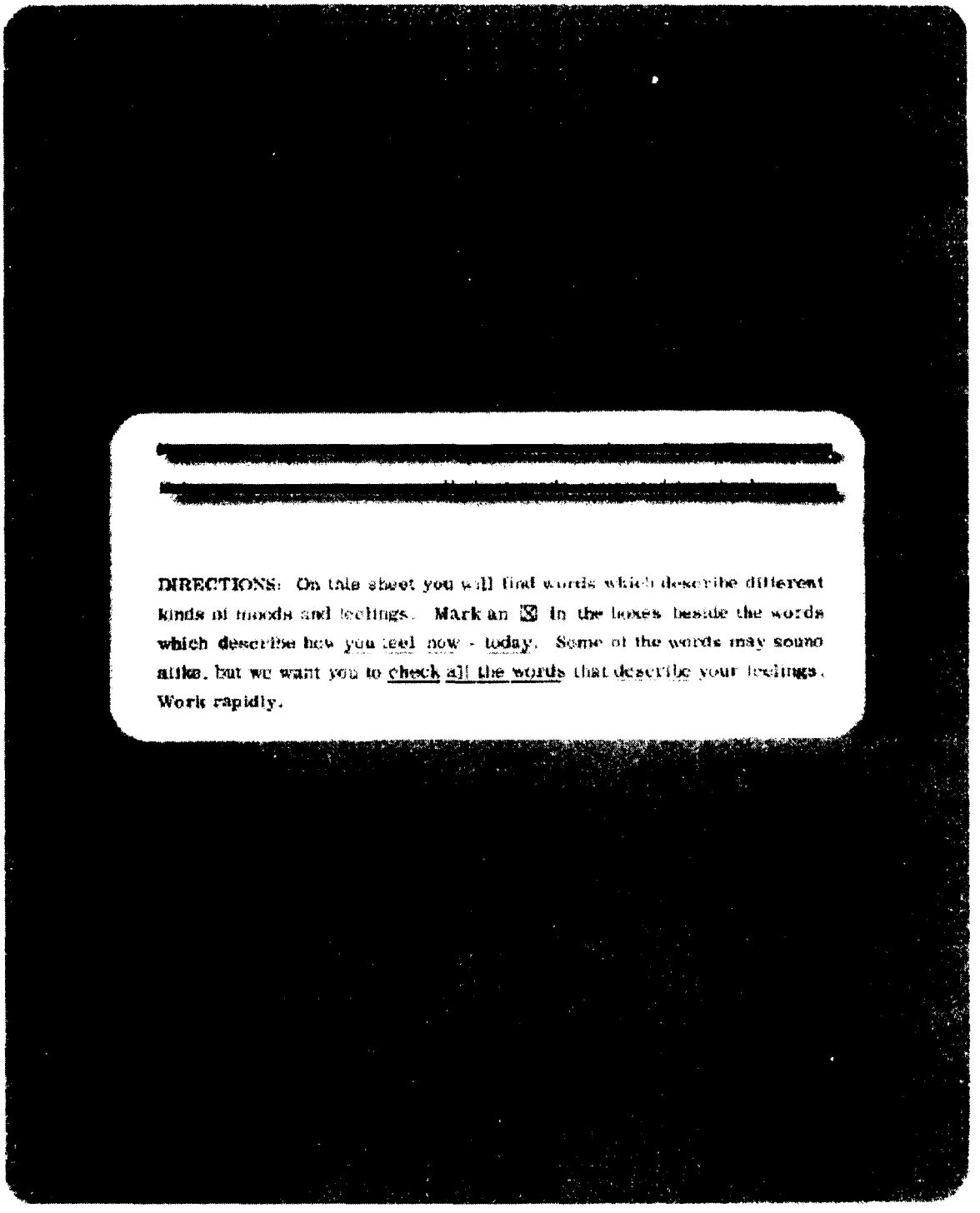
_____

_____

_____

_____

Appendix H



DIRECTIONS: On this sheet you will find words which describe different kinds of moods and feelings. Mark an ☒ in the boxes beside the words which describe how you feel now - today. Some of the words may sound alike, but we want you to check all the words that describe your feelings. Work rapidly.

Appendix H

Appendix I

NAVAL HOSPITAL CAMP PENDLETON
CAMP PENDLETON, CALIFORNIA 92058

CONSENT BY A *SUBJECT* FOR VOLUNTARY PARTICIPATION IN A CLINICAL INVESTIGATION (RESEARCH) STUDY

1. You, _____, have been asked to voluntarily participate in a research project entitled, ***"Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?"*** being conducted at the Naval Hospital Camp Pendleton, Camp Pendleton, CA.

2. WHY IS THE STUDY BEING DONE?

This study is being done to determine an individual's response to stressors that he/she may experience prior to surgery. The information gathered from this project may help medical professionals improve patient care and support future scientific studies.

3. HOW LONG WILL YOU BE PARTICIPATING IN THE STUDY?

The study will begin on the day you agree to participate in the study and will end immediately before you enter the operating room for surgery (i.e., on the day of surgery).

4. WHAT IS INVOLVED IN THE STUDY?

Following your voluntary consent to participate in the study, data collection will take place on two days: Day of Enrollment and Day of Surgery.

Day of Enrollment: Following your preoperative screening on the Preoperative Teaching Unit (1-14 days prior to surgery), you will be asked to complete the Demographic and Deployment Questionnaires, Patient Health Questionnaire-4, Posttraumatic Stress Disorder Checklist-Military, and Walter Reed Army Institute of Research Combat Exposure Scale (see below for a description of each questionnaire).

(a) Demographic Questionnaire: This contains questions used to gather characteristics about individuals, such as gender, age, ethnicity, education level, etc. Additionally, this document will ask

about your past medical history, such as medications you are currently taking, prior surgeries, etc.

(b) Deployment History Questionnaire: This form will be used to gather information related to your military deployment(s), as well as determine which individuals will be asked to complete an additional questionnaire measuring combat exposure (i.e., the Walter Reed Army Institute of Research Combat Exposure Scale).

(c) Walter Reed Army Institute of Research Combat Exposure Scale: Contains 27 questions asking about an individual's exposure to combat-related events. This questionnaire is currently the U.S. Army's most frequently used questionnaire to evaluate a military members exposure to combat in study's evaluating combat stress.

(d) Patient Health Questionnaire-4 (PHQ-4): The PHQ-4 contains four questions; i.e., two questions asking about depression-related symptoms and two questions asking about anxiety-related questions.

(e) Posttraumatic Stress Disorder Checklist-Military (PCL-M): This is a commonly used questionnaire used by the military to assess for PTSD-related symptoms. The form consists of 17 questions asking an individual to relate their military experience(s) to "how bothered" they are by symptoms listed on the PCL-M. The PCL-M is an effective instrument in gauging the likelihood for PTSD; however, it is not intended to diagnose an individual with PTSD.

Note: The anticipated time to complete the consent process and questionnaires provided above is approximately 60 minutes.

Day of Surgery: The following items will be used to evaluate your level of stress (i.e., physical and emotional) on the day of surgery: (a) Visual Analogue Scales for Pain and Stress, (b) Multiple Affect Adjective Checklist-Revised questionnaire, and (c) salivary alpha-amylase. You will be asked to complete these measurements following your arrival to the Same Day Surgery Unit, Preoperative Holding Area, and immediately before entering the operating room. The items used to evaluate stress are explained below.

(a) Visual Analogue Scale for Pain and Stress: This item is commonly used to measure various phenomena, such as pain, stress, or anxiety. The visual analogue scale consists of a 100 mm horizontal line with word descriptors at the ends of this line, such as "no stress" and "very

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(Do not **Subject's Initials:** *this documents w/out prior approval)*

high stress." You will be asked to make a vertical mark along this line that best matches your feeling or perception about a question at a particular moment in time, such as "how stressed do you feel right now."

(b) Multiple Affect Adjective Checklist-Revised questionnaire: This questionnaire is useful in measuring a variety of emotions a person may experience. You will be asked to select words provided on the questionnaire that best describes how you feel at a particular moment in time.

(c) Salivary alpha-amylase: This is a digestive enzyme produced by the salivary glands in the mouth and its role is to begin the breakdown of carbohydrates. The production and secretion of salivary alpha-amylase following a stressful event is almost immediate, thus making it useful in measuring an individual's physical response to stress. The saliva needed to measure the salivary alpha-amylase will be collected using a soft oral swab that will be placed between your upper teeth and cheek area for approximately 3 minutes.

Note: Each period of data collection will require approximately 10-15 minutes with an overall time commitment of approximately 30-45 minutes on the day of surgery.

5. WHAT IS THE EXPERIMENTAL PART OF THE STUDY?

Individuals in this study will be asked to complete psychological questionnaires and submit saliva samples in order to evaluate their physical and emotional stress on the day of surgery. The questionnaires used in this study are as follows: Demographic Data, Deployment History, Walter Reed Army Institute Research Combat Exposure Scale, Patient Health Questionnaire-4, Posttraumatic Stress Disorder Checklist-Military, Visual Analog Scale for Stress and Pain, and the Multiple Affect Adjective Checklist-Revised. Salivary alpha-amylase, found in the saliva, will be used to measure an individual's physical stress response prior to undergoing surgery.

6. HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 120 individuals are needed to participate in this study, and every study subject will be a patient scheduled for surgery at the Naval Hospital Camp Pendleton.

Subject's Initials: _____

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7. WHAT ARE THE RISKS OF THE STUDY?

The primary risks to participate in this study include the unintentional disclosure of private health information, potential for increased stress, and time to complete the survey measures in the preoperative setting. All the information and saliva samples will be de-identified for analyses and only investigators associated with this study will have access to the data. Data security systems include locked storage of paper files and password-protected access to electronic files.

The lead study investigator can address any stress or concern you might have related to this study. Some questions you will be asked to answer may make you think of painful or difficult memories, and for this reason you can stop participating in the study at any time. Furthermore, questionnaires you will be asked to complete may suggest the possibility of a significant anxiety, depression, and/or PTSD disorder. If one or more of the results from the study questionnaire(s) indicate a potential diagnosis for anxiety, depression, or PTSD, and/or the study investigator thinks you might hurt yourself or someone else, you will be referred to a mental health provider at either NHCP's Deployment Health Center or Department of Mental Health. No study-related information, or potential diagnosis received following a mental health consult (if requested), will be made accessible to any military commander(s) and/or military command. Lastly, if you would like to talk to someone about your feelings, the **Military Crisis Line** is available with free and confidential help for service members and their families 24 hours a day. You can call: **1-800-273-8255** anytime, free of charge.

The oral swab used to collect the saliva is an absorbent soft foam material specifically designed to obtain saliva from the mouth. You may or may not experience temporary dryness of the mucosal membrane (oral cavity) following placement of the oral swab in the upper cheek area. All questionnaires and saliva samples will be marked with a subject number; i.e., no patient identification will be used to label the questionnaires or saliva samples. Furthermore, saliva samples will be destroyed following the completion of the study.

It is neither typical nor routine for pregnant patients to undergo elective medical procedures because of potential risks to the unborn child. Therefore, female subjects of childbearing age will have their pregnancy status tested before and/or on the day of surgery, and if found to be pregnant will be excluded from the study. Also, you should promptly advise your doctor and the study researcher identified below if you are now pregnant, if you contemplate becoming pregnant, or if you become pregnant during your participation in the study.

Subject's Initials: _____

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8. ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Your participation in this research project will not be of direct benefit to you personally. However, the results of this study may help us gain important knowledge about stress in combat and noncombat veterans scheduled for elective surgery. In addition, these results will help in the development of future studies and also potentially assist anesthesia providers to identify factors associated with increased preoperative stress.

9. WHAT OTHER OPTIONS ARE THERE?

This research study is not designed to treat any medical condition that you may have; therefore, there are no alternative procedure(s) or course of treatment that would benefit you.

10. WILL I BE PAID TO PARTICIPATE?

You will not be financially compensated for your participation in this study.

11. WHAT IF I AM INJURED AS A RESULT OF PARTICIPATION IN THIS STUDY?

If you suffer any injury directly related to your participation in this research study, immediate medical attention is available at Naval Hospital Camp Pendleton, if applicable.

12. WHAT ABOUT CONFIDENTIALITY?

In all publications and presentations resulting from this research study, information about you or your participation in this project will be maintained in the strictest confidence and will not be released in anyone or in any manner identifying you personally. However, authorized personnel from the Navy Medical Department and from the Food and Drug Administration (FDA), where applicable, may have access to your research file in order to verify that your rights have been adequately protected.

Subject's Initials: _____

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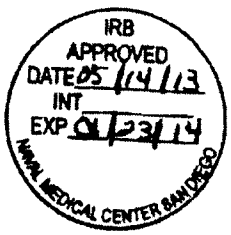

PATIENT AUTHORIZATION TO USE AND/OR DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH (HIPAA)
(In keeping with the Health Insurance Portability and Accountability Protection Act)

What is Confidentiality of records all about?

Naval Hospital Camp Pendleton makes every effort to maintain the confidentiality of protected health information we obtain about you. However, we cannot absolutely guarantee confidentiality because other people may need to see your information in the course of this research study. Most people and organizations will protect the privacy of your information, but may not be required to do so by the law. Also, if the results of this research study are presented at meetings or published, your name will not be used.

What is HIPAA all about?

The Health Insurance Portability and Accountability Act (HIPAA) require that we get your permission to use protected health information about you that is either created by or used in connection with this research study. This permission is called an Authorization. The information we use includes information from your medical records, and name.

What will we do with this information?

Your protected health information will be collected and used during the course of the research study, to monitor your health status, to measure the effects of drugs or devices or procedures, to determine research results, and to possibly develop new tests, procedures, and commercial products.

Your research doctor will use this information to report the results of research to sponsors and federal agencies, like the Food and Drug Administration (FDA). The information may also be reviewed when the research study is audited for compliance. When the study is over, you have the right to see the information and copy it for your records.

Who will we share your information with?

Your information may be shared with any of the following:

- The sponsor of the study, or its agents, such as data repositories.
- Other medical centers, institutions, or research investigators outside of Naval Hospital Camp Pendleton, participating in this research study.

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- State and Federal agencies which have authority over the research, Naval Hospital Camp Pendleton. Good examples are: the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Institute of Health (NIH), the Office of Human Research Protections (OHRP), and the Department of Social Services (DSS) or other.
- This hospital or clinic.
- Accrediting agencies, such as JCAHO.
- A data safety monitoring board, if applicable
- Clinical staff who may not be involved directly in the research study, but who may become involved in your care, if it is possibly related to treatment

For this research study, the study investigator may share this authorization form and records, which identify you to comply with regulatory requirements or for purposes related to this research to: All documented Principal, Associate, and Sub-investigators, and the Medical Monitor.

What if you want to revoke or cancel away your Authorization?

If you decide to participate in this research study, your Authorization for this study will not expire unless you revoke or cancel it in writing to the research doctor. If you revoke your Authorization, you will also be removed from the study, but standard medical care and any other benefit to which you are entitled will not be affected in any way.

Revoking your Authorization only affects the use and disclosure (sharing) of information after your written request has been received. Federal law requires sending study information to the FDA for studies it regulates, like studies of drugs and devices. In a case like this, your information may need to be reported to them and cannot be removed from the research records once it is collected.

Do you have to sign this form?

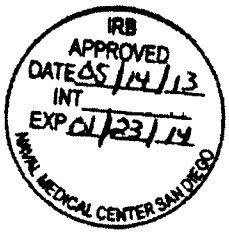
You have the right to refuse to sign this Authorization form and not be a part of this study. You can also tell your study doctor you want to withdraw from the study at any time without revoking the Authorization to use your health information. By signing this research Authorization form, you authorize the use and/or disclosure of your protected health information described above.

This authorization expires 25 years from the date of signature.

13. WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding this research study, you may contact **LT Orlando Rivera, NC, USN, Principal Investigator at (951) 553-8331.**

Subject's Initials: _____



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If you have any questions about your rights as an individual while participating in a research study at the Naval Medical Center, San Diego, you may contact **CDR John Arnold, MC, USN, Chairman, Institutional Review Board at (619) 532-9927, or John D. Malone, M.D., Head, Clinical Investigation Department at (619) 532-6099.**

If you have medical questions or concerns about your participation, you may contact **Dr. Patrick Mullins, LCDR, MC, USN, Medical Monitor, Naval Hospital Camp Pendleton at (760) 725-1511.**

If you believe that you have been injured as a result of your participation in this research study, you may contact **CAPT Mary Ellen Moss, JAGC, USN, Naval Medical Center, San Diego, Legal Department at (619) 532-6475**.

14. WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation in this project is entirely voluntary and your decision not to participate will involve no penalty or loss of benefits to which you are entitled under applicable regulations. If you choose to participate, you are free to ask questions or to withdraw from the study at any time. If you should decide to withdraw from the research project, you can notify **LT Orlando Rivera, NC, USN,** at **951-553-8331** to ensure your timely removal from the study. Your withdrawal will involve no prejudice to your future health care or any loss of rights or benefits to which you are otherwise entitled. Any new significant finding developed during the course of this study, which might affect your willingness to continue participation will be communicated to you.

California Experimental Subject's Bill of Rights

(a) Be informed of the nature and purpose of the experiment.

(b) Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

(c) Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

(d) Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

Subject's Initials: _____

IRB APPROVED DATE 06/14/13 INT _____ EXP 07/23/14 NAVAL MEDICAL CENTER SAN DIEGO

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(e) Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.

(f) Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

(g) Be given an opportunity to ask any questions concerning the experiment or the procedures involved.

(h) Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

(i) Be given a copy of the signed and dated written consent form as provided for by Section 24173 or 24178.

(j) Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

15. CAN I BE TERMINATED FROM THE STUDY?

The investigator may terminate your participation in this study for the following reasons: If you are found to be pregnant and/or taking medications known to interfere with the measurements of salivary alpha-amylase, such as certain high blood pressure medications and/or certain asthma medications. You may also be excluded from the study if you have any metabolic disorder (e.g., diabetes) or undergoing cancer surgery.

16. SIGNATURE

You are making a decision whether or not to participate in the research project above. Your signature indicates that you have had this information presented to you, have had the opportunity to ask questions about the research and your participation, and agree to participate in the study. Further, your signature indicates that you have been provided with a copy of this consent document, a Health Information Portability and Accountability Act (HIPAA) Patient Authorization form, and a document entitled, "California Experimental Subject's Bill of Rights."

Subject's Initials: _____

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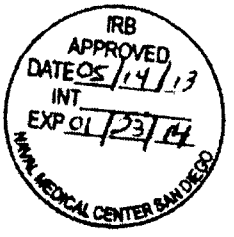
SIGNATURES AND **DATE** SIGNED: **PRINTED** OR **TYPED IDENTIFICATION**:

Patient / Subject	(Date)	Name
Investigator/Researcher	(Date)	Name / Grade or Rank

Subject's Initials: _____

IRB Approval Stamp/Seal Required
(Do not make any alterations to this documents w/out prior approval)



Appendix J

Clinical Investigation Department
Naval Medical Center, San Diego
34800 Bob Wilson Drive, Suite 5
San Diego, CA 92134-1005
Tel: 619-532-9927; FAX: 619-532-8137
Email: mary.massello@med.navy.mil

March 19, 2013

From: Head, Clinical Investigation Department (CID)

To: **LCDR Orlando Rivera, NC, USN**

Subj: **FINAL APPROVAL OF CLINICAL INVESTIGATION PROGRAM (CIP)**
STUDY CIP #NHCP.2012.0104, "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?"

Ref: (a) NAVMEDCEN SDIEGOINST 6500.9A

[select one of the following #1s and delete the other]

1. Two members of the Institutional Review Board (IRB) have reviewed and recommended approval of your application and found that it meets the criteria specified in 63 CFR 60364-60367 categories 3 and 7. Based on the board members findings and recommendation, and his review, the IRB Chairman concurred with the recommendation as specified and reported in the January 23, 2013 IRB meeting minutes. The IRB members and Chairman reviewed all documents attached to the original submission. Naval Medical Center San Diego holds Office of Human Research Protections Federal Wide Assurance number **FWA00002342** and **DOD Navy Assurance number 40005**.

1. The Institutional Review Board (IRB) has reviewed and recommended approval of the application that involves human research subjects, as reported in the January 23, 2013 IRB meeting minutes. This board reviewed all documents attached to the original submission. Naval Medical Center San Diego holds Office of Human Research Protections Federal Wide Assurance number **FWA00002342** and **DOD Navy Assurance number 40005**.

2. **IRB APPROVAL DATE:** January 24, 2013
Type of Review: Expedited Review

3. **CLINICAL INVESTIGATION PROGRAM NUMBER (CIP#):** NHCP.2012.0104
This number is the clinical investigation program number and is required to be included with all correspondence, consent forms, and research data files.

4. **ADVERSE EVENT (AE) REPORTING:** All problems that could possibly effect subject safety must be reported to the IRB within five days: serious AEs must be reported within 24 hours. All deaths, whether or not they are directly related to study procedures, must be reported.

5. **AMENDMENTS:** Prior IRB approval is required before implementing *any* changes to the protocol, including investigator additions or deletions, edits to consent documents or any other modifications to the documentation contained in the original submission package.

6. **EXPIRATION DATE:** Your protocol will expire on January 23, 2014. If the project is to continue, it must be renewed ***prior to the expiration date***.

7. **COMMENT: The Research Administration Office will send you a *Continuing Review Report (CRR) approximately 60 days prior to the expiration of the study.*** The IRB wishes to remind you that, according to the Department of Health and Human Services (DHHS) and NMCSD policy, the renewal of exempt research projects is the ***Investigator's*** responsibility and a renewal application is required ***at least*** annually for all projects involving human subjects.

8. **ARTICLES/ABSTRACTS/POSTERS:** : If you wish to submit an item for publication or presentation, it must be submitted to the CID Medical Editor, Ms. Elisea Avalos.Ms. Avalos can be reached at (619) 532-6134, she will assist in their preparation, will ensure proper acknowledgment of BUMED as sponsor, will obtain command approval and submit them to journals and publications.

9. The Principal Investigator is responsible for obtaining final authorization to begin implementation and recruitment at Naval Hospital Camp Pendleton. The PI is directed to contact Command Research Coordinator, Mary Massello at 619-532-9927 to facilitate the final approval of NHCP's Commander.

10. **QUESTIONS:** Please contact the IRB Research Administration Division (RAD) if you have any questions.

Mary Massello at 619-532-9927

J.D. Malone, MD
Head, Clinical Investigation Department

TRISERVICE NURSING RESEARCH PROGRAM
Fostering Excellence in Military Nursing Science

6 July 2012

Kimberlee T. Eudy
Director, Office of Sponsored Programs
University of San Diego
5998 Alacala Park, Room 264
San Diego, CA 92110-2492
keudy@sandiego.edu

SUBJECT: TriService Nursing Research Program Grant HT9404-12-1-TS16, (N12-P16), "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?" Principal Investigator: LCDR Eric Bopp

Dear Ms. Eudy:

I congratulate Principal Investigator (PI) LCDR Eric Bopp! The TriService Nursing Research Program (TSNRP) Executive Board of Directors approved LCDR Bopp's grant application for funding with stipulations. Given concerns raised during the review process, LCDR Bopp must address the following stipulations:

- Add a combat stress consultant
- Consider adding a control group
- Provide some revision to the informed consent form
- Consider not wearing a uniform when consenting subjects.

I request that the PI respond to the stipulations by **3:00 pm EDT on 20 July 2012.** Please submit the PI's response in a Word document to john.maye@usuhs.edu. Please inform me if it will be difficult for the PI to meet this deadline.

Enclosed are the following documents for the PI's reference: the primary, secondary, and military reviewers' evaluations.

If the PI satisfactorily addresses each stipulation, the Financial Management Office of the Uniformed Services University of the Health Sciences (USU) will process the financial paperwork to encumber the funds for this grant award. Within the next few weeks, you will receive the Notice of Grant Award and Grant Agreement. These documents outline the financial and contractual elements of the grant award. In addition, please review the enclosed USU General Terms and Conditions for Assistance Awards and the TSNRP Supplement to Grant Terms and Conditions.

4301 Jones Bridge Road • Bethesda, MD 20814 • Tel: 301-319-0596 • Fax: 301-319-0603 • www.usuhs.mil/tsnrp

The Institutional Review Board must approve the research study before the PI begins to conduct the study. The PI must forward a copy of the submitted protocol, approved consent form, and IRB approval letter from each performance site to my office as soon as possible. A designated person at the USU will review these documents and decide whether to accept the recommendation of the IRB. My staff will coordinate the USU review process on behalf of the PI. Once these requirements are complete, I will send an official start letter to you. **The PI is not authorized to expend funds or begin the research until I send an official start letter to her**.

All members of the research team must complete training related to the protection of human subjects. The PI must send documentation of this training to the TSNRP office. If any team members are unable to obtain this required training at their facility, a member of my staff or I can provide further information about how to complete an on-line training course.

Each year, the TSNRP sponsors a Post Award Grant Management Workshop for recipients of a grant award and their project director. The workshop is designed to facilitate successful implementation of the study. The Post Award Grant Management Workshop will be held during the summer of 2012. Workshop attendance is mandatory for Principal Investigators who have not previously attended the workshop. More information about the workshop will be forthcoming

Again, congratulations! My staff and I look forward to working with your office and the research team on this endeavor. If you have any questions, please feel free to contact Debra Esty, Senior Grants Manager or myself at (301)319-0596. Thank you for your organization's continued support of military nurse scientists and the TSNRP.

JOHN P. MAYE, CRNA, PhD, CAPT, NC, USN
Executive Director
TriService Nursing Research Program

Enclosures: As stated
cc: LCDR Eric Bopp
ericjbopp@me.com

8 July 2013

Kimberlee T. Eudy
Director, Office of Sponsored Programs
University of San Diego
5998 Alacala Park, Room 264
San Diego, CA 92110-2492
keudy@sandiego.edu

SUBJECT: TriService Nursing Research Program Grant HT9404-12-1-TS16, (N12-P16), "Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?" Principal Investigator: LCDR Eric Bopp

Dear Ms. Eudy:

The TriService Nursing Research Program (TSNRP) has received the human use documentation from the Institutional Review Boards of the Naval Medical Center San Diego and the University of San Diego indicating Initial Approval for the above referenced TSNRP study. The documentation has been reviewed and accepted by the Uniformed Services University of the Health Sciences Office of Scientific Management for Grants and Contracts. Enclosed please find a copy of the acceptance memorandum for your records. This is the **START LETTER** for the study.

If you have any questions, please contact Donna Gentry, Grants Manager, at 301-319-0589 or donna.gentry.ctr@usuhs.edu.

Michael Schlicher, PhD, RN
LTC, AN
Executive Director
TriService Nursing Research Program

Enclosures: As stated
cc: LCDR Eric Bopp
ericjbopp@me.com

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Phone: (301) 295-3303

June 24, 2013

MEMORANDUM FOR LCDR ERIC BOPP, UNIVERSITY OF SAN DIEGO, AND TRISERVICE NURSING RESEARCH PROGRAM

SUBJECT: Acceptance of University of San Diego IRB Initial Review Approval of **TSNRP (N12-P16) [2013-06-206]** for Human Subjects Research Participation

In accordance with Department of Defense Directive 3216.02 dated 8 November 2011, USU accepts the 14 June 2013 Initial Review Approval by the University of San Diego (USD) Institutional Review Board (IRB) regarding the research protocol entitled ***"Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?"***. There are two sites for this study: Naval Hospital Camp Pendleton which operates under the IRB of Naval Medical Center, San Diego, and the University of San Diego. The documents for this action were received by the Office of Scientific Management for Grants & Contracts (OSM) on 19 June 2013.

The purpose of this study is to determine the predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health disorders (i.e., anxiety, depression, and PTSD). This is a prospective, descriptive study that will recruit 120 active duty military members scheduled for elective surgery at Naval Hospital Camp Pendleton. This is a greater than minimal risk study. The medical monitor is Patrick Mullin.

You are required to submit amendments to this protocol, continuing reviews, adverse event reports, and other pertinent information relative to human research protections for this project to this office for review prior to changes being implemented. You are also required to submit human subjects' protection training certification every three years.

If you any questions regarding this action, please call me at 301-295-8999 or contact me at Charles.salter@usuhs.edu.

Charles A. Salter, Ph.D., S. D.
LTC (ret), U.S. Army
Scientific Director,
Office of Scientific Management for Grants & Contracts

cc: Executive Director, TSNRP (LTC Michael Schlicher)
File

Learning to Care for Those in Harm's Way

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June 24, 2013

MEMORANDUM FOR LCDR ERIC BOPP, NAVAL MEDICAL CENTER, SAN DIEGO, AND TRISERVICE NURSING RESEARCH PROGRAM

SUBJECT: Acceptance of Naval Medical Center, San Diego IRB Initial Review Approval of **TSNRP (N12-P16) [#NMCSD.2012.0104]** for Human Subjects Research Participation

In accordance with Department of Defense Directive 3216.02 dated 8 November 2011, USU accepts the 19 March 2013 Initial Review Approval by the Naval Medical Center, San Diego (NMCSD) Institutional Review Board (IRB) regarding the research protocol entitled ***"Is Combat Exposure Predictive of Higher Preoperative Stress in Military Members?"***. There are two sites for this study: Naval Hospital Camp Pendleton which operates under the IRB of Naval Medical Center, San Diego, and the University of San Diego. The documents for this action were received by the Office of Scientific Management for Grants & Contracts (OSM) on 19 June 2013.

The purpose of this study is to determine the predictive relationships between the number of combat experiences and the preoperative psychological and physiological stress response in U.S. military personnel on the day of surgery independent of mental health disorders (i.e., anxiety, depression, and PTSD). This is a prospective, descriptive study that will recruit 120 active duty military members scheduled for elective surgery at Naval Hospital Camp Pendleton. This is a greater than minimal risk study. The medical monitor is Patrick Mullin.

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If you any questions regarding this action, please call me at 301-295-8999 or contact me at Charles.salter@usuhs.edu.

Charles A. Salter, Ph.D., S. D.
LTC (ret), U.S. Army
Scientific Director,
ific Management for Grants & Contracts

cc: Executive Director, TSNRP (LTC Michael Schlicher)
File

Learning to Care for Those in Harm's Way

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