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Cognitive function, stress hormones, heart rate and nutritional status during simulated captivity in military survival training

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HIGHLIGHTS

- Cognitive, hormonal, heart rate and nutritional responses to stress were assessed.
- The study was conducted in an environment designed to simulate wartime captivity.
- Reasoning, attention, working memory and various aspects of mood were degraded.
- Cortisol, DHEA-s, prolactin and testosterone were significantly lower.
- Epinephrine, norepinephrine and neuropeptide-Y and heart rate increased.

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ABSTRACT

Stress influences numerous psychological and physiological processes, and its effects have practical implications in a variety of professions and real-world activities. However, few studies have concurrently assessed multiple behavioral, hormonal, nutritional and heart-rate responses of humans to acute, severe stress. This investigation simultaneously assessed cognitive, affective, hormonal, and heart-rate responses induced by an intensely stressful real-world environment designed to simulate wartime captivity. Sixty males were evaluated during and immediately following participation in U.S. Army Survival, Evasion, Resistance, and Escape (SERE) school, three weeks of intense but standardized training for Soldiers at risk of capture. Simulated captivity and intense mock interrogations degraded grammatical reasoning ($p < 0.005$), sustained-attention ($p < 0.001$), working memory ($p < 0.05$) and all aspects of mood assessed by the Profile of Mood States (POMS) questionnaire: Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigor/Activity, Fatigue/Inertia; Confusion/Bewilderment, and Total Mood Disturbance ($p < 0.001$) It also elevated heart rate ($p < 0.001$); increased serum and salivary cortisol and dehydroepiandrosterone-sulfate (DHEA-s) ($p < 0.01$); elevated serum epinephrine, norepinephrine, and soluble transferrin receptors (sTfR) ($p < 0.01$); increased salivary neuropeptide-Y (NPY) ($p < 0.001$); and decreased serum prolactin and serum and salivary testosterone ($p < 0.001$). Partial recovery was observed immediately after training, but stress-induced changes, particularly in body weight and several of the biomarkers, persisted. This study demonstrates that when individuals were exposed to realistic and controlled simulated captivity, cognition, mood, stress hormones, nutritional status and heart rate are simultaneously altered, and each of these subsequently recovers at different rates.

1. Introduction

Stress influences numerous psychological and physiological processes [25], and its effects have practical implications in a variety of professions and real-world activities. In the medical/surgical profession, the stress of working under intense time pressure, often in a fatigued state, while performing complex life or death procedures has been found to delay task completion, degrade economy of motion, and increase errors, all of which may significantly compromise patient safety [2,3]. In law enforcement professions, such as police, intense anxiety in response to physical attacks or threats of injury by an assailant increases avoidance behavior, reduces the ability to inhibit stimulus-driven processing, decreases shooting accuracy, and degrades performance [71,78]. Stress has been associated with cynicism, emotional

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detachment, excessive aggression, and reduced efficiency among law enforcement officers [18]. Likewise, in military operations, exposure to multiple stressors including sleep deprivation, hunger, dehydration, environmental challenges (heat/cold), psychological strain (fear, anxiety), and exercise-induced fatigue significantly challenge the coping capacities of even the most stress-resistant individuals. As a result, critical cognitive and biological functions important for warfighter health and operational performance are significantly degraded [1,22,49,52–54,63–65,67,69,94,95].

Studies conducted on self-reported stress-sensitive versus resilient individuals, as well as evaluations of the stressful effects of college examinations and of situations in which stress levels are manipulated with laboratory tests such as the cold pressor task, the Stroop test, public speaking, the Trier Social Stress Test, and others [19], have identified a range of cognitive, mood, and perceptual effects of brief, acute stress. These include alterations in episodic, declarative, and working memory [82,86,101]; increased depression, anxiety, agitation, and negativity [97]; degradations in simple and potentially complex decision making [26,43,90–92]; reductions in attention [42,81]; impaired attentional inhibition [88]; changes in perceptual- and psychomotor performance [89]; reduced executive functioning [93], and degradation in sleep quality [28].

Some of the hormonal changes due to exposure to stress include increased cortisol [25] and dehydroepiandrosterone (DHEA) levels [48], as well as reduced testosterone and insulin-like growth factor I (IGF-I) [22]. Physiological changes include increases in heart rate and blood pressure [24,41,44,45]; alterations in skin and body temperature [98]; elevations in electrodermal response and respiratory rate, [72]; and decreased heart rate variability (HRV) [96]. Extensive stress-related changes in the periphery, such as in cortisol and catecholamine levels, and the associated activation of specific brain regions (i.e., locus coeruleus, hippocampus, amygdala, and prefrontal cortex) impact alertness, vigilance, and other functions critical for coping with threatening, stressful circumstances (see [8]).

To comprehensively describe and understand the complex nature of the human stress response, concurrent assessment of behavioral, hormonal, and physiological processes is essential. However, an extensive review of the literature on physiological reactions to stress indicates that few carefully-controlled, applied human stress studies have been conducted. Also, very few studies of the effects of real-world stress, as opposed to laboratory-induced stress, have been performed. Taylor et al. [95] highlight the importance of conducting comprehensive studies in realistically stressful environments to expand our knowledge regarding the consequences of real-life stress exposure, facilitate development of operationally-useful stress-monitoring techniques, and promote the development of improved treatments for persistent stress-induced illnesses such as post-traumatic stress disorder (PTSD). Furthermore, since real-world stress situations appear to be much more stressful than laboratory stress paradigms [64], the findings from real-world studies, as opposed to laboratory evaluations, may permit better generalization to actual occupational settings because of their greater ecological and external validity.

One environment that provides a unique opportunity to study the impact of severe acute stress and simultaneously assess a wide array of psychological, physiological, and biochemical markers is military Survival, Evasion, Resistance, and Escape (SERE) school. Training in SERE school is required for U.S. military personnel at high risk of capture, and the demands of this 2–3 weeklong course appear to substantially exceed those of artificial laboratory situations [13,16,53,64,65,67,94,95]. During the first phase, the academic portion of SERE school, students receive several days of classroom training in survival, evasion, resistance, and escape techniques. Then they participate in a survival and evasion field exercise where they are required to navigate through several miles of unfamiliar hostile territory, locate water, hunt and trap small animals, build small shelters, and locate food while evading "enemy forces." This is particularly challenging since it requires students to deal with hunger, uncertainty, fatigue, and discouragement in a real-world environment. In the final phase of the course, students are "captured" by simulated hostile forces, transported to a mock POW camp, and subjected to highly stressful mock interrogations. This last phase is ultimately the most physically and psychologically demanding, aspect of the training [16]. The timing of each phase can vary across different SERE schools and from class-to-class within a single school, but the same phases, in the same sequence, are included in each.

The fundamental objective of SERE school is to prepare students for possible captivity, and to train them to cope, survive and recover physically and psychologically intact. An important aspect of the training is to "inoculate" participants against the highly stressful conditions that are expected to be experienced by prisoners of war (POWs) by exposing them to stress levels sufficient to activate the body's psychological and biological coping mechanisms, but not to stress the trainees so greatly as to overwhelm them beyond the possibility of recovery [62]. When stress inoculation occurs, it has been hypothesized that an individual's performance is likely to improve during subsequent stressful scenarios, and as a result of the training at SERE school, it is anticipated that the rates of emotional disturbance, physical trauma, PTSD diagnoses, and other mental health conditions that have in the past occurred among service personnel who were captured and detained as POWs will be mitigated [16]. Former POWs who attended SERE school prior to capture have reported that the training was extremely helpful [23].

From a research perspective, the highly standardized, structured nature of SERE training, as well as its demonstrated intensity, provide a unique environment to systematically examine warfighters' responses to stress. As the final portion of the course is designed to simulate the POW captivity experience, it provides an extraordinary opportunity to study the biochemical, nutritional, heart-rate and behavioral changes which occur in response to this particularly demanding military training environment. In addition, mock interrogations offer unique opportunities to explore human responses to an especially stressful, militarily-relevant situation [64,65,67,69].

The objective of the present study was to extend previously published research on acute and chronic stress by comprehensively examining classic markers of stress, such as cortisol and heart rate, in combination with multiple measures of cognitive performance, mood state, and biochemical, nutritional and metabolic markers. In this investigation, these parameters were simultaneously assessed during non-stressful and high-stress SERE-training activities. Changes in nutritional status also were assessed to account for the contribution of this factor to the acute stress of SERE school. It was hypothesized that cognitive performance and mood state would deteriorate as a function of the physiological and biochemical changes induced by stress associated with the capture and interrogation of participants.

2. Method

2.1. Volunteers

The study protocol was approved by the Human Use Review Committee at USARIEM. Volunteers participated in this study after giving their free and informed consent. Investigators adhered to Army Regulation 70–25 and U.S. Army Medical Research and Materiel Command Regulation 70–25 on the use of volunteers in research. Sixty male SERE school students, all enrolled in the US Army Special Forces training course, were recruited. These 60 participants represented approximately 30–40% of the total number of enrolled personnel attending 3 separate SERE school classes over a 3-month period. Enrollment in each course is limited to 100 students, and we estimate that approximately 80 personnel were enrolled in each of the courses from which the subjects for this study were drawn. Approximately 50% of eligible students volunteered for the study and the 20 who were tested from each class were randomly selected from the larger pool of volunteering students. All volunteers were male as females were not permitted in the US Army Special Forces when the study was conducted. Participants were

aged 21–34 years (mean ± SEM, 26.92 ± 0.37 years) and weighed 65–103 kg (mean ± SEM, 85.37 ± 1.03 kg). They had served 4.4 ± 2.7 years (mean ± SD) on active duty. Fifteen of the volunteers were officers and 45 were enlisted personnel. There was no attrition among the volunteers who enrolled.

2.2. Testing schedule

After providing informed consent in the presence of an ombudsman and absence of course instructors or cadre, volunteers completed a demographic questionnaire and were trained on the behavioral tests to be administered. Fig. 1 depicts the study time line. Training sessions were conducted at noon during the academic phase of SERE training on 3 separate days. The last of these training sessions served as a measure of baseline performance for comparison to measures obtained during and immediately following the captivity segment of SERE training. At the start of the captivity phase (capture) a saliva sample was collected. There were two testing sessions conducted during the captivity segment, each immediately following a mock interrogation. The exact timing of testing sessions varied across the three separate SERE-course iterations due to factors beyond study control (testing was not permitted to interfere with the training objectives). The timing of baseline training on the cognitive tests, mood evaluations, and the saliva sampling was consistent across all 3 iterations, with training on cognitive/mood tests occurring at noon and accompanied by concurrent saliva sampling (saliva was also collected on the mornings and evenings of the baseline days). Baseline blood collection occurred only during the morning time in conjunction with the collection of saliva samples. Thus, there was a high degree of concordance in the timing of baseline testing. However, during captivity phase testing periods, the timing varied between the first SERE iteration and the second and third SERE iterations. During the first iteration, the data-collection sessions (cognitive, mood, and hormonal) occurred in the morning following Interrogation 1, the afternoon and evening following Interrogation 2, and in the early afternoon upon release from SERE. During the second and third iterations, the three sessions occurred late at night (following Interrogation 1), mid- to late-afternoon (following Interrogation 2), and late afternoon (upon release).

2.3. Biochemical markers of stress and nutritional status

In order to assess the physiological level of stress and indicators of nutritional status of the volunteers, a number of established markers of these functions were measured in saliva and venous blood samples.

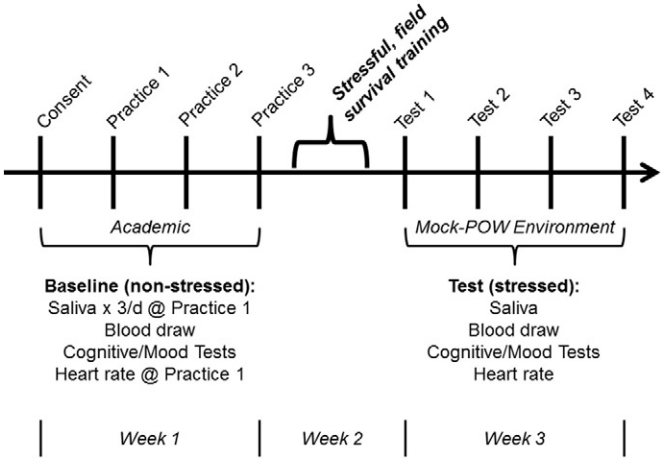

Fig. 1. Timeline of testing and biomarker sampling during the approximately three weeks of SERE training (see text for details). Timing of each phase varies from SERE school to SERE school and can vary within each school.

2.3.1. Venous blood samples

In conjunction with cognitive testing (Fig. 1), 15 ml blood samples were collected. A fasted baseline sample was collected on the last academic training day; captivity-phase collections were conducted immediately (within 5–10 min) after the two mock interrogations; and recovery samples were collected immediately (within 10–20 min) after completion of the captivity phase. Markers associated with stress, including cortisol, epinephrine, norepinephrine, neuropeptide Y (NPY), dehydroepiandrosterone sulfate (DHEA-s), prolactin, and testosterone were assessed. Cortisol is the most widely accepted biological marker of activation of the hypothalamus-pituitary-adrenal axis (HPA) in humans [38,46]. The hormone DHEA-s is an established marker of stress; it appears to persist longer after release than cortisol [68]. NPY elevations have been shown to occur in response to stressful circumstances and may contribute to superior military performance [64,66]. There is substantial evidence that testosterone is suppressed when individuals are exposed to chronic anxiety [20] and that it is acutely sensitive to energy deficit [9]. Epinephrine and norepinephrine are rapidly released in response to stress in order to decrease visceral activity; increase visual acuity; increase brain blood flow and arousal; increase breathing efficiency; release glucose stores for energy; induce vasodilation in muscles; promote vasoconstriction in the periphery; and increase heart rate–the suite of responses associated with the classic fight-or-flight reaction [80]. Soluble transferrin receptor (sTfR) measurements are useful for identifying iron deficiency anemia which might be anticipated after caloric restriction. The circulating sTfR concentration is proportional to cellular expression of the membrane-associated sTfR and increases with increased cellular iron needs and cellular proliferation [47]. Prolactin has been found to play a role in humoral or cell-mediated immunity, and while a great deal of uncertainty about this hormone exists, it appears that prolactin serves an immunomodulatory protective function in response to stress [21].

2.3.2. Saliva samples

Saliva samples for several metabolites associated with the stress response were assessed, including cortisol, testosterone, NPY, and DHEA-s [61,67]. Hormone levels in saliva have been shown to be highly correlated with those in blood [35,38], and since the collection of saliva-based stress markers is far less invasive and disruptive than collection of blood, collection and analysis of saliva is often more practical in real-world environments. In the present study, blood sampling was not possible during initial capture, but saliva sampling was permitted, making it possible to collect additional post-baseline data.

To account for circadian effects, baseline saliva samples were collected in the morning, midday and evening of the classroom phase of training. Samples were also collected during two practice periods (in the morning); at the students' initial capture (in the evening); during each cognitive test session in the captivity phase; and in the late afternoon following the conclusion of training (Fig. 1). Saliva (10 ml) was collected via straw into a cryovial. Prior to saliva collection, volunteers rinsed their mouths two times with water, and then waited approximately five minutes before saliva collection. The samples were stored at -70° C and shipped on dry ice to the Pennington Biomedical Research Center where they were assayed for cortisol, testosterone, DHEA-s, and NPY using standard procedures.

2.4. Heart rate

Electrocardiographic (ECG) data were collected at 256 samples per second using the EquiVital type 1 Sensor Electronics Module (SEM) (Hidalgo Ltd., Cambridge, U.K.). Data from three volunteers were unusable, and so they were deleted from the database. The SEM was secured on the volunteer's chest prior to each mock interrogation and was removed at the conclusion of each data collection session. The total time wearing the monitor during the captivity phase was ~2 h. In addition to wearing the monitor during the captivity phase, volunteers were also asked to

wear it for up to 12 h during the academic instructional phase. This provided an opportunity for volunteers to become familiar with wearing the monitor and provided baseline data for comparison to data obtained during the captivity phase. Heart rates were calculated from R-R wave mean distances over 5 min epochs via VivoSense version 2.0 software (Vivonoetics, Honolulu, HI). During the mock interrogations, volunteers were typically in a standing position, with limited physical stress occurring. During the classroom sessions, subjects were either seated or standing.

2.5. Body weight

Body mass was measured using a calibrated electronic scale (A&A Scales, Prospect Park, NJ). Body mass was assessed at the beginning and end of SERE training, and volunteers wore standard physical-training apparel (i.e. shorts and a t-shirt) when assessed.

2.6. Cognitive tests

To ensure testing did not interfere with SERE training, four computerized cognitive tests were selected that could be conducted rapidly (30–40 min) and are sensitive to operational stressors [5,49,55,85]. Two of these tests were administered to all volunteers – Psychomotor Vigilance Test (PVT) and Match-to-Sample. To minimize the total time required for testing any single volunteer, a split-plot paradigm [37] was employed for two other assessments–one cognitive test (N-back) was administered to one half of the volunteers and another (Grammatical Reasoning) was administered to the other half. Due to the use of the split-plot paradigm and the existence of logistical constraints, there was some variation in the number of volunteers who completed each of the cognitive tests: 30 completed Grammatical Reasoning, 30 completed N-back, 50 completed Match-to-Sample with an 8 s delay, 48 completed Match-to-Sample with a 16 s delay, and 50 volunteers completed the PVT.

2.6.1. Grammatical reasoning

This test, adapted from the Baddeley Grammatical Reasoning Test, assessed language-based logical reasoning and has been used to assess the effects of various treatments on cognitive function [4]. On each trial, the letters AB or BA followed a statement. The volunteer decided whether or not each statement correctly described the order of the two letters. Statements could be positive/negative or active/passive, and a given letter may have preceded or followed the other letter. A session lasted for 32 trials and was made up of the above combination of statements. The time to complete this test was approximately 5 min.

2.6.2. N-back

This test assesses working memory and predicts inter-individual differences in other higher cognitive functions, such as fluid intelligence [34]. It requires on-line monitoring, updating, and manipulation of remembered information and allows for the parametric assessment of different working memory loads. Participants were asked to monitor the identity or location of a series of verbal (letters) stimuli and to indicate when the currently presented stimulus was the same as the one presented "n" trials back (e.g. 1 or 2). Participants were presented with letters one at a time in the center of the monitor and asked to determine if a letter presented was the same as the previous letter (1-back condition) or the one presented 2 letters back (2-back condition). Dependent measures included number of false alarms, number correct, number missed, and total number of correct responses. This task took approximately 10 min to complete.

2.6.3. Match-to-sample

This test assessed short-term spatial memory (working memory) and pattern recognition skills and has been shown to be sensitive to the effects of stress in several previous studies [49,52,54,85]. The volunteer responded by pressing the down arrow key when the word "READY" appeared on the screen. The volunteer was then presented with an 8×8 matrix of a red and green checkerboard on a color screen for 4 s. The sample matrix was removed and was followed by a presentation of a blank screen for either 8 or 16 s. After the delay, the volunteer was required to select one of two matrices which were presented: the original sample matrix vs. a second matrix that differed slightly in that the color sequence of two of the squares was reversed. The 16 s delay trials are more difficult as they require the volunteer to retain the information in working memory for a longer period of time. The task lasted approximately 5 min. A response had to be made within 15 s; otherwise a time-out error was recorded. Correct responses and response times were recorded.

2.6.4. Psychomotor Vigilance Test (PVT)

The PVT assesses simple visual reaction time [15] and is one of the most sensitive tests to the effects of sleep-deprivation and operational stress on human cognitive performance [5,36,58]. A series of stimuli was sequentially presented at random inter-trial intervals on a screen, and the volunteer responded as rapidly as possible when a stimulus appeared. The test required volunteers to maintain attention during a tedious task. Parameters recorded included reaction time, false alarms and number of lapses (long duration responses). A key dependent variable is the occurrence of a lapse as this indicates when a volunteer fails to respond in a timely manner (i.e., >500 ms) or in some cases, fails to respond entirely. This task took approximately 10 min to complete.

2.7. Mood states

The *Profile of Mood States* (POMS) is a widely used, standardized, inventory of mood states [60]. It is sensitive to a variety of nutritional manipulations, environmental factors, sleep loss and sub-clinical doses of various drugs [49–52,54,84]. Volunteers rated a series of 65 mood-related adjectives on a five-point scale, in response to the question, "How are you feeling right now?" Scores on six mood sub-scales (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) were then calculated [60]. It takes <5 min to complete. The POMS was always administered in conjunction with cognitive testing.

2.8. Statistical analyses

Statistical analysis was performed using commercially available statistical software (SPSS 20.0; IBM, Inc., Armonk, NY, USA). For longitudinal comparisons of variables, normally distributed means were compared using repeated measures ANOVA, with a Greenhouse-Geisser correction if sphericity could not be assumed. A Bonferroni correction was applied to all post-hoc analyses. For variables that were not normally distributed (i.e., serum epinephrine and norepinephrine, saliva cortisol, NPY, DHEA-s, and testosterone) a Friedman Test was applied to determine significant differences over time, and post-hoc comparisons were made by a Wilcoxon Signed Ranks' test. Due to time, location, and equipment constraints, not all subjects completed all testing. The number of subjects taking each test is indicated in each table.

3. Results

First, this section examines the effectiveness of SERE Training at inducing stress by presenting results of the biochemical assays of stress and nutrition and changes in heart rate and body weight. Then changes in cognitive performance and mood state associated with these biomarkers of stress are presented.

3.1. Biochemical markers of stress and nutrition

3.1.1. Venous blood samples

The impact of SERE captivity and interrogation was reflected in increased levels of cortisol, DHEA-s, norepinephrine, epinephrine, and sTfR and, as expected, a marked decrease in serum testosterone levels (Table 1). These patterns are similar to those seen in the cognitive and mood data. Significant differences over time were found in values of serum cortisol ($F(2.665, 151.902) = 48.586$, $p < 0.001$), sTfR ($F(2.186, 124.624) = 4.771$, $p = 0.008$), and DHEA-s ($F(1.877, 106.980) = 177.254$, $p < 0.001$). Significant differences were also found for epinephrine (χ^2 (3) = 72.403, $p < 0.01$), norepinephrine (χ^2 (3) = 93.924, $p < 0.01$), ferritin (χ^2 (3) = 115.915, $p < 0.001$), and prolactin (χ^2 (3) = 64.772, $p < 0.001$) which were analyzed by the Friedman test as opposed to ANOVA with post hoc comparisons performed with Wilcoxon Signed Ranks tests due to their significant departure from normality.

3.1.2. Saliva

Saliva markers followed the same general patterns as the other variables in this study. There were marked changes during the captivity and interrogation phases along with a partial recovery at the end of SERE. All saliva biomarker levels, which were analyzed with the Friedman and Wilcoxon Signed Rank tests due to non-normality, were significantly different over the nine collection periods: cortisol (χ^2 (8) = 324.265, $p < 0.001$); NPY (χ^2 (8) = 222.308, $p < 0.001$); DHEA-s ($\chi 2(8) = 272.335$, $p < 0.001$); and, testosterone (χ^2 (8) = 263.562, $p < 0.001$) (Table 2). Although the variation in data-collection sessions across the 3 testing iterations introduced some circadian variation in the hormones assessed, the changes observed were expected. For example, cortisol levels dropped from morning to evening during baseline testing, but at the time of capture, even though the sample was collected in the evening, levels were considerably higher than observed in the evening baseline session. Also, most interrogations were conducted in the later part of the day when cortisol would have been expected to drop, but levels were generally high due to the stress induced by interrogations.

3.2. Heart rates

Heart rates during baseline, Interrogation 1, and Interrogation 2 differed significantly ($F(2, 112) = 234.8$, $p < 0.001$). Post-hoc pairwise comparisons across the respective mean values of 68.7 BPM, 97.6 BPM, and 124.6 BPM demonstrated that heart rate increased 42% from baseline to when interrogation 1 was compared to baseline and 81% when interrogation 2 was compared to baseline (all comparisons were significant).

3.3. Body weight

There was a substantial loss of body weight over the two-week SERE course. Recovery weight ($\overline{X} = 78.68$ kg, SE = 1.03) was significantly lower (t (29) = 55.096, $p < 0.01$, d = 0.86) than baseline weight ($\overline{X} = 85.37$ kg, SE = 1.03). This 6.69 kg mean change is a 7.8% loss in body mass. In previous military field studies, very large, acute changes in body weight have been shown to result from a combination of dehydration, physical activity, and undernutrition [49]. In this study the primary reasons for the observed weight reduction were: 1) during the survival phase of the training, little food was available (participants were required to forage for their sustenance); and 2) during the captivity phase, to simulate a harsh POW environment, very little food was provided by instructors.

3.4. Cognitive tests

Cognitive function was substantially degraded over the course of SERE school. In many cases, the pattern of degradation was consistent across test variables (Fig. 2).

3.4.1. Grammatical Reasoning

Performance on this logical reasoning task was substantially degraded by the stress of SERE training. Significant differences were found for the number of time out errors ($F(1.429, 34.307) = 7.533$, $p < 0.005$) and response times ($F(2.201, 52.823) = 7.533$, $p < 0.001$). In both cases, the most dramatic change was from baseline to interrogation 1.

3.4.2. N-back

Both variations of this working memory task were similarly affected across the testing sessions. There were significant differences detected on the number of correct targets for both sets of N-back tasks, 1-back and 2-back ($F(2.699, 77.399) = 5.600$, $p = 0.002$; and $F(2.692,78.071) = 10.863$, $p < 0.001$); as well as on the number of missed targets ($F(2.669,77.399) = 5.600$, $p = 0.002$; and $F(2.692,78.071) = 10.863$, $p < 0.001$); and the total number of correct responses ($F(1.807,52.393) = 5.542$, $p = 0.008$; and $F(1.935,56.111) = 4.279$, $p = 0.020$). For 1-back, the number of correct targets and total correct were reduced from baseline to

Table 1
Mean or median (MDN) serum biomarker changes over time.

	Baseline	Mock Interrogation 1	Mock Interrogation 2	End of SERE
	$\overline{x} \pm$ SE	$\overline{x} \pm$ SE	$\overline{x} \pm$ SE	$\overline{x} \pm$ SE
Cortisol (μg/dL)	$20.103 \pm 0.38^{b,c,d}$	$23.095 \pm 0.75^{a,c,d}$	$27.234 \pm 0.82^{a,b,d}$	$18.033 \pm 0.59^{a,b,c}$
DHEA-S (μg/dL)	$290.431 \pm 12.66^{b,c,d}$	$519.19 \pm 23.39^{a,c}$	$562.121 \pm 26.07^{a,b,d}$	$542.914 \pm 23.8^{a,c}$
sTfR (nmol/L)	18.966 ± 0.52^{c}	19.724 ± 0.54	$20.121 \pm 0.53^{a,d}$	19.241 ± 0.49^{c}
	Baseline	Interrogation 1	Interrogation 2	End of SERE
	MDN (Range)	MDN (Range)	MDN (Range)	MDN (Range)
Epinephrine pg/ml	$41^{b,c,d}$ (10–143)	$82^{a,d}$ (37–214)	$87^{a,d}$ (24–256)	$66^{a,b,c}$ (17–131)
Norepinephrine pg/ml	$403^{b,c,d}$ (160–985)	905^{a} (408–1171)	944^{a} (471–1334)	$785^{a,c}$ (320–1171)
Ferritin ng/ml	$103.5^{b,c,d}$ (33.9–312)	$233.5^{a,d}$ (87–479)	244.0^{a} (98–524)	$241.5^{a,b}$ (110–509)
Prolactin ng/ml	$12.2^{b,c,d}$ (5.6–31.6)	$8.2^{a,d}$ (2.1–17)	$8.3^{a,d}$ (2.9–26)	$5.1^{a,b,c}$ (2.1–12.5)
Testosterone ng/dl	$472^{b,c,d}$ (206–953)	$84^{a,c,d}$ (20–389)	$177^{a,b,d}$ (72–371)	$157^{a,b,c}$ (36–361)

[a]Significantly different from baseline; [b]Significantly different from Mock Interrogation 1; [c]Significantly different from Mock Interrogation 2; [d]Significantly different from End of SERE.

Table 2
Median (MDN) saliva biomarker changes over time.

Variable	Baseline AM MDN (Range)	Baseline Mid-day MDN (Range)	Baseline PM MDN (Range)	Practice 1 MDN (Range)	Practice 2 MDN (Range)	Capture MDN (Range)	Mock interrogation 1 MDN (Range)	Mock interrogation 2 MDN (Range)	End of SERE MDN (Range)
Cortisol μg/ml	0.451 (0.13–0.90)	0.092 (0.02–0.44)	0.043 (0.01–0.55)	0.073 (0.02–0.82)	0.077 (0.02–0.26)	0.337 (0.02–0.74)	0.249 (0.04–1.04)	0.270 (0.05–0.77)	0.133 (0.05–0.49)
NPY pmol/l	107.00 (49–279)	87.05 (46.1–194.8)	79.70 (45–132)	89.75 (44.8–150.5)	83.40 (39.6–145.1)	144.95 (55.3–780.9)	86.20 (46–374)	117.55 (59.5–368)	106.50 (50.5–388.9)
DHEA-s pg/ml	2844 (680–15,300)	1665 (374–8997)	1595 (276–8716)	1268 (421–4448)	1316 (379–6178)	6894 (1453–1530)	3049 (535–15,300)	3932 (968–15,300)	3427 (856–15,300)
Testosterone pg/ml	101.3 (46.8–176)	70.1 (32.1–162.5)	42.7 (15.9–84.9)	67.1 (33–198.2)	63.85 (39–151.1)	55.25 (28.5–115.9)	34.8 (14.2–80.2)	46.5 (24.2–329.7)	43.1 (13.1–70.5)

Notes: 1) Observe the expected circadian variation during morning-to-evening testing under baseline, but note that even though most saliva sampling during captivity and interrogations occurred in the later part of the day, values were generally higher than would have been expected based on circadian factors due to the stress of SERE training.
2) Non-significant differences in these data are indicated below.

Variable	Non-significant differences	Variable	Non-significant differences
Cortisol	Baseline mid-day and baseline PM Baseline mid-day and practice 1 Practice 1 and practice 2 Capture and mock interrogation 1 Mock interrogation 1 and Mock interrogation 2	NPY	Baseline AM and End of SERE Baseline mid-day and Practice 1 Baseline mid-day and Practice 2 Baseline mid-day and Mock interrogation 1 Practice 1 and practice 2 Practice 1 and Mock interrogation 1 Practice 2 and Mock interrogation 1 Mock interrogation 2 and End of SERE
DHEA-s	Baseline AM and mock interrogation 1 Baseline mid-day and baseline PM Practice 1 and practice 2 Mock interrogation 2 and end of SERE	Testosterone	Baseline mid-day and practice 1 Baseline mid-day and practice 2 Baseline PM and Mock interrogation 2 Baseline PM and end of SERE Practice 1 and practice 2

interrogation 1 and release while the number of misses was increased. For 2-back, the differences in number correct and misses were attributable to changes from baseline to each of the remaining test sessions, and the differences in total correct were attributable to changes from baseline to each of the interrogations. Performance on the 2-back trials was generally worse than performance on 1-back trials as expected due to the greater demands of remembering two of the previously-presented stimuli as opposed to the single stimulus that immediately preceded the current one.

3.4.3. Match-to-sample

Analysis of Match-to-Sample with the 8-second delay and Match-to-Sample with the 16-second delay also revealed performance degradations from baseline to one or more of the subsequent testing sessions. There were statistically-significant changes in the number of correct answers ($F(3, 147) = 76.072$, $p < 0.001$; and $F(3, 141) = 5.197$, $p = 0.002$); the number of incorrect answers ($F(3, 147) = 2.834$, $p = 0.043$; $F(3, 141) = 4.454$, $p = 0.005$); the number of lapses ($F(3, 147) = 12.790$, $p < 0.001$; $F(3, 141) = 11.204$, $p < 0.001$); and the response times ($F(2.347, 115.022) = 6.046$, $p = 0.002$; $F(2.522, 118.553) = 9.321$, $p < 0.001$) on both variations of this task. In most cases, the most pronounced stress-related degradations in performance occurred from baseline to the first interrogation, but there were other differences as well as noted in Fig. 2.

3.4.4. PVT

Sustained attention was likewise affected by the stress of captivity and mock interrogations. There were significant effects on premature responses ($F(3, 147) = 16.422$, $p < 0.001$), number of lapses ($F(2.597, 127.264) = 16.442$, $p < 0.001$), correct answers ($F(3, 147) = 21.504$, $p < 0.001$), and response times ($F(3, 147) = 50.240$, $p < 0.001$). The session effects on premature responses, correct responses, and response times were due to deterioration in performance from baseline compared to the remaining test sessions, and the effect on number of lapses was similar although there were several between-session differences as well (Fig. 2).

3.5. Mood states

As demonstrated by the POMS, there were severe decrements from baseline to the first interrogation, with most aspects of mood improving dramatically when the captivity phase of SERE training ended (Fig. 3). All mood states changed significantly over the course of training (Tension/Anxiety: ($F(2.463, 120.665) = 84.8$, $p < 0.001$); Depression/Dejection: ($F(2.385, 114.460) = 45.931$, $p < 0.001$); Anger/Hostility: ($F(2.766, 129.984) = 44.709$, $p < 0.001$); Vigor/Activity: ($F(2.405, 117.828) = 98.156$, $p < 0.001$); Fatigue/Inertia: $F(2.522, 123.555) = 199.836$, $p < 0.001$); Confusion/Bewilderment: ($F(2.488, 121.902) = 83.505$, $p < 0.001$); and Total Mood Disturbance: ($F(2.496, 122.284 = 134.782)$, $p < 0.001$). Fatigue, Confusion, and Total Mood Disturbance (TMD) increased while Vigor decreased from baseline to interrogation 1, stabilizing at interrogation 2, and recovering at the end of the captivity phase, although not to baseline levels. The changes in the Depression and Anxiety were similar to those of the other subscales, but returned to baseline by the end of SERE. Tension increased from baseline to interrogation 1, significantly decreased by interrogation 2, and decreased again by the end of SERE, though not to baseline values.

4. Discussion

The acute and chronic stress, modest physical demands, and caloric deprivation associated with SERE training: 1) substantially degraded mental and psychological functioning as demonstrated by significant and robust effects on multiple cognitive tasks and mood scales; 2) activated the HPA, as demonstrated by increased levels of the catabolic hormone cortisol and suppressed release of the

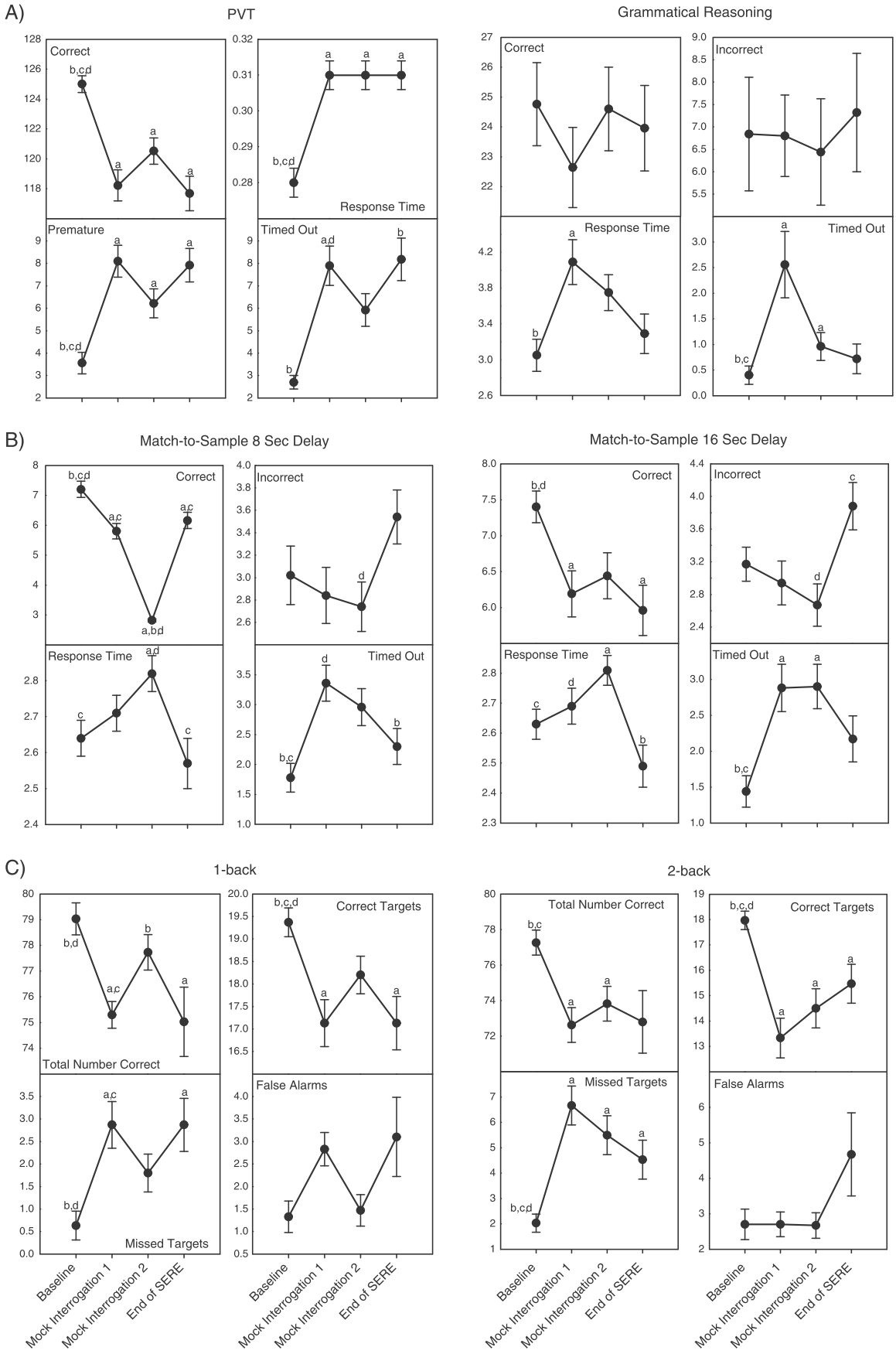

Fig. 2. The impact of SERE training at baseline, mock interrogation 1, mock interrogation 2, and release (End of SERE) on vigilance, logical reasoning and short-term spatial memory as assessed by the (A) Psychomotor Vigilance (PVT) and Grammatical Reasoning tests; (B) Match-to-Sample test; and (C) the N-Back Test. [a]Significantly different from baseline; [b]Significantly different from Mock Interrogation 1; [c]Significantly different from Mock Interrogation 2; [d]Significantly different from End of SERE.

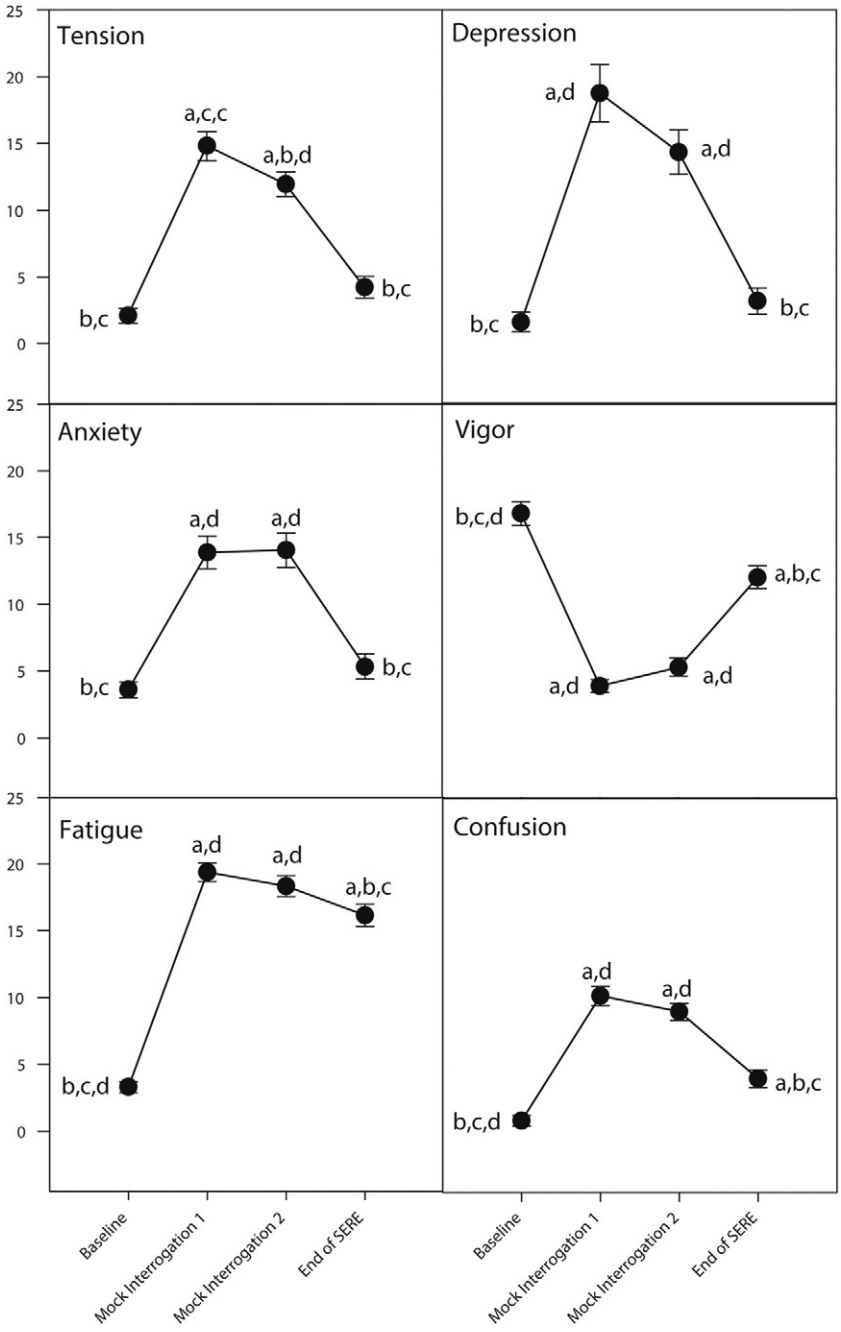

Fig. 3. The impact of SERE training at baseline, mock interrogation 1, mock interrogation 2 and release (End of SERE) on mood states as assessed with the POMS. [a]Significantly different from baseline; [b]Significantly different from Mock Interrogation 1; [c]Significantly different from Mock Interrogation 2; [d]Significantly different from End of SERE.

anabolic hormone testosterone; and 3) induced sympathetic nervous system arousal as indicated by substantially elevated epinephrine, norepinephrine, and heart rate in the absence of highly-strenuous physical activity. All of these changes are recognized as part of the cascade of physiological and psychological events classically associated with stress and restricted energy availability. Few studies have simultaneously assessed these parameters during real-world, psychologically stressful activities such as the intense mock interrogations and forced captivity conducted at SERE school. The limited number of SERE studies that have been conducted suggest that SERE training induces biochemical, heart-rate, and behavioral changes greater than those typically observed in other highly stressful situations, such as skydiving, and in fact have been deemed comparable to those observed in actual combat [53,64–68,94,95]. Return of these parameters to baseline rates was delayed until conclusion of the SERE training experience and, for many dependent measures, recovery did not occur even after the captivity phase had ended, –an additional indication of the severity of stress induced by SERE school.

Response times and other measures of performance on all cognitive tests administered, Grammatical Reasoning, N-back, Match-to-Sample and Psychomotor Vigilance, were significantly ($p \leq 0.05$) degraded from baseline levels. Specifically, out of the 24 cognitive-performance measures evaluated, statistically-significant decrements were found from baseline to the first interrogation session on 16 (67%), and statistically-significant decrements were found from baseline to the second interrogation on 12 (50%). It is unusual to detect significant degradations in so many performance parameters in a single study. These changes

demonstrate that when stress is sufficiently intense, extensive impairments in a broad range of critical cognitive functions, from simple functions like reaction time to more complex components such as logical reasoning and working memory, are certain to occur. The highly statistically-significant deterioration in all elements of cognitive function we assessed would appear to explain, at least in part, the real-world deficits that are consistently observed in a variety of stressful occupations. For example, a laboratory investigation of the effects of severe sleep restriction (i.e., <5 h per day across an entire 7-day period) failed to show the same extensive degradations in attentional capacity that were observed in the present evaluation (see [6]). Errors and accuracy decrements observed in emergency rooms and in surgery, as well as those among police officers in life and death situations and in military personnel during intense combat operations can be explained in part by the cognitive degradations observed here [2,3,12,71].

All 6 mood states assessed, Vigor/Activity, Fatigue/Inertia, Confusion/Bewilderment, Tension/Anxiety, Depression/Dejection, Anger/Hostility, as well as the aggregate mood measure Total Mood Disturbance, were similarly and severely affected ($p < 0.001$). Deterioration most consistently occurred from baseline in comparison to the first stressful phase of SERE school (specifically Interrogation 1), and severe mood disturbances remained during Interrogation 2. Although extensive recovery occurred at the end of the course, the affective status of participants consistently failed to return to pre-stress levels, especially the mood state of Fatigue.

Other investigations have reported somewhat analogous stress-related cognitive and mood deteriorations in sleep-deprived and underfed warfighters engaged in field training activities such as parachute drops, travel in small boats, sustained off-road hiking with heavy load carriage, and exercises designed to simulate combat, including exposure to simulated explosions and gunfire (i.e, [29,49,52,74,75]). However, the degradations in mood observed in this study were qualitatively and quantitatively different from those observed in these other studies, undoubtedly due to the unique stress levels induced by simulated capture, interrogation, forced confinement and other stressors of SERE training [53,64,65,67,95].

While the observed decrements in ratings of vigor, fatigue, and confusion were similar to those noted in prior demanding field studies, the present research revealed far larger changes in tension, depression, and anger associated with the capture/interrogation activities than had been observed elsewhere as a function of demanding physical activity and environmental stressors alone. For example, in the Lieberman et al. [49] study, where underfed soldiers were exposed to continuously strenuous field activities that included simulated explosions and gunfire, ratings of tension increased by 53%, depression increased by 168%, and anger increased by 86%, whereas in the present study, these ratings increased by 797%, 1760%, and 497% respectively. Presumably such changes reflect the beginning of the "stress inoculation" effects of SERE training [62], however longer-duration follow-up assessments as part of future studies are needed to clarify recovery patterns as such extraordinary mood responses may alter susceptibility to subsequent development of chronic conditions such as PTSD in personnel who are exposed to the intense stress of high-intensity combat operations. There appears to be some uncertainty on this point as Morgan et al. [64,65] found that stress-related neurohormonal changes began to dissipate within 24 h of the cessation of survival training, while Matthew et al. [56] noted persistent elevations in self-reported traumatic stress symptoms weeks beyond the conclusion of survival resistance training.

Cortisol, the most widely accepted biological marker of activation of the HPA in humans [38,46], was, not surprisingly, substantially elevated during the capture and interrogation phases of the present study. Similar changes were observed by Morgan et al. [64] in SERE students along with an increase in DHEA-s and NPY. Neuropeptide-Y elevations similar to those observed here were previously shown to have occurred in response to stressful circumstances, and such increases have been associated with reduced psychological dissociation as well as with superior military performance. [64,66]. Prior experience of these endocrine changes may enhance warfighters' resilience to the stresses of a real-world POW experience and other highly stressful environments such as combat.

As a consequence of stress-induced sympathetic nervous system activity, heart rate was substantially elevated at capture and interrogation. During the first interrogation, mean heart rate rose from 68 to 97 BPM, and at the second interrogation, heart rate was 124 BPM. This approximate 80% increase from baseline levels attests to the extremely stressful nature of SERE training procedures and is consistent with elevations in norepinephrine and epinephrine observed. Similar increases are observed in pilots experiencing in-flight emergencies [100], while less-pronounced heart-rate reactions have been observed in other highly stressful settings, such as in astronauts during liftoff (96 BPM), casino gamblers (100 BPM), and people engaged in public speaking and mental arithmetic exercises (110 BPM) [39–41,44].

The decrease in testosterone observed in this study is consistent with findings from an earlier SERE study by Morgan et al. [64] and a stressful infantry field training exercise conducted by an elite Army unit [49]. Testosterone levels are associated with behavioral aspects of social rank, aggression, dominance, and personal success [17,73], all of which can be affected by capture and interrogation. A decline in testosterone is a recognized marker of HPA activation and is associated with energy deprivation. The reductions observed in the present study are consistent with reports that soldiers experiencing severe underfeeding and fatigue during Army Ranger training had substantial reductions in testosterone which gradually recovered during refeeding [22,63]. In the present investigation, the physical demands were not as extensive as those experienced during Ranger training which is conducted for several months, but participants were fed very little throughout the field and captivity phases. Despite efforts of SERE school staff to prevent severe dehydration, the participants in this study appeared to be substantially dehydrated as indicated by their large weight losses. In a previous 2 1/2 day-long field investigation of elite military personnel during which body composition was assessed, 76% of the total mean weight loss of 4.1 kg was due to dehydration [49]. In general, large, rapid losses in body weight must be attributable primarily to dehydration since other body compartments are more stable. Interestingly, at the conclusion of the present study, testosterone levels did not rebound as quickly as cortisol, probably in part because the final assessment occurred immediately after the conclusion of training before volunteers had adequate opportunities to eat, hydrate and begin the process of returning to normal energy balance. Nevertheless, since chronically low testosterone is often found in individuals with PTSD or major depressive disorder (MDD) [70,76], the full time course of recovery of testosterone should be examined in future studies.

Plasma epinephrine and norepinephrine, critical components of the classic fight-or-flight response, increased significantly. In fact, levels of these catecholamines more than doubled during the captivity and interrogation phases of SERE training. Elevations in epinephrine and norepinephrine are part of a normal stress response which has evolved to optimize survival, and this certainly represents an appropriate response when warfighters are in combat or have similar experiences. In such circumstances, decreased non-essential visceral activity, increased brain blood flow and arousal, vasodilation in muscles, peripheral vasoconstriction, and elevated heart rate are adaptive functions [80].

The increases in sTfR observed in this study may have been a response to caloric restriction and/or inflammation [87]. Under such circumstances there is an increased concentration of surface sTfR, especially on bone marrow erythroid precursors, as this serves as a mechanism to sequester needed iron.

4.1. Limitations

Since the present study was a field investigation and not conducted in a controlled laboratory environment, several unavoidable limitations

should be noted. First, there were variations in testing times attributable to the fact that research activities were secondary to meeting the training objectives of SERE School. Unavoidable variation in testing times could have impacted the results to some extent since circadian factors are known to influence cognitive performance, physiology, and hormone release [7,11,30]. Although these variations were expected and addressed by the study design and the analyses conducted, they were nonetheless present (we addressed this issue to some extent by comparing like times of saliva assays). Second, the number of subjects that completed testing on each of the dependent measures varied somewhat due to factors beyond the control of the research staff. Since, as noted previously, the scientific objectives of the present study, a comprehensive evaluation of response to real-world stress, was an "add-on" to the primary objective of SERE school,–the completion of a required military training course,–variations in the number of completed testing sessions were expected. Third, in this study it was not possible to completely separate the individual effects of each of the multiple stressors to which volunteers were exposed. Not only were the psychological stressors of captivity and interrogations present, but the physical stressors of insufficient nutrient intake and sleep restriction were issues as well. No doubt, these all exerted effects on the physiology, mood, and cognition of the volunteers in the present study, but it should be noted that this same combination of stressors is characteristic of what would be experienced in a real-world POW encounter—a fact that supports the relevance of the present work. Fourth, the time course for full recovery from the stressors imposed by the SERE regimen could not be determined from the present evaluation as the volunteers were unavailable for follow-up assessments once they completed SERE school. Since insufficient recovery from severe stress may have long-term health implications, future studies should track and evaluate the time required for complete recovery from SERE school and other intense training environments.

5. Conclusions

The simultaneous assessment of cognitive, affective, hormonal, nutritional and heart-rate responses to the severe real-world stress associated with military SERE training revealed a wide range of significant changes. The captivity and interrogation segments of SERE, in combination with the physical and environmental stressors present in such a realistic scenario, caused substantial degradation in cognition and mood, increased release of catabolic hormones, suppressed anabolic hormone release, and elevated heart rate. Stress-related deficits were observed in two-thirds of the cognitive measures employed, ranging from simple reaction time to complex reasoning and memory, as well as in all of the mood states measured (Vigor, Fatigue, Confusion, Tension, Depression, and Anger). These changes were accompanied by significant elevations in cortisol, DHEA-s, and NPY; a two-fold increase in epinephrine and norepinephrine; and an 80 BPM surge in heart rate—all of which point to extensive HPA activation in conjunction with sympathetic nervous system arousal. In addition, the combination of caloric restriction, modest physical exertion, and possible inflammation resulted in elevated sTfR and significantly lower testosterone.

Although a small number of other investigations have reported somewhat analogous stress-related changes in sleep-deprived and underfed warfighters engaged in demanding field training exercises, to the best of our knowledge none have assessed the decrements associated with the severe and unique stresses of simulated capture, interrogation and forced captivity in such a comprehensive manner. Many of the affected parameters began to recover immediately upon cessation of the training exercise; however, a complete return to baseline often was not observed, and at present, it remains unclear whether full recovery actually occurred and if so, its time course. Although Morgan et al. [66] has shown that in general, the individuals who would attend SERE school may be among those with enhanced resistance to (or tolerance of) high-intensity stress, future studies should fully assess the complete time course of recovery to ensure that the training accomplishes the desired level of stress inoculation without inducing longer-term problematic psychological or metabolic consequences. Recovery characteristics are important given that persistent stress-related dysregulation of HPA and sympathetic nervous system activation has been associated with mental/emotional difficulties, sleep disorders, metabolic/glycemic dysregulation, chronic inflammation, or other adverse outcomes [27].

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