



Salivary Nerve Growth Factor Response to Intense Stress: Effect of Sex and Body Mass Index

***Marcus K. Taylor
Heidemarie K. Laurent
Gerald E. Larson
Mitchell J. Rauh
Melissa D. Hiller Lauby
Douglas A. Granger***



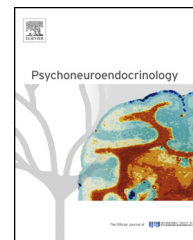
Naval Health Research Center

Report No. 13-44

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. Approved for public release: distribution is unlimited.

This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

***Naval Health Research Center
P.O. BOX 85122
San Diego, California 92186-5122***



SHORT COMMUNICATION

Salivary nerve growth factor response to intense stress: Effect of sex and body mass index



Marcus K. Taylor^{a,b,c,*}, Heidemarie K. Laurent^{b,d,**},
Gerald E. Larson^a, Mitchell J. Rauh^{a,c}, Melissa D. Hiller Lauby^e,
Douglas A. Granger^{b,f}

^a Biobehavioral Sciences Lab, Warfighter Performance Department, Naval Health Research Center, San Diego, CA, USA

^b Institute for Interdisciplinary Salivary Bioscience Research, Arizona State University, Tempe, AZ, USA

^c School of Exercise and Nutritional Sciences, San Diego State University, San Diego, CA, USA

^d Department of Psychology, University of Oregon, Eugene, OR, USA

^e Naval Special Warfare Center, San Diego, CA, USA

^f Johns Hopkins School of Nursing and Bloomberg School of Public Health, Baltimore, MD, USA

Received 28 November 2013; received in revised form 15 January 2014; accepted 11 February 2014

KEYWORDS

Stress;
Nerve growth factor;
Plasticity;
Military;
Survival;
Sex differences;
Body mass index

Summary Ample evidence links stress to psychiatric and neurological disease. Although many studies examine stress hormone secretion and receptor activity, exciting new developments signify a shift in focus to neuromodulatory systems influencing neuronal development, survival, and neuroplasticity. The purpose of this study was to characterize salivary nerve growth factor (sNGF) responses to intense stress exposure in healthy military members undergoing survival training. A second purpose was to explore effects of age, sex, education, and body mass index (BMI). One hundred sixteen military members (80% male) were studied before, during, and 24 h after a stressful mock-captivity exercise. sNGF was measured at all three time points. Reactivity, recovery, and residual elevation of sNGF were computed. General linear modeling with repeated measures evaluated effect of stress exposure, as well as the roles of age, sex, education, and BMI. sNGF increased 137% from baseline to intense stress. During recovery, sNGF remained elevated an average of 67% above baseline (i.e., residual elevation). Men showed greater sNGF reactivity than women quantified by larger absolute T1 – T2Δ (+148.1 pg/mL vs. +64.9 pg/mL, $p < 0.017$). A noteworthy trend of higher sNGF concentrations in low BMI participants was observed ($p = 0.058$). No effects of age or education were shown. This study shows substantial reactivity and residual

* Corresponding author at: Warfighter Performance Department, Naval Health Research Center, 140 Sylvester Road, San Diego, CA 92106, USA. Tel.: +1 619 524 8459; fax: +1 619 553 9859.

** Corresponding author at: 1227 University of Oregon, Eugene, OR 97403, USA. Tel.: +1 541 346 7051.

E-mail addresses: marc.taylor@med.navy.mil (M.K. Taylor), hlaurent@uoregon.edu (H.K. Laurent).

elevation of sNGF in response to intense stress exposure in healthy humans. Further research is needed to refine the sNGF assay, fully characterize the sNGF stress response, delineate correlates and mechanisms, and validate therapeutic applications.

Published by Elsevier Ltd.

1. Introduction

Ample evidence links stress to psychiatric and neurological disease (see [Cohen et al., 1995](#); [McEwen, 2012](#)). At the same time, the fact that stress exposure does not inevitably lead to disorder points to individual differences in stress resilience with important prevention and therapeutic implications. A better understanding of how the stress response operates across multiple physiological systems and determinants of response variability could help to explain differential vulnerability to stress-related diseases by sex, body composition, and other known risk factors. For example, women are known to be at greater risk for affective disorders than men, a difference thought to relate to sex-specific biological responses to stress (e.g., [Ter Horst et al., 2009](#)). However, a definitive answer to the question of how men's and women's stress responses influence disease susceptibility remains elusive, perhaps because of limitations in the scope of physiological stress assessment (typically, hypothalamic–pituitary–adrenal and/or autonomic nervous system activity).

Although many studies examine stress hormone secretion and receptor activity, exciting new developments signify a shift in focus to neuromodulatory systems influencing neuronal development, survival, and neuroplasticity. In particular, nerve growth factor measured in human saliva (sNGF) has recently been shown to respond to acute stress, offering evidence of a neurotrophic stress-responsive system ([Laurent et al., 2013](#)). Further, there is evidence that a dynamic sNGF response to interpersonal conflict stress—i.e., increased reactivity and post-stress recovery—relates to superior psychological adjustment as indexed by stress-related affect and general well-being ([Laurent et al., in press](#); H.K. Laurent, S.L. Laurent, and D.A. Granger, unpublished observations). Some research has documented effects of acute stress on (blood) NGF ([Aloe et al., 1994](#)) while other work suggests no effect ([Lang et al., 2004](#)). Still other studies have linked reduced blood NGF to stress-related psychiatric illness (see [Cirulli and Alleva, 2009](#)). Combined, this work suggests neurotrophic responses could represent a resilience factor that protects certain individuals from adverse effects of stress. Most studies of stress, including the few existing studies of sNGF, involve mild to moderate challenges encountered in daily life. While these provide an important basis for speculation about factors promoting resilience during intense or extreme challenges, further investigation under these more extreme conditions is critical to confirm or refute theories of adaptive stress responses. Convergent findings from mild/moderate and severe stress research would increase confidence that the processes identified in the former apply to conditions such as posttraumatic stress disorder. Thus, an examination of how sNGF responds to severe stress and determinants of differential response could begin to fill important gaps in our knowledge of the basis for health and disease.

The purpose of this study was to characterize sNGF responses to intense stress exposure in healthy military members undergoing survival training. A second purpose was to explore effects of sex, body mass index (BMI), age, and education.

2. Methods

2.1. Military survival training

Survival, Evasion, Resistance, and Escape (SERE) training has been described in earlier reports, ([Morgan et al., 2004](#); [Taylor et al., 2012](#)). US military members who are deemed “high risk of capture” are required to attend this course, which includes a period of mock captivity. After an initial phase of classroom-based didactic training (5 days), students are taken to a field site where they are trained in SERE techniques (7 days). Training tasks include evasion from a simulated enemy and, upon eventual “capture,” students must practice resistance to various forms of simulated exploitation in stressful mock-captivity training challenges. The entire course lasts 12 days, including 1 debrief day after the conclusion of mock captivity.

2.2. Inclusion, exclusion, and compliance criteria

Subjects met inclusion criteria if they were active-duty military members enrolled in SERE training at the Center for Security Forces, SERE Learning Site West (San Diego, California), as part of their military duties and were deemed healthy as indicated by a medical records review conducted by the SERE medical officer. Additional exclusion criteria imposed for this study included smoking; caffeine dependence, any use of anabolic (e.g., DHEA, growth hormone) or ergogenic substance, drug, or supplement (e.g., creatine monohydrate) within the past 3 months; current antihypertensive medication use (e.g., beta-blockers); and current diagnosis of type 1 or type 2 diabetes, with prescribed medication. Compliance requirements were imposed during baseline and recovery assessments. Specifically, subjects were asked to refrain from alcohol ingestion within 12 h of assessments, major meals within 1 h of assessments, and caffeine ingestion within 30 min of assessments. Compliance during mock captivity was implicitly controlled by the training context.

2.3. Protocol

As part of a larger study evaluating stress and health in survival trainees, 116 military members (80.2% male) participated. Half (50.0%) were college educated and two thirds (65.8%) were Caucasian. Mean (SE, range) age, BMI, and

military experience were 25.4 (0.4, 18–46) years, 24.8 (0.3, 18.7–34.0) kg/m² and 4.8 (0.4, 0–15) years, respectively. This protocol was approved by the Naval Health Research Center Institutional Review Board.

Participants completed baseline salivary assessments on the first day of the academic phase of SERE training (Time 1 [T1]; pre-stress). Subsequently, all subjects experienced a rigorous evasion exercise, and then participated in a highly realistic mock-captivity scenario. Assessments were performed again directly after a stressful mock-captivity event (Time 2 [T2]; mock-captivity stress). Finally, approximately 24 h after release from mock captivity (marking completion of field training), assessments were completed a third time (Time 3 [T3]; recovery).

A salivary sample was obtained via the passive drool method (Granger et al., 2007) between 1145 h and 1247 h under baseline, free-living conditions on the first day of academic (classroom) instruction for military survival training. Each subject was asked to rinse his or her mouth with water approximately 10 min prior to sample collection and to avoid the following: brushing teeth prior to collection, using salivary stimulants (e.g., gum, lemon drops), and consuming acidic or high-sugar foods within 20 min prior to collection. After data collection, all samples were immediately placed on dry ice and transferred to Salimetrics, LLC (State College, Pennsylvania) for storage and data processing. Samples were assayed for NGF and cortisol (cortisol was included to confirm and quantify the manipulation effect of survival training). The NGF assay was performed in triplicate using a commercially available enzyme immunoassay kit (Promega NGF Emax immunoassay system Cat.# G7731; Madison, WI) modified for use with saliva. The standard curve measured NGF from 3.9 to 250 pg/mL. The assay has an intra-assay precision of 14.5% and an inter-assay precision of 15.5%. Recovery of NGF added to saliva samples averaged 95.3%. Linearity ranged from 82.3% to 127.2%. Salivary cortisol was assayed in duplicate using a highly sensitive enzyme immunoassay (Salimetrics, LLC, State College, PA). The test uses 25 µL of saliva per determination, has a lower limit of sensitivity of 0.003 µg/dL, standard curve range from 0.012 µg/dL to 3.0 µg/dL, an average intra-assay coefficient of variation of 3.5%, and an average inter-assay coefficient of variation of 5.1%. Method accuracy determined by spike recovery averaged 100.8%, and linearity determined by serial dilution averaged 91.7%.

2.4. Statistical analyses

Data were analyzed using SPSS software version 19.0 (IBM, Armonk, New York). Distribution characteristics for all continuous variables were examined to determine if assumptions of normality were met, following conservative predefined limits (e.g., skewness between –1 and 1 (Leech et al., 2005), kurtosis between –3 and 3). Variables exceeding any of these limits were log-transformed prior to performing the relevant statistical test. All data transformations reduced skewness and kurtosis to acceptable levels. Untransformed means are reported for ease of interpretation. Descriptive analyses were conducted to summarize subject characteristics, and independent *t* tests or chi-square tests compared males and females on demographic and background characteristics. For each hypothesis test, a

theoretically relevant variable was selected as a covariate if it associated with the independent variable and the endpoint of interest, thus qualifying as a potential confounder (MacKinnon et al., 2000). Separate 2 (group) × 3 (time) analysis of variance or analysis of covariance (ANCOVA) with repeated measures evaluated effects of sex, BMI, age, and education differences across time. Greenhouse–Geisser corrections were implemented when sphericity assumptions were not met. Post hoc independent *t* tests or univariate ANCOVA decomposed the observed group effects at each time point, while post hoc paired *t* tests decomposed the overall time effects. Absolute (value 2 – value 1) and relative Δ scores $[(\text{value 2} - \text{value 1}) / \text{value 1}] \times 100\%$ were also computed and then compared across groups via independent *t*-test or univariate ANCOVA. These calculations were used to operationally define “reactivity” (i.e., initial response from baseline to mock-captivity stress), “recovery” (i.e., change from mock-captivity stress to 24-h recovery), and “residual elevation,” (i.e., sustained disruption from baseline to 24-h recovery). Individuals with $\leq 0\%$ relative T1 – T2Δ were classified as non-responders. All formal hypothesis tests were two-sided, and the probability of committing a Type I error was set at .05. Bonferroni corrections were implemented for each family of group, time series, and delta comparisons (absolute and relative) at $.05/3 = .017$. Effect sizes were estimated via partial eta-squared (η_p^2 ; Richardson, 2011).

3. Results

3.1. Nerve growth factor response to intense stress

As shown in Fig. 1, exposure to mock captivity substantially affected sNGF concentrations ($F(2,230) = 58.4$, $p < .001$, $\eta_p^2 = 0.34$). Bonferroni-corrected post hoc comparisons confirmed distinct differences between T1 and T2 ($t(115) = -10.5$, $p < .017$); T2 and T3 ($t(115) = 5.8$, $p < .017$); as well as T1 and T3 ($t(115) = -5.2$, $p < .017$). On average, sNGF increased 136.9% (SE = 15.5%) from baseline to intense stress. During recovery, sNGF remained elevated an average of 67.4% (SE = 11.7%) above baseline (i.e., residual elevation). There were 17 non-responders

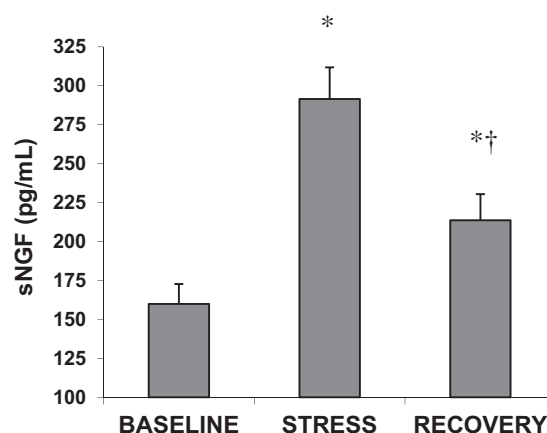


Figure 1 Effect of intense stress exposure on salivary nerve growth factor. *Different from baseline, $p < 0.017$. †Different from stress, $p < 0.017$.

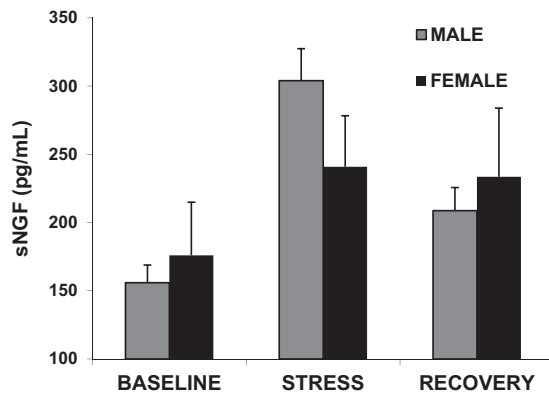


Figure 2 Sex differences in salivary nerve growth factor throughout stress exposure.

(14.7%). Mean (SE) age, BMI and military experience of nonresponders were 24.9 (1.3), 24.7 (0.4), and 4.5 (4.2), respectively. Of the nonresponders, 13 (76.5%) were male and 8 (47.1%) were college educated.

3.2. Cortisol response to intense stress

Exposure to mock captivity profoundly affected cortisol concentrations ($F(2,228) = 264.4$, $p < .001$, $\eta_p^2 = 0.70$). Bonferroni-corrected post hoc comparisons confirmed sizeable differences between T1 and T2 ($t(115) = -16.9$, $p < .017$); T2 and T3 ($t(114) = 21.2$, $p < .017$); as well as T1 and T3 ($t(114) = 5.2$, $p < .017$). On average, cortisol increased 268.2% (SE = 25.0%) from baseline to intense stress. It fully recovered at T3, decreasing an average of 7.5% (SE = 8.3%) below baseline. Weak associations were noted between salivary cortisol and sNGF, both during intense stress (T2; $r(114) = 0.22$, $p = .02$) and with respect to total hormone outputs across all three time points as determined by area under the curve with respect to ground, ($r(113) = .21$, $p = .02$).

3.3. Effect of sex, body mass index, age, and education

Although males and females did not differ in NGF concentrations at baseline ($p = .82$), males showed greater sNGF reactivity than females, quantified by larger absolute T1 – T2Δ (+148.1 pg/mL [SE = 17.4] vs. +64.9 pg/mL [SE = 20.6], $p < 0.017$; see Fig. 2). A noteworthy trend of higher overall sNGF concentrations in low BMI participants was observed (main effect: $F(1,104) = 3.7$, $p = .058$, $\eta_p^2 = 0.03$; see Fig. 3). Neither age ($p = .46$) nor education ($p = .57$) associated with the sNGF trajectory. The salivary cortisol response trajectory was not influenced by sex, BMI, age, or education (all $p > .05$). Small sample size precluded formal investigation of non-responder status by sex, BMI, age, or education.

4. Discussion

This study is the first to our knowledge to show a neurotrophic response to extreme stress in humans, building on previous findings involving moderate stressors. In particular, we found

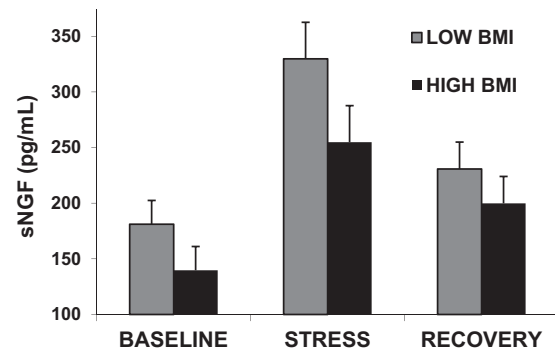


Figure 3 Effect of body mass index (BMI) on salivary nerve growth factor stress trajectory. BMI was dichotomized via median split (cut point = 24.42; group main effect $p = 0.058$). To explore robustness, BMI was dichotomized a second time based on National Institutes of Health (1998) definition of overweight (cut point = 25.0), which yielded a similar effect ($p = 0.105$).

a significant sNGF response to mock captivity in military personnel, as well as individual differences related to sex and BMI. This work sheds further light on a neurotrophic stress-responsive system that could help to explain important links between stress and health.

The marked stress-related rise in sNGF and incomplete post-stress recovery are consistent with sNGF findings in other samples, which have shown non-recovery or a delayed rebound following stress (Laurent et al., in press; Laurent et al., 2013; H.K. Laurent, L. Stroud, B. Brush, and D.A. Granger, unpublished observations). At the same time, the magnitude of the sNGF rise was greater than that detected previously, suggesting a dose-response effect by which higher stress severity elicits higher neurotrophic elevation. The current findings are also consistent with Aloe et al. (1994) findings linking acute stress to plasma NGF concentrations (Aloe et al., 1994) in novice military parachute jumpers, yet inconsistent with Lang et al. (2004) work suggesting no effect of an academic oral presentation on serum NGF of healthy male volunteers. Further investigation of sNGF during and after a range of stressors with longer follow-up periods will be necessary to clarify possible dose-response effects and typical recovery times. The adaptive value of post-stress neurotrophic elevations should also be explored.

Differences in sNGF by sex and BMI could help in understanding differential health vulnerabilities associated with these factors. Given known links between neurotrophin levels and mood disorder, women's blunted neurotrophic responses to severe stress may play a role in the well documented sex imbalance in these disorders. In particular, the failure to launch a robust neurotrophic response during stress could leave central and peripheral neural systems vulnerable to stress-related damage, which in turn could lead to negative mental health sequelae. Similarly, part of the health costs associated with high BMI may be attributable to blunted neurotrophin levels; NGF is known to regulate endocrine and immune function and to provide protection from inflammatory responses (Colafrancesco and Villoslada, 2011). It is also possible that reduced neurotrophin levels represent a downstream effect of physiological changes related to increasing BMI. These findings should be followed up with research that

can address associations with mental and physical health outcomes, as well as directionality of effects.

Limitations of this study should be recognized. Although mock-captivity is a very realistic and ecologically valid psychosocial stressor, it is known to have physical and physiologically stressful elements; thus it is best described as a “composite” stressor. Also, sex hormones are believed to influence neurotrophin activity, but were not controlled in this study. Furthermore, it is noted that several sNGF sample absorbance values fell outside the curve linearity. Some non-NGF material, then, may have been present in saliva after stress which could increase the unspecific binding and, as a result, overestimate stress-induced NGF concentrations. Although the assay used to estimate sNGF reflected current state of the art, it is currently undergoing refinement. Finally, mental/physical health was not assessed in this study. In future work, predictors of neurotrophic response to differing stressors should be related to relevant health outcomes over time to clarify the role of sNGF in stress-health paths. Also, research in larger and more diverse samples will permit closer analysis of non-responders and provide recommendations for possible intervention. Finally, although assessing neurotrophin levels under severe stress conditions represents an important step toward discerning real-world stress effects, it would be informative to compare magnitudes of response and effects on well-being across different types and severities of stress. For now, this study confirms that the human neurotrophic system responds to extreme stress, but that the nature of this response varies across individuals. Combined with findings under moderate stress conditions, this work highlights the importance of stress-responsive neurotrophins for understanding resilience.

Role of the funding sources

This study was supported by a grant from the Office of Naval Research, Code 34. This work was performed under work unit number 61124. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government. Approved for public release; distribution is unlimited. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research (Protocol NHRC.2011.0033).

Conflicts of interest

DAG is founder and Chief Strategy and Scientific Advisor at Salimetrics LLC (State College, PA). DAG's relationship with this entity is managed by the policies of the Conflict of Interest Committee at the Johns Hopkins University and the Office of Research Integrity and Assurance at Arizona State University.

All other authors declare that they have no conflicts of interest.

Acknowledgements

We thank Ms. Michelle LeWark for editorial expertise; Ms. Genieleah Padilla, and LT Ingrid Wilson for study coordination; Ms. Emily Schmied for data management; and Dr. Matthew Koehler for medical oversight.

References

- Aloe, L., Bracci-Laudiero, L., Alleva, E., Lambiase, A., Micera, A., Tirassa, P., 1994. Emotional stress induced by parachute jumping enhances blood nerve growth factor levels and the distribution of nerve growth factor receptors in lymphocytes. *Proc. Natl. Acad. Sci. U. S. A.* 91, 10440–10444.
- Cirulli, F., Alleva, E., 2009. The NGF saga: from animal models of psychosocial stress to stress-related psychopathology. *Front. Neuroendocrinol.* 30, 369–395.
- Cohen, S., Kessler, R.C., Underwood Gordon, L., 1995. *Measuring Stress: A Guide for Health and Social Scientists*. Oxford Press, New York.
- Colafrancesco, V., Villoslada, P., 2011. Targeting NGF pathway for developing neuroprotective therapies for multiple sclerosis and other neurological diseases. *Arch. Ital. Biol.* 149, 183–192.
- Granger, D.A., Kivlighan, K.T., Fortunato, C., Harmon, A.G., Hibel, L.C., Schwartz, E.B., Whembolua, G.L., 2007. Integration of salivary biomarkers into developmental and behaviorally-oriented research: problems and solutions for collecting specimens. *Physiol. Behav.* 92, 583–590.
- Lang, U.E., Anders, D., Danker-Hopfe, H., Hellweg, R., 2004. Measurement of nerve growth factor serum concentration in a psychologically stressful situation in men. *Stress* 7, 39–42.
- Laurent, H.K., Laurent, S.L., Granger, D.A., 2013. Salivary nerve growth factor response to acute psychosocial stress: a new frontier for stress research. *Psychosom. Med.* 75, 744–750.
- Laurent, H.K., Laurent, S.L., Granger, D.A. (in press). Salivary nerve growth factor response to stress related to resilience. *Physiology and Behavior*.
- Leech, L.L., Barrett, K.C., Morgan, G.A., 2005. *SPSS for Intermediate Statistics: Use and Interpretation*, 2nd ed. Lawrence Erlbaum Associates, Mahwah, NJ.
- MacKinnon, D.P., Krull, J.L., Lockwood, C.M., 2000. Equivalence of the mediation, confounding, and suppression effect. *Prev. Sci.* 1, 173–181.
- McEwen, B.S., 2012. Brain on stress: how the social environment gets under the skin. *Proc. Natl. Acad. Sci. U. S. A.* 109, 17180–17185.
- Morgan III, C.A., Southwick, S., Hazlett, G., Rasmusson, A., Hoyt, G., Zimolo, Z., Charney, D., 2004. Relationships among plasma dehydroepiandrosterone sulfate and cortisol levels, symptoms of dissociation, and objective performance in humans exposed to acute stress. *Arch. Gen. Psychiatry* 61, 819–825.
- National Institutes of Health, 1998. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Obes. Res.* 6 (Suppl. 2) 51S–209S.
- Richardson, J.T.E., 2011. Eta squared and partial eta squared as measures of effect size in educational research. *Educ. Res. Rev.* 6, 135–147.
- Taylor, M.K., Padilla, G.A., Stanfill, K.E., Markham, A.E., Khosravi, J.Y., Ward, M.D., Koehler, M.M., 2012. Effects of dehydroepiandrosterone supplementation during military survival training: a randomized, controlled, double blind field study. *Stress* 15, 85–96.
- Ter Horst, G.J., Wichmann, R., Gerrits, M., Westenbroek, C., Lin, Y., 2009. Sex difference in stress responses: focus on ovarian hormones. *Physiol. Behav.* 97, 239–249.

REPORT DOCUMENTATION PAGE

The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB Control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE (DD MM YY) 27 08 13			2. REPORT TYPE Journal article		3. DATES COVERED (from – to) 15 08 11–present	
4. TITLE Salivary Nerve Growth Factor Response to Intense Stress: Effect of Sex and Body Mass Index					5a. Contract Number: 5b. Grant Number: 5c. Program Element Number: 5d. Project Number: 5e. Task Number: 5f. Work Unit Number: 61124	
6. AUTHORS Taylor, Marcus K.; Heidemarie K. Laurent, Gerald E. Larson, Mitchell Rauh, J., Melissa D. Hiller Lauby, & Douglas A. Granger						
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Commanding Officer Naval Health Research Center 140 Sylvester Rd San Diego, CA 92106-3521						
9. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES) Commanding Officer Chief, Bureau of Medicine and Surgery Naval Medical Research Center 7700 Arlington Blvd 503 Robert Grant Ave Falls Church, VA 22042 Silver Spring, MD 20910-7500					8. PERFORMING ORGANIZATION REPORT NUMBER 13-44	
					10. SPONSOR/MONITOR'S ACRONYM(S) NMRC/BUMED	
					11. SPONSOR/MONITOR'S REPORT NUMBER(s)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.						
13. SUPPLEMENTARY NOTES <u>Psychoneuroendocrinology</u> , 2014, May, <u>43</u> , 90-94						
14. ABSTRACT Ample evidence links stress to psychiatric and neurological disease. Although many studies examine stress hormone secretion and receptor activity, exciting new developments signify a shift in focus to neuromodulatory systems influencing neuronal development, survival, and neuroplasticity. The purpose of this study was to characterize salivary nerve growth factor (sNGF) responses to intense stress exposure in healthy military members undergoing survival training. A second purpose was to explore effects of age, sex, education, and body mass index (BMI). One hundred sixteen military members (80% male) were studied before, during, and 24 hours after a stressful mock-captivity exercise. sNGF was measured at all three time points. Reactivity, recovery and residual elevation of sNGF were computed. General linear modeling with repeated measures evaluated effect of stress exposure, as well as the roles of age, sex, education and BMI. sNGF increased 137% from baseline to intense stress. During recovery, sNGF remained elevated an average of 67% above baseline (i.e., residual elevation). Men showed greater sNGF reactivity than women, quantified by larger absolute T1–T2Δ (+148.1 pg/mL vs. +64.9 pg/mL, $p < 0.017$). A noteworthy trend of higher sNGF concentrations in low BMI participants was observed ($p = 0.058$). No effects of age or education were shown. This study shows substantial reactivity and residual elevation of sNGF in response to intense stress exposure in healthy humans. Further research is needed to fully characterize this response, delineate correlates and mechanisms, and validate therapeutic applications.						
15. SUBJECT TERMS stress, nerve growth factor, plasticity, military, survival, sex differences, body mass index						
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UNCL	18. NUMBER OF PAGES 6	18a. NAME OF RESPONSIBLE PERSON Commanding Officer	
a. REPORT UNCL	b. ABSTRACT UNCL	c. THIS PAGE UNCL			18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39-18