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TITLE: Can a Canine Companion Modify Cardiac Autonomic Reactivity and Tone in PTSD?

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14. ABSTRACT Our primary aim is to provide a strong test of the ability of participation in the Service Animal Training Intervention program at the VAPAHCS-Trauma Recovery Program to achieve rehabilitative impacts highly relevant to PTSD as suggested by the civilian literature. These are reductions in cardiac autonomic tone and reactivity and improvements in social experience and function. A second aim is to explore the likely generalizability of these effects under conditions of greater service dog availability.						
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TABLE OF CONTENTS

	<u>Page No.</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	8
5. Changes/Problems	9
6. Products	15
7. Participants & Other Collaborating Organizations	17
8. Special Reporting Requirements	18
9. Appendices	19

- 1. INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The subject of this research is the impact of canine companionship on cardiac autonomic regulation, mood, social experience, and social cognition in U.S. Military Veterans undergoing inpatient treatment for deployment-related posttraumatic stress disorder. Its purpose is to confirm or disconfirm in such Veterans the positive impacts of canine companionship that have been reported in civilian samples. Its scope is the inpatient treatment context; however, its results may have implications for less severely affected populations and similar but less intensive interventions.

- 2. KEYWORDS:**

Posttraumatic stress disorder, animal-assisted therapy, autonomic regulation, autonomic reactivity, mood, sociality, social cognition, sleep, ambulatory monitoring, defense response, facial affect

- 3. ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

The major goals for this project as a whole were to perform strong tests of a set of hypotheses relating canine companionship to autonomic regulation, social experience, and social cognition. The major goals for the first 12 months of this 4-year project were to complete all startup tasks relating related to permissions, staffing, equipment procurement, and data systems development, and to recruit 44-56 participants. All of these goals have been met.

What was accomplished under these goals?

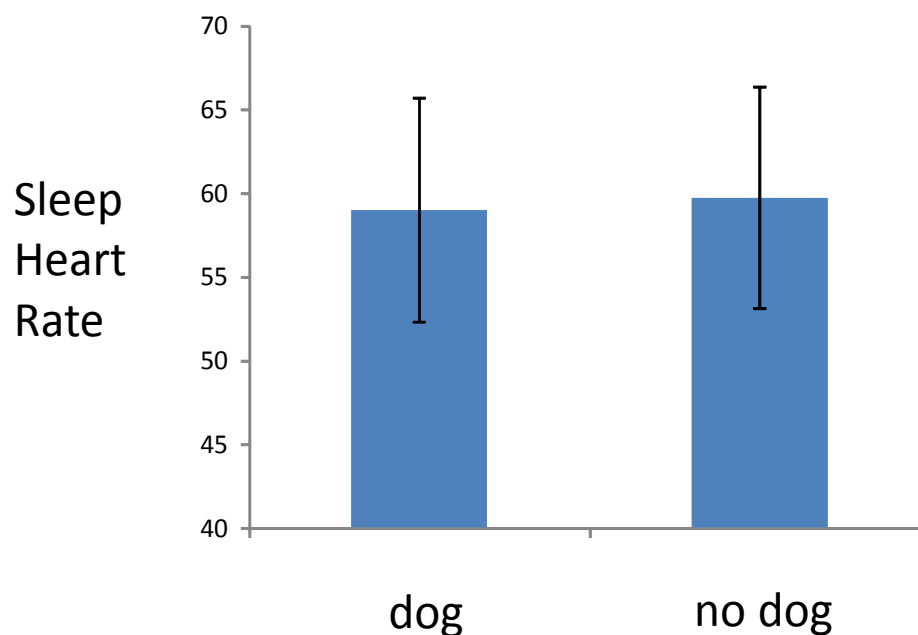
All proposed data acquisition and reduction methodologies are operational. As well, our systems are designed to enable efficient revision of analytic methods and batch re-analysis of large datasets if better methods become available. These ongoing data acquisitions include waking ambulatory heart rate, respiration, and respiratory sinus arrhythmia and activity, sleep heart rate, respiration and respiratory sinus arrhythmia and activity, apnea-hypopnea index estimation, momentary assessments of mood, pain, service animal presence, recent smoking, recent social interactions, weekly lab-based estimates of stress-reactivity and social cognition.

Human-supervised automated data reduction and analysis methods enable us to stay abreast of the large volumes of data collected while maintaining data integrity. All psychometric data are input via efficient scanning/OCR technology.

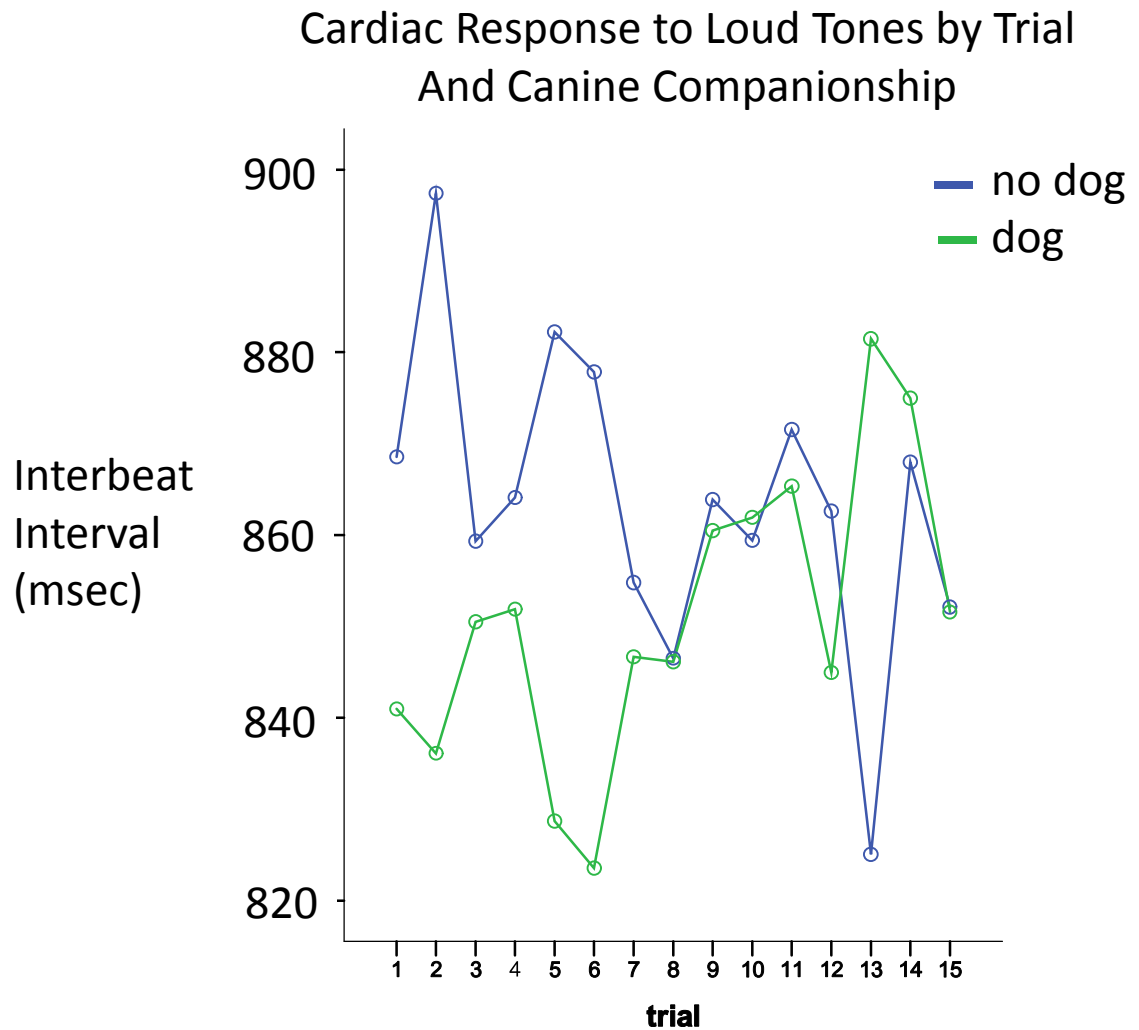
Enrollment since recruitment began in April 2015:

- 42 completed
 - 13 Dog participants
 - 29 Non-dog participants
- 3 currently active (all 3 are dog participants)
- 5 withdrawn (due to d/c from inpatient treatment)
- There have been no AE, SAEs, or UPs.

We are cautious in interpreting our results at this early stage. Below we present preliminary sleep heart rate data from the first 13 participants from the intensive study arm. We believe sleep heart rate is the most reliable outcome pursuant to Hypothesis 1 (*SATI participation will lower basal cardiac autonomic tone measured continuously during waking and sleep for approximately 42 days.*) because 1) it is the autonomic index best protected from nuisance variance, and 2) it derives from a behavioral domain, sleep, that is commonly reported by Veterans to be subjectively improved by the presence of a service animal. Preliminary analyses do not indicate a significant within-subjects effect of service animal companionship (during the prior day and during the night) on sleep heart rate ($t(12) = -0.77, p = 0.46$). We caution that these values, though based on 100+ hours of heart rate data, are unadjusted for certain features of companionship timing and dose. (See below.)

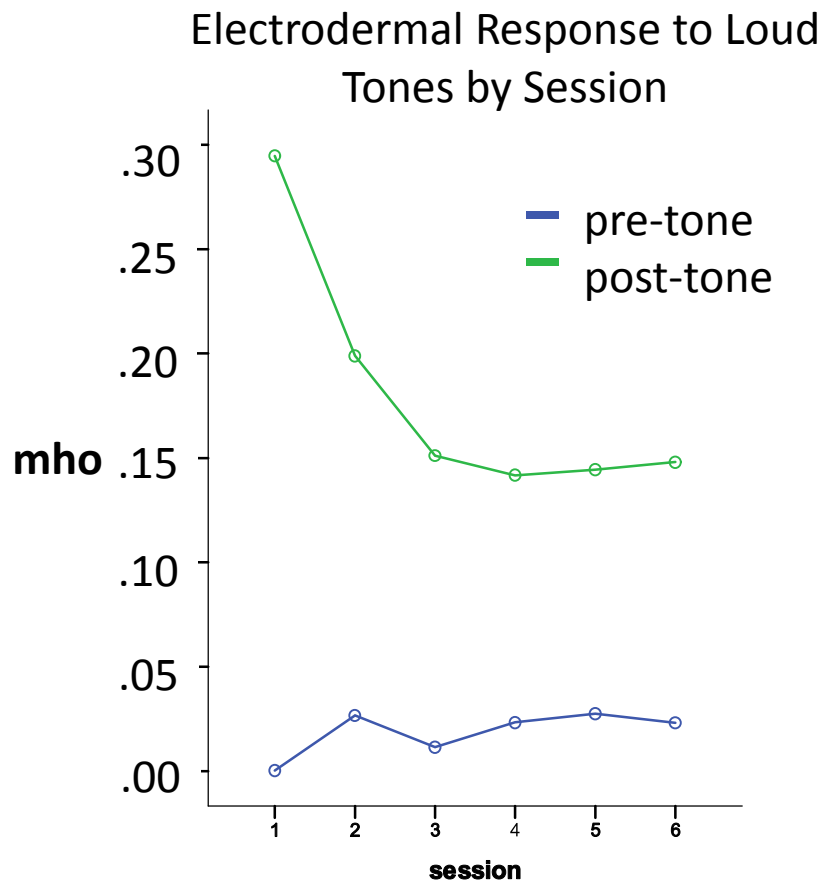


In contrast to the absence of a trend in sleep heart rate, service animal companionship appears to modify reactivity to the loud tones paradigm. A repeated measures ANOVA of cardiac responses to a series of loud tones found, in addition to expected main effects, a significant interaction between trial and dog-presence (see figure below), and a near-significant three-way interaction between dog-presence, response amplitude and trial (not shown).



As indicated by the figure above, participant's peri-tone heart rates accelerated over trials in the absence of their service dog, but decelerated over trials when the dog was present. As we collect continuous data, and employ ~45 second inter-stimulus intervals, we will re-examine this effect in the inter-stimulus intervals and examine respiratory sinus arrhythmia magnitude within these intervals.

Electrodermal responses to the loud tones paradigm have also exhibited an effect of session.



What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Preliminary data from the facial affect preference task were presented as part of the following:

Woodward, S.H., Kaloupek, D.G. FreeSurfer-derived estimate of cranial volume is smaller in chronic severe PTSD. International Society for Traumatic Stress Studies, November, 2015, New Orleans, LA.

What do you plan to do during the next reporting period to accomplish the goals? ”

During the next reporting period, data acquisition and processing will continue as proposed.

- 4. IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

In collaboration with Laura McKee, PhD, we have developed a parenting questionnaire that will enable us to provide a preliminary test of whether participation in the SATI program is associated with improved parenting behavior by self-report.

We have developed an efficient method to extract PRN medication histories from the VA clinical record, which will allow us to test a hypothesis that canine companionship is associated with reduced use of PRN medications such as muscle relaxants.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report. All findings are preliminary.

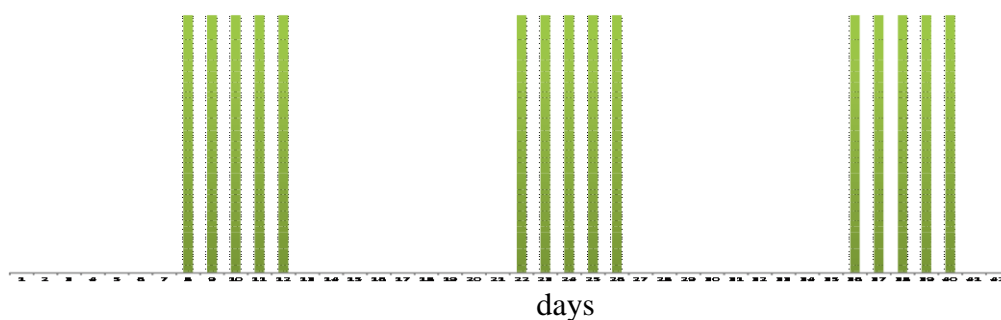
- 5. CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

There are no changes in objectives or scope.

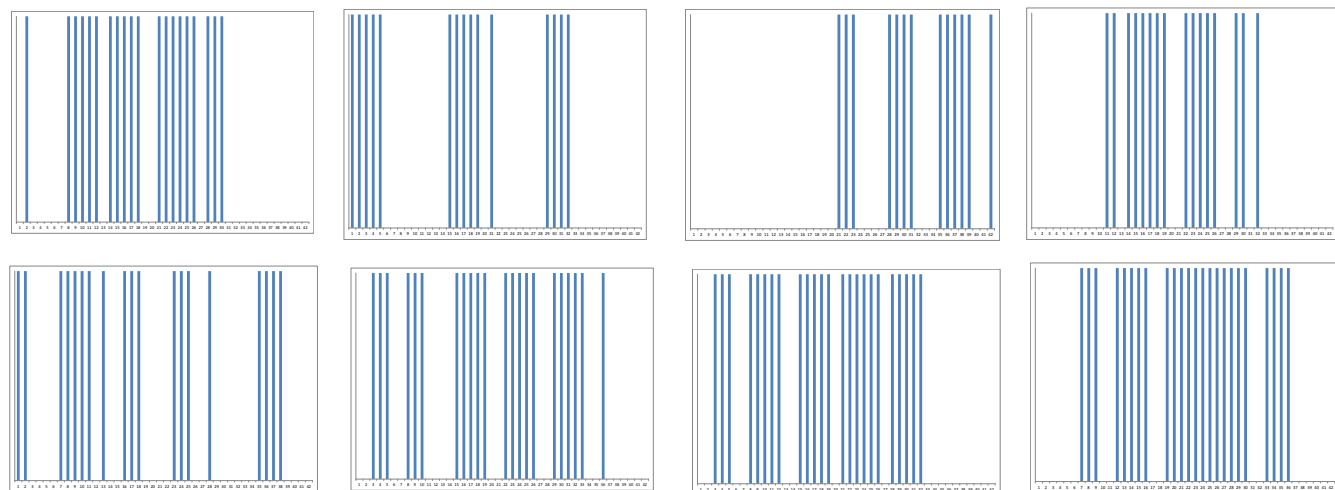
Actual or anticipated problems or delays and actions or plans to resolve them

In the course of proposing this study, we engaged the staff of the Trauma Recovery Program (TRP) and the Service Animal Training Intervention (SATI) in extensive discussions regarding how the latter functioned in the context of the former. The SATI was described as involving regular weekly alternation of 24/7 canine companionship with a typical duration of approximately 6 weeks, as illustrated in the figure below where bars indicate “dog” days. (The 7-day gaps reflect weekends which are typically “non-dog” days due to weekend passes.)



Deviations from this ideal pattern were ascribed to a range of special circumstances. Now that we are, seven months after initiating recruitment, intimately familiar with the operation of the SATI and the many factors that affect scheduling, we can say that deviations from the idealized “dog dosing” schedule are the rule rather than the exception. The figure below captures the range of schedules we have observed.

Some observed dosing schedules



While we are confident that we can accomplish the Aims of the study with the allotted time and budget, adjustments to the methods and analytic strategies are required. We will present these in some detail below. Further detail will be presented on request. We will adhere to the original design until these changes are approved.

The guiding principal common to the reformulations of Hypotheses 1, 2, and 4 is that the SATI intervention will be treated as a single block or “dose” of canine companionship whose duration and “density” vary over participants but can be precisely specified and used as covariates in between-group comparisons. (Density is the percentage of days spent in companionship with the dog over the period of measurement.) This reformulation is quite feasible for the following reasons. More patients apply for inclusion in the SATI than can be accommodated. Among those who apply, assignment to the SATI is, we now know, a quasi-random outcome of the interactions of patient admissions and discharge dates compounded by additional exogenous factors such as dog availability. As a result, the SATI and non-SATI groups will be closely matched on factors which could influence the testing of Hypotheses 1, 2, and 4 such as psychiatric status on admission, inpatient milieu exposure, psychiatric and medical treatments received, treatment response(s), lengths of stay, diet, and exercise, body-mass index, and apnea-hypopnea index. Propensity scores will be used to address any residual bias.

Hypothesis 1 will be reformulated as a between-subjects test comparing changes in sleep heart rate (HR) and respiratory sinus arrhythmia (RSA) across participants who are entered into the service animal training intervention (SATI) vs those who apply but are not entered. The strength of this test is founded on the following:

1. Sleep HR and RSA will be obtained nightly via mattress actigraphy from all patients in the TRP at no cost. They are strong measures of basal cardiac autonomic status that are relatively uncontaminated by nuisance variance as compared to waking heart rate. The validity of sleep HR and RSA as estimated via mattress actigraphy has been shown (Woodward et al., 2007).
2. Actigraphically-estimated sleep duration will be analyzed as co-outcomes of sleep HR and RSA. This feature is analogous to the analysis of waking activity in the original design.
3. Dependent variables will be the slopes of sleep HR, RSA, and sleep duration over the period of the SATI intervention or an analogous epoch for non-SATI participants. Days post-admission will be used as a covariate.
4. As in the original proposal, statistical power will be conditioned on basal HR, arguably the most medically consequential outcome under examination. Beginning with the group difference (~3 BPM) and effect size ($D_{\text{est}} = 0.35$) reported by the largest published comparison of healthy persons with and without pets (Allen, Blascovich, & Mendes, 2002) and extrapolating to a 4-5 BPM decrease in basal HR believed to be cardiologically significant (Jouven et al., 2009; Jouven, Zureik, Desnos, Guerot, & Ducimetiere, 2001; Legeai et al., 2011) yields an effect size of approximately 0.50. Based upon an independent-samples t-test, power to detect such an effect over subsamples of $n = 60$ would be 80%. We would add that the sleep HR slopes to be compared will be based on approximately 120 hour of recording, many times the typical volumes of data.

5. This reformulation of the test of Hypothesis 1 will require twice as many polysomnographic (PSG) estimates of apnea-hypopnea index (AHI). To implement these additional tests at the current staffing level, we will substitute a well-validated single-channel apnea screening system (ApneaLink™) for the current full ambulatory PSG. The ApneaLink system has been validated against gold-standard PSG in two large independent studies (Crowley et al., 2013; Erman, Stewart, Einhorn, Gordon, & Casal, 2007). It costs approximately \$4000. Subject payments for AHI measurement will be reduced from \$50 to \$25 commensurate with the reduced burden of this single-channel study. (Set up time is approximately 10 minutes vs 90 minutes for a full screening PSG.) Adjusting the remaining SATI participant payments accordingly and adding the cost of an additional $80 \times \$25 = \2000 non-SATI subject payments yields a net increase of \$3500. This estimate assumes the attrition rate of these non-SATI participants will approximate that of SATI participants. The total cost of this modification will be approximately \$7500. Budgeting considerations are addressed further below.

Hypotheses 2 and 4 will be reformulated as between-subjects tests comparing change in stress reactivity (Hypotheses 2) and social cognition (Hypothesis 4) over the course of the SATI (or an analogous time period) across SATI and non-SATI participants.

1. Both SATI and non-SATI participants will undergo three laboratory assessments of stress reactivity and social cognition. For SATI participants, these will occur just before beginning the intervention, at the end of week five, and at the end of week six. For non-SATI participants, these will occur analogous times during a window starting at the mean intervention start day post-admission +/- one standard deviation.
2. Dependent variables will be the slopes of autonomic indices of stress reactivity and behavioral and ocular markers of social cognition over 80% of the SATI (week 0 to week 5) or an analogous time period. Days post-admission as well as the duration and density of the SATI intervention will be employed as covariates.
3. As in the reformulation of Hypothesis 1, strong quasi-randomization with residual bias correction via propensity scores will provide strong experimental control over potential confounders of the SATI/non-SATI contrast, including such effects as the reduction of electrodermal responses to the loud tones paradigm reported above.
4. This reformulation sacrifices an attractive feature of the original, a within-subject comparison of laboratory measures of stress reactivity and social cognition with and without a canine companion. This loss will be recouped by randomizing SATI participants to with-dog vs without-dog conditions for the third laboratory session scheduled for week six. Stress reactivity and social cognition indices will be adjusted for session two values obtained one week prior and for companionship “dose” for the intervening week. (The effect of the latter should be attenuated in that ~80% of the SATI intervention will have been completed by that time.)
5. As laboratory sessions have been redistributed rather than added, this modification entails no extra costs in terms of aggregate burden, staffing, or budget.

Hypothesis 3 (*SATI participation will increase positive and reduce negative social interactions with other patients and staff*) will be tested over multiple short-term (day-to-day) transitions from canine-companionship to no-canine-companionship (or vice versa) which are afforded in greater numbers than originally envisioned.

1. Reformulating Hypothesis 3 into a between-subjects test would double the number of ecological momentary assessments (EMA) of mood and social experience and substantially increase aggregate study burden on participants and the Trauma Recovery Program (TRP). This would also apply to the collection of waking ambulatory psychophysiologic data (heart rate, respiration rate, and activity) originally incorporated in Hypothesis 1.
2. The naturalistic variability in service dog scheduling has the effect of affording more opportunities to observe the impact of transitions from accompanied to unaccompanied status. Furthermore, these opportunities may be further increased by instituting mid-week handovers of service animals between participant co-trainers, a feasible modification of the SATI (and the preferred implementation prior to the initiation of this research). These temporally-localized contrasts will be relatively protected from contamination by longer-term trends in TRP and SATI impacts and so may be aggregated from throughout the SATI epoch.
3. We will test the hypothesis that taking possession of a canine companion will, on average, result in significant improvements in the full suite of outcomes assessed via EMA (social experience, mood, smoking, pain, etc.) and ambulatory psychophysiologic recording as compare to the prior day, and conversely, relinquishing a companion canine will result in significant worsening in these same outcomes.

Hypotheses 5 unchanged.

Impacts of Proposed Changes on Recruitment, Staffing, and Budget

To date, recruitment of non-SATI participants has met project targets, leaving approximately 100 additional non-SATI participants to be accrued. It is our judgment that the additional compensation offered for the assessment of AHI and the three laboratory sessions will facilitate recruitment for the non-SATI arm. Insofar as non-SATI participants will now be assigned into one of two groups (those who do and those who do not undergo AHI and laboratory assessments) potential competition for the more remunerative level of participation could arise. This will be managed by the nomination of a limited number of “slots” for the more intensive/remunerative level of non-SATI participation which will empty and refill as a function of the same quasi-random process leading to assignment to the SATI arm.

Staffing and budgeting will not exceed the scope of the original proposal. The proposed increase in expenditures will be funded from the year 1 surplus of approximately \$77,000 (derived principally from unspent salaries.)

The great majority of data collected to date will be utilized in the reformulated hypothesis testing including those from ambulatory psychophysiology, ecological momentary assessment, mattress actigraphy, polysomnography, and all psychometric instruments. Laboratory data collected to date will be comprehensively analyzed.

Summary

We believe this reformulated version of the project will provide strong tests of the original hypotheses or close variants. In general, the reformulated analyses employ more conventional statistical tests than the original. In fact, due to the quasi-random assignment to SATI participation, and the duration and intensity of that intervention, the reformulated study represents a closer approximation of a randomized clinical trial of inpatient treatment augmentation by canine companionship in US Military Veterans with PTSD than the original design.

None.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

As detailed above, future SATI participants will experience a reduction in burden (and commensurate compensation) due to the substitution of a single-channel ApneaLink study for PSG, and a reduction of laboratory sessions from six to three. Approximately 50% of future non-SATI participants will experience an increase in burden (and commensurate compensation) by the addition of the ApneaLink study and three laboratory sessions.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Steven Woodward
 Project Role: Principal Investigator
 Nearest person month worked: 2
 No change

Name: Andrea Jamison
 Project Role: Coordinator
 Nearest person month worked: 10
 No change.

Name: Sasha Gala
 Project Role: Research Assistant
 Nearest person month worked: 10
 No change.

Nothing to report.

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

- 9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

References

- Allen, K., Blascovich, J., & Mendes, W. B. (2002). Cardiovascular reactivity and the presence of pets, friends, and spouses: the truth about cats and dogs. *Psychosomatic Medicine*, 64(5), 727-739. Retrieved from
- Crowley, K. E., Rajaratnam, S. M., Shea, S. A., Epstein, L. J., Czeisler, C. A., Lockley, S. W., . . . Safety, G. (2013). Evaluation of a single-channel nasal pressure device to assess obstructive sleep apnea risk in laboratory and home environments. *J Clin Sleep Med*, 9(2), 109-116. doi:10.5664/jcsm.2400
- Erman, M. K., Stewart, D., Einhorn, D., Gordon, N., & Casal, E. (2007). Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med*, 3(4), 387-392. Retrieved from
- Jouven, X., Empana, J. P., Escolano, S., Buyck, J. F., Tafflet, M., Desnos, M., & Ducimetiere, P. (2009). Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. *American Journal of Cardiology*, 103(2), 279-283. doi:S0002-9149(08)01585-3
- Jouven, X., Zureik, M., Desnos, M., Guerot, C., & Ducimetiere, P. (2001). Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovascular Research*, 50(2), 373-378. doi:S0008636301002309 [pii]
- Legeai, C., Jouven, X., Tafflet, M., Dartigues, J. F., Helmer, C., Ritchie, K., . . . Empana, J. P. (2011). Resting heart rate, mortality and future coronary heart disease in the elderly: the 3C Study. *Eur J Cardiovasc Prev Rehabil*, 18(3), 488-497. doi:1741826710389365
- Woodward, S. H., Arsenault, N. J., Voelker, K., Nguyen, T., Lynch, J., Leskin, G., & Sheikh, J. (2007). Estimating heart rate and RSA from the mattress-recorded kinetocardiogram. *Psychophysiology*, 44(4), 635-638. Retrieved from