



Association between perceived distress and salivary cortisol in veterans with mTBI

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ARTICLE INFO

Keywords:

Subjective distress
Objective markers of distress
Cortisol
Mild traumatic brain injury
Yoga

ABSTRACT

Mild traumatic brain injury (mTBI) is one of the most common injuries experienced by Veterans and can frequently result in a variety of post-concussive symptoms. Post-concussive headaches (PCH), one of the most common symptoms, can persist for years after the injury occurred. The long-lasting impacts of PCH can be extremely distressing for Veterans, thus necessitating the need to find reliable biomarkers that directly relate to subjective feelings of distress. Yoga-based interventions have been shown to improve both subjective and objective markers of stress. Techniques used in yoga, such as the focus on releasing muscular tension, are also recommended as strategies for treating PCH. Thus, yoga-based interventions provide a unique context for the comparison of subjective and objective measures of distress in Veterans with PCH. In this secondary, exploratory analysis, we examined the relationship between perceived distress and cortisol in sixteen Veterans with mTBI and long-term PCH within the context of a yoga intervention feasibility study. The Visual Analogue Scale (VAS), a validated tool for measuring subjective distress, was administered to participants immediately before and after 75-min yoga classes, which occurred twice weekly over eight weeks. Participants also provided salivary cortisol (pre- and post-yoga) at in-person sessions (eight) to compare to changes in VAS scores. We found that VAS scores were significantly reduced within five of the eight assessed yoga classes, but there were no significant changes in cortisol levels. No significant correlations were found between VAS scores and salivary cortisol levels. When looking at how cortisol levels changed over time (i.e., over the series of eight yoga sessions), there was a significant downward trajectory in post-yoga cortisol, but not after taking pre-class cortisol into account (i.e., within yoga session cortisol change over time). Taken together, we found that subjective distress, but not cortisol was reduced by yoga classes. These data suggest that salivary cortisol did not match changes in perceived distress, thus emphasizing the ongoing challenges of relating subjective and objective measures.

1. Introduction

Although both civilian and Veteran populations experience mild traumatic brain injury (mTBI), mTBI is a leading injury sustained by Veterans, as a result of the casualties incurred during the conflicts in Iraq and Afghanistan. Individuals that suffer mTBI can develop persistent

post-concussive symptoms (PCS), with one of the most widely reported symptoms being post-concussive headaches (PCH) [1–3]. Although headaches can be experienced after all types of mTBI, studies suggest that chronic headache prevalence may be up to 4- to 5-times higher in United States Soldiers following a deployment-related concussion [4]. Around 48% of Service Members have persistent PCS past the typical

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<https://doi.org/10.1016/j.cpnec.2022.100123>

Received 3 November 2021; Received in revised form 31 January 2022; Accepted 31 January 2022

Available online 2 February 2022

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resolution timeframe of 3 months [5]. Although PCH typically improves within a year post-injury, a subpopulation will continue to experience PCH for over a year [3]. While PCH can be debilitating and painful, they often coincide with additional cognitive and physiological mTBI-related sequelae – many of which are related to stress dysfunction. For example, mTBI can result in long-term dysregulation of both the autonomic nervous system [6,7] and hypothalamic-pituitary-adrenal (HPA) axis [8,9], resulting in widespread impacts on the ability to maintain an appropriate stress response. Military-incurred mTBI has also been associated with increased prevalence/severity of stress-related disorders, such as post-traumatic stress disorder (PTSD) [10,11]. Both stressful situations and daily levels of perceived stress are positively associated with reported intensities of PCS [12,13], indicating that both psychological and physiological components of stress are fundamentally associated with PCS. Persistent symptoms, such as PCH, can also be inherently distressing. However, an understanding of the relationship between changes in perceived levels of distress and physiological markers in a population that has experienced persistent PCH for over a year remains largely unknown.

A variety of patient reported outcome measures (PROMs) have been developed to target subjective components of distress. Self-report measures, such as the Kessler Psychological Distress Scale and the Visual Analogue Scale (VAS), are both commonly used, validated tools [14,15]. However, studies have shown that other more persistent factors, such as PTSD symptom severity, can influence TBI injury perception, emphasizing both the challenges associated with using subjective PROMs [16, 17] and the need for objective and reliable physiological biomarkers. As levels of perceived distress can vary across individuals, it is essential to better understand the relationship between subjective distress and objective biomarkers. If the specific relationships between non-invasive physiological stress markers and perceived distress can be uncovered, this may allow increased understanding of symptoms, such as PCH, that often accompany TBI.

Salivary cortisol is a well-established and minimally invasive measure for assessing HPA function, thus making it a potentially promising biomarker for assessing distress in those with PCH after mTBI. Elevated cortisol levels in individuals with severe TBI have been linked to worse outcomes in multiple domains (i.e., Glasgow Outcome Scale, Functional Independence Cognitive Measure, Disability Rating Scale) [18,19], further supporting links between physiological stress systems and TBI recovery. A relevant animal study demonstrated that the corticosterone response after experiencing blast-related mTBI can increase risk for development of the PTSD phenotype, emphasizing the intricate relationship between the HPA axis, mTBI, and PTSD [20]. Interestingly, an exploratory analysis in a recent randomized, double-blind, placebo controlled trial showed that Veterans with PCS after mTBI had a larger reduction in symptoms after prolonged exposure treatment augmented with synthetic glucocorticoid hydrocortisone [21]. Yet, few studies have explored how HPA axis biomarkers, such as cortisol, relate to perceptions of distress in Veterans with persistent PCH. Interventions aimed at reducing stress, such as yoga, can offer unique contexts for increased understanding of the relationship between these measures.

Through use of breathing techniques, muscle relaxation, and mindfulness, yoga-based interventions have become a much-discussed tool for targeting stress response systems [22–25]. Yoga interventions have been shown to reduce cortisol levels in those suffering from pain, fatigue, and depression [26–28], suggesting that this non-pharmacological, alternative treatment shows promise for successfully targeting physiological stress systems. Yoga-based interventions can also influence psychological outcomes, such as reducing subjective feelings of pain [29,30] and stress [31,32]. A recent pilot study of a yoga intervention in Veterans showed a significant association between a measurement of total cortisol output and self-reported life satisfaction [33]. However, the assessment of cortisol immediately before and after each individual yoga session was not measured. Yoga-based interventions are an optimal setting for exploring the relationship between

subjective distress and frequently employed physiological stress markers in Veterans with mTBI.

The present study is a secondary analysis from a feasibility and acceptability pilot trial [34], where changes in subjective distress (VAS) and salivary cortisol levels were assessed within the context of a manualized yoga intervention for Veterans with PCH. This exploratory analysis was conducted to evaluate the relationship between subjective distress and cortisol in Veterans with PCH following mTBI and how these two measures respond to an intervention aimed at addressing acute stress, such as the 75-min yoga sessions used in this study.

2. Materials and methods

2.1. Use of human subjects

This protocol was reviewed and approved by local regulatory committees including the Colorado Multiple Institutional Review Board.

2.2. Participants

This is a secondary, exploratory analysis of measures from participants who were enrolled in a feasibility study of a yoga-based intervention [34] and for whom cortisol levels were obtained. In brief, Veterans had to have a history of post-acute mTBI with persistent PCH. Briefly, participants were U.S. Military Veterans receiving care at a mountain state Veterans Affairs Medical Center. Participant samples used in this secondary analysis were only collected in the final two waves of the study, and thus the sample size is limited to $N = 16$. Participants had a history of mTBI and reported persistent PCH for at least 1 year. Full inclusion/exclusion criteria, as well as other details regarding the protocol are outlined in Betthausen et al., 2021.

2.3. Procedures

The study procedure timeline as it pertains to cortisol sampling is depicted in Fig. 1. After completing the first baseline visit, participants then completed an exercise run-in visit (used to familiarize Veterans with yoga poses) prior to randomization. Participants were then block randomized into the Yoga-Now or Yoga-Wait groups (Fig. 1, Visit 1b); the Yoga-Now group began the yoga intervention, *Strength and Awareness in Action: an Intervention for Post-Acute TBI Headaches* (SAA-TBI), shortly after randomization, whereas the Yoga-Wait group received enhanced treatment as usual for the first 8 weeks and then began the SAA-TBI yoga intervention. During the yoga intervention, participants completed 75-min classes twice weekly across 8 weeks (16 total yoga sessions). Veterans were administered the VAS distress measure immediately before and after each of the 16 attended yoga sessions over the course of the 8-week intervention. Salivary cortisol was collected at the same time points for every other session (total of 8 sessions) and was only collected from the 6th and 7th cohorts of participants. For these participants, the second class of each week was provided as an online format, so no cortisol samples could be collected from those sessions. Cohort 7 participants were not randomized and all began the 8-week yoga intervention immediately (no Yoga-Wait group). VAS distress scores and salivary cortisol from the same 8 sessions were used for analyses in the current study.

2.4. VAS distress thermometer measure

Subjective distress was measured using the VAS Distress Thermometer. The VAS is a well-validated self-report tool [15] that allows participants to rate their perceived level of distress at the current moment. The visual thermometer range consists of 1-point ticks starting from 0 (no distress) to 10 (extreme distress).

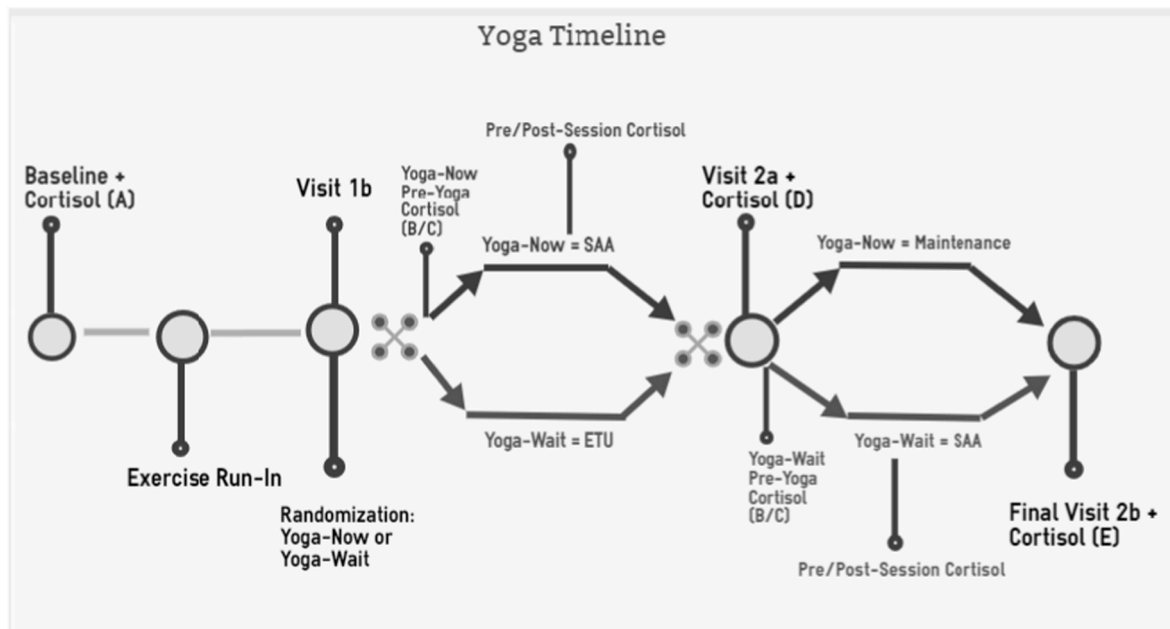


Fig. 1. Infographic depicting study procedure timeline as it pertains to cortisol sampling. After a baseline and exercise run-in sessions, participants were randomized to either immediately begin the 8-week yoga intervention (Yoga-Now) or to wait 8 weeks while undergoing ETU before beginning the intervention (Yoga-Wait). During the SAA yoga intervention, participants attended 75-min yoga sessions twice a week over 8 weeks. VAS distress scores were collected immediately before and after each session. Salivary cortisol was also collected at the same timepoints (pre- and post-yoga sessions) for 8 of the sessions. ETU = Enhanced Treatment as Usual. SAA = Strength and Awareness in Action. VAS = Visual Analogue Scale.

2.5. Cortisol collection and measurement procedures

Saliva for cortisol measurement was collected using Salivette for cortisol testing tubes (Cat. No. SAR-511534500, SciMart, Box Elder, SD, USA). It is well documented that cortisol concentrations follow a circadian rhythm; therefore, sample collection occurred immediately before and after a consistently timed yoga class to control for circadian variation. For saliva collection, participants were provided with a saliva collection kit and instructions (see Supplementary Material). Participants were first instructed to rinse their mouth with water for 10 s to remove potential contaminants (i.e. food, nicotine) and were then told to wait 2–5 min. Participants were instructed to insert the saliva collecting wad in their mouth for 45 s or until saturated. They then removed the wad from their mouth and placed the wad into the collection tube. Saliva was extracted from the wad according to the manufacturer's instructions and frozen at -80°C until further analysis. Total salivary cortisol concentrations were measured using cortisol Enzyme Immunoassay (EIA) kits (Cat. No. ADI-900-071, Enzo Life Sciences, Plymouth Meeting, PA, USA) according to manufacturer instructions. Each sample was run in duplicate and plates were read with a spectrophotometer set at 405 nm (Synergy 4, BioTek, Winooski, VT, USA). The mean of the sample duplicates were used for further analysis. The sensitivity of this assay is $0.0057\ \mu\text{g}/\text{dl}$ and the inter- and intra-assay coefficients of variation for the data collected were 4.4% and 1.63%, respectively.

2.6. Data analysis

All analyses assumed a two-sided test of hypothesis, a significance level of 0.05 and were run in SAS v9.4. Demographic characteristics are summarized as means and standard deviations (SD), medians and ranges and frequencies, as appropriate. The average change in VAS distress thermometer and cortisol (both raw and the natural log transformation of cortisol levels), within each yoga session, were estimated using separate repeated measures analyses which modeled the outcome of post-session value minus pre-session value as a function of time using maximum likelihood estimation. This analysis accounts for the

correlation between yoga sessions within a person and allows for nonlinear changes between sessions (i.e., time is considered categorical, and means are estimated within each session). Mixed-effects models, which account for the correlation between repeated measures over time, were used to determine linear trajectories of VAS and cortisol levels (raw and log transformed) over continuous time. Trajectories for two types of outcomes were estimated for both measures. First, the post-session outcome was modeled as a function of continuous time to determine if there was a significant increase or decrease in the post-session values for each outcome as a participant progressed through sessions. Second, the change (post-session minus pre-session) was modeled as a function of continuous time to determine if there was a significant increase or decrease in the within-session change for each outcome as a participant progressed through sessions. Additionally, for each session, the Spearman correlation between VAS change and cortisol change was calculated.

3. Results

The 16 Veteran participants with measured cortisol were primarily male (75%) and White (69%) with an average age of 38.3 (SD = 7.6). See Table 1 for a full description of demographic and military characteristics.

3.1. Within session VAS and cortisol change

There was a significant decrease in VAS within 5 of the 8 yoga sessions (all $p < 0.01$) with estimated mean decreases ranging from 1.33 to 2.00 points. See Table 2 for all estimated mean changes with 95% confidence intervals (CIs). This was not observed for within-session changes in cortisol levels as there was no significant change in either raw or log-transformed cortisol levels for any session (Table 2).

3.2. VAS and cortisol trajectories

A statistically significant linear decrease over time (i.e., over

Table 1
Demographic and military characteristics (N = 16).

Characteristic	Mean (SD) and Median (range) or N (%)
Age	38.3 (7.6) 34.5 (28, 50)
Gender	
Male	12 (75%)
Female	4 (25%)
Race	
Caucasian/White	11 (69%)
Black or African American	2 (12%)
Multiracial/Other	3 (19%)
Hispanic/Latino	6 (38%)
Military Branch ^a	
Army Active Duty	11 (69%)
Air Force Active Duty	1 (6%)
Navy Active Duty	1 (6%)
Marines Active Duty	3 (19%)
Army Reserve	1 (6%)
Army National Guard	2 (12%)
Number of Deployments	2.6 (2.5) 2 (1, 11)
Number of Combat Tours	2.1 (2.2) 1.5 (0, 9)
Highest Level of Education	
Some College	7 (44%)
Associate's/Bachelor's	6 (37%)
Master's	3 (19%)
Employment Status	
Full-time/Part-time	11 (69%)
Unemployed	3 (19%)
Retired	2 (12%)
Student	3 (19%)
Relationship Status	
Married	10 (63%)
Cohabiting	1 (6%)
Single	5 (31%)

^a Participants may have served in more than one military branch.

Table 2
VAS and cortisol estimated change within yoga session.

Session	VAS		Cortisol ug/dl		Ln (Cortisol)	
	Estimated Mean Change (95% CI)	p-value	Estimated Mean Change (95% CI)	p-value	Estimated Mean Change (95% CI)	p-value
1 (N = 14)	-1.33 (-2.2, -0.48)	0.003	-0.0102 (0.016)	0.43	-0.12 (0.003)	0.06
3 (N = 9)	-1.36 (-2.4, -0.36)	0.009	0.017 (-0.015, 0.049)	0.30	0.067 (-0.086, 0.22)	0.38
5 (N = 11)	-0.50 (-1.5, 0.46)	0.30	-0.025 (-0.053, 0.004)	0.09	-0.11 (-0.25, 0.029)	0.12
7 (N = 9)	-1.78 (-2.9, -0.67)	0.002	-0.016 (-0.048, 0.015)	0.31	-0.071 (-0.22, 0.082)	0.36
9 (N = 7)	-2.00 (-3.3, -0.75)	0.002	-0.021 (0.057, 0.016)	0.26	-0.066 (-0.24, 0.108)	0.45
11 (N = 7)	-1.63 (-2.8, -0.45)	0.008	-0.021 (0.057, 0.016)	0.26	-0.085 (-0.26, 0.089)	0.33
13 (N = 9)	-1.00 (-2.1, 0.11)	0.08	-0.028 (0.061, 0.004)	0.08	-0.12 (-0.28, 0.031)	0.12
15 (N = 4)	-1.25 (-2.9, 0.41)	0.14	-0.011 (-0.059, 0.037)	0.66	-0.060 (-0.29, 0.17)	0.60

sessions) in post-session cortisol levels was observed for raw cortisol levels indicating that post-session levels reduced, on average, by 0.018 µg/dl for each additional session (p = 0.03). A similar result was

observed for the log-transformed post-session cortisol levels ($\beta = -0.005$, $p = 0.03$). These results were not upheld when assessing the within session change in cortisol over time, though there was a trend toward a significantly larger within session decrease over time for the log-transformed cortisol analysis ($\beta = -0.016$, $p = 0.07$). Results are displayed in [Table 3](#).

The analysis for post-session VAS yielded a decreasing trend in post-session VAS over time, indicating that on average, post-session VAS decreased by 0.07 points for each additional session (p = 0.07). This trend was no longer observed when taking pre-session VAS into account as there was no observed association between time and within session change in VAS ($\beta = 0.03$, $p = 0.66$).

3.3. VAS and cortisol change correlations

Across sessions, available paired sample sizes ranged from 4 (final session) to 14 (first session), with a mean of 8.8 (SD = 3.0) and a median of 9. No significant correlations were observed between VAS change and cortisol change for any of the yoga sessions.

4. Discussion

In the current study, the research team explored the relationship between subjective distress and salivary cortisol levels within the context of a yoga intervention for Veterans with persistent headaches after mTBI. We found that participants' subjective distress scores, but not salivary cortisol levels, were significantly reduced following five of the eight assessed yoga classes. These changes in distress scores were not correlated with changes in cortisol levels. When looking at changes in cortisol levels over the series of yoga sessions, there was a significant downward trajectory in post-yoga cortisol, but this effect was no longer significant when accounting for pre-yoga cortisol levels. These findings are consistent with previous studies showing no clear or significant association between perceived stress and cortisol levels and also emphasize the need for careful consideration when selecting clinical trial outcomes [35–37]. Although large observed correlations would be necessary to achieve significance (>0.56), the discrepancy between scores on these measures suggest that subjective distress and physiological stress are measuring different facets of the stress response [38, 39]. Therefore, understanding the interrelation between subjective distress and physiological stress and the extent to which they correspond to changes in stress responsivity over time likely requires more nuanced investigations that consider the context (e.g., type of stress or intervention), the methods and timing of assessment, and individual factors that could moderate the relationship between these two responses [35].

The significant reduction in VAS scores within 5 of the 8 sessions suggest that this measure may be useful for gauging acute changes in perceived distress in this population. VAS measures have been successfully used to measure other TBI-associated symptoms that can often coincide with feelings of distress [40–43], thus adding to the evidence which suggests that these quick self-report tools may provide a method for understanding how interventions alter subjective experiences of one's symptomology. Nevertheless, the level of detail that can be gathered from a single response item thermometer certainly limits the

Table 3
VAS and cortisol trajectories.

Model Outcome	VAS		Cortisol ug/dl		Ln (Cortisol)	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Post-Session	-0.068 (0.04)	0.07	-0.018 (0.008)	0.03	-0.005 (0.002)	0.03
Within Session Change	0.03 (0.07)	0.66	-0.004 (0.002)	0.11	-0.016 (0.009)	0.07

usefulness of the tool in terms of its ability tease apart underlying mechanisms associated with an individual's subjective experience.

Incorporating objective markers of psychological stress may increase understanding of mechanisms of change in mind-body therapies such as yoga, but selection of markers must take into account the specific intervention, the timing of measurement, and sensitivity to change. While salivary cortisol may be a feasible, non-invasive biological marker of psychological stress, its utility in rapidly detecting changes in stress response likely depends on the context of the intervention. In fact, previous research has shown cortisol changes are only seen in specific types of stress-inducing paradigms [35]. The specific type of cortisol analysis may also play an important role. In Zaccari and colleagues' yoga intervention study in Veterans with PTSD, although there were no significant changes in cortisol measurements post-to pre-intervention, changes in cortisol area under the curve with respect to the ground, a measurement of cortisol output, was significantly associated with self-reported improvement in life satisfaction [33].

Specifics of the yoga intervention are also important – though salivary cortisol changes can be detected within acute time frames, it may not be the most sensitive biological marker of acute changes that occur within 75 min yoga sessions. For example, in a recent study, Eda and colleagues demonstrated a significant reduction in salivary cortisol at 120 min post yoga session compared to pre-yoga session levels [44]. However, no significant reductions were observed immediately post or at 60 min post yoga session. Along these lines, studies have also shown that increases in perceived stress and anxiety can precede HPA activation in stress-induction tasks [36], which supports our current findings showing changes only in subjective distress immediately following the yoga intervention.

These findings suggest that other objective biomarkers may better suited for matching changes in distress during acute intervention sessions. As autonomic reactivity is altered in those with mTBI [6,7], measures of such reactivity (e.g., heart rate variability, blood pressure, vagal tone, galvanic skin response) may be better matched to acute ratings of subjective distress. Alternative stress biomarkers (e.g., catecholamines, cortisol, salivary amylase) may also be more readily associated with measured subjective distress in Veterans with PCH. For example, a previous study showed that subjective distress ratings after an acute stress paradigm were correlated with circulating epinephrine in chronically stressed, but not control participants – also highlighting the potential importance of chronic stress states when relating specific biomarkers to distress [45]. Interestingly, the aforementioned study also showed associations between distress scores and immune activity [45]. Given that chronic stress can result in a wide variety of negative health outcomes, physiological systems that are intertwined with the stress response, such as the immune system [46–48], may also be important to consider when measuring distress in Veterans with PCH.

Elucidating which biomarkers are most appropriate for various time points after mTBI is also paramount. In one study, cortisol levels were only increased in certain subgroups in the immediate days after TBI [18]. Whereas salivary cortisol may be helpful for assessing changes immediately post-injury, inflammatory cytokines may be better markers of distress that can accompany long-term PCS.

There are limitations to the current study. It should be noted that this was a secondary analysis from an acceptability and feasibility trial [34], and thus additional studies focusing on the relationship between subjective distress and physiological biomarkers as a primary outcome are needed. We also did not assess salivary cortisol at every single yoga session. Collection at all time points would be useful to fully understand how these measures change over longer intervention periods. As the current population suffers from long-term symptoms, it may also be useful to examine more chronic measures of cortisol, such as hair or fecal samples. Although we controlled for specific factors known to alter salivary cortisol levels, such as sample collection timing and mouth contaminants, we cannot exclude the possibility that additional factors (e.g., smoking, menstrual cycle) may have impacted the results found in

the current study.

The inclusion of measures that directly relate distress to specific symptoms, such as the Symptom Distress Scale [49], could further enhance our understanding of how distress specifically relates to various symptoms associated with long-term PCS. Comparing VAS results with other PROMs typically used to evaluate stress, such as the Perceived Stress Scale or Psychosocial Stress Inventory, may also help increase understanding of how changes in distress may relate to more detailed measures of subjective stress. Finally, it must be noted that the current study only focused on a small sample size of Veterans with long-term PCH after mTBI, thus limiting the generalizability of these findings. Future studies will benefit from larger samples and more diverse populations to improve generalizability.

It is worth noting that the VAS used in the current study asked participants to rate their level of distress at a specific moment in time, which may differ from one's levels of stress. Although distress and stress are often used interchangeably, the terms may be targeting two different subjective components. While stress is often assumed as explicitly negative, stress was originally conceptualized by Hans Selye as “the non-specific response of the body to any demand” [50]. Selye also distinguished between “eustress”, or stress that can result from positive experiences, and “distress” as stress that may result from negative experiences [51]. However, these definitions may be interpreted differently across individuals, where distress might be considered as either more prolonged and/or more severe versions of stress. Means of addressing this include adding specific definitions for both stress and distress to the measure, administering scales for both stress and distress, and/or to conducting qualitative post-interviews help to clarify the participants interpretation of the VAS scale.

Studies also indicated that TBI may result in long-term hypocortisolism [52]. Given that the aim of the current intervention was to reduce, not elicit stress, we may not expect to see changes if cortisol levels are too low at baseline in Veterans with long-term PCH. Further, there may be floor effects, as normal cortisol levels typically fall below 5 µg/dl, and exercise can also increase salivary cortisol levels [53]. A previous study also demonstrated that salivary cortisol was not associated with perceived stress in participants with TBI [54], further adding to the idea that cortisol may not actually measure acute changes in subjective symptoms. An additional thought worth considering is that large fluctuations in salivary cortisol over short periods of time may not necessarily be desired, but reductions in one's subjective experience of distress after a yoga session could be important for daily symptom management. Therefore, tracking cortisol over longer periods of time alongside acute VAS ratings could be used to tease apart the relationship between subjective distress management and HPA function.

Taken together, our results show that a yoga intervention was associated with reduced subjective distress, but not salivary cortisol in Veterans with PCH following mTBI. The study emphasized an ever important need to continue uncovering relationships between subjective and physiological markers when studying interventions. As the current intervention was found to be acceptable [34], yoga-based interventions may be a useful context within which to continue the exploration of biological mechanisms driving perceived distress in this population. Further, these results suggest that yoga could be a useful avenue for managing perceived distress, which could lead to changes in physiology over longer periods.

Funding

This work was supported by the Colorado Traumatic Brain Injury Trust Fund (part of the MINDSOURCE Brain Injury Network) [Contract IHEA #101374]. M.D. was supported by the VA Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs.

Conflicts of interest

Dr. Brenner reports grants from the VA, DOD, NIH, and the State of Colorado, editorial remuneration from Wolters Kluwer, and royalties from the American Psychological Association and Oxford University Press. In addition, she consults with sports leagues via her university affiliation.

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Acknowledgements

The views expressed herein are those of the author(s) and do not reflect the official policy of the U.S. Government. The authors acknowledge the effort and assistance of all team members in helping to successfully complete this study, including Carlee Kreisel, Daniel Matrosic, and Ann Bortz, PsyD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnec.2022.100123>.

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