Neurobiology of Stress 11 (2019) 100180

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

HPA axis function and diurnal cortisol in post-traumatic stress disorder: A systematic review

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A B S T R A C T

Background: There is inconsistency in the literature regarding the nature of hypothalamic-pituitary-adrenal (HPA) axis functionality in post-traumatic stress disorder (PTSD).

Purpose: The review aimed to investigate HPA axis functionality via the diurnal profile of cortisol as it relates to PTSD.

Methods: The authors conducted a systematic review of the literature from June 2017 – March 2019 in accordance with The PRISMA Statement in the following four databases: PubMed, MEDLINE, ScienceDirect and PsycINFO with Full Text. The search strategy was limited to articles in English language, published in peer-reviewed journals within the last decade and human studies. Search terms included "post-traumatic stress disorder" OR "PTSD", AND "hypothalamic pituitary adrenal axis" OR "HPA axis" AND "diurnal cortisol" OR "cortisol". PTSD sufferers of all trauma types, genders and socioeconomic statuses were included provided there was a "healthy" control group and an inclusion of reporting on inter-group measurements of diurnal cortisol profiles as a portrayal of HPA axis functionality.

Results: A total of 10 studies met the criteria for inclusion in this review. The association between HPA axis functionality and PTSD was evaluated by the measurement of salivary and/or plasma cortisol concentrations. Only two studies demonstrated an association between PTSD and diurnal cortisol when compared with respective control groups while three studies found no associations. The remaining five studies found partial, mostly negative associations between PTSD and diurnal cortisol.

Conclusion: Despite some indications of an association between PTSD and dysregulated HPA axis functionality as demonstrated by diurnal cortisol output, the current review has revealed mixed findings. As such, a complete understanding of HPA axis dysregulation as it relates to PTSD remains unestablished. Given the findings, further investigation into the relationship between PTSD trauma-exposed and non-PTSD trauma-exposed individuals and diurnal cortisol is warranted.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a severe stress-related condition that may develop after experiencing a traumatic event. Characterized as an Axis I disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013), PTSD is defined by four symptom clusters: re-experiencing the traumatic event through flashbacks and nightmares, avoidance of reminders of the traumatic event, negative alterations in mood and cognition and hyperarousal which may affect sleep quality and concentration due to a hyper-vigilant state (American Psychiatric Association, 2013; Furtado and Katzman, 2015). In order to be diagnosed with chronic PTSD, these symptoms must lead to functional impairment, cause severe distress within the individual for at least one month and must not be due to the effects of medication or other illnesses (American Psychiatric Association, 2013). Given that PTSD is estimated to have a lifetime prevalence rate between 7 and 12%, it is a substantial public health concern (Zaba et al., 2015).

Post-traumatic stress disorder places an undeniable burden on the sufferer, their families and society considering the mental health stigma, negative social consequences, and substantial annual medical costs (Daskalakis et al., 2013). Additionally, PTSD is correlated with an elevated risk for the development of a variety of co-morbid chronic diseases due to its associated alterations in a number of physiological mechanisms/systems such as the metabolic, immune/inflammatory and central nervous systems as well as influencing epigenetic changes (Perroud et al., 2014). Alterations within the hypothalamic-pituitary-adrenal (HPA) axis are of particular interest as dysregulation of this

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https://doi.org/10.1016/j.ynstr.2019.100180
Received 19 December 2018; Received in revised form 17 April 2019; Accepted 3 June 2019
Available online 04 June 2019
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system has been proposed to accelerate chronic disease progression within the PTSD population (Miller et al., 2007).

Previous studies propose that cortisol is one of the hormones that can represent alterations to HPA axis functionality, particularly with respect to its diurnal rhythm. Typically, the diurnal (i.e. circadian) rhythm of cortisol follows a 24-h cycle, peaking within an hour of waking, gradually declining throughout the day and reaching its lowest point during sleep (Morris et al., 2012; Ryan et al., 2016). From a measurement perspective, findings of diminished diurnal cortisol secretion may be partly attributed to a dampened cortisol awakening response (CAR), described as a rapid burst in cortisol output ensuing post-morning awakening (Clow et al., 2010). Other measurable aspects include the diurnal cortisol slope (i.e. the characteristic decline in cortisol from morning to evening) and the area under the curve, which reflects cumulative cortisol output across the day (Adam and Kumari, 2009; Ryan et al., 2016). Alterations to these parameters, and thus abnormal diurnal cortisol output, may prevent the body's return to homeostasis and dysregulated HPA axis functioning. (Daskalakis et al., 2013; Morris et al., 2012). With respect to dysregulated HPA axis activity and the various regulatory roles of cortisol, such alterations to diurnal cortisol output may have an impact on other physiological processes such as glucose metabolism, digestion, inflammation and memory encoding/retrieving (Meewisse et al., 2007; Reul and Nutt, 2008).

However, discrepancies remain regarding HPA axis dysregulation post-trauma and the consequential nature of cortisol output under sustained stress (Luo et al., 2012). Several studies have exhibited lower than normal diurnal cortisol secretion in PTSD participants, specifically upon awakening and throughout the afternoon whilst opposing findings have been also been reported, and some studies did not detect significant differences between PTSD sufferers and their healthy counterparts (Bremner et al., 2007; Clow et al., 2010; Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013).

Given the extent of inconsistency between research methods and findings regarding cortisol secretion, this systematic review aimed to investigate research within the last decade that assessed HPA axis functionality via the diurnal profile of cortisol as it relates to PTSD.

2. Methods/design

We performed a systematic review in accordance with the established guidelines from The Preferred Reporting Items for Systematic Reviewed and meta-analyses (PRISMA) Statement (Liberati et al., 2009; Moher et al., 2009).

2.1. Search strategy

An electronic literature search of peer-reviewed journal articles was conducted from June 2017 – March 2019 using four databases (PubMed, MEDLINE, ScienceDirect and PsycINFO). Medical subject headings (MeSH) were considered in the development of the search terms. The search was limited to human studies published in English language. Studies prior to 2007 were excluded to ensure that data remained recent. Titles, abstracts and methods were screened by the lead author for relevance based on the selection criteria (Section 2.3) and all duplicates were removed. The articles deemed relevant were selected for further consideration (Fig. 1). The search was further limited to peer-reviewed original research articles with full text available. Review, meta-analysis and other types of articles (e.g. author manuscript, letters to editors) were also excluded. A hand search was undertaken of the reference lists of relevant articles, and those deemed eligible were included with the intent to ensure that all articles relevant to the research had been captured by the search strategy. The abstracts of the articles deemed relevant by the lead author (K.S) were then independently reviewed by a further investigator (A.M) for relevance. If consensus was not reached, the article was moved on to the next stage for a review of the full-text. The full-texts of the remaining eligible studies were independently reviewed by the investigators (K.S and A.M) against the inclusion and exclusion criteria. Disagreements were discussed until consensus was reached in all cases.

2.2. Search terminology

The search terms used included: “post-traumatic stress disorder” OR “PTSD”, AND “hypothalamic pituitary adrenal axis” OR “HPA axis” AND “diurnal cortisol” OR “cortisol”. These were combined using the Boolean operators AND as stated above and OR between other terms. A hand search was undertaken of reference lists with the intent to assure the quality of chosen articles.

2.3. Selection criteria and data extraction

Studies were eligible for inclusion if the following applied: (1) they examined trauma leading to PTSD; (2) they examined the association between PTSD, the HPA axis and diurnal cortisol in adults; (3) studies must have a correlational or longitudinal design (observational, randomized trials); (4) studies must have a healthy control group; (5) they took diurnal cortisol measurements; (6) results were presented as mean ± standard deviation and p values were provided.

All papers identified from the initial electronic search process were imported into EndNote (version X8.1, Thomson Reuters) where all duplicates were removed. Upon completion of the title and abstract reviews, a total of 129 articles were identified for full-text review where 10 were identified as meeting the inclusion criteria. The reasons for excluding each article were recorded.

2.4. Data analysis

After study selection, criteria were followed to maintain the evaluation of the studies within narrow standards. The first and essential criterion was that all details regarding diurnal cortisol collection should be verified, with description of instruments, data collection protocol, and methods.

Data extraction of included studies was organized into a table. This included the following: author and year of publication; number of participants; study population, trauma type(s) study design; focus and outcome of the study; the cortisol measurements taken and statistical significance of study findings.

2.5. Risk of bias

Two independent reviewers used the Physiotherapy Evidence Database (PEDro) scale to assess the quality and risk of bias of each of the studies identified as eligible (see Table 1). The PEDro scale is shown to have good constructive validity (Macedo et al., 2010). It is an 11-item scale that is used to assess the quality of the methodology in the studies (Maher et al., 2003; Verhagen et al., 1998). The PEDro scale measured/assessed the eligibility criteria, randomisation, allocation processes, similarity of baseline groups, the blinding process, near complete data sets obtained for the key outcome, between group statistics reported and measures of variability were included in the selected studies (Verhagen et al., 1998). Criterion one is used to help determine the external validity of the study; criterion two through to nine is designed to help identify whether the study has internal validity; and criterion ten and eleven assist in determining there is sufficient statistical information for the results to be interpreted appropriately (Verhagen et al., 1998). Each of these items was allocated a score in relation to the study. A point was allocated (as represented by an “X”) if the study met the specified criterion and a zero was given when the item did not. This was then used to calculate a total score of bias for the

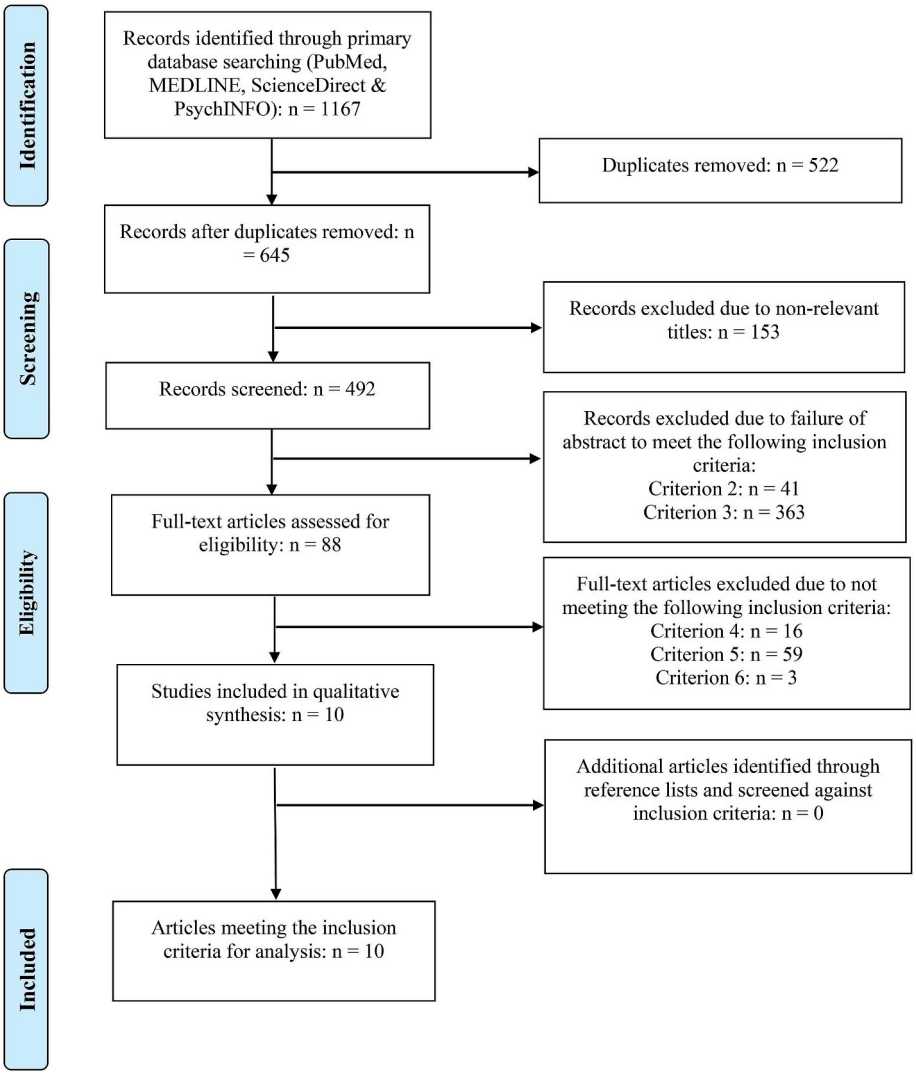

Fig. 1. PRISMA Flow Chart Schematic representation of the flow of information during the different phases of the systematic review. Articles were included if they (1) examined trauma leading to PTSD; (2) examined the association between PTSD, the HPA axis and diurnal cortisol in adults; (3) have a correlational or longitudinal design (observational, randomized trials); (4) have a healthy control group; (5) took diurnal cortisol measurements; (6) presented results as mean ± standard deviation and provided *p* values.

Table 1
The PEDro scale.

Authors and Date	1	2	3	4	5	6	7	8	9	10	11	Total	Risk of bias
Cordero et al. (2017)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Pierce and Pritchard (2016)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Labonté et al. (2014)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Van Liempt et al. (2013)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Wahbeh and Oken (2013)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Eckart et al. (2009)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Metzger et al. (2008)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
DE Kloet et al. (2007)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Gill et al. (2008)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)
Bremner et al. (2007)	X	0	0	X	0	0	0	X	0	X	X	5/11	2/6 (high)

Criteria: 1. eligibility criteria were specified; 2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); 3. allocation was concealed; 4. the groups were similar at baseline regarding the most important prognostic indicators; 5. there was blinding of all subjects; 6. there was blinding of all therapists who administered the therapy; 7. there was blinding of all assessors who measured at least one key outcome; 8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"; 10. the results of between-group statistical comparisons are reported for at least one key outcome; 11. The study provides both point measures and measures of variability for at least one key outcome (Verhagen et al., 1998).
Note: X: the study met the specified criterion; 0: the study did not meet the specified criterion.

study by adding all of the items together. The risk of bias for the studies was established using the criteria from the PEDro scale summating items two to four and seven to nine. The six criteria that were used in the current review i) adequacy of randomization (criterion two); ii) allocation concealment (criterion three); iii) between-group baseline comparability (criterion four); iv) blinding of outcome assessors (criterion seven); v) adequate follow-up (more than 85%) (criterion eight), and; vi) intention to treat analysis (criterion nine). A score of five or six was considered to have a low risk of bias, three to four a moderate risk, and two or less a high risk.

3. Results

3.1. Study design, characteristics and risk of bias

The initial searches resulted in a total of 1167 manuscripts. Following the title, abstract and methods screening as well as removal of duplicates, the number of articles was reduced to 129. From this, 10 studies met the inclusion criteria (Fig. 1) with all selected studies of a cross-sectional design. Risk of bias assessment revealed that all studies demonstrated high risk (Table 1). The studies included in this systematic review are presented in Table 2 with a description of the studies (including population, types of trauma, design) according to their focus investigating HPA axis functionality within PTSD sufferers via their diurnal cortisol profile, the method used to diagnose PTSD, the way in which diurnal cortisol levels were collected and the statistical significance of the study findings.

The main aim of all included studies was to compare cortisol concentrations of PTSD participants with those of their healthy counterparts in order to demonstrate whether HPA axis dysregulation is prevalent within the PTSD population (Table 2).

3.2. Populations assessed

There was a vast range of trauma sources (Table 2) leading to PTSD within the selected eight studies including military and combat exposure (DE Kloet et al., 2007, Eckart et al., 2009, Pierce and Pritchard, 2016, Van Liempt et al., 2013, Wahbeh and Oken, 2013); motor vehicle accidents (Labonte et al., 2014); armed assault (Gill et al., 2008; Labonte et al., 2014); adulthood physical and sexual abuse (Cordero et al., 2017; Gill et al., 2008; Labonte et al., 2014); childhood physical and sexual abuse (Bremner et al., 2007; Cordero et al., 2017; Gill et al., 2008; Labonte et al., 2014); refugee experiences (Eckart et al., 2009), unexpected death of a family member or close friend (Gill et al., 2008); witnessing physical assault or murder of another person (Gill et al., 2008); other (Labonte et al., 2014). Some studies ($n = 4$) only incorporated females (Bremner et al., 2007; Cordero et al., 2017; Gill et al., 2008; Metzger et al., 2008; Pierce and Pritchard, 2016). Three studies included only males and one study consisted of both females and males (DE Kloet et al., 2007; Eckart et al., 2009, Labonte et al., 2014, Van Liempt et al., 2013; Wahbeh and Oken, 2013).

3.3. Control for confounding factors

Through inclusion and exclusion criteria and statistical analyses, the reviewed studies controlled for the following confounding factors that are known to implicate the validity of cortisol concentrations: age (Bremner et al., 2007; Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); gender (Bremner et al., 2007; Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); ethnicity/race (Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); marital status (Cordero et al., 2017; Eckart et al., 2009; Gill et al., 2008; Van Liempt et al., 2013; Wahbeh and Oken, 2013); education (Eckart et al., 2009; Gill et al., 2008; Pierce and Pritchard, 2016, Van Liempt et al., 2013); weight (Bremner et al., 2007, Van Liempt et al., 2013); BMI (DE Kloet et al., 2007, Eckart et al., 2009, Gill et al., 2008, Metzger et al., 2008, Van Liempt et al., 2013, Wahbeh and Oken, 2013); menopausal status (if applicable) (Bremner et al., 2007; Gill et al., 2008); Major Depressive Disorder (MDD) (Bremner et al., 2007; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); psychiatric co-morbidities other than major depressive disorder (Bremner et al., 2007; Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); physical co-morbidities (Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Wahbeh and Oken, 2013); perceived stress (Wahbeh and Oken, 2013); medication (Cordero et al., 2017; Eckart et al., 2009; Gill et al., 2008; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); smoking status (Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Gill et al., 2008; Metzger et al., 2008; Van Liempt et al., 2013; Wahbeh and Oken, 2013); tobacco use (Pierce and Pritchard, 2016); alcohol/substance abuse or dependence (Bremner et al., 2007; Cordero et al., 2017; Eckart et al., 2009; Gill et al., 2008; Metzger et al., 2008; Van Liempt et al., 2013; Wahbeh and Oken, 2013); early life trauma (Bremner et al., 2007; Cordero et al., 2017; Metzger et al., 2008); type of trauma (Bremner et al., 2007; Cordero et al., 2017; DE Kloet et al., 2007; Eckart et al., 2009; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); trauma history (Eckart et al., 2009; Metzger et al., 2008; Van Liempt et al., 2013; Wahbeh and Oken, 2013); years exposed to traumatic conditions (Eckart et al., 2009; Metzger et al., 2008; Van Liempt et al., 2013; Wahbeh and Oken, 2013); time since trauma (DE Kloet et al., 2007, Eckart et al., 2009, Metzger et al., 2008, Pierce and Pritchard, 2016, Van Liempt et al., 2013, Wahbeh and Oken, 2013); sleep duration (Eckart et al., 2009; Van Liempt et al., 2013; Wahbeh and Oken, 2013); time of awakening (Bremner et al., 2007; DE Kloet et al., 2007; Eckart et al., 2009; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013); sample collection time (Bremner et al., 2007; DE Kloet et al., 2007; Eckart et al., 2009; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013).

3.4. Cortisol collection methods and definitions of abnormal cortisol concentrations

All selected studies sought to investigate the association between PTSD and the HPA axis via participants' diurnal cortisol profiles. However, there were variations between studies in the type of sample used to extract cortisol from as well as a lack of a clear definition of abnormal cortisol concentrations in some studies. The majority of studies ($n = 7$) chose to collect cortisol samples solely through participants' saliva (Cordero et al., 2017; Eckart et al., 2009; Gill et al., 2008; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Wahbeh and Oken, 2013). Two studies used plasma samples and the last study measured cortisol in both saliva and plasma samples (Bremner et al., 2007, DE Kloet et al., 2007; Van Liempt et al., 2013) (see Table 2).

In regard to clearly defining abnormal cortisol concentrations, seven studies provided their respective intra- and/or inter-assay coefficients of variation (10% or lower) (Cordero et al., 2017; Eckart et al., 2009; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Van Liempt et al., 2013; Wahbeh and Oken, 2013). Two studies not only provided coefficients of variation but also incorporated distinct definitions of abnormal cortisol levels through comparing their intra- and inter-assay results to either time-dependent reference values or

Table 2
Representation of selected articles examining the relationship between PTSD and diurnal cortisol.

Authors	N	Study Population	Trauma Type(s)	Design	Aim	PTSD Diagnostic Method	Cortisol Sampling	Findings (Significant p values)
Cordero et al. (2017)	36	F; PTSD (18) and HC (18)	IPV	- Cross-sectional - Experimental element: laboratory stressor involving mother and child separation	To examine maternal IPV-PTSD diurnal cortisol compared with controls and in relation to their child's distress	CAPS structured interview and PCL-S	Salivary cortisol collected 30 min after waking, between 2 and 3pm and bedtime. Cortisol was also collected around the laboratory stressor at baseline (before stressor), immediately after stressor, 30 min and 60 min post-stressor	**Maternal PTSD vs. No PTSD** 30 min post-awakening: $p < 0.021$ Bedtime: $p < 0.014$ Group x time interaction: $p < 0.001$
Pierce and Pritchard (2016)	52	F; controls without PTSD (20), controls with PTSD (19), veterans without PTSD (6), veterans with PTSD (7)	War zone	- Cross-sectional - Experimental element: TSST	To examine cortisol concentrations in female veterans and civilians both with and without PTSD	PDS self-report questionnaire	Salivary cortisol collected at bedtime, awakening and after the TSST	**Cortisol after TSST** Veterans PTSD+ and PTSD− Time 1: $p = 0.006$ Time 2: $p = 0.017$ Time 3: $p = 0.018$
Labonte et al. (2014)	46	M and F; Lifetime PTSD (30) and controls never exposed to trauma (16)	MVA, war, armed assault, adulthood physical/sexual abuse, childhood physical/sexual abuse, other	- Cross-sectional - Experimental element: none	To investigate HPA function in subjects with lifetime PTSD vs. healthy controls	CAPS structured interview and the IES-R self-report	Salivary cortisol taken at six-time points throughout the day – awakening, awakening + 30 min, awakening + 45 min, awakening + 60 min, awakening + 8 h, and bedtime	**PTSD vs. No PTSD** Overall: $p < 0.0005$ 30–45 min post-awakening: $p < 0.01$ 45–60 min post-awakening: $p < 0.05$
Van Liempt et al. (2013)	45	M; PTSD (13), TC (17) and HC (15)	War zone	- Cross-sectional - Experimental element: none	To examine sympathetic activity and HPA axis activity during sleep in PTSD	SCID and CAPS structured interview with consensus by two clinicians	Plasma cortisol determined every 20 min from 10pm to 8am and 20 min, 40 min and 60 min post-awakening	**PTSD vs. Trauma Controls and Healthy Controls** No relevant significant results
Wahbeh and Oken (2013)	71	M; PTSD (51) and No PTSD (20)	War zone	- Cross-sectional - Experimental element: none	To measure cortisol in combat veterans with and without PTSD	CAPS structured interview	Salivary cortisol collected upon waking, 30 min after waking and bedtime on two consecutive days	**PTSD vs. No PTSD** Waking: $p < 0.05$ Waking + 30 min: $p < 0.01$ Bedtime: $p < 0.05$
Eckart et al. (2009)	30	M; PTSD (17) and Control (13)	Highly traumatized adult males from Rwanda with and without PTSD	- Cross-sectional - Experimental element: none	To evaluate the diurnal cortisol profile secretion in a population of Rwandan refugees	PDS self-report questionnaire	Salivary cortisol concentrations taken at 7:30am, 8am, 8:30am, 9:30am, 11:30am, 1:30pm, 3:30pm, 5:30pm, 7:30pm and 9pm	**PTSD vs. No PTSD** No relevant significant results
Metzger et al. (2008)	83	F; Current PTSD (40) and Never PTSD (43)	War zone	- Cross-sectional - Experimental element: LD-DST	To assess cortisol levels at 8am and 4pm and the cortisol response to DEX in female Vietnam nurse veterans	CAPS-DX and SCID structured interviews	Salivary cortisol concentrations	**PTSD vs. No PTSD** No relevant significant results
DE Kloet et al. (2007)	83	M; PTSD (28), TC (27), and HC (28)	War zone	- Cross-sectional - Experimental element: LD-DST	To determine the effects of trauma exposure and PTSD on diurnal cortisol rhythm and	Dutch Self Inventory for PTSD (self-report), CAPS structured interview and	Salivary and plasma cortisol concentrations taken on 2 day at 8am, 4pm (1st day) and 8am and 4pm post-DEX (2nd day)	**PTSD vs. Trauma Controls and Healthy Controls**

(*continued on next page*)

Table 2 (*continued*)

Authors	N	Study Population	Trauma Type(s)	Design	Aim	PTSD Diagnostic Method	Cortisol Sampling	Findings (Significant *p* values)
					HPA-axis feedback regulation using low dose DEX	consensus by three clinicians		4pm Post-DEX: $p < 0.001$
Gill et al. (2008)	71	F; PTSD group (26), TC (24), NTC (21)	Childhood physical/sexual abuse, unexpected death of a family member or close friend, adulthood rape or sexual abuse, IPV, physical assault by a non-intimate partner and witnessing physical assault or murder of another person	- Cross-sectional - Experimental element: none	To compare cortisol, DHEA, sIgA and serum production of TNFα, IL-1β and IL-6 among TC, NTC and PTSD participants	CAPS structured interview	Salivary cortisol measurements collected in the morning and evening	**PTSD vs. Trauma Controls and Healthy Controls** Morning: $p < 0.05$
Bremner et al. (2007)	43	F; Abuse + PTSD (19), Abuse Only (11), Controls (no abuse or PTSD) (13)	Early childhood sexual, physical, emotional and/or general abuse	- Cross-sectional - Experimental element: none	To evaluate cortisol, DHEA and estradiol over 24 h	ETI, SCID and CAPS structured interviews	Plasma cortisol levels across 24 h and divided into time blocks (12pm – 8pm, 4am – 2pm, 8pm – 4am and 7pm–10pm)	**PTSD vs. Trauma Controls and Healthy Controls** 12pm - 8pm: $p = 0.044$* *No longer significant when adjusted for body weight

Note indicated by "*"; F: Females; M: Males; TSST: Trier Social Stress Test; PTSD: post-traumatic stress disorder; MVA: Motor vehicle accident; HPA axis: hypothalamic-pituitary-adrenal axis; DEX: dexamethasone; IPV: interpersonal violence; TC: traumatized control; HC: healthy control; NTC: non-traumatized controls; CAR: cortisol awakening response; DHEA: dehydroepiandrosterone; sIgA: salivary immunoglobulin A; TNF: tumor necrosis factor; IL: interleukin; LD-DST: low-dose dexamethasone suppression test; CAPS: clinician-administered PTSD scale; PCL-S: Posttraumatic Symptom Checklist – short version; CAPS-DX: clinician-administered PTSD scale: current and lifetime diagnosis version; SCID: structured clinical interview for DSM-IV; PDS: posttraumatic stress diagnostic scale; IES-R: Impact of Event Scale- Revised; ETI: early trauma inventory.

"*cortisol peaks*" representing elevations in cortisol levels that were three times greater than the coefficient of variation (Bremner et al., 2007, DE Kloet et al., 2007). The remaining study did not include a definition of abnormal cortisol concentrations (Gill et al., 2008). Each selected study tested for statistical significance ($p < 0.05$) when comparing between-group cortisol levels.

4. Discussion

Amongst the reviewed studies, PTSD-associated dysregulated HPA axis functionality was only partially demonstrated. This was evident since two studies indicated an association between PTSD and diurnal cortisol, three studies did not demonstrate any associations, and the five remaining studies observed some, although mostly negative associations. Given the mixed findings, a definitive conclusion on whether PTSD is specifically associated with dysregulated HPA axis function as portrayed by altered diurnal cortisol cannot be determined. However, the studies that did not demonstrate findings for between-group differences, or those that presented circumstantial associations (e.g. at a specific time of day or following experimental methods such as the Trier Social Stress Test) in cortisol still recognize the disruptions to HPA axis functionality that seem to characterize PTSD or suggest alternative contributors that may be responsible for the proposed HPA axis dysregulation (Bremner et al., 2007, DE Kloet et al., 2007, Eckart et al., 2009, Gill et al., 2008, Labonte et al., 2014, Metzger et al., 2008, Pierce and Pritchard, 2016, Van Liempt et al., 2013).

4.1. Heterogeneity of included studies

Hypothalamic-pituitary-adrenal axis dysregulation was only associated with PTSD in two studies (Cordero et al., 2017; Wahbeh and Oken, 2013). The remaining studies that found partial associations only indicated altered diurnal cortisol concentrations in the PTSD-affected populations at specific timepoints or under experimental manipulation. Thus, the limitations and heterogeneity between studies must be addressed. Firstly, there was a lack of uniformity in the method of cortisol collection (see Table 2). Some studies chose to analyze plasma cortisol as opposed to salivary cortisol (Bremner et al., 2007, DE Kloet et al., 2007; Van Liempt et al., 2013). In addition, several different psychological assessments for PTSD diagnosis were used with varying methodology (e.g. structured interview with a psychologist vs. self-report). As a result of inconsistent measuring techniques, the between-study findings are difficult to synthesize which may have contributed to the overall mixed findings. The time of day during which cortisol samples were collected also varied immensely (see Table 2). Given that cortisol levels are highly influenced by time, studies with differing cortisol collection protocols cannot be compared as they exhibit distinctive "*snapshots*" of HPA axis functionality (Ryan et al., 2016; Schumacher et al., 2018). In addition, only four studies provided reference values for cortisol levels to support their mention of the coefficient of variation (Bremner et al., 2007; Cordero et al., 2017, DE Kloet et al., 2007; Van Liempt et al., 2013). Others only included the coefficient of variation for cortisol (Eckart et al., 2009; Labonte et al., 2014; Metzger et al., 2008; Pierce and Pritchard, 2016; Wahbeh and Oken, 2013). The remaining study did not incorporate either (Gill et al., 2008). Considering the methodological differences between studies, direct comparison and synthesis of results is a challenge due to the disparities in the reliability and sensitivity of differing experimental collection and assessment methods as well as external influencing factors (Luo et al., 2012).

Inconsistencies were also apparent between studies and their control for additional confounding factors suggested to influence diurnal cortisol production and secretion. These confounders included age, gender, ethnicity/race, marital status, education, weight, BMI, menopausal status (if applicable), Major Depressive Disorder (MDD), psychiatric co-morbidities other than Major Depressive Disorder (MDD), physical co-morbidities, perceived stress, medication, smoking status, tobacco use, alcohol/substance abuse or dependence, early life trauma, type of trauma, trauma history, years exposed to traumatic conditions, time since trauma, sleep duration, and time of awakening. Therefore, possible influence of confounding factors on study results and, thus, the findings from the current review should be considered (Morris et al., 2012). Although the studies were unable to control for all confounders (either statistically via results analysis or through inclusion and exclusion criteria), the current review recognizes the difficulty in achieving such a task. However, the comparison of results between studies remains questionable since, without complete control over confounding factors, it is impossible to determine the exact nature of HPA axis functionality in PTSD sufferers.

4.2. Cortisol levels as they relate to trauma exposure versus PTSD development

Some findings of hypocortisolism suggest that PTSD development is associated with lower levels of cortisol secretion. Although, several investigations found no statistically significant differences in diurnal cortisol output between the PTSD group and the trauma-exposed control group, thereby attributing decreased cortisol concentrations to trauma exposure rather than PTSD *per se* (DE Kloet et al., 2007, Metzger et al., 2008; Pierce and Pritchard, 2016, Van Liempt et al., 2013). This would suggest that similar exposure to trauma across study participants would dictate analogous findings between groups regardless of PTSD status.

Well-controlled research on highly traumatized refugees conducted by Eckart et al. (2009) supported the notion that altered cortisol is due to trauma exposure, and not PTSD, by reporting results that did not observe significant intergroup differences in cortisol secretion ($p = 0.43$). However, it is difficult to extract a conclusion based on these results due to the strenuous and stressful living conditions that all participants were experiencing at the time of the study. It is possible that the constant disadvantaged living conditions may illustrate a "*building block effect*" such that, under present stress, those with PTSD displayed elevated diurnal cortisol output to match that of the healthy counterparts without PTSD (Steudte et al., 2011). Therefore, while it is possible that trauma exposure alters HPA axis functionality it remains difficult to confirm in the absence of a non-trauma-exposed control group (Metzger et al., 2008).

In addition to trauma exposure, some studies have also proposed that the number of traumatic events may affect cortisol concentrations in study participants (Eckart et al., 2009; Johnson et al., 2008; Pierce and Pritchard, 2016). Contrary to earlier concepts of trauma exposure being a rare event, it is now believed that the majority of the population will experience significant trauma (whether it be through actively experiencing the event or via observation of others enduring trauma) at least once in his or her lifetime (Reul and Nutt, 2008). Previous traumatic experiences may increase the chance of further traumatic incidences and even persuade the likelihood of enlisting in the military wherein further traumatic events are likely to occur (Pierce and Pritchard, 2016). However, this "building block" effect only seems to be correlated with PTSD symptom severity rather than the association between cortisol concentrations and the extent of trauma load (Eckart et al., 2009).

4.3. Cortisol levels as they relate to PTSD severity

Another potential explanation for altered cortisol levels in individuals with PTSD may not be the disorder itself but rather the severity of its associated symptoms. These findings were supported by Gill et al. (2008) by demonstrating that dysregulated HPA axis functioning via lower morning cortisol levels was specifically correlated with PTSD hyperarousal symptoms. While the proposal that relates lower levels of morning cortisol secretion with PTSD symptom severity seems plausible, in order to be applicable to understanding HPA axis functionality

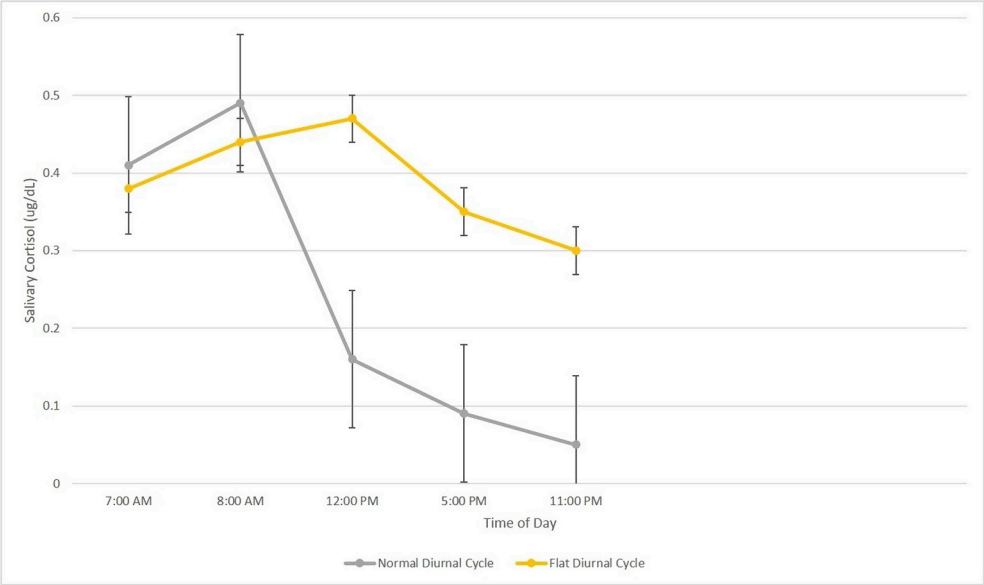

Fig. 2. Normal vs. Flat Diurnal Cycle of Salivary Cortisol
Representative illustration of an example of *normal*, "healthy" diurnal salivary cortisol output as compared with that of "*flat*" diurnal salivary cortisol output characterized by a reduced CAR, gradual increase throughout the day and higher levels overnight, as seen in those suffering from PTSD.

in PTSD, it must be taken into account the entirety of diurnal cortisol output in the PTSD population as compared to those without the disorder. In a "*normal*" diurnal cycle of salivary cortisol there is a peak in concentration approximately 30–45 min after awakening, which slowly tapers off after the first hour (Schumacher et al., 2018). Cortisol levels then seem to rapidly drop as the day progresses until the next morning (Lauc et al., 2004). By contrast, PTSD sufferers appear to exhibit "*flat*" diurnal cortisol profiles, which show a reduced cortisol awakening response (CAR) followed by a slight drop within the first 30 min post-awakening and then a gradual increase in concentration as the day goes on and are characterized by a lesser drop in levels overnight (Lauc et al., 2004) (see Fig. 2). One explanation for this flattened diurnal cortisol profile demonstrated in more severe PTSD cases is the individual's interpretation of how controllable the stress they are undergoing is (Lauc et al., 2004; Miller et al., 2007). More specifically, when one feels they are capable of coping with their stressor, they seem to display a higher CAR perhaps in preparation to actively deal with the situation, as opposed to someone who feels that their stressor is too severe to control (as demonstrated in people with PTSD) and consequently withdraws from the situation as illustrated by a decreased CAR and overall "*flat*" diurnal cortisol profile (Miller et al., 2007).

Whilst current research supports the finding that individuals with PTSD exhibit some form of dysregulation within the HPA axis leading to its chronicity and associated co-morbidities, there is still controversy over how one develops this dysregulation. The disorder may be the result of an increased vulnerable predisposition due to genetic and environmental risk factors occurring prior to a traumatic event which together may alter HPA axis functionality (Het and Wolf, 2007). However, others suggest that alterations in physiological mechanisms and hormones are the result of acquiring the disorder itself (Daskalakis et al., 2013).

4.4. Limitations and strengths

The limitations and strengths of this review should be considered. Firstly, there was a paucity of studies that qualified for selection within this review and, despite meeting the inclusion criteria, all studies were determined to have a high risk of bias (see Table 1). Specifically, a "*high-risk*" assessment may have influenced the resulting associations (or lack thereof) between PTSD and diurnal cortisol. Studies also had a cross-sectional design and, as such, prohibited causality. Although the authors of this review conducted a thorough search of the literature with specified inclusion criteria, there is a possibility that some studies were missed. The included studies also demonstrated low comparability due to a lack of standardization between study design, methodology and confounding factors which could have affected results. It should also be noted that the authors would have liked to include some additional studies for full review, however, those study results were not presented as mean ± standard deviation and/or number values demonstrating statistical significance were not provided. Upon attempt to contact the researchers for their results there was no response so, unfortunately, some studies had to be excluded.

With respect to other similar reviews and meta-analyses, the current review demonstrated findings in line with Klaassens et al. (2012) and Schumacher et al. (2018). Commonalities between these studies and the current review include mixed findings with a mostly negative association for PTSD and cortisol. Furthermore, when significance was demonstrated, it was likely in relation to a subgroup, such as a specific timepoint, before statistical adjustments to confounding factors were made, or in response to an experimental inclusion (Schumacher et al., 2018). The findings from this review mostly oppose alternative suggestions for an association between PTSD and cortisol, particularly hypocortisolism (Morris et al., 2012; Pan et al., 2018). However, the current review offers a unique perspective on the inconsistencies between PTSD and cortisol. Specifically, only studies that investigated diurnal cortisol output were included as were trauma of all types and timepoints whereas Klaassens et al. (2011) and Schumacher et al. (2018) included studies prior to 2007, various cortisol measurements (i.e. those not measuring diurnal rhythm) and Klaassens et al. (2011) excluded childhood trauma. The exclusion of studies that did not measure diurnal cortisol output provides a more comparable view of HPA axis functionality in PTSD sufferers as opposed to one aspect of its functionality (Ryan et al., 2016; Schumacher et al., 2018). Given the complexity of the interactions between the physiological systems and mechanisms and their associated hormones as well as the vast unknowns in psychoneuroendocrinology research itself, the selected studies have established a foundation for HPA axis functionality in PTSD sufferers as portrayed by their diurnal cortisol profiles (Josephs et al., 2017).

4.5. Future directions

The findings of the included studies propose that the HPA axis is not functioning properly in the PTSD population but whether this is associated with diurnal cortisol secretion output is not consistently observed. The observed results are mixed and influenced by multiple

confounders, with an emphasis placed on trauma exposure (DE Kloet et al., 2007, Metzger et al., 2008; Pierce and Pritchard, 2016, Van Liempt et al., 2013). Based on this review, standardization of study design, methodology and protocol for collecting diurnal cortisol should be incorporated. Specifically, future investigations should measure the diurnal rhythm of cortisol for at least two days since this methodology would provide a more comprehensive characterization of HPA axis functionality and diurnal cortisol as it relates to PTSD (Ryan et al., 2016). Furthermore, additional research is needed investigating the potential association between trauma-exposure (as opposed to PTSD status) and dysregulated HPA axis functionality given the findings from the current and similar reviews (Klaassens et al., 2012; Schumacher et al., 2018).

5. Conclusion

Post-traumatic stress disorder is a severely debilitating disorder affecting a multitude of persons from average civilians to first responders and military personnel. Its effects, if left untreated, lead to a number of adverse health outcomes. However, the current systematic review demonstrates that there is only partial, mostly negative, associations between PTSD and HPA axis dysregulation in the context of diurnal cortisol output. Furthermore, the lack of findings that indicated a difference in diurnal cortisol output between PTSD trauma-exposed and non-PTSD trauma-exposed participants may suggest an association between trauma exposure and HPA axis functionality instead. The mixed findings demonstrated by this review have revealed that a complete understanding of the relationship between PTSD and HPA axis functionality remains unestablished. Future investigations should firstly standardize experimental design and methodology with respect to diurnal cortisol measurements and aim to reduce confounding influences on diurnal cortisol output.

Declarations of interest

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

KS and AM led the design of the review. KS conducted the literature searches, imported records, removed duplicates and did an initial screening of abstracts. AM reviewed the abstracts for relevance. KS and AM reviewed the full-texts against inclusion and exclusion criteria and performed the PEDro Scale risk of bias assessment. KS performed data extraction of all articles which was checked by AM and SS. KS led analysis and interpretation of data with the assistance of AM. SS, NN and ND reviewed the interpretation of results until all authors reached consensus. KS led the writing of the review in collaboration with AM. All authors (KS, AM, SS, NN and ND) revised and edited the manuscript. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2019.100180.

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