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High cortisol awakening response in the aftermath of workplace violence exposure moderates the association between acute stress disorder symptoms and PTSD symptoms

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ABSTRACT

Although a majority of people will be exposed to a traumatic event over the course of their lifespan, only a minority will develop post-traumatic stress disorder. Better understanding the factors contributing to the development of this psychopathology is of high importance and could significantly reduce the societal and human costs associated with PTSD. Acute stress disorder symptoms, which refers to clinical manifestations experienced in the aftermath of a traumatic event, have been shown to be associated with subsequent PTSD symptoms. Yet, many people who develop PTSD do not meet criteria for acute stress disorder in the first place, highlighting the need to refine the predictors of PTSD. The secretion of the stress hormone cortisol is dysregulated in PTSD patients. Whether combining clinical and biological measures in the aftermath of trauma could help to better explain subsequent PTSD symptoms remains to be tested. The current prospective study recruited 51 adults who were exposed to a traumatic event in their work setting, i.e. a psychiatric hospital. Acute stress disorder symptoms and cortisol awakening responses were assessed one to five weeks following trauma exposure (Time 1). PTSD symptoms were measured two months following trauma exposure. Results revealed a significant interaction between acute stress disorder symptoms and cortisol awakening response in predicting later PTSD symptoms. The results suggest that higher cortisol awakening response is a protective factor in that it abolishes the relationship between acute stress disorder symptoms and subsequent PTSD symptoms. These results point to the importance of considering multi-level information in the aftermath of trauma, such as clinical and biological measures, in order to better identify individuals who are at higher risk of developing PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating condition with a lifetime prevalence of 9.2% (Breslau et al., 1991; Van Ameringen et al., 2008). Workplace violence in the healthcare sector is common and a systematic review has identified that PTSD is one of the most frequent psychological outcomes following workplace violence exposure (Lanctot and Guay, 2014). Importantly, only a minority of trauma-exposed individuals will develop PTSD. This suggests a great deal of variability in the aftermath of trauma exposure and points to the importance of better characterizing individual differences. Over the last decades, researchers have attempted to identify vulnerability and protective factors that could modulate one's risk of developing PTSD following trauma exposure (Ozer et al., 2008).

Introduced in the DSM-IV, acute stress disorder (ASD) characterizes acute stress reactions in the month following trauma exposure. A systematic review has shown that a majority of people with ASD will develop PTSD, but most people who develop PTSD do not meet ASD criteria in the first place (Bryant, 2011). Although acute stress disorder symptoms remain informative and should be considered further, these results highlight the need to examine other factors in order to refine our ability to identify trauma-exposed individuals who are at higher risk of

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presenting high levels of PTSD symptoms.

From a biological standpoint, the hypothalamic-pituitary-adrenal (HPA) axis, for which cortisol is the main hormonal end-product, has been the focus of many studies in PTSD. Cortisol levels exhibit a sharp increase during the first hour following awakening, which has been named the cortisol awakening response (CAR) (Clow et al., 2004). The CAR is considered a valid marker to assess HPA function and dysfunction (Chida and Steptoe, 2009). In general, most studies have reported lower morning cortisol levels and lower CAR in PTSD samples relative to normal controls with or without a history of trauma exposure (Rohleder et al., 2004; Wessa et al., 2006). However, it is important to note that other groups have found either no differences or opposite findings (Johnson et al., 2008; Laudenslager et al., 2009). In 2007, de Kloet and colleagues found that the CAR was lower in trauma-exposed individuals relative to non-trauma exposed individuals (de Kloet et al., 2007). Importantly, no differences were found between trauma-exposed individuals with and without PTSD (de Kloet et al., 2007). It has also recently been found that higher pre-treatment CAR was predictive of PTSD symptom reduction following psychotherapy in combat-exposed men with PTSD (Rapcencu et al., 2017). Taken together, these results suggest that the CAR is an endocrine marker that is dysregulated in trauma-exposed individuals. Yet, the directionality (lower versus higher CAR) remains a question of debate.

One important factor that should be highlighted with regards to mixed findings pertaining to dysregulated CAR in PTSD individuals is *timing*. In fact, most studies assessing the CAR have been performed in individuals who were already suffering from PTSD, making it difficult to interpret whether the dysregulated CAR pattern was present before trauma exposure or whether it reflects the consequence of chronic stress exposure. Given the clear feasibility issues, few studies have assessed CAR before or right after trauma exposure, making it difficult to document HPA axis profiles prior to the development of the psychopathology. Notwithstanding, a study performed in police officers found that higher CAR during academy training was associated with greater acute stress disorder symptoms and greater peritraumatic dissociation during later police service (Inslicht et al., 2011), but did not have predictive value of subsequent PTSD symptoms. Other studies performed in firefighters and in military personal found no association of CAR prior to trauma exposure and later PTSD symptoms (Heinrichs et al., 2005; van Zuiden et al., 2011). It is important to keep in mind that these studies have assessed CAR months to years prior to trauma exposure. This lag makes it impossible to determine whether the CAR profiles of the individuals were stable over time and actually reflect endocrine profiles at the time of trauma.

Better understanding the risk factors that increase one's vulnerability to develop PTSD following trauma exposure is necessary in order to better identify individuals who require help and treatment early on. Yet, the joint influence of measures, both clinical and biological, taken in the aftermath of trauma on later PTSD symptomatology has not been studied. In this study, we tested how acute stress disorder symptoms and CAR, both measured within the first month following the traumatic experience, influenced the severity of PTSD symptoms measured 1 month after the initial assessment. Given that lower CAR is reported in PTSD populations and that high acute stress symptoms is a risk factor for later PTSD, we hypothesized that individuals exhibiting high acute stress disorder symptoms and low CAR profiles in the aftermath of trauma would have the worse outcome with regards to their subsequent PTSD symptoms.

2. Methods

2.1. Participants

Data used for the current analysis are part of a larger prospective study on workplace violence and its long-term psychological consequences. Two sites were used for the larger study, but the current biomarker sub-study was only conducted on one site, which included 87 participants. All participants were employees in a psychiatric hospital. A total of 51 participants aged between 18 and 65 years old are included in the current study as they completed both Time 1 and Time 2 assessments. They also completed the cortisol sampling procedure adequately.

Potential participants who recently reported being a victim or witness of a violent act at work (physical and/or verbal) were first approached by union representatives and/or human resources staff, who briefly introduced the study. Individuals interested in taking part in the study filled out an informed consent form and Time 1 assessment was scheduled as soon as possible after the event of workplace violence (and this information was added as a potential confounding variable in our analyses). Time 2 was scheduled two months after the traumatic experience. The research project was reviewed and approved by the ethic boards of the Research Institute (i.e., Institut Universitaire en Santé Mentale de Montréal).

2.2. Questionnaires

2.2.1. Acute stress disorder scale (ASDS) (Bryant et al., 2000)

This self-report questionnaire has 19 items, each of which is answered using a scale from 1 (not at all) to 5 (very much), which indicates the frequency at which the participant has experienced a given symptom since the event. Scores for all items were added to generate a total score. Higher scores indicate greater acute stress disorder symptoms.

2.2.2. PTSD checklist (PCL)

The PTSD Checklist-specific for DSM-IV (Weathers et al., 1994) was used to quantify PTSD symptom severity. This self-report questionnaire consists of 17 items which taps onto the DSM criteria for PTSD. For each item, the participant has to indicate the degree to which they have been bothered by specific symptoms in the last month, using a scale from 1 (not at all) to 5 (extremely). Scores for all items were added to generate a total score. Higher scores indicate greater PTSD symptom severity.

2.2.3. Life Event Checklist

Given that previous trauma exposure is a predisposing factor that could modulate one's risk to develop PTSD, all participants were asked to fill the *Life Event Checklist (LEC)*. This questionnaire probes the participant regarding 17 traumatic situations. For each situation, the participants have to report 1) whether it has happened to them, 2) whether they witnessed the situation or whether it happened to someone else, 3) whether they learned about the event that happened to someone close to them, 4) whether they are not sure or 5) whether it does not apply (Gray et al., 2004). A score for the first three categories is calculated for each participant to account for previous trauma exposure in our analyses.

2.3. Potential confounding variables

Given that CAR can be influenced by multiple factors (Stalder et al., 2016), we have gathered information about the following variables in order to account for their contribution in our analyses: sex, age, smoking, and medication use.

2.4. Procedure

At Time 1, which occurred between 5 and 45 days (mean = 26.2, SEM = 1.5) following the potentially traumatic event, participants were asked to fill out the ASDS (predictor) and the LEC (covariate) questionnaires. Participants were provided with a sampling kit to collect basal cortisol (predictor) at home. They were asked to provide salivary samples upon awakening and 30 min following awakening, for three days. Participants were invited to write in a logbook the time at

which they woke up and the time at which they took their two morning samples. Participants were asked to freeze their samples until their next visit to the laboratory. After completion of their saliva samples, participants sent them back to the laboratory via express mail at which point they were immediately frozen in a −20 °C freezer. At Time 2, which occurred two months following the traumatic experience, participants were asked to fill out the PCL questionnaire to assess PTSD symptom severity (outcome).

2.5. Cortisol assays

Analyses were performed at the BioAssay Lab of the Centre for Studies on Human Stress (www.humanstress.ca/saliva-lab). Frozen samples were brought to room temperature and were then centrifuged at 1500xg (3000 rpm) for 15 min. Analyses were performed using a high sensitivity enzyme immune assay kit from Salimetrics State College, PA, catalogue number 1–3102 (sensitivity: 0.012–3 µg/dl). Samples were assayed in duplicates and averaged.

2.6. Treatment of data and statistical analyses

For each of the sampling days, the cortisol awakening response (CAR) was calculated using the following formula: (cortisol value 30 min after awakening – cortisol value at awakening)/cortisol value at awakening * 100. Given that the CAR differs between week days and weekend days (Thorn et al., 2006), only CAR values for working days were included in the average for each participant. Note that seven participants were on sick leave following the event. For these participants, all their sampling days were included.

In order to assess the main effect of ASDS and the CAR as well as the interaction of these factors on PTSD symptoms, we performed a multiple linear regression using SPSS version 25.0. We included previous trauma exposure (coded as the following three categories: being a victim, a witness, or having learned about the trauma of someone else) and the following predictors: ASDS, CAR, as well as the interaction between ASDS and CAR. To decompose a significant interaction, the effect of the predictor was plotted as a function of the other predictor and followed by simple slope tests (Aiken et al., 1991). Analyses were conducted using standardized predictors, which were also used to compute interaction terms.

3. Results

3.1. Sub-sample analyses

As mentioned in the methods section, 87 individuals were recruited for this sub-study assessing stress biomarkers. The current study includes 51 individuals. The 36 participants that are not included in the current analysis either did not complete Time 2 assessment, had their first assessment more than 45 days after the traumatic event, did not complete cortisol samples, or did not follow the sampling instructions. An exploratory analysis revealed no group differences with regards to the distribution of sex, age category, and type of trauma exposure, all ps > 0.05. Importantly, both groups had comparable acute stress disorder symptoms, $t_{85} = 0.76$, $p > 0.05$. We are therefore confident that the findings reported in the current manuscript are representative of the full study sample.

3.2. Descriptive preliminary analyses

3.2.1. Type of traumatic event

Most of the participants (70.6%) reported being victim of physical violence (e.g., being hit, bitten), 13.7% reported being victim of psychological violence (e.g., harassment, threat), and 15.7% reported another type of event (e.g., witnessing aggression).

Table 1
Main effects of previous trauma exposure, acute stress disorder symptoms (ASDS), and cortisol awakening response (CAR) on PTSD Checklist (PCL) symptoms. The table depicts both the unadjusted and the adjusted model (which included the following covariates: age, sex, smoking, medication, and number of days between the traumatic event and Time 1).

	Unadjusted			Adjusted		
	B	SE	p	B	SE	p
Intercept	22.55	1.67	< 0.001	29.00	6.04	< 0.001
Age	–	–	–	−1.59	0.75	0.042
Sex	–	–	–	−1.08	1.89	0.572
Smoking	–	–	–	1.35	2.69	0.618
Medication	–	–	–	0.85	2.04	0.681
Days between trauma and Time 1	–	–	–	0.01	0.08	0.876
Previous trauma exposure (victim)*	0.82	0.37	0.031	0.99	0.38	0.012
Previous trauma exposure (witness)	0.08	0.46	0.861	−0.17	0.50	0.731
Previous trauma exposure (having learned)	−0.32	0.43	0.457	−0.64	0.46	0.172
Acute Stress Disorder Symptoms (ASDS)*	6.43	1.05	< 0.001	6.47	1.10	< 0.001
Cortisol Awakening Response (CAR)	−0.27	0.82	0.747	−0.05	0.82	0.950
ASDS X CAR*	−3.60	1.42	0.015	−3.31	1.48	0.031
Adjusted R^2	69.7%			70.7%		

3.2.2. Potential confounding variables

Our sample was mostly composed of women (57% of the sample) and age was distributed in the following manner: 18–25 years old: 11.8%, 26–35 years old: 25.5%, 36–45 years old: 11.8%, 46–55 years old: 29.4%, 56–65 years old: 21.6%). 11.8% of the participants reported smoking more than 10 cigarettes per day. 21.6% of the participants reported taking antidepressant medication, 3.9% reported using anxiolytics, and 31% of the women used hormonal contraceptives (either hormonal intrauterine device or oral contraceptive pill). Two participants reported recreational use of marijuana. Because removing these two participants did not affect the results, we have therefore decided to keep them in our analyses.

3.3. Main analysis

The multiple linear regression revealed a significant effect of previous trauma exposure (as a victim) [$F(1,44) = 4.946$, $p = 0.031$] and a significant main effect of ASDS [$F(1,44) = 37.762$, $p < 0.001$] on PTSD (Table 1). The analysis also revealed a significant interaction between ASDS and CAR [$F(1,44) = 6.471$, $p = 0.015$] (Table 1). Simple slope tests showed that the effect of ASDS was significant when CAR levels were low (-1SD, $B = 10.296$, $p < 0.001$), but not when they were high (+1SD, $B = 2.563$, $p = 0.313$) (Fig. 1). This result suggests that cortisol awakening response moderates the association between acute stress disorder symptoms and subsequent PTSD symptoms.

This model was ran again including the following potential confounding variables: age, sex, number of days between the traumatic event and T1, use of medications (antidepressants, anxiolytics, and hormonal contraceptives; coded as 0 or 1), smoking (coded as 1 when participants smoked more than 10 cigarette/day). All results remained statistically significant (Table 1 depicts the results for both the unadjusted and the adjusted models).

4. Discussion

Our goal was to examine the relationship between clinical and biological measures, assessed in the aftermath of trauma, in predicting subsequent PTSD symptomatology. Our results revealed that higher cortisol awakening response (CAR) moderated the association between

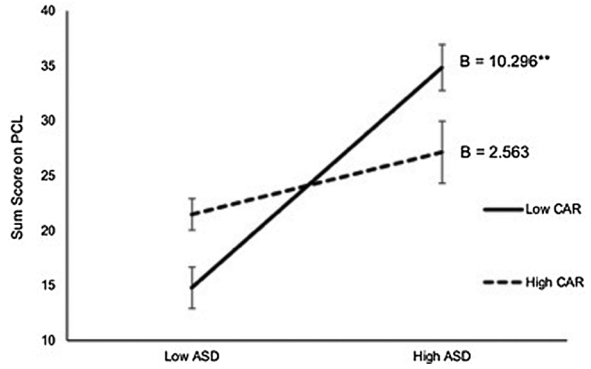

Fig. 1. Post-traumatic checklist (PCL) unadjusted predicted means based on regression models including previous trauma exposure, acute stress symptoms (ASD) symptoms, and cortisol awakening response (CAR). **p < 0.001.

acute stress disorder symptoms and subsequent PTSD symptomatology. Moreover, the model tested in the current manuscript explained 70% of the variance in PTSD symptom severity in our sample.

Higher severity of acute stress disorder symptoms in the aftermath of trauma was predictive of subsequent PTSD symptoms. This result supports previous findings from the literature that have proposed an important role of acute symptomatology to identify individuals at higher risk of developing PTSD (Bryant, 2017, 2011). The current study brings some nuances to this result, by showing that the positive association between acute stress disorder symptoms and PTSD symptoms is only significant if individuals display low CAR. In fact, for individuals exhibiting high CAR in the aftermath of the traumatic event, the relationship between acute symptoms and subsequent PTSD symptoms was not significant.

Given the quasi-experimental design of the current study, it is not possible to conclude whether the CAR pattern is a predisposing factor that was present before the traumatic experience or whether the CAR pattern is in response to the traumatic event. Either way, it looks like maintaining and/or adopting higher CAR patterns following trauma exposure might attenuate the known relationship between ASDS and PTSD symptoms. It was previously shown that higher cortisol awakening responses measured months to year prior to trauma exposure was associated with greater acute stress disorder symptoms and greater peritraumatic dissociation (Inslicht et al., 2011). Our findings might seem to contradict those results. However, our study sampled cortisol in the aftermath of trauma whereas the other studies sampled CAR months to years prior to trauma exposure. It is therefore impossible to conclude whether individuals in that study had similar endocrine profiles when they were exposed to trauma. Moreover, these authors and others have reported that the CAR was not predictive of PTSD symptoms (Heinrichs et al., 2005; Inslicht et al., 2011; van Zuiden et al., 2011). Importantly, our analyses did not find a main effect of CAR on PTSD symptoms. In fact, higher CAR was protective against PTSD symptoms for those who exhibited high acute symptoms in the aftermath of trauma (interaction term).

4.1. Clinical considerations

These results could have important clinical implications. In fact, the current findings highlight the need to assess both psychological symptoms and biological profiles in individuals immediately after trauma exposure. Individuals who would display a high-risk profile, i.e., those exhibiting high acute stress disorder symptoms and low CAR, could be targeted for an intervention, which could be psychological but also potentially pharmacological. Whether the protective nature of higher CAR must be endogenously driven remains to be determined. Future studies could try to pharmacologically modulate CAR patterns in individuals presenting high acute stress disorders in order to test whether it acts by moderating the risk of later endorsing PTSD symptoms. Testing various interventions in the aftermath of trauma and assessing their impact based on individual differences could also be informative. Indeed, our results suggest that individuals exhibit a high degree of variability with regards to psychological and hormonal profiles in the aftermath of trauma. It is therefore possible to hypothesize that response to interventions could be modulated based on the individual's profile. This could eventually lead to personalized medical interventions that can more precisely remediate normal functioning.

It is important to highlight the fact that women are more vulnerable to develop PTSD than men (Breslau et al., 1991; Kessler et al., 1995). Moreover, previous studies have often tested cortisol patterns in specific trauma-exposed populations who were often more represented by one sex than the other, for example, police officers, firefighters, or military personal (Heinrichs et al., 2005; Inslicht et al., 2011; Rapcencu et al., 2017; van Zuiden et al., 2011). The current study included both men and women. Including sex as a covariate in our statistical model did not change the results, suggesting no significant sex differences for our dataset. Notwithstanding, a larger sample would have allowed for analyses that assess the moderating effects of sex on cortisol functioning and trauma symptomatology.

The findings that we have obtained are promising and suggest that higher CAR in the aftermath of trauma could dampen the relationship between ASD and subsequent PTSD symptoms. However, it is important to consider alternative explanations with regards to the current findings. In fact, the CAR's magnitude is likely influenced by various environmental and individual factors that could also promote or hinder one's resilience when confronted to trauma. Therefore, in this study, CAR was measured and moderated the relationship between ASD and PTSD symptoms. However, future studies should consider other peritraumatic factors, such as stress levels or sleep quality, to only name a few examples. This will likely provide valuable information about the potential modulators of CAR in the aftermath of trauma.

5. Limitations

Some limitations warrant consideration. First, this study was performed in a sample of workers from a psychiatric hospital, which therefore prevents the generalization of the findings to other populations. It is important to keep in mind that the nature of their work might be stressful and we do not have data on chronic stress levels prior to trauma exposure, which might have an influence on the results. Future studies should therefore take into consideration stress levels prior to the traumatic event. For example, sampling hair in order to quantify hair cortisol levels in the days following trauma exposure would allow obtaining an objective measure of cortisol secretion in the months preceding the traumatic event. It would in fact be interesting to assess the impact of the participants' stress levels prior to trauma to see how this could contribute to the vulnerability to develop PTSD.

Second, our participants did not undergo an extensive screening with regards to physical and psychological conditions that could potentially impact cortisol levels. Similarly, no data regarding body mass index were collected. Although we have controlled for medication use in our analyses and this did not affect the results, these variables should definitely be assessed more thoroughly in future studies. It is not possible at this point to conclude if the different patterns of CAR resulted from the traumatic event or were rather present before the traumatic event. Having the possibility to sample cortisol during the days preceding or following the event would be optimal. Finally, the breadth of PTSD symptomatology is rather limited. In fact, most participants did not meet the diagnostic criteria for PTSD at Time 2. Nonetheless, our results suggest a robust moderating effect of cortisol on the relationship between ASD and PTSD symptoms. It remains to be determined whether such results would show similar patterns of associations in more symptomatic populations.

6. Conclusions

Our results suggest that higher cortisol awakening response in the aftermath of trauma could act as a protective factor by attenuating the relationship between acute stress disorder symptoms and subsequent PTSD symptoms. These results highlight the importance of considering clinical and biological variables in the aftermath of trauma in order to refine our detection tools and to better identify individuals at greater risk of suffering from PTSD.

Declarations of interest

None.

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