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DOES CHILDHOOD ADVERSITY INFLUENCE CORTISOL RESPONSE TO A SOCIAL STRESSOR: EVALUATING PARTICIPANT SEX AS A MODERATOR

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ABSTRACT

The ways in which individuals respond to stressors can impact their health and well-being, both in positive and negative ways. Childhood adversity is thought to negatively influence the stress response in adults and affect cortisol levels such that total cortisol output and cortisol sensitivity (i.e., degree of increase/decrease) are both lower in response to certain stressors (Merkulov et al., 2017; Khoury et al., 2019). Importantly, biological sex is related to differences in cortisol responses to stressors and may explain differential long-term consequences of stress in males and females. This study aimed to evaluate the effect of childhood adversity on the cortisol response to a social stressor and determine whether or not the association differed in males and females. Data regarding childhood adversity and biological sex was collected through self-report questionaries. Cortisol was collected via salivary samples collected before and after the Trier Social Stress Test, a laboratory induced social stressor that requires participants to give a 5-minute speech about how well the individual would fit into a hypothetical position of employment, followed by a 5-minute mental arithmetic task. Saliva was collected once before the stressor, as soon as the stressor ended, and every 10 minutes for 40 minutes after that. A significant bivariate correlation was observed between childhood adversity and total cortisol output (r = - .266, p = .029). However, this association was attenuated when including participant age, sex, and body mass index in the model. Additionally, females demonstrated lower total cortisol output (r =-.449, p < .001) and lower cortisol sensitivity (i.e., the degree of increase/decrease in cortisol over time) (r = -.533, p < .001) in response to the stressor than males. Support was not identified for the hypothesis that childhood adversity and cortisol in response to a stressor would be more strongly associated in females as compared to males. Data

from the present study provide further support for sex differences in cortisol responses to stressors and highlight that further research is needed to develop a further understanding of the impact of childhood adversity on stress and health.

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Chapter 1

Introduction

The impact of stress on health

Stress has a significant impact on mental and physical health. In America, 55% of people report experiencing stress daily, making stress a relevant and problematic issue that many people face (Ray, 2019). The HPA (hypothalamic pituitary adrenal) axis plays an important role in stress by activating the "fight or flight" response (i.e. the sympathetic nervous system) and increasing levels of cortisol, the body's main stress hormone (Kudielka & Kirschbaum, 2005). Cortisol increases availability of blood glucose, decreases growth and digestion, and suppresses immune function. Cortisol also plays other roles, including reducing inflammation and controlling blood pressure and heart rate (Dickerson & Kemeny, 2004). While cortisol is important for the stress response to decrease heart rate and blood pressure, it can also have a negative effect on health if cortisol levels are dysregulated. If cortisol secretion is too low during the sympathetic response to a stressor, the parasympathetic nervous system is slower to activate, resulting in an elongated sympathetic response. This means that there are higher levels of cortisol for a longer period of time and the "fight or flight" response is harder to turn off. (Power et al., 2012). Some of the physiological consequences of prolonged or chronic stress can be atherosclerosis, heart attack, and strokes (McEwen, 2008). Chronic stress can lead to elevated baseline cortisol due to glucocorticoid resistance, meaning that there are high levels of cortisol being produced but receptors don't bind it, resulting in elevated circulating cortisol and prolonged HPA axis activation (Hannibal & Bishop, 2014; Rodriguez et al., 2016). There are

several causes for a dysregulated stress response in adults, but one of the most well-known is exposure to adversity in childhood.

Childhood adversity and health

Adverse events in childhood can have several different influences on well-being throughout the lifespan. In general, childhood adversity is defined as experiencing emotional, sexual, or physical abuse, neglect, bullying, discrimination, poverty, or various forms of family dysfunction (Bartlett & Sacks, 2019). These events can happen once or be repeated over time. Maltreatment in childhood can negatively affect someone's personality, physical health, and mental health (Patten et al., 2016; Oh et al., 2018). Further research has shown that adverse childhood events can lead to obesity, alcoholism, drug abuse, lower education status, liver and lung disease, heart disease, and poverty (Flaherty et al., 2006). Although these events are experienced in childhood, they can have negative effects throughout a lifetime. Statistically, 45% of US children have experienced at least one adverse childhood event, while further research shows that 1 in 10 children experience at least 3 adverse events during early life (Ray, 2019). Experiencing multiple events puts the child at a higher risk for developing the negative consequences associated with childhood adversity (Ray, 2019). Some other known consequences of childhood adversity are an increased risk for comorbidities, early mortality, and other physical and psychological issues (Thomson & Jaque, 2018). Research has determined that exposure to childhood adversity increases risk for developing a mood disorder such as PTSD, depression, and anxiety (McLaughlin et al., 2010). Notably, studies have shown that childhood adversity has an impact on the stress response and cortisol levels in adults, which could be one of the

mechanisms linking childhood adversity with poor mental and physical health outcomes (Bartlett & Sacks, 2019; Patten et al., 2016; Oh et al., 2018).

Although childhood adversity is a psychological stressor, it has been found to cause the opposite effect on cortisol in comparison to other psychological stressors. Meta-analytic findings support that childhood adversity is associated with blunted cortisol responses to psychologically stressful events in adulthood (Power et al., 2012). A blunted cortisol response to stress is associated with prolonged sympathetic arousal, which is in large part due to inadequate activation of the parasympathetic nervous system (Heim et al., 2000). Not surprisingly, prolonged sympathetic arousal is associated with increased risk of cardiovascular events and all-cause mortality (e.g., Power et al., 2012). Childhood adversity may result in lower cortisol output because of the type of stressor and how the individual copes with it (Heim et al., 2000). Repeated exposure to stressors and hyper activation of the HPA axis changes the cascade biologically and results in a hypo-active and a less responsive HPA system (Khoury et al., 2019). One study proposed an attenuation hypothesis, predicting that hypersecretion of cortisol from stressful events happens initially, which causes the HPA axis to adapt and downregulate cortisol in response to future stressors (Trickett et al., 2011). This could be explained by an increase of the negative feedback loop sensitivity, which would also downregulate glucocorticoid receptors (Trickett et al., 2011). When high levels of cortisol are sensed, the negative feedback mechanism tells the stress response to decrease (Khoury et al., 2019). If there are high levels of cortisol consistently, the glucocorticoid receptors become less sensitive and cause cortisol to bind to less receptors. Typically, individuals with glucocorticoid resistance produce higher levels of cortisol to compensate for the lack of sensitivity in glucocorticoid receptors (Merkulov et al., 2017; Khoury et al., 2019). This resistance to cortisol is seen frequently as a result of chronically

increased cortisol levels due to psychological disorders such as depression, PTSD, and bipolar disorder (Merkulov et al., 2017).

The limited availability of cortisol can be detrimental to health because the desired effect (i.e., reduced inflammation, increased blood glucose, lower heart rate and blood pressure) will be delayed or less likely to occur. If the cortisol response to stressors is blunted as early as childhood, it can result in delayed development, growth, behavioral issues, higher BMI, and poor immune functioning (Ouellet-Morin et al., 2011). Since cortisol helps the body defend against potentially harmful mechanisms of the stress response, such as inflammation, the parasympathetic nervous system being underactive because of a lack of cortisol can make an individual more vulnerable to sleep dysfunction, cardiovascular disease, and other stress related disorders (Ouellet-Morin et al., 2011; Heim et al., 2000). In the long term, an individual can develop autoimmune disorders, asthma, and chronic pain (Heim et al., 2000).

Sexual abuse in childhood

General childhood adversity is an established psychological stressor that can result in a dysregulated cortisol response (Heim et al., 2000); however, sexual abuse may be particularly problematic. Indeed, adults who reported experiencing sexual abuse as children had a greater suppression of cortisol than other forms of adversity (Davis & Petretic-Jackson, 2000). Children who experience sexual abuse are also more likely to develop psychological issues, interpersonal relationship difficulties, and mood disturbances (Davis & Petretic-Jackson, 2000). Since sexual abuse has been associated with worse outcomes compared to other childhood maltreatments, it is

important to analyze the relationships between cortisol levels and childhood adversity as a whole, and cortisol levels and sexual abuse specifically.

Biological sex, stress, and cortisol

Biological sex plays a significant role in many health aspects, including prevalence of disease, susceptibility, and severity of disease. Available research has indicated that males and females respond differently, both biologically and psychologically, to stressors (Verma et al., 2011), which may underlie sex differences in health more broadly. For example, females that experienced previous stress tended to show lower levels of cortisol in response to a stressor when compared to males (Verma et al., 2011). One explanation for this finding is that stressors may be interpreted differently in men and women and it may take more effort in men to confront the stressor (Liu et al., 2017). This may be a mechanism that explains why females are at a higher risk to suffer from autoimmune disorders, while males are more likely to report heart disease and infectious diseases (Kudielka & Kirschbaum, 2005). The hypocortisol response that females show after childhood adversity has been linked to autoimmune diseases such as lupus and asthma (Kudielka & Kirschbaum, 2005).

Animal studies have indicated that early life adversity affects the development of brains in males and females in different ways, leading to different adaptation styles to stressors as adults (Bath, 2020). Such studies suggest that neural development can be impacted by early life adversity in mice. For example, in both sexes, an adverse environment in early life was associated with adaptation of a fear learning style, where fear becomes a response to neutral stimuli, and maturation of the amygdala at an earlier age, meaning it has higher level connectivity and

functioning earlier in life (Bath, 2020). Yet, female mice raised in adversity exhibit depressive behaviors, attention learning impairments, faster maturation of the amygdala, delayed sexual maturation, and weakened contextual expression of fear, when compared to males (Bath, 2020, McLaughlin et al., 2014). These developmental differences indicate that sexes react differently to early life adversity. The differences developed in early life as a response to stress could lead to different physiological reactions to stressors as adults, along with negative health outcomes throughout the lifespan.

A similar study on humans analyzed brain differences of males and females after early life adversity found that females were twice as likely to develop psychological issues related to the previous adversity compared to males (Helpman et al., 2017). This association with psychological issues after early adversity was due to an enlarged, overactive amygdala and altered endocrine system functioning (Helpman et al., 2017). The amygdala is the region of the brain that processes fear, and it is also involved in stress (Schumann et al., 2011). When the amygdala is overactive, risk-taking behaviors increase, along with anxiety, inappropriate social skills, and stress dysregulation (Schumann et al., 2011). Females developing an overactive amygdala after adversity in this study indicates that here are structural differences that adversity can cause in biological sexes. While potential sex differences in the HPA axis and early life adversity are largely unknown, Helpman et al. reported that there is a sex-specific association in HPA functioning and the limbic system. Specifically, there was a negative association between cortisol and brain connectivity in females, while a positive association was identified in males (Helpman et al., 2017). Additionally, women tend to have lower cortisol output in response to psychological stressors, specifically (Kudielka et al., 2009). However, biological sex has not been evaluated as a moderator of the association between childhood adversity and cortisol in response to a stressor in previous work.

Measurement of cortisol

Cortisol can be measured in several different ways during a research study. Cortisol can be measured in urine, blood, hair, or saliva, and the time point it is measured has significance (El-Farhan et al., 2017). Often, baseline cortisol is measured in research at one single point in time. This measurement can provide an indicator of disease states, adrenal function, and some levels of stress (Fraser et al., 1999). Yet, cortisol follows a diurnal pattern, meaning that levels reach a maximum shortly after waking up in the morning and slowly decline throughout the day (Adam et al., 2017). The increase in cortisol levels immediately after waking up is called the cortisol awakening response. As a result, time of day is an important consideration within research studies measuring cortisol, particularly when one time point is utilized (Adam et al., 2017). Multiple measurements of cortisol throughout the day can help researchers account for the cortisol awakening response, the diurnal nature of cortisol, and natural fluctuations of cortisol levels (Admon et al., 2017). Measuring cortisol throughout the day can help determine some disease states and an overall picture of health but aren't necessarily accurate for measuring the acute stress response. Similarly, hair is a common way to measure cortisol and this technique is beneficial for cortisol measurement over time. Cortisol levels can be detected in hair for up to 3 months (Wright et al., 2015). When analyzing chronic stress, hair is a useful technique, but acute stress should be measured with salivary or serum cortisol (Wright et al., 2015).

Although both salivary and serum measures of cortisol in response to acute stress can be utilized, cortisol is more prominent in saliva than in serum (Aardal-Eriksson et al., 1998). Salivary cortisol measurements measure free cortisol and is the preferred measurement for many studies (Levine et al., 2006). Saliva measurements have been shown to be more strongly associated with adrenocorticotrophic hormone (ACTH), which is a precursor to cortisol, than

serum (Aardal-Eriksson et al., 1998). Lastly, saliva works better with endocrine tests that are dynamic, such as when the HPA axis is purposefully stimulated by a stressor in a laboratory setting (Aardal-Eriksson et al., 1998).

Another consideration when measuring cortisol is the number of data collection points. Single measurement cortisol assessments are good for acute, immediate stress reactions, but they don't measure the prolonged stress response beyond the singular point in time (Lee et al., 2015). The accuracy of single measurements can also vary across participants depending on the consistency of the timing of the measurement. Collection points of cortisol at multiple times after a stressor allows researchers to track fluctuations in cortisol and generate data regarding the degree of increase and decrease before, during, and after a stressor (Admon et al., 2017). Typically, salivary cortisol rises from 5-20 minutes after a stressor, peaking around 20 minutes (Kudielka & Kirschbaum, 2005). An important statistical approach can be utilized for cortisol if it is measured at least three times that are spaced out every 10 or 15 minutes after the stressor (Guevara et al., 2019; Fekedulegn et al., 2007). This approach is frequently referred to as calculating the "area under the curve" (AUC) (Fekedulegn et al., 2007). Two types of AUC can be measured; AUC with respect to ground (i.e., AUC_g) measures the total cortisol output in response to a stressor during the measurement timeframe. AUC with respect to increase/decrease (i.e., AUC_i) measures the degree of increase/decrease in cortisol due to the stressor as baseline levels of cortisol are removed from the equation in order to reflect sensitivity to the stressor over time. These two measurements have been used in many research studies and found to be useful when collecting samples at multiple time points and in describing how stress and health are related in relation to stressors (Fekedulegn et al., 2007).

Hypotheses

This study examined associations between sexual abuse, total childhood adversity, biological sex, and cortisol responses to a stressor. Given the information discussed previously, it was hypothesized that individuals with a history of childhood adversity would have less total cortisol output (lower AUC_g score) in response to a stressor and less cortisol sensitivity (lower AUC_i score). It was also hypothesized that those who reported sexual abuse in childhood would have lower AUC_g and lower AUC_i values in comparison to those who did not report experiencing childhood sexual abuse. It was hypothesized that there would be a stronger association between each independent variable (i.e. total adversity and sexual abuse) and dependent variable (i.e. AUC_g and AUC_i) among females in comparison to males. Specifically, it was hypothesized that total childhood adversity and sexual abuse would be more strongly, and negatively, associated with AUCg and AUCi among females in comparison to males.

Chapter 2

Methods

This study consisted of 71 participants with ages ranging from 45-70 (M=60.62, SD=6.19). Participants were recruited from several sources, including flyers in public spaces, an ad in a local newspaper, and a website containing information about local active research studies. Volunteers were excluded from the study if they were pregnant or nursing, regularly taking non-steroidal anti-inflammatory drugs, or working night shifts. On the day of the study, participants were asked not to participate in strenuous exercise, consume caffeine, or eat foods high in fat. All participants were scheduled at 8:00am in order to reduce the effect of diurnal variation.

Participants were asked 10 questions about adverse childhood events as well, answering yes or no to each question. The Adverse Childhood Experiences (ACEs) questionnaire was the questionnaire used in the study and was originally created by Felitti et al. (1998). Some of the questions included, “Did a parent or other adult in the household often or very often…swear at you, insult you, put you down, or humiliate you? Or act in a way that made you afraid that you might be physically hurt?” “Did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?” and, “Was a household member depressed or mentally ill, or did a household member attempt suicide?” (Felitti et al. 1998). These questions were aimed to establish if the participant had experienced adverse childhood experiences, and if so, how many. For each of these questions the responses were coded 1 = yes and 0 = no. The total adversity score was a summation of these values. Sexual abuse was measured in one specific question, “Did a parent or other adult in the household touch or fondle you or have you touch their body in a sexual way? Or attempt or actually have oral, anal, or vaginal intercourse with you?”

Responses were coded the same for these questions, 1 = yes and 0 = no. These values were summed into a sexual abuse score.

The Trier Social Stress Test (TSST) is used frequently in laboratory settings to evaluate responses to social stressors. During the TSST, the participants were asked to provide a speech in order to convince a panel of experts to hire them for a hypothetical position of employment. They were told to prepare for 3 minutes beforehand and that their speech would be recorded for behavioral analysis. “Panel members,” which included two trained research assistants from the lab, were not allowed to answer questions or offer encouragement and were told to maintain neutral affect throughout administration of the TSST. After the speech, participants engaged in an arithmetic task, in which they were asked to count backwards from 2023 in 17-digit increments as quickly as possible for 5 minutes or until completion. With each mistake, the participant was asked to restart counting backwards from 2023.

Saliva samples were obtained before and after the TSST, using Salivette collection devices (Sarstedt, Inc., Newton, NC, USA) in which participants were asked to chew on a piece of synthetic cotton before placing it in a sealed tube. One sample was collected immediately before the test to establish a baseline. Additionally, samples were collected immediately after the TSST and every 10 minutes afterwards for a period 40 minutes. Six samples were collected in total. Salivette collection tubes were stored in a -80F degree freezer after collection. After data collection for the entire study had been completed, salivary cortisol levels were analyzed using an enzyme immunoassay kit (Salimetrics, State College, PA, USA). Intra-assay CV values range from 4-7% and. inter-assay CV values range from 3-11% (Salimetrics, 2016; Davis et al., 2020).

Covariates

Participant age and body mass index (BMI) were included as covariates in the analyses described below. Age and BMI have a known association with cortisol that could impact results if not taken into account (Trickett et al., 2011; Bjorntorp & Rosmond, 2000). Participant age was self-reported, and BMI was calculated by obtaining participant height and weight during the study visit (kg/m^2, kg = weight, m = height).

Statistical analysis

Statistical analysis software, SPSS, was used for data analysis (IBM, 2017). Descriptive statistics and frequencies were run and analyzed to evaluate the data. All variables included in the study demonstrated normal distributions and statistical outliers were not identified. A correlation table depicting Pearson correlations was also generated. Lastly, the, PROCESS macro (Hayes, 2018) was used for regression analysis to evaluate biological sex as a potential moderator of associations between childhood adversity and total cortisol output (AUC_g) and cortisol sensitivity (AUC_i).

Chapter 3

Results

Table 1 displays the descriptive statistics for the variables in the study, Table 2 presents the Pearson correlations between study variables.

Table 1. Descriptive statistics

Variable	Number (%)	Mean	Std. Deviation
Male	15 (22.4)		
Female	52 (77.6)		
High school grad/GED	9 (13.4)		
Some college	11(16.5)		
Trade school	4 (6.0)		
Bachelor's degree	20 (29.9)		
Graduate degree	23 (34.3)		
Total adversity		1.045	1.408
AUC_g (total output)		34.053	19.513
AUC_i (sensitivity)		1.911	16.366
Age		60.730	6.355
BMI		27.534	5.766

Note. BMI = body mass index

Table 2. Pearson correlations between study variables

Variable	1	2	3	4	5	6
1. Total adversity	-	.514**	.197	-.266*	-.039	-.182
2. Sexual abuse	-	-	.064	-.107	.070	-.171
3. Sex	-	-	-	-.449**	-.533**	-.202
4. AUC_g (total output)	-	-	-	-	.465**	.171
5. AUC_i (sensitivity)	-	-	-	-	-	-.018
6. BMI	-	-	-	-	-	-

Note. * = $p < .05$; ** = $p < .01$, BMI = body mass index

As expected, greater childhood adversity was associated with lower total cortisol output (AUC_g; $r = -.266$, $p = .029$). Total adversity and sexual abuse were positively correlated ($r = .514$, $p < .001$) and females demonstrated lower AUC_g ($r = -.449$, $p < .001$) and AUC_i (r = -.533, p = .000) than males. Total cortisol output (AUC_g) and cortisol sensitivity (AUC_i) were positively associated ($r = .465$, $p = .000$).

Table 3. Regression analyses examining sex and total adversity predicting AUC_g (i.e. total cortisol output)

DV	coeff	*SE*	t	*P*
Constant	60.435	16.871	3.582	.001
Total adversity	3.482	9.647	.361	.719
Sex	-16.762	6.160	-2.721	.008
Total adversity x Sex	-3.130	5.024	-.623	.536
BMI	.215	.387	.555	.581

Note. BMI = body mass index

Table 4. Regression analyses examining sex and total adversity predicting AUC_i (i.e. cortisol sensitivity)

DV	coeff	*SE*	t	*p*
Constant	48.337	13.562	3.564	.001
Total adversity	3.367	7.755	.434	.666
Sex	-21.208	4.952	-4.282	.000
Total adversity x Sex	-1.466	4.039	-.363	.718
BMI	-.341	.311	-1.095	.278

Note. BMI = body mass index

Table 5. Regression analyses examining sex and sexual abuse predicting AUC_g (i.e. total cortisol output)

DV	coeff	*SE*	t	*p*
Constant	53.328	16.410	3.250	.002
Sexual abuse	48.296	27.349	1.766	.082
Sex	-15.684	5.648	-2.777	.007
Sexual abuse x Sex	-28.240	14.622	-1.931	.058
BMI	.334	.386	.867	.390

Note. BMI = body mass index

Table 6. Regression analyses examining sex and sexual abuse predicting AUC_i (i.e. cortisol sensitivity)

DV	coeff	*SE*	t	*p*
Constant	42.716	13.030	3.278	.002
Sexual abuse	37.374	21.717	1.721	.090
Sex	-19.093	4.485	-4.257	.000
Sexual abuse x Sex	-18.424	11.610	-1.587	.118
BMI	-.274	.307	-.894	.375

Note. BMI = body mass index

Total adversity was no longer associated with AUC_g when including biological sex and BMI in the linear regression models (see Table 3). The interactions between total adversity and

biological sex were non-significant. Biological sex continued to be associated with lower AUC_g ($p = .008$) and AUC_i ($p = .000$) (See Table 3 and 4) among females in comparison to males. Similarly, the interaction between sexual abuse and biological sex was not significant in predicting AUC_g ($p = .058$) and AUC_i ($p = .118$) (See Table 5 and 7); however, it should be noted that the interaction between sexual abuse and biological sex in predicting AUC_g trended towards significance, indicating that further research among studies with greater statistical power is warranted. Participant BMI was not associated with AUC_g or AUC_i in any of the models ($p =$ .278 to .581).

Chapter 4

Discussion

The primary goal of this study was to evaluate the association between childhood adversity and cortisol in response to a social stressor, with participant sex as a potential moderator. Childhood adversity was associated with a lower cortisol output, as expected, when using bivariate Pearson correlations; however, when biological sex and BMI were added to the analyses, the association between adversity and total cortisol output became non-significant. These findings align with those reported in previous research, with notable associations between childhood adversity and dysregulated HPA responses (Bunea et al., 2017). Cortisol levels have been found to be significantly lower in those who experience childhood adversity (Trickett et al., 2011). The association between variables in the present study was no longer significant after biological sex and BMI were analyzed as moderators. This could be due to the small sample size and a homogenous pool of participants in the present study and/or non-significant findings in prior research studies that were not published due to the focus on significant associations in the research literature.

As hypothesized, females demonstrated lower cortisol output (AUC_g) and cortisol resistance (AUC_i) than males. This corresponds with previous data which has reported that males often have higher cortisol in response to a stressor (Liu et al., 2017). The mechanisms behind this difference are not well known, but one report suggested structural and developmental brain differences in females and males when exposed to early life adversity which could potentially result in females having lower cortisol levels (Bath, 2020). Although the data did not support biological sex as a moderator of the association between adversity and cortisol, the interaction between sexual abuse and biological sex trended towards significance when predicting AUC_g. As

a result, although the hypothesis was not supported statistically, present study findings suggest that the interaction between sexual abuse and biological sex in predicting cortisol responses to social stressors should be evaluated in future research. It will be important to include samples that have a more balanced distribution of males and females in future research studies. The present study included relatively few male participants, which limits statistical power to detect differences between groups. Furthermore, it may be beneficial to focus on recruiting participants who report experiencing childhood adversity. The present study sample reported relatively low levels of adversity, which suggests that present study results may underestimate the strength of hypothesized effects. Focusing on those who have experienced adversity, as opposed to including a community sample, would address this concern. A previous retrospective cohort study had a sample with over half the participants reporting adverse childhood events and found significant association between childhood adversity and risk for negative health outcomes (Hillis et al., 2001). This suggests that a study focused on participants with high childhood adversity levels could lead to identification of significant findings.

Contrary to expectations, sexual abuse was not associated with AUC_i or AUC_g. Previous studies have shown that sexual abuse in childhood can potentially lead to lower levels of cortisol both in childhood and adulthood (King et al., 2008; Trickett et al., 2011). These differing outcomes could be a result of the present study having very few participants who reported being sexually abused. Once again, the study may be underestimating the hypothesized effects of sexual abuse on cortisol as a result. Focusing recruitment on those who report experiencing sexual abuse as children may alleviate this concern, in addition to using measurement strategies that evaluate sexual abuse continuously rather than categorically (i.e., yes/no). These two methodological approaches may yield stronger effect than those found in the current study.

In addition to recruiting participants who have experienced adversity, other biomarkers could be studied to measure the effects of stress from adverse childhood events on the stress response in adults. While cortisol is a traditional indicator of activation of the HPA axis, other measurements could be beneficial in measuring different stages of the stress response to get more well-rounded and potentially significant data. Measuring stress hormones other than cortisol, such as CRH and ACTH, can give a more holistic measure of the entire HPA axis response (Spencer & Deak, 2017). CRH stimulates the secretion of ACTH, which in turn stimulates the secretion of cortisol (Hänsel et al., 2010). By measuring levels of CRH and ACTH, data could show which part of the HPA response is most directly impacted by stress or childhood adversity. It could also indicate dysregulation in the cortisol negative feedback loop and help in pinpointing which mechanism is affected most by childhood adversity. Previous research has analyzed CRH and ACTH levels in response to acute stress (Spencer & Deak, 2017). Studies such as this have been able to report on different measures on hypocortisolism and could be a beneficial added marker to measure the consequences of stress (Spencer & Deak, 2017; Allen, 2020). Directly measuring glucocorticoid resistance could also be a beneficial additional measurement. Research has demonstrated that chronic stress can lead to glucocorticoid resistance, a potentially harmful adaptation to prolonged HPA axis activation (Cohen et al., 2012). Glucocorticoid resistance can result in increased inflammation, and as such, inflammatory biomarkers could be a useful measurement as well (Cohen et al., 2012). Cytokines are known markers of inflammation. The pro-inflammatory cytokine (IL-6) has been shown to increase in response to psychosocial stressors (Hänsel et al., 2010), making IL-6 an excellent candidate marker to study among those who have experienced adversity. Tumor necrosis factor-alpha (TNF-α) is another pro-inflammatory marker in the acute stress response (Jensen et al., 2019), which could be an

indicator of the magnitude of the immediate reaction to a social stressor. Associations between greater childhood trauma and more pro-inflammatory cytokines have been established in previous data (Hartwell et al., 2013). While these biomarkers have been well-studied, measuring them in combination with childhood adversity and biological sex may be beneficial to future studies. By measuring how stress impacts the HPA response and inflammation, more data can be available that could lead to improved preventative measures and treatment of stress related illnesses.

Limitations

A significant limitation for this study was the uneven representation of male and female participants, which limits the ability to detect sex differences. Reports of childhood adversity were also relatively low across participants, and therefore, present study data may underestimate the strength of the association between childhood adversity and cortisol in response to the TSST, Additionally, childhood adversity could be underreported due to recall bias that can be associated with traumatic and sensitive events (Iversen et al., 2007), which could limit the ability to identify significant effects. Adversity was measured categorically by answering yes or no qustions. Approaching data collection more dynamically could have been useful to gather more information about specific types of adversity. Another limitation is that the TSST is not a situation that is commonly encountered in everyday life. This test is useful for generating stress in a laboratory setting; however, the experiences are likely not similar to experience in their lives. Furthermore, the demographic representation of participants was relatively homogenous. Participants were generally healthy, mostly white, and from a small city in Pennsylvania. These

factors limit the ability to generalize the study findings to other populations. Lastly, this study could be limited because there are other biomarkers that weren't accounted for in this study. The current study focused on cortisol, but a variety of stress relevant biomarkers, such as CRH, ACTH, and pro-inflammatory cytokines are available.

Chapter 5

Conclusion

In the present study, females demonstrated lower cortisol output, and lower cortisol sensitivity, when faced with a social stressor than males. Such findings may aid in explaining biological sex differences in mental and physical health. Present study hypotheses for associations between childhood adversity and cortisol output, with biological sex as a potential moderator of these associations, were not supported; however, trend level findings provide evidence that more research is needed to evaluate study hypotheses. Larger sample sizes are needed in future studies, along with a focus on recruiting those who have experienced adversity, in order to move the field forward. An even distribution of males and females in future studies to test for biological sex differences would also be useful. Addressing the limitations of the present study in future research could lead to a better understanding of how to prevent serious health outcomes such as cardiovascular disease, mental health issues, and autoimmune disorders among those who have experienced childhood adversity.

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ACADEMIC VITA

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Education

The Pennsylvania State University**,** University Park, PA / August 2017- May 2021

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Honors and Awards

Schreyer Honors College / 2017-2021

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Research and Academic Experience

EMRAP Internship / BBH 495 / Summer 2019

Summer intern for Emergency Medicine Research Associate Program in Hershey, Pa, networked, shadowed, observed, and learned from physician assistants and physicians in the emergency department

Research Assistant, The DRIVES Lab / The Pennsylvania State University / Spring 2019

Examined the bidirectionality between cognition, stress, and biological markers of health

Professional and Work Experience

Emergency Department Patient Care Technician / UPMC Carlisle Hospital / May 2020-Present

Works closely and continuously with patients, partnering with nurses and other professionals to communicate observations and patient needs vital to the safety and comfort of the patient

Assists with procedures and performs a variety of basic and advanced skills such as EKG, phlebotomy, vitals and cardiac monitoring, catheter insertion/removal, and splinting

Resident/Nursing Assistant / Elmcroft Senior Living / September 2019-March 2020

Assists residents in activities of daily living and personal care, fulfilling needs such as support during showers, toileting, and eating

Provides emotional and physical support in the later stages of adult's lives and has been trained to handle sensitive situations of those afflicted with dementia and Alzheimer's

Home Care Assistant / Messiah Lifeways / May-August 2019

Provided a variety of personal care and assistance to activities of daily living to older adults both in a skilled nursing facility and in their homes

Performed nursing assistant duties and worked closely with nursing/hospice staff to ensure patient comfort and safety

Other Activities

Leader for Wyldlife / 2017-Present

YoungLife Christian outreach ministry at State College Area Middle Schools

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An outdoor, service based day that aims to better the campus and community

Committee Member for Rules and Regulations committee for THON / 2018