

Stress, Trauma, and Cortisol: Exploring Current Insights into the Neurobiological Influences of PTSD

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ABSTRACT

A considerable amount of literature has been generated on the role of cortisol in the symptomology of post-traumatic stress disorder (PTSD). This comprehensive critical review delves into the intricate nature of cortisol, trauma, and stress. Through examining four recent studies around the neurobiological contributors to PTSD, this writing will review methodology, results, and implications for future research. The first review will emphasize the importance of exploring variability in acute and chronic PTSD presentations. It specifically looks at the aspects of tissue sample types and a trend of lower cortisol levels in trauma-exposed individuals compared to non-trauma-exposed individuals. The second review uses a machine learning algorithm to explore a significant correlation between trauma symptom measures and specific cortical networks. Additionally, this review also includes a 2021 study that followed hair cortisol levels across PTSD treatment to reflect that increased levels are associated with a significant reduction in PTSD symptom scores and that childhood maltreatment did not show a significant association for changes in PTSD across treatment. The final review demonstrated that hair cortisol levels and post-trauma symptoms did not differ significantly between children who experienced refugee flight and those born in Germany. Explorations of mother and child hair cortisol levels revealed statistically significant associations. Noteworthy findings within this review highlight implications for communities such as survivors of forced migration, mother and child relationships, and inpatient-level treatment of PTSD. The articles are synthesized and then connected by a common thread of their contributions to updating the current understanding of the neurobiological factors of PTSD.

Keywords: PTSD, Trauma, Stress, PTSS, Cortisol, HPA-axis, Neurobiological

The term trauma stems from medical terminology used to describe an unexpected and impactful injury to an anatomical feature or organ of the body from an external force [1]. An important factor in the medical term involves the body's activation of the autonomic nervous system in response to this unexpected force [1]. The term trauma has expanded to include both physiological and psychological injuries. Posttraumatic stress disorder (PTSD) is a psychological disorder that includes symptoms that have a pervasive impact on multiple areas of functioning. It is estimated that 1 in 11 adults will experience PTSD in their lifetime [2]. For adolescents (ages 13 -18), the lifetime prevalence is 8% [2]. Importantly, PTSD is not appropriated equally amongst populations. There is a disparity for PTSD based on socio-demographic factors. Women are twice as likely to have PTSD compared to men [2]. There are also three racial/ethnic groups who are disproportionately represented in higher rates of PTSD when compared to the White population: U.S. Latinos,

African Americans, and Native Americans/Alaska Natives [2]. The disparities become even more blatant when considering the impact a diagnosis of PTSD may have on one's well-being. Having an understanding of the contributors to PTSD furthers improvements in the conceptualization, treatment, and identification of PTSD. In this writing, we will explore the most recent empirical findings around biological aspects of PTSD, with a specific emphasis on the role of cortisol.

Neurobiological Aspects of PTSD

There are various neurobiological factors that highlight and inform how PTSD is understood. The hippocampus region of the brain plays a key role in memory formation and regulation. This area is impacted in individuals with PTSD, as demonstrated by structural issues that contribute to memory deficits and intrusive experiences for individuals with PTSD [3]. Similarly, changes to the amygdala, spurred by increased amygdala activation, influence heightened emotional responses and the inability to downregulate negative emotions with PTSD [4]. The existing literature on the neurobiological aspects of PTSD has

highlighted the role of the prefrontal cortex in general for PTSD. Neurobiological indicators also provide evidence of resilience and plasticity.

Neurological mechanism models consider the neurological systems and their involvement in the physiological and psychological symptoms of PTSD. The neurological mechanism model primarily focuses on two stress response systems. The first is the sympathetic adrenal-medullary system (SAM) [5]. In moments of stress, the sympathetic nervous system activates the adrenal medulla, releasing adrenaline and noradrenaline into the bloodstream to initiate coping. This can be observed in what is often termed the fight or flight response. This hypersensitive SAM manifests in the form of exaggerated responses and heightened reactivity. The hypothalamic pituitary adrenal axis (HPA Axis) system releases the stress hormone cortisol [5]. The hormones released in the hypothalamus signal the adrenal glands to release cortisol [5]. These signals impact emotion regulation in relation to the limbic system. Led by the corticotropin-releasing hormone (CRH), this is exhibited as anxiety and heightened fear responses, while the CRH antagonist reduces anxiety and stress reactions [5].

Cortisol

A central hormone in the neurological system is the hormone Cortisol. Cortisol is a glucocorticoid secreted by the adrenal cortex that contributes to breaking proteins down into glucose. This process makes fats available for energy, which increases blood flow and responsiveness. Stress hormones, such as cortisol, may cause atrophy in the hippocampus, which can contribute to difficulty processing contextual cues for safety in PTSD [5].

The literature on the importance of the neurobiological interactions that contribute to symptoms of PTSD is abundant. The functional and structural neurobiological changes can have both immediate and long-term effects. Knowledge of the biological aspects of PTSD empowers individuals by providing them a perspective of their symptoms that separates what they are experiencing from a choice or moral failure. Biological insights have also contributed to prevention efforts, early detection, and personalization of treatment. In this writing, we will explore some recent studies on the role of cortisol in association with PTSD in an attempt to highlight the most recent knowledge and critique the study designs used to generate this knowledge.

A Critical Review of the Current Trends

Tissue Sample Meta-Analysis

Introduction

In Van den Heuvel et al.'s meta-analysis, researchers set out to build upon the understanding of cortisol's role in PTSD by synthesizing data from studies evaluating basal cortisol levels in patients with a diagnosis of PTSD versus non-PTSD diagnosed control groups by tissue type used for cortisol measurement [6]. They began by establishing the importance of focusing on endocrine-mediated stress response, particularly involving cortisol. This opened with a review of the existing literature that shows that cortisol is the chief stress hormone [6]. Previous studies have used traditional methods of sampling blood, saliva, and urine to assess acute cortisol levels. However, methods have developed in recent years using hair and nails, which can contribute to observing retrospective patterns [6]. Notably, Van

den Heuvel et al. highlight the inconsistent findings that have been found in PTSD-related cortisol dysregulation [6]. The rationale provided for this variation within the literature involved methodological differences, variations in the tissue sample types, and potential confounding factors related to trauma exposure [6]. In addition, more recent studies suggest lower cortisol levels in PTSD, particularly when analyzing saliva samples [6]. With this review, the authors establish an aim to provide clarity around the association between basal cortisol levels and PTSD.

Methodology

The authors then described the methods used to conduct this study. This study utilized The Cochrane Collaboration guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to promote transparency and reporting of systematic review findings. The authors also shared that a search was conducted to find other similar systematic reviews around the subject matter of PTSD and cortisol to help develop the necessity of what differentiates their study from others. The other studies were more so looking to evaluate HPA axis function in PTSD and evaluating 24-hour urinary cortisol levels in PTSD patients.

The Van den Heuvel et al. study utilized two reviewers to conduct standardized screening of the included studies independently [6]. The search strategy encompasses electronic databases, trial registries, and reference lists of relevant studies [6]. Restrictions were not placed on the publication date, publication status, or language for this meta-analysis [6]. The specified search terms to locate relevant studies included 'PTSD' and 'cortisol' and relevant synonyms to those terms [6]. An independent peer review using the PRESS methodology was facilitated by an information specialist [6].

This study considered the variation in designs of the studies to be reviewed. Participants across the studies were adults aged 18 years and older with a current DSM/ICD criteria-determined diagnosis of PTSD at the time of their study. Further inclusion criteria extended to studies with medical or psychiatric comorbidity. They also focused on studies whose outcomes focused on baseline or basal cortisol measurements across different tissue samples and time periods. Responses to stress tests were not utilized. Study selection involved rigorous screening of titles, abstracts, and full texts using a systematic eligibility form to document the rationale for inclusion and exclusion. There was an emphasis placed on subgroup analyses comparing PTSD patients to control groups.

Data was determined to be abstracted by two independent reviewers using the RED Cap database application. The RED Cap form covered study characteristics, participant demographics, trauma-related information, PTSD details, physical data, cortisol-related data, and the methodological aspects of the studies. The study also adhered to HIPAA regulations due to the sensitivity of the protected health information utilized in this study. A risk of bias assessment, a modified Newcastle-Ottawa Scale, was performed by the reviewers to ensure quality and inter-rater reliability. This tool used components from the Cochrane Risk of Bias tool and Agency for Healthcare Research and Quality (AHRQ) guidelines. Inter-rater reliability was measured using the kappa statistic. The Grading of

Recommendations, Assessment, and Evaluation (GRADE) approach was applied as well. The study data was then analyzed using qualitative synthesis to summarize the information as organized via evidence tables. A comprehensive examination of heterogeneity dynamics, such as study design, populations, and outcome measurements, was utilized. A meta-analysis was then conducted for each tissue type sampled through standardized mean difference (SMD) and Hedge's g for studies with smaller sample sizes. A random effects model was then used for the heterogeneity, with sensitivity analyses and meta-regression to explore the potential moderators. Potential moderators involved factors such as the publication year, age of participants, sex, trauma type, time that has passed since the trauma occurred, PTSD severity, psychiatric comorbidity, and sampling details. Analyses were also made to address the impacts of study effects and bias.

Results and Discussion

The results indicated that most studies anticipated and demonstrated that individuals with PTSD will generally have lower levels of cortisol than those who were not exposed to trauma or in the control group who were trauma-exposed but not diagnosed. The authors also hypothesized that the directionality of cortisol levels across different tissue types would be consistent and that there would be variability in statistical significance. They found that this variability was partially attributed to the time window of cortisol measurement and the tissue type that was sampled. Results were disseminated through publication in peer-reviewed journals, especially open-access options. These findings were also presented at relevant conferences. These findings help to contribute to the understanding of the variability in the acute and chronic displays of basal cortisol secretion in PTSD.

Critique and Implications for Future Research

Overall, this study utilized a rigorous screening process. The authors explained in great detail the criteria and methodology for looking at data across such varied sources. Attention was also paid to the importance of standardization. Although there was emphasis on the design variability, some variability added to the study's overall design is a limitation. Using studies across languages adds to the generalizability and open-access framework. However, there is room for losses in translation. There was also substantial methodological heterogeneity in the cortisol measurement and sample types, affecting the consistency and comparability of the results. The variability in study designs could also impact the findings. A similar limitation can also be found in the varying definitions of trauma due to the inclusion of various forms of trauma exposure. However, the methodology was clear and replicable. There was attention paid to potential confounds and moderators for the variables. The authors used clear approaches and models to control the quality of the evidence. The researchers met their goal of exploring the variability in cortisol levels in PTSD-diagnosed individuals and control groups in relation to the type of sampling, particularly in acute versus chronic presentations of PTSD. The authors also seem to be setting up further exploration around identifying specific aspects of tissue sample type in PTSD studies. The findings of the review hold the potential to enhance the utility of cortisol as a biomarker and to synthesize the current understanding.

Mapping PTSD via Machine Learning

In the Zandvakili et al. study, machine learning was used to explore differences in PTSD symptom subgroups based on brain functional connectivity in the cortical and subcortical regions of the brain [7]. The researchers in this study began by characterizing the pervasive condition of PTSD based on the range of symptoms experienced (e.g., intrusive thoughts, avoidance, hyperarousal, mood concerns, and cognitive impairments). These indicators are reflected in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria of intrusion, avoidance, cognition/mood, and hyperarousal domains. They set the stage around the complexities of the symptomology while highlighting the distress and functional impairments they cause. Zandvakili et al. also highlighted the difficulties in pinpointing a unified biological marker [7]. To address this gap, the researchers used functional neuroimaging to examine the neural circuits and their correlation with each symptom domain. Their study innovates from previous functional imaging studies in that they are using machine learning and its potential to predict and identify more precisely. Zandvakili et al. state that their research objective is to determine if the combination of both technologies, machine learning, and neuroimaging, can establish clearer links between specific neural circuits and PTSD symptom profiles [7].

Methodology

In the next section, Zandvakili et al. clearly state their method and study design. Magnetic resonance imaging data were collected from 50 participants at Brown University using a 3T MRI scanner [7]. The dataset used in this study was from pretreatment baseline scanning from prior studies [7]. The participants were between 37 and 59 years old on average [7]. All participants were diagnosed PTSD based on DSM-5 criteria, and 38% identified as women [7]. Self-reported PTSD indications were assessed via the PTSD checklist for the DSM-5 (PCL-5), a 20-question scale rating the severity of symptoms and categorizing them into the four PTSD subscales [7]. In alignment with common occurrence, participants were included who had co-morbid DSM-5 diagnoses of depression [7].

The authors then explained their procedure for selecting a neurobiological region of interest. Functional connectivity analyses on 100 cortical and subcortical regions of interest (ROIs) were chosen based on the existing literature on the functional networks in PTSD [7]. Functional connectivity analysis involved extracting functional MRI time courses, creating cross-correlation matrices, and bivariate Pearson correlations between ROI [7].

Next, the specifics of the machine learning components were explained. Least-angle regression (LARS) on this dimensionality-reduced dataset was used to predict the four PCL-5/DSM-5-based subscale categories [7]. To validate the predictions, the study was rerun on a randomly permuted dataset through 5000 iterations [7]. This analysis included a rigorous validation process. Results were visualized in connectome plots, highlighting the top 1% strongest weights of implicated brain connection regions.

Results and Discussion

The results indicated that PCL subscales were decidedly correlated with each other (Pearson correlation coefficient $r = 0.38$ and 0.50), which is expected for the related symptoms of a psychological

construct [7]. The machine learning algorithm, using feature selection and LARS regression, was able to predict the total PCL-5 score ($R^2 = 0.29$, $p=0.030$) as well as the subscale scores for the intrusion ($R^2 = 0.33$, $p=0.412$) and avoidance clusters ($R^2 = 0.23$, $p=0.164$) [7]. These results demonstrate that the models operated significantly better than chance at predicting total PCL-5 scores and for two specific subscales. When plotting the connections, they depicted that numerous connectivity patterns accurately projected PTSD symptoms within the profiles. Connectivity patterns between right rostral anterior cingulate and left pars orbitals that were positive were related to higher intrusion symptoms and overall PCL-5 score [7]. Functional connectivity patterns highlighted specific brain regions associated with symptom severity. Unique connectivity profiles distinguished intrusion from avoidance symptoms, and a disrupted cross-network connectivity was observed in individuals with severe symptoms [7]. Both areas in the cortex and subcortex were specified, which could provide more information on how stress hormones, such as cortisol, influence these areas. This can even develop into methods of using cortisol as a warning signal with its associated areas during trauma and post-trauma.

Zandvakili et al. emphasized their novel two-step machine learning algorithm in that it effectively predicts individual-level self-reported PTSD symptoms [7]. This study's supervised learning algorithm offers a valuable alternative to previous machine learning studies. They restated their findings around the functions of the distinct cortical networks and symptom severity. In regards to their observed limitations, they highlighted that the model did not predict arousal and cognition/mood symptoms. They then gave their rationale for why that might be, such as algorithmic bias towards certain symptomology, sample size limits, or variations in how those symptom groups present [7]. They highlight that one area for future study would involve expanding on the neuro biomarkers for PTSD using this methodology. After acknowledging the general limitations of secondary neuroimaging analyses, they concluded by highlighting the success and utility of their findings.

Critique and Implications for Future Research

There were notable limitations around the sample size of 50, which speaks to future implications for improved generalizability testing. The study's cross-sectional design also limits the ability to communicate a casual relationship from these findings. Although the inclusion of the depression co-morbidity speaks to effectiveness studies and how this disorder might present in the real-world setting, this could have been a potential confound or a hindrance to some of their findings in the criteria domains. Additionally, the data was selected based on individuals who participated in previous studies, which might confound if the participants were truly representative of the broader population of individuals with PTSD.

This article was selected for this review due to its innovative methodology and utility for future explorations of brain regions, neurotransmitters, and neurohormones in relation to PTSD symptomology, such as cortisol. It would also be important to utilize more diverse samples to ensure generalizability of this method and model to various types of PTSD and to assess symptom presentation across subgroups. Studies using this model could also explore and compare results using

data meeting PTSD criteria in comparison to healthy or non-diagnosed control groups. It would also be useful to compare these results longitudinally, including a measurement of the impact or moderation of treatment. The authors were innovative in adopting a two-step machine-learning algorithm. This study also demonstrated the potential of using resting-state functional connectivity in prediction. This study also carries significant clinical relevance in identifying biological markers and linking them to symptoms and symptom severity. The authors were mindful of validity and bias considerations at multiple steps throughout the methodology and analysis. In summary, this study makes significant contributions to the understanding of the neurobiological underpinnings and functions of PTSD. Importantly, it also inspires multiple avenues for more specified neurobiological explorations of the SAM and HPA Axis systems and their related regions.

The Predictive Role of Hair Cortisol Concentrations in PTSD Treatment Outcome

Introduction

The next two articles utilize a hair-sampling method for cortisol research. The hair sampling technique has gained popularity in recent years as ongoing efforts to refine and enhance its capacities are developing. A study by Hummel et al. explored hair cortisol concentrations' predictive role in treatment outcomes for individuals receiving inpatient care for PTSD [8]. The researchers highlighted that psychological treatment of PTSD has a non-response rate of up to 50%, generally [8]. The use of hair cortisol analysis allows for a more reliable appraisal of cortisol secretion over periods of time. The authors then shared their intent to explore hair cortisol concentrations (HCC), non-response to treatment, and the role of a history of childhood maltreatment. Essentially, they were aiming to identify characteristics of non-response. Hummel et al. summarized previous findings that pre-treatment bedtime salivary cortisol, urinary cortisol excretion, and salivary cortisol awakening response in individuals with PTSD were lower [8]. It was also found that while basal cortisol levels decreased for responders to psychotherapy treatment, cortisol levels increased for responders [9]. However, the follow-up and meta-analytic reviews of these findings have produced mixed results [8]. Hummel et al. explained that the current mixed findings on the role of cortisol might be due to varied assessment strategies (e.g., plasma, saliva, urine) in capturing what is occurring with long-term cortisol secretion [8]. This then brought to the forefront the importance of the recent development of hair cortisol analysis due to its ability to capture accumulative cortisol secretion over periods of several months [8]. Childhood maltreatment has also been used as a predictor of reduced treatment response [8]. For that reason, both were used as independent variables within this study. The primary objectives were to assess whether diminished HCC during treatment predicted less of a reduction in PTSD symptoms across treatment and to compare this to the predictive role of childhood maltreatment.

Methodology

This study used a prospective design in a natural treatment setting. Participants included 52 patients undergoing PTSD treatment at a specialist inpatient clinic in Germany. A rigorous inclusion and exclusion process ensured homogeneity within the sample to enhance the validity of the findings [8]. Treatment within this

study included multimodal trauma-focused psychotherapy using individual, group, movement, and art therapy [8]. Patients also practiced facilitated relaxation techniques and psychoeducation [8]. The data involved collecting hair cortisol concentrations to measure cumulative cortisol secretion over an extended period. The authors shared that a chromatography-tandem mass spectrometry liquid protocol was used on the hair [8]. The hair samples were collected at specified intervals pre-, post-, and follow-up post-treatment. Childhood maltreatment was assessed by the severity score on the Childhood Trauma Questionnaire (CTQ) [8]. CTQ data was provided for 45 of the 52 patients [8]. The primary outcome measure utilized the posttraumatic diagnostic scale (PDS) score. Secondary dependent variables or outcomes measured symptom severity via the symptom checklist-90-revised (SCL-90-R), the Beck Depression Inventory (BDI), and the CTQ score.

The data analysis was conducted using linear-mixed effect regressions for the exploration of clinical PTSD symptoms [8]. Sensitivity analyses were performed for the subsample of verified PTSD diagnoses [8]. To explore the associations between HCC and symptom severity a regression analysis was used [8]. A regression analysis was also used to explore associations between HCC and the outcome variables, and the predictive analysis assessed HCC change over time in relation to treatment [8].

Results and Discussion

Hummel et al. found that an increased HCC corresponded with a significant reduction in PTSD symptom scores from pretreatment to both post-treatment and follow-up [8]. This suggests a potential link between the body's long-term stress response and the effectiveness of PTSD treatment. Individuals with higher HCC levels at the start of treatment may respond more positively to treatment and have a lasting reduction in PTSD symptoms. Pre-treatment HCC did not demonstrate significant associations with changes in PTSD symptomology during treatment or follow-up. However, pre-treatment levels of HCC were associated with a smaller reduction in overall psychological symptoms post-treatment [8]. This suggests that while HCC levels prior to treatment may not directly relate to changes in PTSD, they could be associated with the overall psychological well-being of individuals long-term. Additionally, changes in HCC during treatment were not predictive of changes in PTSD symptoms or secondary measures [8]. Childhood maltreatment did not show significant associations with changes in PTSD symptoms or secondary outcome measures during treatment or in the follow-up [8].

In summary, the findings did not corroborate the hypotheses that pre-treatment HCC would predict changes in PTSD symptoms over the progression of inpatient treatment [8]. However, it was found that subordinate pre-treatment HCC was associated with less improvement in overall clinical symptomology from baseline to discharge [8]. This finding lost statistical significance when including baseline dissociative symptoms [8]. Overall, this study found that pre-treatment HCC might have predictive value for general psychological symptomology rather than PTSD-specific symptoms. The authors shared that HCC has been used to predict treatment responses to anxiety and depression symptoms, which might add to their findings [8]. In addition,

there is more to be explored around the relevance of dissociative symptoms in moderating the relationship between cortisol levels and symptom change. Although changes in HCC over the course of inpatient treatment are not predictive of changes in PTSD symptoms in relation to treatment, HCC might be better used to measure other relationships between PTSD symptoms and cortisol. There is more to be explored in whether general HPA axis activity pre and post-psychotherapy may serve as a predictor for treatment outcome. The authors shared limitations in the study, such as having a relatively small sample size and limits to the generalizability of the findings [8]. There might also be some confounds introduced around the variability of treatment due to not providing a standardized treatment protocol [8]. Also, the study did not control for the impact of medication intake on HCC in these patients [8]. Hummel et al. shared that future studies would benefit from more standardized protocols and should consider larger sample sizes [8].

Critique and Future Implications for Research

This study was insightful in that it contributes to the potential role of cortisol as measured by HCC in monitoring general symptom change. These findings underscore the complexity of the relationship between cortisol regulation and symptoms. As the authors stated, there were some limitations. Having a small and homogeneous sample impacts the statistical power and generalizability. The emphasis on ecological validity and mirroring current routine care had impacts on the methodological rigor in regard to treatment protocol standardization. In addition, the sample was comprised exclusively of female patients. The authors also alluded to the lack of standardization in the treatment protocol. I would imagine that PTSD, being treated on an inpatient level, would be highly variable and co-morbid in its presentation and treatment. In addition, inpatient treatment is primarily about acute stabilization versus long-term treatment, which might have varied implications on what is meant by PTSD treatment. It would be interesting to see how these results would materialize if utilizing PTSD-specific treatment such as cognitive behavioral therapy, cognitive processing therapy, eye-movement desensitization and reprocessing therapy, narrative exposure therapy, or dialectical behavioral therapy.

As stated, there is more to be explored around the importance of dissociative symptoms and their role in PTSD treatment, as evidenced by cortisol levels. With the emergence of research on adverse childhood experiences (ACEs) and their influence on long-term physiological and neurobiological effects, there is also more to be explored around the interplay between childhood maltreatment, PTSD, and cortisol.

This study's emphasis on real-world applicability, although contributing to some standardization issues, was a strength in that it reflects the challenges and complexities of treating chronic PTSD. Research in non-controlled settings is important and valuable. The study also had a strong longitudinal design in the collection of pre-post-and follow-up treatment measures. Overall, this study was selected due to its use of HCC. Findings exhibiting the use of HCC as a measure of long-term cortisol output provide a more stable reflection of how cortisol operated over time. This can contribute to many innovations and potentials in exploring cortisol concentration in relation to psychological conditions.

Hair Cortisol in Trauma-Exposed Refugee Mother-Child Dyads

Introduction

A 2020 study by Lembcke et al. used HCC technology to investigate if children's cortisol levels in response to traumatic events are associated with their mothers' cortisol and whether or not this association can be moderated by positive parenting factors such as maternal affection [10]. This specific article was included in this review due to its incorporation of PTSD experiences related to immigration trauma, which involves the interplay of social determinants of health and the complexities of racial/ethnic marginalization. This is an important consideration that can be expanded upon to explore trauma(s) specified towards people of color (POC) and the little that is known about the intergenerational impacts of these trauma(s).

The introduction provides a comprehensive background on the challenges faced by children who are refugees. As a refugee, adversity can be experienced before, during, and after forced displacement. The authors outlined observable manifestations of post-traumatic stress symptoms (PTSS) in children, ranging from intrusive memories to socially withdrawn behaviors [10]. Due to the vulnerability of children, this highlights the increased impacts for children who are refugees. Lembcke et al. also reviewed the literature on how these experiences can be exacerbated when the primary caregiver is also experiencing PTSS [10]. Conversely, positive parenting practices can serve as mitigating factors for all children who experience symptoms of mental health conditions, including refugees [11]. This introduction then shifts to a discussion on the impact of adverse experiences on the HPA axis, demonstrating the role of cortisol release in response to stress and trauma. The cited studies were selected by Lembcke et al. to highlight the detrimental effects of prolonged cortisol exposure [10]. The authors then introduce HCC as a reliable biomarker tool in assessing cumulative cortisol release.

The present study's aim is then outlined as a way to examine the potential connections amongst mother-child dyads regarding PTSS, using HCC and exploring parenting practices as a potential moderating variable. The interconnectedness of these factors is highlighted by the authors via figures and frameworks. According to Lembcke et al. these complicated associations may go back and forth between mother and child, which is influenced by both environmental and genetic factors [10]. The first research question explores whether children born prior to forced displacement differ in HCC, PTSS, and maternal affection when compared to children who were born post fleeing. The authors hypothesize that exposure to war and displacement may indirectly influence these factors [10]. The authors seem to use the term flight experiences to represent fleeing from one area to another due to unsafe circumstances. This question poses important implications for understanding the indirect effects of war-related adversities on children and families. Research question two examines the affiliation of mothers' and children's HCC by distinguishing between war-exposed samples and their German born children. The findings could provide clarity around functional biological synchrony or synchronous neurobiological rhythms between mother and child. The existing literature has established synchrony in mother-child dyads with PTSS [10]. However, the correlation between HCC levels of the mother and child has produced mixed results [10]. The third question seeks

to predict children's PTSS based on the HCC levels within the mother-child dyad, basically testing if mother-child dyad HCC can serve as a predictor. The author summarizes this section by acknowledging the potential confounding factors such as socio-economic factors, characteristics of the experience when fleeing, health status, and hair characteristics [10]. The authors hypothesize that they might explain some of the variance; however, the PTSS will be the most significant contributor to HCC [10].

Methodology

Data collection for this study occurred between July 2017 and October 2018 [10]. Eligibility criteria included Syrian and Iraqi refugees who arrived in Germany within the four year timespan leading up to 2017 [10]. Participants also had to have a child under 5 years old [10]. Exclusion criteria included developmental disorders and certain chronic health and genetic disorders [10]. Recruitment occurred across various settings, such as cultural centers, vocational schools, refugee camps, and online platforms [10]. Materials explaining the study were sure to consider hesitancy and address distrust and religious factors. The researchers shared that about 50% of those considered declined participation due to factors such as distrust [10]. The research assistants were 4 Arabic-speaking female researchers [10]. Their specific ethnic and cultural factors were also considered when interacting with participants. This was an important and thoughtful consideration by the research team. Consistency training for hair strand collection was utilized [10].

The final participation number was comprised of 42 dyads. Mothers ranged in age from 24 to 34 on average. The participating children were 5 to a few months old in age [10]. The children in this study included 23 girls and 19 boys [10]. HCC was assessed using strands collected using a posterior vertex of the scalp [10]. There appeared to be very strict controls around the operations involving hair strand collection. Liquid chromatography-tandem mass spectrometry was employed for the cortisol extraction, similar to the previous study utilizing HCC.

The preschool PTSD scale of the Child Behavior Checklist in Arabic was used to assess PTSS in the children [10]. The mothers' PTSS was measured using the Arabic-adapted PTSD scale of the Harvard Trauma Questionnaire [10]. The authors reported psychometric validity and reliability data for the measures. Affection from the mothers was observed utilizing the Parenting Interactions with Children Checklist of Observation Linked to Outcomes (PICCOLO), which accounted for seven types of affectioned behaviors [10]. The confounding factors, such as health status, were measured and documented.

The mean values for PTSS and maternal affection scales were utilized due to missing data [10]. Cohen's *d* was utilized for the comparison of subgroups, and Hedge's *g* was used for unequal sample-sized groups [10]. Hierarchical linear regression was used to assess correlations and predictive capacity. The median split of the difference between mother-children HCC levels was split into typical and atypical HCC dyad groups.

Results and Discussion

Normality was established for all variables except for HCC, which was then log-transformed [10]. The authors then shared their descriptive statistics. Confounding factors, differences,

and associations were also explored and shared. Significant differences were not found in HCC levels, PTSS, or maternal affection between children who experienced flight and those born in Germany. Atypical dyads did have a statistically significant correlation between maternal and child HCC [10]. Children in the atypical HCC dyads had lower levels of HCC ($M = 1.18$, $SD = 0.65$) on average compared to the typical group [$M = 2.48$, $SD = 0.63$]; $t(33) = -5.97$, adjusted $p < .001$, $d = -2.02$] [10]. Children's and mothers' HCC were correlated in a positive trend ($r = .21$, $p = .221$, $n = 35$) but statistical significance was only demonstrated in the atypical HCC dyads ($r = .69$, $p = .002$, adjusted $p = .007$, $n = 17$) [10]. This might indicate disrupted physiological synchrony. The positive tendency between children's HCC and PTSS contradicts what is typically seen in adult populations. Children who lived through refugee flight were equally as likely to fall into the atypical or typical HCC dyad group [10]. It was revealed that children who experienced flight had significantly lower levels of maternal affection when compared to those born in Germany after a follow-up t-test was performed [10].

The results indicated that affection from the mothers was not significantly correlated with children's and mothers' HCC across the sample at large. However, maternal affection tended to be positively correlated with both children's ($r = .39$, $p = .108$, $n = 18$) and mothers' HCC ($r = .84$, $p = .045$, adjusted $p = .268$, $n = 18$) in the typical HCC group [10]. This would suggest that mothers and children with higher levels of PTSS and elevated cortisol levels were connected with maternal affection. In conjunction, maternal affection was negatively associated with children's ($r = -.35$, $p = .186$, $n = 17$) and mothers' ($r = -.05$, $p = .863$, $n = 17$) HCC levels in atypical HCC dyads [10]. An association between children's HCC and PTSS was not found [10]. However, the HCC difference between children and mothers was significantly correlated with children's PTSS scores [10]. The hierarchical linear regression indicated the predictive value of HCC difference in PTSS scores [10].

Within the discussion, the authors highlighted nuanced connections from their findings. For instance, the high levels of PTSS in children who were born to refugee parents in Germany suggest much to be explored around the indirect impacts of systemic trauma exposure. The predictive capacity of affection was also restated. The authors did express limitations around the small sample size, lack of norm data for HCC levels, and differences in the length of hair samples for the mothers [10]. Overall, maternal HCC, PTSS, and affection were important influences on children's HCC and PTSS, beyond whether the children experienced fleeing the country or directly experienced trauma.

Critique and Implications

As previously stated, the importance of this study spans beyond the HCC technology advancements but also involves the use of neurobiological measures to explore the impacts of structural and systemic-related stress. There were some barriers regarding sample size, which, if replicated with a larger sample, could enhance the external validity and generalizability and possibly better answer some of the stated research questions. This study might have also benefitted from a comparison to a non-refugee control group. In addition to more established confidence in

the causality of the associations, there would be more cross-over experiences of PTSS and HCC levels for those who have experienced similar forced immigration and the adversities involved with that experience, even though it is not diagnosed or self-reported. There would also be expansion and specification around types of trauma associated with forced migration when attempting to pinpoint the role of cortisol and the HPA axis. As the researchers shared in their limitations, norm data for general HCC would have added to an increased understanding of the observed levels of HCC within this study and how they fall into typical functioning. There are varied ways this study can be built upon and strengthened.

The Lembcke et al. study also had various strengths [10]. The emphasis on mother-child dyads highlighted the systemic importance of caregiver-child relationships in understanding trauma. The study, in general, found an innovative way to include and address the multiple stressors and adversities that are associated with forced immigration. From a social determinants of health perspective, this type of research could have profound implications for knowledge, clinical, and policy understanding. The mother-child HCC dyads provide valuable insights into cortisol synchrony.

Conclusion

As these recent studies show, understanding the most current literature provides nuanced information on the latest developments and trends within the field. This ensures awareness of developments in theories and findings. A more comprehensive view of the role and functions of cortisol has yielded some potential inconsistencies or gaps within the literature. However, this body of work has also provided ample space for further exploration and clarification. The neurobiological frameworks and theories for conceptualizing psychopathology are alive and well. The stress hormone cortisol will continue to play a major role in these advancements.

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