

Stress and immune biomarkers interact with parenting behavior to shape anxiety symptoms in trauma-exposed youth

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ABSTRACT

The relations between stress, HPA-axis, and the immune system have been extensively studied; however, no study to date addressed the joint contribution of immune and HPA biomarkers to the development of anxiety in youth exposed to chronic trauma as mediated by mother-child interaction patterns. A unique cohort of war-exposed children and their mothers, compared to matched controls, were followed from infancy and the current study reports findings from early adolescence (mean age = 11.66, SD = 1.23; N = 111; exposed = 58 control = 53). Youth and mothers' salivary cortisol (CT) and secretory immunoglobulin (s-IgA) levels were measured three times during a 4-hour lab visit, mother-child interaction patterns were quantified from a joint task, and children's anxiety symptoms diagnosed. Trauma-exposed children had higher levels of CT and s-IgA, exhibited more anxiety symptoms, and showed lower social collaboration with mother during the joint task. Trauma-exposed mothers had higher CT and s-IgA levels and showed less supportive parenting during mother-child interaction. Structural equation modeling defined three bio-behavioral paths by which trauma increases anxiety in youth. While the first path charted a behavioral link from exposure to child anxiety via diminished maternal support, the other two paths described mediated biological paths, one through HPA-axis functioning, the other via the immune system. Paths via the child's HPA and immune system were mediated by the parallel maternal variable. Findings are the first to describe the complex bio-behavioral interplay of stress and immune biomarkers and parenting behavior in shaping to the development of risk and resilience trajectories in youth growing up amidst chronic trauma.

1. Introduction

The relations between stress and the immune system in general and their interdependence in the context of chronic trauma in particular have been extensively studied (Boscarino, 2004; Heim et al., 2008; Segerstrom and Miller, 2004a,b). Stress-induced hormonal alterations have been linked with changes in the immune system as well as with behavioral, emotional, and cognitive processes that lead to physical illness and psychiatric problems (De Bellis and Zisk, 2014; Lupien et al., 2009). Such negative effects of stress on physical and mental health is particularly noted during periods of brain maturation and studies have repeatedly shown that trauma carries greater effects on the developing child (Anda et al., 2006; Heim and Nemeroff, 2001). Neural and behavioral plasticity are higher during childhood and adolescence, rendering youth more susceptible to the long-term consequences of prolonged trauma. It is thus important to study the mutual influences of

stress and immune responses as they interact in the developing child.

Exposure to war and terror are examples of "mass trauma" where large populations are exposed to the same natural disaster or stressful events at the same time (Masten and Narayan, 2012). Coping with such events requires different mechanisms from those involved in coping with other forms of trauma as the entire family is typically exposed to the same traumatic events and affected mothers may have limited resources to contain the child's fears. Following such trauma, child social abilities and biological systems interact to define trajectories of risk and resilience and shape well-being and health (Heim and Nemeroff, 2001). Since exposure to war and terror is associated with uncertainty (Shaw, 2003), the daily experience of fear, stress, and anxiety increase (Ulmer-Yaniv et al., 2018), markedly increasing the prevalence of anxiety disorders in war-exposed children (Halevi et al., 2016; Heim and Nemeroff, 2001). In addition, many children exposed to war-related stressors suffer from other psychiatric problems, including depression,

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disruptive behaviors, and somatic symptoms (Allwood et al., 2002; Halevi et al., 2016).

Following mass trauma, maternal sensitivity, empathy, and social attunement serve as important protective factors and buffer against the development of psychopathology in children (Feldman and Vengrober, 2011; Masten and Narayan, 2012; Scheering and Zeanah, 2001). Maternal relational behavior is shaped by the mother's psychiatric symptoms and both maternal parenting behavior and maternal psychopathology are influenced by the mother's stress response and hormonal levels. Maternal psychopathology and maladaptive parenting contribute to the sense of instability that is already present in the child's life and may exacerbate the traumatic effects. In contrast, the mother's supportive presence and empathic behavior exert a general 'social buffering' effect that regulates the child's hormonal, immune, and behavioral systems (Ulmer-Yaniv et al., 2018). Consistent with our "bio-behavioral synchrony" model (Feldman, 2012a, 2015, 2016), such biobehavioral maternal influences define the paths by which maternal physiology and behavior modulate the child's stress response in a system-specific manner.

Adrenocortical activation is the major hormonal response to stress that organizes physiological and psychological adaptation following exposure to stressors (Sapolsky et al., 2000). Traumatic experiences and chronic stress can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in both adults and children, resulting in altered cortisol (CT) secretion (Chrousos, 2009). In trauma-exposed adults, such dysregulation is often reflected in hypocortisolism, although some studies showed hypercortisolism or no difference between stress-exposed and control individuals (Klaassens et al., 2012; Miller et al., 2007). In children, most studies reported that trauma exposure leads to elevated CT levels (Carrion et al., 2002; Cicchetti et al., 2010; De Bellis and Zisk, 2014; Pfeffer et al., 2007), however other studies report lower basal CT levels in trauma-exposed children (Goenjian et al., 1996; King et al., 2001). Consistent with most research, we have previously shown that war-exposed children and mothers had higher CT levels compared to non-exposed controls (Feldman et al., 2013; Halevi et al., 2017).

Stress, trauma, and adrenocortical activation are associated with marked alterations in various components of the immune system (McEwen and Stellar, 1993). Among these, Immunoglobulin A (IgA), which functions as a first-line protector of the body from pathogens, has been extensively investigated. IgA is the most common antibody in the human mucous and levels of its secreted form (s-IgA) in saliva provide a well-validated biomarker of immune-system functioning (Bosch et al., 2002; MacPherson et al., 2008). S-IgA secretion is modulated by physical and psychological stressors (Engeland et al., 2016) as mediated by the degree of anxiety caused by these stressors (Graham et al., 1988; Ulmer-Yaniv et al., 2018; Vermeer et al., 2012). However, results regarding basal levels and responsiveness of s-IgA following acute and chronic stress are contradictory, and evidence shows both excessive and insufficient s-IgA production even after exposure to the same stressors (Bosch et al., 2002; Segerstrom and Miller, 2004a,b).

Notably, most studies on s-IgA have been conducted in adults and very few studies examined the effect of chronic trauma on s-IgA levels in children or adolescents. In one seminal study, adolescents who experienced adverse childhood experiences, including institutionalization or physical abuse, exhibited high levels of salivary s-IgA, particularly against herpes simplex virus (HSV), representing a failure of their cellular immune processes to limit viral (Shirtcliff et al., 2009). Similarly, nine-year old children exposed to chronic war-related stress displayed high levels of s-IgA compared to controls (Ulmer-Yaniv et al., 2018). The stress-induced changes in s-IgA levels may be related to the adrenocortical activation, evidenced by the reported association between CT and s-IgA following prolonged stress, specifically in children (Watamura et al., 2010). However, the results of other studies examining the association between these biomarkers are inconsistent, with studies reporting negative, positive, or no correlation between CT and s-IgA levels (Laurent et al., 2015; Sanchez-Martin et al., 2001;

Watamura et al., 2010; Wayforth, 2007).

Although several studies addressed the relations between stress, hormones, immunity, anxiety, and parental behavior, no prior study to our knowledge integrated all components in a single study to test their joint impact on the development of anxiety disorders in stress-exposed youth. Furthermore, previous studies focused on either adults or children, not on both partners of the caregiving dyad, and nearly no research exists on these factors in early adolescence (Hostinar et al., 2014). In the current study, we investigated the multi-dimensional biobehavioral interplay between the HPA axis, the immune system, and the development of anxiety disorders in youth growing up amidst chronic trauma. We followed a unique cohort of war-exposed adolescence and their mothers living in Sderot, a small Israeli town located less than a mile from the Gaza border and exposed to repeated missile and rockets attack since 2001, with significant exacerbation of the situation in 2005, 2008, and 2014. During the past 12 years, there have been six military operations when the city was under siege and suffered dozens of daily missiles attacks for weeks. Sirens warning of incoming missiles allow citizen 7–15 seconds to reach shelter before explosion. Even during relatively calm periods threats are looming and occasional missiles are launched every few days in addition to the constant fear from tunnel-digging from Gaza. Overall, Sderot and its surrounding area suffered dozens of casualties with hundreds of injured individuals and significant property and infrastructure damage, leading to severe psychological distress among its citizens.

We hypothesized that exposed mothers and children will show elevated levels of CT and s-IgA and that exposed children would display more anxiety symptoms and less social collaboration. We expected that biomarkers in mother and child would be inter-related, consistent with the bio-behavioral synchrony theory (Feldman, 2015). Finally, based on previous findings we build a theoretical model, and assumed that the mother's supportive and sensitive style, as well as her stress biomarkers will shape the child's parallel variables, and that together these factors would explain the association between trauma exposure and anxiety in youth.

2. Methods

2.1. Participants

Participants were children and their mothers recruited in two groups; the war-exposed group included families living in the same frontline neighborhoods in Sderot and exposed to repeated war-related trauma and the control group included families living in comparable towns in central Israel who were screened for other trauma. In the initial stage, 232 families of children aged 1.5–5 years ($M = 2.76$, $SD = 0.91$) were recruited, of whom 47.6% were males and 47.1% firstborns. The control group matched the research group in age, sex, socioeconomic status as well as mother's age and education (see Feldman and Vengrober, 2011).

In the current stage of this study we revisited 111 children and their mothers from the initial cohort. Attrition was mainly related to inability to locate the families or families moving out of Sderot. No demographic differences were found between families who did or did not participate in the current stage in terms of child's age, gender, family income, and maternal education. At the current stage, children were in early adolescence ($M = 11.66$, $SD = 1.23$) and the sample included 44 males and 67 females (see Table 1 for demographic comparison). The study was approved by the local Institutional Review Board and all parents signed informed consent.

2.2. Procedures

Mothers and children arrived to lab and visits lasted approximately 4 h and included neuropsychological, physiological and behavioral procedures. Upon arrival, saliva sample were collected (T1), and

Table 1
Comparisons between groups in main demographic variables.

| | Control | Exposed | t/χ^2 | Effect size (Cohen's d/Φ) |
|--------------------------------|-------------------------|-------------------------|---------------------------------|---------------------------------|
| Gender | | | | |
| Female | 36 (67.9%) | 31 (53.4%) | $\chi^2_{(1)} = 2.42, p > 0.05$ | 0.15 |
| Child Age | M = 11.55 (SD = 1.14) | M = 11.76 (SD = 1.31) | $t_{(107)} = 0.90, p > 0.05$ | 0.17 |
| Mother age | M = 41.26 (SD = 4.40) | M = 40.06 (SD = 5.81) | $t_{(109)} = -1.22, p > 0.05$ | 0.23 |
| Mother education | | | | |
| High school education | 9 (17.0%) | 18 (31.0%) | $\chi^2_{(1)} = 2.97, p > 0.05$ | 0.16 |
| Above high school | 44 (83.0%) | 40 (69.0%) | | |
| Maternal marital status | | | | |
| Married | 49 (92.5%) | 56 (96.6%) | $\chi^2_{(1)} = 0.91, p > 0.05$ | 0.09 |
| SES (1-9) | M = 4.52 (SD = 1.42) | M = 4.13 (SD = 1.02) | $t_{(107)} = -1.66, p > 0.05$ | 0.31 |

following, mothers and children played together for 7 min using an "Etch a Sketch". This is a game where mother and child each controls one of two knobs that enable the drawing of either vertical or horizontal lines. Dyads need to coordinate their activity to create a drawing. Ten min after the joint task, a second saliva sample was collected (T2). At this point, mother and child separated and completed different tasks. At the end of the session, a final salivary sample was collected (T3, 1.5 h from T2).

2.3. Measures

2.3.1. Mother-child interactions

Interactions were coded using our well-validated Coding Interactive Behavior Manual (CIB) (Feldman, 1998). The CIB is a global rating system including multiple scales each rated from 1 to 5 that are integrated into theoretically-meaningful constructs. The CIB has been validated in multiple studies across numerous cultures, ages, and psychopathologies with good psychometric properties (for review: Feldman, 2012b). Two constructs were used here: *Maternal supportive style* included the codes of maternal positive affect, acknowledgement of child communication, creative involvement, and enthusiastic, energetic focus. *Child social collaboration*, included scales addressing the child's positive affect, compliance and regulation, involvement, and frustration tolerance.

2.3.2. Anxiety symptoms

Children's anxiety level was evaluated using the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997). We used two source of information: mother-report and the child's self-report, as it was previously found that this combination is more reliable for assessment of child psychopathology (Kendall and Flannery-Schroeder, 1998) and a mean score of the two informants total anxiety score was used in the current analysis.

2.3.3. Samples collection

Salivary samples from mother and child were collected at 3 time-points during the visit (upon arrival, 10 min after the interaction and before departure - see Supplementary Tables 1 and 2 for additional information), by passive drool. In order to precipitate the mucus, samples underwent three freeze-thaw cycles, freeze at -70°C and thaw at 4°C . After the fourth cycle the tubes were centrifuged twice at $1500 \times g$ (4000 rpm) for 20 min. Supernatants collected and the aliquots stored at -20°C until assayed.

2.3.4. S-IgA

Determination of s-IgA was performed, using a commercial s-IgA ELISA kit (EUROIMMUN AG; Luebeck, Germany). The kit provides a quantitative in vitro assay for s-IgA in human saliva. On the assay day, all samples were thawed completely, and s-IgA levels were measured according to the kit's instructions. Samples preparation was performed by Freedom-Evo (Tecan Group, LTD.) an automatic liquid handler, and

Table 2

Means and standard errors for main study variables.

| | Control | | Exposed | |
|----------------------------|--------------|------------|--------------|------------|
| | M | SeM | M | SeM |
| s-IgA Mother (AUCg) | 4,652,669.31 | 303,084.00 | 5,738,277.77 | 407,457.97 |
| s-IgA Child (AUCg) | 5,050,087.17 | 267,197.43 | 6,205,578.57 | 36,0168.56 |
| CT Mother (AUCg) | 444,457.92 | 23,022.35 | 524,648.70 | 30,854.26 |
| CT Child (AUCg) | 403,598.43 | 27,094.48 | 489,153.55 | 29,724.70 |
| Maternal Supportive Style | 3.73 | 0.13 | 3.18 | 0.12 |
| Child Social Collaboration | 4.02 | 0.09 | 3.64 | 0.14 |
| Anxiety Symptoms | 18.60 | 1.07 | 22.25 | 1.37 |

the readings and calculations were conducted by Magellan V.7 software (Tecan Austria GmbH). The intra-assay coefficient of samples and controls was 5.7%, and inter-assay coefficients for samples and controls were less than 10.83%.

2.3.5. Cortisol

The concentration of CT was determined by using a commercial ELISA kit (Salimetrics, USA). Measurements performed according to the kit's instructions. In addition to the manufacture low and high controls: 1060 ± 270 , 9700 ± 2430 pg/ml, three in-house controls were included in each plate (250, 900, 1200 pg/ml), thus to correlate between plates measured in different periods. Concentration of CT calculated by using MatLab-7 according to relevant standard curves. The intra-assay coefficient of variance of manufacture and in-house controls low and high range controls was 7.54%. The inter-assay coefficient of variance of samples was 16.11%.

2.4. Statistical analysis

Consistent with prior research, CT and s-IgA were measured by computing area under the curve with respect to the ground (AUCg; Pruessner et al., 2003), to accurately assess total overall production. *T*-tests were used to compare study variables between exposed and controls. Next, Pearson correlations assessed relationships between study variables. Finally, for a comprehensive model on the direct and mediated paths leading from war-exposure to anxiety symptoms as mediated by mother and child biomarkers and behavior, we conducted a path analysis using lavaan 0.5–23.1097 package (Rosseel, 2012) in R 3.4.4 (R Core Team, 2014; RStudio, 2015). The model was conducted controlling for time of saliva collection. Path analysis was based on maximum likelihood estimations and the following indicators were used to evaluate the model fit: chi-square values, and their degrees of freedom and p-values, with good fit indexed by non-significant values; root mean square error of approximation (RMSEA), values that are < 0.06 are considered to indicate a good fit; comparative fit index (CFI), and Tucker-Lewis index (TLI), values > 0.95 are considered to indicate a

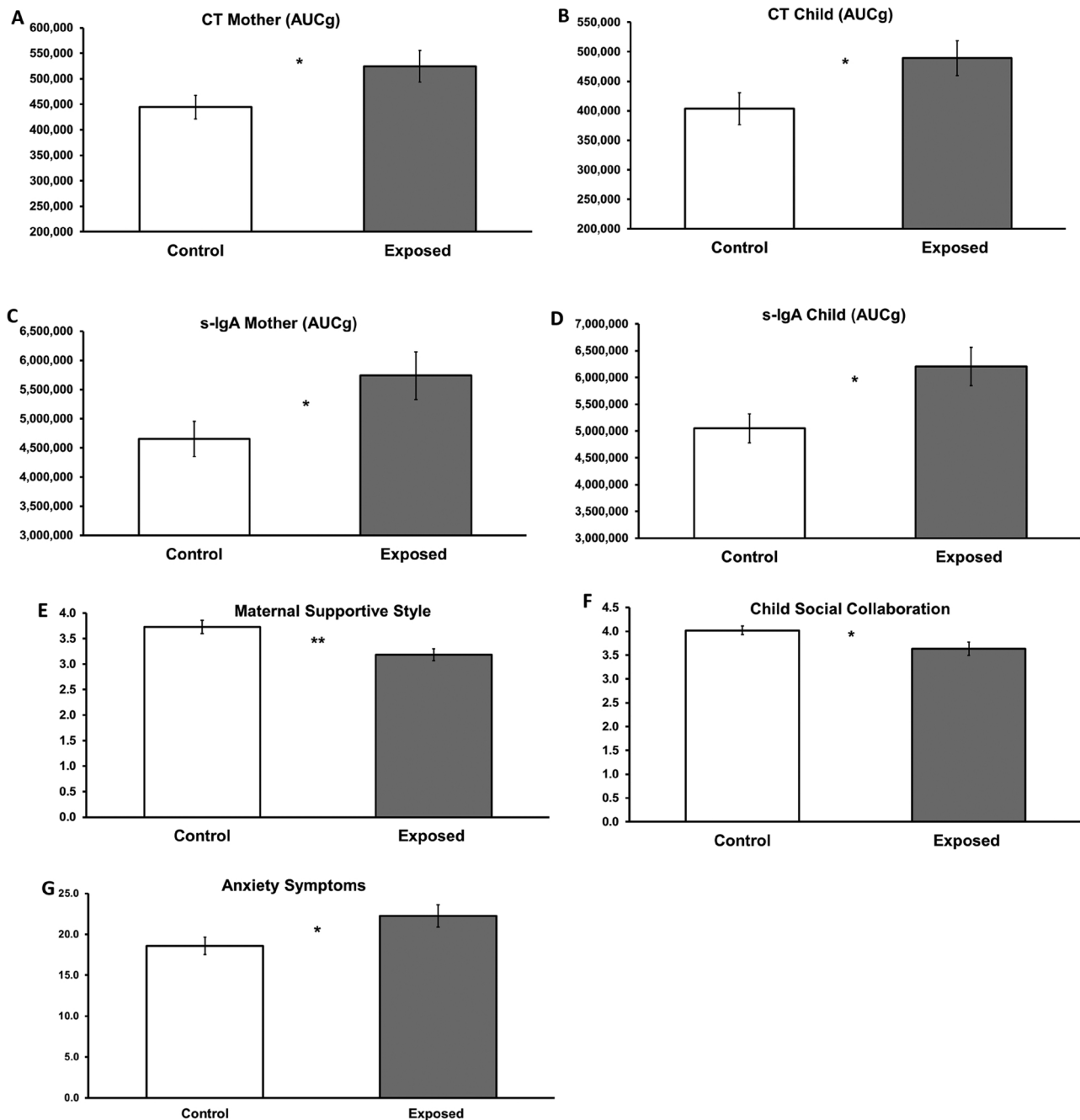


Fig. 1. Differences between groups in study variables.

Note: Mothers in the exposed group had significantly higher levels of cortisol (CT) ($t_{(90)} = -2.07, p < .05$, Cohen's $d = .43$) and secretory immunoglobulin A (s-IgA) ($t_{(91)} = -2.12, p < .05$, Cohen's $d = .44$), and lower levels of maternal supportive style ($t_{(98)} = 3.10, p < .01$, Cohen's $d = .62$). Similarly, children in the exposed group had significantly higher levels of CT ($t_{(84)} = -2.10, p < .05$, Cohen's $d = .46$), s-IgA ($t_{(88)} = -2.52, p < .05$, Cohen's $d = .54$), anxiety symptoms scores ($t_{(106)} = -2.06, p < .05$, Cohen's $d = .40$), and lower levels of child social collaboration ($t_{(92)} = 2.25, p < .05$, Cohen's $d = .47$). * $p < .05$, ** $p < .01$. Significant differences were examined using t-tests.

good fit (Hu and Bentler, 1999). To assess significance of the mediation effects, we used Hayes's (2013) procedure and calculated the 95% confidence intervals of 5000 bias-corrected and accelerated bootstrapping analyses (Hayes, 2013; MacKinnon et al., 2004). In cases where the value zero is not included in the confidence interval indicate a significant statistical effect at $\alpha < .05$.

3. Results

Visual examination of the distributions using density and q-q plots showed that all variables were normally-distributed. However, Jarque-

Bera test revealed that child social collaboration and anxiety symptoms scores were not normally distributed ($p < 0.05$) and these variables were log-transformed.

Differences between groups in study variables appear in Fig. 1 and Table 2. T-tests revealed that exposed mothers and children had significantly higher CT and s-IgA levels compared to controls and children displayed more anxiety symptoms. Notably, these differences remained significance even after controlling for mothers' anxiety (using STAI-T) and the time of measurements during the day ($p < 0.05$). Exposed mothers showed less supportive parenting and exposed children exhibited lower social collaboration.

Table 3
Pearson correlations of study variables.

| Variable | 1 | 2 | 3 | 4 | 5 | 6 |
|-------------------------------|--------|--------|-------|-------|-------|--------|
| 1. s-IgA Mother (AUCg) | | | | | | |
| 2. s-IgA Child (AUCg) | .32** | | | | | |
| 3. CT Mother (AUCg) | -.03 | .09 | | | | |
| 4. CT Child (AUCg) | .23 | 0.1 | .43** | | | |
| 5. Maternal Supportive Style | -.30** | -.19 | -.06 | -.14 | | |
| 6. Child Social Collaboration | -.23* | -.31** | -.23* | -.27* | .30** | |
| 7. Anxiety Symptoms | 0.19 | .23* | .21 | .29** | -.20* | -.31** |

* $p < .05$.
** $p < .01$.

Mothers' and children's CT, s-IgA and social behaviors were inter-related (Table 3). Elevated child's s-IgA and CT were associated with reduced social collaboration and more anxiety symptoms. Maternal s-IgA was associated with less collaborative parenting, and both maternal s-IgA and CT correlated with reduced child's collaboration. Anxiety symptoms correlated with less supportive parenting and child's collaboration.

Finally, we used path analysis to test our model on the role of mothers and children biomarkers and behaviors as mediating the link between war exposure and anxiety disorders (Fig. 2). The overall model provided good fit to the data $\chi^2_{(25)} = 18.18, p = .803, RMSEA = .000$ with lower 90% CI = .000 and higher 90% CI = .05 PCLOSE = .951, CFI = 1.00, TLI = 1.08.

We identified three parallel paths leading from war exposure to child anxiety and three additional converging paths.

- (a) *Mediation by immune function.* The first path linked war exposure with higher maternal s-IgA, which led to elevated child s-IgA levels leading to more anxiety symptoms. Test of mediation indicated that this indirect path was significant (95%CI = .003, .059).
- (b) *Mediation by HPA axis.* The second path linked exposure with increased maternal CT, correlating with higher child CT levels, similarly leading to more anxiety symptoms, and test of mediation was significant (95%CI = .003, .065).
- (c) *Mediation by maternal and child social behavior.* The third path considered social behaviors; exposure reduced the mother's

supportive parenting, leading to lower child social collaboration, and culminating in more anxiety disorders and test of mediation was significant (95%CI = .001, .041).

In addition, three junction paths were connected with the direct paths. First, direct path from exposure to child's s-IgA was added to the first path (95%CI = .001, .017). Second, increase in mothers' CT directly linked to lower child collaboration, which combined with the second path (95%CI = .001, .004). Finally, maternal s-IgA joined the third path, and the increase in maternal s-IgA levels was associated with decrease in both supportive parenting and child collaboration (95%CI = .000, .002).

4. Discussion

Childhood trauma has been defined as “an environmentally induced complex developmental disorder” (De Bellis and Zisk, 2014). Adapting a broad developmental neuroscience perspective that considers how multiple systems and relational patterns evolve over time to shape risk and resilience (Feldman, 2016, 2015) we examined the unique and joint contributions of stress and immune biomarkers and mother-child interactive patterns to adolescents' anxiety disorders in the context of chronic early trauma. Findings indicate that children exposed to war-related trauma exhibit significantly more anxiety disorders at the transition to adolescence. Such increased anxiety is accompanied by alterations in neuroendocrine and immune systems implicated in the stress response, lower parental support, and reduced social collaboration skills. Our results also underscore the critical role of the mother's stress and immune physiology and parenting behavior for the development of risk and resilience in the context of chronic trauma and show that maternal physiology and behavior mediate the effects of war on the child in a system-specific manner. Three mediated paths led from trauma exposure to anxiety symptoms; the first via activation of the HPA-axis, the second through immune stimulation, and the third comprised a behavioral effect of trauma on the dyadic relationship. Consistent with our *bio-behavioral synchrony* model (Feldman, 2012a, 2017), we found that the two biological paths interacted with the behavioral path to shape of risk and resilience trajectories in youth experiencing early life stress (Feldman, 2015).

Trauma-exposed children had elevated CT levels that correlated with their mothers' CT levels, and such endocrine coupling of maternal

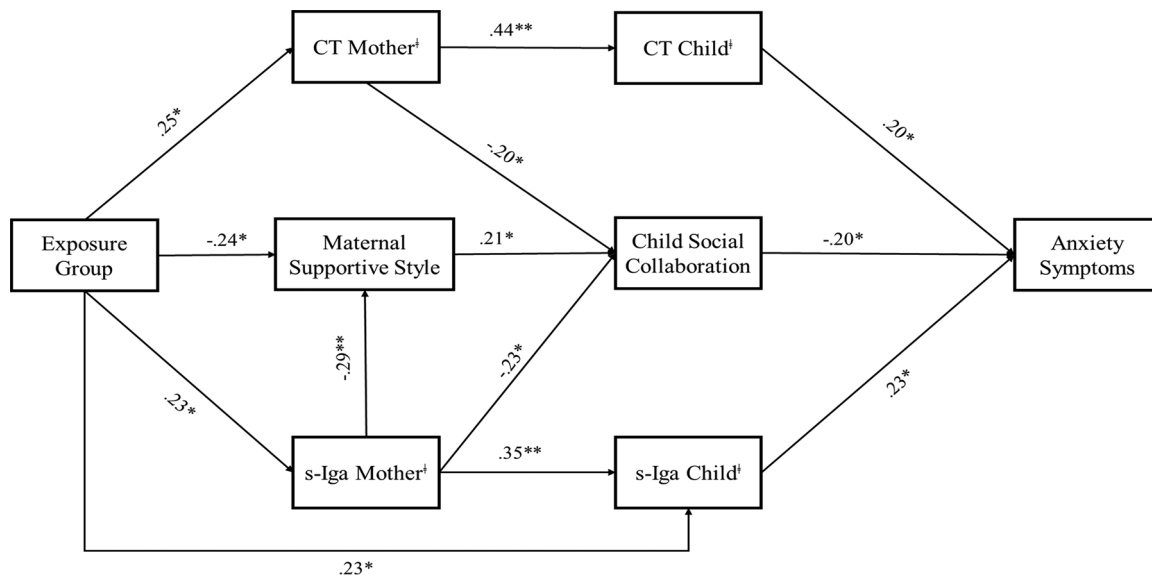


Fig. 2. Path-analysis linking exposure group with Anxiety Symptoms scores, with biomarkers and mother-child behaviors as mediators. Note: Coefficients represent standardized regression weights. The overall model provided an adequate fit to the data: $\chi^2_{(25)} = 18.18, p = .803, RMSEA = .000$ with lower 90% CI = .000 and higher 90% CI = .05 PCLOSE = .951, CFI = 1.00, TLI = 1.08. * $p < .05$, ** $p < .01$. † Controlling for time of the saliva measurements.

and child stress response is consistent with prior research and becomes particularly strong under conditions of early life stress, such as maternal depression (Halevi et al., 2017; Pratt et al., 2017). In combination, maternal and child's CT mediated the link between trauma exposure and anxiety symptoms. Augmented CT secretion in trauma-exposed children and adolescents has been previously reported (Carrion et al., 2002; Cicchetti et al., 2010; De Bellis and Zisk, 2014; Pfeffer et al., 2007), as well as the link between early stress exposure and anxiety outcomes (Heim and Nemeroff, 2001). Still, very few studies addressed the relations between CT and anxiety following trauma (for example Pfeffer et al., 2007). In general, levels of CT in individuals suffering anxiety disorders vary and depend on the specific anxiety disorder (Zorn et al., 2017). Our findings are consistent with research in adolescence that showed associations between anxiety problems and elevated CT levels (Schiefelbein and Susman, 2006), higher morning CT, and higher CT awakening response (Greaves-Lord et al., 2007). As such, our results indicate that greater HPA reactivity in mother and child charts one pathway of risk for the development of anxiety symptoms in the context of chronic early stress.

Authors suggest that behavioral and emotional reactivity to stress, as well as activity of the neurobiological systems that underlie stress responsiveness, increase at the transition to adolescence (Dahl and Gunnar, 2009). For instance, animal studies show that in contrast to adults, juvenile rats have a potentiated release of adrenocorticotrophic hormone and glucocorticoids after repeated exposure to stress (Romeo et al., 2006). In humans, adolescence is characterized by a sharp increase in the prevalence of affective psychopathology, particularly depression and anxiety (Paus et al., 2008), and the onset of such disorders is partially related to the stress associated with this developmental stage (Dahl and Gunnar, 2009). Adolescence-associated elevation in HPA reactivity may explain this heightened sensitivity to stress and psychopathology during this period (Lupien et al., 2009). Studies have shown that as adolescents get older their HPA axis activity increases following exposure to a public performance stressor (Gunnar et al., 2009; Stroud et al., 2009). Furthermore, in both animal and human studies adolescence is considered a time when the effects of early exposure to stress become evident (Lupien et al., 2009). Thus, the present trauma-related CT elevation may reflect the cumulative effects of earlier trauma exposure. Although there is no clear evidence that elevated CT levels are causally linked to anxiety, other components of the HPA axis, which are likely elevated in trauma-exposed children, have a causal effect on anxiety. For instance, studies in animal models demonstrate that chronic over-expression of corticotropin releasing hormone (CRH) in the amygdala induces elevated levels of anxiety (Keen-Rhinehart et al., 2009). Furthermore, CRH projections of the locus coeruleus also play an important causal role in mediating the effects of stress on anxiety (McCall et al., 2015) and future research should thus assess the role of CRH in mediating the effects of chronic early stress on anxiety in humans.

Levels of salivary s-IgA in trauma-exposed mothers and children were similarly elevated in comparison to controls and higher s-IgA was associated with more anxiety symptoms. This is consistent with ours (Ulmer-Yaniv et al., 2016, Ulmer-Yaniv et al., 2018) and others' studies (Laurent et al., 2015) demonstrating the effects of psychological stress on increased s-IgA. The relation between stress and s-IgA could be mediated, at least partly, by alterations in physical health and the presence of sub-clinical conditions in the exposed children that influence the overall functioning of the immune system, including s-IgA production (Bosch et al., 2002). Consistent with our findings, a prior study showed that childhood adversity resulted in failure of the adaptive immune system to control virus reactivation, leading to higher s-IgA levels to HSV (Shirtcliff et al., 2009). The global stress response includes activation of various immune processes that serve to prepare the organism for potential harm even before exposure to actual immune challenges (Segerstrom and Miller, 2004a, 2004b). Moreover, stress induces the production of danger signals that elevate those immune

functions that serve as first line of defense against pathogen invaders, such as inflammatory cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α), and s-IgA (Segerstrom and Miller, 2004a,b). Thus, in our sample it is possible that either actual immune challenges (such as the release of latent viruses from immune control) and/or preparatory responses to imminent danger led to increased inflammatory tone and elevated s-IgA. This possibility is supported by a prior study showing exaggerated interleukins 6 (IL-6) responses in adolescents exposed to chronic early stress (Elwenspoek et al., 2017) and by a recent meta-analysis reporting elevated IL-6 in adults with childhood trauma (Baumeister et al., 2016). The inflammatory responses and production of s-IgA may be causally related given that stress-induced alterations in the autonomic nervous system induce IgA secretion mediated by elevations in inflammatory cytokines, such as IL-6 (Bosch et al., 2002).

Our findings demonstrate associations between s-IgA and anxiety in the context of early trauma. A prior longitudinal study showed sharper slope of diurnal s-IgA changes in children with high versus low anxiety levels and longitudinal links between greater anxiety at age 9–12, higher s-IgA at age 12–15, and more anxiety at age 15–18, suggesting ongoing negative mutual influences of anxiety and s-IgA. It should be noted, however, that results on the associations of anxiety and s-IgA are mixed. Ma et al. (2018) found no significant correlation and Keller et al. (2010) similarly showed no correlation with self-reported anxiety, albeit this finding could be explained by the reluctance of adolescents to disclose their anxiety (Silverman and Ollendick, 2005). As such, in the current study we chose to utilize both maternal and child's report of the child's anxiety symptoms. In combination, these findings point to the dynamic developmental nature of s-IgA production (Ide et al., 2016) and its complex impact on anxiety symptoms, which requires much further research in various high-risk conditions.

The third path mediating the link between trauma exposure and youth anxiety described the relational behavior of mother and child. Specifically, trauma exposure was associated with less maternal sensitivity and support, which led to lower child social collaboration, culminating in heightened anxiety. The relationship between children and their primary caregiver is crucial for their well-being, particularly in context of chronic stress and trauma (Feldman et al., 2014; Scheering and Zeanah, 2001; Shaw, 2003). Mother-child adrenocortical and immune linkage, the coupling of maternal and child's CT and s-IgA, was high, consistent with prior research (Halevi et al., 2017; Ulmer-Yaniv et al., 2018) and maternal CT and s-IgA levels were associated not only with the respective biological variable in the child but also with the degree of child collaboration in the joint task. Overall, these findings underscore the multiple ways in which mothers shape their offspring's biological and behavioral adaptation to stress by signaling the amount of environmental danger via multiple physiological and social cues (Ruttle et al., 2011).

Limitations of this study include the lack of stress markers other than cortisol; still, cortisol is only one component in a complex interactive network implicated in the stress response. Similarly, s-IgA is only one component in the immune system and future studies should assess additional innate and adaptive immune parameters. Additionally, we did not include the time of military operations as a covariate, and have no specific data regarding the individuals' level of exposure. Another limitation concerns the lack of a detailed oral and overall health screening. It should be noted, however, that children's visit to the laboratory were cancelled in case of sickness of any kind. In sum, our study is the first, to our knowledge, to characterize the interactive influences of maternal stress and immune biomarker and observed maternal behavior to the development of risk and resilience in the context of chronic early trauma. Much future research and targeted interventions should take into account the important role of maternal physiology and behavior in shaping children's stress responses, mental and physical health across child development and specifically during periods of transition, such as the transition to adolescence.

Declaration of interest

Karen Yirmiya, Amir Djalovski, Shai Motsan, Orna Zagoory-Sharon and Ruth Feldman have no conflict of interest to declare.

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