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Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors

Amy Lehrner^{1,*}, Linda M. Bierer^{1,2}, Vincent Passarelli¹, Laura C. Pratchett^{1,2}, Janine D. Flory^{1,2}, Heather Bader¹, Iris R. Harris¹, Aarti Bedi¹, Nikolaos P. Daskalakis^{1,2}, Iouri Makotkine^{1,2}, and Rachel Yehuda^{1,2}

¹James J. Peters Veterans Affairs Medical Center, Bronx, New York

²Traumatic Stress Studies Division, Department of Psychiatry, Icahn School of Medicine at Mount Sinai

Abstract

Intergenerational effects of trauma have been observed clinically in a wide range of populations, and parental PTSD has been associated with an increased risk for psychopathology in offspring. In studies of Holocaust survivor offspring, parental PTSD, and particularly maternal PTSD, has been associated with increased risk for PTSD, low basal urinary cortisol excretion and enhanced cortisol suppression in response to dexamethasone. Such findings implicate maternally derived glucocorticoid programming in the intergenerational transmission of trauma-related consequences, potentially resulting from *in utero* influences or early life experiences. This study investigated the relative influence of Holocaust exposure and PTSD in mothers and fathers on glucocorticoid sensitivity in offspring. Eighty Holocaust offspring and 15 offspring of non-exposed Jewish parents completed evaluations and provided blood and urine samples. Glucocorticoid sensitivity was evaluated using the lysozyme suppression test (LST), an *in vitro* measure of glucocorticoid receptor sensitivity in a peripheral tissue, the dexamethasone suppression test (DST), and 24 hour urinary cortisol excretion. Maternal PTSD was associated with greater glucocorticoid sensitivity in offspring across all three measures of glucocorticoid function. An interaction of maternal and paternal PTSD on the DST and 24-hr urinary cortisol showed an effect of decreased glucocorticoid sensitivity in offspring with paternal, but not maternal, PTSD. Although indirect, these findings are consistent with the hypothesis that epigenetic programming may be involved in the intergenerational transmission of trauma-related effects on glucocorticoid regulation.

Keywords

PTSD; risk factor; glucocorticoid receptor; cortisol; dexamethasone suppression test; intergenerational; Holocaust; trauma

*Corresponding author: Amy Lehrner, PhD, Mental Health Care Center, James J. Peters Veterans Affairs Medical Center, 526 OOMH PTSD 116/A, 130 West Kingsbridge Road, Bronx, New York 10468 amy.lehrner@va.gov.

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The intergenerational transmission of the effects of trauma from survivors to their children has been observed primarily in populations in which the first generation was exposed to chronic and severe threat and horror such as occurred during the Holocaust, the Cambodian Khmer Rouge genocide, and the Israeli occupation of Gaza and the West Bank (Yehuda et al., 1998a; Field et al 2011; Palosaari et al., 2013). Transmission to offspring of trauma-related consequences or vulnerability following a single, acute trauma has also been noted (Yehuda et al., 2005; Chemtob et al., 2010). Parental posttraumatic stress disorder (PTSD) appears to be a salient factor in the transmission of at least some of these effects (Leen-Feldner et al., 2013). For example, the presence of PTSD in Holocaust exposed parents is associated with lower urinary cortisol excretion in non-exposed offspring (Yehuda et al., 2000; Yehuda et al., 2002). Parental PTSD and associated symptoms may affect caregiving behavior which shapes the early “environment” of the offspring (Yehuda et al., 2001; Zerach et al., 2012). Alternatively, it is possible that genetic risk factors that interact with trauma exposure to produce PTSD may be transmitted to offspring (Binder et al., 2008). In the former circumstance, maternal and paternal PTSD might have different effects on offspring as a result of distinct roles and involvement in childrearing. This would explain the previously observed finding that severity of maternal, but not paternal, PTSD symptoms was associated with Holocaust offspring PTSD (Yehuda et al., 1998b). Lower levels of cortisol and higher glucocorticoid responsiveness were also observed, primarily in relation to maternal PTSD (Yehuda, et al., 2008). Further, maternal psychopathology and early adverse experiences have been associated with glucocorticoid alterations (e.g., Essex et al., 2011; Azak et al., 2013). Taken together, these findings raise the possibility of underlying maternally derived epigenetic mechanisms. Such mechanisms are also suggested by findings from a cohort of babies born to mothers exposed to the 9/11 terrorist attacks during pregnancy. Low salivary cortisol was observed in babies of mothers who developed PTSD following exposure in the 2nd or 3rd trimester (Yehuda et al., 2005). Ostensibly, these mothers “transmitted” a tendency for low cortisol levels via *in utero* glucocorticoid programming. Importantly, the pattern of low cortisol excretion and increased HPA axis sensitivity noted in prior studies of offspring is similar to that observed in individuals with PTSD (Yehuda et al., 2007), and has been associated with increased risk for the development of PTSD in a recent, prospective study in a large military sample (van Zuiden et al., 2012).

While the influences of maternal behavior on offspring stress responsivity have been extensively studied in animal models (Champagne and Meaney, 2006; Mychasiuk et al., 2011), recent investigations also show paternal influences on offspring biology, leading to an increased interest in the differential impacts of maternal and paternal stress and PTSD-like behaviors on offspring in animal studies (e.g., Darnaudéry and Maccari, 2008). For example, paternal exposure to chronic variable stress in both adolescent and adult mice was associated with changes in sperm microRNA content resulting in reduced, rather than enhanced, HPA axis responsivity in offspring (Rodgers et al., 2013). Interestingly, chronic social defeat stress in male rats resulted in increased anxiety- and depression- like behavioral phenotypes and basal corticosterone levels in the offspring. However, *in vitro* fertilization experiments showed that this model of transgenerational transmission may not only involve the sperm (Dietz et al., 2011). Early postnatal paternal stress in rats has also been shown to affect offspring behavioral stress responses and DNA methylation patterns in brain tissue (Franklin et al., 2010). Understanding the mechanisms underlying the transmission of vulnerability from parent to child has important implications for the prevention and treatment of stress- and anxiety-related disorders.

The Lysosome Stimulation Test (LST) was developed to provide an *in vitro* measure of glucocorticoid receptor sensitivity in a peripheral tissue (Yehuda et al., 2004). The most

widely used clinical test of glucocorticoid sensitivity, the Dexamethasone Suppression Test (DST), measures the strength of negative feedback inhibition in the HPA axis following the oral ingestion of dexamethasone (DEX). However, as with any measure, the DST has some limitations. For example, the test is affected by the bioavailability of DEX (Guthrie, 1991), and depends on subject compliance with DEX ingestion (usually at home at a specific time) and timely arrival for blood drawing procedures 9 hours following ingestion. Furthermore, in non-clinical populations there can be a reluctance to ingest a “steroid” analogue.

Because glucocorticoids inhibit lysozyme activity, an *in vitro* administration of graded concentrations of DEX to peripheral blood mononuclear cells (PBMCs) can directly measure glucocorticoid responsiveness (i.e., the concentration at which lysozyme activity is diminished by 50%, or the IC_{50-DEX} value). IC_{50-DEX} has been robustly correlated with cortisol suppression as assessed by the DST (Yehuda et al., 2003), and lower IC_{50-DEX} values, indicating increased sensitivity, have been associated with PTSD in veterans (Yehuda et al., 2004). Enhanced sensitivity on the IC_{50-DEX} has also been associated with younger age of first trauma, indicating responsiveness to early environmental experiences (Yehuda et al., 2004).

The current study was designed to examine maternal versus paternal influences on glucocorticoid sensitivity in Holocaust offspring as assessed by the LST. Previous work with this population demonstrated an association between parental PTSD and enhanced glucocorticoid sensitivity demonstrated by the DST, indicating that offspring of Holocaust survivors with PTSD had greater cortisol suppression to DEX compared with demographically comparable controls (Yehuda et al., 2007). It was hypothesized that maternal PTSD would exert a stronger influence on offspring glucocorticoid sensitivity than paternal PTSD, and that maternal PTSD would associate with higher sensitivity in offspring. Because concurrent offspring symptomatology (i.e., anxiety and depression) can be related to HPA axis functioning, the influence of these symptoms on the results was examined. Finally, the role of childhood family environment (as retrospectively reported by offspring) on glucocorticoid sensitivity was evaluated to determine whether such factors account for the effects of parental PTSD.

Methods

Participants

The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine (MSSM), and all subjects provided written informed consent prior to participation. Participants were recruited through print and online advertisements in Jewish news outlets, second generation and other Jewish electronic mailing lists, advertisements at MSSM, and by word-of-mouth. Of the 120 participants recruited from 2010 through 2012, 94 were offspring of at least one Holocaust survivor and 26 were Jewish comparison subjects. 95 participants met eligibility criteria and completed at least one biological collection. Of these, 80 were offspring of at least one Holocaust survivor and 15 were Jewish comparison subjects. The sample contained 66 women and 29 men. Participants ranged from 23 to 68 years of age ($M \pm SD$; 56.6 ± 8.5). Table 1 provides descriptive information on the numbers of participants with maternal and paternal Holocaust exposure and PTSD. Parental Holocaust exposure was defined as being interned in a Nazi concentration camp, having witnessed or experienced torture, or having to flee for one's life or hide during the Nazi era. Comparison subjects were demographically similar (i.e., similar ages and gender distribution) adult biological children of Jewish parents who were not in Nazi-occupied Europe immediately before and during WWII. Exclusion criteria for all subjects included any history of psychotic disorder or bipolar illness, and significant current alcohol or drug use. Exclusion criteria for comparison subjects included parental PTSD as assessed by family history

interview. Medical information was obtained for all participants using a medical checklist and lab report of blood panels, with review by an M.D (LMB). Individuals were excluded from participation if they had a current major medical condition (e.g., lupus, cancer) or were taking oral or inhaled steroids, androgen, or spironolactone.

Clinical Evaluation

Axis I diagnoses were determined by doctoral level psychologists based on the Structured Clinical Interview for the DSM-IV (SCID; Spitzer et al., 1995). Parental PTSD was determined by consensus of at least three clinicians based on the Parental PTSD Questionnaire (PPQ), a Likert-type scale on which offspring rate Holocaust-survivor parents across the 17 DSM-IV PTSD criteria, as well as by clinical interview data from the offspring. The PPQ has been previously validated against independent diagnostic assessments of Holocaust survivors by clinicians (Yehuda et al., 2006). Participants also completed additional self-report measures assessing depression (Beck Depression Inventory, BDI; Beck et al., 1961), anxiety (Spielberger State Trait Anxiety Inventory, STAI; Spielberger, 1968), parental bonding (Parental Bonding Inventory, PBI; Parker, 1989) childhood abuse and neglect (Childhood Trauma Questionnaire, CTQ; Bernstein et al., 1997), and childhood family environment (e.g., family cohesion, expressiveness, conflict, organization, and control) (Family Environment Scale, FES; Moos & Moos, 1986)

Biological Assessment

Blood samples were obtained between 0800 h and 0830h on two consecutive mornings. The Day 1 blood was obtained for the measurement of plasma cortisol and extraction of PBMCs for determination of the lysozyme IC_{50-DEX} . The night before the Day 2 blood draw, participants ingested 0.5 mg of dexamethasone at 2300 h. Day 2 blood was measured for plasma cortisol and dexamethasone level in 90 participants (5 offspring declined to ingest DEX). Lysozyme activity was assessed in PBMCs following the *in vitro* administration of increasing concentrations of DEX to wells containing $3.5-4.0 \times 10^5$ cells (PBMCs). Procedures for the preparation of leukocytes and lysozyme activity assay were developed in our lab and have been previously described (Yehuda et al., 2003). In this cohort, IC_{50-DEX} was negatively associated with cortisol suppression following the low-dose DST, controlling for age, gender, DEX levels and BMI ($r=-0.23$, $df=81$, $p=.036$). For analysis of 24 hour urinary cortisol excretion, participants collected all urine for a 24 hour period in 2 liter polyethylene bottles kept in freezers in the participant's residence. Participants generally planned to stay home on collection days, and scheduled collection on days that were not expected to be particularly stressful or involve unusual activity. Completeness of collections was determined by history at the time of delivery of the urine collection, and by reference to urinary creatinine concentrations and total volume ($> 600ml$). 91 participants collected urine; 79 collections were deemed adequate for valid analysis of urinary cortisol. Day 1 and 2 plasma cortisol, post-DST dexamethasone, and urinary cortisol were determined by RIA. The intra- and inter-assay coefficients of variation were 2.3% and 6.1% for cortisol, 8.0% and 9.0% for dexamethasone, respectively.

Statistical Analyses

Offspring and comparison groups were compared using χ^2 tests for categorical descriptors and t-tests for continuous variables. Because not all Holocaust exposed parents developed PTSD, two dichotomous variables were created to indicate the presence or absence of maternal and paternal PTSD. The presence or absence of maternal and paternal Holocaust exposure was also denoted by two dichotomous variables. ANCOVA was used to compare groups with maternal and paternal PTSD (and their interaction) with respect to IC_{50-DEX} , cortisol suppression on the DST, and 24 hour urinary cortisol excretion, controlling for the

effects of maternal and paternal Holocaust exposure and covariates associated with the outcome variables. This approach differentiates the unique effects of maternal and paternal PTSD after controlling for Holocaust exposure. Bonferroni post hoc analyses were used to explore any significant main effects or interactions.

Analyses were also conducted to evaluate whether offspring clinical symptoms and diagnoses or indicators of childhood environment (i.e., exposure to childhood abuse, early family environment, or parental bonding) were independently associated with offspring IC_{50-DEX}. ANCOVA was used to test the relationships of dichotomous variables with offspring IC_{50-DEX}; regression was used for dimensional variables. In the event of a significant association with IC_{50-DEX}, this variable was included as a covariate in the primary ANCOVA analyses to determine if such a factor would attenuate the association between respective parental exposure and/or PTSD and glucocorticoid sensitivity. Given the gender imbalance in the sample and the large age range, as well as the known association of these variables with endocrine measures, age and gender were used as covariates in all analyses.

Results

Sample characteristics and comparisons between the offspring and control groups are reported in Table 2. The groups were not significantly different in age, gender, BMI or education. The offspring group was more likely than the comparison group to have a current anxiety disorder diagnosis and to report symptoms of depression and anxiety on self report measures. Offspring were also more likely to report more child abuse and neglect on the Childhood Trauma Questionnaire. Offspring had higher 24-hour urinary cortisol levels than controls. There were no group differences in IC_{50-DEX}, or in any baseline or post-DST measure of plasma cortisol or glucocorticoid sensitivity.

Glucocorticoid sensitivity and urinary cortisol

Maternal PTSD was associated with lower IC_{50-DEX}, indicative of higher glucocorticoid sensitivity, controlling for the effects of maternal and paternal Holocaust exposure, paternal PTSD, gender, and age ($F_{1,86}=5.98$, $p=.016$; see Fig 1A). Bonferroni post hoc analyses revealed that offspring with maternal PTSD have significantly lower IC_{50-DEX} than offspring with paternal PTSD in the absence of maternal PTSD. In addition, offspring with paternal PTSD only have significantly higher IC_{50-DEX} than offspring without any parental PTSD. The severity of maternal PTSD, as assessed by the number of maternal PTSD symptoms positively endorsed by Holocaust offspring on the PPQ, was also associated with lower levels of offspring IC_{50-DEX} in a regression analysis ($\beta = -.41$, $p=.006$), controlling for age and gender, while the number of paternal PTSD symptoms were not significantly associated with offspring IC_{50-DEX}.

There was an interaction of maternal and paternal PTSD on offspring cortisol suppression following ingestion of DEX, such that maternal PTSD appeared to moderate the effect of paternal PTSD. Offspring with paternal PTSD in the absence of maternal PTSD had the lowest percent suppression (69.57%), whereas the presence of PTSD in both parents was associated with the highest percent suppression (82.49%), controlling for maternal and paternal Holocaust exposure, DEX level, age, gender, and BMI ($F_{1,78}=4.82$, $p=.031$; see Fig 1B). Bonferroni post hoc analyses did not reveal any significant group differences. There was a similar interaction of maternal and paternal PTSD on offspring urinary cortisol levels, controlling for maternal and paternal Holocaust exposure, age gender, and BMI ($F_{1,70}=4.89$, $p=.030$). Bonferroni post hoc analyses revealed that offspring with paternal PTSD only had higher urinary cortisol levels than offspring with PTSD in both parents. Gender was a significant covariate, reflecting significantly higher levels of urinary cortisol in men ($M \pm SD$;

70.07±24.10) compared with women (50.22±23.19) ($t_{77}=3.42$, $p=.001$), but the study was not powered to further explore this effect.

Clinical Symptoms and Diagnoses

Clinician diagnosed depression and anxiety were not associated with offspring IC_{50-DEX} in an ANCOVA controlling for age and gender (F 's < 1.40, p 's > .24). Similarly, self-reported symptoms of depression or anxiety as assessed by the BDI and STAI were not significantly associated with offspring IC_{50-DEX} in a regression analysis, including age and gender as covariates. Because these analyses indicated that offspring psychopathology did not associate with IC_{50-DEX}, no further analyses were conducted.

Childhood environment

The effects of childhood abuse, parental bonding, and childhood family environment were also investigated for their potential to account for the effects of maternal and paternal PTSD on offspring endocrine measures. Of the five subscales assessed by the CTQ, emotional abuse had the highest maximum value and was the only scale directly correlated with IC_{50-DEX}. Emotional abuse was also positively associated with both maternal and paternal PTSD ($r=.301$, $p=.003$; $r=.318$, $p=.002$, respectively). In a regression analysis, emotional abuse was significantly associated with offspring IC_{50-DEX}, controlling for age and gender ($\beta=-.21$, $p=.044$). When emotional abuse was included in the primary ANCOVA that included parental PTSD and Holocaust exposure, the main effect of maternal PTSD on IC_{50-DEX} was unchanged ($F_{1,85}=4.81$, $p=.031$), and emotional abuse was a significant covariate ($F_{1,85}=4.39$, $p=.039$).

Maternal and paternal care and overprotection as assessed by the Parental Bonding Inventory were not significantly associated with offspring IC_{50-DEX} in a regression analysis that also included age and gender. In a separate regression analysis that included five measures of childhood family environment (family cohesion, expressiveness, conflict, organization, and control) as assessed by the FES, family conflict emerged as a significant correlate of IC_{50-DEX} ($\beta=-.29$, $p=.037$). When family conflict was included as a covariate in the ANCOVA including maternal and paternal PTSD and Holocaust exposure, the main effect of maternal PTSD was unchanged. Interestingly, family conflict was correlated with paternal, but not maternal, PTSD ($r=.36$, $p<.0005$).

Discussion

The major finding in this study is the demonstration of greater glucocorticoid sensitivity as indicated by both the LST and the DST, and lower urinary cortisol excretion in offspring, in association with maternal PTSD. Previous studies have demonstrated lower urinary cortisol levels in offspring in association with maternal PTSD (Yehuda et al., 2007b). Additionally, higher cortisol suppression in response to dexamethasone has been demonstrated in an independent cohort of Holocaust offspring in association with parental PTSD (Yehuda et al., 2007a). The current study used three unique measures of HPA axis function and tested specific contributions of maternal vs. paternal PTSD, controlling for respective parental Holocaust exposure. In all three measures, maternal PTSD was associated with increased glucocorticoid sensitivity in offspring. Furthermore, the results of the DST and 24-hr urinary cortisol excretion indicated an association with paternal PTSD in the opposite direction for offspring with paternal PTSD only, that is, of decreased sensitivity on the DST and increased 24-hr urinary cortisol excretion. Interestingly, when paternal PTSD was present in the context of maternal PTSD, offspring showed increased glucocorticoid sensitivity and diminished urinary cortisol, consistent with the effects observed in those with maternal

PTSD only. These findings contribute substantially to our understanding of intergenerational endocrine effects and are the first to differentiate between maternal and paternal influences.

The analyses were designed to evaluate effects of maternal and paternal PTSD, respectively, while controlling for effects of Holocaust exposure as well as PTSD in the other parent. Holocaust offspring represent a unique sample in which to evaluate intergenerational transmission of the effects of parental trauma exposure and PTSD, since Holocaust exposure did not depend on genetic, familial, or behavioral risk factors of the survivor. Moreover, the trauma itself was similar for both mothers and fathers when exposed. In this sample, a sufficient proportion of Holocaust survivors did not develop PTSD, allowing for a test of the effects of parental symptoms, rather than exposures, in mediating effects on offspring. Offspring clinical characteristics such as self-reported or clinician diagnosed depression or anxiety were not independently associated with IC₅₀-DEX, indicating that glucocorticoid receptor sensitivity was not simply a reflection of clinical state. When indicators of childhood family environment and parental bonding were analyzed, emotional abuse and family conflict emerged as potential moderators of the effects of parental PTSD on glucocorticoid sensitivity in offspring, although their inclusion in the model did not account fully for the main effect of maternal PTSD. Interestingly, family conflict was associated with the presence of paternal, rather than maternal, PTSD.

Although studies of HPA axis development have traditionally only investigated maternal influences, there is increasing evidence for paternal influences on offspring behavior, development, and HPA axis functioning (e.g., Essex et al., 2011; Mills-Koonce et al., 2011). Recently, opposite effects of paternal and maternal parenting on offspring cortisol variability in the context of genetic and prenatal risk factors have been observed in 4 year-old children in a longitudinal adoption study with normal (i.e., non-psychiatric or traumatized) parents (Marceau et al., 2013). In rodent models, paternal stress has been associated with higher corticosterone in offspring (Dietz et al., 2011), and paternal stress in adolescence or adulthood associated with reduced HPA axis responsivity (Rodgers et al., 2013). In the current study, paternal PTSD appears to exert differential effects depending on the maternal context. It is possible that fathers with PTSD express their symptoms differently when mothers are also symptomatic, contributing to an overall increase in conflict within the family. This conjecture is supported by the finding of an association of family conflict with paternal (but not maternal) PTSD. When mothers are more functional and less symptomatic, perhaps fathers with PTSD are more absent or withdrawn. It is also possible that mothers without their own PTSD are able to buffer the effects of paternal PTSD on their children, helping to contain or explain PTSD-related behaviors by fathers and to provide support. The findings of relative non-suppression on the DST and of higher urinary cortisol associated with paternal PTSD are consistent with the higher levels of IC₅₀-DEX observed in offspring with paternal PTSD, and with prior observations that paternal, but not maternal, PTSD is associated with the development of major depressive disorder (Yehuda et al., 2008), a disorder linked to higher glucocorticoid levels and reduced GR sensitivity (Holsboer, 2000). Clearly, the effects of paternal PTSD on offspring warrant further study.

To the extent that maternal PTSD results in an altered “environment” for offspring, the findings are suggestive of potential epigenetic influences on glucocorticoid receptor sensitivity (Yehuda et al., 2007b). This interpretation is supported by observations of similar interaction effects of maternal and paternal PTSD on offspring glucocorticoid receptor gene methylation (in preparation). That the effects of maternal and paternal PTSD were generally distinguishable, and in some cases in opposing directions, argues against genetic explanations for the observed findings in offspring as these would most likely confer effects in the same direction. That all three measures show similar results provides strong support for glucocorticoid programming as relevant to the observed effects in offspring. The

measures used each describe distinct aspects of HPA axis regulation, and are thus only modestly correlated. While the shared variance accounted for by the two tests of glucocorticoid sensitivity, the LST and DST, was smaller than previously reported in a healthy (non-psychiatric) sample (Yehuda et al., 2003), it was still significant, and importantly, maternal PTSD was associated with each of the three measures in this study. The association of IC₅₀-DEX with emotional abuse in childhood also replicates a similar association between IC₅₀-DEX and childhood trauma in a sample of combat veterans (Yehuda et al., 2004), and suggests that this measure is a relevant indicator of developmental history, consistent with glucocorticoid programming.

The effects of maternal and paternal PTSD on the offspring's early environment can be wide-ranging, including altered attachment and parenting behaviors that can influence early glucocorticoid receptor programming (Kappeler and Meaney, 2010). Variation in maternal care in rodents results in epigenetic modifications of genes regulating HPA axis activity in offspring (Liu et al., 1997; Weaver et al., 2004). However, the question remains whether there are even earlier origins of glucocorticoid programming than post-natal parenting influences. Maternal transmission of the effects of trauma might result from *in utero* exposure to high levels of glucocorticoids during vulnerable periods of fetal development, or from pre-conception stress-induced alterations in oocytes (Drake and Seckl, 2011). In the current sample, offspring were born either after liberation or after parents had escaped to safety, with the majority born approximately a decade thereafter. This was to ensure that the exposure to *in utero* effects reflected post-war symptoms or adjustment rather than direct war-related influences such as prolonged starvation or physical life threat. The effects of paternal stress exposure on offspring in animal models have been primarily attributed to pre-conception influences on gamete development (Franklin and Mansuy, 2010; Franklin et al., 2010; Rodgers et al., 2013). However, paternal effects may also influence *in utero* and postnatal offspring environments (Dietz et al., 2011; Yehuda, 2011).

Because the majority of offspring (63%) had two Holocaust survivor parents, and because among the survivors the mothers had higher rates of PTSD (66%) than the fathers (53%), this study is limited by the relatively smaller number of offspring with *only* paternal PTSD. Nonetheless, a significant interaction of maternal and paternal PTSD showing opposite directional effects on the DST and urinary cortisol was observed, but requires replication. Despite the disproportionate number of female participants, including gender as a covariate did not significantly change the results for IC₅₀-DEX or cortisol suppression on the DST. Gender was a significant correlate of urinary cortisol. We did not hypothesize differences according to offspring gender, and such differences should be investigated in future research designed and powered to investigate the effects of parental PTSD on male versus female offspring.

The findings of this study are significant because they contribute to a small but emerging literature on parental contributions to offspring biology and psychology in clinical samples. This line of research is important because of its potential to highlight potential epigenetic, molecular and behavioral mechanisms associated with enduring, and even intergenerational, effects of stress. Future investigations should focus on the assessment of epigenetic processes such as DNA methylation or histone acetylation affecting expression of glucocorticoid or other related genes, as well as the possibility of sex-linked genetic influences that might explain the differences observed in offspring attributable to maternal vs. paternal effects.

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Offspring Glucocorticoid Sensitivity

Figure 1.

A. Mean IC₅₀-DEX values for offspring based on the presence or absence of maternal and paternal PTSD, controlling for parental Holocaust exposure, gender, and age ($F_{1,86}=5.98$, $p=.016$). Error bars represent standard errors.

B. Mean percent suppression of cortisol in offspring following the low-dose (.05mg) DST based on the presence or absence of maternal and paternal PTSD, controlling for parental Holocaust exposure, DEX level, age, gender, and BMI ($F_{1,78}=4.82$, $p=.031$). Error bars represent standard errors.

Table 1
Rates of maternal versus paternal Holocaust exposure and PTSD

	PTSD			
	None	Maternal Only	Paternal Only	Both Parents
None	15	-	-	-
				15 (15.8%)
Holocaust Exposure	Maternal Only	1	7	0
				1*
				9 (9.5%)
	Paternal Only	4	0	7
				11 (11.6%)
Both Parents	11	15	4	30
				60 (63.2%)
Total	31 (32.6%)	22 (23.2%)	11 (11.6%)	31 (32.6%)
				95 (100%)

* Note: there is one father unexposed to the Holocaust with PTSD as a result of combat experience in WWII.

Table 2
Characteristics of Offspring and Control Groups

	Offspring n=80 M± SD or %	Comparison N=15 M± SD or %	t(df)p or χ^2 (df) p	
Age	56.20 ± 7.89	58.67 ± 11.19	<i>t</i> (93)=1.0	<i>p</i> = <i>ns</i>
Gender	F=57, M=23	F=9, M=6	χ^2 (1)=0.75	<i>p</i> = <i>ns</i>
BMI	26.18 ± 4.95	27.54 ± 4.99	<i>t</i> (93)=-0.97	<i>p</i> = <i>ns</i>
Years of Education	17.49 ± 2.48	18.20 ± 2.37	<i>t</i> (93)=-1.03	<i>p</i> = <i>ns</i>
BDI	11.88 ± 8.25	7.0 ± 3.12	<i>t</i> (93)=-3.98	<i>p</i> =.000
STAI	42.45 ± 22.45	28.17 ± 11.99	<i>t</i> (91)=-3.58	<i>p</i> =.001
MDD	5 (5.4%)	0 (0%)	χ^2 (1)=1.02	<i>p</i> =.59
Anxiety disorder	39 (41.1%)	3 (3.2%)	χ^2 (1)=4.57	<i>p</i> =.03
CTQ Total	8.34 ± 2.52	6.77 ± 1.93	<i>t</i> (92)=-2.28	<i>p</i> =.025
CTQ Emotional Abuse	2.27 ± 1.00	1.61 ± .75	<i>t</i> (93)=-2.95	<i>p</i> =.007
FES Conflict	29.01 ± 7.30	26.62 ± 4.65	<i>t</i> (91)=-1.61	<i>p</i> =.12
24 hr urinary cortisol	n=66 58.63 ± 25.23	n=13 42.66 ± 19.68	<i>t</i> (77)=2.15	<i>p</i> =.035

Abbreviations: BMI, body mass index; BDI, Beck Depression Inventory; STAI, State/Trait Anxiety Inventory total score; MDD, clinician diagnosis of current Major Depressive Disorder; Anxiety disorder, clinician diagnosis of current Axis I anxiety disorder; CTQ, Childhood Trauma Questionnaire; FES conflict, Family Environment Scale conflict subscale