ORIGINAL ARTICLE

Affiliation buffers stress: cumulative genetic risk in oxytocin–vasopressin genes combines with early caregiving to predict PTSD in war-exposed young children

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Research indicates that risk for post-traumatic stress disorder (PTSD) is shaped by the interaction between genetic vulnerability and early caregiving experiences; yet, caregiving has typically been assessed by adult retrospective accounts. Here, we employed a prospective longitudinal design with real-time observations of early caregiving combined with assessment of genetic liability along the axis of vasopressin–oxytocin (OT) gene pathways to test G × E contributions to PTSD. Participants were 232 young Israeli children (1.5–5 years) and their parents, including 148 living in zones of continuous war and 84 controls. A cumulative genetic risk factor was computed for each family member by summing five risk alleles across three genes (OXTR, CD38 and AVPR1a) previously associated with psychopathology, sociality and caregiving. Child PTSD was diagnosed and mother–child interactions were observed in multiple contexts. In middle childhood (7–8 years), child psychopathology was re-evaluated. War exposure increased propensity to develop Axis-I disorder by threefold: 60% of exposed children displayed a psychiatric disorder by middle childhood and 62% of those showed several comorbid disorders. On the other hand, maternal sensitive support reduced risk for psychopathology. G × E effect was found for child genetic risk: in the context of war exposure, greater genetic risk on the vasopressin–OT pathway increased propensity for psychopathology. Among exposed children, chronicity of PTSD from early to middle childhood was related to higher child, maternal and paternal genetic risk, low maternal support and greater initial avoidance symptoms. Child avoidance was predicted by low maternal support and reduced mother–child reciprocity. These findings underscore the saliency of both genetic and behavioral facets of the human affiliation system in shaping vulnerability to PTSD as well as providing an underlying mechanism of post-traumatic resilience.

INTRODUCTION

Exposure to trauma, especially when lengthy, repeated and potentially lethal, contributes to the development of post-traumatic stress disorder (PTSD) in some individuals but not in others and identifying those with greater vulnerability or resilience is among the central goals of PTSD research.[1–3] Repeated exposure to traumatic events during the first years of life, when critical brain structures are maturing, carries an even greater risk for psychopathology.[4–6] Research has demonstrated genetic involvement in PTSD and suggests that similar to most complex behavioral disorders, risk for PTSD is likely determined by the interaction of genetic dispositions and early caregiving experiences.[7–11] Yet, characterization of the early environment has been poorly assessed and typically relies on adult recollection of caregiving, accounts often colored by current mental state. To move the study of G × E interaction in the etiology of PTSD forward, there is a need to integrate features of the rearing environment with genetic vulnerability focused on key neurobiological systems that underpin affiliative and attachment behavior. Such research may be most fruitful if conducted prospectively beginning in early childhood and combining real-time assessments of parenting with genetic biomarkers of parents and child.

However, to date, no study has integrated genetic liability with direct observations of parent–child relatedness toward further understanding of post-traumatic risk and resilience.

Research detailing the pervasive effects of early caregiving on PTSD in children and adults provides evidence for the critical role of parenting in shaping vulnerability for PTSD throughout life and implicates genetic and epigenetic mechanisms in these effects.[12–15] These studies lend support to the notion that affiliation and its underlying neurobiology may be the key elements in understanding the etiology of PTSD. Specifically, since oxytocin (OT) and vasopressin have been shown to have a crucial role in affiliative behaviors in both animals and humans,[16–20] it is reasonable to test biomarkers in this peptidergic neural path for vulnerability to PTSD. Such neurogenetic analysis may offer unique insights on the disorder and, importantly, suggest new directions for targeted and personalized pharmacotherapy.[21,22] OT, a nine amino-acid neuropeptide, provides the neurohormonal substrate for mammalian social bonding and has been implicated in human parental care, empathy and critical sociocognitive processes impaired in PTSD.[16–20] Several single-nucleotide polymorphisms (SNPs) on the OT receptor gene (OXTR), including rs53576, rs2254298 and

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rs1042778 have been associated with lower parental sensitivity and parent–child reciprocity[23–25] and with disorders involving social dysfunctions, such as autism, depression and schizophrenia.[26–28] In addition, *CD38*, an ectoenzyme that mediates the release of OT from hypothalamic neurons through the mobilization of calcium, supports mammalian affiliation, and the CC genotype on the CD38 rs3796863 SNP has been linked with risk for autism and lower parent–child reciprocity.[23,24,29] Vasopressin (AVP), a structurally related neuropeptide to OT, is similarly involved in mammalian bonding and territorial behavior, and variability in a promoter region repeat polymorphism in *AVPR1A* is associated with decreased maternal behavior[30] and social–emotional deficits.[18] Recent studies demonstrate that cumulative genetic risk, an index computed by combining several SNPs in the *OXTR* gene associated with social dysfunction, provides a better risk estimate than each SNP alone.[31] Cumulative genetic risk on the *OXTR* and *CD38* genes has been found to have a role in the cross-generation transfer of children's social reciprocity,[24] and family studies show contribution of both parental and child *OXTR* and *AVPR1A* in autism.[32] These studies suggest that computing a combined risk index using information for all three genes (*OXTR*, *CD38* and *AVPR1a*) and assessing such index in mother, father and child may provide an informative indicator of PTSD vulnerability and resiliency. This notion is consistent with recent conceptualization on the importance of building cumulative genetic risk indicators in the study of psychopathology and wellness.[33]

The current study aimed to address the issue of risk and resilience in PTSD by utilizing a prospective longitudinal design beginning in early childhood and integrating a gene-by-environment model with ethologically based behavioral approach. We examined the role of the human affiliation system in PTSD and calculated a cumulative risk index for each family member by combining five risk alleles on the *OXTR*, *CD38* and *AVPR1a* genes previously linked with social and attachment deficits.[16,18] Genetic risk was complemented by ecological observations of parent–child interactions in multiple contexts. War-exposed young children (1.5–5 years) were recruited from Sderot, Israel, located 10 km from the Gaza border (34 formap) during a period of continuous missile attacks and followed into middle childhood in comparison with non-exposed controls. Such setting provides a 'natural experiment' to study G × E effects in the etiology of PTSD: it describes a singular setting where the source of trauma is identical across participants whereas genetic dispositions and caregiving experiences are used to differentiate those who did or did not develop PTSD.

Four hypotheses were proposed. First, repeated trauma exposure during the first years of life will markedly increase child's propensity to develop psychiatric disorder by middle childhood. Second, children experiencing less supportive parenting will be more susceptible to develop psychiatric disorders in middle childhood. Third, G × E effect will emerge, with child genetic risk interacting with early trauma exposure to increase risk for psychopathology. Finally, among exposed children, chronicity of PTSD will be related to both genetic risk and parenting so that greater genetic risk and less supportive parenting will differentiate children with chronic PTSD from those whose early PTSD has recovered by middle childhood. Similarly, for exposed children, we further examined the contribution of genetic risk and parenting to child symptomatology in the four post-traumatic symptom clusters in young children: re-experiencing, avoidance, hyperarousal, fears-and-aggressions as well as to the degree of developmental regression.

MATERIALS AND METHODS

Detailed methods appear in Supplementary Material, and briefly described here:

Participants

At time 1 (early childhood:1.5–5 years), 232 children and their parents participated ($M = 33.08$ months, s.d. = 10.89), including 47.6% males and 47.1% firstborns. War-exposed group included 148 families from Sderot, Israel, located 10 km from the Gaza border (Supplementary Figure 1). During this period (2005–2008), Sderot citizens were exposed to repeated rocket attacks, had only 15 s to enter protected spaces after sirens and were exposed to frequent mortar shelling with no sirens. Eighty-four children were recruited from comparable non-exposed towns in the Tel-Aviv area. Controls matched the exposed group in age, gender, birth-order, maternal and paternal age and education and maternal employment and marital status. The study was approved by the Institutional Review Board and parents signed informed consent.

At time 2 (middle childhood: 7–8 years), 210 families were revisited ($M = 92.15$ months, s.d. = 8.36).

Procedure

Time 1: Psychiatric Interview. Child PTSD was evaluated by maternal interview and direct observations using the diagnostic classification: Zero-to-Three[34] a validated system using DSM-IV criteria for children under 5.[35,36] Maternal interview was conducted while child was present and mother and child were videotaped for later coding. Interview elicited detailed information on trauma exposure, specific symptoms and developmental regression. Following, mothers completed the Child Post-Traumatic Symptoms Scale, which includes 58 symptoms in the four PTSD symptom categories at this age: re-experiencing, avoidance, hyperarousal, fears-and-aggression, and assesses developmental regression with good reliability and validity.[37] PTSD was diagnosed in 56 (37.8%) exposed young children.

Mother–child free play

Ten minutes of mother–child free play was filmed.

Table 1. Genotypes on the *OXTR*, *CD38*, and *AVPR1a* genes included in the Cumulative Genetic Risk Index

	Genotype		Prevalence of high-risk genotype		
	High risk	Low risk	Child	Mother	Father
OXTR rs1042778	TT	GG, GT	11.5%	7.7%	8.1%
OXTR rs2254298	GG	AA, AG	42.6%	43.0%	41.8%
OXTR rs53576	AA, AG	GG	44.3%	44.4%	40.0%
CD38 rs3796863	CC	AA, AC	33.6%	32.8%	37.4%
AVPR1A RS3	327 bp[a]	Non-327	22.6%	14.5%	20.4%
Cumulative risk mean (s.d.)			1.56 (1.18)	1.42 (1.10)	1.56 (1.09)
Correlations			Child–mother: $r = 0.53$***	Child–father, $r = 0.42$***	Mother–father: $r = 0.19$**

Note: cumulative genetic risk is computed for each family member by combining the number of high-risk genotypes on each of the five single-nucleotide polymorphisms. **$P < 0.01$, ***$P < 0.001$. [a]At least one 327-bp repeat.

DNA collection

Genotyping. DNA of mother, father and child was extracted from 20 ml of mouthwash samples using Master Pure kit (Epicentre, Madison WI, USA). Genotyping of *OXTR*, *CD38* and *AVPR1A* is described elsewhere[23–27,30,31] and Supplementary Materials. A cumulative genetic risk factor was computed for each individual by summing the number of genetic risk variations associated with psychiatric risk or social difficulties (Table 1). These included the *OXTR* rs1042778 TT genotype, associated with greater risk for autism[26] and lower empathy in healthy adults;[38] *OXTR* rs2254298 GG genotype, associated with smaller amygdala volume in two independent samples[39,40] and risk for major depression;[27] the A allele (AA or AG) on the *OXTR*rs53576, related to risk for autism,[41] lower empathy[42] and non-optimal parenting;[25] the CC genotype on the *CD38* rs3796863, linked with greater risk for autism in two independent samples[43,44] and non-optimal parenting;[23,24] and the 327 bp allele on the *AVPR1A* RS3, associated with lower altruism and non-optimal mothering.[30,45,46] Risk scores ranged from 0 (no risk) to 5 (risk on all five SNPs).

Time 2: The Development and Well-Being Assessment includes structured interview and questionnaire that generates ICD-10 and DSM-IV diagnoses in children 4–16 years.[47] The Development and Well-Being Assessment is well validated, including large epidemiological study in Israel.[48]

Behavior coding

Trauma evocation and play sessions were coded with the Coding Interactive Behavior (CIB) Manual,[49] a well-validated rating system for adult–child interactions that include multiple codes aggregated into theoretically meaningful composites. The CIB has been validated universally with good psychometric properties.[50] Coding was conducted by two trained coders blind to other information with reliability, performed on 20% of the sample, averaged, intraclass $r = 0.94$.

Maternal support during trauma evocation

The mother's supportive style during the evocation of traumatic experiences describes the mother's stress-regulating style during moments of distress, a parental style long known as the central marker of secure attachment.[51] The construct included the following scales: attention to child's verbal and nonverbal signals, acknowledging child's emotions and stressful expression, mother provides supportive presence to child's experiences, competence in regulating child's distress, mother expresses a wide affective range and mother provides affectionate touch (alpha = 0.89).

Dyadic reciprocity during free play

The *Dyadic Social Reciprocity* construct, a central component of the parent–child synchronous style in early childhood, was used. The construct includes the following scales: give-and-receive reciprocity, mutual adaptation and fluency, (alpha = 0.89). Social reciprocity describes the synchronous maternal style, a central component of growth-promoting mothering in the preschool years, which has shown individual stability in two longitudinal samples from infancy to adolescence and predicts social–emotional competencies.[52,53]

Statistical analysis

The entire sample of war-exposed and control families was used to test the first three hypotheses, whereas the fourth hypothesis was tested on the war-exposed group only. The first hypothesis that war-exposed children were more likely to develop psychiatric disorders, was tested with χ^2 analysis. To examine the first three hypotheses: that war exposure would increase child's propensity for psychopathology, that sensitive parenting would decrease risk for psychopathology and that genetic risk would interact with war exposure (G × E) to predict risk for psychiatric disorders, we conducted a hierarchical ordinal regression. Significant interactions were probed using Hayes'[54] approach. Heteroscedasticity was examined using Breusch–Pagan and the Koenker tests and corrected by the Heteroscedasticity-Consistent method[55] and normal distribution was determined by the Kolmogorov–Smirnov test and Lilliefors Significance Correction. We tested the fourth hypothesis, using multivariate analyses of variance (MANOVAs), and examined differences in (a) genetic risk and (b) parenting behavior between exposed children with chronic PTSD versus those whose early PTSD has recovered by middle childhood. Following the

MANOVA analysis, hierarchical regressions predicted PTSD symptomatology and developmental regression from cumulative genetic risk and parenting in exposed children.

RESULTS

Distributions of psychiatric disorders in war-exposed and control children

War exposure increased child's propensity to receive psychiatric diagnosis *by* threefold. Among war-exposed children, 60.3% received Axis-I diagnosis by middle childhood, compared with only 20.2% among controls, $X^2 = 43.92$, $P < 0.001$. In addition to PTSD, exposed children were more likely to suffer anxiety disorders, conduct disorders and ADHD (Figure 1). Among diagnosed war-exposed children, 38.1% had one disorder, 33.3% two disorders, 22.6% three disorders and 6% four or more comorbid disorders. Comorbidity was higher in exposed, compared with control children, $X^2 = 27.66$, $P < 0.001$.

Exposure, genetic risk and parenting effects in child psychiatric disorders

Unstandardized ordinal regression coefficients and odd ratios for predicting the propensity for child Axis-I diagnosis are presented in Table 2 and Supplementary Table 1. Results indicate that the likelihood of war-exposed children to receive Axis-I disorder diagnoses was significantly greater than controls. Maternal support decreased the likelihood of child psychopathology: one-point increase in maternal support was linked with 39% decrease in the propensity for child Axis-I diagnosis. These findings support our first two hypotheses (Figures 2a and b). Finally, an exposure x child's genetic risk interaction emerged (Figure 2c, Supplementary Figure 1). Among the exposed group, one-point increase in child's cumulative genetic risk was linked with 77% increase in the likelihood of Axis-I disorder ($b = 0.55$, $\exp(b) = 1.77$, $P < 0.01$). Conversely, among the non-exposed group, child's cumulative genetic risk was unrelated to child's disorder. This G × E effect confirms our third hypothesis.

Chronicity versus recovery of PTSD in war-exposed children

Of the trauma-exposed children, 56 were diagnosed with PTSD in early childhood. Of these, 23 maintained the diagnosis in middle childhood (41%), 33 remitted (58%) and two were not seen at follow-up. MANOVA conducted for the chronic versus recovered PTSD children on genetic risk of mother, father and child revealed an overall effect of genetic risk, Wilks' $F(3,50) = 7.63$, $P = 0.001$,
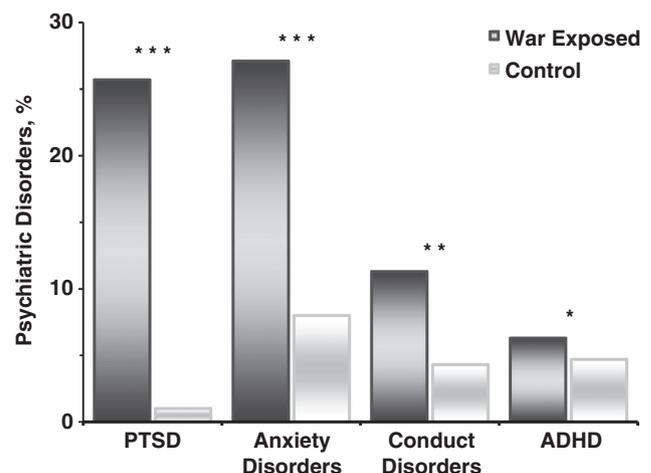

Figure 1. Prevalence of psychiatric disorders in war-exposed and control children. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 2. Unstandardized ordinal regression coefficients and odd ratios predicting propensity for child Axis-I psychiatric disorder

	Axis-I psychiatric diagnosis	
	b	Exp (b)
Exposure group	0.75***	2.12
Child's cumulative risk	0.22	1.24
Father's cumulative risk	0.06	1.06
Mother's cumulative risk	0.28	1.32
Mother–child reciprocity	0.06	1.06
Maternal support	−0.50*	0.61
Exposure group x child's cumulative risk	0.35*	1.42
Exposure group x reciprocity	0.13	1.13
Exposure group x maternal support	−0.17	0.84
Child's cumulative risk x reciprocity	0.30	1.35
Child's cumulative risk x maternal support	0.10	1.11
Exposure group x child's cumulative risk x reciprocity	−0.15	0.87
Exposure group x child's cumulative risk x maternal support	0.03	1.03
	$R^2 = 24.3\%$	

Note: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; exp(b) are odd ratios; R^2 refers to Cox and Snell's pseudo R^2.

Figure 2. Trauma exposure, supportive parenting and cumulative genetic risk on the vasopressin–oxytocin pathway in relation to child psychopathology in middle childhood. Proportions of children-Please provide he displaying Axis-I disorders in (**a**) war-exposed and control children (**b**) children experiencing high versus low maternal support in early childhood and (**c**) war-exposed and control children with high and low genetic risk. **$P < 0.01$, ***$P < 0.001$.

effect size (ES) = 0.23. Univariate tests showed that child genetic risk, $F(1,50) = 21.24$, $P < 0.001$, ES = 0.21, mother genetic risk, $F(1,50) = 12.76$, $P < 0.001$, ES = 0.15, and father genetic risk, $F(1,50) = 4.33$, $P < 0.05$, ES = 0.06, were each significantly higher in the chronic as compared with the recovered PTSD children (Figure 3). A similar MANOVA conducted for the two parenting behaviors, maternal support and mother–child reciprocity, showed an overall main effect: Wilks' $F(2,51) = 6.45$, $P = 0.004$, ES = 0.15. Univariate tests showed a significant effect for maternal support, $F(1,51) = 12.83$, $P = 0.003$, ES = 0.16 but not for reciprocity (Figure 3). These results confirm our fourth hypothesis.

In addition, we tested whether children with chronic PTSD had more symptoms in the various symptom clusters and whether they showed a greater developmental regression in early childhood compared with recovered children. Children with chronic PTSD had initially more avoidance, $F(1,53) = 28.81$, $P < 0.001$ and fears-and-aggression, $F(1,53) = 21.21$, $P < 0.001$, symptoms and showed greater developmental regression, $F(1,53) = 17.92$, $P < 0.001$, in early childhood than remitted children.

Predicting PTSD symptomatology in war-exposed children

Hierarchical regression predicted child's post-traumatic symptomatology and developmental regression from genetic risk and parenting behavior among the war-exposed group. Standardized regression coefficients are presented in Supplementary Table 2. Results indicate that higher maternal support predicted lower avoidance and hyperarousal symptoms. Greater mother–child reciprocity was independently predictive of lower avoidance symptoms. Finally, mother's cumulative genetic risk was associated with more developmental regression.

DISCUSSION

Our study, among the first to follow trauma-exposed children from infancy to middle childhood, indicates that lengthy exposure to war-related trauma increased the prevalence of child psychopathology by threefold: 60% of children growing up in zones of continuous political violence received an Axis-I diagnosis by middle childhood and 62% of those diagnosed had more than
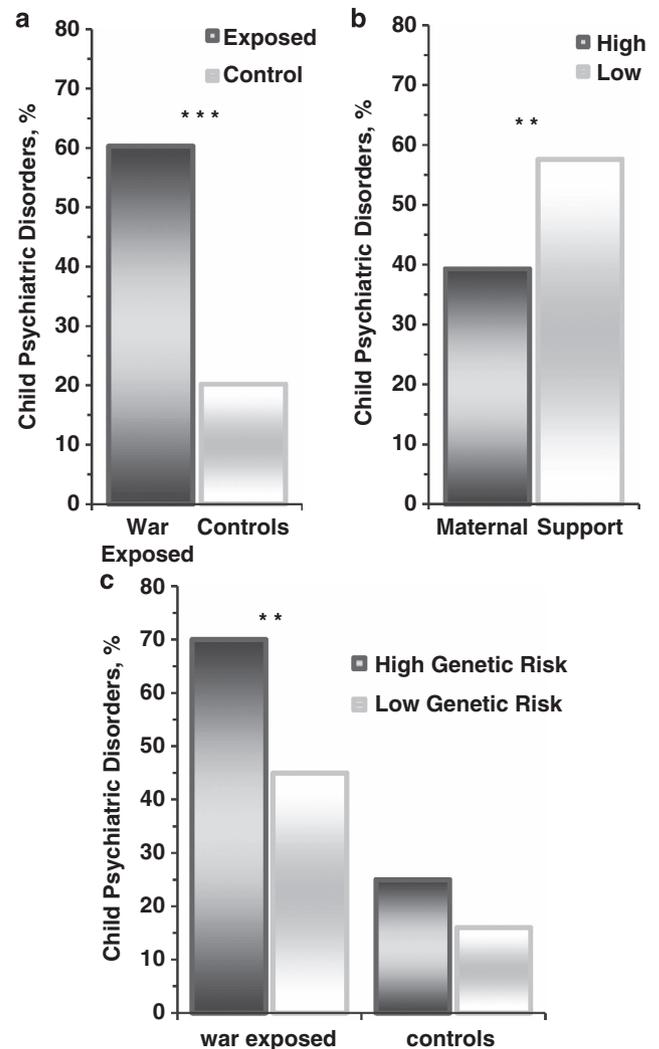
one disorder. Such high incidence of psychopathology was noted even when follow-up took place during a period of relative calm. As millions of the world's children are growing up amidst armed conflict, racial or tribal violence or repeated terror attacks, these data should raise much concern regarding their future well-being. However, although considerable psychopathology is observed following trauma exposure, not all children are equally vulnerable to such stressors. Importantly, our findings are first to demonstrate the involvement of both biological (OT–vasopressin genotype) and behavioral (sensitive caregiving) facets of the human affiliative system in contributing to differential sensitivity to developing PTSD. We computed a genetic risk index that combines for each individual the cumulative risk alleles from some of the most researched genetic biomarkers on the extended OT neuropathway.[16] We found that in the context of early and persistent exposure to trauma, greater child genetic risk increased the propensity to develop psychiatric disorder by middle childhood, demonstrating for the first time G×E effect for the OT–vasopressin neuropathway in high-risk children. In addition, maternal sensitive support during moments of stress, considered
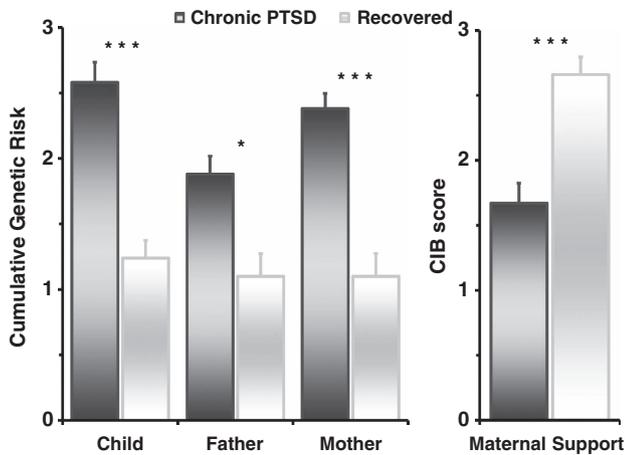
Figure 3. Cumulative genetic risk in mother, father and child and supportive parenting in children with chronic versus recovered PTSD. Chronic PTSD was observed in 23 children (41%) who received PTSD diagnosis in both early childhood (1.5–5 years) and middle childhood (7–8 years). Recovered PTSD was observed in 33 children (58%) whose initial PTSD diagnosis was remitted by middle childhood. $*P < 0.05$, $***P < 0.001$.

the central behavioral marker of secure attachment,[51] was associated with resilience. Maternal support generally reduced the risk for developing psychopathology and among trauma-exposed children supportive parenting differentiated children with chronic PTSD from those whose early PTSD has remitted by middle childhood.

Until recently, it was thought that young children lack the cognitive mechanisms to understand, memorize or coherently describe overwhelming experiences, and that the formal diagnosis of PTSD is inappropriate at this age.[56] However, more recent studies showed that young children display a clear and detectable PTSD constellation following traumatic events, such as hurricane Katrina, the 9/11 attack, domestic violence, motor vehicle accidents or war-related trauma.[34–37,57,58] These authors also argued for a more behavior-based approach in diagnosing childhood PTSD, substituting observations of behavior during trauma evocation for memorized accounts and adding a fears-and-aggression symptom cluster as an important index of the young child's expression of horror. Using such behavioral approach, we found that 62% of young children with PTSD retain their diagnosis in middle childhood when external conditions were calmer with only occasional reminders. In the one study assessing PTSD longitudinally in children exposed to the Beslan terror attack, the authors reported low spontaneous recovery.[59] Our findings similarly show that 41% of children diagnosed with PTSD retained their diagnosis 2–3 years later and moreover highlight the joint genetic and parenting contributions to PTSD chronicity. Children with chronic PTSD had higher genetic risk than those who recovered and greater genetic risk was also observed for their mothers and fathers. In addition, these children received caregiving characterized by minimal maternal support during moments of stress. It is thus possible that children showing chronic PTSD were growing up in what we suggest is a 'dysfunctional OT environment', evidenced by the high genetic risk in mother, father and child. Furthermore, children developing chronic PTSD initially showed higher avoidance and fears symptoms. These findings are consistent with research in young adults that found that initial avoidance symptoms predicted PTSD chronicity.[60] The current results help define the group at highest risk among trauma-exposed children and are especially important for identifying those most in need for intervention. The results also spotlight a particular neural pathway that may be a worthwhile target for future drug therapy.

OT and vasopressin are the central biological players of the human affiliation system, without which attachment bonds and the unique form of human sociality could not have evolved.[16–20] Importantly, the extended OT system is bio-behavioral in essence. Infant brain OT is shaped through patterns of maternal care and is highly epigenetic.[61] OT receptors are widely distributed throughout the body and brain; the system maintains coordination with the hypothalamic-pituitary-adrenal axis, reward and immune systems; and OT shows online response to moments of stress or to expressions of sensitive caregiving.[18] Our findings implicating such bio-behavioral system in the etiology of PTSD emphasize the need to adapt a complex, dynamic, cross-generational G×E perspective. Our findings further suggest that it is important to build attachment-based interventions for trauma-exposed young children, perhaps in combination with OT administration, that include social behaviors known to induce OT, such as social gaze, physical proximity or reciprocal exchanges. Such interventions should be combined with teaching caregivers to provide a soothing presence to downregulate child arousal during moments of stress or utilize reciprocity to diminish avoidance.

Our findings highlight the critical role of human attachment, in terms of both affiliative biology and attachment behavior, in risk and resilience for PTSD. To date, most research on the underlying mechanisms in PTSD examined threat-rated processes, including fear conditioning, habituation and extinction.[62] It has been argued that such narrow focus cannot encompass the broad post-traumatic phenotype or address the psychobiology of resilience or even post-traumatic growth.[1,2] Notably, the current findings underscore attachment as one potential mechanism in post-traumatic resilience. The mother's supportive containment of the child's stress during trauma reminders, a central component of secure maternal–child attachment, emerged as a critical maternal style, associated with child propensity for psychopathology, chronicity of PTSD and severity of avoidance symptoms. Animal studies underscore the essential role of the mother's physical presence and online responsivity for downregulating stress, shaping hypothalamic-pituitary-adrenal neurocircuitry and building arousal-modulating mechanisms.[61,63] These diverse findings are consistent with research showing that PTSD is associated with inability to detect and respond to safety signals[64] and suggest that uncontained mothering combined with early trauma may have a casual role in the disorder. Greater mother–child social reciprocity enables children to rework traumatic experiences through give-and-receive social exchanges and was found to predict lower avoidance, a critical factor in PTSD chronicity. Finally, the differential effects of OT on war-exposed versus non-exposed children accord with 'differential susceptibility' models, which suggest that children at genetic risk are more susceptible to their environments,[65] and extend these models to include the vasopressin–OT neuropathways. It thus appears that supportive parenting is especially critical for children with dysfunctional OT system who are growing up in environments of continuous trauma.

Limitations of the study relate to the need for longer follow-up in order to prospectively examine effects of the rearing environment on PTSD in adolescence and young adulthood. For a fuller attachment-based study, father–child and child–peers interactions should have also been included. The OT system interacts with other neurobiological systems, including the reward, hypothalamic-pituitary-adrenal and immune systems and assessing these would have given a fuller picture. Overall, our results contribute to understanding PTSD by adding a behavior focus to a largely mentally based disorder, highlighting attachment processes lacking from most PTSD research and advocating a resilience rather than a risk-based focus. As current studies on PTSD attempt to integrate findings from human and animal studies,[1,3] our behavior-based approach may provide mid-point between animal models and the self-report methodology of PTSD

research to include ecological contexts, daily routines and nonverbal patterns for broader understanding of PTSD and toward targeted novel interventions. It has been suggested that pharmacological and behavioral therapies for PTSD have come to an impasse, leaving many patients without a clear road to recovery.[66,67] The current findings, pointing to deficits in the extended OT system in PTSD, may lead to new pharmacological treatments, possibly in combination with behavioral therapies. Finally, further research is required to understand how extended periods of war impact children's brains, endocrinological systems and the epigenome. Much needs to be learned about how repeated traumatic events experienced in early childhood coalesce into a full-blown disorder. Such research may inform the construction of novel interventions to assist the millions of war-exposed children growing up around the world for the sake of both the suffering families and our future society.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)