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

R Feldman1,2, A Vengrober1 and RP Ebstein3

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–oxygen (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.

Keywords: gene-by-environment; mother-child relationship; oxytocin; PTSD; vasopressin

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...
rs1042778 have been associated with lower parental sensitivity and parent–child reciprocity, and with disorders involving social dysfunctions, such as autism, depression and schizophrenia. 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. 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 and social-emotional deficits. 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. 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, and family studies show contribution of both parental and child OXTR and AVPR1A in autism. 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.

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. 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 (Supplementary Figure 1) during a period of continuous missile attacks and followed into middle childhood in 10 km from the Gaza border (34 formap) during a period of child interactions in multiple contexts. War-exposed young children are 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).

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

| Genotype | Prevalence of high-risk genotype |
|----------|---------------------------------|
|          | Child | Mother | Father |
| OXTR rs1042778 | High risk | Low risk |                   |
| TT | 11.5% | 7.7% | 8.1% |
| GG | 42.0% | 43.0% | 41.8% |
| AA, AG | 44.3% | 44.4% | 40.0% |
| OXTR rs2254298 | AA, AC | CC | Non-327 |
| 327 bp* | 33.6% | 32.8% | 37.4% |
| CD38 rs3796863 | 22.6% | 14.5% | 20.4% |
| AVPR1A RS3 | 1.56 (1.18) | 1.42 (1.10) | 1.56 (1.09) |
| Correlations | Child–mother: | Child–father: | Mother–father: |
| r = 0.53*** | r = 0.42*** | 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. 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 elsewhere23–27,30,31 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 autism45 and lower empathy in healthy adults;18 OXTR rs2254298 GG genotype, associated with smaller amygdala volume in two independent samples39,40 and risk for major depression;27 the A allele (AA or AG) on the OXTR rs53576, related to risk for autism,45 lower empathy46 and non-optimal parenting;22 the CC genotype on the CD38 rs2796863, linked with greater risk for autism in two independent samples52,53 and non-optimal parenting;23,24 and the 327 bp allele on the AVPR1A R53, associated with lower altruism and non-optimal mothering.39,45,46 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.57 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,69 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.15 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.71 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 χ² 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 Approach. Heteroscedasticity was examined using Breusch–Pagan and the Koenker tests and corrected by the Heteroscedasticity-Consistent method 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, χ² = 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, χ² = 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, **
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 markers 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

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    | 0.26 | 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   |

Note: *P < 0.05, **P < 0.01, ***P < 0.001; exp(b) are odd ratios; R² refers to Cox and Snell’s pseudo R².

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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} 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.\textsuperscript{57} It has been argued that such narrow focus cannot encompass the broad post-traumatic biology of resilient address the psychological and even post-traumatic growth.\textsuperscript{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 responsibility for downregulating stress, shaping hypothalamic-pituitary-adrenal neurocircuitry and building arousal-modulating mechanisms.\textsuperscript{61,63} These diverse findings are consistent with research showing that PTSD is associated with inability to detect and respond to safety signals\textsuperscript{64} and suggest that uncontained mothering combined with early trauma may have a causal 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\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.

**ACKNOWLEDGMENTS**

This study was supported by NARSAD independent investigator award to RF.

**REFERENCES**

1. Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: A critical review. Prog Brain Res 2008; 167: 151–168.
2. Layne CM, Warren JS, Watson PJ, Shalev AY. Risk, vulnerability, resistance, and resilience: toward an integrative conceptualization of post-traumatic adaptation. In: Friedman MJ, Keane TM (eds). Handbook of PTSD. Guilford: New York, NY, USA, 2007, pp 497–520.
3. Daskalakis NP, Yehuda R, Diamond DM. Animal models in translational studies of PTSD. Psychoneuroendocrinology 2013; 38: 1895–1911.
4. Lataster J, Myin-Germeys I, Lieb R, Wittchen HU, van Os J. Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. Acta Psychiatr Scand 2012; 125: 388–399.
5. Dannlowski U, Stuhmann A, Beutelmann V, Zwanzer P, Lenzen T, Grotegerd D et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatry 2012; 71: 286–293.
6. Fairbank JA, Putnam FW, Harris WW. The prevalence and impact of child traumatic stress. In: Friedman MJ, Keane TM, Resick PA (eds). Handbook of PTSD. Guilford: New York, NY, USA, 2007, pp 229–251.
7. Pitman RK, Rasmussen AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci 2013; 13: 769–787.
8. Mehta D, Binder EB. Gene x environment vulnerability factors for PTSD: the HPA axis. Neuropharmacology 2012; 62: 654–662.
9. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am J Psychiatry 2002; 159: 1675–1681.
10. Gillespie CF, Pfifer J, Bradley B, Ressler KJ. Risk and resilience: genetic and environmental influences on development of the stress response. Depression Anxiety 2009; 26: 984–992.
11. Broekman BF, Off M, Boer F. The genetic background to PTSD. Neurosci Biobehav Rev 2007; 31: 948–963.
12. Kaplow JB, Saxe GN, Putnam FW, Pyneos RS, Lieberman AF. The long-term consequences of early childhood trauma: a case study and discussion. Psychiatry 2006; 69: 362–375.
13. Mehta D, Klenget T, Conneely KN, Smith AK, Altmann A, Pace TW et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. Proc Natl Acad Sci USA 2013; 110: 8302–8307.
14. Perroud N, Paoloni-Giacobino A, Prada P, Olié E, Saltmann M, Nicoara R et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Transl Psychiatry 2011; 1: e59.
15. Zovick IB, Sweatt JD. Epigenetic mechanisms in learned fear: implications for PTSD. Neuropsychopharmacology 2013; 38: 77–93.
16. Ebstein RP, Knafo A, Mankuta D, Chew SH, Lai PS. The contributions of oxytocin and vasopressin pathways to human behavior. Horm Behav 2012; 61: 359–79.
17. Ross HE, Young LJ. Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front Neuroendocrinol 2009; 30: 534–547.
18. Feldman R. Oxytocin and social affiliation in humans. Horm Behav 2012; 61: 380–391.
19. Insel TR. The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. Neuron 2010; 65: 768–79.
20. Carter CS. Oxytocin pathways and the evolution of human behavior. Annu Rev Psychol 2013; 65: 17–39.
21. Off M, Langeland W, Witteveen A, Denys D. A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder. CNS Spectr 2010; 15: 522–530.
22. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci 2011; 12: 524–538.
23. Feldman R, Zagoory-Sharon O, Weisman O, Schneidman I, Gordon I, Mazo R et al. Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. Biol Psychiatry 2012; 72: 175–181.
24. Feldman R, Gordon I, Influs M, Gutirriz T, Ebstein RP. Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity. Neuropsychopharmacology 2013; 38: 1154–1162.
25. Bakermans-Kranenburg MJ, Van Uzendoom MH. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Soc Cog Affect Neurosci 2008; 3: 128–134.
26. Lerer E, Levi S, Salomon S, Darvasi A, Yirmiya N, Ebstein RP. Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. Mol Psychiatry 2008; 13: 980–988.
27. Aptar-Levi Y, Feldman M, Vakart A, Ebstein RP, Feldman R. Impact of maternal depression across the first six years of life on the child's mental health, social engagement, and empathy: The moderating role of oxytocin. Am J Psychiatry 2013; 170: 1161–1168.
28. Montag C, Brockmann EM, Bayerl M, Rujescu D, Müller DJ, Gallint J. Oxytocin and oxytocin receptor gene polymorphisms and risk for schizophrenia: a case-control study. World J Biol Psychiatry 2013; 14: 500–508.
29. Higashida H, Yokoyama S, Kikuchi M, Munesue T. CD38 and its role in oxytocin secretion and social behavior. Horm Behav 2012; 61: 351–358.
30. Avinun R, Ebstein RP, Knafo A. Human mental behavior is associated with arginine vasopressin receptor 1 A gene. Biol Lett 2012; 8: 894–896.
31. Schneidman I, Kanat-Maymon Y, Ebstein RP, Feldman R. Cumulative risk on the oxytocin receptor gene (OXTR) underpins empathic communication difficulties at the first stages of romantic love. Soc Cog Affect Neurosci 2013 (e-pub ahead of print).
32. Israel S, Lerer E, Shalev I, Uzevovsky F, Reibold M, Bachner-Melman R et al. Molecular genetic studies of the arginine vasopressin 1a receptor (AVPVR1a) and the oxytocin receptor (OXTR) in human behaviour: from autism to altruism with some notes in between. Prog Brain Res 2008; 170: 435–449.
33. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry 2009; 14: 746–754.
34. Zero To Three. Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood: Revised Edition (dc:0-3r). Zero to Three Press: Washington, DC, USA, 2005.
35. Chu AF, Lieberman AF. Clinical implications of traumatic stress from birth to age five. Annu Rev Clin Psychol 2010; 6: 469–494.
36. Scheeringa MS, Zeanah CH, Cohen JA. PTSD in children and adolescents: toward an empirically based algorithm. Depression Anxiety 2011; 28: 770–782.
37. Feldman R, Vengrober A. Post-traumatic stress disorder in infants and young children exposed to war-related trauma. J Am Acad Child Adolesc Psychiatry 2011; 50: 654–658.
38. Wu N, Li Z, Su Y. The association between oxytocin receptor gene polymorphism (OXTR) and trait empathy. J Affect Disord 2012; 138: 468–472.
39. Furman DJ, Chen MC, Gotlib IH. Variant in oxytocin receptor gene (OXTR) underpines empathic communication difficulties at the first stages of romantic love. Soc Cog Affect Neurosci 2013 (e-pub ahead of print).
40. Israel S, Lerer E, Shalev I, Uzevovsky F, Reibold M, Bachner-Melman R et al. Molecular genetic studies of the arginine vasopressin 1a receptor (AVPVR1a) and the oxytocin receptor (OXTR) in human behaviour: from autism to altruism with some notes in between. Prog Brain Res 2008; 170: 435–449.
41. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry 2009; 14: 746–754.
42. Zero To Three. Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood: Revised Edition (dc:0-3r). Zero to Three Press: Washington, DC, USA, 2005.
43. Chu AF, Lieberman AF. Clinical implications of traumatic stress from birth to age five. Annu Rev Clin Psychol 2010; 6: 469–494.
