

## NEWS AND COMMENTARY

## Preventive Treatment in Stress-Related Disorders

## Countering posttraumatic LHPA activation in refugee mothers and their infants

E Ullmann<sup>1,2</sup>, SR Bornstein<sup>2,3</sup>, RS Lanzman<sup>4</sup>, C Kirschbaum<sup>5</sup>, S Sierau<sup>1</sup>, M Doehner<sup>1</sup>, P Zimmermann<sup>6</sup>, H Kindler<sup>7</sup>, M Schauer<sup>8</sup>, M Ruf-Leuschner<sup>8</sup>, JM Fegert<sup>9</sup>, K von Klitzing<sup>1</sup> and U Ziegenhain<sup>9</sup>

*Molecular Psychiatry* (2018) **23**, 2–5; doi:10.1038/mp.2017.235; published online 14 November 2017

During the recent wave of refugees, Germany was one of the primary host countries, particularly for families with infants and toddlers. In 2016, 722,370 first-time Visa applications were submitted. Of those, 11% (78,192) were submitted for children younger than 4 years of age. However, public authorities were not fully prepared to accommodate and provide medical and psychological care for this large number of refugee families. After cases of violence against women and children, an Independent Commissioner for Issues of Sexual Child Abuse by the Federal Government issued a checklist of minimum standards for the protection of children in refugee shelters. This checklist aided operators to systematically introduce protective measures for children (for example, personnel standards, spatial standards such as separate living areas for families and sanitary areas separated by gender). These guidelines highlight the need for better accommodations; however, infants of refugee families in Germany are still an understudied and underserved group.<sup>1</sup> Although refugee families are highly diverse, recent research revealed a high prevalence of clinically relevant symptoms (for example, depressiveness or psychosis) in adult refugees.<sup>2</sup> In particular, trauma and stressor-related disorders are prevalent in subjects recently relocated to Germany.<sup>2,3</sup> Since a considerable number of these adults are parents, these data imply an elevated developmental risk for their infants.<sup>4</sup> International data support this view, since older refugee children have a high risk of mental health problems, including posttraumatic stress disorder (PTSD), depression, anxiety and somatic complaints.<sup>5</sup>

Exposure to potentially traumatic experiences predispose individuals for mental health problems, which suggests that more frequent and/or severe exposure to trauma is associated with higher vulnerability, called a ‘building block effect’.<sup>6</sup> Indeed, many refugee children living in Germany, as a host country, endured traumatic experiences in their home countries coupled with traumatic events during their flight and stressful experiences during their acculturation processes. Refugees have experienced not only direct exposure to flight and war-related events (for example, injury and death by shellfire confrontation and loss of close relatives), but also domestic violence in refugee families.<sup>7</sup> Pathogenesis of mental burdening in the war-affected refugee

population, as well as child abuse and neglect, is still a rarely acknowledged and understudied stressor.<sup>5</sup> Studies revealed that PTSD symptoms in refugee mothers residing in Germany positively correlate with family violence experienced as a child and that lower cognitive abilities occur among children (aged ≤56 months) from depressed mothers.<sup>8,9</sup> Given the high prevalence of trauma sequelae in adult refugees, violent and maltreating parental behavior in this population may frequently occur to produce psychophysiological outcomes in their children.<sup>10</sup>

However, not all children exposed to frequent and severe traumatic events actually develop mental health problems. The few studies that focus on possible protective factors imply that individual factors, such as emotional regulation and coping skills, serve resilient functions in refugee children. Other factors between adults and children can also determine the degree of resiliency in refugee children, such as caregiver mental health, secure attachment regulation and extended social support.<sup>11</sup> Positive parenting can be a major protective factor for children encountering stressful situations and may buffer external, stress-induced effects on their stress-regulatory systems and ultimately their health.<sup>12</sup> The impact of violence on infants and young children has long-lasting effects, because they endure stressful situations during a critical developmental period.

## BIOLOGICAL VARIANCE OF CHRONIC MENTAL BURDENING

Early exposure to stress, especially in the context of violence, can induce alterations in brain structure and function.<sup>13</sup> Growing evidence suggests that exposure to external violence triggers a sequence of biological changes that enable the infantile brain to cope with adverse experiences.<sup>14</sup> Adults with early stressful experiences show activated inflammatory responses and glucocorticoid hyperactivation, as well as epigenetically and genetically changes after extreme and/or chronic mental burdening (Table 1). These data suggest that early life stressful events predispose an individual to develop a heightened biological basis for fear that then conflicts with behavioral problems and learning capacity. The limbic system, including hippocampus and amygdala, was the initial focus to assess the effects of childhood abuse on brain development. Both the hippocampus and amygdala are densely populated with glucocorticoid receptors (GR). Excessive exposure to glucocorticoids can induce reversible atrophy of dendritic

<sup>1</sup>Department for Child and Adolescent Psychiatry, Psychotherapy, and Psychosomatics, University of Leipzig, Leipzig, Germany; <sup>2</sup>Department of Medicine, Technische Universität Dresden, Carl Gustav Carus, Dresden, Germany; <sup>3</sup>Faculty of Life Sciences & Medicine, Endocrinology and Diabetes, Kings College London, London, UK; <sup>4</sup>Department of Diagnostic and Interventional Radiology, University Hospital Düsseldorf, Düsseldorf, Germany; <sup>5</sup>Department of Psychology, Technische Universität Dresden, Dresden, Germany; <sup>6</sup>Department of Psychology/Developmental Psychology, University of Wuppertal, Wuppertal, Germany; <sup>7</sup>German Youth Institute, Munich, Germany; <sup>8</sup>Center of Excellence for Psychotraumatology, University of Konstanz, Konstanz, Germany and <sup>9</sup>Department for Child and Adolescent Psychiatry, Psychotherapy, and Psychosomatics, University of Ulm, Ulm, Germany. Correspondence: Dr E Ullmann, Department of Medicine, University of Dresden, Fetscherstraße 74, Dresden D-01307, Germany. E-mail: enrico.ullmann@uniklinikum-dresden.de

**Table 1.** Biological variances in mental burdening subjects

<i>Eco-phenotypes</i>	<i>Eco-genotypes</i>	<i>Genotypes</i>
Limbic system-hippocampus/amygdala <sup>15</sup>	FKBP5 <sup>18</sup>	Genome-wide associations <sup>22</sup>
Sensory cortex-Prefrontal cortex (PFC) <sup>16</sup>	NR3C1 <sup>19</sup>	Telomeres <sup>23</sup>
Ant.cingulate cortex (ACC) <sup>17</sup>	CRFR2 <sup>20</sup>	
	CRHR1 <sup>21</sup>	

Abbreviations: CRFR2, Corticotropin-releasing factor receptor type 2; CRHR1, corticotropin releasing hormone receptor 1; FKBP5, FK binding protein 5; group C, member 1; NR3C1, nuclear receptor subfamily 3.

cellular processes in the hippocampus, in particular the Cornu Ammonis (CA, especially the CA3 subfield) and suppress neurogenesis within the dentate gyrus. In contrast, glucocorticoids can stimulate dendritic arborization and new spine formation on pyramidal cells in the amygdala, which increases volume.<sup>15</sup> GR also localize on glial cells in the cerebral cortex, mainly the prefrontal cortex, which shows decreased gray matter volume following stress-related experiences.<sup>16</sup> Anterior cingulate cortex volume reduction is one of the most consistent findings related to mentally burdening.<sup>17</sup>

In addition, glucocorticoids play a key role in the physiology of the limbic-hypothalamic-pituitary-adrenal axis. GR density correlates with stress adaptation, as demethylation processes at the FK binding protein 5 reduce GR density and limbic-hypothalamic-pituitary-adrenal activity in early childhood traumatized subjects.<sup>18</sup> Moreover, parenting stress and maternal mental burdening, as well as symptoms of attention deficit hyperactivity disorder and brain volume, correlate with changes in the nuclear receptor subfamily 3, group C, member 1 (*NR3C1*), a gene that encodes for the GR with a central role in stress responses.<sup>19</sup> Corticotropin-releasing factor receptor type 2 may also influence stress-regulation of anxiety-related symptoms in animals and humans.<sup>20</sup> Another potential biomarker for limbic-hypothalamic-pituitary-adrenal axis activity is the corticotropin releasing hormone receptor 1 (*CRHR1*) gene, which is associated with anxiety, depression and PTSD.<sup>21</sup> Finally, genome-wide association studies show an overlap between schizophrenia and PTSD and telomere erosion were found in subjects after childhood abuse using longitudinal observations.<sup>22,23</sup> Hair samples from refugees with PTSD can show elevated glucocorticoid-cortisol-levels, which indicates a 'load factor' of the limbic-hypothalamic-pituitary-adrenal axis without ultra- and circadian variabilities.<sup>24</sup>

### RELATIONSHIP-BASED EARLY INTERVENTION AS A PREVENTIVE STRATEGY

Studies indicate that infants and toddlers from refugee families are at risk to develop mental and physical health symptoms and developmental problems, despite limited empirical data. The high prevalence of clinically relevant symptoms in adult refugees emphasizes this prognosis, as parental health directly affects their infant's mental and physical health. However, clinical practice with refugee populations reveals that infants from refugee families represent a diverse group along a continuum from low to high risk. Thus, there is a critical need for a cost-effective, anticipatory social policy that focuses on early preventive intervention and simultaneously provides individually tailored components according to risk level. According to attachment theory, infants develop two key skills through interactions with care-givers—the ability to physiologically self-regulate and acquire social-cognitive competencies through executive functioning.<sup>25</sup> However, mental health problems from parents can impair appropriate and adequate

caregiving. Thus, refugee infant mental health crucially depends on the quality of attachment relationships and parental mental health. We and others propose that improving attachment security can reduce mental health problems in high-risk infants.<sup>26</sup> The biological basis that underlies this concept suggests a universally comprehensive and independent process from cultural conditions or socialization practices. However, refugee mental health is a particular concern, because they often experience extremely stressful events during a formative stage of development. Many refugees, both adult and infants, are exposed to multiple and cumulative risks.<sup>5</sup> Among these, exposure to violence is the factor with the strongest evidence to predispose an individual for subsequent psychological and mental health problems. The accumulation and interaction of multiple risk factors combined with a lack of buffering protective factors provide the prototypical rationale for selective preventive interventions.

Moreover, providing early and preventive intervention for refugee infants also offers the opportunity to promote successful cultural integration. Independent of the degree of protection and their final residence status, systematic early preventive intervention matters. Although international research somehow reveals smaller effects from these factors on parental competencies, comprehensive, preventative psychosocial health and developmental programs compared to psychotherapeutic interventions and early intervention programs for children are vital to promote productive coping mechanisms and successful integration into new cultures. In particular, programs starting early in infancy were positively evaluated to provide 'a healthy start to life'.<sup>27</sup> These programs predominantly utilize attachment-based practices, which focus explicitly on enhancing parental sensitive behaviors and infant attachment security. These programs are incorporated primarily in practice fields and show promising results, as the 'Ulm Model' was successfully tested in mothers with a migration background living in Germany.<sup>28</sup> A hallmark of these programs is that they do not directly target a specific health or non-specified problem in the mother, *per se*. Instead, they focus on improving the relationship between mother and their child in a resource-oriented manner. Such programs make parenting easier and more enjoyable, such as increasing infants' self-regulatory capacities. Thus, this approach has a better acceptance among skeptical or even distrustful parents. Incorporating video reviews as a feedback mechanism supports verbal communication with refugee mothers. A related universal and low-threshold preventive program is 'Opstapje', a home-based early intervention program targeted to improve a child's cognitive and language development by enhancing caregiver's age-appropriate caregiving and scaffolding.<sup>29</sup> Opstapje is also culturally sensitive and has been evaluated with migration families in Germany and the Netherlands. An improvement in caregiver's sensitive autonomy support during play was significantly associated with an increase in children's interest and engagement with the learning environment and their IQ. Comparable to the Ulm Model, Opstapje focuses on promoting positive and sensitive parenting utilizing scaffolding in caregivers and cognitive and language development milestones. In that perspective, both programs fulfill one criteria that defines program success, namely supporting early childhood development.

The importance of maternal traumatic experiences, specifically the sequelae in the trauma-spectrum for mother–infant relationships and infant mental health indicates that the inclusion of an additional specific trauma-focused intervention for mothers is needed. 'Narrative Exposure Therapy' is an effective, short-term and culturally universal intervention for trauma victims, in particular those exposed to multiple and severe traumatic stressors.<sup>30</sup> NET has been proven to be highly effective among refugee populations.

**Table 2.** PRECURE 0-3 longitudinal designed collaboration project starting in prenatal period

Diagnosis	Assess mental and physical health in war refugee children, including cognitive and motor development and long-term stress-hormone levels in hair across various ages Assess mental health in war refugee mothers, including long-term stress-hormone levels in hair across the lifespan
Treatment	Prove the feasibility of the application of Narrative Exposure Therapy (NET) within a stepped care approach for refugee mothers Prove the benefits of videotaped dyadic interaction between mother and their toddler, including home care visits (Ulm Model, Opstapje)

Our consortium, including most authors here, aim to test and implement a stepped-care approach into regular and interdisciplinary service delivery in Germany (PRECURE 0–3). Our model consists of two previously discussed intervention components to promote sensitive maternal behaviors across the risk spectrum and incorporates maternal trauma therapy as indicated (Table 2). Thus, PRECURE 0–3 addresses the low to high risk continuum in refugee infants. In addition, it includes a psychoeducational tool for all participating families and a standardized procedure for professionals to use in cases of child endangerment.

PRECURE 0–3 provides culturally-sensitive, early preventive intervention components for infants from refugee families in Germany. We aim to promote infant mental health via a cascade model of prevention that provides individually tailored interventions appropriate for the maternal risk to provide inadequate care and to address trauma sequelae. To our knowledge, no proven culturally sensitive, stepped-care approach for infants from refugee families is currently implemented in regular and interdisciplinary service delivery. In addition, no approach to date systematically screens both the infant mental health risks and the functionality of maternal care, while simultaneously addressing each infant's specific needs and integrating a low-threshold, short-term trauma therapy for mothers in need. The flexibility of the approach can improve cultural sensitivity of the assessment tools and promote infant and maternal mental health at the onset of participation in the program. Given the critical impact of violence on infant behavior and health development, there is an urgent need for systematic and regular early preventive intervention for infants from refugee families. Overall, the project will inform policy and clinical decision making for social services, child protection, medical and child-psychiatric services to ensure the program's feasibility and assess the effects of our integrative intervention approach. Once successfully conducted, our program will provide an economical, stepped-care model with culturally sensitive interventions for regular interdisciplinary service delivery in communities with proven feasibility and effectiveness in the German social service system. We believe our program will stimulate programs in other countries to better assist refugee families. We will collaborate with other practitioners and funding agencies to evaluate the long-term effects of our program.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### REFERENCES

- 1 v Ludovica G, Liebau E, Peter F, Weinhardt F. *Viele Kinder von Geflüchteten besuchen eine Kita oder Grundschule—Nachholbedarf bei den unter Dreijährigen und der Sprachförderung von Schulkindern*. German Institute for Economic Research—weekly report, vol. 19, 2017.
- 2 Miller GA, Elbert T, Rockstroh B. Judging psychiatric disorders in refugees. *Lancet* 2005; **366**: 1604–1605, author reply 5.
- 3 Ullmann E, Barthel A, Tache S, Bornstein A, Licinio J, Bornstein SR. Emotional and psychological trauma in refugees arriving in Germany in 2015. *Mol Psychiatry*. 2015; **20**: 1483–1484.
- 4 Fegert J, Diehl C, Leyendecker K, Hahlweg K. *Aus Kriegsgebieten geflüchtete Familien und ihre Kinder: Entwicklungsrisiken, Behandlungsangebote, Versorgungsdefizite—short report*. Federal Scientific Council in Family Affairs, Germany, 2017; <https://www.bmfsfj.de/blob/119734/9715f720b0090d71d4cbe797586a9cec/kurzgutachten-gefluechtete-familien-data.pdf>.
- 5 Slone M, Mann S. Effects of war, terrorism and armed conflict on young children: a systematic review. *Child Psychiatry Hum Dev* 2016; **47**: 950–965.
- 6 Schauer M, Neuner F, Karunakara U, Klaschik C, Robert C, Elbert T. PTSD and the building block effect of psychological trauma among West Nile Africans. *Eur Soc Trauma Stress Stud Bull* 2003; **10**: 5–6.
- 7 Catani C, Jacob N, Schauer E, Kohila M, Neuner F. Family violence, war, and natural disasters: a study of the effect of extreme stress on children's mental health in Sri Lanka. *BMC Psychiatry* 2008; **8**: 33.
- 8 Ruf-Leuschner M, Roth M, Schauer M. Traumatized mothers—traumatized children? Transgenerational trauma exposure and trauma sequelae in refugee families. *Z Klin Psychol Psychother* 2014; **43**: 1–16.
- 9 Liu Y, Kaaya S, Chai J, McCoy DC, Surkan PJ, Black MM et al. Maternal depressive symptoms and early childhood cognitive development: a meta-analysis. *Psychol Med* 2017; **47**: 680–689.
- 10 Ullmann E, Licinio J, Barthel A, Petrowski K, Stalder T, Bornstein SR et al. Persistent LHPA activation in german individuals raised in an overprotective parental behavior. *Sci Rep* 2017; **7**: 2778.
- 11 Bonanno GA, Mancini AD. The human capacity to thrive in the face of potential trauma. *Pediatrics* 2008; **121**: 369–375.
- 12 Kryski KR, Dougherty LR, Dyson MW, Oliino TM, Laptook RS, Klein DN et al. Effortful control and parenting: associations with HPA axis reactivity in early childhood. *Dev sci* 2013; **16**: 531–541.
- 13 Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *J Neuropsychiatry Clin Neurosci* 2008; **20**: 292–301.
- 14 Teicher MH, Samson JA. Annual research review: enduring neurobiological effects of childhood abuse and neglect. *J Child Psychol Psychiatry* 2016; **57**: 241–266.
- 15 Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neurosci Res* 1996; **26**: 235–269.
- 16 Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *J Neurosci* 2010; **30**: 7466–7472.
- 17 Sarrieau A, Dussaillant M, Agid F, Philibert D, Agid Y, Rostene W. Autoradiographic localization of glucocorticosteroid and progesterone binding sites in the human post-mortem brain. *J Steroid Biochem* 1986; **25**: 717–721.
- 18 Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* 2013; **16**: 33–41.
- 19 Schechter DS, Moser DA, Paoloni-Giacobino A, Stenz L, Gex-Fabry M, Aue T et al. Methylation of NR3C1 is related to maternal PTSD, parenting stress and maternal medial prefrontal cortical activity in response to child separation among mothers with histories of violence exposure. *Front Psychol* 2015; **6**: 690.
- 20 Henckens MJ, Printz Y, Shamgar U, Dine J, Lebow M, Drori Y et al. CRF receptor type 2 neurons in the posterior bed nucleus of the stria terminalis critically contribute to stress recovery. *Mol Psychiatry*; advance online publication, 23 August 2016; doi: 10.1038/mp.2016.133.
- 21 Rogers J, Raveendran M, Fawcett GL, Fox AS, Shelton SE, Oler JA et al. CRHR1 genotypes, neural circuits and the diathesis for anxiety and depression. *Mol Psychiatry* 2013; **18**: 700–707.
- 22 Duncan LE, Ratanatharathorn A, Aiello AE, Almli LM, Amstadter AB, Ashley-Koch AE et al. Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. *Mol Psychiatry*; advance online publication, 25 April 2017; doi: 10.1038/mp.2017.77.

- 23 Shalev I, Moffitt TE, Sugden K, Williams B, Houts RM, Danese A *et al.* Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. *Mol Psychiatry* 2013; **18**: 576–581.
- 24 Mewes R, Reich H, Skoluda N, Seele F, Nater UM. Elevated hair cortisol concentrations in recently fled asylum seekers in comparison to permanently settled immigrants and non-immigrants. *Transl psychiatry* 2017; **7**: e1051.
- 25 Madigan S, Bakermans-Kranenburg MJ, Van Ijzendoorn MH, Moran G, Pederson DR, Benoit D. Unresolved states of mind, anomalous parental behavior, and disorganized attachment: a review and meta-analysis of a transmission gap. *Attach hum dev* 2006; **8**: 89–111.
- 26 Pine DS, Costello J, Masten A. Trauma, proximity, and developmental psychopathology: the effects of war and terrorism on children. *Neuropsychopharmacology* 2005; **30**: 1781–1792.
- 27 Bakermans-Kranenburg MJ, van IMH, Juffer F. Less is more: meta-analyses of sensitivity and attachment interventions in early childhood. *Psychol Bull* 2003; **129**: 195–215.
- 28 Pillhofer M, Spangler G, Bovenschen I, Kuenster AK, Gabler S, Fallon B *et al.* Pilot study of a program delivered within the regular service system in Germany: effect of a short-term attachment-based intervention on maternal sensitivity

in mothers at risk for child abuse and neglect. *Child Abuse Negl* 2015; **42**: 163–173.

- 29 van tuijl C, Iseman PP, Rispens J. Efficacy of an intensive home-based educational intervention programme for 4- to 6-year-old ethnic minority children in the Netherlands. *Int J Behav Dev* 2001; **25**: 148–159.
- 30 Schauer M, Neuner F, Elbert T. *Narrative exposure Therapy (NET). A Short-Term Intervention for Traumatic Stress Disorders*. Hogrefe & Huber Publishers: Cambridge/Göttingen, 2011.



This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/4.0/>

© The Author(s) 2018