Behavioral Sciences and the Law
Behav. Sci. Law **33**: 701–721 (2015)
Published online 11 September 2015 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/bsl.2200

Epigenetic Alterations Associated with War Trauma and Childhood Maltreatment

Laura Ramo-Fernández, Lic.-Biol.*, Anna Schneider, Dipl.-Psych.†, Sarah Wilker, Ph.D.† and Iris-Tatjana Kolassa, Ph.D.†

Survivors of war trauma or childhood maltreatment are at increased risk for trauma-spectrum disorders such as post-traumatic stress disorder (PTSD). In addition, traumatic stress has been associated with alterations in the neuroendocrine and the immune system, enhancing the risk for physical diseases. Traumatic experiences might even affect psychological as well as biological parameters in the next generation, i.e. traumatic stress might have transgenerational effects. This article outlines how epigenetic processes, which represent a pivotal biological mechanism for dynamic adaptation to environmental challenges, might contribute to the explanation of the long-lasting and transgenerational effects of trauma. In particular, epigenetic alterations in genes regulating the hypothalamus–pituitary–adrenal axis as well as the immune system have been observed in survivors of childhood and adult trauma. These changes could result in enduring alterations of the stress response as well as the physical health risk. Furthermore, the effects of parental trauma could be transmitted to the next generation by parental distress and the pre- and postnatal environment, as well as by epigenetic marks transmitted via the germline. While epigenetic research has a high potential of advancing our understanding of the consequences of trauma, the findings have to be interpreted with caution, as epigenetics only represent one piece of a complex puzzle of interacting biological and environmental factors.

INTRODUCTION

Reports of violent or traumatic events, such as the East Ukraine crisis or the Syria conflict but also severe civilian violence, including childhood maltreatment or sexual violence, dominate our daily newspapers. The ephemerality of such news creates a sharp contrast to the long-lasting, but often invisible, consequences for the survivors of trauma and violence.

Trauma survivors are at increased risk to develop disorders of the trauma spectrum such as post-traumatic stress disorder (PTSD) or depression. While the latter can arise in response to different environmental stressors, PTSD is unique among the psychiatric disorders as it requires experience of a traumatic event to manifest. These psychological disorders may take a chronic course and are associated with low levels of social and economic functioning, higher rates of suicidality and less active societal participation

*Correspondence to: Laura Ramo-Fernández, Lic.-Biol., Clinical and Biological Psychology, Institute of Psychology & Education, Ulm University, Albert-Einstein-Alle 47, 89069, Ulm, Germany. E-mail: laura.ramo@uni-ulm.de
† Clinical and Biological Psychology, Ulm University, Germany

(Sareen et al., 2005; Stansfeld, Clark, Rodgers, Caldwell, & Power, 2010). However, the consequences of trauma and violence are not limited to psychosocial functioning, but can be extended to physical health. Trauma survivors show changes in the immune and the neuroendocrine system (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Hunter, Minnis, & Wilson, 2011) and a higher risk for infections, diabetes, cardiovascular disease or even cancer (Norman et al., 2012). Epigenetic modifications might represent one piece in the puzzle of the link between traumatic stress exposure and associated health consequences (Bick et al., 2012). Finally, the impact of traumatic experiences can even be transmitted to the next generation, referred to as a transgenerational cycle of trauma and maltreatment. Among the complex factors accounting for this transgenerational transmission, epigenetic alterations could play a pivotal role.

After introducing the field of epigenetics to the reader, this selective literature review describes the psychological and biological consequences of war trauma and childhood maltreatment. It is followed by an explanation of how epigenetic alterations might partially account for these trauma-associated alterations. The next section is devoted to the transgenerational transmission of trauma, violence and PTSD. Again, we start by explaining risk factors on the behavioral level and proceed with illuminating alterations on the biological level, with a focus on how epigenetic processes could mediate the transmission to the next generation.

An Introduction to Epigenetics

Shortly after Rosalind Franklin started her studies on deciphering the molecular structure of DNA and James Watson and Francis Crick described the DNA double helix structure (Watson & Crick, 1953), the belief that DNA carries important biological information that flows in a unique single direction was widely disseminated. The so called "central dogma" of molecular biology stated that biological information is transcribed from DNA into RNA, which is translated into proteins (Crick, 1970). However, the veracity of the central dogma was called into question for two reasons: First, studies suggested the existence of DNA modifications that were acquired throughout life—epigenetic mechanisms (Holliday & Pugh, 1975; Jaenisch & Bird, 2003); and second, because genetic risk factors alone did not completely explain the estimated heritability for the majority of diseases and traits, commonly referred to as the "missing heritability problem" (Chaufan & Joseph, 2013; Manolio et al., 2009). As an example, according to twin studies, genetic factors were estimated to account for at least 60% of individual variability in schizophrenia risk (Picchioni & Murray, 2007). However, the genetic risk factors reliably identified by large-scale meta-analyses explained only a small proportion of the total phenotypic variance (Gershon, Alliey-Rodriguez, & Liu, 2011). Explanations for the missing heritability include methodological issues (e.g., small sample sizes, inadequate selection of control groups, imprecise definition of phenotypes, neglect of gene × environment interactions, and a focus on samples with European ancestry) as well as reasons more inherent to genetic association studies. The latter comprises (1) the small effect sizes of single genetic risk factors, (2) the fact that genes act in pathways, which would require the modulation of complex gene × gene interaction analyses, (3) the existence of non-additive genetic effects (e.g. dominance and epistasis) and (4) the potential impact of rare variants or structural variations such as copy number variations, which are much more difficult to study in population-based studies (diLalla & Gottesman, 1991; Gershon et al.,

DOI: 10.1002/bsl

2011; Manolio et al., 2009). Finally, epigenetic modifications of the genetic loci under investigation might influence gene expression and hence mask the effects of the genetic risk factor. Accordingly, the investigation of epigenetic modifications could contribute to our understanding of the remaining variability in disorder liability (Slatkin, 2009).

Epigenetic mechanisms are long-term DNA modifications that do not affect the sequence but do modulate gene regulation and expression. The most extensively described epigenetic mechanism in the context of psychiatry is DNA methylation, which consists of the addition of a methyl group to a cytosine residue followed by guanosine, referred to as "CpG sites" (Jaenisch & Bird, 2003). Since epigenetic modifications are crucial for the cellular differentiation process (i.e., the fact that all cells carry the same DNA but exert different functions; Morgan, Santos, Green, Dean, & Reik, 2005), they need to be at least somewhat stable. However, epigenetic modifications could be also responsible for environmentally shaped gene expression in order to adjust to life's demands (Francis, 2011), which would imply at least partial flexibility. The discovery of enzymes responsible for dynamic epigenetic changes, including DNA methyltransferases and histone acetyltransferases (Ramchandani, Bhattacharya, Cervoni, & Szyf, 1999; Rice & Allis, 2001; Strahl & Allis, 2000), provided the first evidence that epigenetic processes could indeed flexibly respond to environmental influences. This idea is reflected in the concept of behavioral epigenetics, which describes behavioral adaptations by epigenetically shaped gene expressions in response to difficult life experiences.

Among the complex interacting biological and environmental factors that could account for the consequences of trauma and its transgenerational transmission (see Fig. 1), this selective literature review predominantly focuses on the role of epigenetic processes. Epigenetic processes could be of particular importance in the field of trauma, as they can flexibly adapt to environmental challenges (in contrast to genes) and these adaptions can also become at least partly stable (in contrast to mRNA and proteins).

LONG-LASTING EFFECTS OF WAR TRAUMA AND MALTREATMENT

Posttraumatic Stress Disorder and the Building Block Effect of War Trauma

PTSD is characterized by (1) intrusive re-experiencing of the traumatic event in the form of recurrent dreams, thoughts, sensations or flashbacks, (2) avoidance of potentially trauma reminding thoughts or activities, (3) emotional numbing as well as persistent alterations in mood and cognition and (4) a heightened state of alertness or arousal (American Psychiatric Association, 2013). As indicated in the introduction, the experience of a traumatic event is a necessary condition to develop PTSD. Yet, the development of PTSD after a single traumatic experience seems to be the exception rather than the rule. While 50–60% of study participants reported at least one potential traumatic experience in western non-war countries, only 5–10% of them developed PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Kessler et al., 2005). Studies investigating PTSD in

DOI: 10.1002/bsl

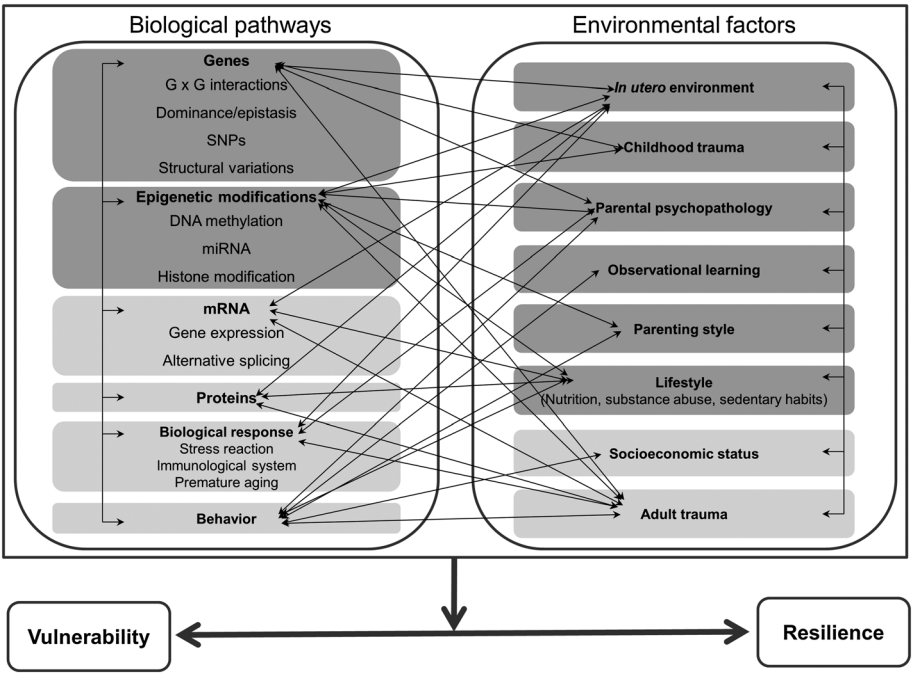

Figure 1. Epigenetic modifications represent one piece of the complex puzzle linking trauma experiences to an elevated risk of psychopathology and adverse physical health consequences. The arrows indicate interacting pathways between the biological and environmental factors that are more commonly described in the literature. The dark grey color represents the major contributors to the transgenerational transmission of the possible consequences of trauma, which include not only internal factors such as (epi)genetic variants, but also behavioral responses such as lifestyle and parenting imitation.

war affected countries reported higher prevalence rates, ranging from 16% lifetime prevalence reported in Ethiopia up to 37% in Algeria (de Jong et al., 2001). Another survey showed current prevalence rates of up to 40% among West Nile refugees (Neuner et al., 2004). The detrimental effects of war trauma on psychological well-being can be explained by the so-called "building block effect" of traumatic load (Schauer et al., 2003): It has been repeatedly shown that the number of different traumatic event types experienced increases the risk of developing PTSD in a dose–response manner (Brewin, Andrews, & Valentine, 2000; Dunmore, Clark, & Ehlers, 2001; Fawzi et al., 1997; Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Neugebauer et al., 2009; Neuner et al., 2004), while the likelihood of spontaneous remission from PTSD decreases with accumulating trauma exposure (Kolassa, Ertl, Kolassa, Onyut, & Elbert, 2010). Furthermore, there seems to be no ultimate resilience towards PTSD: Neuner et al. (2004) investigated 3,339 West Nile refugees in Uganda and showed that the probability of developing PTSD approximated 100% after having experienced extreme levels of traumatic stress. Accordingly, this important environmental risk factor should be included in every study examining individual risk factors for PTSD. However, one important critical point is the lack of consistency when measuring "trauma load" (Maier, 2007). For instance, it is not clear whether the frequency of traumatic events, the severity or the age should also be considered (Wilker et al., in press). It is also unclear whether it is adequate to define trauma load as the unweighted sum of traumatic events, or whether some events, such as interpersonal violence (Breslau et al., 1998) and sexual violence in

DOI: 10.1002/bsl

particular (Maercker, Michael, Fehm, Becker, & Margraf, 2004; Maercker et al., 2009; Schoedl et al., 2010), should be given more weight, as they are associated with a higher risk of PTSD.

Childhood Maltreatment and Associated Psychological Consequences

Childhood maltreatment comprises sexual, physical and emotional abuse as well as physical and emotional neglect (Butchart, Harvey, Mian, & Furniss, 2006; Cicchetti & Toth, 2005; Myers, 2011) and can have a detrimental impact on a child's development and psychological as well as physical health throughout life (Schury & Kolassa, 2012). In a U.S. survey with 4,503 children and adolescents (aged one month up to 17 years), Finkelhor, Turner, Shattuck, and Hamby (2013) reported a lifetime prevalence of 9.6% for physical abuse, 14.9% for emotional abuse and 14.6% for neglect by caregivers, and 9.5% for any sexual victimization by adults and peers. Thombs et al. (2006) reported a similar prevalence, with higher rates of physical and emotional abuse among boys and higher rates of sexual abuse among girls. Concerning child sexual abuse, a global meta-analysis based on 331 independent samples estimated a general prevalence of 11.8%, with a prevalence of 18% in female samples and 7.6% in male samples (Stoltenborgh, van IJzendoorn, Euser, & Bakermans-Kranenburg, 2011).

The potentially adverse consequences of childhood maltreatment are manifold: On the one hand, experiencing maltreatment during childhood can lead to an increased risk for internalizing behavioral problems (e.g., depression, anxiety), presumably more common among women (Ackerman, Newton, McPherson, Jones, & Dykman, 1998; Fergusson, Boden, & Horwood, 2008; Moylan et al., 2010; Norman et al., 2012), and externalizing behavioral problems (e.g., aggressive behavior, delinquency), more often observed in men (Ackerman et al., 1998; Evans, Davies, & DiLillo, 2008; Moylan et al., 2010). On the other hand, the experiences of abuse can repeat themselves: Victims of childhood maltreatment are at increased risk to be abused during adulthood or to become involved in relationships with abusive partners (Barrios et al., 2015; Bensley, Van Eenwyk, & Wynkoop Simmons, 2003). Moreover, the risk of becoming perpetrators themselves and abusing their spouses and children (Duke, Pettingell, McMorris, & Borowsky, 2010; Ehrensaft et al., 2003; Gil-González, Vives-Cases, Ruiz, Carrasco-Portiño, & Álvarez-Dardet, 2008), or of becoming involved in offending and violent crime, is elevated in childhood maltreatment survivors (Thornberry, Henry, Ireland, & Smith, 2010). In addition, increased levels of substance or alcohol abuse as well as engagement in risky sexual behaviors were observed in survivors of childhood maltreatment compared with non-maltreated individuals (Thornberry et al., 2010; Widom, Ireland, & Glynn, 1995; Wilson & Widom, 2008).

Potential Health Consequences of Trauma and Childhood Maltreatment

Both childhood maltreatment and war-related traumatic experiences can have negative consequences on physical health. In particular, childhood maltreatment is associated with an increased likelihood of cardiovascular disease, diabetes and obesity (Batten, Aslan, Maciejewski, & Mazure, 2004; Danese & Tan, 2014; Suglia, Clark, Boynton-

DOI: 10.1002/bsl

Jarrett, Kressin, & Koenen, 2014; Thomas, Hypponen, & Power, 2008). Similarly, trauma survivors were found to be more vulnerable to infection, cancer, chronic lung disease, diabetes and cardiovascular problems (Brown et al., 2010; Norman et al., 2012). Furthermore, the risk of developing any physical disease increases with the number of traumatic event types (Scott et al., 2013). Hence, the building block effect seems not to be limited to mental disease, but also extends to the biological level.

Next to lifestyle factors associated with childhood and adult trauma exposure (including smoking, alcohol and substance abuse, and poor nutrition), trauma-associated neuroendocrinological as well as immunological alterations are likely to contribute to the enhanced physical health risk. Upon trauma exposure, the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis are activated, resulting in the release of catecholamines and cortisol, respectively. Furthermore, PTSD has been found to be associated with endocrinological deregulations. While the literature consistently points towards increased catecholamine levels in PTSD (Pervanidou & Chrousos, 2012; Yehuda, Southwick, Giller, Ma, & Mason, 1992; Young & Breslau, 2004), evidence regarding cortisol levels is more heterogeneous. Yet, the majority of studies points towards lower cortisol levels (Heim & Nemeroff, 2009; Pace & Heim, 2011; Yehuda, Halligan, & Bierer, 2002) and increased sensitivity of glucocorticoid receptors in PTSD (Yehuda, Golier, Yang, & Tischler, 2004). However, adding to the complexity of the cortisol literature, childhood maltreatment survivors rather present a lower density of central and peripheral glucocorticoid receptors, higher cortisol levels, general insensitivity to cortisol and disrupted stress reactivity (Carpenter et al., 2007, 2009; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). These opposed findings in PTSD versus childhood maltreatment could be due to a higher vulnerability of the developing brain structures (Kellermann, 2013). Since the immune system and the endocrine system interact via peptide hormones, neurotransmitters and cytokines, it is not surprising that trauma survivors with PTSD show immunological alterations too. In more detail, traumatic stress seems to be followed by a reduction in the count of naïve and regulatory T lymphocytes as well as an increase of memory T cells (Sommershof et al., 2009). Moreover, spontaneous production of pro-inflammatory cytokines by isolated leukocytes (Gola et al., 2013) and circulating levels of pro-inflammatory cytokines (Carpenter et al., 2010; von Känel et al., 2007) seem to be increased in association with childhood maltreatment and PTSD.

Not only do individuals with PTSD present an increased risk and an earlier onset of age-related diseases, but the aforementioned immunological alterations are also indicative of a prematurely aged immune system. Similarly, the examination of age-related biomarkers indicates premature aging in trauma survivors: Shorter telomere length—a robust biomarker for premature aging—was associated with childhood maltreatment and exposure to chronic stress (Epel et al., 2004; Tyrka et al., 2010). Furthermore, increased DNA breakage accumulation has been observed in peripheral blood mononuclear cells of trauma-exposed individuals with and without PTSD (Morath et al., 2014). Moreover, comparing the GlycoAgeTest in individuals with and without PTSD also pointed towards accelerated physiological aging in trauma survivors with PTSD (Moreno-Villanueva et al., 2013).

But how can traumatic stress lead to long-lasting endocrinological and immunological changes? The following section describes how enduring epigenetic modifications might explain some of the observed alterations in trauma survivors.

DOI: 10.1002/bsl

EPIGENETIC PROCESSES MAY ACCOUNT FOR THE LONG-LASTING CONSEQUENCES OF TRAUMA

Epigenetics of War Trauma and PTSD

The majority of studies investigating survivors of adult trauma focused on epigenetic correlates of PTSD. Since intrusive memories for the traumatic experiences form a hallmark of the disease, and PTSD patients present distinct memory impairments, the disorder has been conceptualized as a disorder of pathological memory formation (Brewin, 2011). Recent work highlighted the essential mediating role of epigenetic marks in the molecular mechanisms of memory formation (Levenson & Sweatt, 2005) and showed that inhibition of the DNA methyltransferase blocks long-term potentiation and memory consolidation in rat hippocampi (Miller & Sweatt, 2007). Moreover, mRNA levels of *de novo* DNA methyltransferase undergo upregulation after fear conditioning (Miller & Sweatt, 2007). Since glucocorticoids are central players in emotionally driven memory consolidation, they are essential for the biological characterization of PTSD (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Roozendaal, Okuda, de Quervain, & McGaugh, 2006) and represent a pivotal target for epigenetic investigations aiming to explain pathological memory formation in PTSD. In this context, Vukojevic et al. (2014) investigated DNA isolated from human saliva and found an association between epigenetic alterations in the gene encoding the glucocorticoid receptor (*NR3C1*) and human healthy memory performance, as well as intrusive memory symptoms in male PTSD patients. Moreover, higher DNA methylation at the *NR3C1* promoter exon 1_F was associated with less intrusive memory symptoms in male but not in female survivors of the Rwandan genocide (Vukojevic et al., 2014). The gender-specific and complex interaction between methylation of *NR3C1*, memory formation and PTSD risk is not yet completely understood, but represents an interesting starting point for the investigation of epigenetic alterations in memory-related genes.

Within this framework, a greater number of glucocorticoid receptors in lymphocytes and changes of circulating cortisol levels of war combatants with PTSD have been observed (de Kloet et al., 2007; Yehuda, Lowy, Southwick, Shaffer, & Giller, 1991), and reduced methylation of *NR3C1* promoter has been assumed to account for the observed alterations in glucocorticoid signaling (Seckl & Meaney, 2006). Consistently, Labonté and colleagues reported an increased expression of glucocorticoid receptor variants in T lymphocytes in individuals with lifetime PTSD compared with controls, an effect that was accompanied by lower overall methylation of *NR3C1* in individuals with PTSD (Labonté, Azoulay, Yerko, Turecki, & Brunet, 2014). Similarly, Yehuda and co-workers observed lower methylation in the promoter region of the *NR3C1* gene in peripheral blood mononuclear cells from veterans with PTSD and a 39% higher relative expression of the glucocorticoid receptor gene in PTSD cases compared with controls (Yehuda et al., 2015). Finally, a higher number of glucocorticoid receptors in peripheral blood mononuclear cells of soldiers before war service has been indicated as a vulnerability factor for PTSD development after deployment: The odds ratio for the presence of PTSD symptoms after deployment increased 7.5-fold with every increment of 1,000 receptors counted (van Zuiden et al., 2010).

As previously mentioned, PTSD-related health problems might stem from alterations in immune function (Baker et al., 2001; Gola et al., 2013; Hoge et al., 2009; von Känel et al., 2007), which might be partly mediated by epigenetic changes

DOI: 10.1002/bsl

(Smith et al., 2011). A comparison of whole blood DNA methylation in more than 14,000 genes between PTSD cases and healthy controls showed epigenetic changes of immune activation in PTSD patients, as some genes regulating the innate and the adaptive immune system were significantly less methylated (Uddin et al., 2010). Methylation signatures of immune activation mechanisms were also found in peripheral blood cells investigated in an African American population with a PTSD diagnosis compared with healthy controls (Smith et al., 2011).

While these studies do not yet allow for causal interferences between PTSD, increased expression of proinflammatory cytokine genes and decreased concentrations of neuroprotective chemokines, they suggest a chronic immune system activation in PTSD that correlates with corresponding alterations on the epigenetic level. Whether epigenetic alterations represent a risk factor or a consequence of PTSD is not yet clear (Rusiecki et al., 2013; Sipahi et al., 2014). Nevertheless, in interaction with the identified genetic risk factors and the number of traumatic events experienced, epigenetic signatures could contribute to the explanation of interindividual variance of psychiatric outcomes following war-trauma exposure, thus representing a promising approach for future research.

Epigenetic Mechanisms Following Childhood Maltreatment

Pioneering studies by Meaney and colleagues presented experimental evidence for the potential programming role of infant adversity in rats. They suggested as early as 1996 that early environmental regulation of glucocorticoid receptor gene (*NR3C1*) expression was mediated by mother–infant interaction. Offspring experiencing high maternal care (in terms of licking and grooming in laboratory rats) had fewer anxiety-like behaviors and responded with a decreased HPA-axis reactivity to stressful experiences (Meaney et al., 1996). In order to understand why maternal care provoked a reduced response to stress, the same group studied DNA methylation levels of the *NR3C1* promoter and its hippocampal expression. The offspring of high-caring mothers showed an increased *NR3C1* expression rate and a lower methylation level (Weaver et al., 2004; Weaver, Meaney, & Szyf, 2006). This observation could explain the previously mentioned reduced stress reactivity in high maternal care pups. In more detail, the negative feedback of the HPA axis, which is required for a timely termination of the stress response, is strengthened by higher *NR3C1* expression. Similar studies in animal models support the idea that methylation could be a key modulator of the stress response after early-life adversity (Fagiolini, Jensen, & Champagne, 2009; Murgatroyd et al., 2009; Oh et al., 2013). Even more surprising are first indicators for changes of DNA methylation in germline cells, suggesting transgenerational effects of early-life adversity, as persistent and maintained across generations. For example, methylation increase has been observed in sperm cells of male mice exposed to unpredictable maternal separation combined with unpredictable maternal stress (Franklin et al., 2010). Together, these data suggest that maternal behavior can have profound consequences on the offspring's behavioral and neuroendocrine response to stress.

Postmortem analyses in human brain mirrored the results from earlier animal research regarding the effects of early-life stress (McGowan et al., 2009): Hippocampal cells from suicide completers with a history of childhood maltreatment showed higher methylation levels of the exon 1_F *NR3C1* promoter and significantly less expression of *NR3C1* mRNA compared with suicide completers without childhood trauma and controls who died suddenly or accidentally (McGowan et al., 2009). Enhanced *NR3C1*

DOI: 10.1002/bsl

promoter methylation after experiences of childhood maltreatment were also found in several studies investigating peripheral tissue (see Daskalakis & Yehuda, 2014, for a review). Moreover, a positive correlation between the severity, repetition and sexual character of childhood abuse and *NR3C1* promoter methylation levels has been observed (Perroud et al., 2011, 2013), indicating a cumulative effect of childhood maltreatment, similarly to the building block effect of traumatic load (Schury & Kolassa, 2012).

Contrary to these results, epigenetic analysis in war veterans with PTSD showed lower methylation of the *NR3C1* promoter (Labonté et al., 2014; Vukojevic et al., 2014; Yehuda et al., 2015). This suggests that epigenetic modifications might differ depending on the developmental timing of trauma exposure, resulting in either hypo- or hyper-gene expression. Correspondingly, Mehta et al. (2013) compared the gene expression and methylation profiles between PTSD patients with and without a history of childhood maltreatment and found almost no overlap in the gene expression profile of the two groups, an effect that was mirrored by distinct epigenetic signatures.

Another gene involved in HPA axis regulation that is found to be subject to trauma-related epigenetic changes is *FKBP5*, which encodes for a chaperon-like protein that downregulates cortisol binding and glucocorticoid receptor translocation into the cell nucleus. Accordingly, FKBP5 decreases the sensitivity of the glucocorticoid receptor to glucocorticoids. Since binding of glucocorticoids to the glucocorticoid receptor is essential for a termination of the stress response via a negative feedback loop, increased FKBP5 expression might be associated with a prolonged stress response (Binder, 2009). PTSD risk following childhood maltreatment has been associated with certain genetic variations of the *FKBP5* gene (Binder et al., 2008; Klengel et al., 2013; Xie et al., 2010). Furthermore, lower methylation levels of the *FKBP5* gene were observed in individuals with childhood abuse who were also carriers of a genetic risk factor at the *FKBP5* locus (Klengel et al., 2013). Thus, the authors hypothesized that the increased cortisol release resulting from early life events induces epigenetic changes in the promoter area of the gene (Klengel et al., 2013). Accordingly, there seems to be a complex interaction between genetic makeup, environment and consequent epigenetic changes, which warrants further investigations.

While the aforementioned targeted epigenetic studies mainly focused on genes involved in HPA-axis regulation, first epigenome-wide studies allow identification of broad methylation changes that introduce new potential biological pathways related to childhood adversity. So far reported pathways include, among others, cellular signaling cascades (Naumova et al., 2012), neural communication (Naumova et al., 2012), estrogen receptor response (Bick et al., 2012) and developmental pathways (Khulan et al., 2014). Furthermore, a recent study investigating peripheral blood cells aimed to establish genome-wide DNA methylation changes in the promoters of genes that were mostly involved in embryonal development and inflammatory regulation (Suderman et al., 2014).

TRANSGENERATIONAL TRANSMISSION OF TRAUMA AND VIOLENCE

There is mounting evidence that the consequences of trauma and violence could be transmitted to the next generation. For instance, children of Holocaust survivors with PTSD are at increased risk to develop PTSD themselves (Yehuda, Bell, Bierer, &

DOI: 10.1002/bsl

Schmeidler, 2008). Furthermore, parental early adversity is believed to be a risk factor for maltreatment of their own offspring (Dixon, Browne, & Hamilton-Giachritsis, 2008). In a sample of 135 parents with a history of childhood maltreatment, 6.7% abused their own children during the first 13 months (Dixon et al., 2008) while only 0.4% of the non-abused control parents abused their offspring. Many different factors, which are detailed hereafter, could account for this transgenerational transmission of trauma and violence. Foremost, beginning with risk factors on the behavioral level, the experience of trauma and violence, especially if it occurs in early development stages, could repeat itself—a process termed re-victimization. Individuals who have been sexually abused during childhood are at increased risk to experience sexual and physical re-victimization as adults (Arata, 2000; Classen, Palesh, & Aggarwal, 2005; Messman-Moore, Long, & Siegfried, 2000). Moreover, the experience of different types of abuse increases the likelihood of abusive experiences in adulthood (Chiu et al., 2013), including intimate partner violence. Additionally, experiencing childhood abuse has been linked to a higher probability of engagement with a violent intimate partner (Whitfield, Anda, Dube, & Felitti, 2003; WHO, 2005). Besides physical injuries such as head, neck or facial injuries (Wu, Huff, & Bhandari, 2010), victims of inter-personal violence showed stress-related symptoms including loss of appetite, gastrointestinal dysfunction (Campbell, 2002; Coker, Smith, Bethea, King, & McKeown, 2000; Leserman & Drossman, 2007) and hypertension (Coker et al., 2000; Letourneau, Holmes, & Chasedunn-Roark, 1999; Silverman, Decker, Reed, & Raj, 2006). Furthermore, higher prevalence rates of anxiety disorders, PTSD, sleeping disorder and alcohol and drug abuse were observed in victims of intimate partner violence (Campbell, 2002; Carbone-López, Kruttschnitt, & Macmillan, 2006; Krug, Mercy, Dahlberg, & Zwi, 2002; Pico-Alfonso et al., 2006).

Intimate partner violence and childhood maltreatment are correlated, and individuals who abuse their partners often also tend to maltreat their children (Appel & Holden, 1998). Indeed, parent–child interaction can be negatively affected by parental history of childhood maltreatment and intimate partner violence (Buist, 1998; Malta, McDonald, Hegadoren, Weller, & Tough, 2012). In more detail, abused mothers showed an enhanced psychological aggression and physical punishment, less parental warmth and problems in establishing boundaries (Banyard, 1997; Barrett, 2009; Letourneau et al., 2011; Peled & Gil, 2011). To summarize, adults who were abused in childhood have a higher probability of abusing their own children, and they more often become involved in violent intimate relationships in which they re-experience victimization and may fail to protect the children from their violent partner (Dixon, Browne, & Hamilton-Giachritsis, 2005), which can be referred to as a 'cycle of maltreatment' (Widom, 1989).

Survivors of childhood maltreatment, especially survivors of sexual abuse, are not only at increased risk to become violent towards their own family but are also more likely to become involved in delinquency, to carry a weapon for self-protecting reasons, to be arrested and to commit different types of crime (Currie & Tekin, 2012; Smith & Thornberry, 1995; Widom, 1989). Nevertheless, it is important to emphasize that the majority of childhood maltreatment survivors do not become perpetrators. As most previous studies assessed violent outcome retrospectively, representative prospective cohort studies are warranted to derive a valid estimate of the association between maltreatment and future violent behavior.

Another factor involved in the transgenerational transmission of violence is the occurrence of violent behavior during pregnancy. Violent relationships are associated

DOI: 10.1002/bsl

with higher rates of unintended pregnancies, which are in turn related to an increased risk of inter-partner violence during pregnancy (Curry, Perrin, & Wall, 1998; Gazmararian et al., 1995; Goodwin et al., 2000; Saltzman, Johnson, Gilbert, & Goodwin, 2003). Exposure to stress and violence can lead to serious complications during pregnancy as well as premature birth and low birth weight of the newborn, associated with adverse effects on the child's future psychological health (Cokkinides, Coker, Sanderson, Addy, & Bethea, 1999; Curry et al., 1998; Fernandez & Krueger, 1999; Schmuel & Schenker, 1998; Silverman et al., 2006). Presumably, maternal stress can program brain development and stress system plasticity of the fetus (DiPietro, Novak, Costigan, Atella, & Reusing, 2006; O'Donnell et al., 2012). During pregnancy, the developing fetus is protected from maternal glucocorticoid levels by enzymatic inactivation of cortisol in the placenta. However, when maternal cortisol levels are too high, the buffering function of the respective placental enzyme is reduced (Cottrell & Seckl, 2009). Fetal cortisol exposure programs the activity of the HPA-axis (Seckl, 2004) and is associated with low birth weight, increased risk of impaired neurodevelopment and psychiatric diseases later in life (Talge, Neal, & Glover, 2007). For instance, infants of mothers who experienced the September 11th event during pregnancy and subsequently developed PTSD had a lower birth weight and showed more severe depressive symptoms (Yehuda & Bierer, 2009; Yehuda et al., 2005). Acute stress during pregnancy was furthermore associated with subsequent development of PTSD and lower cortisol levels in mothers and their babies (Yehuda et al., 2005). This data supports the aforementioned idea that maternal stress exposure and hence elevated glucocorticoid levels during pregnancy can influence the child's reactivity to stress. The underlying epigenetic processes taking place during *in utero* development after episodes of maternal stress will be discussed in the next section.

To conclude, on the behavioral level, trauma and maltreatment can have adverse transgenerational consequences. As parents abused in childhood have a higher probability for re-victimization, trauma-related psychopathology and violent behavior, their offspring is also at an increased risk for traumatic experiences. Observational learning and imitation of poor lifestyle habits as well as sedentary lifestyle, smoking and alcohol consumption could be additional behavioral mechanisms accounting for the cycle of maltreatment, which also impact physical health. On a biological level, next to the genetic transmission of risk (diLalla & Gottesman, 1991), violence or stress exposure *in utero* is likely to impact the unborn's stress system, presumably via epigenetic mechanisms.

Transgenerational Epigenetics

If psychological and behavioral distress consequent to trauma and childhood maltreatment can be passed on the next generation, how can this transmission be biologically explained? This enigma could be partially solved by investigating epigenetics. It has already been shown that epigenetic modifications occurring in a germline cell can become stable in the next generation, if fecundation occurs (Bale, 2014).

Chronic and unpredictable maternal separation in mice induced behavioral alterations not only in the affected offspring, but also in their own pups (Franklin et al., 2010). In more detail, increased depression and anxiety-like behavior as well as methylation modifications of sperm cells in numerous stress- and emotion-regulation-related genes have been observed, suggesting enduring epigenetic marks that can be transgenerationally

DOI: 10.1002/bsl

transmitted (Franklin et al., 2010). Besides DNA methylation, microRNAs (miRNAs) can also regulate gene transcription and have been implicated in the transmission of the effects of early life stress (Gapp et al., 2014; Zucchi et al., 2013). An experiment conducted by Zucchi et al. (2013) indicated that, if pregnant rats were exposed to stressors such as restraint or forced swimming, 336 miRNAs were differentially expressed in their offspring. When a miRNA binds to its mRNA-target, it represses expression through degradation of the mRNA (Khraiwesh et al., 2010). The putative gene targets for miRNA that appeared differentially expressed were related to neurotransmission, neurodevelopment, brain pathologies and stress responsivity. This indicates that the developing brain is particularly vulnerable to stress exposure during gestation (Zucchi et al., 2013).

Another experiment showed alterations in miRNA expression, metabolism and behavior after traumatic stress in early life up to the third generation in mice (Gapp et al., 2014). In response to maternal stress and unexpected maternal separation, the relative miRNA levels were altered in germ cells, serum and brain of the first generation. This was accompanied by behavioral alterations, including increased depressive behavior and reduced fear in experimental tests (Gapp et al., 2014). The resulting offspring revealed upregulation of several miRNAs in serum, plasma and brain, but interestingly not in sperm. However, the third generation showed behavioral symptoms similar to those of the first and second generations of mice, except changes in miRNA of the sperm cells. These findings suggest an alternative mechanism mediating the transfer of adaptive changes to subsequent generations, which might include other epigenetic marks such as histone modifications. Last, the authors injected sperm RNAs purified from early-stress exposed mice into fertilized mouse oocytes, which reproduced behavioral alterations (Gapp et al., 2014), suggesting the existence of a RNA-dependent processes in the inheritance of acquired traits after early traumatic stress in mammals.

In humans, it has been reported that parental PTSD is not only a risk factor for PTSD in the offspring, but also leads to transgenerational effects on the epigenetic level (Yehuda & Bierer, 2009). In more detail, differential effects of maternal and paternal PTSD on the methylation of their children's *NR3C1* 1_F promoter have been observed. If only the father was diagnosed with PTSD the promoter region was hypermethylated, while if both parents suffered from PTSD methylation was significantly decreased (Yehuda et al., 2014). The authors discussed that mothers were the primary caregivers in their sample and might have buffered the stress associated with parental PTSD, while PTSD in both parents might lead to unpredictable stress in the offspring, resulting in epigenetic changes mimicking those of individuals with PTSD (Yehuda et al., 2014).

Psychosocial difficulties during pregnancy may also affect the methylation pattern and stress responsiveness in developing babies. An increased depressed maternal mood in the third trimester has been associated with increased neonatal methylation of exon 1_F of the *NR3C1* promoter (Oberlander et al., 2008). Furthermore, maternal exposition to war or rape during pregnancy has been associated with higher DNA methylation of the *NR3C1* promoter region in newborns (Mulligan, D'Errico, Stees, & Hughes, 2012; Rodney & Mulligan, 2014). Similarly, Radtke and colleagues (2011) reported a positive correlation between maternal exposure to intimate partner violence during pregnancy and the *NR3C1* DNA methylation level in their teenage children (Radtke et al., 2011). Even though the mental health status of the children was not assessed, these findings point towards an epigenetic transmission of prenatal stress and children's psychological health.

DOI: 10.1002/bsl

In sum, parental and prenatal exposure to adversities such as war or partner violence can lead to enduring changes in the next generation, partly via epigenetic processes. However, the exact molecular mechanisms remain to be illuminated, since a genome-wide loss of DNA methylation occurs following fertilization (Morgan et al., 2005). If methylation in the DNA inherited from maternal and paternal stem cells is erased in the very first stage of development and reprogrammed across next stages, why can parental methylation traces be found in the offspring after birth? Although it is not entirely clear how the "memory" of parental methylation pattern can be maintained, broader epigenetic machinery is likely to interact. Presumably non-coding RNAs or chromatin structure modifications could store the information to later guide the methyltransferases and define where to add methyl groups to the DNA (Yan, 2014). It is further important to ask whether the observed methylation patterns in offspring are truly inherited or whether they appear as a consequence of a modified parenting model in the event that parents went through adversities during their own childhood. Research indicates that both processes seem to be of importance. On the one hand, animal models show changes in behavior up to two generations after early life trauma, which could affect methylation in their offspring (Gapp et al., 2014; Weaver et al., 2004). On the other hand, cross-fostering studies reveal that methylation marks at specific sites can be at least partially reversed by environmental enrichment (Bredy, Zhang, Grant, Diorio, & Meaney, 2004). In addition, maternal pregnancy stress has been shown to directly induce methylation changes in babies (Mulligan et al., 2012; Oberlander et al., 2008; Radtke et al., 2011). However, further investigations of parenting behavior after a history of childhood maltreatment and methylation changes in parents and their descendants are needed to completely understand the transgenerational programming of the epigenome.

LIMITATIONS AND FURTHER DIRECTIONS

This review has summarized current literature regarding the effect of childhood and war trauma on methylation status. The majority of the summarized studies investigated peripheral blood cells. Since DNA methylation is a core mechanism for cellular functional differentiation, it is difficult to clarify if methylation changes in blood cells mirror the methylation status of the brain. While this empirical research question can of course not be addressed in human studies, future animal research can help to clarify whether the observed methylation changes are global or cell specific.

One caveat when interpreting the literature on the biological consequences of war and childhood trauma is the aforementioned alterations in lifestyle frequently observed in trauma survivors (Zhou, Enoch, & Goldman, 2014). As survivors of violence exposure show higher rates of smoking, alcohol and drug consumption (Campbell, 2002; Carbone-López et al., 2006; Krug et al., 2002; Pico-Alfonso et al., 2006), the effects of adverse lifestyle are difficult to disentangle from the effects of the stress per se. Therefore, when interpreting the literature, one should be aware of the complex interplay of genetics, perinatal environment, lifestyle factors, observational learning and associated epigenetic changes. Accordingly, it becomes obvious that epigenetic processes only represent one piece in a very complex puzzle. Nevertheless, the flexibility in response to environmental demands as well as the potential heritability render epigenetic processes an interesting candidate for future research.

Concerning the transgenerational aspects of trauma and childhood maltreatment, most studies have focused on the mother–child transmission (prenatal and postnatal)

DOI: 10.1002/bsl

of epigenetic marks. Initial evidence also highlights the important role of the father in transmitting the potentially adverse effects of early trauma and war. Therefore, epigenetic research on sperm cells from fathers exposed to war and on their children could provide important hints about the transgenerationality of paternal trauma.

Epigenetic plasticity is thought to be of importance for the adaptation to adverse environments and might help to explain interindividual variation in behavior. As indicated earlier in the article, the majority of trauma survivors shows a relative resilience and does not respond with the development of psychological disorders. Furthermore, while female childhood maltreatment and trauma survivors are at increased risk to develop internalizing behavior problems such as PTSD or depression, male survivors rather respond with antisocial and violent behavior. However, it is still not exactly clear which processes mediate the different behavioral consequences of trauma and childhood maltreatment and the observed gender effects. A biological/epigenetic approach might help to promote a better understanding of human development and behavior after traumatic experiences.

Furthermore, individuals vary not only in their reaction to traumatic experiences, but also in their responsiveness to trauma-focused psychotherapy, with approximately one-third of trauma survivors not benefitting from therapy (Bradley, Greene, Russ, Dutra, & Westen, 2005). Preliminary evidence from 16 trauma survivors receiving psychotherapy indicates that some epigenetic marks might represent predictors of therapy success, while others can be modified in the course of successful therapeutic treatment (Yehuda et al., 2013). Hence, research on the epigenetic processes accompanying successful recovery from trauma-related disorders could shed light on the underlying biological processes and help to develop personalized treatments for PTSD.

Finally, it is important to emphasize that epigenetic marks could help to draw attention to the profound consequences of war trauma and childhood maltreatment, which can even proceed to the next generation. While the public media rather focus on the visible physical wounds and economic needs caused by war, terrorism or natural disasters, the invisible, psychological wounds are at least as disastrous and can lead to life-long impaired psychosocial functioning, increased risk of physical diseases and even a transgenerational transmission of risk. With epigenetic research, it finally became feasible to begin to shed light on these long-lasting consequences, and to support the psychological findings with biological data. On a public health policy level, these findings could support arguments for an enhanced awareness for the psychological consequences of trauma in first help providers and physicians, as well as an increased availability of mental health care services, especially for highly traumatized populations such as refugees and asylum seekers.

ACKNOWLEDGMENTS

We thank Daniela Conrad for helpful comments on an earlier version of this manuscript.

REFERENCES

Ackerman, P. T., Newton, J. E. O., McPherson, W. B., Jones, J. G., & Dykman, R. A. (1998). Prevalence of posttraumatic stress disorder and other psychiatric diagnoses in three groups of abused children (sexual, physical, and both). *Child Abuse and Neglect*, *22*(8), 759–774.

DOI: 10.1002/bsl

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*(5th ed. pp.). Washington, DC: Author.
Appel, A. E., & Holden, G. W. (1998). The co-occurrence of spouse and physical child abuse: A review and appraisal. *Journal of Family Psychology*, *12*(4), 578.
Arata, C. M. (2000). From child victim to adult victim: A model for predicting sexual revictimization. *Child Maltreatment*, *5*(1), 28–38.
Baker, D., Ekhator, N., Kasckow, J., Hill, K., Zoumakis, E., Dashevsky, B., … Chrousos, G. (2001). Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. *Neuroimmunomodulation*, *9*(4), 209–217.
Bale, T. L. (2014). Lifetime stress experience: Transgenerational epigenetics and germ cell programming. *Dialogues in Clinical Neuroscience*, *16*(3), 297–305.
Banyard, V. (1997). The impact of childhood sexual abuse and family functioning on four dimensions of women's later parenting. *Child Abuse and Neglect*, *21*(11), 1095.
Barrett, B. (2009). The impact of childhood sexual abuse and other forms of childhood adversity on adulthood parenting. *Journal of Child Sexual Abuse*, *18*(5), 489–512.
Barrios, Y. V., Gelaye, B., Zhong, Q., Nicolaidis, C., Rondon, M. B., Garcia, P. J., … Mascaro Sanchez, P. A. (2015). Association of childhood physical and sexual abuse with intimate partner violence, poor general health and depressive symptoms among pregnant women. *PLoS One*, *10*(1), e0116609.
Batten, S. V., Aslan, M., Maciejewski, P. K., & Mazure, C. M. (2004). Childhood maltreatment as a risk factor for adult cardiovascular disease and depression. *Journal of Clinical Psychiatry*, *65*(2), 249–254.
Bensley, L., Van Eenwyk, J., & Wynkoop Simmons, K. (2003). Childhood family violence history and women's risk for intimate partner violence and poor health. *American Journal of Preventive Medicine*, *25* (1), 38–44.
Bick, J., Naumova, O., Hunter, S., Barbot, B., Lee, M., Luthar, S. S., Raefski, A., … (2012). Childhood adversity and DNA methylation of genes involved in the hypothalamus–pituitary–adrenal axis and immune system: Whole-genome and candidate-gene associations. *Development and Psychopathology*, *24* (4), 1417–1425.
Binder, E. (2009). The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*, *34*(Suppl. 1), 186–195.
Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., … Tang, Y. (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *Journal of the American Medical Association*, *299*(11), 1291–1305.
Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta- analysis of psychotherapy for PTSD. *American Journal of Psychiatry*, *162*(2), 214–227.
Bredy, T. W., Zhang, T. Y., Grant, R. J., Diorio, J., & Meaney, M. J. (2004). Peripubertal environmental enrichment reverses the effects of maternal care on hippocampal development and glutamate receptor subunit expression. *European Journal of Neuroscience*, *20*(5), 1355–1362.
Breslau, N., Kessler, R. C., Chilcoat, H. D., Schultz, L. R., Davis, G. C., & Andreski, P. (1998). Trauma and posttraumatic stress disorder in the community: The 1996 Detroit Area Survey of Trauma. *Archives of General Psychiatry*, *55*(7), 626–632.
Brewin, C. (2011). The nature and significance of memory disturbance in posttraumatic stress disorder. *Annual Review of Clinical Psychology*, *7*, 203–227.
Brewin, C., Andrews, B., & Valentine, J. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology*, *68*(5), 748–766.
Brown, D., Anda, R., Felitti, V., Edwards, V., Malarcher, A., Croft, J., & Giles, W. (2010). Adverse childhood experiences are associated with the risk of lung cancer: A prospective cohort study. *BMC Public Health*, *10*(1), 20.
Buist, A. (1998). Childhood abuse, parenting and postpartum depression. *Australian and New Zealand Journal of Psychiatry*, *32*(4), 479–487.
Butchart, A., Harvey, A. P., Mian, M., & Furniss, T. (2006). *Preventing child maltreatment: A guide to taking action and generating evidence*. Geneva, Switzerland: World Health Organization.
Campbell, J. C. (2002). Health consequences of intimate partner violence. *Lancet*, *359*(9314), 1331–1336.
Carbone-López, K., Kruttschnitt, C., & Macmillan, R. (2006). Patterns of intimate partner violence and their associations with physical health, psychological distress, and substance use. *Public Health Reports*, *121*(4), 382–392.
Carpenter, L. L., Carvalho, J., Tyrka, A. R., Wier, L. M., Mello, A. F., & Mello, M. F. (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, *62*(10), 1080–1087.
Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology*, *35*(13), 2617–2623.
Carpenter, L. L., Tyrka, A. R., Ross, N. S., Khoury, L., Anderson, G. M., & Price, L. H. (2009). Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biological Psychiatry*, *66*(1), 69–75.

DOI: 10.1002/bsl

Chaufan, C., & Joseph, J. (2013). The "missing heritability" of common disorders: Should health researchers care? *International Journal of Health Services*, *43*(2), 281–303.
Chiu, G. R., Lutfey, K. E., Litman, H. J., Link, C. L., Hall, S. A., & McKinlay, J. B. (2013). Prevalence and overlap of childhood and adult physical, sexual, and emotional abuse: A descriptive analysis of results from the Boston Area Community Health (BACH) Survey. *Violence and Victims*, *28*(3), 381–402.
Cicchetti, D., & Toth, S. L. (2005). Child maltreatment. *Annual Review of Clinical Psychology*, *1*(1), 409–438.
Classen, C. C., Palesh, O. G., & Aggarwal, R. (2005). Sexual revictimization: A review of the empirical literature. *Trauma, Violence, and Abuse*, *6*(2), 103–129.
Coker, A. L., Smith, P. H., Bethea, L., King, M. R., & McKeown, R. E. (2000). Physical health consequences of physical and psychological intimate partner violence. *Archives of Family Medicine*, *9*(5), 451.
Cokkinides, V. E., Coker, A. L., Sanderson, M., Addy, C., & Bethea, L. (1999). Physical violence during pregnancy: Maternal complications and birth outcomes. *Obstetrics and Gynecology*Part 1, *93*(5), 661–666.
Cottrell, E. C., & Seckl, J. R. (2009). Prenatal stress, glucocorticoids and the programming of adult disease. *Frontiers in Behavioral Neuroscience*, *3*, 19.
Crick, F. (1970). Central dogma of molecular biology. *Nature*, *227*(5258), 561–563.
Currie, J., & Tekin, E. (2012). Understanding the cycle: Childhood maltreatment and future crime. *Journal of Human Resources*, *47*(2), 509–549.
Curry, M., Perrin, N., & Wall, E. (1998). Effects of abuse on maternal complications and birth weight in adult and adolescent women. *Obstetrics and Gynecology*, *92*(4), 530–534.
Danese, A., Pariante, C. M., Caspi, A., Taylor, A., & Poulton, R. (2007). Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(4), 1319–1324.
Danese, A., & Tan, M. (2014). Childhood maltreatment and obesity: systematic review and meta-analysis. *Molecular Psychiatry*, *19*(5), 544–554.
Daskalakis, N. P., & Yehuda, R. (2014). Site-specific methylation changes in the glucocorticoid receptor exon 1 F promoter in relation to life adversity: Systematic review of contributing factors. *Frontiers in Neuroscience*, *8*, 369.
de Jong, J. T., Komproe, I. H., Van Ommeren, M., El Masri, M., Araya, M., Khaled, N., … van De Put, W. (2001). Lifetime events and posttraumatic stress disorder in four postconflict settings. *Journal of the American Medical Association*, *286*(5), 555–562.
de Kloet, C., Vermetten, E., Bikker, A., Meulman, E., Geuze, E., Kavelaars, A., … Westenberg H. (2007). Leukocyte glucocorticoid receptor expression and immunoregulation in veterans with and without posttraumatic stress disorder. *Molecular Psychiatry*, *12*(5), 443–453.
de Quervain, D., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology*, *30*(3), 358–370.
diLalla, L. F., & Gottesman, I. I. (1991). Biological and genetic contributors to violence—Widom's untold tale. *Psychological Bulletin*, *109*(1), 125–129.
DiPietro, J. A., Novak, M. F. S. X., Costigan, K. A., Atella, L. D., & Reusing, S. P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development*, *77*(3), 573–587.
Dixon, L., Browne, K., & Hamilton-Giachritsis, C. (2005). Risk factors of parents abused as children: A mediational analysis of the intergenerational continuity of child maltreatment (Part I). *Journal of Child Psychology and Psychiatry*, *46*(1), 47–57.
Dixon, L., Browne, K., & Hamilton-Giachritsis, C. (2008). Patterns of risk and protective factors in the intergenerational cycle of maltreatment. *Journal of Family Violence*, *24*(2), 111–122.
Duke, N. N., Pettingell, S. L., McMorris, B. J., & Borowsky, I. W. (2010). Adolescent violence perpetration: Associations with multiple types of adverse childhood experiences. *Pediatrics*, *125*(4), e778–e786.
Dunmore, E., Clark, D. M., & Ehlers, A. (2001). A prospective investigation of the role of cognitive factors in persistent Posttraumatic Stress Disorder (PTSD) after physical or sexual assault. *Behaviour Research and Therapy*, *39*(9), 1063–1084.
Ehrensaft, M. K., Cohen, P., Brown, J., Smailes, E., Chen, H., & Johnson, J. G. (2003). Intergenerational transmission of partner violence: A 20-year prospective study. *Journal of Consulting and Clinical Psychology*, *71*(4), 741.
Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(49), 17312–17315.
Evans, S. E., Davies, C., & DiLillo, D. (2008). Exposure to domestic violence: A meta-analysis of child and adolescent outcomes. *Aggression and Violent Behavior*, *13*(2), 131–140.
Fagiolini, M., Jensen, C. L., & Champagne, F. A. (2009). Epigenetic influences on brain development and plasticity. *Current Opinion in Neurobiology*, *19*(2), 207–212.
Fawzi, M., Pham, T., Lin, L., Nguyen, T., Ngo, D., Murphy, E., & Mollica, R. (1997). The validity of posttraumatic stress disorder among Vietnamese refugees. *Journal of Traumatic Stress*, *10*(1), 101–108.
Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). Exposure to childhood sexual and physical abuse and adjustment in early adulthood. *Child Abuse and Neglect*, *32*(6), 607–619.

DOI: 10.1002/bsl

Fernandez, F. M., & Krueger, P. M. (1999). Domestic violence: Effect on pregnancy outcome. *Journal of the American Osteopathic Association*, *99*(5), 254–256.
Finkelhor, D., Turner, H., Shattuck, A., & Hamby, S. (2013). Violence, crime, and abuse exposure in a national sample of children and youth: An update. *JAMA Pediatrics*, *167*(7), 614–621.
Francis, R. C. (2011). *Epigenetics: How environment shapes our genes*. New York, NY: W.W. Norton & Company.
Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., … Vizi, S. (2010). Epigenetic transmission of the impact of early stress across generations. *Biological Psychiatry*, *68*(5), 408–415.
Gapp, K., Jawaid, A., Sarkies, P., Bohacek, J., Pelczar, P., Prados, J., … Farinelli, L. (2014). Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. *Nature Neuroscience*, *17*(5), 667–669.
Gazmararian, J. A., Adams, M. M., Saltzman, L. E., Johnson, C. H., Bruce, F. C., Marks, J. S., & Zahniser, S. C. (1995). The relationship between pregnancy intendedness and physical violence in mothers of newborns. *Obstetrics and Gynecology*, *85*(6), 1031–1038.
Gershon, E. S., Alliey-Rodriguez, N., & Liu, C. (2011). After GWAS: Searching for genetic risk for schizophrenia and bipolar disorder. *American Journal of Psychiatry*, *168*(3), 253–156.
Gil-González, D., Vives-Cases, C., Ruiz, M. T., Carrasco-Portiño, M., & Álvarez-Dardet, C. (2008). Childhood experiences of violence in perpetrators as a risk factor of intimate partner violence: A systematic review. *Journal of Public Health*, *30*(1), 14–22.
Gola, H., Engler, H., Sommershof, A., Adenauer, H., Kolassa, S., Schedlowski, M., … Groettrup, M. (2013). Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells. *BMC Psychiatry*, *13*(1), 40.
Goodwin, M., Gazmararian, J., Johnson, C., Gilbert, B., Saltzman, L., & Group, P. W. (2000). Pregnancy intendedness and physical abuse around the time of pregnancy: Findings from the pregnancy risk assessment monitoring system. *Maternal and Child Health Journal*, *4*(2), 85–92.
Heim, C. M., & Nemeroff, C. B. (2009). Neurobiology of posstraumatic stress disorder. *CNS Spectrums*, *14*(Suppl. 1), 13–24.
Hoge, E. A., Brandstetter, K., Moshier, S., Pollack, M. H., Wong, K. K., & Simon, N. M. (2009). Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and Anxiety*, *26*(5), 447–455.
Holliday, R., & Pugh, J. E. (1975). DNA modification mechanisms and gene activity during development. *Science*, *187*(4173), 226–232.
Hunter, A. L., Minnis, H., & Wilson, P. (2011). Altered stress responses in children exposed to early adversity: A systematic review of salivary cortisol studies. *Stress*, *14*(6), 614–626.
Jaenisch, R., & Bird, A. (2003). Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. *Nature Genetics*, *33*, 245–254.
Kellermann, N. P. (2013). Epigenetic transmission of holocaust trauma: Can nightmares be inherited? *Israel Journal of Psychiatry and Related Science*, *50*(1), 33–39.
Kessler, R. C., Birnbaum, H., Demler, O., Falloon, I. R. H., Gagnon, E., Guyer, M., … Howes, M. J. (2005). The prevalence and correlates of nonaffective psychosis in the National Comorbidity Survey Replication (NCS-R). *Biological Psychiatry*, *58*(8), 668–676.
Kessler, R., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, *52*(12), 1048–1060.
Khraiwesh, B., Arif, M. A., Seumel, G. I., Ossowski, S., Weigel, D., Reski, R., & Frank, W. (2010). Transcriptional control of gene expression by microRNAs. *Cell*, *140*(1), 111–122.
Khulan, B., Manning, J., Dunbar, D., Seckl, J., Raikkonen, K., Eriksson, J., & Drake, A. (2014). Epigenomic profiling of men exposed to early-life stress reveals DNA methylation differences in association with current mental state. *Translational Psychiatry*, *4*(9), e448.
Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J., Pariante, C., … Pace, T. (2013). Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. *Nature Neuroscience*, *16*(1), 33–41.
Kolassa, I.-T., Ertl, V., Kolassa, S., Onyut, L., & Elbert, T. (2010a). The probability of spontaneous remission from PTSD depends on the number of traumatic event types experienced. *Psychological Trauma: Theory, Research, Practice and Policy*, *3*(3), 169–174.
Kolassa, I.-T., Kolassa, S., Ertl, V., Papassotiropoulos, A., & De Quervain, D. (2010b). The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-O-methyltransferase Val (158)Met polymorphism. *Biological Psychiatry*, *67*, 304–308.
Krug, E. G., Mercy, J. A., Dahlberg, L. L., & Zwi, A. B. (2002). The world report on violence and health. *Lancet*, *360*(9339), 1083–1088.
Labonté, B., Azoulay, N., Yerko, V., Turecki, G., & Brunet, A. (2014). Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. *Translational Psychiatry*, *4*, e368.
Leserman, J., & Drossman, D. A. (2007). Relationship of abuse history to functional gastrointestinal disorders and symptoms: Some possible mediating mechanisms. *Trauma, Violence, and Abuse*, *8*(3), 331–343.
Letourneau, E. J., Holmes, M., & Chasedunn-Roark, J. (1999). Gynecologic health consequences to victims of interpersonal violence. *Women's Health Issues*, *9*(2), 115–120.

DOI: 10.1002/bsl

Letourneau, N., Young, C., Secco, L., Stewart, M., Hughes, J., & Critchley, K. (2011). Supporting mothering: Service providers' perspectives of mothers and young children affected by intimate partner violence. *Research in Nursing and Health*, *34*(3), 192–203.

Levenson, J. M., & Sweatt, J. D. (2005). Epigenetic mechanisms in memory formation. *Nature Reviews Neuroscience*, *6*(2), 108–118.

Maercker, A., Michael, T., Fehm, L., Becker, E. S., & Margraf, J. (2004). Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. *British Journal of Psychiatry*, *184*(6), 482–487.

Maercker, A., Mohiyeddini, C., Müller, M., Xie, W., Hui Yang, Z., Wang, J., & Müller, J. (2009). Traditional versus modern values values, self-percieved interpersonal factors, and posttraumatic stress in Chinese and German crime victims. *Psychology and Psychotherapy*, *82*(2), 219–232.

Maier, T. (2007). Weathers' and Keane's, "The criterion A problem revisited: Controversies and challenges in defining and measuring psychological trauma.". *Journal of Traumatic Stress*, *20*(5), 915–916.

Malta, L., McDonald, S., Hegadoren, K., Weller, C., & Tough, S. (2012). Influence of interpersonal violence on maternal anxiety, depression, stress and parenting morale in the early postpartum: A community based pregnancy cohort study. *BMC Pregnancy and Childbirth*, *12*(1), 153.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., … McCarthy, M. I. (2009). Finding the missing heritability of complex diseases. *Nature*, *461*(7265), 747–753.

McGowan, P., Sasaki, A., D'Alessio, A., Dymov, S., Labonté, B., Szyf, M., … Turecki, G. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, *12*(3), 342–348.

Meaney, M. J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., … Sharma, S. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. *Developmental Neuroscience*, *18*(1/2), 49–72.

Mehta, D., Klengel, T., Conneely, K., Smith, A., Altmann, A., Pace, T., … Rex-Haffner, M. (2013). Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(20), 8302–8307.

Messman-Moore, T. L., Long, P. J., & Siegfried, N. J. (2000). The revictimization of child sexual abuse survivors: An examination of the adjustment of college women with child sexual abuse, adult sexual assault, and adult physical abuse. *Child Maltreatment*, *5*(1), 18–27.

Miller, C. A., & Sweatt, J. D. (2007). Covalent modification of DNA regulates memory formation. *Neuron*, *53*(6), 857–869.

Morath, J., Moreno-Villanueva, M., Hamuni, G., Kolassa, S., Ruf-Leuschner, M., Schauer, M., … Elbert, T. (2014). Effects of psychotherapy on DNA strand break accumulation originating from traumatic stress. *Psychotherapy and Psychosomatics*, *83*(5), 289–297.

Moreno-Villanueva, M., Morath, J., Vanhooren, V., Elbert, T., Kolassa, S., Libert, C., … Bürkle, A. (2013). N-glycosylation profiling of plasma provides evidence for accelerated physiological aging in post-traumatic stress disorder. *Translational Psychiatry*, *3*, e320.

Morgan, H. D., Santos, F., Green, K., Dean, W., & Reik, W. (2005). Epigenetic reprogramming in mammals. *Human Molecular Genetics*, *14*(Suppl. 1), 47–58.

Moylan, C., Herrenkohl, T., Sousa, C., Tajima, E., Herrenkohl, R., & Russo, M. J. (2010). The effects of child abuse and exposure to domestic violence on adolescent internalizing and externalizing behavior problems. *Journal of Family Violence*, *25*(1), 53–63.

Mulligan, C., D'Errico, N., Stees, J., & Hughes, D. (2012). Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. *Epigenetics*, *7*(8), 853–857.

Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmuhl, Y., & Fischer, D. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nature Neuroscience*, *12*, 1559–1566.

Myers, J. E. B. (2011). *The APSAC handbook on child maltreatment*(3rd ed. pp.). Thousand Oaks, CA: SAGE Publications.

Naumova, O. Y., Lee, M., Koposov, R., Szyf, M., Dozier, M., & Grigorenko, E. L. (2012). Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. *Development and Psychopathology*, *24*(01), 143–155.

Neugebauer, R., Fisher, P. W., Turner, J. B., Yamabe, S., Sarsfield, J. A., & Stehling-Ariza, T. (2009). Posttraumatic stress reactions among Rwandan children and adolescents in the early aftermath of genocide. *International Journal of Epidemiology*, *38*(4), 1033–1045.

Neuner, F., Schauer, M., Karunakara, U., Klaschik, C., Robert, C., & Elbert, T. (2004). Psychological trauma and evidence for enhanced vulnerability for posttraumatic stress disorder through previous trauma among West Nile refugees. *BMC Psychiatry*, *4*, 34.

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. *PLoS Medicine*, *9*(11), e1001349.

O'Donnell, K. J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T. G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11β-HSD2. *Psychoneuroendocrinology*, *37*(6), 818–826.

DOI: 10.1002/bsl

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*, *3*(2), 97–106.
Oh, J. E., Chambwe, N., Klein, S., Gal, J., Andrews, S., Gleason, G., … Shaknovich, R. (2013). Differential gene body methylation and reduced expression of cell adhesion and neurotransmitter receptor genes in adverse maternal environment. *Translational Psychiatry*, *3*, 218.
Pace, T. W., & Heim, C. M. (2011). A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. *Brain, Behavior, and Immunity*, *25*(1), 6–13.
Peled, E., & Gil, I. B. (2011). The mothering perceptions of women abused by their partner. *Violence Against Women*, *17*(4), 457–479.
Perroud, N., Paoloni-Giacobino, A., Prada, P., Olié, E., Salzmann, A., Nicastro, R., … Guillaume, S. (2011). Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: A link with the severity and type of trauma. *Translational Psychiatry*, *1*, e59.
Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M. E., Furrer, S., … Ardu, S. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational Psychiatry*, *3*, e207.
Pervanidou, P., & Chrousos, G. P. (2012). Metabolic consequences of stress during childhood and adolescence. *Metabolism, Clinical and Experimental*, *61*(5), 611–619.
Picchioni, M. M., & Murray, R. M. (2007). Schizophrenia. *British Medical Journal*, *335*(7610), 91–95.
Pico-Alfonso, M. A., Garcia-Linares, M. I., Celda-Navarro, N., Blasco-Ros, C., Echeburúa, E., & Martinez, M. (2006). The impact of physical, psychological, and sexual intimate male partner violence on women's mental health: Depressive symptoms, posttraumatic stress disorder, state anxiety, and suicide. *Journal of Women's Health*, *15*(5), 599–611.
Radtke, K. M., Ruf, M., Gunter, H. M., Dohrmann, K., Schauer, M., & Meyer, A. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry*, *1*, 1–6.
Ramchandani, S., Bhattacharya, S. K., Cervoni, N., & Szyf, M. (1999). DNA methylation is a reversible biological signal. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(11), 6107–6112.
Rice, J. C., & Allis, C. D. (2001). Gene regulation: Code of silence. *Nature*, *414*(6861), 258–261.
Rodney, N. C., & Mulligan, C. J. (2014). A biocultural study of the effects of maternal stress on mother and newborn health in the Democratic Republic of Congo. *American Journal of Physical Anthropology*, *155*(2), 200–209.
Roozendaal, B., Okuda, S., de Quervain, D. J. F., & McGaugh, J. L. (2006). Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience*, *138*(3), 901–910.
Rusiecki, J. A., Byrne, C., Galdzicki, Z., Srikantan, V., Chen, L., Poulin, M., … Liying, Y. (2013). PTSD and DNA methylation in select immune function gene promoter regions: A repeated measures case–control study of U.S. military service members. *Frontiers in Psychiatry*, *4*, 56.
Saltzman, L., Johnson, C., Gilbert, B., & Goodwin, M. (2003). Physical abuse around the time of pregnancy: An examination of prevalence and risk factors in 16 states. *Maternal and Child Health Journal*, *7*(1), 31–43.
Sareen, J., Cox, B. J., Afifi, T. O., de Graaf, R., Asmundson, G. J. G., ten Have, M., & Stein, M. B. (2005). Anxiety disorders and risk for suicidal ideation and suicide attempts. *Archives on General Psychiatry*, *62*(11), 1249–1257.
Schauer, M., Neuner, F., Karunakara, U., Klaschik, C., Robert, C., & Elbert, T. (2003). PTSD and the "building block" effect of psychological trauma among West Nile Africans. *European Society for Traumatic Stress Studies Bulletin*, *10*(2), 5–6.
Schmuel, E., & Schenker, J. G. (1998). Violence against women: The physician's role. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *80*(2), 239–245.
Schoedl, A. F., Costa, M. C. P., Mari, J. J., Mello, M. F., Tyrka, A. R., Carpenter, L. L., & Price, L. H. (2010). The clinical correlates of reported childhood sexual abuse: An association between age at trauma onset and severity of depression and PTSD in adults. *Journal of Child Sexual Abuse*, *19*(2), 156–170.
Schury, K., & Kolassa, I.-T. (2012). Biological memory of childhood maltreatment: Current knowledge and recommendations for future research. *Annals of the New York Academy of Sciences*, *1262*(1), 93–100.
Scott K. M., Koenen K. C., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M. C., Benjet, C., … Bruffaerts, R. (2013). Associations between lifetime traumatic events and subsequent chronic physical conditions: A cross-national, cross-sectional study. *PLoS One*, *8*(11), e80573.
Seckl, J. R. (2004). Prenatal glucocorticoids and long-term programming. *European Journal of Endocrinology*, *151*(Suppl. 3), 49–62.
Seckl, J. R., & Meaney, M. (2006). Glucocorticoid "programming" and PTSD risk. *Annals of the New York Academy of Sciences*, *1071*(1), 351–378.
Silverman, J. G., Decker, M. R., Reed, E., & Raj, A. (2006). Intimate partner violence victimization prior to and during pregnancy among women residing in 26 U.S. states: Associations with maternal and neonatal health. *American Journal of Obstetrics and Gynecology*, *195*(1), 140–148.

DOI: 10.1002/bsl

Sipahi, L., Wildman, D. E., Aiello, A. E., Koenen, K. C., Galea, S., Abbas, A., & Uddin, M. (2014). Longitudinal epigenetic variation of DNA methyltransferase genes is associated with vulnerability to post-traumatic stress disorder. *Psychological Medicine*, *44*(15), 3165–3179.
Slatkin, M. (2009). Epigenetic inheritance and the missing heritability problem. *Genetics*, *182*(3), 845–850.
Smith, A. K., Conneely, K. N., Kilaru, V., Mercer, K. B., Weiss, T. E., Bradley, B., … Tang, Y. (2011). Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *156*(6), 700–708.
Smith, C., & Thornberry, T. P. (1995). The relationship between childhood maltreatment and adolescent involvement in delinquency. *Criminology*, *33*(4), 451–481.
Sommershof, A., Aichinger, H., Engler, H., Adenauer, H., Catani, C., Boneberg, E. M., … Elbert, T. (2009). Substantial reduction of naive and regulatory T cells following traumatic stress. *Brain, Behavior, and Immunity*, *23*, 1117–1124.
Stansfeld, S. A., Clark, C., Rodgers, B., Caldwell, T., & Power, C. (2010). Repeated exposure to socioeconomic disadvantage and health selection as life course pathways to mid-life depressive and anxiety disorders. *Social Psychiatry and Psychiatric Epidemiology*, *46*(7), 549–558.
Stoltenborgh, M., van IJzendoorn, M. H., Euser, E. M., & Bakermans-Kranenburg, M. J. (2011). A global perspective on child sexual abuse: Meta-analysis of prevalence around the world. *Child Maltreatment*, *16*(2), 79–101.
Strahl, B. D., & Allis, C. D. (2000). The language of covalent histone modifications. *Nature*, *403*(6765), 41–45.
Suderman, M., Borghol, N., Pappas, J., Pinto Pereira, S., Pembrey, M., Hertzman, C., … Power, C. (2014). Childhood abuse is associated with methylation of multiple loci in adult DNA. *BMC Medical Genomics*, *7*(1), 13.
Suglia, S., Clark, C., Boynton-Jarrett, R., Kressin, N., & Koenen, K. (2014). Child maltreatment and hypertension in young adulthood. *BMC Public Health*, *14*(1), 1149.
Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry*, *48*(3/4), 245–261.
Thomas, C., Hypponen, E., & Power, C. (2008). Obesity and type 2 diabetes risk in midadult life: The role of childhood adversity. *Pediatrics*, *121*(5), e1240–e1249.
Thombs, B. D., Bernstein, D. P., Ziegelstein, R. C., Scher, C. D., Forde, D. R., Walker, E. A., & Stein, M. B. (2006). An evaluation of screening questions for childhood abuse in 2 community samples: Implications for clinical practice. *Archives of Internal Medicine*, *166*(18), 2020–2026.
Thornberry, T. P., Henry, K. L., Ireland, T. O., & Smith, C. A. (2010). The causal impact of childhood-limited maltreatment and adolescent maltreatment on early adult adjustment. *Journal of Adolescent Health*, *46*(4), 359–365.
Tyrka, A. R., Price, L. H., Kao, H.-T., Porton, B., Marsella, S. A., & Carpenter, L. L. (2010). Childhood maltreatment and telomere shortening: Preliminary support for an effect of early stress on cellular aging. *Biological Psychiatry*, *67*(6), 531–534.
Tyrka, A. R., Price, L. H., Marsit, C., Walters, O. C., & Carpenter, L. L. (2012). Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PLoS One*, *7*(1), e30148.
Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., & de Los Santos, R. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 9470–9475.
van Zuiden, M., Geuze, E., Willemen, H. L. D. M., Vermetten, E., Maas, M., Heijnen, G. J., & Kvelaars, A. (2010). Pre-existing high glucocorticoid receptor number predicting development of posttramatic stress symptoms after military deployment. *American Journal of Psychiatry*, *168*(1), 89–96.
von Känel, R., Hepp, U., Kraemer, B., Traber, R., Keel, M., Mica, L., & Schnyder, U. (2007). Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. *Journal of Psychiatric Research*, *41*(9), 744–752.
Vukojevic, V., Kolassa, I.-T., Fastenrath, M., Gschwind, L., Spalek, K., Milnik, A., … Heck, A. (2014). Epigenetic modification of the glucocorticoid receptor gene is linked to traumatic memory and post-traumatic stress disorder risk in genocide survivors. *Journal of Neuroscience*, *34*(31), 10274–10284.
Watson, J. D., & Crick, F. H. (1953). Molecular structure of nucleic acids. *Nature*, *171*(4356), 737–738.
Weaver, I., Cervoni, N., Champagne, F., D'Alessio, A., Sharma, S., Seckl, J., … Dymov, S. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, *7*(8), 847–854.
Weaver, I., Meaney, M. J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(9), 3480–3485.
Whitfield, C. L., Anda, R. F., Dube, S. R., & Felitti, V. J. (2003). Violent childhood experiences and the risk of intimate partner violence in adults: Assessment in a large health maintenance organization. *Journal of Interpersonal Violence*, *18*(2), 166–185.
Widom, C. (1989). The cycle of violence. *Science*, *244*(4901), 160–166.
Widom, C., Ireland, T., & Glynn, P. J. (1995). Alcohol abuse in abused and neglected children followed-up: Are they at increased risk? *Journal of Studies on Alcohol*, *56*(2), 207–217.

DOI: 10.1002/bsl

Wilker, S., Pfeiffer, A., Kolassa, S., Koslowski, D., Elbert, T., & Kolassa, I.-T. (in press). How to quantify exposure to traumatic stress?—Reliability and predictive validity of measures for cumulative trauma exposure in a post-conflict population. *European Journal of Psychotraumatology*.

Wilson, H. W., & Widom, C. S. (2008). An examination of risky sexual behavior and HIV in victims of child abuse and neglect: A 30-year follow-up. *Health Psychology*, *27*(2), 149.

World Health Organization (WHO). (2005). *The World Health Report* (2005). *Make every mother and child count*. Geneva: Author.

Wu, V., Huff, H., & Bhandari, M. (2010). Pattern of physical injury associated with intimate partner violence in women presenting to the emergency department: A systematic review and meta-analysis. *Trauma, Violence, and Abuse*, *11*(2), 71–82.

Xie, P., Kranzler, H. R., Poling, J., Stein, M. B., Anton, R. F., Farrer, L. A., & Gelernter, J. (2010). Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology*, *35*(8), 1684–1692.

Yan, W. (2014). Potential roles of noncoding RNAs in environmental epigenetic transgenerational inheritance. *Molecular and Cellular Endocrinology*, *398*(1/2), 24–30.

Yehuda, R., Bell, A., Bierer, L. M., & Schmeidler, J. (2008). Maternal, not paternal PTSD, is related to increased risk for PTSD in offspring of Holocaust survivors. *Journal of Psychiatric Research*, *42*(13), 1104–1111.

Yehuda, R., & Bierer, L. M. (2009). The relevance of epigenetics to PTSD: Implications for the DSM-V. *Journal of Traumatic Stress*, *22*(5), 427–434.

Yehuda, R., Daskalakis, N. P., Desarnaud, F., Makotkine, I., Lehrner, A. L., Koch, E., … Flory, J. D. (2013). Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Frontiers in Psychiatry*, *4*, 118.

Yehuda, R., Daskalakis, N. P., Lehrner, A., Desarnaud, F., Bader, H. N., Makotkine, I., … Flory, J. D. (2014). Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in holocaust survivor offspring. *American Journal of Psychiatry*, *171*(8), 872–880.

Yehuda, R., Engel, S. M., Brand, S. R., Seckl, J., Marcus, S. M., & Berkowitz, G. S. (2005). Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *Journal of Clinical Endocrinology and Metabolism*, *90*, 4115–4118.

Yehuda, R., Flory, J. D., Bierer, L. M., Henn-Haase, C., Lehrner, A., Desarnaud, F., … Makotkine, I. (2015). Lower methylation of glucocorticoid receptor gene promoter 1 F in peripheral blood of veterans with posttraumatic stress disorder. *Biological Psychiatry*, *77*(4), 356–364.

Yehuda, R., Golier, J. A., Yang, R. K., & Tischler, L. (2004). Enhanced sensitivity to glucocorticoids in peripheral mononuclear leukocytes in posttraumatic stress disorder. *Biological Psychiatry*, *55*(11), 1110–1116.

Yehuda, R., Halligan, S. L., & Bierer, L. M. (2002). Cortisol levels in adult offspring of Holocaust survivors: relation to PTSD symptom severity in the parent and child. *Psychoneuroendocrinology*, *27*(1/2), 171–180.

Yehuda, R., Lowy, M. T., Southwick, S. M., Shaffer, D., & Giller, E. L. Jr. (1991). Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. *American Journal of Psychiatry*, *148*, 499–504.

Yehuda, R., Southwick, S., Giller, E. L., Ma, X., & Mason, J. W. (1992). Urinary catecholamide excretion and severity of PTSD symptoms in Vietnam combat veterans. *Journal of Nervous and Mental Disease*, *180*(5), 321–325.

Young, E. A., & Breslau, N. (2004). Cortisol and catecholamines in posttraumatic stress disorder: An epidemiologic community study. *Archives of General Psychiatry*, *61*(4), 349–401.

Zhou, Z., Enoch, M. A., & Goldman, D. (2014). Gene expression in the addicted brain. *International Review of Neurobiology*, *116*, 251–273.

Zucchi, F. C. R., Yao, Y., Ward, I. D., Ilnytskyy, Y., Olson, D. M., Benzies, K., … Kovalchuk, O. (2013). Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. *PLoS One*, *8*(2), e56967.

DOI: 10.1002/bsl