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Experiencing community and domestic violence is associated with epigenetic changes in DNA methylation of *BDNF* and *CLPX* in adolescents

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Abstract

Experiencing violence changes behavior, shapes personalities, and poses a risk factor for mental disorders. This association might be mediated through epigenetic modifications that affect gene expression, such as DNA methylation. The present study investigated the impact of community and domestic violence on DNA methylation measured in saliva collected from 375 individuals including three generations: grandmothers ($n = 126$), mothers ($n = 125$), and adolescents ($n = 124$, 53% female). Using the Infinium HumanMethylation450 BeadChip array, in adolescents, we detected two CpG sites that showed an association of DNA methylation and lifetime exposure to community and domestic violence even after FDR correction: *BDNF*_cg06260077 (logFC -0.454, $p = 3.71E\text{-}07$), and *CLPX*_cg01908660 (logFC $= -0.372$, $p = 1.38E\text{-}07$). Differential DNA methylation of the CpG *BDNF*_cg06260077 associated with exposure to violence was also observed in the maternal but not the grandmaternal generation. *BDNF* (brain-derived neurotrophic factor) and *CLPX* (caseinolytic mitochondrial matrix peptidase chaperone subunit) genes are involved in neural development. Our results thus reveal altered molecular mechanisms of developmental and intergenerational trajectories in survivors of repeated violent experiences.

KEYWORDS

adolescents, BDNF, DNA methylation, epigenetics, intergenerational, violence

1 | INTRODUCTION

Violence is a public health problem worldwide (Krug, Mercy, Dahlberg, & Zwi, 2002). A quarter of individuals have reported to be physically abused as children and one in five women sexually abused as a child (Butchart, Mikton, Dahlberg, & Krug, 2015). Growing up in a violent home or neighborhood not only impacts a child's safety and physical health but also increases the risk for psychopathology (Margolin & Gordis, 2000). Chronic exposure to community violence (e.g., crime-related events, use of weapons, physical aggression) and family violence (e.g., parental interpersonal violence) predicts the development of post-traumatic stress disorder (PTSD), depression, anxiety, and behavioral problems (Elbert & Schauer, 2002; Fitzpatrick & Boldizar, 1993; Fowler, Tompsett, Braciszewski, Jacques-Tiura, & Baltes, 2009; Gorman-Smith & Tolan,

1998; Hecker, Fetz, Ainamani, & Elbert, 2015; White, Bruce, Farrell, & Kliewer, 1998). Furthermore, a history of childhood adversities is associated with smaller prefrontal cortex and hippocampus (Teicher, Anderson, & Polcari, 2012; Teicher & Samson, 2016), shortened telomeres (Shalev et al., 2013), adaptations of the hypothalamic-pituitary-adrenal (HPA) axis (Miller, Chen, & Zhou, 2007), and elevated inflammation (Kiecolt-Glaser et al., 2003). Increasing evidence concerning the molecular consequences of childhood adversities suggests epigenetic mechanisms to be involved in the biological embedding of early life experiences (Hecker, Radtke, Hermenau, Papassotiropoulos, & Elbert, 2016; Klengel et al., 2013; Mehta et al., 2013; Radtke et al., 2015; Romens, McDonald, Svaren, & Pollak, 2015).

Epigenetic modifications provide potential mechanisms by which the environment is linked to gene expression without changing the DNA sequence. These modifications may alter the levels of gene expression (either silencing genes or increasing transcriptional activity; Champagne & Curley, 2011) and involve a broad range of phenomena (dosage compensation and genomic imprinting) and mechanisms (chromatin organization and histone modifications; Jirtle & Skinner, 2007). Epigenetic studies of early stress in humans have focused mainly on DNA methylation, a biochemical process that involves the covalent addition of a methyl group to cytosines in DNA.

A growing body of research has shown that variations in DNA methylation of different genes, are linked with early adversities, especially those involved in the HPA axis (Melas & Forsell, 2015; Monk, Spicer, & Champagne, 2012; Oberlander et al., 2008; Romens et al., 2015; Serpeloni, Radtke, Hecker, & Elbert, 2016; Yehuda et al., 2015). Differential DNA methylation of genes involved in HPA axis regulation provides a possible mechanism through which early adversities can be translated into changes in gene expression. For instance, a study of suicide victims with a history of child abuse revealed an increase in site-specific methylation of a glucocorticoid receptor gene (*NR3C1*) in the hippocampus, as compared to those without a history of child abuse (McGowan et al., 2009). In a different study, children exposed to physical maltreatment had greater methylation of the *NR3C1* gene (Romens et al., 2015). Childhood adversities have also been associated with differential methylation (hypo- or hypermethylated) in other genes, for instance: the proopiomelanocortin gene (*POMC*; Hecker et al., 2016), the FK506 binding protein 5 gene (*FKBP5*; Klengel et al., 2013), and the serotonin transporter gene (*SLC6A4*, Kang et al., 2013*)*. Moreover, DNA methylation has been suggested as a biological mechanism involved in the transgenerational impact of stress (Yehuda & Bierer, 2008). Changes in methylation of different genes during childhood, such as the *NR3C1*, *FKBP5*, and *SLC6A4* have been associated with prenatal stress (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013;

Devlin, Brain, Austin, & Oberlander, 2010; Monk et al., 2016; Oberlander et al., 2008; Paquette et al., 2014; Radtke et al., 2011; Serpeloni et al., 2019). Furthermore, transgenerational epigenetic effects of prenatal stress have been shown in the third generation. Grandchildren whose maternal grandmother was exposed to violence during pregnancy showed differential methylation in genes involved in circulatory system processes when compared with grandchildren whose grandmothers had no or few events of violence during pregnancy (Serpeloni et al., 2017).

Although early life stress has been associated with DNA methylation, it has not been investigated whether lifetime exposure to chronic stress, such as community and domestic violence, is associated with changes in DNA methylation in different periods of life (childhood and adulthood). Understanding to what extent interpersonal violence (i.e., community and domestic violence; Krug et al., 2002) affects the stress response is fundamental in establishing the biological mechanisms that lead to stress-related disorders. In the present study, we therefore investigated the association of exposure to violence with genome-wide DNA methylation. Variation in DNA methylation was analyzed in three different cohorts (adolescents, mothers, grandmothers). We hypothesized that the group of individuals exposed to high levels of community and domestic violence would report more emotional problems as well as differential DNA methylation compared with the group exposed to low or no levels of violence.

2 | METHOD

2.1 | Participants

The study was carried out with families living in São Gonçalo, a city located in the state of Rio de Janeiro, Brazil. São Gonçalo has a population of more than 1 million, with a high proportion of low-income families and high levels of community and domestic violence (Assis et al., 2009). The study cohort represents a convenience sample ($N = 375$) from a project ($N = 386$) that investigated the transgenerational impact of prenatal stress across three generations. The participants were recruited via the local Family Strategy Program (Serpeloni et al., 2017, 2019). The families were invited to participate in the study if the child, mother, and grandmother were living in the city of São Gonçalo. From the original sample, we selected all family triads from whom we had information about lifetime exposure to domestic and community violence: 124 adolescents (*M* age = 13.67 years, *SD* = 2.51, range = 8–20 years; 53% female), 125 mothers (*M* age = 38.63 years, *SD* = 6.26, range = 25–60 years), and 126 grandmothers (*M* age = 64.70 years, *SD* = 8.17, range = 46–88 years) were included in the analyses. Participants' characteristics are shown in Table 1.

TABLE 1 Participants' sociodemographic and psychopathological data divided into groups based on exposure to community and domestic violence (CDV)

| | CDV[a] | | | | | | | | |
| | Adolescents (N = 124) | | | Mothers (N = 125) | | | Grandmothers (N = 126) | | |
	CDV+ (n = 34) mean (SD) or n (%)	CDV− (n = 90) mean (SD) or n (%)	p, χ^2 or ANOVA	CDV+ (n = 38) mean (SD) or n (%)	CDV− (n = 87) mean (SD) or n (%)	p, χ^2 or ANOVA	CDV+ (n = 24) mean (SD) or n (%)	CDV− (n = 102) mean (SD) or n (%)	p, χ^2 or ANOVA
Sociodemographic									
Age (years)	14.55 (2.65)	13.38 (2.38)	<0.05	37.32 (6.39)	39.19 (6.15)	ns	63.24 (7.80)	65.02 (8.25)	ns
Sex (female)	16 (47.06)	50 (55.55)	ns	–	–		–	–	
Education (years)	8.33 (2.43)	7.39 (2.50)	ns	10.32 (3.23)	11.03 (2.73)	ns	6.04 (3.30)	5.75 (2.92)	ns
Family income (USD)	452.26 (350.80)	467.28 (306.00)	ns	519.83 (355.48)	459.37 (315.14)	ns	316.06 (279.05)	306.92 (215.34)	ns
Mental health									
PTSD severity[b,c]	11.29 (11.11)	4.52 (6.59)	<0.001	8.37 (8.52)	2.10 (3.96)	<0.001	4.58 (8.81)	3.08 (4.95)	<0.05
Depression severity[d]	3.73 (5.01)	1.14 (1.78)	<0.001	6.45 (5.47)	2.24 (3.53)	<0.001	3.95 (4.39)	2.46 (2.86)	<0.05
Anxiety (adults)[e]	–	–		7.68 (3.68)	3.68 (3.88)	<0.001	4.29 (4.27)	2.47 (3.41)	<0.05

Note: Dashes indicate no data available. Abbreviations: CDV = community and domestic violence; *ns* = not significant.
[a]Things I have seen and heard (Richters & Martinez, 1990). [b]UCLA Post-Traumatic Stress Disorder Reaction Index for DSM-IV (Steinberg et al., 2004). [c]Posttraumatic Stress Diagnostics Scale (Foa, 1995). [d]Patient-Health-Questionnaire–9 (Richardson et al., 2010). [e]Generalized Anxiety Disorder–7 (Spitzer et al., 2006).

The study received approval from the Ethics Committee of the University of Konstanz (DE) and the National Commission for Ethics in Research (CONEP/BR). We obtained written informed consent from the adult participants as well as written informed consent from parents and written assent from the youth.

2.2 | Measures

The interviews were carried out individually at the participants' home. The beginning of the interview consisted of collecting sociodemographic information, including date of birth, years of education, and family income. The following measures were used:

2.2.1 | Community and domestic violence

Exposure to community and domestic violence (CDV) was assessed using the survey, "Things I have seen and heard" (Richters & Martinez, 1990). This scale measures types of violence both witnessed and directly experienced at home and in the community. Two questions were modified in the adult version: "Grownups were nice to me during childhood" and "Heard adults yelling at each other during childhood." Of the original 20 items, six items were added asking about direct exposure to events, based on the questions of witnessing an event (e.g., "Somebody threatened to shoot me" or "Somebody threatened to stab me"). This modification resulted in 26 items. Within the items, four are specifically about violence exposure in the home setting and two more about weapons and drugs in the home. Items are reported on a 5-point Likert scale ranging from 0 (*never*) to 4 (*many times*). A total score reflecting overall exposure to violence was calculated by summing across all items assessing exposure to violence. Four items not directly assessing violence were omitted from this score ("I feel safe at home," "I feel safe at school/work," "Grownups are nice to me/ Grownups were nice to me during childhood," and "I feel safe in the neighborhood"). The score was generated by summing all the items and ranges from zero to 88. Under the assumption that the greatest effect of stress on DNA methylation is observed in higher exposure to adversities (Cao-Lei et al., 2014), we divided the participants in two groups: CDV+ (high exposure to violence) and CDV− (low or no exposure to violence). The summed scores were standardized separately for each generation to allow selecting the highest exposed group based on the third quartile: Child, CDV− ($n = 90$) and CDV+ ($n = 34$); mother, CDV− ($n = 87$) and CDV+ ($n = 38$); grandmother, CDV− ($n = 102$) and CDV+ ($n = 24$).

2.2.2 | Traumatic events

Lifetime exposure to potentially traumatizing events of the adolescents was determined using the UCLA PTSD Index for DSM-IV (Steinberg, Brymer, Decker, & Pynoos, 2004). The UCLA event checklist is a structured interview with 13 dichotomous (yes/no) items, measuring witnessed or self-experienced forms of traumatic events (e.g., serious accident, natural disasters, sexual abuse). A trauma lifetime score was calculated by summing up all the items answered with *yes*. Potentially traumatizing events in adults were assessed using a 17 trauma-related-event checklist (e.g., natural catastrophes, physical and sexual assault). This questionnaire is an adapted version of a checklist developed by Neuner et al. (2004), which had previously shown high intertest reliability and statistically significant accordance with the event list of the Composite International Diagnostics Interview (Ertl et al., 2011). The checklist has been used successfully in a number of previous studies (Hermenau, Hecker, Schaal, Maedl, & Elbert, 2013). Items are reported on a scale ranging from 0 (*never*) to 4 (*many times*). The possible scores range from zero to 68. The lifetime exposure to traumatic events sum scores were *z*-standardized separately for each generation.

2.2.3 | Mental health

PTSD symptom severity in the youth generation was assessed using the UCLA PTSD Index for DSM-IV (Steinberg et al., 2004). In the adolescent sample, Cronbach's α was 0.88. For adults, PTSD symptom severity in the past month was assessed using the Post-Traumatic Stress Diagnostic Scale (PDS; Foa, 1995). Cronbach's α was 0.87 for the mothers and 0.86 for the grandmaternal generation. Depression symptom severity was assessed with the Patient Health Questionnaire (PHQ-9; Richardson et al., 2010). Cronbach's α was 0.80, 0.85, and 0.78 for children, mothers, and grandmothers, respectively. Anxiety symptom severity in adults was assessed with the Generalized Anxiety Disorder (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006). Cronbach's α for the mothers was 0.81 and 0.83 for the grandmothers.

2.2.4 | DNA methylation

Saliva samples (2 ml) for DNA methylation analysis were collected using the Oragene●Discover (OGR-500) Collection Kit (DNA Genotek, ON, Canada). DNA methylation profiling of the three generations was performed using the Infinium HumanMethylation450 BeadChip Kit by the Queen Mary University of London Genome Center according to standard protocols. Briefly, 500 ng genomic DNA was prepared and hybridized according to manufacturer's specification (Illumina, catalog #WG-914-1002, Part #15019522 Rev. A, 2010). Family biological relationships were validated. Samples that were contaminated, had insufficient genotyping quality, or had problems during bisulfite conversion were excluded. Quality control and probe filtering (X or Y chromosome, cross-hybridizing with other genomic locations, and single nucleotide polymorphism)

were performed (Chen et al., 2013). To control for cell type heterogeneity bias in mothers and adolescents, we extracted the beta values using the *minfi* R package (Aryee et al., 2014), imported them into GLINT 1.0.3 (Rahmani et al., 2017), and extracted factor scorings as described in Serpeloni et al. (2017). No sign of cellular heterogeneity in our sample was found (see online supporting information, Table S1). For further details regarding the preprocessing procedure, we have provided an R script of the pipeline published here (Serpeloni et al., 2019).

2.3 | Statistical analysis

2.3.1 | Genome-wide DNA methylation profile

All analyses were conducted using R 3.2.1. To investigate to what extent CDV impacts genome-wide DNA methylation profiles, we performed linear regressions using the *limma* R package (Ritchie et al., 2015). Logit-transformed beta values (M values; Du et al., 2010) were subjected to a robust linear regression model to identify significantly differentially methylated probes in association with CDV exposure. The results were adjusted for multiple testing using the Benjamini-Hochberg method to control for the false discovery rate (FDR). Exposure to other traumatic events was included as a covariate in the model to account for possible confounding effects. Sex and age were both added as covariates for the youth generation, and age was added for the maternal and grandmaternal generation. We checked whether the significant CpGs associated with violence exposure in the youth generation could be replicated in the maternal and grandmaternal generation.

3 | RESULTS

Lifetime exposure to CDV was significantly positively correlated ($p < 0.001$) with all mental health variables in the three generations (Table 1). PTSD current diagnostic criteria were met by 18% of adolescents, 5% of mothers, and 3% of grandmothers. To investigate to what extent CDV impacts DNA methylation in the youth generation, we performed an epigenome-wide association analysis. Two CpG sites were significantly (FDR < 0.05) associated with lifetime exposure
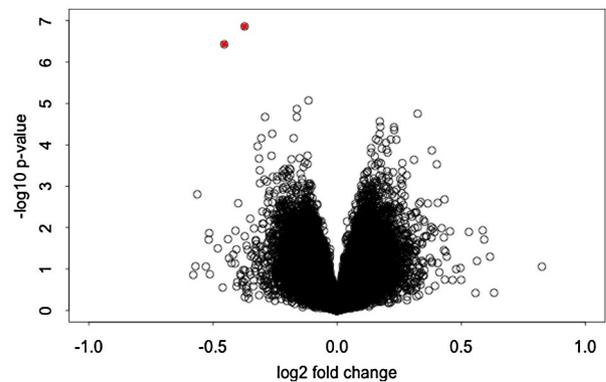

FIGURE 1 CpG sites significantly associated with lifetime CDV in the adolescents. Volcano plot of the results from the genome-wide methylation analysis using a linear regression (*limma* R package). The two CpG sites shown in red were differentially methylated in relation to adolescents' lifetime exposure to CDV after correction for multiple comparisons: *CLPX*_cg01908660 (FDR < 0.05) and *BDNF*_cg06260077 (FDR < 0.05)

to more severe CDV after corrections for multiple comparisons (Table 2, Figure 1), both sites showing decreased DNA methylation: *CLPX*_cg01908660, caseinolytic mitochondrial matrix peptidase chaperone subunit, (logFC = −0.372, $p = 1.38E-07$) and *BDNF*_cg06260077, brain-derived neurotrophic factor, (logFC −0.454, $p = 3.71E-07$). The *CLPX*_cg01908660 is located in a promoter region (TSS200) of the gene CLPX within a CpG island. The *BDNF*_cg06260077 is located in an untranslated region in an upstream region (5'UTR). Although this region is not involved in the determination of the peptide sequencing that builds a protein, it might have a regulatory function.

We then investigated whether DNA methylation patterns associated with CDV in the youth generation could also be observed in the adult generations. The two CpG probes significantly associated with CDV were used as candidate CpG sites, on which we applied linear regression models (controlling for age) to investigate the same sites in mothers and grandmothers. Increased lifetime exposure to CDV was associated with decreased DNA methylation of *BDNF*_cg06260077 in the maternal, (ß = −0.15, $p < 0.01$), but not in the grandmaternal generation, (ß = 0.002, $p = 0.72$). To test whether differences in methylation levels had a significant heritable component (i.e., heritability), we regressed offspring's versus mother's values

TABLE 2 Results of the genome-wide methylation analysis

CpG	chr	logFC	*p*	Adj.*p*	Gene
cg01908660	chr15	−0.3726898	1.38E-07	<0.05	*CLPX*
cg06260077	chr11	−0.4544887	3.71E-07	<0.05	*BDNF*

Note: Two significant CpG sites were associated with lifetime CDV (FDR < 0.05) in the adolescents. Genome-wide methylation analysis was performed to assess the association of CDV with differential methylation status. Abbreviations: CpG = CpG identification according to Illumina ID; chr = chromosome where probe is located; logFC = log2 fold change, negative and positive values indicate the direction of methylation; $p = p$ value based on the genome-wide methylation analysis; Adj.p = adjusted p value corrected for false discovery rate (FDR) using Benjamini-Hochberg; Gene = associated gene of each CpG probe.

using Pearson's correlation test. *BDNF*_cg06260077 methylation of the youth and maternal generation was not significantly correlated ($r = -0.09$, $p = 0.34$). The lack of correlation between generations suggests a minor or absent heritable component for the methylation of these particular CpG sites. There was no correlation between DNA methylation and the presently assessed mental health variables (PTSD and depression) in any of the three generations (Table 3).

4 | DISCUSSION

We examined the association of lifetime exposure to CDV by measuring genome-wide DNA methylation. Our data revealed that the experience of more violent events was significantly associated with decreased DNA methylation of CpGs located in two protein-coding genes: brain-derived neurotrophic factor (*BDNF*) and caseinolytic mitochondrial matrix peptidase chaperone subunit (*CLPX*).

Nonhuman animal model studies suggest that regulation of BDNF in the hippocampus might be influenced by epigenetic modifications (Tsankova et al., 2006). BDNF protein levels are a key mediator of brain plasticity and can modulate learning and memory in response to stress (Gray, Milner, & McEwen, 2013). Therefore, disruption of BDNF expression during sensitive periods in development may alter neural development and functioning, possibly contributing to either vulnerability for psychopathology or resilience (Bath, Schilit, & Lee, 2013). Given that stress promotes changes in *BDNF* expression through effects on the hippocampus (Duman & Monteggia, 2006; Smith, Makino, Kvetnansky, & Post, 1995), it may well be possible that the observed

TABLE 3 Spearman correlations of BDNF and CLPX with CDV per generation

	*BDNF*_cg06260077 rho	*CLPX*_cg01908660 rho
Youth		
CDV	−0.24**	−0.23**
PTSD	−0.04	−0.15
Depression	−0.04	−0.04
Mother		
CDV	−0.18*	0.10
PTSD	−0.01	−0.05
Depression	−0.03	−0.05
Grandmother		
CDV	0.04	0.04
PTSD	0.02	−0.06
Depression	0.03	−0.03

Note: Abbreviations: rho = Spearman correlations; CDV = community and domestic violence; PTSD = post-traumatic stress disorder.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.

methylation change results from the exposure to violence. Such chronic stress may contribute to cognitive deficits such as learning and memory impairment (Calabrese, Guidotti, Racagni, & Riva, 2013; Sterlemann et al., 2010). It thus might be interesting to test cognitive functioning in relation to BDNF methylation. Pathways involving BDNF signaling are considered candidates in stress-related disorders (Bath et al., 2013), where changes in DNA methylation in the *BDNF* gene has been suggested as a biomarker for early detection of psychopathology (Kundakovic et al., 2015). Indeed, differential methylation of *BDNF* was found in individuals with bipolar disorder, major depression, and eating disorders (D'Addario et al., 2012; Fuchikami et al., 2011; Thaler et al., 2014). We have assessed a set of trauma-related symptoms but could not find correlations with the BDNF methylation. This does not exclude nonlinear or more complex relationships. Usually it is reported in the literature that hypermethylation is associated with suppression of gene transcription (Miranda & Jones, 2007). However, there is also evidence that hypomethylation can be associated with decreased gene expression (Chahrour et al., 2008). Moreover, both increases and decreases in BDNF methylation have been associated with stress (Braithwaite, Kundakovic, Ramchandani, Murphy, & Champagne, 2015; Fuchikami et al., 2011; Kim et al., 2017; Roth, Zoladz, Sweatt, & Diamond, 2011). While stress alters HPA functioning, changes in the inherent HPA dynamics with nonlinear feedback loops may not allow unidirectional predictions of any given parameter.

We also observed that the mitochondria-related gene *CLPX* is associated with lifetime exposure to CDV. A growing body of research suggests that dysfunctional mitochondria may affect key cellular processes that contribute to the development of psychiatric disorders, such as depression, anxiety, schizophrenia, and bipolar disorder (Burroughs & French, 2007; Clay, Sillivan, & Konradi, 2011; Gardner et al., 2003; Karabatsiakis et al., 2014; Manji et al., 2012). *CLPX*, for example, was reported to be differentially expressed in the postmortem brain of individuals with bipolar disorder (Sun, Wang, Tseng, & Young, 2006). However, again, we could not observe significant linear correlations between methylation and the assessed psychopathology.

Both *BDNF* and *CLPX* are implicated in aging. BDNF modulates age-related changes in hippocampal function (Sambataro et al., 2010), and its levels in peripheral blood decrease significantly with increasing age (Lommatzsch et al., 2005). Reduced levels of serum BDNF were linked with hippocampal shrinkage and memory decline in late adulthood (Erickson et al., 2010; Komulainen et al., 2008). Therefore, chronic stress may contribute to the cognitive deficits associated with aging such as learning and memory (Calabrese et al., 2013; Sterlemann et al., 2010). The mitochondria-related gene *CLPX* has also been implicated in aging. In fact,

dysfunction of mitochondria is associated with aging and age-related diseases, playing a central role in aging (Jensen & Jasper, 2014; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). This may explain why *BDNF*_cg06260077 methylation was associated with interpersonal violence in adolescents and during middle adulthood (mothers) but not during late adulthood (grandmothers). In our study, we investigated the association of lifetime stress in three generations. We found the same CpG located within the *BDNF* gene associated with stress in the adolescent and maternal generation. Intergenerational effects of trauma might be considered (Yehuda et al., 2015). Future longitudinal studies considering stress exposure during different developmental periods, including before conception, during pregnancy, after birth, and childhood, may shed light on the epigenetic influences.

It should be noted that we analyzed the methylation levels in saliva. Despite tissue-specific patterns, DNA methylation in *BDNF* of peripheral cell populations has been shown to predict changes in the brain as well as behavioral vulnerabilities (Kundakovic et al., 2015; Stenz et al., 2015). Gene expression in the brain, as well as the functional implications thereof such as the extent to which it may affect or predict psychiatric disorders, remains to be investigated. The many more differences that did not survive correction also remain of interest for replication samples. But, already, our results support the impact of violent environments on DNA methylation of genes, especially those associated with stress regulation.

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SUPPORTING INFORMATION

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Table S1

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