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Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review

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Abstract

The early-life social environment can induce stable changes that influence neurodevelopment and mental health. Research focused on early-life adversity revealed that early-life experiences have a persistent impact on gene expression and behaviour through epigenetic mechanisms. The hypothalamus-pituitary-adrenal (HPA) axis is sensitive to changes in the early-life environment that associate with DNA methylation of a neuron-specific exon 1_7 promoter of the glucocorticoid receptor (GR; *NR3C1*). Since Weaver et al published the initial findings in 2004, numerous reports have investigated GR gene methylation in relationship to early-life experience, parental stress and psychopathology. We conducted a systematic review of this growing literature, which identified 40 articles (13 animal and 27 human studies) published since 2004. The majority of these examined the GR exon variant 1_F in humans or the GR1_7 in rats, and 89% of human studies and 70% of animal studies of early-life adversity reported increased methylation at this exon variant. All the studies investigating exon $1_F/1_7$ methylation in conditions of parental stress (one animal study and 7 human studies) also reported increased methylation. Studies examining psychosocial stress and psychopathology had less consistent results, with 67% of animal studies reporting increased exon 1_7 methylation and 17% of human studies reporting increased exon 1_F methylation. We found great consistency among studies investigating early life adversity and the effect of parental stress, even if the precise phenotype and measures of social environment adversity varied among studies. These results are encouraging and warrant further investigation to better understand correlates and characteristics of these associations.

Keywords

glucocorticoid receptor; epigenetics; DNA methylation; social environment; early-life adversity; systematic review

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Introduction

There is substantial theoretical and empirical research supporting an association between early-life environmental adversity and poor lifetime mental health outcomes (1–12). A critical issue concerns the molecular mechanisms that account for such strong and long-lasting effects. There is evidence suggesting that early-life environmental influences induce changes in stable epigenetic states that regulate gene expression and ultimately, complex neural functions. Thus in both rodents and nonhuman primates the early-life environment, including the quality of maternal care, regulates hypothalamus-pituitary-adrenal (HPA) axis function in adulthood (13–15). Variations in the early social environment in rodents, modeled by maternal care, reveal profound and persistent alterations in gene expression and behaviour that are mediated through epigenetic mechanisms, including changes in DNA methylation (16). The offspring of mothers with an increased frequency of pup licking/grooming (i.e., high LG mothers) show increased hippocampal glucocorticoid receptor (GR; *NR3C1*) expression, greater negative feedback regulation over hypothalamic corticotropin releasing factor (CRF) and more modest responses to stress compared to the offspring of low LG mothers (16–18). Variations in maternal LG are linked to an epigenetic modification of a neuron-specific exon 1_7 GR promoter (16) such that increased maternal LG associates with decreased methylation of the exon 1_7 promoter and increased hippocampal GR expression.

Subsequent studies in humans have expanded on the findings in rats. Accordingly, evidence for a long-term effect of early-life adversity (ELA) on the epigenetic state of the human genome was observed while investigating the methylation state of the GR gene in the hippocampus of individuals who died by suicide and had histories of child abuse (19). ELA in humans reprograms the DNA methylation patterns of the GR gene exon 1_F ($GR1_F$; $GR1_7$ homologue in rats) promoter and decreases $GR1_F$ expression in the hippocampus of suicide completers with a history of child abuse compared to non-abused suicide completers and healthy controls (19). An earlier study reported that children born to mothers with depression, irrespective of SSRI use, exhibited higher $GR1_F$ methylation levels (20). Since these first reports, several studies have investigated the effect of environmental adversity, measured by ELA or exposure to parental stress, on GR gene methylation, using both animal models and human samples. These studies also used different designs, measures of adversity, and tissue samples, and investigated methylation of diverse GR gene sequences. A growing number of studies have also been investigating the relationship between psychological stress or psychopathology and GR methylation. We conducted a systematic review of the growing literature investigating the relationship between environmental experience, stress and GR gene methylation.

Methods

Study identification

We performed a search of association studies of the GR gene and DNA methylation. The primary search was carried out through the National Library of Medicine (NLM) PubMed and a replication search was conducted through the Web of Knowledge database. The search included publications from 2004 up to July 2014 using the Weaver et al. (16) study as a

starting point. The Medical Subject Headings (MeSH) terms used were '("glucocorticoid receptor" OR NR3C1) AND (epigenetics OR "DNA methylation")'. Additional articles were found by scanning the list of references of the original publications and review articles. Only articles in English and those investigating humans or other mammals were included.

Study selection

The studies included in this systematic review met the following criteria: (a) use of a case–control or cohort design; (b) use of at least one analysis investigating DNA methylation of the GR gene in response to a change or perturbation in social environment; and (c) inclusion of studies independent from one another. Analyses based on the same set of data were excluded. In such cases, only the larger or more representative sample was retained. Studies in which a control group was absent also were not included.

Data extraction

Information for each study was extracted based on nine variables: 1) Species (human or nonhuman), 2) Study (experimental) group; 3) Sex; 4) Sample size; 5) Methodology (DNA methylation assessment); 6) Tissue(s) investigated; 7) Subject age at tissue collection; 8) Region or first exon variant(s) investigated; and 9) Effect on methylation (see tables 1–3). Studies were then grouped according to a broad classification of the study criteria and attributed to tables 1, 2 or 3. Within each table, animal- and human-based studies were considered independently.

Results

There is a growing number of studies reporting changes in GR gene methylation in association with social environment and stress. Our search identified a total of 430 articles. Of these, 173 were review papers and were excluded. Another 210 articles were excluded due to lack of relevance to the topic of this review. Seven studies were removed because they were not independent, as they investigated samples for which results had been reported elsewhere. In all, 40 articles met all the specified criteria. These were then sorted based on whether they addressed GR gene methylation changes in response to ELA (22 articles; Table 1), parental stress (9 articles; Table 2), or psychological stress/psychopathology (11 articles; Table 3) (two studies were included in two tables because they addressed both ELA and psychological stress (21) or parental stress and psychological stress (22)). Within each table, the articles were further subdivided into animal studies, human studies using peripheral tissues, and human studies using CNS tissue.

Sample type: species and tissues studied

Among the animal studies included, all used either rat (8 out of 13 studies) or mouse (5 out of 13 studies). All animal studies examined brain tissue, and 1 compared brain tissue and fecal matter (23), while another compared brain tissue and adrenal tissue (24). The brain region studied varied, including cortical and subcortical regions.

In the human studies, the majority of articles reported on GR gene methylation in peripheral tissues, where the term peripheral refers to tissues other than the CNS. In the "human

peripheral studies" category, 21 of the 24 articles used blood tissue, while 2 used saliva (25, 26), 1 used buccal epithelial cells (27) and 1 used placental tissue (28). Of the 3 studies examining brain tissue (the "human central tissues" category), all examined tissues from the limbic and cortical regions (19, 29, 30), and focused in particular on the hippocampus. In addition, Labonté and colleagues examined the anterior cingulate cortex (ACC), while Alt and colleagues investigated the amygdala, inferior prefrontal gyrus, cingulate gyrus and nucleus accumbens.

GR gene region examined—The GR gene in humans and rodents consists of 11 exons including untranslated first exon variants (31). Nine untranslated first exon variants each possessing their own promoter region have been identified in humans ($1_{A, I, D, J, E, B, F, C \text{ and } H}$) and in rats ($1_{1, 4\text{-}11}$). We found significant heterogeneity in the reporting and identification of the specific regions of the first exon variants that were studied. Specifically, there was no consistency in how CpG sites were identified and labeled, making the determination of overlapping regions difficult. This made detecting consistency in findings at the sequence level among studies challenging. We compiled the sequence data that we were able to retrieve from information published in all the human studies and located the regions within the GR gene containing the first exon variants investigated (see supplemental figure 1).

Early-life adversity

Experimental groups—To ensure the maximum impact of the review and allow for the comparison of results, we carefully selected articles that used similar criteria to define ELA.

In animal models, early-life experience was characterized by the use of maternal care models in 6 studies (16, 32–35) or maternal separation models in 4 studies (36–38).

Human studies defined ELA as exposure to traumatic events in childhood, including emotional, physical or sexual abuse, neglect, early parental death and other traumatic events. All studies included subjects who had been exposed to childhood abuse, with variations in the type of abuse included. In addition, 3 studies included early parental death as a marker of ELA (25, 39, 40).

GR region studied—The majority of studies included in this review examined exon 1_7 (10 out of 10 animal studies), or exon 1_F (10 out of 12 human studies). One study also examined exon 1_D, while two studies also examined exon 1_B and 1_C, and three studies examined exon 1_H. Of the 10 studies examining exon 1_7 and the 10 studies examining exon 1_F, 9 and 6, respectively, included examination of the binding site for the transcription factor NGFI-A (a.k.a., Egr-1, Zyf-268; table 1 and supplemental figure 1), which regulates GR gene transcription (19, 41).

Effect on methylation—As the majority of studies reported on exon $1_7/1_F$, we focused our comparisons on this particular variant. In the ELA group, all 10 animal studies examining GR gene methylation investigated exon 1_7, and 7 studies (70%) reported a significant increase in methylation in the exon 1_7 promoter, while three studies reported no change in exon 1_7 methylation status (22, 33, 36). Of the 10 human studies examining exon

1_F methylation, 9 reported increased promoter methylation with ELA (90%). Of these, one study reported increased methylation at CpG sites labelled by the authors as CpGs 3, 6, and 7 in the whole sample, while a socioeconomic-matched subsample exhibited a decrease in methylation level of a single CpG (CpG2), located before the NFGI-A binding site (CpGs 3 &4), in conjunction with increased methylation at CpGs 3, 5 and 6 (42). One study reported no change in $GR1_F$ methylation status in response to ELA (21) (figure 1). A single study reported on exon 1_D methylation, and found decreased methylation in blood samples of adolescents with early-life stress (40). In addition, one study reported no change in methylation of exons 1_B and 1_C in peripheral tissues (21), while another found increased methylation in brain tissues of subjects with childhood abuse (29). Three studies reported on the methylation status of exon 1_H, with one study reporting no change (21), one reporting increased methylation (40) and one reporting decreased methylation (29). Additionally, one study reported decreased GR gene methylation, but did not specify the region investigated (43).

Parental stress

Experimental groups—One animal study (44) used a variety of non pain-inducing, non-habituating stressors over the course of 7 days to stress mouse dams. Human studies examined the methylation status of children of women who had experienced anxiety and mood disorders (20, 28), pregnancy-related anxiety (45), violence (46) or war stress (47, 48) during pregnancy. Another study examined the effects of parental stress on GR gene methylation in adolescence (27), and one additional study studied the methylation patterns of individuals whose parents had experienced war, but not necessarily during pregnancy (49) (table 2).

GR gene region—Most studies in this group examined exon 1_7 (for the animal study) or exon 1_F (7 of 8 human studies), and the sites analyzed spanned the NFGI-A binding site. One study also examined exons 1_D and 1_B (45).

Effect on methylation—Interestingly, all 8 studies investigating exon $1_F/1_7$ (including the animal study) reported an increased methylation of exon $1_7/1_F$ in offspring of parentally-stressed individuals (figure 2). Of these, two studies also reported decreased methylation at specific CpG sites and in particular conditions. For example, Hompes and colleagues reported a decreased methylation at a position labelled by the authors as CpG 36 (near the NGFI-A binding site) only during trimesters 1 and 2 in women reporting a fear of changes associated with their pregnancy (45). Additionally, in the study of the offspring of Holocaust survivors, maternal experience of Holocaust was associated with decreased methylation of exon 1_F, while paternal experience of Holocaust was associated with increased exon 1_F methylation (49). Of note, the study investigating Holocaust survivors recruited participants born after the end of World War II, and therefore did not necessarily include mothers who experienced stress during pregnancy, but rather before pregnancy. Only one study examined other exon 1 variants, reporting increased methylation of exon 1_D in the children of women experiencing fear of delivery in all trimesters or fear of the integrity of the baby in the first trimester, and decreased methylation of exon 1_B in the children of women with fear of

delivery (45). Finally, an additional study investigated a single CpG located downstream of the 1_H promoter (in the gene body) and found no change in methylation status (27).

Psychological stress/Psychopathology

Experimental groups—Three animal studies used acute or chronic stress models to assess the impact of social stressors on GR gene methylation (24, 50). In addition, 8 studies examined the effects of psychopathologies on human GR gene methylation. Specifically, studies included response to stress (51), borderline personality disorder (52), bulimia nervosa (21), post-traumatic stress disorder (PTSD) (53–55) and depression (30, 56) (table 3).

GR gene region—Most studies in this group examined exon 1_7 (3 animal studies) or exon 1_F (6 of the 8 human studies). In addition, 3 studies examined exon 1_B (21, 30, 55), 2 studies examined exons 1_C and 1_H (21, 55), and 1 study examined exons 1_J and 1_E (30). Of the 8 studies examining exon $1_7/1_F$, 6 specified that they included examination of the binding site for NGFI-A.

Effect on methylation—Two of the three animal studies included in this group reported increased exon 1_7 methylation in stressed animals, but studies reporting on human psychological stress/psychopathology had more varied results. One study reported increased methylation of exon 1_F (52), while three reported no change (21, 30, 53), and two reported decreased methylation (30, 54). Among the other exon variants examined, there was no consensus on the effects of psychological stress/psychopathology on methylation status. Exons 1_J and 1_E showed no change in methylation, exon 1_B was unchanged in two studies (21, 30) and had decreased methylation in one study (54), exon 1_C was hypermethylated in one study (21), hypomethylated in one study (55) and unchanged in one study (51). Finally, exon 1_H was hypomethylated in one study (21) and unchanged in another (55).

Conclusion

Since the publication of Weaver et al. 2004, there has been a surge in interest in GR gene methylation changes associated with altered social environment and stress, as evidenced by the number of articles that have since been published on the subject. We conducted a systematic review of all studies that investigated GR gene methylation in relation to various psychological stressors, including parental stress, adverse early-life social environments in animals, such as interventions affecting early environment, ELA in humans, and psychological stress or psychopathology in adults.

Most of these studies investigated the GR exon variant 1_F and studies considering early-life and in utero adversity mostly reported increased methylation at this exon. In particular, negative early-life social environments were associated with greater exon 1_F methylation in the large majority of studies (70% of animal ELA studies and 90% of human ELA studies assessing exon 1_F; 100% of parental stress studies assessing exon 1_F). In studies of gestational stress, it is important to note that 4 studies collected tissue samples at birth (20, 28, 45, 47), and it is therefore unclear whether the observed changes would persist into adulthood. However, the other studies included used adolescent or adult subjects (27, 46, 48,

49). When combined with the ELA studies, these findings show a compelling consensus of increased exon 1_F methylation in conjunction with stress in early life (16 out of 17 studies; human studies from Tables 1 and 2, combined, that investigated exon 1_F).

The strength of the association between adverse postnatal social environments and $GR1_F$ methylation in humans is consistent with the original report from McGowan et al. (16). Inter-individual differences in DNA methylation can be tissue- and cell type-specific, yet we found multiple reports of associations between the quality of childhood experience and the methylation status of the exon 1_F NR3C1 gene promoter in readily-accessible peripheral cells. Perroud et al. (57, 58) used peripheral blood lymphocytes to show that childhood maltreatment associates with increased exon 1_F methylation and, importantly, that promoter methylation status was closely correlated with both the frequency and severity of maltreatment (also see (42)). Interestingly, Tyrka et al. (39) reported that increased methylation of the exon 1_F NR3C1 gene promoter in leukocytes, associated with disruption of normal parent-offspring interactions or maltreatment, was linked to an attenuated cortisol response to the Dex/CRH test. In this study, and that of Melas et al. (25), childhood parental loss was associated with increased methylation of the exon 1_F NR3C1 gene promoter (note the Melas et al. study used salivary DNA, which is primarily of leukocyte origin (59)).

These findings appear despite the significant evidence of tissue-specific DNA methylation profiles (60–63), leading to the question of how a ‘social adversity-related’ epigenetic signal might appear in cell populations as diverse as peripheral blood cells and CNS-derived cells. One possibility is that social adversity activates stress responses that include signals such as steroid hormones (e.g., glucocorticoids) or cytokines, which act in multiple cell types and might initiate a coordinated remodelling of the epigenome at specific sites. While this reasoning is a matter of speculation, it does suggest a pathway by which the epigenetic imprint associated with social adversity might appear in a range of cell types, thus enabling meaningful population analyses of the effects of childhood environmental conditions on the epigenome. This also suggests that the nature of specific epigenetic marks across multiple tissues might be context specific: environmental conditions of sufficient biological impact, such as social adversity, might lead to coordinated changes that would enhance the probability of detecting specific epigenetic states across multiple tissues. This might also support the inclusion of epigenetic analyses of peripheral samples within intervention programs targeting brain-based phenotypes. The merits of this approach will become apparent with future studies focusing on a broader range of genomic targets, including genome-wide analyses (e.g. (27)).

The stability of DNA methylation is also a point of interest (64). Recent evidence supports the hypothesis that epigenetic plasticity is sustained in the brain throughout adulthood, potentially as a mechanism to cope with the evolving demands of the environment, yet there are clear moments during development when plasticity is heightened, and these may be more strongly associated with the establishment of life-long epigenetic modifications (reviewed in (65)). Another important consideration is that the studies cited here report low overall levels of methylation. This is consistent with the fact that strong CpG promoters, such as those from the GR gene, have generally low levels of methylation (66).

There has been great consistency regarding the increased methylation of the NGFI-A binding site within exon1_F. There are also reports of differential methylation at other sites of the GR promoter that are not associated with NGFI-A binding (tables 1–3). However, the functional implications of such differential methylation have not been empirically tested, and further investigation of these sites is warranted. Although NGFI-A is enriched in the brain, it appears to be expressed ubiquitously (67), and belongs to the early growth response family of proteins, which contain a zinc-finger motif, allowing for interactions with target DNA regions (68). NGFI-A is activated by a range of stimuli, including neurotransmitters and cellular stimulation, and is a key contributor to T lymphocyte proliferation (69). Therefore, blocking NGFI-A binding-sites in the GR gene promoter in peripheral tissues (blood and saliva, in which the majority DNA-contributing cells are lymphocytes) is likely to actively contribute to the regulation of GR expression.

The activity of the HPA axis is governed by corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), both of which are subject to GR-mediated feedback regulation at multiple levels within the axis and inhibition from extra-hypothalamic sites. Hippocampal GR activation associates with the inhibition of hypothalamic CRF synthesis and dampened HPA activity (70). Studies with adults reveal that childhood maltreatment is associated with an increased HPA response to stress (71, 72). Subsequent statistical analyses revealed that childhood abuse was the strongest predictor of ACTH responsiveness, followed by the number of abuse events, adulthood traumas and depression. An interaction term of childhood and adulthood trauma proved to be the most potent predictor of ACTH responses, suggesting that a history of childhood abuse per se is related to increased stress reactivity, which is further enhanced when additional trauma occurs in adulthood (71, 73). Among women with no history of MDD, childhood trauma was similarly associated with and increased ACTH response to stress (71).

There is evidence for elevated CSF levels of CRF in adults associated with a history of childhood maltreatment (74, 75), poor quality of parental care (76) and childhood stressful experience (77). Heim et al. (74) showed that CSF CRF concentrations were correlated with the severity and duration of physical and sexual abuse, and high CRF may arise due to GR down-regulation and impaired negative feedback inhibition, as supported by early reports linking childhood abuse with higher cortisol response to the DEX/CRH challenge test in adults (71, 78). Recent work has shown that some subjects having experienced childhood abuse exhibit lower levels of cortisol, with marked differences depending on gender (79–82), time of cortisol sampling (79), source tissue (83), type of abuse (84, 85), and the presence of concurrent psychiatric (71, 78) or other health conditions (84). Importantly, decreased cortisol may not be exclusively linked to PTSD (83, 86), as has often been supposed (87, 88); rather, decreased cortisol production may reflect an adaptation to chronically stressful situations, whereas elevated cortisol production may prime individuals to react to unpredictable stressors, and these situations may both constitute ELA (81). Currently, it is difficult to draw conclusions on the overall impact of GR methylation variations on basal and reactive cortisol levels, as the majority of studies investigating GR promoter methylation did not measure cortisol levels.

These findings suggest that childhood adversity stably influences HPA responses to stress. Childhood adversity moderates the relation between stressful life events in adulthood and depression, with increased risk for depression or anxiety in response to moderately stressful circumstances among individuals with a history of childhood adversity (5, 10, 89). This is consistent with the idea that childhood maltreatment sensitizes neural and endocrine responses to stress, thus establishing a vulnerability for mood disorders.

Recent rodent studies suggest that epigenetic programming of HPA function occurs at multiple levels of the HPA axis in addition to effects on hippocampal GR expression. Environmental conditions that increase the frequency of LG in the rat are associated with decreased paraventricular CRF expression (18, 90–92). Avishai-Eliner et al. (93) showed that this maternally-regulated decrease in CRF expression is accompanied by an increased hypothalamic expression of the transcriptional repressor NRSF and NRSF binding to a 21 bp sequence within the regulatory region (intron) of the *Crh* gene (94). Korosi et al. (95) showed that augmented maternal care reduced the number of excitatory synapses onto CRF neurons. A study where CRF expression was increased through disruption of maternal care in the mouse (96) showed enhanced glutamatergic transmission to hypothalamic CRF neurons in the offspring (97). Moreover, prolonged periods of maternal separation alter the methylation state of the promoter for the *avp* gene, increasing hypothalamic AVP synthesis and HPA responses to stress (98). Maternal separation of neonatal mice also produces an enduring hypomethylation of the *POMC* gene, which encodes for the ACTH pro-hormone, proopiomelanocortin (99), increased POMC mRNA expression and increased basal and CRF-induced levels of ACTH. These findings extend previous studies of hippocampal GR regulation and reveal that the quality of postnatal maternal care in rodents epigenetically programs gene expression at multiple levels of the HPA axis to regulate both basal and stress-induced activity.

The initial reports of epigenetic regulation of hippocampal GR expression are now accompanied by reports of environmentally-regulated alterations in the methylation status of multiple genes directly implicated in HPA function. Likewise, in humans, childhood maltreatment associates with differential methylation of the *FKBP5* gene, which encodes for a functional regulator of GR signalling. FKBP5 alters glucocorticoid receptor function by decreasing ligand binding and impeding translocation of the receptor complex to the nucleus. Childhood maltreatment produces an FKBP5 genotype-specific demethylation of a distal enhancer, resulting in increased FKBP5 expression, and decreased GR signalling (100). A remarkable feature of these findings is the co-ordinated epigenetic effects on multiple genes, in multiple tissues, that collectively serve to increase HPA responsivity to stress in response to early social adversity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Evans E, Hawton K, Rodham K. Suicidal phenomena and abuse in adolescents: a review of epidemiological studies. Child abuse & neglect. 2005; 29:45–58. [PubMed: 15664425]
2. Ystgaard M, Hestetun I, Loeb M, Mehlum L. Is there a specific relationship between childhood sexual and physical abuse and repeated suicidal behavior? Child abuse & neglect. 2004; 28:863–875. [PubMed: 15350770]
3. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. Lancet. 2009; 373:68–81. [PubMed: 19056114]
4. Collishaw S, Pickles A, Messer J, Rutter M, Shearer C, Maughan B. Resilience to adult psychopathology following childhood maltreatment: evidence from a community sample. Child abuse & neglect. 2007; 31:211–229. [PubMed: 17399786]
5. McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Archives of general psychiatry. 2010; 67:124–132. [PubMed: 20124112]
6. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. The American journal of psychiatry. 2003; 160:1453–1460. [PubMed: 12900308]
7. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychological medicine. 1997; 27:1101–1119. [PubMed: 9300515]
8. Afifi TO, Enns MW, Cox BJ, Asmundson GJ, Stein MB, Sareen J. Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. American journal of public health. 2008; 98:946–952. [PubMed: 18381992]
9. Widom CS. Posttraumatic stress disorder in abused and neglected children grown up. The American journal of psychiatry. 1999; 156:1223–1229. [PubMed: 10450264]
10. Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Archives of general psychiatry. 2007; 64:49–56. [PubMed: 17199054]
11. Widom CS, White HR, Czaja SJ, Marmorstein NR. Long-term effects of child abuse and neglect on alcohol use and excessive drinking in middle adulthood. Journal of studies on alcohol and drugs. 2007; 68:317–326. [PubMed: 17446970]
12. Lansford JE, Dodge KA, Pettit GS, Bates JE, Crozier J, Kaplow J. A 12-year prospective study of the long-term effects of early child physical maltreatment on psychological, behavioral, and academic problems in adolescence. Archives of pediatrics & adolescent medicine. 2002; 156:824–830. [PubMed: 12144375]
13. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annual review of neuroscience. 2001; 24:1161–1192.
14. Levine A, Cohen D, Zadik Z. Urinary free cortisol values in children under stress. The Journal of pediatrics. 1994; 125:853–857. [PubMed: 7996355]
15. Higley JD, Hasert MF, Suomi SJ, Linnoila M. Nonhuman primate model of alcohol abuse: effects of early experience, personality, and stress on alcohol consumption. Proceedings of the National Academy of Sciences of the United States of America. 1991; 88:7261–7265. [PubMed: 1871131]
16. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. Nature neuroscience. 2004; 7:847–854.
17. Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science. 1999; 286:1155–1158. [PubMed: 10550053]

18. Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science. 1997; 277:1659–1662. [PubMed: 9287218]
19. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature neuroscience. 2009; 12:342–348.
20. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics: official journal of the DNA Methylation Society. 2008; 3:97–106. [PubMed: 18536531]
21. Steiger H, Labonte B, Groleau P, Turecki G, Israel M. Methylation of the glucocorticoid receptor gene promoter in bulimic women: associations with borderline personality disorder, suicidality, and exposure to childhood abuse. The International journal of eating disorders. 2013; 46:246–255. [PubMed: 23417893]
22. Desarnaud F, Jakovcevski M, Morellini F, Schachner M. Stress downregulates hippocampal expression of the adhesion molecules NCAM and CHL1 in mice by mechanisms independent of DNA methylation of their promoters. Cell adhesion & migration. 2008; 2:38–44. [PubMed: 19262122]
23. Liberman SA, Mashoodh R, Thompson RC, Dolinoy DC, Champagne FA. Concordance in hippocampal and fecal Nr3c1 methylation is moderated by maternal behavior in the mouse. Ecology and evolution. 2012; 2:3123–3131. [PubMed: 23301177]
24. Witzmann SR, Turner JD, Meriaux SB, Meijer OC, Muller CP. Epigenetic regulation of the glucocorticoid receptor promoter 1(7) in adult rats. Epigenetics: official journal of the DNA Methylation Society. 2012; 7:1290–1301. [PubMed: 23023726]
25. Melas PA, Wei Y, Wong CC, Sjoholm LK, Aberg E, Mill J, et al. Genetic and epigenetic associations of MAOA and NR3C1 with depression and childhood adversities. Int J Neuropsychopharmacol. 2013; 16:1513–1528. [PubMed: 23449091]
26. Weder N, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, et al. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. Journal of the American Academy of Child and Adolescent Psychiatry. 2014; 53:417–424 e415. [PubMed: 24655651]
27. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, Neumann SM, et al. Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. Child Dev. 2013; 84:58–75. [PubMed: 21883162]
28. Conradt E, Lester BM, Appleton AA, Armstrong DA, Marsit CJ. The roles of DNA methylation of NR3C1 and 11beta-HSD2 and exposure to maternal mood disorder in utero on newborn neurobehavior. Epigenetics: official journal of the DNA Methylation Society. 2013; 8:1321–1329. [PubMed: 24135662]
29. Labonte B, Yerko V, Gross J, Mechawar N, Meaney MJ, Szyf M, et al. Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. Biological psychiatry. 2012; 72:41–48. [PubMed: 22444201]
30. Alt SR, Turner JD, Klok MD, Meijer OC, Lakke EA, Derijk RH, et al. Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. Psychoneuroendocrinology. 2010; 35:544–556. [PubMed: 19782477]
31. McCormick JA, Lyons V, Jacobson MD, Noble J, Diorio J, Nyirenda M, et al. 5′-heterogeneity of glucocorticoid receptor messenger RNA is tissue specific: differential regulation of variant transcripts by early-life events. Mol Endocrinol. 2000; 14:506–517. [PubMed: 10770488]
32. Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, Meaney MJ, et al. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2005; 25:11045–11054. [PubMed: 16306417]
33. Henningsen K, Dyrvig M, Bouzinova EV, Christiansen S, Christensen T, Andreasen JT, et al. Low maternal care exacerbates adult stress susceptibility in the chronic mild stress rat model of depression. Behavioural pharmacology. 2012; 23:735–743. [PubMed: 23075705]

34. Kosten TA, Huang W, Nielsen DA. Sex and litter effects on anxiety and DNA methylation levels of stress and neurotrophin genes in adolescent rats. Developmental psychobiology. 2014; 56:392–406. [PubMed: 23460384]
35. Kosten TA, Nielsen DA. Litter and sex effects on maternal behavior and DNA methylation of the Nr3c1 exon 1 promoter gene in hippocampus and cerebellum. International journal of developmental neuroscience: the official journal of the International Society for Developmental Neuroscience. 2014; 36C:5–12. [PubMed: 24721039]
36. Daniels WM, Fairbairn LR, van Tilburg G, McEvoy CR, Zigmond MJ, Russell VA, et al. Maternal separation alters nerve growth factor and corticosterone levels but not the DNA methylation status of the exon 1(7) glucocorticoid receptor promoter region. Metabolic brain disease. 2009; 24:615–627. [PubMed: 19816761]
37. Kember RL, Dempster EL, Lee TH, Schalkwyk LC, Mill J, Fernandes C. Maternal separation is associated with strain-specific responses to stress and epigenetic alterations to Nr3c1, Avp, and Nr4a1 in mouse. Brain and behavior. 2012; 2:455–467. [PubMed: 22950049]
38. Kundakovic M, Lim S, Gudsnuk K, Champagne FA. Sex-specific and strain-dependent effects of early life adversity on behavioral and epigenetic outcomes. Frontiers in psychiatry. 2013; 4:78. [PubMed: 23914177]
39. Tyrka AR, Price LH, Marsit C, Walters OC, Carpenter LL. Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: preliminary findings in healthy adults. PloS one. 2012; 7:e30148. [PubMed: 22295073]
40. van der Knaap LJ, Riese H, Hudziak JJ, Verbiest MM, Verhulst FC, Oldehinkel AJ, et al. Glucocorticoid receptor gene (NR3C1) methylation following stressful events between birth and adolescence. The TRAILS study. Translational psychiatry. 2014; 4:e381. [PubMed: 24713862]
41. Weaver IC, D'Alessio AC, Brown SE, Hellstrom IC, Dymov S, Sharma S, et al. The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2007; 27:1756–1768. [PubMed: 17301183]
42. Romens SE, McDonald J, Svaren J, Pollak SD. Associations Between Early Life Stress and Gene Methylation in Children. Child Dev. 2014
43. Guillemin C, Provencal N, Suderman M, Cote SM, Vitaro F, Hallett M, et al. DNA methylation signature of childhood chronic physical aggression in T cells of both men and women. PloS one. 2014; 9:e86822. [PubMed: 24475181]
44. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2008; 28:9055–9065. [PubMed: 18768700]
45. Hompes T, Izzi B, Gellens E, Morreels M, Fieuws S, Pexsters A, et al. Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. Journal of psychiatric research. 2013; 47:880–891. [PubMed: 23566423]
46. Radtke KM, Ruf M, Gunter HM, Dohrmann K, Schauer M, Meyer A, et al. Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. Translational psychiatry. 2011; 1:e21. [PubMed: 22832523]
47. Mulligan CJ, D'Errico NC, Stees J, Hughes DA. Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. Epigenetics: official journal of the DNA Methylation Society. 2012; 7:853–857. [PubMed: 22810058]
48. Perroud N, Rutembesa E, Paoloni-Giacobino A, Mutabaruka J, Mutesa L, Stenz L, et al. The Tutsi genocide and transgenerational transmission of maternal stress: epigenetics and biology of the HPA axis. The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry. 2014; 15:334–345.
49. Yehuda R, Daskalakis NP, Lehrner A, Desarnaud F, Bader HN, Makotkine I, et al. Influences of Maternal and Paternal PTSD on Epigenetic Regulation of the Glucocorticoid Receptor Gene in Holocaust Survivor Offspring. The American journal of psychiatry. 2014

50. Tran L, Chaloner A, Sawalha AH, Greenwood Van-Meerveld B. Importance of epigenetic mechanisms in visceral pain induced by chronic water avoidance stress. Psychoneuroendocrinology. 2013; 38:898–906. [PubMed: 23084728]
51. de Rooij SR, Costello PM, Veenendaal MV, Lillycrop KA, Gluckman PD, Hanson MA, et al. Associations between DNA methylation of a glucocorticoid receptor promoter and acute stress responses in a large healthy adult population are largely explained by lifestyle and educational differences. Psychoneuroendocrinology. 2012; 37:782–788. [PubMed: 21978868]
52. Dammann G, Teschler S, Haag T, Altmuller F, Tuczek F, Dammann RH. Increased DNA methylation of neuropsychiatric genes occurs in borderline personality disorder. Epigenetics: official journal of the DNA Methylation Society. 2011; 6:1454–1462. [PubMed: 22139575]
53. Yehuda R, Daskalakis NP, Desarnaud F, Makotkine I, Lehrner AL, Koch E, et al. Epigenetic Biomarkers as Predictors and Correlates of Symptom Improvement Following Psychotherapy in Combat Veterans with PTSD. Frontiers in psychiatry. 2013; 4:118. [PubMed: 24098286]
54. Yehuda R, Flory JD, Bierer LM, Henn-Haase C, Lehrner A, Desarnaud F, et al. Lower Methylation of Glucocorticoid Receptor Gene Promoter 1 in Peripheral Blood of Veterans with Posttraumatic Stress Disorder. Biological psychiatry. 2014
55. Labonte B, Azoulay N, Yerko V, Turecki G, Brunet A. Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. Translational psychiatry. 2014; 4:e368. [PubMed: 24594779]
56. Na KS, Chang HS, Won E, Han KM, Choi S, Tae WS, et al. Association between glucocorticoid receptor methylation and hippocampal subfields in major depressive disorder. PloS one. 2014; 9:e85425. [PubMed: 24465557]
57. Perroud N, Dayer A, Piguet C, Nallet A, Favre S, Malafosse A, et al. Childhood maltreatment and methylation of the glucocorticoid receptor gene NR3C1 in bipolar disorder. The British journal of psychiatry: the journal of mental science. 2014; 204:30–35. [PubMed: 23743517]
58. Perroud N, Paoloni-Giacobino A, Prada P, Olie E, Salzmann A, Nicastro R, et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. Translational psychiatry. 2011; 1:e59. [PubMed: 22832351]
59. Thiede C, Prange-Krex G, Freiberg-Richter J, Bornhauser M, Ehninger G. Buccal swabs but not mouthwash samples can be used to obtain pretransplant DNA fingerprints from recipients of allogeneic bone marrow transplants. Bone marrow transplantation. 2000; 25:575–577. [PubMed: 10713640]
60. Davies MN, Volta M, Pidsley R, Lunnon K, Dixit A, Lovestone S, et al. Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. Genome biology. 2012; 13:R43. [PubMed: 22703893]
61. Liang P, Song F, Ghosh S, Morien E, Qin M, Mahmood S, et al. Genome-wide survey reveals dynamic widespread tissue-specific changes in DNA methylation during development. BMC genomics. 2011; 12:231. [PubMed: 21569359]
62. Xin Y, Chanrion B, Liu MM, Galfalvy H, Costa R, Ilievski B, et al. Genome-wide divergence of DNA methylation marks in cerebral and cerebellar cortices. PloS one. 2010; 5:e11357. [PubMed: 20596539]
63. Xin Y, O'Donnell AH, Ge Y, Chanrion B, Milekic M, Rosoklija G, et al. Role of CpG context and content in evolutionary signatures of brain DNA methylation. Epigenetics: official journal of the DNA Methylation Society. 2011; 6:1308–1318. [PubMed: 22048252]
64. Ziller MJ, Gu H, Muller F, Donaghey J, Tsai LT, Kohlbacher O, et al. Charting a dynamic DNA methylation landscape of the human genome. Nature. 2013; 500:477–481. [PubMed: 23925113]
65. Auger CJ, Auger AP. Permanent and plastic epigenesis in neuroendocrine systems. Frontiers in neuroendocrinology. 2013; 34:190–197. [PubMed: 23707698]
66. Weber M, Hellmann I, Stadler MB, Ramos L, Paabo S, Rebhan M, et al. Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. Nature genetics. 2007; 39:457–466. [PubMed: 17334365]
67. Watson MA, Milbrandt J. Expression of the nerve growth factor-regulated NGFI-A and NGFI-B genes in the developing rat. Development. 1990; 110:173–183. [PubMed: 2081458]

68. O'Donovan KJ, Tourtellotte WG, Millbrandt J, Baraban JM. The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. Trends in neurosciences. 1999; 22:167–173. [PubMed: 10203854]
69. Perez-Castillo A, Pipaon C, Garcia I, Alemany S. NGFI-A gene expression is necessary for T lymphocyte proliferation. The Journal of biological chemistry. 1993; 268:19445–19450. [PubMed: 8366092]
70. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrine reviews. 2000; 21:55–89. [PubMed: 10696570]
71. Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biological psychiatry. 2008; 63:398–405. [PubMed: 17825799]
72. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA: the journal of the American Medical Association. 2000; 284:592–597.
73. Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depression and anxiety. 2002; 15:117–125. [PubMed: 12001180]
74. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008; 33:693–710. [PubMed: 18602762]
75. Lee R, Geracioti TD Jr, Kasckow JW, Coccaro EF. Childhood trauma and personality disorder: positive correlation with adult CSF corticotropin-releasing factor concentrations. The American journal of psychiatry. 2005; 162:995–997. [PubMed: 15863804]
76. Lee RJ, Gollan J, Kasckow J, Geracioti T, Coccaro EF. CSF corticotropin-releasing factor in personality disorder: relationship with self-reported parental care. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2006; 31:2289–2295. [PubMed: 16880775]
77. Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, Nemeroff CB, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2004; 29:777–784. [PubMed: 14702025]
78. Rinne T, de Kloet ER, Wouters L, Goekoop JG, DeRijk RH, van den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. Biological psychiatry. 2002; 52:1102–1112. [PubMed: 12460693]
79. Power C, Thomas C, Li L, Hertzman C. Childhood psychosocial adversity and adult cortisol patterns. The British journal of psychiatry: the journal of mental science. 2012; 201:199–206. [PubMed: 22790680]
80. Elzinga BM, Roelofs K, Tollenaar MS, Bakvis P, van Pelt J, Spinhoven P. Diminished cortisol responses to psychosocial stress associated with lifetime adverse events a study among healthy young subjects. Psychoneuroendocrinology. 2008; 33:227–237. [PubMed: 18096322]
81. Seltzer LJ, Ziegler T, Connolly MJ, Prososki AR, Pollak SD. Stress-induced elevation of oxytocin in maltreated children: evolution, neurodevelopment, and social behavior. Child Dev. 2014; 85:501–512. [PubMed: 23865588]
82. Doom JR, Cicchetti D, Rogosch FA, Dackis MN. Child maltreatment and gender interactions as predictors of differential neuroendocrine profiles. Psychoneuroendocrinology. 2013; 38:1442–1454. [PubMed: 23333253]
83. Steudte S, Kirschbaum C, Gao W, Alexander N, Schonfeld S, Hoyer J, et al. Hair cortisol as a biomarker of traumatization in healthy individuals and posttraumatic stress disorder patients. Biological psychiatry. 2013; 74:639–646. [PubMed: 23623187]

84. Bublitz MH, Parade S, Stroud LR. The effects of childhood sexual abuse on cortisol trajectories in pregnancy are moderated by current family functioning. Biological psychology. 2014; 103C:152–157. [PubMed: 25220484]

85. Bublitz MH, Stroud LR. Childhood sexual abuse is associated with cortisol awakening response over pregnancy: preliminary findings. Psychoneuroendocrinology. 2012; 37:1425–1430. [PubMed: 22341730]

86. Lovallo WR, Farag NH, Sorocco KH, Cohoon AJ, Vincent AS. Lifetime adversity leads to blunted stress axis reactivity: studies from the Oklahoma Family Health Patterns Project. Biological psychiatry. 2012; 71:344–349. [PubMed: 22112928]

87. Yehuda R, Seckl J. Minireview: Stress-related psychiatric disorders with low cortisol levels: a metabolic hypothesis. Endocrinology. 2011; 152:4496–4503. [PubMed: 21971152]

88. Ehlert U. Enduring psychobiological effects of childhood adversity. Psychoneuroendocrinology. 2013; 38:1850–1857. [PubMed: 23850228]

89. Wichers M, Geschwind N, Jacobs N, Kenis G, Peeters F, Derom C, et al. Transition from stress sensitivity to a depressive state: longitudinal twin study. The British journal of psychiatry: the journal of mental science. 2009; 195:498–503. [PubMed: 19949197]

90. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain research Molecular brain research. 1993; 18:195–200. [PubMed: 8497182]

91. Fenoglio KA, Brunson KL, Avishai-Eliner S, Stone BA, Kapadia BJ, Baram TZ. Enduring, handling-evoked enhancement of hippocampal memory function and glucocorticoid receptor expression involves activation of the corticotropin-releasing factor type 1 receptor. Endocrinology. 2005; 146:4090–4096. [PubMed: 15932935]

92. Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ. Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2005; 30:2192–2204. [PubMed: 15920504]

93. Avishai-Eliner S, Gilles EE, Eghbal-Ahmadi M, Bar-El Y, Baram TZ. Altered regulation of gene and protein expression of hypothalamic-pituitary-adrenal axis components in an immature rat model of chronic stress. Journal of neuroendocrinology. 2001; 13:799–807. [PubMed: 11578530]

94. Seth KA, Majzoub JA. Repressor element silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) can act as an enhancer as well as a repressor of corticotropin-releasing hormone gene transcription. The Journal of biological chemistry. 2001; 276:13917–13923. [PubMed: 11278361]

95. Korosi A, Shanabrough M, McClelland S, Liu ZW, Borok E, Gao XB, et al. Early-life experience reduces excitation to stress-responsive hypothalamic neurons and reprograms the expression of corticotropin-releasing hormone. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2010; 30:703–713. [PubMed: 20071535]

96. Rice CJ, Sandman CA, Lenjavi MR, Baram TZ. A novel mouse model for acute and long-lasting consequences of early life stress. Endocrinology. 2008; 149:4892–4900. [PubMed: 18566122]

97. Gunn BG, Cunningham L, Cooper MA, Corteen NL, Seifi M, Swinny JD, et al. Dysfunctional astrocytic and synaptic regulation of hypothalamic glutamatergic transmission in a mouse model of early-life adversity: relevance to neurosteroids and programming of the stress response. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2013; 33:19534–19554. [PubMed: 24336719]

98. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmuhl Y, Fischer D, et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nature neuroscience. 2009; 12:1559–1566.

99. Wu Y, Patchev AV, Daniel G, Almeida OF, Spengler D. Early-life stress reduces DNA methylation of the Pomc gene in male mice. Endocrinology. 2014; 155:1751–1762. [PubMed: 24506071]

100. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nature neuroscience. 2013; 16:33–41.

101. Kosten TA, Huang W, Nielsen DA. Sex and litter effects on anxiety and DNA methylation levels of stress and neurotrophin genes in adolescent rats. Developmental psychobiology. 2013

102. Martin-Blanco A, Ferrer M, Soler J, Salazar J, Vega D, Andion O, et al. Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. Journal of psychiatric research. 2014

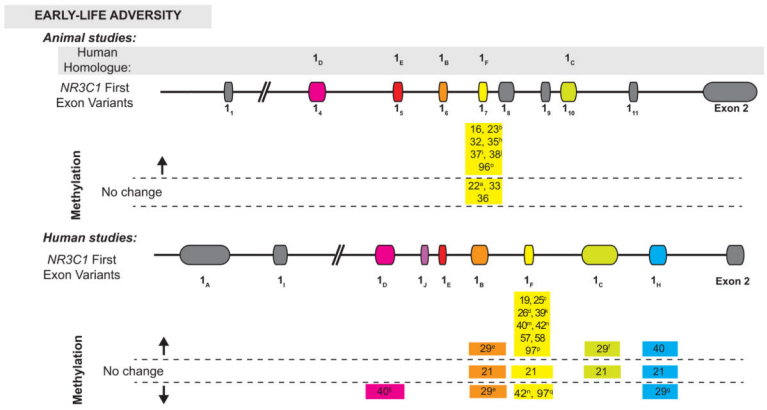

Figure 1. Early-life adversity findings in animal and human studies

Significant findings reported from animal and human studies examining the effects of early-life adversity according to the *NR3C1* first exon variant investigated. Publications are numbered according to their position in the reference list. Upward arrow indicates increased methylation while downward arrow indicates decreased methylation. Results were reported as mean methylation of the region investigated unless otherwise indicated by the footnotes.

a. GR gene CpG methylation undetectable in all conditions. b. Hippocampus only at CpG 1 and 2, NGFI-A site; ↑ methylation correlated to decreased nursing frequency. c. CpG 35 (NGFI-A site is CpG 37 & 38). d. For 6 promoter-associated CpGs. e. CpG 6 & 8, ↑ methylation of both abused and non-abused compared to controls; CpG11, ↓ methylation of both abused and non-abused compared to controls; hippocampus only. f. CpGs 8, 9, 12 & 13; hippocampus only. g. hippocampus only. h. Cerebellum; CpGs −127 & −10; single sex males and mixed-litter females compared to mixed-sex males. i. CpG 13,14, 17, DBA/2J only. j. C57BL/6J, hippocampus and males only. k. CpG 1 & 3 only (NGFI-A site is CpG 3 & 4). l. Repeated exposure to non-physical, non-sexual abuse. m. Single exposure to sexual abuse only. n. ↓ CpG 2 in subset of subjects only; ↑ CpGs 3, 6 and 7 whole sample, 3, 5 & 6 in subset; NGFI-A site at CpG 3 & 4. o. CpGs at −99 & −57 for all females in hippocampus; CpGs −118, −116, −114 in single-sex females in nucleus accumbens; CpG −57 in males vs. females in nucleus accumbens.

p. Reached significance with physical abuse, trend with emotional neglect.

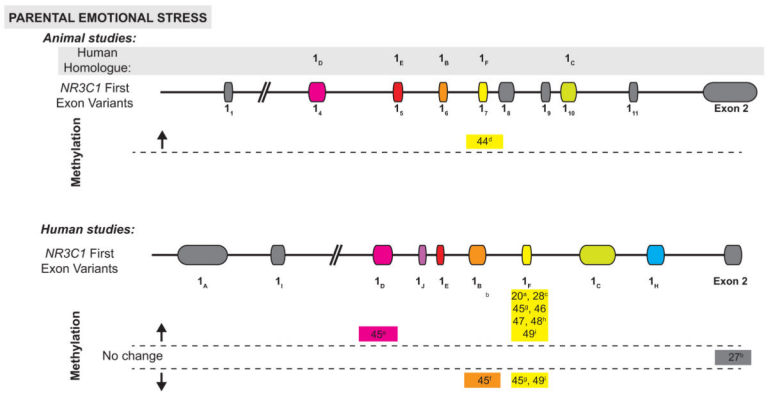

Figure 2. Parental stress findings in animal and human studies

Significant findings reported from animal and human studies examining the effects of parental stress according to the *NR3C1* first exon variant investigated. Publications are numbered according to their position in the reference list. Upward arrow indicates increased methylation while downward arrow indicates decreased methylation. Results were reported as mean methylation of the region investigated unless otherwise indicated by the footnotes. a. CpG 1–3, NFGI-A site. b. indicates a sampling downstream of region 1H, within the gene body. c. CpG2, depression only. d. Early gestation group only; CpGs −523 & −496. e. CpG 12 & 13 with fear of delivery all trimesters; CpG 25 & 28 with fear of integrity of the baby T1. f. CpG 6 with fear of delivery. g. Site- and parameter-specific: CpG 38/39 (near NGFI-A site) ↓ with fear of changes T1 & 2; CpG 36 ↑ with fear of integrity T1 & 2; CpG 36 ↑ with fear of delivery T3. h. Total region for children; CpGs 1, 5 & 8 for mothers. i. ↑ methylation with paternal PTSD only in the absence of maternal PTSD.

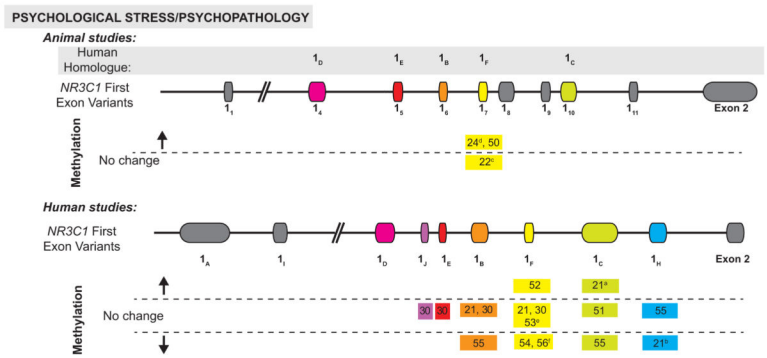

Figure 3. Psychological stress/psychopathology findings in animal and human studies

Significant findings reported from animal and human studies examining the effects of psychological stress/psychopathology according to the *NR3C1* first exon variant investigated. Publications are numbered according to their position in the reference list. Upward arrow indicates increased methylation while downward arrow indicates decreased methylation. Results were reported as mean methylation of the region investigated unless otherwise indicated by the footnotes.

a. CpGs 10 & 21; BN vs. no eating disorder. b. In BN+BPD vs. BN no BPD/no eating disorder. c. no detectable methylation on NR3C1 CpGs. d. Acute stress group – ↑ methylation at several CpG sites in hippocampus only; Chronic stress group – ↑ methylation in response to psychosocial stress in adrenal and pituitary, ↑ methylation in adrenal and ↓ methylation in the pituitary in response to restraint stress. e. No change over time and no difference between responders and non-responders. f. CpGs 3 & 4.

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Table 1

Early-life adversity affects GR gene methylation

	Study	Experimental Group	Species	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_6	1_7	NGFI-A site?	1_{10}
Animal Studies	1 Weaver et al. 2004 (16)	Maternal care model (LG-ABN)	Rat	100	5 animals per group	Sodium bisulfite treatment + sequencing (Frommer 1992)	Hippocampus	P6, 21 and 90		↑	Y	
	2 Weaver et al. 2005 (32)	Maternal care model (LG-ABN)	Rat	100	4–6 animals per group	Sodium bisulfite treatment + sequencing (Frommer 1992)	Hippocampus	P90		↑	Y	
	3 Desarnaud et al. 2008 (22)	Maternal separation and pup handling	Mouse	NR	5 animals per group	Sodium bisulfite treatment (EZ DNA Methylation Kit, *Zymo Research*) + sequencing (ABI Prism 3100 Genetic Analyzer, *Applied Biosystems*)	Hippocampus	P25		no Δ[a]	Y	
	4 Daniels et al. 2009 (36)	Maternal separation (daily for 3h) from P2 to P14	Rat	100	3 animals per group	Sodium bisulfite treatment (EZ DNA Methylation-Gold Kit, *Zymo Research*) + sequencing (Frommer 1992)	Hippocampus	P21		no Δ	Y	
	5 Kember et al. 2012 (37)	Maternal separation on P9 for 24h	Mouse	100	C57BL/6 control: 10 C57BL/6 maternally separated: 8 DBA/2J control: 12 DBA/2J maternally separated: 6	Sodium bisulfite treatment (EZ-96 DNA Methylation Kit, *Zymo Research*) + EpiTYPER platform (*Sequenom*)	Hippocampus	14- to 15-week-old		↑[b]	NR	
	6 Henningsen et al. 2012 (33)	Maternal care model (LG-ABN)	Rat	100	4 animals per group	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + sequencing (Beckman Coulter Genomics)	Dentate gyrus	12-week-old		no Δ	Y	
	7 Liberman et al. 2012 (23)	Maternal care model (LG-ABN) - lower nursing frequency on P1	Mouse	45	Hippocampus: 22 Fecal bolus: 19	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + pyrosequencing (Pyromark MD system and Pyro Q-CpGt 1.0.9, *Qiagen*)	Hippocampus Feces	P35		↑[c]	Y	
	8 Kosten et al. 2014a (101)	Maternal care model (single sex vs. mixed sex litters)	Rat	49	Mixed males: 11 Moxed females: 12 Single-sex males: 9 Single-sex females: 9	Sodium bisulfite treatment (EZ-96 DNA Methylation Kit D5004, *Zymo Research*) + sequencing (ABI 3730 XL, *Applied Biosystems*)	Hippocampus Nucleus accumbens	P35		↑[d]	Y	
	9 Kundakovic et al. 2013 (38)	Maternal separation (daily for 2h) from P1 to 14	Mouse	C57BL/6J: 46 Balb/c: 50	6 animals per sex per rearing condition	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + pyrosequencing (PyroMark Q24 Pyrosequencer, *Qiagen*)	Prefrontal cortex Hippocampus	P40		↑[e]	Y	
	10 Kosten et al. 2014b (35)	Low maternal care (female only vs. mixed vs. male only)	Rat	48	Mixed males: 20 Mixed females: 20 Male single-sex: 10 Female single-sex: 12	Bisulfite treatment + pyrosequencing (PyroMark Q96 MD Pyrosequencing System, *Qiagen*)	Hippocampus Cerebellum	P35		↑[f]	Y	

	Study	Experimental Group	Sex(% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
Human Peripheral Studies	11 Perroud et al. 2011 (58)	Sexually abused	BPD: 6 MDD, low maltreatment: 35	BPD: 101 MDD, low maltreatment[g]: 99 MDD + PTSD: 15	Sodium bisulfite treatment (EZ DNA Methylation Gold-Kit, *Zymo Research*) + pyrosequencing (PSQ 96 Gold reagent kit, *Biotage*)	Blood	BPD: 30.76 MDD (low maltreatment): 41.63 MDD + PTSD: 37.33					↑	N			

	Study	Experimental Group	Sex(% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
				MDD + PTSD: 27 MDD + PTSD: 27												
	12 Tyrka et al. 2012 (39)	Early-life trauma	41	99	Sodium bisulfite treatment (EZ DNA Methylation Kit, *Zymo Research*) + pyrosequencing (PyroMark Software, *Qiagen*)	Blood	27.3 (mean)					↑[h]	Y			
	13 Steiger et al. 2013 (21)	Bulimia nervosa with childhood abuse	0	BN with childhood abuse: 32 BN without childhood abuse: 32 No BN or abuse: 32	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + EpiTYPER platform (*Sequenom*)	Blood	BN: 26.05 (mean) No eating disorder: 23.67 (mean)				no Δ	no Δ	Y	no Δ	no Δ	
	14 Melas et al. 2013 (25)	Depressed (current) with childhood adversity - early parental death	0	Depression: 93 Control: 83	Sodium bisulfite treatment (EZ Methylation Gold-Kit, *Zymo Research*) + EpiTYPER platform (*Sequenom*)	Saliva	Depressed: 55 (median) Control: 56 (median)					↑[i]	Y			
	15 Perroud et al. 2014a (57)	Bipolar disorder (currently treated) with childhood trauma	44	BD: 99	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + pyrosequencing (Pyro Q-CpG Software, *Biotage*)	Blood	44.6 (mean)					↑	N			
	16 Van der Knaap et al. 2014(40)	Early-life trauma	50	Initial study: 468 Confirmation study: 454	Sodium bisulfite treatment (EZ-96 DNA Methylation Kit, *Zymo Research*) + EpiTYPER platform (*Sequenom*)	Blood	16.3 (mean)	↓[j]				↑[k]	Y		↑	
	17 Weder et al. 2014 (26)	Abused or neglected children removed from parental care	42	Maltreated: 94 Non-traumatised: 96	Sodium bisulfite treatment (EZ-96 DNA methylation kit, *Zymo Research*) + Illumina 450K Methylation BeadChip (*Illumina*) / + EpiTYPER platform (*Sequenom*)	Saliva	5–14 (10.2 mean)					↑[l]	NR			
	18 Martìn-Blanco et al. 2014 (102)	Borderline personality disorder with / without childhood abuse	15	281	Sodium bisulfite treatment (EpiTech Bisulfite Kit, *Qiagen*) + Pyrosequencing (PyroMark Q24, *Qiagen*)	Blood	29.4 (mean)					↑[m]	N			
	19 Romens et al. 2014 (42)	Abused or neglected children removed from parental care	54	Total: 56 Maltreatment: 18 Controls: 38	Sodium bisulfite treatment (EZ Methylation Gold-Kit, *Zymo Research*) + pyrosequencing (PSQ 96 MA, *Qiagen*)	Blood	11–14 (12.11 mean)					↓/↑[n]	Y			
	20 Guillemin et al. 2014 (43)	Chronic physical abuse in childhood	0	Control: 14 Abused: 5	MeDIP + Microarray (180K promoter tiling array, *Agilent*); Validation by qPCR *(Roche)* / Sodium bisulfite treatment (EZ-96 DNA Methylation Kit, *Zymo Research*) + Infinium Human Methylation450 Bead Chip *(Illumina)*	Blood	Control: 24.19 Abused: 25									↓[o]
n Central	21 McGowan et al. 2009	Abused suicides	100	Abused suicides: 12 Non-abused suicides: 12 Controls: 12	Sodium bisulfite treatment + sequencing (Cequation 8800, *Beckman-Coulter*)	Hippocampus	SA: 34.2 (mean) SNA: 33.8 (mean) Controls: 35.8 (mean)					↑	Y			

Study	Experimental Group	Sex(% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
22 Labonte et al. 2012 (29)	Abused suicides	100	Hippocampus: 21 abused suicides, 21 non-abused suicides, 14 controls BA24: 22 abused suicides, 14 non-abused suicides, 14 controls	Sodium bisulfite treatement (*Qiagen*) + pyrosequencing (*EpigenDx*)	Hippocampus Anterior cingulate cortex (BA 24)	*Hippocampus* SA: 37.3 (mean) SNA: 40.8 (mean) Controls: 39.8 (mean) *BA 24* SA: 36.1 (mean) SNA: 37.3 (mean) Controls: 35.8 (mean)				↓/↑[p]			↑[q]	↓[r]	

NR: Not reported.

[a] GR gene CpG methylation undetectable in all conditions.

[b] CpG 13,14, 17, DBA/2J only.

[c] Hippocampus only at CpG 1 and 2, NGFI-A site; ↑ methylation correlated to decreased nursing frequency.

[d] CpGs at -99 & -57 for all females in hippocampus; CpGs -118, -116, -114 in single-sex females in nucleus accumbens; CpG -57 in males vs. females in nucleus accumbens.

[e] C57BL/6J, hippocampus and males only.

[f] Cerebellum; CpGs -127 & -10; single sex males and mixed-litter females compared to mixed-sex males.

[g] Due to small sample size, emotional neglect was not considered.

[h] CpG 1 & 3 only (NGFI-A site is CpG 3 & 4).

[i] CpG 35 (NGFI-A site is CpG 37 & 38).

[j] Repeated exposure to non-physical, non-sexual abuse.

[k] Single exposure to sexual abuse only.

[l] For 6 promoter-associated CpGs.

[m] Reached significance with physical abuse, trend with emotional neglect.

[n] ↓ CpG 2 in subset of subjects only; ↑ CpGs 3, 6 and 7 whole sample, 3, 5 & 6 in subset; NGFI-A site at CpG 3 & 4.

[o] Sampling region not specified.

[p] CpG 6&8, ↑ methylation of both abused and non-abused compared to controls; CpG11, ↓ methylation of both abused and non-abused compared to controls; hippocampus only.

[q] CpGs 8, 9, 12 & 13; hippocampus only.

[r] hippocampus only.

Table 2

Parental stress affects GR gene methylation

	Study	Experimental Group	Species	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_6	1_7	NGFI-A site?	1_{10}
Study Animal	1 Mueller et al. 2008 (44)	Offspring of 7-day stress-exposed dams (early, mid and late gestation)	Mouse	100	4–5 animals per group	Sodium bisulfite treatement (EZ DNA Methylation Kit, *Zymo Research*) + pyrosequencing (PSQ HS96 Pyrosequencing system, *Biotage*)	Brain	4 months		↑[a]	Y	

	Study	Experimental Group	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
Human Peripheral Studies	2 Oberlander et al. 2008 (20)	Third trimester maternal depressed/anxious mood	SRI exposed: 44 Depressed, no SRI: 42 Control: 48	SRI exposed: 33 Depressed, no SRI: 13 Control: 36	Bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + pyrosequencing (PyroMark MD System, *Biotage*)	Cord blood	At birth					↑[b]	Y			
	3 Radtke et al. 2011 (46)	Intimate partner violence during pregnancy	32	25	Sodium bisulfite treatment (Frommer 1992) + sequencing (BigDye Terminator 3.1 Cycle Sequencing Kit, *Applied Biosystems*)	Blood	Mother: 25.2 (mean) Child: 14.1 (mean)					↑	Y			
	4 Mulligan et al. 2012 (47)	Exposure to varying degree of maternal stressors - war stress	Not reported	25 mother-child dyads	Sodium bisulfite treatment (EZ DNA Methylation Kit, *Zymo Research*) + sequencing (*Applied Biosystems*)	Cord blood	At birth					↑	Y			
	5 Hompes et al. 2013 (45)	Pregnancy-related anxiety over 3 trimesters	Not reported	83 mother-child dyads	Sodium bisulfite treatment (MethylDetector Bisulfite Modification Kit, *ActiveMotif*) + EpiTYPER (*Sequenom*)	Cord blood	At birth	↑[c]			↓[d]	↑/↓[e]	Y			
	6 Conradt et al. 2013 (28)	*In utero* exposure to maternal mood-disorder	Depression: 48.5 Anxiety: 45.6 Healthy: 48.2	Depression: 66 Anxiety: 57 Healthy: 398	Bisulfite treatment (Pyromark PCR Kit, *Qiagen*) + pyrosequencing (PyroMark MD, *Qiagen*)	Placenta	At birth					↑[f]	Y			
	7 Essex et al. 2013 (27)	Childhood stress exposure	45	109	Sodium bisulfite treatment (EZ DNA Methylation Kit, *Zymo Research*) + Infinium Human Methylation 27 BeadChip Assay (*Illumina*)	Buccal epithelium	15.1 (mean)									no Δ[g]
	8 Perroud et al. 2014b (48)	Women exposed to the Tutsi genocide during pregnancy and their children	Non-exposed: 48 Exposed: 36	Exposed mother-child dyads: 25 Non-exposed mother-child dyads: 25	Sodium bisulfite treatment (EZ Methylation Gold-Kit, *Zymo Research*) + pyrosequencing (PSQ 96 Gold reagent kit, *Biotage*)	Blood	Mothers: 39–52[h] Children: 17–18					↑[i]	Y			
	9 Yehuda et al. 2014 (49)	Parental exposure to the Holocaust	No parental PTSD: 48 Paternal PTSD: 36	No parental PTSD: 31 Paternal PTSD: 11 Maternal PTSD: 22 Bi-parental PTSD: 31	EpiTect Bisulfite Kit, *Qiagen*) + sequencing (*Genewiz*)	Blood	None: 57.13 (mean) Paternal: 47.64 (mean)					↑/↓[j]	Y			

Study	Experimental Group	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
		Maternal PTSD: 18 Maternal PTSD: 18 Bi-paternal PTSD: 19				Maternal: 57.36 (mean) Both: 58.68 (mean)									

[a] Early gestation group only; CpGs -523 & -496.

[b] CpG 1–3, NFGI-A site.

[c] CpG 12 & 13 with fear of delivery all trimesters; CpG 25 & 28 with fear of integrity of the baby T1.

[d] CpG 6 with fear of delivery.

[e] Site- and parameter-specific: CpG 38/39 (near NGFI-A site) ↓ with fear of changes T1 & 2; CpG 36 ↑ with fear of integrity T1 & 2; CpG 36 ↑ with fear of delivery T3.

[f] CpG2, depression only.

[g] indicates a sampling downstream of region 1_H, within the gene body.

[h] Mother's ages estimated based on age at birth (28+/−6) and the age of children at assessment.

[i] Total region for children; CpGs 1, 5 & 8 for mothers.

[j] ↑ methylation with paternal PTSD only in the absence of maternal PTSD.

Table 3

Psychological stress and psychopathology affect GR gene methylation

	Study	Experimental Group	Species	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_6	1_7	NGFI-A site?	1_{10}
Animal Studies	1 Desarnaud et al. 2008 (22)	Social defeat and exposure to rat	Mouse	NR	5 animals per group	Sodium bisulfite treatment (EZ DNA Methylation Kit, *Zymo Research*) + sequencing (ABI Prism 3100 Genetic Analyzer, *Applied Biosystems*)	Hippocampus	NR		no Δ [a]	Y	
	2 Witzmann et al. 2012 (24)	Acute or chronic stress	Rat	100	6 animals per group	Sodium bisulfite treatment (EpiTect Bisulphite kit, *Qiagen*) + pyrosequencing (Pyromark ID using Pyrogold reagents, *Biotage*)	Paraventricular nucleus (PVN) Hippocampus Adrenal Pituitary	10–12-week-old		↑[b]	Y[c]	
	3 Tran et al. 2013 (50)	Repeated (7 day) water avoidance stress	Rat	100	6 animals per group	Sodium bisulfite treatment (EZ DNA Methylation-Gold kit, *Zymo Research*) + pyrosequencing (*EpigenDX*)	Amygdala	Adult		↑	Y	

	Study	Experimental Group	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
Human Peripheral Studies	4 De Rooij et al. 2012 (51)	Variations in acute stress reactivity	47	675	Methylation-sensitive enzymatic restriction (*AciI and HinfI*) + qPCR (SYBR Green, *Sigma*)	Blood	55–60							no Δs		
	5 Dammann et al. 2011 (52)	Borderline personality disorder	Control: 0 BPD: 8	Control: 11 BPD: 26	COBRA and/or Sodium bisulfite treatment + pyrosequencing (PyroMark Q24, *Qiagen*)	Blood	33					↑	N			
	6 Steiger et al. 2013 (21)	Bulimia nervosa with childhood abuse	0	BN with childhood abuse: 32 BN without childhood abuse: 32 No BN or abuse: 32	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + EpiTYPER platform (*Sequenom*)	Blood	BN: 26.05 (mean) No eating disorder: 23.67 (mean)				no Δ	no Δ	Y	↑[d]	↓[e]	
	7 Yehuda et al. 2013 (53)	Combat veterans with PTSD and prolonged exposure to psychotherapy: responders and non- responders	88	Responders: 8 Non-responders: 8	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + sequencing (*Genewiz*)	Blood	Responders: 41 Non-responders: 58					no Δ [f]	Y			
	8 Labonté et al. 2014 (55)	Post-traumatic stress disorder and negative trauma experience	50	PTSD: 30 Controls: 16	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + Epityper (*Sequenom*)	Blood	PTSD: 43.4 Controls: 36.9				↓			↓	no Δ	
	9 Yehuda et al. 2014 (54)	Combat veterans with or without post-traumatic stress disorder	100	PTSD: 61 Controls: 61	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + Sequencing (*Genewiz*)	Blood	PTSD: 34.2 Controls: 33.0					↓	Y			
	10 Na et al. 2014 (56)	Major Depression Disorder	MDD: 24 Controls: 29	Total: 117 MDD: 45 Controls: 72	Sodium bisulfite treatment (EZ DNA Methylation-Gold kit, *Zymo Research*) +	Blood	18–65 MDD: 41.6 (median)					↓[g]	Y			

	Study	Experimental Group	Sex (% male)	Sample size	DNA Methylation Assessment	Tissue(s)	Age at Sample Collection	1_D	1_J	1_E	1_B	1_F	NGFI-A site?	1_C	1_H	Other
					Pyrosequencing (Pyromark ID, *Varionostic*)		Controls: 40.72 (median)									
Human Central Studies	11 Alt et al. 2010 (30)	Lifetime diagnosis of major depressive disorder	MDD: 67 Controls: 50	MDD: 6 Controls: 6	Sodium bisulfite treatment (EpiTect Bisulfite Kit, *Qiagen*) + Pyrosequencing (Pyromark ID, *Varionostic*)	Amygdala Hippocampus Inferior prefrontal gyrus Cingulate gyrus Nucleus accumbens	MDD: 75.5 Controls: 72.5		no Δs	no Δs	no Δs	no Δs	Y			

[a] no detectable methylation on NR3C1 CpGs.

[b] Acute stress group – ↑ methylation at several CpG sites in hippocampus only; Chronic stress group – ↑ methylation in response to psychosocial stress in adrenal and pituitary, ↑ methylation in adrenal and ↓ methylation in the pituitary in response to restraint stress.

[c] Acute stress – hippocampus only; Chronic stress – adrenal only.

[d] CpGs 10 & 21; BN vs. no eating disorder.

[e] In BN+BPD vs. BN no BPD/no eating disorder.

[f] No change over time and no difference between responders and non-responders.

[g] CpGs 3 & 4.