



Epigenetics of childhood trauma: Long term sequelae and potential for treatment

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ABSTRACT

Childhood trauma (CT) can have persistent effects on the brain and is one of the major risk factors for neuro-psychiatric diseases in adulthood. Recent advances in the field of epigenetics suggest that epigenetic factors such as DNA methylation and histone modifications, as well as regulatory processes involving non-coding RNA are associated with the long-term sequelae of CT. This narrative review summarizes current knowledge on the epigenetic basis of CT and describes studies in animal models and human subjects examining how the epigenome and transcriptome are modified by CT in the brain. It discusses psychological and pharmacological interventions that can counteract epigenetic changes induced by CT and the need to establish longitudinal assessment after CT for developing more effective diagnostics and treatment strategies based on epigenetic targets.

Abbreviations: 5-HT(1AR), serotonin (receptor 1A); 5-HTTLPR, serotonin transporter-linked polymorphic region; 5(h)mC, 5-(hydroxy)methylation; A2ar, adenosine A2A receptor; ABN, arched-back nursing; ACE, adverse childhood experience; AVP, arginine vasopressin; BAGE, B-melanoma antigen sequence; BDNF, brain derived neurotrophic factor; bLA, basolateral amygdala; BN, bulimia nervosa; BPD, borderline personality disorder; BSD, bulimia spectrum disorder; CAI, childhood abuse index; CECA-Q, childhood experience of care and abuse questionnaire (Bifulco et al., 1994); CFS, chronic fatigue syndrome; CPI, CpG island; CRH, corticotropin releasing hormone; CT, childhood trauma; CTI, childhood trauma interview (Fink et al., 1995); CTQ-SF, childhood trauma questionnaire – short form (Bernstein et al., 2003); CTQ, childhood trauma questionnaire (Bernstein et al., 1998); CTS, conflicts tactics scale (Straus, 1979); CU(M)S, chronic unpredictable (mild) stress; DA, dopamine; Dex, Dexamethasone; DName, DNA methylation; DNHS, Detroit Neighborhood Health Study; DNMT1, DNA methyltransferase 1; DRD, dopamine receptor D; EGR1, early growth response 1; ETISR-SF, early trauma inventory – short form (Bremner et al., 2007); FEP, first episode psychosis; FHR-P, familial high risk for schizophrenia; FKBP5, FK506 binding protein 5; GAD1, glutamate decarboxylase 1; GR, glucocorticoid receptor; GRIN2B, ionotropic glutamate receptor NMDA type subunit 2B; H3K4me3, trimethylation at the 4th lysine residue of histone H3; H3K9ac, acetylation at lysine residue 9 of histone 3; HDAC, histone deacetylase; Hdac1, histone-deacetylase 1; Hip, hippocampus; HPA, hypothalamus-pituitary-adrenal; Hyp, hypothalamus; I-DBT, intensive dialectical behavior therapy; i.c.v., intracerebro-ventricular; i.h., intrahippocampal; i.n., intranasal; KITLG, Kit-ligand; LES, life events scale; LG, licking/grooming; LINE-1, long interspersed nuclear element 1; MAOA, monoamine oxidase A; McArthur CVI, McArthur Community Violence Instrument (Steadman et al., 1998); MD, maternal deprivation; MDD, major depressive disorder; MeCP2, methyl.CpG binding protein 2; MS, maternal separation; NAc, nucleus accumbens; NGFI-A, nerve growth factor inducible protein A; NR3C1, glucocorticoid receptor gene; OXT(R), oxytocin(receptor); PA, physical abuse; PBI, parental bonding instrument (Parker, 1989); Pcdh, protocadherin; PFC, prefrontal cortex; PND, postnatal day; Pp1c, Protein phosphatase 1; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; REST, repressor element-1 silencing transcription factor; SA, sex abuse; SCZ-AR, acutely relapsed schizophrenia; SDS, social defeat stress; SES, sexual experience survey (Koss and Oros, 1982); SHIP, Study of Health in Pomerania (Völzke et al., 2011); SLC6A4, serotonin transporter gene; SPAQ, sexual and physical abuse questionnaire (Kooiman et al., 2002); SPR, surrogate peer reared; SPS, single prolonged stress; TSA, Trichostatin A; TSST, Trier social stress test (Kirschbaum et al., 1993); WBCs, white blood cells.

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1. Introduction

Adverse experiences such as physical, sexual and emotional abuse during childhood can be detrimental to the psychological and physical development of a child. Up to 1 billion children and adolescents across the world are exposed to violent behavior (data in 2015; Hillis et al., 2016), and violence and maltreatment in childhood account for 45% of all childhood- and 25–32% of adult-onset disorders. This is a major concern for society and public health (Green et al., 2010). Individuals who experience adverse conditions during childhood exhibit greater vulnerability to psychological illnesses including depression, post-traumatic stress disorder (PTSD), bipolar and anxiety disorders (Huh et al., 2017; Palmier-Claus et al., 2016), as well as psychosis and schizophrenia (Misiak et al., 2017; Wells et al., 2020) in adulthood. They also have increased tendency towards aggression, addictive drug abuse and suicide (Aas et al., 2017; Chistiakov and Chekhonin, 2019; Teixeira et al., 2017). Childhood adversity can also negatively impact physical health and increase the risk for adulthood obesity (Hemmingsson, 2018), cardiovascular diseases (Appleton et al., 2017; Suglia et al., 2018), chronic pain (Burke et al., 2017) and cancer (Brown et al., 2010; Holman et al., 2016). The high prevalence of childhood trauma (CT) and its long-lasting impact on mental and physical health make it necessary to better understand the biological processes underlying the pathologies caused by CT. This is essential for early diagnostics, and for the development of interventions that can attenuate or overcome these pathologies.

CT has multiple consequences on the brain and body. It interferes with brain development, and can lead to structural abnormalities in grey matter volume and white matter integrity. Furthermore, CT alters the functional connections between key brain regions such as the prefrontal cortex, hippocampus and amygdala (Teicher et al., 2016). These brain structures are important for cognitive functions and behavior, since they are sensitive to stressful stimuli partially due to the presence of stress hormone receptors, such as the glucocorticoid receptor, in these regions. Accumulating evidence suggests that stressful stimuli in early postnatal life can lead to epigenetic changes in sensitive brain regions, and dysregulate neuroendocrine signaling and immunological cascades, sometimes until adulthood (Bick et al., 2012; Vaiserman and Koliada, 2017). Epigenetic processes modified by CT include changes in DNA methylation (DNAm) and histone modifications, and alterations in the level of non-coding RNA (ncRNA), especially microRNAs (miRNAs) (Hoffmann and Spengler, 2014). Among the most studied molecular pathways in relation to CT-induced epigenetic changes is the hypothalamus-pituitary-adrenal (HPA) axis, implicated in regulation of stress response (Jiang et al., 2019). Many other signaling pathways also undergo epigenetic modifications after CT, in particular signaling peptides and molecules such as brain-derived neurotrophic factor (BDNF), which is important for neurodevelopment (Bondar and Merkulova, 2016) and oxytocin, a hormone that regulates social bonding (Baracz et al., 2020). Epigenetic alterations in the signaling cascades involving neurotransmitters serotonin and dopamine are also implicated in the long-term sequelae of CT. This is of importance, given their known role in the etiology of depression and schizophrenia (Houwing et al., 2017; Howes et al., 2017). However, molecular mechanisms by which early adverse experiences affect the brain and increase the risk for developing neuropsychiatric diseases are highly complex and remain only partially defined.

This review discusses studies on epigenetic factors associated with CT and its long-term effects on brain physiology and behavior. It summarizes evidence of trauma-induced epigenetic alterations from animal and human studies. A particular focus is placed on the link between reported epigenetic changes and their implication in molecular pathways thought to underlie neuropsychiatric symptoms. The possibility of exploiting epigenetic factors for the design of potential treatment approaches is also discussed.

2. Methods

This narrative review is based on the use of PubMed for the initial search of relevant manuscripts published between 2000 and 2020 using the following keywords: “((childhood trauma) OR (childhood adversity) OR (early life trauma) OR (early life adversity) OR (early trauma) OR (early adversity) OR (adverse childhood experience)) AND ((epigenetics) OR (epigenetic) OR (epigenetic therapy) OR (epigenetic treatment) OR (DNA methylation) OR (histone modifications) OR (non-coding RNA) OR (microRNA) OR (miRNA))”. More studies were identified from the bibliography of the selected manuscripts, and additional relevant papers were included during the reviewing process (Fig. 1). Studies from both animal models and humans were selected based on the following criteria: 1) They report changes in DNAm, histone modifications or ncRNA, in response to adverse experiences in early postnatal life or adolescence. 2) The reported changes are related to the brain or behavioral phenotypes and persist till adulthood. Studies focusing on the reversal of identified CT-induced epigenetic changes were also included. Case reports, reviews, letters and editorials were excluded. Information about model organism, environmental exposure, observed epigenetic changes in brain, associated phenotype, and sample sizes was extracted from each animal study. For human studies, assessment of CT, observed epigenetic changes, associated symptoms, sample size, and country of origin of study participants is reported. This information was independently collected and cross-validated by the three co-authors K. M. Thumfart, M. Flachsmann and K. Bright.

3. Involvement of epigenetic factors in the sequelae of CT

CT can interfere with many signaling pathways in the brain, but

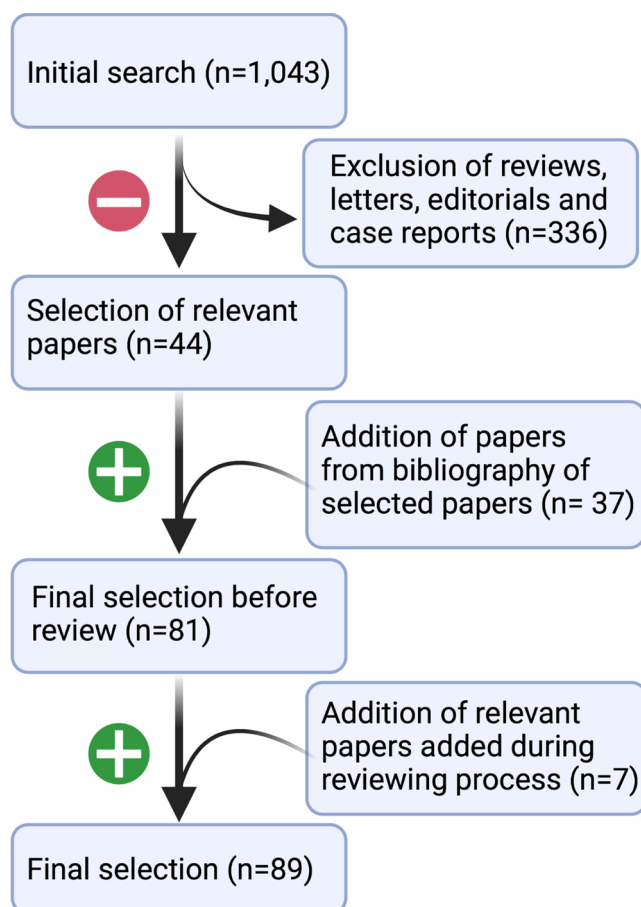


Fig. 1. Flow chart summarizing the selection of papers.

pathways involving the HPA axis, BDNF, oxytocin, and neurotransmitters like dopamine and serotonin, and their associated epigenetic changes have been the most examined. We therefore structured the review along these pathways and systematically compared results obtained in animal models and human subjects in relation to the long-term sequelae of CT.

3.1. Evidence from animal studies

Rodents, and to a lesser extent non-human primates, have been widely used to model CT in preclinical studies. Paradigms such as maternal separation, natural variations in maternal care, early weaning, and social isolation have been used to study pathways implicated in the effects of early trauma on stress response, behavior, and cognitive functions in adulthood (Table 1).

3.1.1. Epigenetic dysregulation of key molecular pathways

3.1.1.1. HPA axis. Initial evidence suggesting that early life experiences can affect the epigenetic landscape in the brain derives from studies investigating variations in maternal care in rats (Weaver et al., 2004). In lactating female rats, the level of licking/grooming and arched-back nursing varies greatly across individual females and is an important determinant of the pups' health. Pups raised by a low-grooming mother have increased DNAm and lower histone acetylation at the promoter of the glucocorticoid receptor (GR) gene Nr3c1 in the hippocampus when adult. GR is an important mediator of stress responses in the brain that provides a negative feedback response to glucocorticoid action in the hypothalamus and pituitary (De Kloet et al., 1998). Cortisol release is also increased in these rats, indicating hyperactivity of the HPA axis (Weaver et al., 2004). More recent studies of exposure to various stressors in early life have confirmed GR downregulation and HPA axis hyperactivity in adolescent and adult rats. Increased DNAm of the Nr3c1 gene by low licking-grooming was observed in the hippocampus and nucleus accumbens in adolescent rats (Kosten et al., 2014). The increase was more pronounced in females than males, suggesting a sex-specific effect. Further, rats exposed to maternal separation between postnatal day (PND) 1 and 21 also have reduced histone H3 acetylation at the Nr3c1 promoter I7 in the hippocampus in adulthood, resulting in GR downregulation (Park et al., 2017). Similar changes in HPA axis response also occur in rats subjected to maternal separation during PND 2 to 14 (Uchida et al., 2010), or after chronic unpredictable mild stress in adolescence (PND 56-77) leading to GR downregulation in the basolateral amygdala (Xu et al., 2017). However, in mice exposed to maternal separation from PND 1 to 10, hypermethylation of the CpG island shore of the Nr3c1 exon I7 promoter has been associated with GR upregulation in the hypothalamus. This may be due to decreased binding of the transcriptional repressor YY1 that can lead to dis-inhibition of GR transcription (Bockmühl et al., 2015). While most studies investigated DNAm changes at Nr3c1 gene in various brain regions after early life adversity, recent evidence also implicated histone modifications. Maternal separation from PND 1 to 21 decreases histone acetylation at GR promoter in the hippocampus in both young adult and middle-aged mice, leading to GR downregulation (Seo et al., 2020). This effect is accompanied by an upregulation of histone deacetylase 5, suggesting that acetylation of many other histone residues is likely altered in the hippocampus.

Apart from changes in DNAm and histone acetylation, other factors have been implicated in GR and HPA axis dysregulation in response to early life stressors. FKBP5 binding protein 5 (FKBP5) and miR-124, which both negatively regulate GR function, are persistently upregulated in the basolateral amygdala of rats exposed to chronic unpredictable mild stress from PND 28 for 21 days (Xu et al., 2017). FKBP5 expression is induced by increased glucocorticoid levels via binding of glucocorticoids to glucocorticoid responsive elements in the FKBP5

gene. FKBP5 then associates with GR and prevents its activation, thereby providing negative feedback for glucocorticoid signaling (Wochnik et al., 2005). FKBP5, miR-124a and miR-18a are also increased in the prefrontal cortex and hippocampus of adolescent rats after chronic unpredictable mild stress from PND 21 for 21 days, while GR expression is decreased (Xu et al., 2019). Both of these miRNAs were shown to directly repress GR expression (Vreugdenhil et al., 2009), suggesting a combined effect of FKBP5 and direct action of miRNAs on the regulation of GR activity. Further, alterations in the arginine-vasopressin gene expression in the paraventricular nucleus of the hypothalamus can also contribute to HPA axis hyperresponsiveness after early life trauma (Murgatroyd et al., 2009). In particular, maternal separation from PND 1 to 10 decreases DNAm at the arginine-vasopressin gene and prevents transcriptional repression by the methyl CpG-binding protein 2 (MeCP2) leading to arginine-vasopressin upregulation, and HPA axis hyperactivity in adulthood (Murgatroyd et al., 2009).

In conclusion, most animal studies on HPA dysregulation after early life trauma showed GR downregulation in hippocampus, basolateral amygdala and nucleus accumbens and linked this effect to hypermethylation at Nr3c1 exon I7 promoter and/or decreased histone acetylation (Kosten et al., 2014; Park et al., 2017; Seo et al., 2020; Weaver et al., 2004). However, other studies reported opposite epigenetic changes in hypothalamus, suggesting different epigenetic signatures of early life trauma in different brain areas (Bockmühl et al., 2015). In some cases, no epigenetic change in GR was observed in the hippocampus or nucleus accumbens after early life stress (Murgatroyd et al., 2009), possibly due to the variance in the use of stressors, stress induction at different time points, and tissue examination at various stages after stress (Seo et al., 2020).

3.1.1.2. BDNF. Besides GR and associated HPA axis dysregulation, neurotrophins such as BDNF have been implicated in the short- and long-term effects of CT. BDNF is involved in important neurodevelopmental processes, such as the differentiation and growth of neurons, and its expression can be modified by life experiences (Branchi et al., 2004). Exposure of rat pups to stressed mothers during their first week of life increases DNAm at the BDNF locus in prefrontal cortex associated with decreased BDNF expression (Roth et al., 2009). Other mechanisms or factors, like histone acetylation and miRNAs, also likely contribute to BDNF regulation in relation to early adversity. Several miRNAs including miR-16, miR-124a, and miR-206 have been shown to directly target BDNF (Bahi and Dreyer, 2013; Lee et al., 2012; Sun et al., 2013). They are also upregulated in the hippocampus of rats after maternal separation during PND 1 to 11, or in mice subjected to early social isolation starting from PND 21 for 5 weeks (Bahi, 2016; Bahi et al., 2014; Bai et al., 2012; Chang et al., 2020). In both models, this correlated with decreased BDNF expression and depressive-like phenotypes in adulthood. Further, maternal separation in rat pups from PND 2 to 14 coupled with single prolonged stress in adulthood (PND 80) increases histone deacetylase 2 and lowers global H3K9ac levels in the hippocampus (Sun et al., 2020). These changes correlate with lower BDNF mRNA and protein levels, suggesting that the BDNF locus is affected by stress-induced deacetylation via histone deacetylase 2.

Like for GR, most studies reported BDNF downregulation and epigenetic changes at its locus in mice and rats, but in some cases no change was observed (Kosten et al., 2014). Nonetheless, it appears that several mechanisms likely contribute to BDNF downregulation after CT, including increased DNAm (Roth et al., 2009), decreased histone acetylation (Sun et al., 2020) and miRNAs dysregulation (Bahi, 2016; Chang et al., 2020), suggesting a combinatorial epigenetic response. The higher consistency of results in studies investigating BDNF compared to HPA axis may be due to the analyses of the same brain regions, particularly the hippocampus and prefrontal cortex, as opposed to analyses of several different brain regions in studies of glucocorticoid response.

Table 1
Summary of animal studies

Reference	Model	Environmental exposure	Epigenetic changes	Associated phenotype	Sample size
1 (Weaver et al., 2004)	Rat	Low LG and ABN	Altered cytosine methylation, histone acetylation and transcription factor (NGFI-A) binding to the GR promoter (Hip)	Higher HPA stress responses	4-5/group
2 (Kosten et al., 2014)	Rat	Different litter gender composition and associated variation in maternal LG	Elevated DNAm of the GR gene (Nr3c1) in (Hip and NAc)	Increased anxiety behavior	9-12/group
3 (Park et al., 2017)	Rat	MS (PND1–21) and chronic restraint stress (PND56–77)	Reduced histone H3 acetylation at GR promoter I7 (Hip)	Reduced GR expression	12/group
4 (Uchida et al., 2010)	Rat	MS (PND2-14); repeated restraint stress (at 8 weeks old)	Increased expression of REST4 and target gene mRNAs and miRNAs (mPFC)	Higher HPA stress responses; increased depression-like behavior and anhedonia	6-8/group
5 (Xu et al., 2017)	Rat	CUMS or Dex administration (from PND28 for 21 days)	Decreased GR expression, increased FKBP5 and miR-124a expression (bIA)	Permanent depressive-like behaviors and memory impairment	6/group
6 (Bockmühl et al., 2015)	Mouse	MS (PND1-10)	Increased GR expression through CPI shore hypermethylation (decreased binding of YY1 transcriptional repressor) (Hyp)	Higher cortisol response to stress	9-10/group
7 (Seo et al., 2020)	Mouse	MS (PND1-21)	Decreased histone acetylation (increased HDAC5) and increased repressive methylation at GR exon I7 promoter (Hip)	Decreased GR, depressive behavior in middle-aged mice	7-13/group
8 (Xu et al., 2019)	Rat	CUMS or Dex administration (from PND28 for 21 days)	Decreased GR and increased FKBP5, miR-124a and miR-18a expression (PFC and Hip); decreased miR-511 expression (PFC)	Anhedonia, altered locomotor behavior, anxiety, cognitive impairment	6/group
9 (Murga-troyd et al., 2009)	Mouse	MS (PND1-10)	increase in AVP expression, DNAm decrease and less repressive binding of MeCP2 (Hyp, PVN)	corticosterone hypersecretion and alterations in passive stress coping and memory	8-10/group
10 (Roth et al., 2009)	Rat	Expose rat pups to stressed caretakers that show abusive behaviors (PND1-7)	Increase in <i>BDNF</i> DNAm resulting in decreased <i>BDNF</i> expression (PFC)	females had increased self-grooming and rearing	4-9/group
11 (Bai et al., 2012)	Rat	MD (PND1-13); CUS (at 10 weeks old for 3 weeks)	Differential expression of <i>BDNF</i> mRNA and miR-16 (Hip)	Depressive-like behaviors	6/group
12 (Bahji, 2016)	Rat	Neonatal isolation model of autism (from PND1-11)	Increased expression of miR-124a and reduced expression of <i>BDNF</i> (Hip)	Decreased social interaction, increased repetitive- and anxiety-like behaviors	6/group
13 (Chang et al., 2020)	Mouse	Social isolation from PND21 for 5 weeks	Increased miR-206 (Hip)	<i>BDNF</i> -dependent increased stress-induced attack-behavior	7-8/group
14 (Sun et al., 2020)	Rat	MS (PND2-14); SPS in adulthood (PND80)	Decreased H3K9ac and increased Hdac2 levels (Hip)	Reduced <i>BDNF</i> levels, increased synaptic damage, anxiety, depression	10-12/group
15 (Beery et al., 2016)	Rat	Low LG (PND1-21)	Increased DNAm at several OxtR CpGs (mononucleocytes) or at an individual CpG (Hip)	Lower weight, lower cortisol response	16-28/assay
16 (Zhang et al., 2010)	Rat	Low LG (PND1-21)	DNMT1 significantly higher, increased DNAm at <i>GAD1</i> gene and lower acetylation (Hip)	Decrease of <i>GAD1</i> levels, hippocampal serotonin (5-HT) and NGFI-A	4-8/group
17 (Liu et al., 2017)	Rat	Prolonged stress in adolescence (PND28-33; PTSD-like model protocol)	Reduced miRNA-135a and elevated 5-HT1AR (PFC); increased miRNA-16 expression (Hip)	Anxiety-like behaviors and spatial memory damage	10/group
18 (Sasagawa et al., 2017)	Mouse	MS coupled with social isolation (PND1-14)	Lower DRD1 expression through elevated DNAm in female mice (NAc, striatum)	Altered reward-seeking behavior in female mice	4-9/group
19 (Zhang et al., 2013)	Rat	MD from P1-14 and CUS (at 10 weeks old)	Higher miR-504 expression and lower DR D1 and D2 (NAc)	Depressive-like behaviors	17-22/group
20 (Zhang et al., 2015)	Rat	MD from PND1-14 and CUS (at 10 weeks old)	Increased DRD2 expression; differential expression of miRNA-9 and miRNA-326 (striatum, NAc)	Depressive-like behaviors, enhanced susceptibility to late life stress	11-15/group
21 (McGowan et al., 2011)	Rat	Low LG (PND1-21)	DNAm and acetylation changes in several promoters, exons and gene ends; specifically, <i>Pcdh</i> family affected (Hip)	Higher transcription in several affected loci	3-4/group for epigenetic assays 8/group for gene expression
22 (Suri et al., 2014)	Mouse	MS (PND2-14)	Age-dependent, opposing regulation of Hdacs and HMTs - decreased in young adults; enhanced in middle-aged life (Hip)	Enhanced anxiety in young adulthood	9-12/group
23 (Bahari-Javan et al., 2017)	Mouse	MS (PND1-21)	Demethylation of <i>Hdac1</i> gene and increase in expression (Hip)	Development of schizophrenia-like phenotypes	5-6/group
24 (Reshetnikov et al., 2020)	Mouse	MS (PND2-14) + SDS (PND110–PND124)	Genome-wide landscape of H3K4me3 (PFC)	Higher cortisol and anxiety after SDS	7-9/group
25 (Kronman et al., 2021)	Mouse	MS and low home cage nesting material (PND10-17)	enriched H3K9me1 at PND21; suppressed H3K79me1/2 in adulthood (males only); increased <i>Dot1l</i> and <i>Kdm2b</i> expression (NAc)	Impaired social interaction, less exploration, depressive-like	3/group for histone modifications

(continued on next page)

Table 1 (continued)

Reference	Model	Environmental exposure	Epigenetic changes	Associated phenotype	Sample size
26 (Anier et al., 2014)	Rat	MS (PND2-15)	Decreased global DNAm; Increased DNAm of Pp1c and A2ar promoters (Nac)	behavior, increased susceptibility to adult stress Increased response to cocaine-induced locomotor activity and exploratory behavior	5-8/group for proteins 6/group
27 (Borba et al., 2021)	Rat	MD (PND1-10)	Increased HDAC and DNMT (PFC + Hip in females; Hip in males)	Depressive-like behavior, altered spontaneous locomotor activity	4-5/group
28 (Massart et al., 2014)	Monkey	SPR monkeys	Altered 5hmC and 5mC enriched at promoters of a subset of highly expressed genes associated with early-adversity (PFC)	Mental health pathologies	3-4/group
29 (Papale et al., 2017)	Mouse	Exposure to different daily stressor (PND12-18)	Altered 5hmC and gene expression (Hyp)	Anxiety-like behaviors in adult female mice	10–12/group

3.1.1.3. Oxytocin. The neuropeptide oxytocin has been implicated in the infant response to maternal care and is therefore another potential candidate for mediating the long-term effects of early adversity on the adult brain (Bales and Perkeybile, 2012). While a role for the oxytocin system has been extensively studied with respect to early environments and social behaviors, little is known about its epigenetic regulation in response to early life adversity. DNAm likely contributes, since several CpGs in the oxytocin receptor gene (*Oxtr*) are hypermethylated in blood and hippocampus of rats exposed to low maternal care (Beery et al., 2016). This is specific to these regions, since methylation was not altered in the hypothalamus or striatum of the same rats, suggesting differential regulation of *Oxtr* DNAm across tissues as reported earlier (Harony-Nicolas et al., 2014). More studies will be required to confirm these findings and identify the mechanisms of epigenetic regulation in different brain regions.

3.1.1.4. Neurotransmitter signaling. Alterations in neurotransmitter systems have been implicated in the long-term sequelae of early life trauma, not only in affected individuals, but also in their progeny (Franklin et al., 2011; Razoux et al., 2017). Rats with low-grooming mothers have lower serotonin levels in the hippocampus, and higher DNAm and lower H3K9ac at the glutamic acid decarboxylase (*GAD1*) promoter. The elevated DNAm and lower acetylation at this locus decrease serotonin-induced NGFI-A binding to the *GAD1* promoter, thus downregulating *GAD1* expression (Zhang et al., 2010). Besides direct DNA modifications, miR-135 has also been implicated in the regulation of serotonergic activity, by targeting both, the serotonin transporter and receptor 1A (Issler et al., 2014). Adolescent rats (PND 28-33) exposed to an inescapable electrical foot shock causing PTSD-like symptoms in adulthood, have lower miR-135a level and increased serotonin receptor 1A expression in the prefrontal cortex (Liu et al., 2017).

Dopamine signaling can also be dysregulated by epigenetic mechanisms in response to early life adversity. Downregulation of the dopamine receptor D1 has been associated with increased DNAm at its promoter in nucleus accumbens in a mouse model of maternal separation coupled with social isolation in the first two weeks of postnatal life (Sasagawa et al., 2017). This also resulted in behavioral alterations in reward seeking behavior albeit only in females. Aside from DNAm-dependent mechanisms, miRNAs have also been implicated in changes in dopamine signaling in response to CT. In adult mice exposed to maternal deprivation from PND 1 to 14 followed by chronic unpredictable stress at 10 weeks of age, miR-504 is increased in the nucleus accumbens and dopamine receptor D1 and D2 are downregulated (Zhang et al., 2013). This is opposite to a previous study reporting upregulation of D1 receptor through miR-504 binding to the D1 receptor gene 3'-UTR determined by luciferase assays (Huang and Li, 2009). These discrepancies can possibly be explained by experimental differences like in vivo vs. in vitro settings and need further evaluation. Bioinformatic predictions revealed that besides miR-504, miR-9 is a potential regulator of dopamine receptor expression. Consistently,

miR-9 is decreased in nucleus accumbens and striatum, and correlates with increased dopamine receptor D2 expression in rats subjected to maternal deprivation at PND 1 to 14 (Zhang et al., 2015).

In summary, these studies suggest a tight epigenetic control of the interplay between serotonin, dopamine and glutamate signaling pathways in response to early life adversity. However, the regulation of dopamine receptors and effector miRNAs is still controversial, highlighting the necessity for expanding the research to other brain regions and epigenetic marks such as acetylation, and taking into account different times of exposure and stress models (Sasagawa et al., 2017; Zhang et al., 2015, 2013).

3.1.2. Changes in global epigenome and the epigenetic machinery

Detecting changes in epigenetic factors at specific genes, and relating them to behavioral responses and brain alterations has provided information about the effects of early life adversity. However, identifying the mechanisms responsible for these changes is necessary to determine their causal implication. The epigenetic machinery is a complex ensemble of biochemical cascades involving multiple enzymes that regulate DNAm, histone posttranslational modifications and ncRNA expression.

In rats, poor maternal care was shown to affect DNAm and histone modifications on large genomic regions, for instance, on chromosome 18 (McGowan et al., 2011). In this region, changes in DNAm and histone acetylation occur in several clusters at multiple loci in both genic and inter-genic regions. Functional assays for epigenetic enzymes, such as histone deacetylases (HDACs) and histone methyltransferases (HMTs) in mice subjected to maternal separation from PND 2 to 14, showed an age-dependent dysregulation of these histone modifying enzymes in hippocampus (Suri et al., 2014). In this study, HDACs and HMTs were oppositely regulated, with decreased level in young adulthood and enhanced level in middle-aged life, translating into differential enrichment of histone acetylation and methylation modifications at specific gene loci (Suri et al., 2014). Another study in mice showed that maternal separation at PND 1 to 21 leads to demethylation at the *Hdac1* locus resulting in increased HDAC1 mRNA and protein in the hippocampus (Bahari-Javan et al., 2017). This increase was associated with the development of schizophrenia-like phenotypes in adulthood, further highlighting a major role for epigenetic enzymes for proper behavioral functioning. Further, global alterations in histone methylations, namely H3K4me3, were observed in the prefrontal cortex of mice undergoing maternal separation from PND 2 to 14 followed by adult stressors (Reshetnikov et al., 2020). Lastly, early life stress induced by maternal separation and low nesting material between PND 10 and 17 induces upregulation of the histone modifying enzymes DOT1L and KDM2B in type 2 medium spiny neurons in nucleus accumbens (Kronman et al., 2021). This is associated with enriched H3K9me1 at PND 21, and decreased H3K79me1 and H3K79me2 in adulthood, albeit in males only. Additionally, higher levels of DOT1L and KDM2B in nucleus accumbens correlate with higher behavioral susceptibility to adult

stress, supporting a central role of these histone modifying enzymes in the long-term effects of early stress, probably in a sex-specific manner (Kronman et al., 2021).

Apart from global changes in histone modifications and associated enzymes, early life experiences can also influence the expression of DNA-methyltransferases (DNMTs) (Anier et al., 2014; Zhang et al., 2010). Expression of DNMT1, -3a, and -3b is increased in the nucleus accumbens of young and adult rats exposed to maternal separation from PND 2 to 15 (Anier et al., 2014). This increase is associated with a global decrease in DNAm, but an increase in methylation at specific sites involved in cocaine addiction, such as the promoter regions of Pp1c (Protein phosphatase 1 catalytic subunit gamma) and A2ar (Adenosine A2A receptor), suggesting that global and gene-specific methylation may have different regulatory mechanisms. Also, sex was shown to influence the differential activity of epigenetic modifiers in response to CT (Borba et al., 2021). Maternally deprived (PND 1-10) female rats show an increase in DNMT and HDAC enzymes in prefrontal cortex and hippocampus, whereas in males only the hippocampus is affected.

Hydroxy-methylation (5hmC) is an additional epigenetic mark that can be affected by early-life events and is associated with phenotypical changes in adulthood. Studies in monkeys and mice show that different traumatic experiences in early life can lead to enriched 5hmC at the promoter of genes associated with early adversity in the prefrontal cortex (Massart et al., 2014). For instance, in female mice subjected to chronic stress between PND 12 and 18, which exhibit anxiety-like behaviors in adulthood, stress-related isoforms of several genes including the mineralocorticoid receptor Nr3c2 and the presynaptic cell adhesion molecule Neurexin 1 have altered 5hmC and expression in the hypothalamus, consistent with previous suggestion that 5hmC is involved in alternative splicing (Khare et al., 2012; Papale et al., 2017).

Together, these studies suggest a global dysregulation of several epigenetic modifiers including DNMTs, HDACs and HMTs (Bahari-Javan et al., 2017; Suri et al., 2014) (Anier et al., 2014; Zhang et al., 2010) leading to changes in DNAm and histone posttranslational modifications. Some of the CT-induced effects seem to be sex- (Borba et al., 2021) or age-dependent (Suri et al., 2014), which needs to be taken into account for future studies. Also, further studies are needed to determine, how such global alterations can lead to changes at specific loci associated with neuropsychiatric pathologies (Anier et al., 2014).

3.2. Evidence from human studies

Inspired by studies in animal models, translational work in epigenetics has examined the relationship between the epigenome and neuropsychiatric disorders in patients with a history of CT. Blood and saliva have mostly been used as biological samples until now, with analyses in the brain still being scarce, due to limited tissue accessibility. These analyses have implicated the epigenome in the long-lasting consequences of CT in humans (Table 2).

3.2.1. Epigenetic dysregulation of key molecular pathways

3.2.1.1. HPA axis. Initial evidence that CT is associated with epigenetic changes in humans came from a study in post-mortem hippocampal tissue from suicide victims with a history of childhood abuse (McGowan et al., 2009). Akin to rodent studies, the NR3C1 F1 promoter region was found to be hypermethylated and had reduced transcription factor binding, which correlated with a decreased level of GR mRNA. Consistently, NR3C1 promoter hypermethylation in white blood cells of patients from two cohorts, one affected by bipolar disorder and the other by major depressive disorder, was associated with sexual, physical or emotional abuse, and neglect in childhood (Perroud et al., 2011). This was confirmed in another independent cohort of bipolar patients, where NR3C1 promoter hypermethylation further correlated with physical abuse in childhood, as well as disease severity (Martin-Blanco et al.,

2014).

Different methylation sites of the NR3C1 gene were found to be altered in opposite directions in patients suffering from major depressive disorder compared to patients with a history of CT. While depression was associated with decreased DNAm at CpG sites 5-13, CT was associated with an increase in DNAm at CpG sites 1-4 (Bustamante et al., 2016). This is consistent with the results of another study on healthy adults showing increased rates of DNAm at several CpGs of the NR3C1 gene after parental neglect or loss, suggesting that CT alone influences DNAm in this region, independently from any psychiatric conditions (Tyrka et al., 2012). In contrast, reduced methylation of exon 1 F of NR3C1 across the whole promoter region and at several individual CpG was reported in a larger cohort of adults with a history of childhood adversity (Tyrka et al., 2016), as well as in adults with a history of childhood emotional abuse, although not significantly (Vangeel et al., 2018). A loss of DNAm at the NR3C1 promoter was further reported in schizophrenia patients with a history of CT (Misiak et al., 2020b). However, DNAm was increased in patients with relapse of schizophrenia compared to those after the first episode of psychosis, suggesting that the methylation status might dynamically change in schizophrenia patients over several psychotic episodes. No correlation between CT and methylation at the NR3C1 promoter was observed in some cases (Alexander et al., 2018). However, methylation levels at the CpG12 of the NR3C1 promoter were associated with HPA responsiveness in people who underwent moderate to severe CT.

These inconsistent findings suggest that the interaction between CT, differential DNAm of NR3C1 promoter and HPA axis responsiveness is complex and likely involves additional modulating factors. Indeed, several miRNAs known to regulate GR functioning are also differentially expressed after CT. A whole-genome methylation analysis of leukocytes that compared patients with bipolar disorder and a history of severe CT to patients with depression and mild CT showed differential methylation of a CpG site close to miR124-3 that was associated with the severity of trauma (Prados et al., 2015). MiR-124 is an noteworthy candidate because it targets GR, is highly abundant in neurons, and has been implicated in several neuropsychiatric diseases (Saab and Mansuy, 2014). Similarly, miR-15a is significantly increased in peripheral blood of subjects who were exposed to CT (Volk et al., 2016). One of the targets of miR-15 is FKBP5, which is known to play a role in the transcriptional activation of GR in response to cortisol. Consistently, an upregulation of miR-15 in response to dexamethasone administration has also been observed in healthy controls, further highlighting a role for miR-15 in the regulation of GR response.

Intriguingly, the dysregulation of HPA axis response after CT implicates a complex interplay of genetic and epigenetic mechanisms. It was found that child abuse-related risk for PTSD and the rs1360780 locus of the FKBP5 gene are significantly associated (Klengel et al., 2013). Only CT-exposed individuals carrying a specific risk allele (rs1360780 A/T) have decreased DNAm in intron 7 of FKBP5, which also correlates with the severity of CT. However, in people carrying the protective allele (rs1360780 C/G), this correlation is either absent or positive, suggesting that different genetic predispositions can lead to distinct changes in FKBP5 methylation after CT. Moreover, persistent DNAm changes are observed in response to CT but not to later traumatic events, indicating that there may be sensitive time periods for the priming of the epigenetic state of the FKBP5 gene (Klengel et al., 2013). The effect of CT on FKBP5 methylation status was further investigated in a cohort of young women exposed to CT (Ramo-Fernández et al., 2019). In line with previous studies, these women had significant demethylation of the FKBP5 gene, only when carrying the risk allele, as well as higher DNAm at the GR locus, suggesting a genotype specific relation between FKBP5 and NR3C1 functioning. In addition, lower methylation of the corticotropin releasing hormone receptor gene was observed in women with a history of CT (Ramo-Fernández et al., 2019).

Further, CT-associated demethylation of a specific CpG (site 4) of the FKBP5 locus close to a glucocorticoid response element of intron 7 was

Table 2
Summary of human studies

Reference	Assessment of CT	Epigenetic changes	Associated phenotype	Sample size	Country
1 (McGowan et al., 2009)	CECA-Q	Decreased GR mRNA; increased DNAm of NR3C1 promoter. decreased NGFI-A binding (Hip)	Suicide	12/group	Canada
2 (Perroud et al., 2011)	CTQ	Increased DNAm of NR3C1 promoter (WBCs)	BPD, MDD	101 BPD patients; 99 MDD patients; 15 MDD patients with past/current PTSD	France, Switzerland
3 (Martin-Blanco et al., 2014)	CTQ-SF	Increased NR3C1 promoter DNAm (blood)	BPD	281 subjects with BPD	Spain
4 (Bustamante et al., 2016)	CTS and CTQ	Increased DNAm on EGR1 TF binding site of NR3C1 gene (blood)	Lower GR expression (leukocytes)	152 adults from DNHS	USA
5 (Tyrka et al., 2012)	PBI, Childhood Parental Loss, CTQ	Increased DNAm at several CpG sites at the NR3C1 promoter (blood)	Attenuated cortisol responses to the Dex/CRH test in adulthood	99 healthy patients	USA
6 (Tyrka et al., 2016)	Parental death and/or desertion and CTQ	Decreased NR3C1 promoter DNAm (blood)	Attenuated cortisol responses to the Dex/CRH test; higher anxiety symptoms	340 healthy adult participants	USA
7 (Vangeel et al., 2018)	CTQ-SF on CFS patients	Decreased NR3C1 DNAm (blood)	CFS, Dysregulation of HPA axis	80 CFS patients 91 controls (females only)	Belgium
8 (Misiak et al., 2020b)	CECA-Q	Decreased NR3C1 DNAm (blood)	Better attention and memory, and higher general functioning in psychotic patients	40 FEP 45 SCZ-AR 39 FHR-P 58 controls	Poland
9 (Alexander et al., 2018)	CTQ	Differential DNAm of NR3C1-1 F CpG12 (blood)	Different peak cortisol levels in response to TSST	98 CT exposed, 102 controls	Germany
10 (Prados et al., 2015)	CTQ and clinical interview	Differential methylation of CpG site close to miR124-3 (leukocytes)	No associated phenotype tested	96 BPD subjects (high level of CT), 93 MDD subjects (low level of CT)	Switzerland
11 (Volk et al., 2016)	Loss/separation of a parent; severe PA or SA; neglect	Increased levels of miR-15a (blood)	No associated phenotype tested	20/group	Italy
12 (Klengel et al., 2013)	CTQ	Allele-specific FKBP5 DNA demethylation of intron 7 (blood)	Predisposition to PTSD; tightening the feedback loop between FKBP5 and GR, leading to GR resistance	30 CT, 46 controls 56 (replication cohort)	USA
13 (Ramo-Fernández et al., 2019)	CTQ	Decreased DNAm of FKBP5 and CRHR1; increased NR3C1 methylation, (leukocytes)	Increased FKBP5 expression in response to Dex	117 women	Germany
14 (Misiak et al., 2020a)	CECA-Q	Lower DNAm at intron 7 of the FKBP5 locus (leukocytes)	Better cognitive performance and general functioning in schizophrenic patients	40 FEP 45 SCZ-AR 58 controls	Poland
15 (Bustamante et al., 2018)	CTS and CTQ	No association of DNAm at FKBP5 with CT (blood)	CT associated with depression symptom severity	112 adults from DNHS	USA
16 (Klinger-König et al., 2019)	CTQ	No main effect for CT on FKBP5 methylation (blood)	No association of CT and phenotype reported	3965 (1841 + 2124) subjects of SHIP	Germany
17 (Alexander et al., 2020)	CTQ	No association between FKBP5 DNAm and CT (blood)	No association of FKBP5 methylation and cortisol response	200 healthy individuals	Germany
18 (Houtepen et al., 2016)	CTQ and Early Trauma Inventory	Higher DNAm at KITLG locus (blood)	Blunted cortisol stress reactivity	85 healthy individuals (blood) Replication cohorts: 45 (blood); 225 (buccal cells)	Netherlands
19 (Frach et al., 2020)	CTQ	No association between DNAm at KITLG with CT (monocytes)	Lower stress response	60	Germany
20 (Cattane et al., 2019)	CECA-Q	Downregulation of miR-125b-1-3p in subjects exposed to CT (blood)	Enhanced vulnerability of developing Schizophrenia	52 controls (cohort 1); 17 controls, 32 SZ patients (cohort 2)	Italy
21 (Lutz et al., 2018)	CECA-Q	Decreased 5hmC at intron 2 of kappa opioid receptor (anterior insula)	Decreased GR binding and decreased kappa expression	33 controls 30 suicide victims with history of CT and 32 without	Canada
22 (Perroud et al., 2013)	CTQ	BPD and frequency of CT associated with higher DNAm at BDNF locus (leukocytes)	Changes in depression and hopelessness scores and impulsivity	115 subjects with BPD, 52 controls	Switzerland
23 (Thaler et al., 2014)	CTI	Hypermethylation of BDNF promoter (lymphocytes)	Higher levels of BN	64 BN patients, 32 normal eaters	Canada
24 (Peng et al., 2018)	ETISR-SF	Hypermethylation at BDNF and NR3C1 gene (leukocytes)	Association with depressive symptoms	119 Monozygotic twin pairs	USA
25 (Ferrer et al., 2019)	CTQ	Higher DNAm at BDNF promoter (blood)		64 MDD patients, 70 healthy controls	Spain

(continued on next page)

Table 2 (continued)

Reference	Assessment of CT	Epigenetic changes	Associated phenotype	Sample size	Country
26 (Fachim et al., 2020)	CTQ	Hypermethylation at BDNF in association with CT + FEP (blood)	Poorer cognitive functioning (attention, executive function, visual and verbal memory) Association with FEP	58 FEP patients, 59 controls, 29 unaffected siblings of patients	Brazil
27 (Wang et al., 2018)	CTQ	Hypomethylation of BDNF (blood)	Less responsiveness to escitalopram treatment	142 MDD patients	China
28 (Hossack et al., 2020)	ACE scores	No association of BDNF or NR3C1 methylation, but higher DNAm at SCL6A4 locus (blood)	Higher risk for PTSD	170 active military members	USA
29 (Unternaehrer et al., 2015)	PBI	Greater DNAm at BDNF and OXCR genes (blood)	No phenotype reported	45 low maternal care; 40 high maternal care	Switzerland
30 (Smearman et al., 2016)	CTQ	Higher DNAm at two CpG sites at OXCR (blood)	No direct correlation with depression and anxiety symptoms	393 African American adults	USA
31 (Gouin et al., 2017)	SES and CAI	Higher DNAm at two promoter CpGs and two CpGs of intron 1 of OXCR (in females only) (blood)	Childhood trajectories of anxiousness	46	Canada
32 (Womersley et al., 2020)	CTQ-SF	No epigenetic alterations at OXTR related to CT (blood)	Reduced left hippocampal volumes in risk allele carriers with CT	63 Caucasian	South Africa
33 (Parianen Lesemann et al., 2020)	CTQ	No direct association of CT with DNAm at OXT and OXTR gene (saliva)	CT-associated decreasing N170 intensity in participants with high to medium DNAm of OXT	81 women	Netherlands
34 (Robakis et al., 2020)	CTQ	1580 CpGs associated with CT, but no strong correlation with OXTR DNAm (buccal cells)	Attachment insecurity and depression severity	54 women	USA
35 (Beach et al., 2011)	Childhood SA	Overall hypermethylation of SLC6A4 gene (lymphoblasts)	Antisocial personality disorder	155 women	USA
36 (Vijayendran et al., 2012)	Childhood SA	Two CpGs of SLC6A4 gene associated with CT (lymphoblasts)	No robust association of DNAm and SLC6A4 expression	158 women	USA
37 (Kang et al., 2013)	parental loss, financial hardship, PA and SA	Increased SLC6A4 promoter DNAm (leukocytes)	Worse clinical representation of MDD	108 subjects with MDD	Korea
38 (Booij et al., 2015)	CTQ	Hypermethylation of SLC6A4 (blood)	MDD; smaller hippocampal volume	33 subjects with MDD 36 controls	Canada
39 (Duman and Canli, 2015)	CTQ	Increased global DNAm in (LL)allele carriers of 5-HTTLPR; increased F3 DNAm in (S)allele carriers (blood)	Increased SLC6A4 mRNA after TSST in (LL)-allele carriers	105 Caucasian males; 71 for TSST	USA
40 (Shen et al., 2020)	CTQ	Hypermethylation at TPH2-5-203 CpG (males) or at TPH2-10-60 CpG (females); (blood)	Reduced antidepressant response	291 MDD patients; 100 controls	China
41 (Groleau et al., 2014)	CTI	Higher DRD2 DNAm in women with BSD + CT (blood)	Low-DA associated traits – BSD and BPD	52 women with BSD; 19 controls	Canada
42 (Checknita et al., 2018)	CTS (PA); SES, SPAQ, McArthur CVI (SA)	Hypermethylation of MAOA exon 1, hypomethylation at intronic CpG15 (saliva)	More diagnoses of alcohol and drug dependence, anxiety disorders	114 women	Sweden
43 (Engdahl et al., 2021)	parental death, severe financial or family problems (2 at least)	Increased methylation levels of 3 specific CpGs at the GRIN2B locus (saliva)	No association of smoking/drinking behavior or depression	186	Sweden
44 (Loureiro et al., 2021)	CTQ	No change in GRIN2A, GRIN2B and LINE-1 DNAm but hypermethylation at GRIN1	Possible liability to psychosis	40 controls 40 FES patients 23 siblings of FES patients	Brazil
45 (Labonté et al., 2012)	adapted CECA-Q	248 significant promoter loci hypermethylated, 114 hypomethylated (Hip)	Inversely correlated gene expression with altered methylation	41 suicide victims	Canada
46 (Lutz et al., 2017)	CECA-Q	Dysregulated global DNAm, enriched at myelin-related genes (cingulate cortex)	Lower density of oligodendrocytes and lower myelin thickness	27 CT and MDD 25 MDD only 26 controls	Canada
47 (Lutz et al., 2021)	CECA-Q	Altered histone modification and DNAm landscape (amygdala)	Gene expression altered in immune-related pathways	17 controls, 21 suicide victims (history of CT and MDD)	Canada
48 (Mehta et al., 2013)	CTQ	69.3% of gene expression changes related to DNAm changes in PTSD patients + CT only (blood)	Non-overlapping gene expression profiles of PTSD patients + CT and without CT	108 trauma-exposed but no PTSD; 29 PTSD; 32 PTSD + CT;	USA
49 (Misiak et al., 2015)	ETISR-SF	Decreased LINE-1 DNAm in FES patients; Decreased BAGE DNAm with higher trauma score (leukocytes)	First-episode schizophrenia (FES)	48 controls; 48 FES patients	Poland
50 (Bahari-Javan et al., 2017)	CTS	Hdac1 mRNA levels increased (blood)	Development of schizophrenia-like phenotypes	38 SZ + CT; 39 SZ no CT	USA, Germany, Spain

found in cohorts of schizophrenic patients (Misiak et al., 2020a). However, this association was only present in first-episode psychosis patients and not in patients suffering from acute-relapsing schizophrenia, suggesting dynamic alterations in epigenetic regulation along the course of the disease. Contrary to the above-mentioned studies, some studies report no association between FKBP5 methylation and exposure to CT. In a cohort of adults from the Detroit Neighborhood Health Study (DNHS), some of which were suffering from depressive symptoms, no association between the FKBP5 methylation status and previous exposure to CT was found, even though depressive symptoms correlated highly with CT and FKBP5 upregulation (Bustamante et al., 2018). Similarly, no association between FKBP5 methylation and CT was found in subjects from the Study of Health in Pomerania (SHIP) cohort. However, lower FKBP5 methylation levels occurred in currently depressed people and study participants carrying the risk allele of rs1360780 (Klinger-König et al., 2019). When studying a healthy cohort, FKBP5 demethylation could not be reproduced even when taking into account the risk allele proposed earlier (Alexander et al., 2020).

While most HPA axis related studies focused on the methylation and expression pattern of GR and FKBP5, Kit ligand gene (KITLG) methylation is also functionally relevant for the programming of stress reactivity in humans (Houtepen et al., 2016). A whole methylome analysis on blood of healthy individuals revealed a strong association between KITLG hypermethylation, CT and blunted cortisol responsiveness to the Trier social stress test. However, the association between CT and KITLG could not be reproduced in monocytes, leaving the role of this locus unclear (Frach et al., 2020). Further, miR-125b-1-3p was downregulated in three independent investigations, i.e., brain samples of rats that underwent prenatal stress, human blood samples of patients with schizophrenia with a history of CT, and human hippocampal progenitor cells treated with cortisol, indicating a role for miR-125 in cortisol response (Cattane et al., 2019). Finally, stress response via GR is interconnected with other signaling systems, such as endogenous opioid signaling, which can be influenced by CT. Analyses of postmortem tissues showed that individuals with a history of CT have downregulated kappa opioid receptors in the anterior insula (Lutz et al., 2018). This downregulation can be attributed to lower 5hmC levels at the intron 2 site, resulting in less transcriptional activation of the kappa gene by GR.

Overall, human studies on the long-term epigenetic effects of CT on the HPA axis have been rather inconsistent. While several studies reported hypermethylation at the NR3C1 locus (Bustamante et al., 2016; Martin-Blanco et al., 2014; McGowan et al., 2009; Peng et al., 2018; Perroud et al., 2011; Tyrka et al., 2012), others reported loss of methylation or no association with CT (Alexander et al., 2018; Hossack et al., 2020; Misiak et al., 2020b; Tyrka et al., 2016; Vangeel et al., 2018). Similarly, FKBP5 methylation after CT has been reported to be decreased (Klengel et al., 2013; Misiak et al., 2020a; Ramo-Fernández et al., 2019) or not changed (Alexander et al., 2020; Bustamante et al., 2018; Klinger-König et al., 2019). This might be due to major differences between cohorts and assessment, as psychiatric background (Misiak et al., 2020a), genetics (Klinger-König et al., 2019), and tissue type (Frach et al., 2020) can all have a confounding effect on the epigenetic dysregulation of the HPA axis after CT.

3.2.1.2. BDNF. Similar to its regulation in rodent studies, epigenetic mechanisms that regulate BDNF expression after CT are now being discovered in humans. A positive correlation between the severity of CT and increasing DNAm of the BDNF promoter was found in circulating leukocytes of patients with bipolar disorder and a history of CT (Perroud et al., 2013). Similarly, several other studies have reported BDNF hypermethylation in association with CT and often co-morbid psychiatric diseases in adulthood such as bipolar disorder, bulimia nervosa or depression (Peng et al., 2018; Thaler et al., 2014). Furthermore, CT- and depression-associated BDNF hypermethylation is associated with marked cognitive dysfunction in patients and several SNPs could worsen

this phenotype (Ferrer et al., 2019). This indicates an interplay between genetic predisposition, epigenetic regulation in response to early life experiences, and psychiatric disease state. Lastly, an association of BDNF hypermethylation with CT was found in a study on first-episode psychosis patients and matched controls. However the association was only present in patients suffering from psychosis, suggesting a possible contribution of psychotic episodes to the methylation state (Fachim et al., 2020).

Even though most studies proposed a hypermethylation of the BDNF gene in response to CT, others could not reproduce this and even found contradictory results. Negative correlation between CT and BDNF methylation status was found in a cohort of depressive patients with history of CT (Wang et al., 2018), whereas no association was found in war veterans with prior exposure to CT (Hossack et al., 2020).

To summarize, akin to animal studies, most human studies observed increased BDNF methylation (Fachim et al., 2020; Ferrer et al., 2019; Peng et al., 2018; Perroud et al., 2013; Thaler et al., 2014), while only a few studies reported hypomethylation or no change after CT (Hossack et al., 2020; Wang et al., 2018). We have to consider, however, that these few contradicting studies did not include appropriate control groups and focused on depressed patients and military personnel, where possibility of recent traumatic exposures is high. Hence, the generalizability of these results remains limited.

3.2.1.3. Oxytocin. In humans, the oxytocin system has been the focus of several studies on prenatal exposure to stress and its intergenerational impact. Also, studies on adults or children with psychopathologies related to attachment and social deficits often assessed a potential role of oxytocin (for review see: (Kraaijenvanger et al., 2019)). A long-term epigenetic impact of CT on the oxytocin system was first explored in a comparison of people who have received low or high maternal care during their childhood respectively (Unternaehrer et al., 2015). A specific OXTR site (TS2) was found to be hypermethylated in adults that had experienced low maternal care, indicating that parenting has a long-lasting impact on the epigenetic landscape of OXTR. Later, CpG sites cg04523291 and cg02192228 located in exon 3 of the OXTR gene were found to be hypermethylated in adults with a history of CT (Smeerman et al., 2016). These CT-related changes could, however, not predict psychopathologies in adulthood, whereas several single nucleotide polymorphisms (SNPs) and other methylation sites indeed showed correlations (Smeerman et al., 2016). Furthermore, two CpG sites in the promoter region and intron 1 of OXTR, were significantly hypermethylated in only women with CT (Gouin et al., 2017). The lack of significant association of CT and OXTR methylation in men unlike in women may suggest a higher vulnerability of women to persistent changes at this locus. On the contrary, more recent studies failed to detect any association of OXTR or oxytocin gene methylation status with previous CT in both genders (Parianen Lesemann et al., 2020; Robakis et al., 2020; Womersley et al., 2020). Nevertheless, oxytocin gene methylation does seem to play a modulatory role in adult behavioral phenotypes observed after CT. Response to threatening faces, an indicator of hypervigilance observed in individuals with history of CT who suffer from social phobia and/or social anxiety correlates with oxytocin gene methylation (Parianen Lesemann et al., 2020). Furthermore, an interaction of the rs2254298 A risk allele of the OXTR gene and childhood emotional neglect was associated with reduced left hippocampal volume, emphasizing a more indirect impact of CT on shaping OXT signaling and related social behaviors (Womersley et al., 2020).

In conclusion, there are discrepancies between earlier studies reporting hypermethylation at several sites of the OXTR locus, and later studies that failed to detect differences in OXTR DNAm after CT. This could possibly be due to methodological developments over time, or the effects of gender (Gouin et al., 2017), genotype, and type of CT (Womersley et al., 2020) on epigenetic modifications of oxytocin related loci in response to early stress.

3.2.1.4. Neurotransmitter signaling. As shown in animal studies, persistent epigenetic dysregulation of several neurotransmitter systems, including serotonergic, dopaminergic and GABAergic signaling, have also been implicated in the long-term sequelae of CT in humans. Aberrant hypermethylation at the serotonin transporter gene (SLC6A4) in response to childhood sexual abuse in humans predicted the susceptibility to antisocial personality disorder (Beach et al., 2011). Further, sexual abuse in childhood was significantly associated with the methylation of specific CpGs, one of them immediately downstream of the SLC6A4 promoter region (Vijayendran et al., 2012). While there was no strong evidence for a direct correlation between CT-related DNAm alterations and SLC6A4 expression, methylation at the shore of the CpG island was able to predict the expression of a splice variant, whereas DNAm of CpGs in the center of the CpG island predicted overall gene expression, suggesting that differential methylation likely regulates SLC6A4 mRNA abundance.

Accumulating evidence further supports the idea of SLC6A4 hypermethylation in response to CT and its impact on later psychological wellbeing. In depressive patients, a history of several different types of CT including parental loss or physical and sexual abuse were significantly correlated with SLC6A4 promoter hypermethylation and the severity of clinical symptoms (Kang et al., 2013). Further, hippocampal development is closely linked to serotonin signaling, since the hippocampus is highly innervated by the serotonergic system and implicated in several neuro-psychiatric diseases. Indeed, hypermethylation of the SLC6A4 locus was associated with CT, being male, and having smaller hippocampal volume (Booij et al., 2015).

Similar to the BDNF gene, SLC6A4 has long been known to have a common polymorphism located in its promoter region (Heils et al., 1996). This serotonin transporter-linked polymorphic region can either consist of a short (S) or long (L) allele, differing in transcriptional activity and susceptibility to psychiatric diseases. Homozygous L-allele carriers of this polymorphism that were exposed to early life stress, show increased global methylation, while S-allele carriers had increased methylation at a specific SLC6A4 site only, namely the F3 locus. However, in either case, SLC6A4 mRNA expression remains unperturbed after CT in the absence of an acute stressor (Duman and Canli, 2015). Upon exposure to social stress in the form of Trier social stress test, homozygous L-allele carriers responded with increased SLC6A4 mRNA expression whereas S-allele carriers did not (Duman and Canli, 2015). Also, L-carriers with a history of CT had the highest SLC6A4 expression change in response to the stress test. These results suggest an interaction between CT-induced changes in the serotonergic system and lasting alterations of the cortisol response in adults.

While most research around the serotonergic system focused on the serotonin transporter gene SLC6A4, the tryptophan hydroxylase locus TPH2, which encodes a key rate-limiting enzyme in serotonin biosynthesis, is also implicated in the epigenetic response to adverse experiences in early life (Shen et al., 2020). The TPH2 locus exhibits several differentially methylated CpGs in response to CT, which vary strongly between women and men and are associated with the response to anti-depressant treatment. This reiterates the previously observed sex-dimorphism in the epigenetic dysregulation of serotonin signaling after CT and puts forward a plausible prognostic value of CT exposure in determining the treatment efficacy of anti-depressants (Shen et al., 2020).

Similar to animal studies, epigenetic dysregulation of the dopaminergic system has been a consistent theme in human CT studies. Adult subjects with CT who also developed bulimia-spectrum disorder, had increased DNAm at the dopamine receptor D2 gene promoter compared to adults with no eating disorder. This indicates a potential epigenetic contribution to persistent dysregulation of dopaminergic signaling in response to early adversity (Groleau et al., 2014). Additionally, the gene coding for monoamine oxidase, an enzyme involved in metabolism of serotonin and dopamine among other neurotransmitters, is differentially regulated at the epigenetic level after CT (Checknita

et al., 2018). Notably, sexual abuse led to hypermethylation of exon 1 of the monoamine oxidase gene that was associated with increased risk of alcohol and drug dependence as well as vulnerability to depression and anxiety symptoms in women (Checknita et al., 2018).

Finally, glutamate signaling has been implicated the long-term epigenetic sequelae of CT (Engdahl et al., 2021). Previous results on the effects of adverse prenatal exposures and data from depressed suicide victims had shown a role for the ionotropic glutamate receptor NMDA type subunit 2B gene, which is important for synaptic plasticity and involved in mental and cognitive development (Alavian-Ghavanini et al., 2018; Gray et al., 2015). Indeed, people suffering from CT had elevated levels of DNAm at 3 out of 4 of the studied CpGs at this gene, with females being more affected than males (Engdahl et al., 2021). However, DNAm changes at the subunit 2B gene could not be replicated in a cohort of first-episode schizophrenia patients and their non-affected siblings (Loureiro et al., 2021). In this cohort, a history of CT correlated with hypermethylation at the subunit 1 gene of the NMDA receptor in siblings of schizophrenia patients only, suggesting that a familial predisposition to psychosis may influence the effect of CT at this locus.

In summary, most studies report hypermethylation at both serotonin as well as dopamine related loci (Beach et al., 2011; Booij et al., 2015; Checknita et al., 2018; Groleau et al., 2014; Kang et al., 2013) similar to some observations from animal models (Sasagawa et al., 2017). Still, genetic predisposition seems to play a big role in the epigenetic response of neurotransmitter systems to CT as exemplified by studies on polymorphic regions (Duman and Canli, 2015) and different study outcomes in cohorts with familial predispositions (Loureiro et al., 2021), highlighting the need to report genetic differences in epigenetic studies.

3.2.2. Changes in global epigenome and the epigenetic machinery

Several genome-wide analyses have now been performed in human cohorts that provide a broader view on the epigenetic alterations after CT in humans. In this regard, the post-mortem analyses are noteworthy as they allow epigenetic inspection of the brain after CT in region-specific manner. In hippocampal tissue obtained from suicide victims, 68.5% of the significant loci showed higher methylation, and 31.5% lower methylation in people with a history of CT compared to control samples (Labonté et al., 2012). Comparison with a matched gene expression dataset additionally confirmed a negative correlation between gene expression and methylation status, indicating a major impact of CT on hippocampal gene expression in adulthood through altered methylation profiles (Labonté et al., 2012). Similarly, dysregulated DNAm was found in post-mortem cingulate cortex samples of people with a history of CT (Lutz et al., 2017). Genomic sites close to myelin-related pathways were especially affected with differential expression of 35 myelin-related genes. Subsequently, post-mortem cingulate from individuals with CT showed lower myelination and oligodendrocyte density. Further, the global epigenetic landscape was significantly altered in post-mortem lateral amygdala samples of patients with a history of CT and depression compared to control samples (Lutz et al., 2021). Integration of DNAm, histone modification and gene expression data indicated immune-related pathways as the most prominently changed.

The profiling of blood samples from individuals with CT that further develop different psychopathologies provide additional insights about long-term epigenetic effects of CT in humans and represent the potential of using epigenetic modifications as biomarkers. PTSD patients with a history of CT showed highly distinct gene expression patterns compared to PTSD patients with no CT (Mehta et al., 2013). Moreover, PTSD-related gene expression changes in those suffering from early traumatic experiences, were correlated to methylation changes at the same genomic site in 69.3% of the cases, whereas only 33.6% were correlated in PTSD patients without previous CT. This suggests a prominent contribution of CT to PTSD-related DNAm changes with a functional relevance for gene expression (Mehta et al., 2013). Also,

long-term differential methylation of repetitive elements, such as long interspersed nuclear elements (LINE) and B-melanoma antigen (BAGE) sequences may be involved in the response to CT (Misiak et al., 2015). In a cohort study, patients who developed psychosis after CT had significantly lower LINE-1 methylation in comparison to those who did not develop psychosis after CT. Similarly, BAGE methylation status was negatively correlated with total trauma, indicating that DNAm at repeat element sites may generally be more affected by CT than adult disease status (Misiak et al., 2015). However, correlations between CT and LINE-1 methylation status were not detected in a recent cohort of psychosis patients, leaving the association of CT and repeat element methylation unclear (Loureiro et al., 2021). One recent study on CT-induced genome-wide DNAm changes identified 1580 differentially methylated regions, three of which are associated with insecure attachment style, and six with perinatal depression (Robakis et al., 2020). Moreover, 38.9% of significant alterations were localized to promoter regions mostly associated with genes involved in metabolic and cellular processes, or regulatory functions.

Besides DNAm alterations, also histone modifications have been proposed to play a role in mediating the long-term effects of early life traumatic experiences. Similar to findings from rodent studies, HDAC mRNA was found to be upregulated in patients with a history of CT, suggesting a conserved role for HDAC dysregulation in the long-term mediation of CT-induced schizophrenic phenotypes in mammals (Bahari-Javan et al., 2017). Together, genome-wide studies of the epigenetic landscape in human have revealed brain region-specific alterations in response to CT (Labonté et al., 2012; Lutz et al., 2021, 2017). Moreover, the importance of the disease state in combination with CT was highlighted by several studies (Mehta et al., 2013; Misiak et al., 2015), and may explain some of the discrepancies found in human studies on CT.

4. Therapies based on epigenetics

Epigenetics can be dynamically regulated, and epigenetic marks can be acquired and removed throughout life in a dynamic and adaptable fashion (Wong et al., 2010). Their dynamic nature allows the possibility to reverse or correct their alterations, for instance via psychological and pharmacological interventions, to mitigate their long-term impact on gene expression and behavior. Several strategies have exploited environmental and pharmacological manipulations to reverse epigenetic alterations and/or behaviors induced by CT, and initial evidence indicates that therapeutic effects of psychotropic drugs may implicate epigenetic signaling (Table 3).

4.1. Evidence from animal studies

Human studies on epigenetic interventions, especially pharmacological ones, in relation to the long-term sequelae of CT remain scarce, due to the limited tissue accessibility and for ethical reasons. Thus, animal models have been widely used to identify conditions that allow a reversal of CT-induced epigenetic changes. In rats, low maternal care is associated with higher hippocampal methylation at the GR promoter and lower H3K9 acetylation at the same genomic region, correlating with lower hippocampal expression of GR and higher HPA responses to stress (Weaver et al., 2006, 2005, 2004). Cross fostering starting at 12 h after birth reverses these epigenetic changes highlighting the dynamics of the epigenetic landscape in early life and therapeutic potential of early interventions (Weaver et al., 2004). Intracerebroventricular injections of the HDAC inhibitor Trichostatin A at PND 90 for 7 days significantly decreased DNAm on the GR promoter, increased hippocampal GR expression and modulated HPA response of adult rats, which had experienced low maternal care (Weaver et al., 2004). The opposite methylation status, an increase of DNAm, could be induced by intracerebroventricular injections of methionine (Weaver et al., 2005). Methionine is converted into S-adenosyl-methionine, which acts as a

donor of methyl groups for DNA methylation, thereby inducing hypermethylation (Detich et al., 2003). Both Trichostatin A and methionine influenced hippocampal methylation status in adult rats in the opposing directions, highlighting their potential in partially reversing transcriptomic changes in the hippocampus induced by high or low maternal care in early life respectively, leading to different behavioral outcomes (Weaver et al., 2006). Besides Trichostatin A, other HDAC inhibitors can also reverse epigenetic marks induced by early life adversity. In a rat model of maternal separation, administration of the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) increased the acetylation at H4K12 in the lumbar spinal cord after it had been reduced by maternal separation during PND 2 and 12 (Moloney et al., 2015). This epigenetic reversal was accompanied by normalization of stress-induced pain and defecation behaviors (Moloney et al., 2015). Likewise, schizophrenia-like phenotypes induced by maternal separation between PND 15 and 21 in rats could be reversed by the Hdac1 inhibitor Entinostat even when applied in adulthood (Bahari-Javan et al., 2017). In contrast, 8-day intraperitoneal injections of the HDAC inhibitor valproic acid in early adulthood did not rescue behavioral and epigenetic alterations induced by early life stress applied through maternal and sibling separation at PND 2 to 9 (Kao et al., 2012). Only valproic acid administration prior to daily separation could reverse the observed decrease in H3K9 mono- and tri-methylation in frontal cortex and normalized the associated decrease in fear-potentiated startle (Kao et al., 2012).

Like for HDACs, specific inhibitors of HDMs have been used to reverse the effects of CT. In adolescent rats (PND 21–35) subjected to early postnatal maternal separation, intraperitoneal administration of the HDM inhibitor As-8351 counteracted the decreased H3K4m3 of OXTR and rescued OXTR expression (Wei et al., 2020). Likewise, H3K79me3 overexpression in the nucleus accumbens induced by maternal separation during PND 10 to 17 could be rescued by intraperitoneal administration of the DOT1L-inhibitor pinometostat in mice, and reduced the susceptibility to adult stress (Kronman et al., 2021). Finally, miRNAs can also be targeted in vivo to rescue behavioral phenotypes. Hippocampal and intra-nasal delivery of miR-206 antagonists was recently shown to reverse miR-206 upregulation in a mouse model of early social isolation from PND 21 for 5 weeks. This intervention also normalized hippocampal BDNF level and the abnormal stress-induced attack behavior in mice (Chang et al., 2020). This study exemplifies the potential of miRNA therapeutics in neuropsychiatric disease. Considering the effectiveness and easy applicability of intranasal drug administration, such treatment also has great potential for translation in human in the future.

In addition to pharmacological manipulation of epigenetic modifiers or targets, animal studies have revealed that the therapeutic effects of known psychotropic medications may also be mediated by epigenetic pathways. Selective serotonin reuptake inhibitors (SSRIs) and other anti-depressants modulate miRNAs and epigenetic changes caused by early life trauma. In rat hippocampus, the anti-depressants fluoxetine and ketamine, and electroconvulsive shock therapy were observed to correct alterations in miR-598-5p induced by maternal separation at PND 2 to 12, and fluoxetine also reverses stress-induced change of miR-451 (O'Connor et al., 2013). Similarly, the SSRI paroxetine hydrochloride normalizes the decrease in miR-135a and the associated increase in serotonin receptor 1A expression in prefrontal cortex, and the increase of miR-16 in the hippocampus in rats. It also ameliorates anxiety-like behaviors and spatial memory deficit induced by stress in early adolescence (PND 28–33) (Liu et al., 2017). Furthermore, the SSRI escitalopram reversed an increase in striatal miR-326 induced by maternal deprivation at PND 1 to 14 in rats (Zhang et al., 2015) and in another rat study counteracted the downregulation of BDNF and the decrease of H3 acetylation induced by maternal separation at PND 1 to 21 (Park et al., 2018). Moreover, stressed rats treated with escitalopram showed a decrease in a methyl-binding transcriptional repressor as well as DNMT1 and DNMT3a mRNA levels compared to non-treated rats (Park et al., 2018). Similarly, intracerebroventricular administration of

Table 3
Epigenetic therapies

Reference	Model organism	Type of CT	Type of Treatment	Duration of Treatment	Epigenetic changes	Sample Size
1 (Weaver et al., 2004)	Rat	Low LG-ABN	i.c.v. infusions of TSA	PND90 for 7 consecutive days	Reversal of hypermethylation on GR promoter and H3K9ac (Hip)	Acetylation: 4/group Methylation: 5/group
2 (Weaver et al., 2005)	Rat	High LG-ABN	i.c.v. infusions of Methionine	PND90 for 7 consecutive days	Reversal of hypomethylated status of GR promoter (Hip)	4/group
3 (Weaver et al., 2006)	Rat	Low LG-ABN	i.c.v. of TSA or Methionine	PND90 for 7 consecutive days	TSA induced “maternal care” genes in low LG-ABN offspring; Methionine repressed them in high LG-ABN offspring (Hip)	10/group
4 (Moloney et al., 2015)	Rat	MS (PND2-12)	i.p. injection of suberoylanilide hydroxamic acid (SAHA)	PND60 for 5 consecutive days	Reversal of the reduced H4K12 acetylation (lumbar sacral spinal cord)	6/group
5 (Bahari-Javan et al., 2017)	Mouse	MS (PND15-21)	i.p. injections of MS-275 (Entinostat)	PND130, daily injections for 10 days	HDAC inhibitor rescues HDAC1 overexpression due to hypomethylation at GR binding site (Hip)	Controls: 34 MS: 33 (treated: 8; untreated: 14)
6 (Kao et al., 2012)	Rat	Daily 1-hr maternal and sibling separation (PND2-9)	i.p. injection of valproic acid (VPA)	PND2-9; prior to daily separation	Reversed the separation-decreased H3K9 mono- and tri- methylation (frontal cortices)	8/group
7 (Wei et al., 2020)	Rats	NMS (PND1-20; long-term separation)	Treatment with HDM inhibitor As-8351 (i.p)	daily from PND21-35	Rescue of H3K4me3 downregulation at OXTR gene and its expression (mPFC)	9/group
8 (Kronman et al., 2021)	Mouse	MS and low home cage nesting material (PND10-17)	Treatment with DOT1L-inhibitor pinometostat (i.p.)	10 mg/kg twice per day over 10 days	Reversal of higher stress susceptibility and H3K79me2 protein levels (NAc)	8-10/group
9 (Chang et al., 2020)	Mouse	Social isolation from PND21 for 5 weeks	Antagomir-206 (i.h. or i.n.)	PND49 one time application	Decreased stress-induced attack behavior; increased BDNF	6-7/group
10 (O'Connor et al., 2013)	Rat	MS (PND2-12)	Fluoxetine, ketamine and ECT	In adulthood: Fluoxetine: 21 days; Ketamine: 1x only; ECT: 10 days	All: reversal of miR-598-5p decrease Fluoxetine: reversal of miR-451 decrease (Hip)	7-10/ group
11 (Liu et al., 2017)	Rat	Inescapable stress during adolescence (PND28-33)	Paroxetine hydro-chloride and corticotropin-releasing factor antagonist (CP-154,526)	PND34; intragastrical injections of PH and/or i.p. injections of CP-154,526 for 14 days	Reversal of miRNA-135a downregulation and 5-HT1AR over-expression (PFC); alleviation of miRNA-16 over-expression (Hip)	10/group
12 (Zhang et al., 2015)	Rat	MD PND1-14 and CUS at 14 weeks	i.p injection of Escitalopram	14-week old adults; Daily for 4 weeks	Normalization of microRNA-326 over-expression (striatum)	11-15 /group
13 (Park et al., 2018)	Rat	MS (PND1-21)	i.p injection of Escitalopram	PND56; Daily injection for 3 weeks	Restoration of BDNF protein, mRNA and histone H3 acetylation levels (Hip)	12/group
14 (Roth et al., 2009)	Rat	stressed-abusive mother (mal-treatment) PND1-7	i.c.v. injection of zebularine	Adulthood; 7 consecutive days	Reversed hypermethylation of BDNF promoter and normalized BDNF mRNA levels (PFC)	Methylation: 2-5/group mRNA: 4-6/group
15 (Ignacio et al., 2017)	Rat	MD (PND1-10)	i.p. injections of Quetiapine	PND50 for 14 consecutive days	Reversal of enhanced DNMT activity (Hip)	10-12/group
16 (Xu et al., 2019)	Rat	CUMS or Dex injection in adolescence (PND28-48)	s.c injection of GR antagonist RU486	Daily, 30 min before CUMS/Dex injections (21 days)	Decreased GR and increased FKBP5 levels normalized; partially reversed miR-124a and miR-18a levels (PFC + Hip)	20/group
17 (Borba et al., 2021)	Rat	MD (PND1-10)	Environ-mental enrichment	3 h daily for 20 or 40 days	Rescue of HDAC and DNMT overexpression (PFC + Hip)	4-5/group
18 (Brody et al., 2016a)	Human	Racial discrimination	Supportive family environment during adolescence	3 years	Lower epigenetic aging (blood)	2 cohorts: 322; 294
19 (Brody et al., 2016b)	Human	Parental depressive symptoms; harsh parenting	Increasing family-based protective parenting processes	7 weeks (2 h/week)	Lower epigenetic aging (blood)	Treated: 242; Controls: 157
20 (Perroud et al., 2013)	Human	CTQ	I-DBT	4 weeks	Reversal in CT associated BDNF hypermethylation (blood)	BPD patients 115; Controls: 52

(continued on next page)

Table 3 (continued)

Reference	Model organism	Type of CT	Type of Treatment	Duration of Treatment	Epigenetic changes	Sample Size
21 (Wang et al., 2018)	Human	LES and CTQ	Escitalopram	8 weeks	Reversal of CT induced BDNF hypomethylation (blood)	85 MDD patients

the DNA-methylation inhibitor zebularine in adulthood could alleviate hypermethylation of the BDNF promoter in the prefrontal cortex in rats raised by stressed mothers during PND 1 to 7. Also, the zebularine treatment reinstated normal BDNF levels, suggesting common pathways of action between zebularine and escitalopram (Roth et al., 2009). Also, the atypical anti-psychotic quetiapine can partially reverse the epigenetic and behavioral effects of early-life stress. Increased hippocampal HDAC and DNMT activity in rats exposed to maternal deprivation between PND 1 and 10 was reversed by intraperitoneal injection of quetiapine during adulthood and normalized depressive-like behaviors (Ignacio et al., 2017).

Because the HPA axis plays a central role in the stress response, modulators of the HPA axis have also been used to reverse the long-term effects of CT, and have been proposed to implicate epigenetic mechanisms. Injecting the corticotropin-releasing factor antagonist CP-154,526 into adult rats exposed to inescapable stress during adolescence (PND 28–33) reversed stress-induced decrease in miR-135a and increase in serotonin receptor 1A expression in the prefrontal cortex, as well as the increase of miR-16 in the hippocampus, similar to the effects of the SSRI paroxetine (Liu et al., 2017). Further, injection of the GR antagonist RU486 30 minutes before chronic unpredictable mild stress or dexamethasone treatment at adolescence (PND 28–48) partially prevented the elevation of miR-124a and miR-18 in the prefrontal cortex and hippocampus due to the stressors (Xu et al., 2019). Collectively, these studies suggest the involvement of several epigenetic factors in the behavioral effects of anti-depressants, psychotropic medication, and HPA axis modulators. However, it is not clear if the epigenetic changes induced by the drugs directly mediate the therapeutic effects.

Finally, non-pharmacological interventions such as environmental enrichment can have beneficial effects on behavior and metabolism in rodents that suffered through early life traumatic experiences (Gapp et al., 2016; Kempermann, 2019). However, few have examined whether CT-induced epigenetic changes in the brain can be reversed through such an intervention. Recent evidence supports this idea, as increased HDAC and DNMT levels in the prefrontal cortex and hippocampus of maternally deprived rats at PND 1 to 10 could be fully reversed by 3 hours of daily environmental enrichment for 40 days, paving the way for non-pharmacological treatments against the long-term effects of CT (Borba et al., 2021).

4.2. Evidence from human studies

Inspired by animal work demonstrating the reversibility of environmentally-induced phenotypes, a few studies in humans have examined the therapeutic benefit of environmental/social environment and psychotropic medications. Analyses of epigenetic age by DNAm in adults who underwent racial discrimination or harsh parenting in childhood indicated accelerated aging (Brody et al., 2016a, 2016b). This accelerated epigenetic aging could be counteracted by a supportive environment during adolescence in two independent cohorts (Brody et al., 2016a). Family-centered prevention programs were also effective in decreasing epigenetic age in children with depressed parents and harsh parenting (Brody et al., 2016b). Intensive dialectical behavior therapy could also normalize BDNF hypermethylation and improve associated depressive symptoms in several bipolar disorder patients with CT. These results suggest that psychotherapeutic intervention can have effects on DNA methylation at specific loci associated with CT (Perroud et al., 2013).

A link between DNAm in people with a history of CT and response to antidepressant treatment has been suggested (Shen et al., 2020; Wang et al., 2018). Lower BDNF DNAm after CT predicted a worse outcome of an 8-week antidepressant treatment with escitalopram (Wang et al., 2018). Similarly, interactions between antidepressant treatment, previous exposure to CT and associated DNAm alterations at the TPH2 locus were shown, but an effect of treatment on the epigenetic status was not examined (Shen et al., 2020).

5. Discussion

This review summarizes the current knowledge on the involvement of epigenetic factors in mediating the long-term effects of CT. By including both animal as well as human studies from the past 20 years, we provide a comprehensive overview about the existing knowledge related to the long-term epigenetic effects of CT, and further elaborate on possible treatment strategies that can mitigate these long-term effects through epigenetic mechanisms. The examination of animal and human studies indicates an overwhelming focus of this research on a particular set of molecular and endocrine signaling cascades, including the HPA axis, small signaling proteins/peptides such as BDNF and oxytocin, and neurotransmitter systems, which are the main focus of this review (for graphical summary see: Fig. 2). However, further pathways such as immunologically-related ones may be considered for future evaluations of long-term epigenetic changes after CT, to achieve a more profound insight into the long-term effect of CT on brain and behavior.

5.1. Discrepancies in epigenetic studies of CT

A parallel evaluation of human and animal studies reveals several contradictory findings that could be due to variance between study designs, sample sizes, model systems, type and severity of CT, and timing and type of tissue examination. While animal studies allow to minimize several confounding factors through the use of inbred strains, controlled environments and established paradigms, confounding factors in human studies are multifarious and difficult to exclude. For instance, ethnicity was reported to influence gene methylation (Houtepen et al., 2016), thus further studies with more homogenous cohorts would help clarify the association between CT and epigenetics. Also, genetic factors must be taken into account as they have been shown to influence the likelihood of epigenetic changes, symptom severity and responsiveness to treatment (Ferrer et al., 2019; Klengel et al., 2013; Wang et al., 2018). Collectively, some factors such as age, body mass index, ethnicity, contraceptives, menstruation cycle etc., have been considered and adjusted for in some studies. However, the same factors are not always taken into consideration. Further, new factors may appear, for instance, the influence of somatic and blood parameters on DNA methylation such as reported for FKBP5 (Klinger-König et al., 2019). Thus, better knowledge about potential confounding factors, adapted statistical tools, and better study design (Provenzi et al., 2018) could aid in gaining more accurate insight on the consequences of CT at the cellular, tissue, and organism level in future. An additional drawback of studies in humans is that most molecular analyses are conducted on saliva or blood samples, thus provide no information about the state of affairs in the brain. Further, most human studies are retrospective, which increases potential biases such as use of different instruments e.g. childhood trauma questionnaire versus childhood trauma screener, and potential recall bias. More longitudinal studies are needed to better

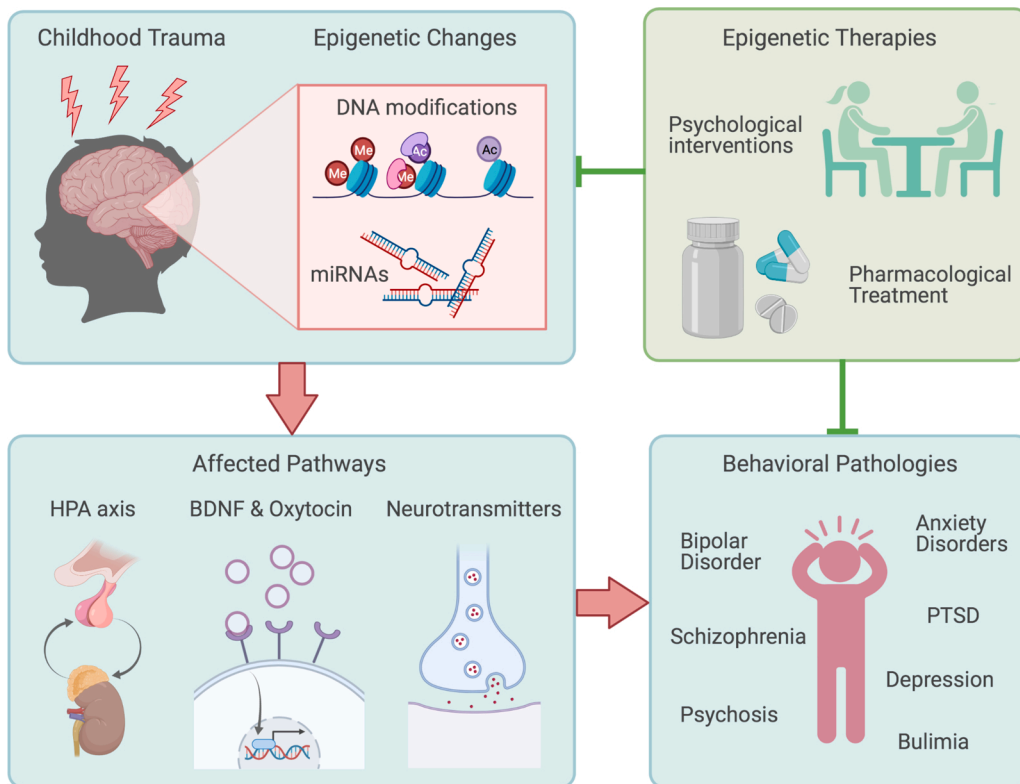


Fig. 2. Graphical summary of the topics reviewed.

CT leads to alterations in DNA modifications and dysregulation of miRNAs in several brain regions. These molecular changes affect important pathways involved in brain development and functioning, particularly the HPA axis, BDNF, oxytocin and neurotransmitter signaling, thereby increasing the risk for developing affective and psychotic disorders in adulthood. Several psychological and pharmacological interventions have demonstrated a reversal of these epigenetic changes and improvement of psychiatric symptoms, suggesting epigenetic marks as possible target to counteract the long-term sequelae of childhood trauma. Created with BioRender.com.

determine the effects of CT on the epigenome over long periods of time ideally till adulthood in relation to the severity, type and duration of CT.

Another important consideration is whether the identified epigenetic changes are a consequence of CT or a by-product of neuropsychiatric manifestations. This is particularly difficult to study in retrospective studies. Notably, PTSD patients with a history of CT have differential global DNAm pattern compared to patients without CT, suggesting that global DNAm is altered in an exposure-dependent manner in relation to the disease (Mehta et al., 2013). Moreover, several epigenetic “phenotypes” often related to CT, were found to be associated with a higher risk to develop PTSD, suggesting that CT increases the susceptibility to stressors later in life by influencing epigenetic patterns. So far, many studies on PTSD patients have focused on FKBP5, whose methylation was shown to be influenced by CT and to be associated with the predisposition to PTSD (Klengel et al., 2013). Thus, changes in FKBP5 can have a strong impact on the stress response, probably due to its close interaction with GR. The epigenetic difference between PTSD patients with CT and those with no stress could also be an important determinant of treatment response. Several studies have shown treatment resistance in PTSD patients with a history of CT and it is possible that the epigenetic status of certain loci can predict the efficiency of treatment (Shen et al., 2020; Wang et al., 2018). Further investigations are needed to examine how CT impacts the epigenome and whether a combination of epigenetic modulators can enhance treatment response in psychiatric diseases caused by CT.

Another important observation is that most studies only examine DNAm, and rare studies assess other epigenetic factors. It is recognized that CT alters multiple epigenetic processes that converge on the same molecular cascades. For instance, BDNF dysregulation has been a consistent feature in several CT studies, even though different epigenetic mechanisms including promoter DNAm, histone acetylation, and miRNAs (Bahí, 2016; Bai et al., 2012; Chang et al., 2020; Roth et al., 2009; Sun et al., 2020) were associated with decreased BDNF expression. Future parallel investigations of these different mechanisms should help to delineate the specific contributions of each of these mechanisms

and their potential influences on each other as mediators of the long-term influence of CT. Moreover, recent methodological advances also allow the parallel investigation of transcriptomics and epigenomics on a genome wide level, facilitating the identification of new target genes and pathways that are altered in response to CT (Arranz et al., 2021; Wiegand et al., 2021). By combining genome-wide and loci-specific observations on a transcriptomic and epigenetic level, information on the interplay between global and local epigenetic changes after CT can be expanded and possibly be used for intervention strategies.

5.2. Future directions and potential of epigenetic therapies for prevention and treatment of psychopathologies after CT

One of the biggest challenges in this type of research is translating findings from rodent models to humans, where access to brain tissue is rarely possible. The availability of induced pluripotent stem cells (iPSCs) offers the possibility to establish 3D neuronal cultures and brain organoids from fibroblasts collected from children or adults with a history of CT. There is evidence that iPSC-derived cultures preserve epigenetic signatures from donor cells (Kim et al., 2010). Therefore, it is plausible that these models continue to carry epigenetic alterations induced by CT, and could be used for mechanistic studies and high-throughput screening of potential mitigating factors. Advances in human imaging have also made it possible to track some epigenetic modifications in patients *in vivo*. For example, [¹⁸F] FAHA demonstrates sites of differential HDAC activity whereas [¹⁸F] FDG indirectly illuminates sites of neuronal hypomethylation (Couto and Millis, 2015). Future human studies could take advantage of such imaging modalities to track epigenetic changes in specific brain regions after exposure and assess their link with the appearance of neuropsychiatric symptoms. They could also be used to assess responses to therapies with a broad prognostic perspective.

With the accumulating evidence of the involvement of epigenetic factors in the long-term sequelae of CT, this field has started to gain

critical therapeutic relevance. Several studies have reported a reversal of CT-induced epigenetic changes through psychological intervention (Brody et al., 2016a, 2016b; Perroud et al., 2013) in humans or the use of anti-depressants in animal models (Liu et al., 2017; O'Connor et al., 2013; Park et al., 2018; Zhang et al., 2015). To further elaborate on the effects of established treatment procedures, epigenetic changes would need to be assessed longitudinally and tracked before, during, and after the treatment period. Besides the exploitation of existing treatments, new therapeutic interventions directly targeting epigenetic modifiers may be considered. Studies in animals suggest that histone modifying enzymes, particularly HDAC inhibitors, can be targeted for therapeutic purposes (Bahari-Javan et al., 2017; Kao et al., 2012; Moloney et al., 2015; Weaver et al., 2006). Several HDAC inhibitors are currently investigated in clinical trials for therapies in oncology, neurodegenerative and inflammatory diseases (for review see Bondarev et al., 2021), providing a plausible option for future therapies to reverse CT-induced epigenetic changes. However, off-target effects of HDAC inhibitors could limit their wide use. While current evidence suggests changes in the epigenetic machinery and in the epigenetic profile of specific loci after CT, it is not clear if overall changes in DNAm/histones are countered by other epigenetic or non-genomic changes that result in target-specific functional changes only. This has direct implications when considering epigenetic therapies, where use of broad-based epigenetic modifiers, such as HDACs may have undesired effects due to their non-specific actions. Since the effects of CT across tissues or brain regions are different, epigenetic therapies for certain brain regions may be envisaged, for example, using liposomes that can cross the blood-brain barrier and deposit epigenetic modifiers specifically to particular neuronal or glial lineages. Besides HDACs, non-genomic therapy could also target miRNAs. A number of miRNA-based clinical trials are currently underway for treatment of cancer, cardiovascular diseases, and brain disorders like amyotrophic lateral sclerosis (ALS) (Chakraborty et al., 2021). The pleiotropic nature of miRNA targets and functions also raises the issue of off-targets effects. However, their ease in packaging, and their relative target specificity makes them an attractive therapeutic option.

The possibility of a highly specific epigenetic therapy after CT at this point remains hypothetical in humans. Current advances in CRISPR technologies allow site-specific alterations of the methylation status *in vitro*, which can definitely help gaining knowledge about causative links between epigenetic changes and behavior in health and disease (for review see Goell and Hilton, 2021). However, the use of CRISPR-based epigenetic editing in clinical settings still requires extensive work and preclinical assessment, and needs careful safety evaluation.

6. Conclusion

This review provides concrete evidence for involvement of epigenetic mechanisms in the long-term sequelae of CT in both animals and humans. The functional relevance of epigenetic changes in humans still needs to be established with the help of innovative tools to detect and treat epigenetic changes in neuronal tissue after CT.

Declaration of Competing Interest

The authors declare no conflict of interests.

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