The epigenome under pressure: On regulatory adaptation to chronic stress in the brain

Arzate-Mejia, Rodrigo G ; Carullo, Nancy V N ; Mansuy, Isabelle M

DOI: https://doi.org/10.1016/j.conb.2023.102832

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

The epigenome under pressure: On regulatory adaptation to chronic stress in the brain

Rodrigo G. Arzate-Mejia[a], Nancy V. N. Carullo[a] and Isabelle M. Mansuy

Abstract

Chronic stress (CS) can have long-lasting consequences on behavior and cognition, that are associated with stable changes in gene expression in the brain. Recent work has examined the role of the epigenome in the effects of CS on the brain. This review summarizes experimental evidence in rodents showing that CS can alter the epigenome and the expression of epigenetic modifiers in brain cells, and critically assesses their functional effect on genome function. It discusses the influence of the developmental time of stress exposure on the type of epigenetic changes, and proposes new lines of research that can help clarify these changes and their causal involvement in the impact of CS.

Addresses

Laboratory of Neuroepigenetics, Brain Research Institute, Medical Faculty of the University of Zurich and Institute of Neurosciences, Department of Health Science and Technology of the Swiss Federal Institute of Technology, Neuroscience Center Zurich, Switzerland

Corresponding author: Mansuy, Isabelle M. (mansuy@hifo.uzh.ch), (imansuy@ethz.ch)

(Arzate-Mejia R.G.), (Carullo N.V.N.), (Mansuy I.M.)

[a] Equal contribution.

Current Opinion in Neurobiology 2024, **84**:102832

This review comes from a themed issue on **Neurobiology of Disease 2024**

Edited by **Eric Nestler** and **Erik Musiek**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.conb.2023.102832

Introduction

Situations that are demanding or threatening trigger a physiological stress response that allows an individual to cope and adapt to the perceived challenges [1]. In mammals, the stress response is mediated by the concomitant activation of the locus coerulus/noradrenaline pathway and the hypothalamic-pituitary-adrenocortical (HPA) axis in the brain, which leads to heightened alertness, enhanced memory formation and mobilization of energy resources. Activation of the HPA axis results in the secretion of glucocorticoids in circulation, which bind to glucocorticoid receptors in many cells across the body [2]. Since glucocorticoid receptors are nuclear receptors, their activation causes epigenetic and transcriptional changes in the cell nucleus [3]. Periods of dynamic brain development in early postnatal life and adolescence are particularly sensitive to stress and the brain has heightened susceptibility during these periods. This review focuses on the effects of chronic stress (cs) during these time periods. The majority of the presented findings are derived from rodent models in which CS is induced by physical challenge such as restraint or forced swim, or social challenge such as maternal separation in early life or social defeat in adulthood. In the most severe paradigms, stressors are delivered unpredictably which intensifies their effects on the animals.

Epigenetic regulation of gene expression

The genome is compacted and highly organized in the form of chromatin in the cell nucleus. The fundamental unit of chromatin is the nucleosome which consists of an octamer of histone proteins (H2A, H2B, H3 and H4) that wraps around the DNA. Chromatin is the context upon which transcriptional control takes place, mediated primarily by the activity of transcription factors (TFs) and epigenetic mechanisms. Epigenetic mechanisms here are molecular processes that mark chromatin and modify genome activity without changing the DNA sequence [4].

At least five different epigenetic mechanisms involved in the control of gene expression can be distinguished 1) chemical modifications of the DNA, particularly CpG methylation (5-methyl cytosine, 5mC), 2) histone post-translational modifications (HPTMs) such as acetylation, methylation and phosphorylation, and histone variants, 3) nucleosome remodeling, 4) non-coding RNAs and 5) chromatin three-dimensional (3D) organization [5]. Modifications to DNA and histones are catalyzed by epigenetic enzymes called writers such as DNA methyltransferases (DNMTs) and histone acetyl- and methyl-transferases, and are removed by erasers such as DNA demethylases (TETs) and histone deacetylases (HDACs) and demethylases (HDMs). Importantly, the recruitment of writers and erasers is

mediated primarily by TFs and non-coding RNAs but can also be mediated by HPTMs themselves [6,7].

Chromatin structure can also vary as a function of the arrangement of nucleosomes due to electrostatic interactions between HPTMs, the binding of TFs and the activity of ATP-dependent chromatin remodellers [8]. Epigenetic mechanisms can impact chromatin 3D organization by influencing the dynamics of long-range interactions between enhancers and promoters and by segregating the genome in the nuclear space into active (eu-) or inactive (hetero-) chromatin [9,10].

Epigenetic mechanisms functionally operate mainly at regulatory elements such as enhancers and promoters in the genome and are highly interdependent and reversible [5]. They are tightly controlled during development and are major determinants of cell differentiation and maturation in the brain that can respond and modify genome activity and functions upon experience [11,12].

Effects of CS on the epigenome

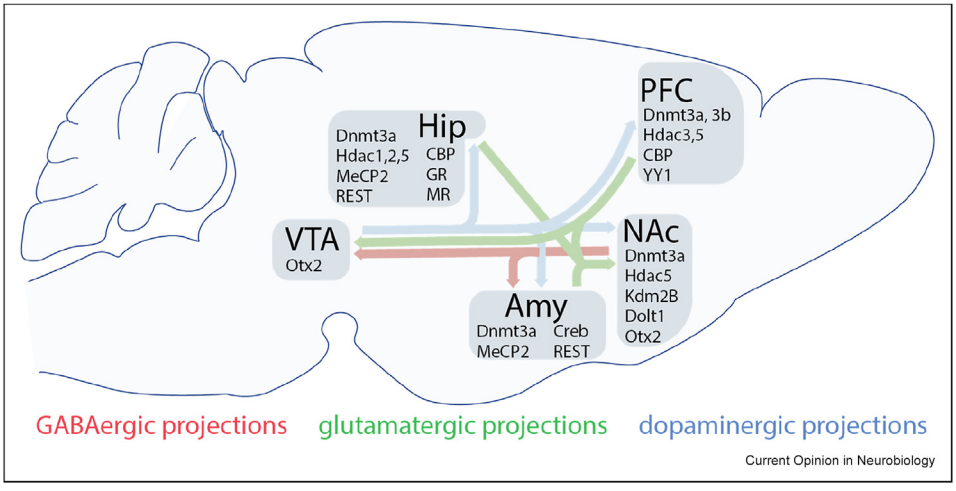
Most brain regions respond to stress, and include the hippocampus involved in learning and memory, the prefrontal cortex (PFC) involved in executive functions and impulse control, the amygdala, the core emotion center, and the ventral tegmental area and nucleus accumbens (NAc), areas for reward and aversion processing (Figure 1). While a healthy stress response is a form of adaptation, CS such as prolonged conflict, threat, fear or pressure can persistently affect brain functions by altering gene expression [13] and neuronal connectivity [14,15]. Changes in different brain regions can converge to alter multiple circuits and neurotransmitter pathways resulting in large and complex effects on brain functions and behavior (Figure 1). The lasting effects of CS on the brain are in part mediated by transcriptional changes and epigenetic mechanisms that are differentially regulated across the animal's lifespan [16].

Irrespective of time of exposure, CS affects the level and genome-wide deposition of epigenetic modifications. These modifications have been primarily profiled in bulk tissue, and in some cases in specific cellular populations such as sub-types of neurons and glia [17,18]. The recent application of proteomic approaches and the simultaneous characterization of genome-wide deposition of HPTMs and DNA methylation have begun to uncover the true complexity of the regulatory response of brain cells to CS [18–22]. The effects of CS on the epigenome are multiple and several epigenetic processes are simultaneously acting across brain regions in a cell-type and gender-specific manner in rodents and humans [18,21]. Further, the epigenomic response to CS evolves over time, resulting in different regulatory responses at the time of exposure and after cessation of CS [18]. Below, we summarize recent findings, particularly on HPTMs, that highlight their involvement of epigenetic factors in the effects of CS on the brain.

CS simultaneously affects different epigenetic processes

The relative abundance of HPTMs and histone variants can be modified by CS in the brain [18–20]. Mice exposed to maternal separation and low home cage nesting from PND10 to 17 have altered level of euchromatin-associated HPTMs e.g. H3K79me2 and

Figure 1



Epigenetic regulators in the brain affected by CS. Scheme showing epigenetic enzymes including writers and erasers of DNA methylation and HPTMs, genes coding for TFs or gene regulation affected by CS in major brain nuclei and connecting projections involving GABAergic (red), glutamatergic (green) and dopaminergic (blue) circuits. Amygdala (Amy), hippocampus (Hip), nucleus accumbens (NAc), prefrontal cortex (PFC), ventral tegmental area (VTA).

H4K5ac and heterochromatin-associated e.g. H3K9me1 in nucleus accumbens (NAc) that persist across time after exposure (at PND21, PND35 and adulthood) [18]. Such stress had first been shown to increase the level of H3K27me1 in NAc, similarly to chronic social defeat stress in adult males [20]. Both stress paradigms also resulted in lower level of the euchromatin-associated histone variant H3.3 in NAc [19]. The changes in HPTMs and histone variants were modest and affected primarily males, with only a trend in females [18]. These findings have at least two important implications: 1) different epigenetic mechanisms can be simultaneously affected by CS in the same brain region, and 2) CS can impact the same epigenetic modification e.g. H3K27me1 and H3.3, independently of time of exposure and experimental paradigm. Data from humans with a history of adverse childhood events (ACE) support these findings. Individuals with ACE have changes in the deposition of promoter- and enhancer-associated marks H3K4me1,3 and H3K27ac, the elongation-associated mark H3K36me3, the repressive marks H3K27me3 and H3K9me3, and DNA methylation at thousands of genomic regions in the amygdala, in turn affecting H3K27ac deposition at gene bodies [21]. Therefore, brain cells can respond to CS by altering the abundance and genomic-deposition of both euchromatin- and heterochromatin-associated HTPMs, likely reflecting the dynamic activation and repression of gene transcription associated with CS. In this regard, a key question is whether the observed effects occur simultaneously in every cell type of the brain region under analysis or rather represent regulatory responses of specific cell types in that region. The 2nd is probably the case at least for the effect of CS in early life on the level H3K79me2 in NAc [18]. In this case, expression of the histone H3K79 methyl-transferase *Dot1l* was altered in dopaminergic medium spiny neurons of NAc in adult males [18], suggesting that epigenomic responses to CS may result from cell-type specific changes in the expression of epigenetic modifiers.

CS results in transient and long-lasting effects on epigenetic modifications

The longitudinal characterization of changes to the epigenome due to CS started to reveal the dynamics of the regulatory response to CS and its potential lasting consequences [18,23]. Maternal separation from PND10 to 17 differentially alters HPTMs in NAc across life [18]. For instance, while H3K27me1 is increased 4 days after the end of stress (PND21) and remains high in adulthood [18], H3K9me1 is significantly reduced at PDN21 but back to normal in adulthood [18]. Other HPTMs such as H3K79me1-2 are significantly altered only in adulthood [18], suggesting a complex dynamic of HPTMs including transient, long-lasting and deferred effects. Likewise, in mice exposed to maternal separation from PND2 to 15, the level of H4K8ac, H4K12ac and H4K5ac is first decreased at PND21 but then increases at PND60 in the neocortex [24]. Such temporal dynamics of HPTMs changes is also observed if CS is applied in adolescence or adulthood. In adolescent rats exposed to inescapable foot shock from PND21 to 26, the level of H3K9me2 increases in the hippocampus and PFC at PND28 and adulthood, suggesting an enduring effect of CS [23]. Thus, the effects of CS can unfold overtime, highlighting an unappreciated complexity whose functional consequences are unknown.

CS differentially affects the abundance and genomic distribution of epigenetic modifications

With some notable exceptions [18,20,22], it is common practice to characterize the level or genomic distribution of a given epigenetic mark in a tissue after stress. These two features provide important but different information and do not necessarily correlate. A change in the level of a HPTM does not predict if this HPTM is also differentially distributed on the genome. For instance, while H3K79me2 (measured by mass spectrometry) is overall lower after CS in early life, its genomic distribution (profiled by ChIP-seq) is modified, thus the mark is re-localized rather than reduced genome-wide [18]. In contrast, H3K27me1 is increased by chronic social defeat in NAc of susceptible individuals, and its genomic deposition is also consistently increased but only at intronic regions [20]. This suggests that additional mechanisms determine the precise genomic localization of a HPTM, but these mechanisms remain unknown. When assessing the epigenomic effects of CS, it is therefore important to measure both, the level and genomic distribution of HPTMs for a more accurate characterization.

Genotype influences the response of the epigenome to CS in the brain

Genotype also strongly influences the response of the epigenome to CS. In mice, the effects of maternal separation on histone acetylation in the neocortex are strain-specific, and are evident in Balb/cJ mice but not in C57Bl/6J mice [24]. In humans, allelic variants at the enhancer of cis−trans prolyl isomerase *Fkbp5*, a co-chaperone that regulates steroid hormone receptors and a major regulator of glucocorticoid signaling in the stress response, influence their own DNA methylation, resulting in decreased DNA methylation in individuals with a history of childhood trauma [25]. Several other polymorphisms in *Fkbp5* locus can alter long-range DNA interactions and impact *Fkbp5* transcription [25]. This in turn alters Fkbp5 level and glucocorticoid sensitivity as observed in stress-related conditions such as post-traumatic stress disorder and major depression [26]. These findings highlight the influence of the genetic background on the epigenetic and transcriptional response to stress.

Transcriptional implications of changes in the epigenome induced by CS

Functionally, the epigenomic effects of CS have been correlated with transcriptional changes and behavioral phenotypes. However, whether epigenetic changes are causally linked to transcription or are a by-product of transcriptional activity is an unresolved question. Recent elegant mechanistic assays investigating the direct contribution of epigenetic modifications to gene expression have revealed unexpected findings challenging long-standing assumptions about the role of epigenetic modifications on gene transcription [27–30]. These findings have profound implications for the interpretation of the effects of CS on the epigenome and transcription.

Transcriptional implications of CS-induced changes in DNA methylation

Ample evidence from rodents and humans indicates that CS induces genome-wide changes in DNA methylation in brain cells. These changes primarily occur at intergenic regions and gene bodies and have been correlated with alterations in gene expression [22,31,32]. In mice exposed to brief maternal separation from PND4 to 6, the level of DNA methylation is altered at thousands of genomic regions in the hypothalamus. This mainly includes intergenic and intronic regions of genes involved in synapse assembly and neuron migration, as well as a subset of promoters [32]. Functionally, the effect of DNA methylation on transcription is influenced by genomic location. At promoter elements, direct inhibition of TF binding is the prevailing mode of gene repression by DNA methylation [33]. This mechanism of action is consistent with the observation that CS can increase DNA methylation at promoter elements of genes involved in the regulation of the HPA axis e.g. *Nr3c1* encoding the glucocorticoid receptor [34] and of neuronal growth e.g. *Bdnf* [35]. This results in transcriptional repression of these genes, likely as a consequence of TF binding disruption [36]. Therefore, modulation of DNA methylation by CS at promoters may directly affect gene expression via differential TF binding. Importantly, differences in DNA methylation at regulatory elements can persistently alter TF binding, a phenomenon associated with chromatin memory [37,38] that may explain long-lasting effects of CS on transcription.

The functional consequences of changes in DNA methylation at gene bodies is less direct and require careful interpretation. On one side, it is likely that some of the reported alterations in DNA methylation at genes in the context of CS have been misclassified and actually affect intragenic enhancers and alternative promoters. Indeed, the majority of tissue-specific enhancers are located in introns [39] and the activity of some enhancers is affected by DNA methylation, mainly via changes in TF binding [40,41]. In this context, intragenic DNA methylation at regulatory elements has been shown to regulate cell-type specific gene expression [41] and to restrict transcriptional initiation at canonical transcription start site (TSS) by suppressing spurious transcriptional initiators [42]. For cases where DNA methylation at genes is not located at regulatory elements, the observed differences in methylation could influence alternative splicing [43]. They may also alter the rate of RNA Pol II initiation at long and highly methylated genes in the brain, via interaction with the methyl-DNA-binding repressor protein MeCP2 [44]. Genic DNA methylation may also be just a co-transcriptional event, since it is known that it can be established during transcriptional elongation, via recruitment of *de novo* DNA methyltransferases by the elongation-specific HPTM H3K36me2, -3 [45]. Therefore, it is plausible that a subset of genic changes in DNA methylation due to CS derive from co-transcriptional effects reflecting alterations in transcription. Today, available evidence that changes in genic DNA methylation induced by CS have functional consequences is only correlative, which warrants more mechanistic work.

Transcriptional implications of CS-induced changes in HPTMs

Changes in HPTMs have been implicated in the observed effects of CS on transcription that ultimately affect behavior and cognition [18,20]. The direct influence of HPTMs on the regulation of gene expression has however recently been questioned [27]. Accumulating evidence in different model organisms and cell-types challenges the prevailing view that HPTMs are instructive for transcription, particularly transcriptional activation [28–30]. Thus, caution should be used when suggesting a relationship between changes in HPTMs and transcription in the context of CS, particularly in correlative analysis derived from genome-wide datasets. For instance, CS has been reported to affect the abundance and deposition of HPTMs classically associated with transcriptional activation such as H4K5ac, H4K8ac, H4K12ac, H3K4me3 and H3K27ac [18,20,21,24]. Similarly to what has been reported for DNA methylation, the majority of these changes occur at gene bodies [21], thus with uncertain effects on transcription. Current evidence indeed does not support a direct role for histone H3K4 methylation and H3K27ac in the maintenance of transcriptional states since these HPTMs are largely dispensable for steady-state transcription [28–30]. Further, inhibition of transcription is sufficient to induce the loss of H3K27ac genome-wide [29], suggesting that for some HPTMs, their observed pattern of genome occupancy might reflect a co-transcriptional event rather than HPTMs governing transcription. However, HPTMs may support stimulus-dependent gene expression. Histone acetylation is important for transcriptional bursting of activity-dependent genes such as *c-Fos* in neurons [46].

H3K4me3 may affect transcription since its deposition is mutually exclusive with DNA methylation [47]. Therefore, it is reasonable to suggest that while changes in HPTMs deposition at stimulus-dependent promoters or enhancers may directly affect transcriptional activation, changes at genic or intergenic regions are rather an indirect effect of transcription, that may be mediated by differential activity or expression of TFs, as has been reported for Oxt2 in the context of CS in early life [48].

Other HPTMs with less characterized role in transcription such as H3K79me2 and H3K37me1 have recently been shown to be altered by CS and may influence transcriptional programs leading to behavioral and cognitive deficits [18,20]. In a mouse model of CS in early life, H3K79me2 deposition was increased at loci encoding TFs in NAc. This increase was prominent at gene bodies and partially correlated with gene expression [18]. Remarkably, reduction of H3K79-methyltransferase *Dot1l* in NAc dopaminergic neurons in adult mice exposed to CS in early life reversed their impairment in social interaction, decreased anxiety and improved stress coping [18]. Conversely, *Dolt1* over-expression phenocopied the behavioral phenotype. These manipulations also altered NAc transcriptome. Importantly, systemic administration of an inhibitor of DOT1L could rescue behavior after CS [18]. Together, these results suggest that the activity of DOT1L is relevant to sustain behavioral abnormalities induced by CS in early life. However, it should be noted that histone modifiers can have non-histone targets and non-catalytic activity that can influence gene expression [27,49]. DOT1L can physically interact with other regulatory proteins such as the estrogen receptor [50] and is involved in different nuclear processes beyond gene transcription in different cell types [51]. Therefore, in the absence of specific manipulations for instance, using catalytic mutants and assessing their effect on transcription in appropriate cell types [27], it is difficult to establish a direct functional link between altered HPTMs and behavioral phenotypes.

Effects of CS on the expression of epigenetic modifiers

One of the possible routes by which CS alters the epigenome is by directly affecting the transcription and synthesis of epigenetic modifiers. CS can dysregulate the expression of epigenetic modifiers distinctly in different cell types, brain regions and in females and males (Figure 1 and Table 1). Below, we highlight some of the expression patterns of epigenetic modifiers observed as a consequence of CS exposure and discuss their implications for the epigenome.

CS can alter the expression of antagonistic epigenetic modifiers. For example, it can lead to simultaneous transcriptional activation of both, a writer and eraser of the same histone modification. Maternal separation and low home cage nesting from PND10 to 17 results in transcriptional up-regulation of the histone H3K79 methyl-transferase *Dot1l* and its associated histone-demethylase *Kdm2b* in dopaminergic medium spiny neurons of NAc in adult males [18]. Such concomitant transcriptional activation of a writer and eraser of the same HPTM may explain the co-existence of regions that gain and loose H3K79me2 in NAc in response to CS.

CS can also differentially affect the expression of similar types of epigenetic regulators such as histone modifiers, depending on time of exposure and genetic background. In adult mice exposed to maternal separation from PND2 to 15, the expression of *Hdac1*, *3*, 7, *8*, and *10* is decreased specifically in the neocortex in Balb/cJ but not in C57Bl/6J mice, and this effect emerges only if exposure occurs before PND21 [24]. In contrast, in adult mice exposed to chronic social defeat stress for 10 days, the expression of *Hdac5* and *8* and S*irt2*, *3* and *6* is decreased in PFC [52]. These observations suggest that the type of experience, the developmental time of exposure and the genetic background influence the regulation of epigenetic modifiers across brain regions in the context of CS.

CS can also alter the expression of specific epigenetic modifiers independently of time of exposure and stress paradigm. For example, CS systematically alters the expression of *de novo* DNA methyltransferase *Dnmt3a* across brain regions. In mouse pups at PND7, *Dnmt3a* expression is transiently down-regulated in the hippocampus by low maternal care [53] while in adults exposed to chronic social defeat stress for 10 days, *Dnmt3a* is down-regulated in PFC [54]. Further, in a rat model of post-traumatic stress, protein level of Dnmt3A is reduced in NAc [22]. The functional outcome of these changes is indeed different. In pups, they resulted in reduced DNA methylation of LINE-1 (L1) retrotransposon promoter and increased L1 transcription and retrotransposition in neurons [53]. In adults, lower *Dnmt3a* transcription in PFC correlated with increased anxiety-like behavior while *Dnmt3a* over-expression in PFC decreased anxiety [54]. In adult rats exposed to traumatic stress, reduction of Dnmt3A resulted in widespread changes in DNA methylation that differed between resilient and susceptible animals [22]. These observations highlight the context-dependency of the effects of dysregulation of an epigenetic modifier by CS.

Further, CS can differentially affect epigenetic modifiers as a function of susceptibility or resilience to stress. In adult mice, chronic social defeat stress for 10 days increases the expression of ACF ATP-dependent chromatin-remodeling complex in NAc only in susceptible individuals. Remarkably, in humans suffering from depression, the expression of members of the ACF chromatin-remodeling complex is also up-regulated in

Table 1

CS effects on the expression of epigenetic modifiers and TFs in the brain.

Epigenetic factor/TF	Species	Sex	Model of stress exposure	Age of exposure	Details of stress model	Time of measurement	Analysed brain region	Effect on mRNA	Effect on protein	Reference
Dnmt1	Rat (Wistar)	Male	Maternal separation (MS)	PD2	3 h separation PD2-14	1 day after MS cessation	mPFC	Up-regulated by MS	ND	[61]
Dnmt3a	Rat (Sprague Dawley)	Male	Chronic unpredictable stress (CUS)	3-week-old	CUS for 14 consecutive days	5–7 days after CUS cessation	mPFC and prelimbic cortex	Down-regulated by CUS	Reduced by CUS	[62]
	Mouse (C57Bl/6J)	Male	Chronic social defeat stress (CSDS)	9-week-old	CSDS for 10 consecutive days	11 days after CSDS cessation	Hippocampus	ND	Lower number of neurons expressing high level of Dnmt3a in CSDS-susceptible animals	[63]
	Mouse (C57Bl/6J)	Male	CSDS	9-week-old	CSDS for 10 consecutive days	After last day of CSDS	PFC, central amygdala (CeA) and CA1 of hippocampus	Down-regulated in PFC by CSDS; Up-regulated in CeA by CSDS	ND	[54]
	Rat (Wistar)	Male	MS and MS + stressful social experience (SSE)	PD5	3 h separation PD5-10	PD31 (Adolescence) PD81 (Adult)	Amygdala	Up-regulated by MS and MS + SSE in Adolescents and Adults	ND	[64]
	Rat (Wistar)	Male	MS	PD2	3 h separation PD2-14	1 day after MS cessation	mPFC	Up-regulated by MS (and handling)	Increased by MS	[61]
	Mouse (C57Bl/6J)	Male	Differences in maternal care	PD1-14	High and low-maternal care	PD0, PD7 and PD21	Hippocampus	Reduced expression in low-maternal care pups at PD7	ND	[53]
	Mouse (C57Bl/6J)	Male	CSDS	Adult(?)	CSDS for 10 consecutive days	1 and 11 days after CSDS cessation	NAc	Up-regulated by CSDS	ND	[65]
Dnmt3b	Rat (Sprague Dawley)	Male	CUS	3-week-old	CUS for 14 consecutive days	5–7 days after CUS cessation	PFC	Down-regulated in CUS	ND	[62]
	Rat (Wistar)	Male	MS	PD2	3 h separation PD2-14	1 day after MS cessation	mPFC	Up-regulated by MS (and handling)	ND	[61]
HDAC1	Mouse (Swiss-Webster)	Male	Social isolation (SI)	>3-week-old	Housed individually for 4–6 weeks	NIA	Hippocampus	Up-regulated by SI (susceptible)	ND	[66]
	Mouse (Balb/cJ)	Male	MS	PD2	3 h separation PD2-15	PD21, PD28 and PD60	Forebrain neocortex (FN) and Hippocampus	PD21 and PD28: Up-regulated by MS in FN PD60: Down-regulated by MS in FN	ND	[24]
HDAC2	Mouse (C57Bl/6J)	Male	Chronic restrain stress (CRST)	7-week-old	CRST for 14 consecutive days	17 days post CRST	Hippocampus	Down-regulated by CRST	Reduced in CA1 and CA3 pyramidal neurons	[67]

	Mouse (C57Bl/6J)	Male	MS	PD9	24 h MS	PD14-21	Ventral tegmental area (VTA)	ND	Increased by MS in the nuclear fraction of dopaminergic neurons	[68]
HDAC3	Mouse (Balb/cJ)	Male	MS	PD2	3 h separation until PD15	PD21, PD28 and PD60	FN and Hippocampus	PD21 and PD28: Up-regulated by MS in FN PD60: Down-regulated by MS in FN	ND	[24]
HDAC5	Rat (Sprague Dawley)	Male	Maternal separation (MS)	PD1	3 h separation PD1-21	PD78	Hippocampus	Up-regulated by MS	ND	[69]
	Rat (Sprague Dawley)	Male	Restraint stress (RS)	8 week-old	2 h per day for 3 weeks	PD78	Hippocampus	Up-regulated by MS	ND	[69]
	Mouse (C57BL/6)	Male	Chronic restraint stress (CRST)	7 week-old	2 h restrain per day for 14 days	17 days post CRST	Hippocampus	Down-regulated by CRST	ND	[67]
	Rat (Sprague Dawley)	Male	Chronic unpredictable stress (CUS)	8 week-old	CUS for 28 days	1 day post CUS	Hippocampus	ND	Increased by CUS	[70]
	Mouse (C57BL/6)	Male	Social defeat stress (SDS)	Adult (NIA of specific age)	SDS daily for 10 days	1 day post SDS	NAc	Down-regulated by SDS	ND	[71]
	Rat (Sprague Dawley)	Male	Chronic unpredictable stress (CUS)	8 week-old	CUS for 28 days	1 day post CUS	Hippocampus and Prefrontal cortex	Up-regulated by CUS in both areas	Increased by CUS in both areas	[72]
HDAC7	Mouse (C57BL/6)	Male	Social defeat stress (SDS)	6–8 weeks old	SDS for 10 days	5 days post SDS	NAC, Hippocampus and Prefrontal cortex	Up-regulated by SDS in Nac	Increased by SDS in Nac	[73]
	Mouse (Balb/cJ)	Male	Maternal separation (MS)	PD2	3 h separation until PD15	PD21, PD28 and PD60	Forebrain neocortex and Hippocampus	PD21: Down-regulated by MS in FN PD28: Down-regulated by MS in FN PD60: Down-regulated by MS in FN	ND	[24]
HDAC8	Mouse (Balb/cJ)	Male	Maternal separation (MS)	PD2	3 h separation until PD15	PD21, PD28 and PD60	Forebrain neocortex and Hippocampus	PD21: Up-regulated by MS in FN PD28: Up-regulated by MS in FN PD60: Down-regulated by MS in FN	ND	[24]
HDAC10	Mouse (Balb/cJ)	Male	Maternal separation (MS)	PD2	3 h separation until PD15	PD21, PD28 and PD60	Forebrain neocortex (FN) and hippocampus	PD21: Up-regulated by MS in FN PD28: Up-regulated by MS in	ND	[24]

(*continued on next page*)

Table 1. (*continued*)

Epigenetic factor/TF	Species	Sex	Model of stress exposure	Age of exposure	Details of stress model	Time of measurement	Analysed brain region	Effect on mRNA	Effect on protein	Reference
								FN PD60: Down-regulated by MS in FN		
Suv39h1	Mouse (C57BL/6)	Male	Chronic restraint stress (CRST)	7 week-old	2 h restraint per day for 14 days	17 days post CRST	Hippocampus	Down-regulated by CRST	Reduced in CA1 and CA3 pyramidal neurons	[67]
Ga9	Mouse (C57BL/6)	Male	Chronic restraint stress (CRST)	7 week-old	2 h restraint per day for 14 days	17 days post CRST	Hippocampus	Down-regulated by CRST	ND	[67]
Jmjd2a	Mouse (C57BL/6)	Male	Chronic restraint stress (CRST)	7 week-old	2 h restraint per day for 14 days	17 days post CRST	Hippocampus	Down-regulated by CRST	ND	[67]
MeCP2	Mouse (Swiss Webster)	Male	Social isolation (SI)	>3 week-old	Housed individually for 4–6 weeks	NIA	Hippocampus	Up-regulated in SI (aggressive)	ND	[66]
	Rat (Wistar)	Male	Maternal separation (MS) Maternal separation + Stressful social experience (MS + SSE)	PN5	3 h separation PD5-10	PD31 (Adolescence) P81 (Adult)	Amygdala	Up-regulated by MS and MS + SSE in adolescents and adults	ND	[64]
	Mouse (C57BL/6n)	Male	Maternal separation (MS)	PN1	3 h separation PD1-10	PD10 and 6 week-old	PVN AVP-expressing neurons	No change	No change; increased levels of MeCP2-S438 phosphorylation at PD10	[74]
Tet2	Mouse (Swiss Webster)	Male	Social isolation (SI)	>3 week-old	Housed individually for 4–6 weeks	NIA	Hippocampus	Down-regulated SI (aggressive)	ND	[66]
Tet3	Rat (Wistar)	Male	Maternal separation (MS) Maternal separation + Stressful Social Experience (MS + SSE)	PN5	3 h separation PD5-10	PD31 (Adolescence) P81 (Adult)	Amygdala	Up-regulated by MS in adolescents; up-regulated by MS + SSE in adolescent and adult	ND	[64]
REST	Rat (Wistar)	Male	Maternal separation (MS) Maternal separation + Stressful Social Experience (MS + SSE)	PN5	3 h separation PD5-10	PD31 (Adolescence) P81 (Adult)	Amygdala	Up-regulated by MS in adolescents but down-regulated in adults Up-regulated by MS + SSE in adolescents and adults	ND	[64]
	Rat (Sprague Dawley)	Male	Maternal separation (MS)	PD2	1 h from PD2-8	P28-31	Hippocampus	ND	Decreased by MS in the dentate gyrus of the hippocampus	[57]

HSP90	Rat (Wistar)	Male	Maternal separation (MS) Maternal separation + Stressful Social Experience (MS + SSE)	PN5	3 h separation PD5-10	PD31 (Adolescence) P81 (Adult)	Amygdala	Up-regulated by MS and MS + SSE in adolescents and adults	ND	[64]
CBP	Rat (Sprague Dawley)	Male	Chronic unpredictable stress (CUS)	8 week-old	CUS for 28 days	1 day post CUS	Hippocampus and Prefrontal cortex	Down-regulated by CUS in both areas	Decreased by CUS in both areas	[72]
Suz12	Mouse (C57BL/6)	Male	Social Defeat Stress (SDS)	Adult (NIA)	SDS for 10 days	24 h post SDS	NAc	Up-regulated by SDS in Nac of susceptible animals	ND	[20]
Dot1l	Mouse (C57BL/6)	Male and female	Maternal separation (MS) and low home cage nesting	PD10-17	4 h daily for 8 days	PD21, PD35 and PD70-80 (Adult)	NAc	Up-regulated by MS in NAc of adult males and females	Increased by MS in NAc of PD21 and adult males	[18]
Kdm2b	Mouse (C57BL/6)	Male and female	Maternal separation (MS) and low home cage nesting	PD10-17	4 h daily for 8 days	PD21, PD35 and PD70-80 (Adult)	NAc	Up-regulated by MS in NAc of adult males and females	ND	[18]
BAZ1A	Mouse (C57BL/6)	Male and female	Social Defeat Stress (SDS)	7–8 week-old	SDS for 10 days	48 h, 10- and 28-days post SDS	NAc and mPFC	Up-regulated by SDS in Nac of susceptible animals	Increased in Nac of SDS-susceptible animals (48 h after SDS)	[20]
GR	Rat (Long-Evans)	Male	Maternal care: high and low-maternal care	Adult	Maternal care: high and low-maternal	PD6 and PD90	Hippocampus	Down-regulated in individuals exposed to low-maternal care	Decreased in individuals exposed to low-maternal care	[34,36]
MR	Mouse (C57BL/6)	Male and Female	Maternal separation and unexpected maternal stress (MSUS)	PD1	3 h MSUS from PD1-14	Adult	Hippocampus	Down-regulated by MSUS	ND	[75]
Otx2	Mouse (C57BL/6)	Male	Maternal separation (MS) and low home cage nesting	PD10-17	4 h daily for 8 days	PD10, PD21, PD45 and PD70	VTA	Down-regulated by maternal separation (MS) and low home cage nesting at P21	Decreased cells expressing OTX2 protein in VTA at PD17	[48]

ND; not determined.
NIA; no information available.

NAc of post-mortem brain tissue [55], suggesting a conserved molecular response to CS operating at the level of chromatin structure. Interestingly, in adult male mice, expression of the SWI-SNF ATP-dependent chromatin-remodeling complex in dopaminergic neurons of NAc is necessary for the social avoidance phenotype induced by chronic social defeat stress [56]. This indicates that chromatin remodeling is key for the molecular and behavioral consequences of CS.

Further to epigenetic modifiers, CS can also alter the expression of TFs and co-factors. While TFs are not epigenetic factors *per se*, they are essential for the regulation and the establishment of epigenetic features and their activity can be modulated by epigenetic mechanisms. TFs can be dysregulated transiently e.g. OTX2 [48] or persistently e.g. GR [34], and be differentially expressed during development e.g. REST [57] in rodents and humans. At the functional level, a transient change in abundance or activity of TFs has been proposed to prime the epigenome [38,48] while a persistent change may modify the overall regulatory landscape of the genome. In adults, CS can persistently alter the expression of TFs. In male mice subjected to chronic unpredictable stress, the transcriptional level of the TF YY1 is down-regulated specifically in excitatory neurons of PFC [58]. The selective ablation of YY1 in these neurons increases the susceptibility to stress, and affects transcription and the deposition of HTPMs such as H3K27ac [58], further highlighting the crosstalk between TFs, epigenetic regulation and control of gene expression.

Perspectives

We envision at least four areas of focus that could help better understand the epigenetic effects of CS in the brain and their impact on behavior and cognition. First, it is imperative to distinguish the temporal dynamic of epigenetic changes identified in the context of CS. Not all changes are enduring or represent a form of molecular memory. Epigenetic changes can be transient and present only at the time of exposure and shortly after, long-lasting and persistent after exposure, or deferred and be expressed only later e.g. in adulthood in the case of postnatal exposure. Therefore, time course analyses to evaluate changes to the epigenome at different time points are essential to distinguish the dynamics of the observed molecular changes. Second, causality between epigenetic changes due to CS and effects observed on gene expression should be examined in the relevant cellular context. Modeling epigenetic modifications in specific regulatory elements of loci of interest e.g. using CRISPR tools is a strategy to demonstrate such causality. Third, the interplay between genetic variability and history of stress exposure must be examined to determine if changes in the epigenome are linked to a genetic background of susceptibility e.g. reflected by genetic variants. The genetic make-up of individuals has a major effect on the emergence of stress-induced phenotypes and their molecular effects. Fourth, integrated profiling of the different epigenetic marks and mechanisms regulating gene expression in the context of stress is needed. These marks and mechanisms do not act separately but are interrelated and cooperate to modify chromatin structure and organization and modulate co-factors and TFs. Multimodal experimental approaches that characterize multiple levels of epigenetic information would greatly benefit the mechanistic understanding of epigenomic effects of stress. Efforts should also be made to develop a unifying molecular theory of the long-lasting effects of CS on genome activity and provide experimental evidence for these effects. The possibility that CS can affect individuals across generations, in some cases by involving epigenetic factors in the germline is an important area of research and a paradigm shift in the understanding of the complex traits and their pathologies [59].

Conclusions

Exposure to stress, in particular when chronic, can induce changes in the epigenome of brain cells. These changes are cell-type specific, affect different brain regions and are influenced by genetic background, sex and developmental time of exposure. At the functional level, changes to the brain epigenome have been correlated with changes in basal gene expression. In some cases, they have been suggested to influence stimulus-dependent transcriptional responses in the brain and prime genome activity, and therefore represent a source of molecular susceptibility of future regulatory responses. While in the past two decades, the field has made enormous progress in documenting changes and correlating them with differences in gene expression and phenotypes, more mechanistic work is needed to obtain a more integrative and holistic understanding of the origin of epigenetic effects due to stress and their impact on genome function and brain activity. The recent use of tools for epigenetic editing and for manipulating the expression of epigenetic regulators *in vivo* is shifting the field from correlation to causality [18,20,60]. However, the true nature, timing and dynamics of epigenetic changes triggered by CS and their influence on basal or stimulus-dependent transcriptional programs remain not fully known.

Declaration of competing interest

No financial interest. RGAM and NVC wrote the manuscript, IMM corrected and finalized the manuscript, IMM raised funds for her lab and for RGAM and NVC.

Data availability

No data was used for the research described in the article.

Acknowledgments

The Mansuy lab is funded by the University Zürich, the ETH Zürich, the Swiss National Science Foundation grant number 31003A_175742/1, ETH grants (ETH-10 15-2 and ETH-17 13-2), the National Centre of Competence in Research (NCCR) RNA&Disease funded by the Swiss National Science Foundation (grant number 182880/Phase 2 and 205601/Phase 3), European Union Horizon 2020 Research Innovation Program Grant number 848158, European Union projects FAMILY and HappyMums funded by the Swiss State Secretariat for Education, Research and Innovation (SERI), the Hochschulmedizin Flagship project STRESS, FreeNovation grant from Novartis Forschungsstiftung, and the Escher Family Fund. RGA-M received an ETH Postdoctoral Fellow grant number 20-1 FEL-28. NVNC received a UZH Postdoctoral fellowship grant number FK 21-038.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. O'Connor DB, Thayer JF, Vedhara K: **Stress and health: a review of psychobiological processes**. *Annu Rev Psychol* 2020, **72**:1–26.

2. McEwen BS, Akil H: **Revisiting the stress concept: implications for affective disorders**. *J Neurosci* 2020, **40**:12–21.

3. Gray JD, Kogan JF, Marrocco J, McEwen BS: **Genomic and epigenomic mechanisms of glucocorticoids in the brain**. *Nat Rev Endocrinol* 2017, **13**:661–673.

4. Cavalli G, Heard E: **Advances in epigenetics link genetics to the environment and disease**. *Nature* 2019, **571**:489–499.

5. Allis CD, Jenuwein T: **The molecular hallmarks of epigenetic control**. *Nat Rev Genet* 2016, **17**:487–500.

6. Millán-Zambrano G, Burton A, Bannister AJ, Schneider R: **Histone post-translational modifications — cause and consequence of genome function**. *Nat Rev Genet* 2022, **23**:563–580.

7. Statello L, Guo C-J, Chen L-L, Huarte M: **Gene regulation by long non-coding RNAs and its biological functions**. *Nat Rev Mol Cell Biol* 2021, **22**:96–118.

8. Clapier CR, Iwasa J, Cairns BR, Peterson CL: **Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes**. *Nat Rev Mol Cell Biol* 2017, **18**:407–422.

9. van Steensel B, Furlong EEM: **The role of transcription in shaping the spatial organization of the genome**. *Nat Rev Mol Cell Biol* 2019, **20**:327–337.

10. Schoenfelder S, Fraser P: **Long-range enhancer–promoter contacts in gene expression control**. *Nat Rev Genet* 2019, **20**:437–455.

11. Marco A, Meharena HS, Dileep V, Raju RM, Davila-Velderrain J, Zhang AL, Adaikkan C, Young JZ, Gao F, Kellis M, *et al.*: **Mapping the epigenomic and transcriptomic interplay during memory formation and recall in the hippocampal engram ensemble**. *Nat Neurosci* 2020, **23**:1606–1617.

12. Fernandez-Albert J, Lipinski M, Lopez-Cascales MT, Rowley MJ, Martin-Gonzalez AM, Blanco B del, Corces VG, Barco A: **Immediate and deferred epigenomic signatures of in vivo neuronal activation in mouse hippocampus**. *Nat Neurosci* 2019, **22**:1718–1730.

13. ** Cerniauskas I, Winterer J, de Jong JW, Lukacsovich D, Yang H, Khan F, Peck JR, Obayashi SK, Lilascharoen V, Lim BK, *et al.*: **CS induces activity, synaptic, and transcriptional remodeling of the lateral habenula associated with deficits in motivated behaviors**. *Neuron* 2019, **104**:899–915.e8.
This paper provides the most comprehensive behavioural, physiological and molecular characterization of the effects of CS in mice with a focus on the lateral habenula.

14. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, Hare TA, Bookheimer SY, Tottenham N: **Early developmental emergence of human amygdala–prefrontal connectivity after maternal deprivation**. *Proc Natl Acad Sci U S A* 2013, **110**:15638–15643.

15. Franklin TB, Saab BJ, Mansuy IM: **Neural mechanisms of stress resilience and vulnerability**. *Neuron* 2012, **75**:747–761.

16. Thumfart KM, Jawaid A, Bright K, Flachsmann M, Mansuy IM: **Epigenetics of childhood trauma: long term sequelae and potential for treatment**. *Neurosci Biobehav Rev* 2022, **132**:1049–1066.

17. * Catale C, Bussone S, Iacono LL, Viscomi MT, Palacios D, Troisi A, Carola V: **Exposure to different early-life stress experiences results in differentially altered DNA methylation in the brain and immune system**. *Neurobiol Stress* 2020, **13**:100249.
This study provides a characterization of the effect of different types of CS early in life on DNA methylation across brain regions and cell-types.

18. ** Kronman H, Torres-Berrío A, Sidoli S, Issler O, Godino A, Ramakrishnan A, Mews P, Lardner CK, Parise EM, Walker DM, *et al.*: **Long-term behavioral and cell-type-specific molecular effects of early life stress are mediated by H3K79me2 dynamics in medium spiny neurons**. *Nat Neurosci* 2021, **24**:667–676.
First comprehensive characterization of the effect of CS early in life on the abundance of histone modifications in NAc and their variation over time. Functional validation of the role of HMTs in long-lasting behavioral effects of CS early in life.

19. Lepack AE, Bagot RC, Peña CJ, Loh Y-HE, Farrelly LA, Lu Y, Powell SK, Lorsch ZS, Issler O, Cates HM, *et al.*: **Aberrant H3.3 dynamics in NAc promote vulnerability to depressive-like behavior**. *Proc Natl Acad Sci U S A* 2016, **113**:12562–12567.

20. ** Torres-Berrío A, Estill M, Ramakrishnan A, Kronman H, Patel V, Minier-Toribio A, Issler O, Browne CJ, Parise EM, van der Zee Y, *et al.*: **Monomethylation of lysine 27 at histone 3 confers lifelong susceptibility to stress**. *bioRxiv* 2023, https://doi.org/10.1101/2023.05.08.539829.
First evidence of the role of H3K27me1 in CS in the NAc across life and stress paradigms.

21. Lutz P-E, Chay M-A, Pacis A, Chen GG, Aouabed Z, Maffioletti E, Théroux J-F, Grenier J-C, Yang J, Aguirre M, *et al.*: **Non-CG methylation and multiple histone profiles associate child abuse with immune and small GTPase dysregulation**. *Nat Commun* 2021, **12**:1132.

22. Warhaftig G, Zifman N, Sokolik CM, Massart R, Gabay O, Sapozhnikov D, Vaisheva F, Lictenstein Y, Confortti N, Ahdoot H, *et al.*: **Reduction of DNMT3a and RORA in the nucleus accumbens plays a causal role in post-traumatic stress disorder-like behavior: reversal by combinatorial epigenetic therapy**. *Mol Psychiatry* 2021, **26**:7481–7497.

23. Zhao M, Wang W, Jiang Z, Zhu Z, Liu D, Pan F: **Long-term effect of post-traumatic stress in adolescence on dendrite development and H3K9me2/BDNF expression in male rat hippocampus and prefrontal cortex**. *Front Cell Dev Biol* 2020, **8**:682.

24. Levine A, Worrell TR, Zimnisky R, Schmauss C: **Early life stress triggers sustained changes in histone deacetylase expression and histone H4 modifications that alter responsiveness to adolescent antidepressant treatment**. *Neurobiol Dis* 2012, **45**:488–498.

25. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TWW, Mercer KB, Mayberg HS, Bradley B, *et al.*: **Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions**. *Nat Neurosci* 2013, **16**:33–41.

26. Zannas AS, Provençal N, Binder EB: **Epigenetics of post-traumatic stress disorder: current evidence, challenges, and future directions**. *Biol Psychiatry* 2015, **78**:327–335.

27. Morgan MAJ, Shilatifard A: **Reevaluating the roles of histone-modifying enzymes and their associated chromatin modifications in transcriptional regulation**. *Nat Genet* 2020, **52**:1271–1281.

28. Boileau RM, Chen KX, Blelloch R: **Loss of MLL3/4 decouples enhancer H3K4 monomethylation, H3K27 acetylation, and gene activation during embryonic stem cell differentiation**. *Genome Biol* 2023, **24**:41.

29. Wang Z, Chivu AG, Choate LA, Rice EJ, Miller DC, Chu T, Chou S-P, Kingsley NB, Petersen JL, Finno CJ, *et al.*: **Prediction of histone post-translational modification patterns based on nascent transcription data**. *Nat Genet* 2022, **54**:295–305.

30. Sankar A, Mohammad F, Sundaramurthy AK, Wang H, Lerdrup M, Tatar T, Helin K: **Histone editing elucidates the functional roles of H3K27 methylation and acetylation in mammals**. *Nat Genet* 2022, **54**:754–760.

31. ** Kuehner JN, Walia NR, Seong R, Li Y, Martinez-Feduchi P, Yao B: **Social defeat stress induces genome-wide 5mC and 5hmC alterations in the mouse brain**. *G3 (Bethesda)* 2023, **13**: jkad114.
This paper provides a longitudinal characterization of the effect of chronic social defeat stress on 5mC and 5hmC in the cortex of susceptible and resilient adult mice.

32. Fitzgerald E, Sinton MC, Wernig-Zorc S, Morton NM, Holmes MC, Boardman JP, Drake AJ: **Altered hypothalamic DNA methylation and stress-induced hyperactivity following early life stress**. *Epigenetics Chromatin* 2021, **14**:31.

33. Kaluscha S, Domcke S, Wirbelauer C, Stadler MB, Durdu S, Burger L, Schübeler D: **Evidence that direct inhibition of transcription factor binding is the prevailing mode of gene and repeat repression by DNA methylation**. *Nat Genet* 2022, **54**: 1895–1906.

34. Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ: **Epigenetic programming by maternal behavior**. *Nat Neurosci* 2004, **7**: 847–854.

35. Kundakovic M, Gudsnuk K, Herbstman JB, Tang D, Perera FP, Champagne FA: **DNA methylation of BDNF as a biomarker of early-life adversity**. *Proc Natl Acad Sci U S A* 2015, **112**: 6807–6813.

36. Weaver ICG, D'Alessio AC, Brown SE, Hellstrom IC, Dymov S, Sharma S, Szyf M, Meaney MJ: **The transcription factor nerve growth factor-inducible protein A mediates epigenetic programming: altering epigenetic marks by immediate-early genes**. *J Neurosci* 2007, **27**:1756–1768.

37. Kremsky I, Corces VG: **Protection from DNA re-methylation by transcription factors in primordial germ cells and pre-implantation embryos can explain trans-generational epigenetic inheritance**. *Genome Biol* 2020, **21**:118.

38. Arzate-Mejia RG, Mansuy IM: **Remembering through the genome: the role of chromatin states in brain functions and diseases**. *Transl Psychiatry* 2023, **13**:122.

39. Borsari B, Villegas-Mirón P, Pérez-Lluch S, Turpin I, Laayouni H, Segarra-Casas A, Bertranpetit J, Guigó R, Acosta S: **Enhancers with tissue-specific activity are enriched in intronic regions**. *Genome Res* 2021, **31**:1325–1336.

40. Kreibich E, Kleinendorst R, Barzaghi G, Kaspar S, Krebs AR: **Single-molecule footprinting identifies context-dependent regulation of enhancers by DNA methylation**. *Mol Cell* 2023, **83**:787–802.e9.

41. Blattler A, Yao L, Witt H, Guo Y, Nicolet CM, Berman BP, Farnham PJ: **Global loss of DNA methylation uncovers intronic enhancers in genes showing expression changes**. *Genome Biol* 2014, **15**:469.

42. Neri F, Rapelli S, Krepelova A, Incarnato D, Parlato C, Basile G, Maldotti M, Anselmi F, Oliviero S: **Intragenic DNA methylation prevents spurious transcription initiation**. *Nature* 2017, **543**: 72–77.

43. Linker SM, Urban L, Clark SJ, Chhatriwala M, Amatya S, McCarthy DJ, Ebersberger I, Vallier L, Reik W, Stegle O, *et al.*: **Combined single-cell profiling of expression and DNA methylation reveals splicing regulation and heterogeneity**. *Genome Biol* 2019, **20**:30.

44. Boxer LD, Renthal W, Greben AW, Whitwam T, Silberfeld A, Stroud H, Li E, Yang MG, Kinde B, Griffith EC, *et al.*: **MeCP2 represses the rate of transcriptional initiation of highly methylated long genes**. *Mol Cell* 2020, **77**:294–309.e9.

45. Baubec T, Colombo DF, Wirbelauer C, Schmidt J, Burger L, Krebs AR, Akalin A, Schübeler D: **Genomic profiling of DNA methyltransferases reveals a role for DNMT3B in genic methylation**. *Nature* 2015, **520**:243–247.

46. Chen L-F, Lin YT, Gallegos DA, Hazlett MF, Gómez-Schiavon M, Yang MG, Kalmeta B, Zhou AS, Holtzman L, Gersbach CA, *et al.*: **Enhancer histone acetylation modulates transcriptional bursting dynamics of neuronal activity-inducible genes**. *Cell Rep* 2019, **26**:1174–1188.e5.

47. Hanna CW, Taudt A, Huang J, Gahurova L, Kranz A, Andrews S, Dean W, Stewart AF, Colomé-Tatché M, Kelsey G: **MLL2 conveys transcription-independent H3K4 trimethylation in oocytes**. *Nat Struct Mol Biol* 2018, **25**:73–82.

48. * Peña CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, Issler O, Loh Y-HE, Leong T, Kiraly DD, *et al.*: **Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2**. *Science* 2017, **356**: 1185–1188.
Evidence for the contribution of TFs in long-lasting effects of CS early in life.

49. Aubert Y, Egolf S, Capell BC: **The unexpected noncatalytic roles of histone modifiers in development and disease**. *Trends Genet* 2019, **35**:645–657.

50. Nassa G, Salvati A, Tarallo R, Gigantino V, Alexandrova E, Memoli D, Sellitto A, Rizzo F, Malanga D, Mirante T, *et al.*: **Inhibition of histone methyltransferase DOT1L silences ERα gene and blocks proliferation of antiestrogen-resistant breast cancer cells**. *Sci Adv* 2019, **5**, eaav5590.

51. Farooq Z, Banday S, Pandita TK, Altaf M: **The many faces of histone H3K79 methylation**. *Mutat Res Rev Mutat Res* 2016, **768**:46–52.

52. Erburu M, Muñoz-Cobo I, Domínguez-Andrés J, Beltran E, Suzuki T, Mai A, Valente S, Puerta E, Tordera RM: **CS and antidepressant induced changes in Hdac5 and Sirt2 affect synaptic plasticity**. *Eur Neuropsychopharmacol* 2015, **25**: 2036–2048.

53. Bedrosian TA, Quayle C, Novaresi N, FredH Gage: **Early life experience drives structural variation of neural genomes in mice**. *Science* 2018, **359**:1395–1399.

54. Elliott E, Manashirov S, Zwang R, Gil S, Tsoory M, Shemesh Y, Chen A: **Dnmt3a in the medial prefrontal cortex regulates anxiety-like behavior in adult mice**. *J Neurosci* 2016, **36**: 730–740.

55. * Sun H, Damez-Werno DM, Scobie KN, Shao N-Y, Dias C, Rabkin J, Koo JW, Korb E, Bagot RC, Ahn FH, *et al.*: **ACF chromatin-remodeling complex mediates stress-induced depressive-like behavior**. *Nat Med* 2015, **21**:1146–1153.
This paper shows that CS in adult mice differentially affects chromatin structure genome-wide in the NAc of susceptible but not resilient mice.

56. Zayed A, Baranowski C, Compagnion A-C, Vernochet C, Karaki S, Cuttoli RD, Saint-Jour E, Bhattacharya S, Marti F, Vanhoutte P, *et al.*: **SWI/SNF chromatin remodeler complex within the reward pathway is required for behavioral adaptations to stress**. *Nat Commun* 2022, **13**:1807.

57. Rodenas-Ruano A, Chávez AE, Cossio MJ, Castillo PE, Zukin RS: **REST-dependent epigenetic remodeling promotes the developmental switch in synaptic NMDA receptors**. *Nat Neurosci* 2012, **15**:1382–1390.

58. ** Kwon DY, Xu B, Hu P, Zhao Y-T, Beagan JA, Nofziger JH, Cui Y, Phillips-Cremins JE, Blendy JA, Wu H, *et al.*: **Neuronal Yin Yang1 in the prefrontal cortex regulates transcriptional and behavioral responses to CS in mice**. *Nat Commun* 2022, **13**:55.
Comprehensive characterization of transcriptional effects of CS in adult in PFC. Evidence for cell-type specific changes in the expression of YY1 and its direct contribution to behavioural abnormalities due to stress.

59. van Steenwyk G, Mansuy IM: *Stress: Genetics, Epigenetics and Genomics*. 2021, https://doi.org/10.1016/b978-0-12-813156-5.00029-7.

60. Heller EA, Cates HM, Peña CJ, Sun H, Shao N, Feng J, Golden SA, Herman JP, Walsh JJ, Mazei-Robison M, *et al.*: **Locus-specific epigenetic remodeling controls addiction- and depression-related behaviors**. *Nat Neurosci* 2014, **17**: 1720–1727.

61. Urb M, Anier K, Matsalu T, Aonurm-Helm A, Tasa G, Koppel I, Zharkovsky A, Timmusk T, Kalda A: **Glucocorticoid receptor stimulation resulting from early life stress affects expression of DNA methyltransferases in rat prefrontal cortex**. *J Mol Neurosci* 2019, **68**:99–110.

62. Wei J, Cheng J, Waddell NJ, Wang Z-J, Pang X, Cao Q, Liu A, Chitaman JM, Abreu K, Jasrotia RS, *et al.*: **DNA methyltransferase 3A is involved in the sustained effects of CS on synaptic functions and behaviors**. *Cereb Cortex* 2020, **31**:1998–2012.

63. Hammels C, Prickaerts J, Kenis G, Vanmierlo T, Fischer M, Steinbusch HWM, van Os J, van den Hove DLA, Rutten BPF: **Differential susceptibility to chronic social defeat stress relates to the number of Dnmt3a-immunoreactive neurons in the hippocampal dentate gyrus**. *Psychoneuroendocrinology* 2015, **51**:547–556.

64. Karen C, Rajan KE: **Social behaviour and epigenetic status in adolescent and adult rats: the contribution of early-life stressful social experience**. *Cell Mol Neurobiol* 2019, **39**:371–385.

65. LaPlant Q, Vialou V, Covington HE, Dumitriu D, Feng J, Warren BL, Maze I, Dietz DM, Watts EL, Iñiguez SD, *et al.*: **Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens**. *Nat Neurosci* 2010, **13**:1137–1143.

66. Matrisciano F, Pinna G: **PPAR-α hypermethylation in the hippocampus of mice exposed to social isolation stress is associated with enhanced neuroinflammation and aggressive behavior**. *Int J Mol Sci* 2021, **22**:10678.

67. Lee J-E, Kwon H-J, Choi J, Han P-L: **Stress-induced epigenetic changes in hippocampal Mkp-1 promote persistent depressive behaviors**. *Mol Neurobiol* 2019, **56**:8537–8556.

68. Shepard RD, Gouty S, Kassis H, Berenji A, Zhu W, Cox BM, Nugent FS: **Targeting histone deacetylation for recovery of maternal deprivation-induced changes in BDNF and AKAP150 expression in the VTA**. *Exp Neurol* 2018, **309**:160–168.

69. Seo MK, Ly NN, Lee CH, Cho HY, Choi CM, Nhu LH, Lee JG, Lee BJ, Kim G-M, Yoon BJ, *et al.*: **Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus**. *Neuropharmacology* 2016, **105**:388–397.

70. Liu D, Qiu H-M, Fei H-Z, Hu X-Y, Xia H-J, Wang L-J, Qin L-J, Jiang X-H, Zhou Q-X: **Histone acetylation and expression of mono-aminergic transmitters synthetases involved in CUS-induced depressive rats**. *Exp Biol Med* 2013, **239**:330–336.

71. Renthal W, Maze I, Krishnan V, Covington HE, Xiao G, Kumar A, Russo SJ, Graham A, Tsankova N, Kippin TE, *et al.*: **Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli**. *Neuron* 2007, **56**:517–529.

72. Li H-Y, Jiang Q-S, Fu X-Y, Jiang X-H, Zhou Q-X, Qiu H-M: **Abnormal modification of histone acetylation involved in depression-like behaviors of rats induced by chronically unpredicted stress**. *Neuroreport* 2017, **28**:1054–1060.

73. Qian W, Yu C, Wang S, Niu A, Shi G, Cheng Y, Xu N, Jin Q, Jing X: **Depressive-like behaviors induced by chronic social defeat stress are associated with HDAC7 reduction in the nucleus accumbens**. *Front Psychiatry* 2021, **11**:586904.

74. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, Fischer D, Holsboer F, Wotjak CT, Almeida OFX, Spengler D: **Dynamic DNA methylation programs persistent adverse effects of early-life stress**. *Nat Neurosci* 2009, **12**:1559–1566.

75. Gapp K, Soldado-Magraner S, Alvarez-Sánchez M, Bohacek J, Vernaz G, Shu H, Franklin TB, Wolfer D, Mansuy IM: **Early life stress in fathers improves behavioural flexibility in their offspring**. *Nat Commun* 2014, **5**:5466.