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Epigenetic mechanisms impacted by chronic stress across the rodent lifespan

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ABSTRACT

Exposures to stress at all stages of development can lead to long-term behavioural effects, in part through changes in the epigenome. This review describes rodent research suggesting that stress in prenatal, postnatal, adolescent and adult stages leads to long-term changes in epigenetic regulation in the brain which have causal impacts on rodent behaviour. We focus on stress-induced epigenetic changes that have been linked to behavioural deficits including poor learning and memory, and increased anxiety-like and depressive-like behaviours. Interestingly, aspects of these stress-induced behavioural changes can be transmitted to offspring across several generations, a phenomenon that has been proposed to result via epigenetic mechanisms in the germline. Here, we also discuss evidence for the differential impact of stress on the epigenome in males and females, conscious of the fact that the majority of published studies have only investigated males. This has led to a limited picture of the epigenetic impact of stress, highlighting the need for future studies to investigate females as well as males.

1. Introduction

Harmful or stressful environments during all stages of development can have a long-lasting and persistent impact, in part through changes to the epigenome, which has functional consequences for a wide range of regulatory mechanisms including chromatin organization, and RNA transcription and splicing. Epigenetic regulation is a broad term which refers to mechanisms underlying the dynamic changes in epigenetic marks, as well as differential expression of non-coding RNAs, the partial replacement of histones with histone variants H3.3 and H2A.Z., and altered higher order chromatin organization, like looping (Bannister and Kouzarides, 2011; Bowman and Poirier, 2015; Rothbart and Strahl, 2014; Watson and Tsai, 2017; Wozniak and Strahl, 2014). Epigenetic marks are reversible chemical modifications to DNA or histones (Dupont et al., 2009) which include DNA methylation and hydroxymethylation, and post-translational modifications of histones like acetylation, phosphorylation, methylation, ubiquitylation, ADP-ribosylation, beta-hydroxybutyrylation and crotonylation, which can occur in over 50 distinct sites (Hamilton and Nestler, 2019).

Changes to the epigenome all ultimately impact gene expression by affecting the level of compaction of chromatin and the ease at which transcriptional machinery can access the DNA strand (Bowman and Poirier, 2015; Bruggeman and Yao, 2019). Certain epigenetic marks are associated mainly with facilitating or repressing expression of the associated gene. For instance, DNA methylation in promoter regions tend to repress gene transcription, while DNA hydroxymethylation tends to activate gene transcription, again by impacting chromatin compaction (Bruggeman and Yao, 2019). Histone acetylation occurs at lysine residues and generally acts to loosen chromatin allowing access to the DNA strand, thereby increasing transcription rates (Bowman and Poirier, 2015). In contrast, histone methylation occurs at lysine and arginine residues and can facilitate or repress gene transcription depending on the specific residue and whether it is mono-, di-, or trimethylation. The rate of gene transcription can additionally be regulated by non-coding RNAs, a class of RNAs which includes microRNAs (miRNAs), small interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs). These non-coding RNAs can affect both transcriptional and post-transcriptional processes by regulating heterochromatin formation, and targeting histone modifications and DNA methylation to specific loci, or by regulating mRNA degradation thereby mediating post-transcriptional gene silencing (Holoch and Moazed, 2015). Non-coding RNAs, in particular, have been the recent focus of research into mechanisms for the transgenerational effects of stress (Gapp and Bohacek, 2018).

The stress response engages and affects a wide range of brain structures involved in stress coping, emotional regulation, cognitive

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function, and learning and memory, including the prefrontal cortex (PFC), amygdala, hippocampus, hypothalamus, thalamus, and nucleus accumbens (Andersen and Teicher, 2008; Godoy et al., 2018). The impact of stress at each developmental stage depends partly on the maturational state of these different brain areas at the time of stress exposure, which determines factors like the rate of neurogenesis, pruning, and glucocorticoid and mineralocorticoid receptor expression. Thus, each brain area has a distinct developmental timeline, and so any insult experienced by an individual can affect different brain regions at different stages of their maturation (Andersen and Teicher, 2008; Tottenham and Galván, 2016). During stages of increased and accelerated development, referred to as sensitive periods (Andersen and Teicher, 2008), brain regions are more sensitive to environmental influences including stress exposure, and are more likely to show long-lasting effects of negative events (Romeo, 2017). These sensitive periods could result from high levels of neurogenesis or pruning occurring at these maturational stages. For example, extensive neurogenesis occurs during gestation, but different regions experience peak neurogenesis at different stages of gestation. In mice, the amygdala, several thalamic nuclei, and cortical layers V and VI undergo peak neurogenesis during mid-gestation (Bayer et al., 1993; Finlay and Darlington, 1995). In contrast, the hippocampus, nucleus accumbens, and cortical layers II, III, and IV undergo peak neurogenesis during late gestation, a period when the hippocampal commissure is also formed (Ashwell et al., 1996; Bayer et al., 1993; Finlay and Darlington, 1995). This could suggest that for stress manipulations that impact neurogenesis, mid-gestation is more likely to be a period of increased vulnerability for the amygdala and thalamus, and late gestation is a period of increased vulnerability for the hippocampus and nucleus accumbens.

While it is evident that stress can impact epigenetic mechanisms, it is still unclear if there is a critical period during development when particular brain areas are more susceptible to the epigenetic impact of stress, and whether this is similar in both males and females. This review aims to organize the current literature describing the long-term neural epigenetic effects of chronic stress during prenatal and postnatal development, adolescence and adulthood in order to highlight possible patterns in differential epigenetic regulation occurring as a result of stress exposure across the lifetime. We will also discuss the involvement of epigenetic mechanisms in animal models of neuropsychiatric illnesses that are often precipitated by stress. Due to the broad scope of this review, we are unable to discuss all the publications in this field but have instead chosen to highlight common and differential neural epigenetic mechanisms across the lifespan with a focus on causal, rather than correlative findings. A particular emphasis will be placed on sex differences related to the epigenetic impact of stress.

2. The impact of prenatal stress on epigenetic regulation

Prenatal development is a pivotal period in brain development, and insults during this period can have significant effects on the individual throughout their lifetime. Stress during prenatal development results in reorganization and alterations in dendritic morphology in the PFC and altered hippocampal and amygdala plasticity in rodents (Cheng et al., 2019; Holmes and Wellman, 2009; Huizink et al., 2004; Liston et al., 2006). Stress during later stages of gestational development, in particular, show pronounced adverse effects, likely because during early gestation the placenta acts to reduce the negative impact of stress by limiting the amount of maternal glucocorticoids that reach the developing fetus (Brown et al., 1996; Yang, 1997). At a behavioural level, rodent models have shown that long-term cognitive deficits related to learning and memory have emerged as a consistent behavioural consequence of acute or chronic prenatal stress (Benoit et al., 2015; Markham et al., 2010; Mueller and Bale, 2007; Yang et al., 2006). These deficits in spatial memory are consistently observed across different stressors, including prenatal exposure to chronic unpredictable stress (CUS), chronic variable stress, and foot shock stress (Benoit et al., 2015; Markham et al., 2010; Yang et al., 2006), strongly suggesting that different stressors are acting upon converging pathways leading to this behavioural phenotype in adulthood.

Several lines of evidence have suggested that histone acetylation plays an important role in the negative impact of prenatal stress on memory. In male and female mice, chronic unpredictable stress 4 weeks prior to, and then throughout pregnancy, results in offspring with deficits in spatial memory, and decreased histone 3 lysine 14 (H3K14) acetylation in the hippocampus (Benoit et al., 2015). Sex differences in the effects of prenatal chronic unpredictable stress have been observed, with female mice exposed to prenatal stress showing a greater decrease in H3K14 acetylation, in addition to a female-specific elevation of DNA methyltransferase 1 (Dnmt1) levels in the hippocampus (Benoit et al., 2015). This sex difference was observed at a molecular level, but both males and females exposed to prenatal stress showed similar behavioural deficits in the Morris Water Maze making it difficult to draw a clear correlation between these epigenetic marks and behaviour in this test. However, prenatal stress results in a host of differential behaviours in males and females related to learning and memory; prenatally stressed males, but not females, show impaired object recognition memory and impaired cued fear extinction (Markham et al., 2010). Thus, it is possible that females have compensatory epigenetic mechanisms that limit the impact of prenatal stress on non-spatial forms of memory.

In addition to its impact on memory, prenatal stress, in the form of chronic mild stress during early gestation (embryonic day 1–7), but not mid- or late-gestation, results in increased depression-like behaviours specifically in males and not females, on the tail suspension test and the forced swim test (Mueller and Bale, 2008). Males subjected to early prenatal stress also demonstrate altered reward-seeking behaviour, with reduced basal sucrose intake but increased bingeing on sucrose following a stressor, as well as increased hypothalamic-pituitary-adrenal (HPA) axis responsivity. This is associated with increased expression of the gene that encodes corticotropin releasing factor (*Crf)* in the central nucleus of the amygdala, decreased expression of the gene that encodes the glucocorticoid receptor, *Nr3c1*, in the CA3 and DG subregion of the hippocampus, reduced DNA methylation of the *Crf* promoter and increased DNA methylation of *Nr3c1* promoter in the hypothalamus and the amygdala (Mueller and Bale, 2008). This early gestational stress has also been shown to have transgenerational effects on offspring. Investigation of offspring of prenatally stressed sires showed dysmasculinization of mRNA and miRNA expression in brain taken on postnatal day 1, as well as increased HPA response to a stressor and shorter anogenital distance in male adults (Morgan and Bale, 2011).

Repeated restraint stress during mid- and late-gestation has been suggested to result in a broader schizophrenia-like phenotype in rodents, both at a behavioural and epigenetic level (Matrisciano et al., 2013, 2018; Palacios-García et al., 2015). This includes hyperactivity, reduced social interaction, and deficits in prepulse inhibition and fear conditioning, behavioural abnormalities that could be reversed by administration of a histone deacetylase inhibitor, valproic acid, or an atypical antipsychotic with demethylation activity, clozapine (Matrisciano et al., 2013). Behavioural changes were associated with increased *Dnmt1* and *Dnmt3a* mRNA expression in the frontal cortex and hippocampus, particularly in GABAergic neurons, increased Dnmt1 and decreased reelin and glutamic acid decarboxylase 1 (Gad1) protein expression, and increased Dnmt1 and Mecp2 binding to *Reln* and *Gad1* promoters in the frontal cortex (Matrisciano et al., 2013). Increased methylation and hydroxymethylation of *Reln* and *Gad1* promoter were also observed (Matrisciano et al., 2013, 2018; Palacios-García et al., 2015), and many of these changes in epigenetic regulation and gene expression have been proposed mechanisms for schizophrenia.

In addition to its effects on schizophrenia-like behaviours, repeated restraint stress during mid- and late-gestation also increases anxiety-like behaviours and alcohol intake in Swiss albino ND4 adult male mice (Dong et al., 2018). These behavioural findings were associated with a

30% reduction in spine density in the pyramidal neurons of the medial PFC, as well as decreased expression of genes and proteins associated with synaptic formation including activity regulated cytoskeleton associated protein (*Arc*), spinophilin (*Spn*), and TrkB (*TrkB*) (Dong et al., 2018). Increased methylation of the promoter regions of *Arc* and *Spn*, as well as decreased H3K14 acetylation on *TrkB*, the gene which encodes a Bdnf receptor, was also observed and could be mediating this decreased expression although causal evidence was not provided in this study (Dong et al., 2018). The association between a stress-induced increase in alcohol consumption and differential epigenetic regulation is not exclusive to stress during the prenatal period (see section 5.0-The impact of adult stress on epigenetic regulation). However, combined with research by Benoit et al. (2015), this suggests that H3K14 acetylation may be a histone modification that is particularly sensitive to prenatal stress, as it appears to be affected by at least two types of stressors during this developmental period. The long-term impact of prenatal stress can be due to the direct effects of the stress itself or could be the result of the impact of prenatal stress on subsequent maternal care provided to the pups. It is also possible that sex differences are present in the epigenetic effects of prenatal stress related to schizophrenia-like behaviours, increased alcohol intake and anxiety-like behaviours but this is currently difficult to assess as the studies described above were only performed in males. It is crucial that future investigation of these effects include the behavioural and epigenetic assessment of both males and females.

3. The impact of early-life stress (ELS) on epigenetic regulation

Early life stress (ELS) paradigms result in persistent neuroanatomical and behavioural effects, which include depressive-like and anxiety-like behaviours that present themselves in a sex-dependent manner (Franklin et al., 2010; Goodwill et al., 2019; Johnson et al., 2018; Kalinichev et al., 2002; Nishi et al., 2014; White et al., 2020). Natural fluctuations in maternal care provided by rat dams have been used to demonstrate that low levels of maternal licking and grooming results in lower levels of *Nr3c1*, and that this is associated with increased methylation and reduced levels of H3K9 acetylation of the associated promoter region of the gene in the hippocampus, and reduced glucocorticoid feedback sensitivity, when compared to adult rats that received high levels of licking and grooming (Weaver et al., 2004). Causal evidence for the role of epigenetic modifications in HPA axis responsivity was provided by treating rat offspring of low licking and grooming dams with an Hdac inhibitor (trichostatin A; TSA). This modified the epigenetic profile of the glucocorticoid receptor promoter region and HPA axis response such that low licking-grooming offspring became more similar to high licking-grooming offspring (Weaver, 2005; Weaver et al., 2004). Conversely, treatment with a methyl group donor (methionine infusion) could affect the high licking-grooming offspring to more closely resemble low licking-grooming offspring (Weaver, 2005).

While the above-described studies are based on natural fluctuations in maternal care, most ELS manipulations are based on treatments that ultimately alter the maternal care received by experimental pups during a period of postnatal development when the pups are reliant on their dams for food and other care (Franklin et al., 2010; Weiss et al., 2011). Many ELS paradigms are maternal separation paradigms that involve separation of the pups from their dams, generally for a period of 3 h per day. This results in inconsistent maternal care provided to the pups (Weiss et al., 2011), which ultimately leads to long-term anxiety-like and depressive-like behaviours that have been associated with epigenetic changes in brain and germ cell (Franklin et al., 2010; Ignácio et al., 2017; Weiss et al., 2011). While many of these studies are purely correlational, the use of pharmaceuticals has strengthened the link between aberrant behaviour induced by ELS and differential epigenetic regulation. For example, 3 h of maternal separation per day from PND1 to PND10 leads to increased depressive-like behaviours including increased time spent immobile in the forced swim test, and reduced locomotor activity in the open field, in addition to increased Hdac and Dnmt activity in the hippocampus and nucleus accumbens. However, both the depressive-like behaviours and the increased Dnmt activity in the hippocampus can be rescued by administering the antipsychotic quetiapine (Ignácio et al., 2017). Perhaps downstream of its broader impact on epigenetic regulators in the hippocampus, periods of maternal separation effects the epigenetic state of *Bdnf*, a gene whose expression has been linked to depressive-like behaviours. ELS results in an upregulation of Mecp2 at the Bdnf IV promoter, decreased H3 and H4 acetylation at the Bdnf IV promoter, and a decrease in overall Bdnf expression and Bdnf IV expression, all likely contributing to the reduced Bdnf expression also observed (Seo et al., 2016). The aberrant epigenetic marks and reduced Bdnf could be rescued by chronic treatment with an anti-depressant, escitalopram, suggesting a potential mechanism for its anti-depressant actions (Seo et al., 2016). In addition to its effects in hippocampus, ELS also leads to widespread changes in epigenetic regulation in the adult amygdala including increased *Dnmt3a* and Mecp2, decreased Rest, and increased H3K9ac, H3K9me2, H3K9me3, H3K14ac, H3K4me2, and H3K4me3 (Karen and Rajan, 2019).

Exposure to certain ELS paradigms can modulate susceptibility and resilience to future stress exposure in adulthood (Kronman et al., 2021; Marrocco et al., 2019; Peña et al., 2017; Reshetnikov et al., 2021; Zhang et al., 2015). Three hours of maternal separation between PND2 and PND14 leads to increased susceptibility to CSDS in adulthood, with these mice presenting increased anxiety-like behaviours in the elevated plus maze compared to mice exposed to CSDS without a history of ELS (Reshetnikov et al., 2021). The increased susceptibility to CSDS following ELS was associated with increased adrenal corticosterone levels and altered levels of a marker of active gene transcription, H3K4me3, throughout the genome, although this only corresponded to expected changes in gene transcription in two genes related to circadian rhythm and glutamate signalling (*Dbp* and *Sorcs3*). Epigenetic changes related to susceptibility and resilience have also been found outside the PFC in the nucleus accumbens. A recent study by Kronman et al. (2021) discovered that H3K79me2 dynamics within the D2 medium spiny neurons (MSNs) of the nucleus accumbens plays an important role in the modulation of future susceptibility to stress after ELS-exposure. In this study, mice were exposed to a variation of the maternal separation paradigm involving maternal separation for 4 h a day from P10 to P17 combined with limited nesting material. This manipulation increases susceptibility to future chronic social defeat stress (CSDS) without causing long-term depressive-like behaviours on its own (Kronman et al., 2021; Peña et al., 2017). They found that ELS resulted in down-regulation of H3K79me2 in D2 MSNs of the nucleus accumbens, as well as altered expression of the enzymes responsible for writing (Dot1L) and erasing (Kdm2B) this methylation in males, with some aspects of this phenotype also present in females. Importantly, knockdown of *Dot1L*, or overexpression of *Kdm2b* in D2 MSNs could reverse the behavioural susceptibility resulting from ELS, and overexpression of *Dot1L* and knockdown of *Kdm2b* in these neurons could induce behavioural susceptibility in normally reared mice suggesting a causal link between the aberrant epigenetic regulation described and the behavioural output related to stress susceptibility (Kronman et al., 2021). This same ELS treatment also induced increased expression of a stimulus-dependent H3 gene, *H3f3b*, in the nucleus accumbens, suggesting increased histone variant turnover/dynamics in this brain area (Lepack et al., 2016).

Long-term effects of ELS have been induced in the absence of maternal separation by using a scarcity-adversity model that involves raising pups in an environment with a wire grid bottom, and limited nesting material, between the ages of PND2-12. This results in a blunted corticosterone response when subjected to an acute forced swim stress in adulthood (Marrocco et al., 2019), a phenotype which mirrors that which is observed in some depressed patients (Huber et al., 2006; Stetler and Miller, 2005). This treatment also resulted in increased baseline expression of H3K9me3, a repressive histone marker (Kouzarides, 2007), in CA1 and CA3 subregions of the hippocampus compared to

controls (Marrocco et al., 2019). Interestingly, exposure to an acute stressor in male mice resulted in a downregulation of H3K9me3 in mice exposed to ELS, but an upregulation in controls (Marrocco et al., 2019), a finding that further highlights that ELS may affect the epigenetic response to subsequent stressors, a mechanism that could underlie resilience or susceptibility to disease (Kronman et al., 2021; Marrocco et al., 2019).

While the studies presented above focused on males, it is clear that at the level of the epigenome, genome and behaviour, ELS affects males and females differently (Alyamani and Murgatroyd, 2018; Coley et al., 2019; Goodwill et al., 2019; Kalinichev et al., 2002; Viola et al., 2019; White et al., 2020). To further investigate potential causes for the observed sex differences, Keller et al. (2019) investigated whether ELS paradigms could cause dams to treat males and females differently (Keller et al., 2019). Using a scarcity-adversity model of low nesting material, they found that, specifically in this adverse early environment, females received more maltreatment from the dams than males. This is an important consideration, since differences in maternal care are known to have a long-term impact on epigenetic regulation (Champagne and Curley, 2009; Riyahi et al., 2019; Weaver et al., 2004) but it is often difficult to tease apart whether epigenetic and behavioural sex differences observed after postnatal stress are a direct result of the exposure to the stressor or if they, in part, can stem from environmental factors related to differential treatment from the dams.

Maternal or paternal ELS can additionally lead to the inheritance of behavioural phenotypes related to susceptibility and resilience to stress in the offspring (Coley et al., 2019; Franklin et al., 2010; Gapp et al., 2014, 2016; Rodgers et al., 2013; Roth et al., 2009; Weiss et al., 2011). Since the stress experience does not alter the DNA sequence of the parents, this inheritance must occur through epigenetic mechanisms, alterations in maternal care, or a combination of these factors. Mounting evidence proposes that sperm RNAs, both small RNAs and long non-coding RNAs, are involved in the transgenerational transmission of stress (Gapp et al., 2014, 2020; Rodgers et al., 2013, 2015). Causal evidence for the role of small RNAs and long non-coding RNAs in the transgenerational transmission of stress is provided from experiments involving the injection of these RNAs into control female oocytes. These RNAs can either be collected from treated male mice, be specific miRNAs identified to be dysregulated in treated male mice, or be antisense strands that neutralize identified dysregulated miRNAs (Gapp et al., 2014, 2020; Rodgers et al., 2013, 2015; Wang et al., 2021).

However, research to this point has highlighted that transgenerational transmission of stress is complex, and there are differences between generations as well as between sexes (Coley et al., 2019; Franklin et al., 2010; Zaidan and Gaisler-Salomon, 2015). A study by Franklin et al. (2010) used a maternal separation model of early life stress (maternal separation with unpredictable stress; MSUS) in C57B1/6J mice to investigate the inter- and transgenerational transmission of behavioural alterations, while also investigating epigenetic changes caused by this variable stressor in the male germline. They found increased methylation in the promoter-associated CpG islands of *Mecp2* and *Cnr1* and decreased methylation of *Crfr2* in F1 MSUS sperm (Franklin et al., 2010) and in female F2 MSUS cortex. Similar results were found in F2 MSUS sperm except that no significant change in *Cnr1* methylation was found (Franklin et al., 2010). While the mechanism for the observed parallel between germ cell and subsequent offspring was not found, examples of incomplete erasure of DNA methylation across generations have been shown (Hackett et al., 2013; Tang et al., 2015). Maternal separation in rats results in increased methylation of the *Bdnf* exon IV promoter region in the dorsal hippocampus in both males and females, but only decreased *Bdnf* expression in females, showing that differences in methylation do not always translate to differences in expression; differences at the protein level were not investigated in this study (Coley et al., 2019). Increased *Bdnf* methylation and decreased *Bdnf* expression was also observed in both male and female offspring of ELS breeding pairs (Coley et al., 2019). Increased *Bdnf* methylation, associated with decreased *Bdnf* (exon IX), as a result of ELS is also observed in the mouse PFC in both the animals exposed to the stress and in the offspring of females exposed to the stress (Roth et al., 2009). This is true even when ELS offspring are cross-fostered to untreated female dams, suggesting that this transmission is not due to changes in maternal care received by the pups. However, altered responses from the offspring to the dam resulting in different maternal care provided cannot be ruled out with this type of cross-fostering design (Roth et al., 2009).

The intergenerational transmission of DNA methylation resulting from ELS is paralleled in the transmission of stress-induced behavioural phenotypes (Coley et al., 2019; Franklin et al., 2010). F1 MSUS males, but not females, spend more time floating during the forced swim test (Franklin et al., 2010). Interestingly, this depressive-like behaviour was transmitted to F2 female and F3 male offspring. Anhedonia, another depressive-like behaviour, was present only in F1 MSUS males, and did not get transmitted to future generations (Franklin et al., 2010). F1 MSUS males and F2 MSUS females exhibited a deficiency in behavioural control with a shorter latency to enter aversive areas of behavioural arenas (Franklin et al., 2010). It is also important to note that ELS can also lead to inheritance of both positive and negative traits in the offspring (e.g., inheritance of resilience after chronic stress exposure in the parental generation; (Franklin et al., 2011), and that transmission of altered methylation induced by ELS is, at least in part, reversible by paternal enrichment (Gapp et al., 2016).

4. The impact of adolescent stress on epigenetic regulation

Adolescence is a significant period of brain development and, perhaps as a result, adolescents are thought to be more sensitive to epigenetic and behavioural changes following stress exposure compared to adults (Rowson et al., 2019). For example, Lander et al. (2017) compared the effects of stress induced by social isolation during mid-adolescence and adulthood, and found that mice stressed in adolescence were particularly affected (Lander et al., 2017). Mice stressed at adolescence showed physiological effects including decreased weight gain, and behavioural effects such as increased social and object exploration, and impaired reversal learning and extra-dimensional set-shifting (EDSS) in the water T-maze compared to controls, but mice stressed in adulthood were not affected in these measures. Similar susceptibility to adolescent stress was observed using CSDS (Mouri et al., 2018). One day of social defeat in adolescence was sufficient to induce social avoidance but 10 days of social defeat during adulthood was required to develop the same impairment, and the effects were more persistent when the stress was performed in adolescent mice. The long-term behavioural deficits resulting from adolescent stress have been associated with changes in histone acetylation. CSDS in adolescence results in a significant downregulation of total Bdnf and isoform IV transcripts, and increased levels of H3K9me2, but not H3K9ac or H3K4ac, proximal to the Bdnf IV promoter in the medial PFC (Xu et al., 2018). Similarly, inescapable foot shock stress (IFS) experienced during adolescence also results in increased H3K9me2 and Bdnf down-regulation in the hippocampus and PFC (Zhao et al., 2020), and daily predator odour exposure during adolescence increases acetylation of H3, but not H4, at the promoter of the monoamine oxidase A gene in the PFC (Márquez et al., 2013). This points to an important role for H3 post-translational modifications in the long-term impact of adolescent stress, a finding which is further supported by the fact that antidepressant treatment with tranylcypromine rescued aberrant Bdnf expression, histone H3 methylation, and the chronic inflexibility observed in stressed mice (Xu et al., 2018).

Within the adolescent period, there may be specific developmental windows that are critical for the effects of stress on epigenetic regulation of brain function. In support of this suggestion, adolescent isolation stress in both male and female mice that were additionally genetically at-risk for neuropsychiatric-like disorders leads to schizophrenia-like and depressive-like behaviours including impaired prepulse inhibition

and forced swim test performance (Niwa et al., 2013). Underlying these behavioural deficits was a significant decrease in dopamine levels and this was associated with increased HPA axis responsivity, increased DNA methylation of the tyrosine hydroxylase (*Th*) promoter, increased DNA methylation in an intronic glucocorticoid response element (GRE) of the *Bdnf* gene and decreased methylation of an intronic GRE of the *Fkbp5* (Niwa et al., 2016) in VTA neurons that project to the frontal cortex. Administration of RU486, a glucocorticoid receptor antagonist, during weeks 5–6 successfully normalized the effects of stress on behaviour, dopamine levels, and the epigenetic state of the *Th*, *Bdnf*, and *Fkbp5* genes. These findings suggest that the period from 5 to 6 weeks of age represents a developmental stage when epigenetic regulation related to the development of the dopaminergic system may be particularly sensitive to glucocorticoids. In addition to sensitive periods within adolescence, there is also evidence that sex influences how adolescent stress affects the brain. A study by Rowson et al. (2019) specifically looked at the sex differences seen after chronic stress exposure during adolescence. They found that females exposed to chronic adolescent stress showed a significant global reduction in DNA methylation levels in the hippocampus, but males did not. Together, these findings suggest that while adolescence is a developmental period that is particularly sensitive to stress insults, several factors, including the timing of stress exposure, sex, and the combination of stressors experienced, interact to produce unique effects on behaviour and cognition through a combination of changes in corticosteroid function, neurotransmission, and epigenetics.

Similar to findings resulting from postnatal stress, there is evidence for sex-specific inter- and trans-generational inheritance of adolescent stress (Zaidan and Gaisler-Salomon, 2015). Corticotropin releasing factor type 1 (Crf1) expression was increased in stressed females, as well as the neonate F1 offspring, but was decreased in the brain of male and female neonate F2 offspring (Zaidan and Gaisler-Salomon, 2015). This was also true for corticosterone levels and the authors proposed that these differences between two generations of offspring may be due to a combination of altered maternal care and a potential adaptive response or mechanism to stress across generations (Zaidan and Gaisler-Salomon, 2015). Chronic social instability during adolescence and a brief period of early adulthood (PND27-76) results in both social avoidance and anxiety-like behaviours in the open field and elevated plus maze and similar anxiety-like behaviours and social avoidance were observed in female offspring of sires who themselves did not display any behavioural deficits (Saavedra-Rodríguez and Feig, 2013). This intergenerational effect is similar to social anxiety observed in mice exposed to MSUS early stress, where the males act as 'silent' carriers of a behavioural deficit (Franklin et al., 2011). Although the mechanism for this is not known, it has been suggested to be the result of an epigenetic mechanism (Franklin et al., 2011; Saavedra-Rodríguez and Feig, 2013).

5. The impact of adult stress on epigenetic regulation

Findings from studies looking at the impact of chronic stress during adulthood highlight differential histone acetylation as a possible mechanism. Li et al. (2017) used a CUS model of depression in male Sprague-Dawley rats and measured the expression levels of two histone acetylation regulators, Hdac5 and Cbp, as well as the acetylation levels of H3K14, H3K23, and H4K16, a sub-set of lysine residues known to be important for transcription (Li et al., 2017). The CUS-group had reduced levels of H3K14ac, H3K23ac, and H4K16ac, potentially as a result of higher Hdac5 mRNA and protein, and lower Cbp mRNA and protein present in forebrain areas (Li et al., 2017). Viana Borges et al. (2019) further corroborated these findings, in part, when they reported that adult male Wistar rats exposed to CUS had reduced H3K9ac in hippocampus, and that CUS in combination with isolation housing also showed an upregulation of *Hdac5*, although this effect was buffered in pair-housed animals (Viana Borges et al., 2019). Causal evidence for an important role of Hdac5 in the long-term behavioural impact of chronic stress has also come from experiments using CSDS models in mice (Covington et al., 2009; Renthal et al., 2007). CSDS results in depressive-like behaviour, social avoidance and downregulates *Bdnf* transcripts III and IV, but chronic imipramine administration (a tricyclic antidepressant) can reverse this downregulation, potentially as a result of increased histone acetylation in male mice (Tsankova et al., 2006). The increased acetylation observed after chronic imipramine treatment was associated with a downregulation of *Hdac5*, and viral-mediated *Hdac5* overexpression prevented the therapeutic effects of imipramine, further suggesting an important role for Hdac5 in depressive-like behaviour, resilience to disease and/or susceptibility to neuropsychiatric disease, at least in male rodents (Tsankova et al., 2006). Evidence that overexpression of Hdac5 and downregulation of certain Bdnf transcripts may be involved in depressive-like behaviour is not limited to adult stress, as shown by the study by Seo et al., 2016; See section 3.0-The impact of early-life stress (ELS) on epigenetic regulation).

To strengthen the correlation between the epigenome and behaviour, studies have incorporated concepts of naturally-occurring individual differences related to susceptibility and resilience to their analyses. Male mice that are susceptible or resilient to CSDS are differentially impacted at the level of the epigenome suggesting a behavioural correlation to the mechanism. Susceptibility has been associated with decreased expression of a protein that likely regulates synaptic structure, RAS-related C3 botulinum toxin substrate 1 (Rac1) in the nucleus accumbens, as this was observed in male mice susceptible to the depressive-like effects of CSDS, and in mice exposed to social isolation stress (Golden et al., 2013; Wilkinson et al., 2009). This change is potentially mediated by a stress-induced repressive chromatin state (i.e., reduced H3 acetylation, increased H3K9me3, increased H3K27me3) of the promoter region proximal to its transcriptional start site (Golden et al., 2013; Wilkinson et al., 2009). Importantly, chronic treatment with MS-275, an Hdac inhibitor, can reverse both the depressive-like behaviours and the change in Rac1 expression in male mice exposed to CSDS further linking depressive-like behaviours and changes in epigenetic regulation (Golden et al., 2013).

However, mice that show limited or no behavioural response to CSDS also show differential epigenetic regulation compared to control mice suggesting that resiliency is not just the absence of an effect. Mice resilient to CSDS have increased delta-Fosb expression in D1-MSNs while susceptible animals have increased delta-Fosb expression in D2 MSNs (Lobo et al., 2013). Causal evidence was provided by fusing *Fosb* to G9a to induce gene-targeted histone methylation in D1-MSNs, or by fusing *Fosb* to p65 to induce gene-targeted histone acetylation in D2 MSNs (Hamilton et al., 2018). This gene-specific artificial epigenetic manipulation promotes stress susceptibility, while resilience can also be induced if these epigenetic manipulations are performed in the opposite sub-group of MSNs (Hamilton et al., 2018). These findings suggest that epigenetic control of *Fosb* in nucleus accumbens is sufficient to bias a behavioural phenotype towards either stress susceptibility or resilience. Additionally, mice resilient to CSDS have decreased expression of a gene encoding a DNA methyltransferase, *Dnmt3a*, in the PFC, and of a gene encoding the histone methyltransferase *G9a* in the hippocampus (Mallei et al., 2019). The effect of CSDS on *Dnmt3a* in the cortex appears to be subregion specific, as a similar CSDS protocol induced an increase in *Dnmt3a* in whole cortex which was not dependent on the stress susceptibility or resilience of the animal (Bilen et al., 2020).

Similar to findings following CSDS, adult male mice exposed to repeated restraint stress exhibit depressive-like behaviors and this was associated with a downregulation of *G9a*, and reduced H3K9me2 at the oxytocin and vasopressin promoters in the basolateral amygdala, effects that could be reversed by exercise (Kim et al., 2016). CSDS also decreased *Setdb1*/Setdb1, which is primarily responsible for tri-methylating lysine 9, specifically in adult male cortex of susceptible mice, and this was associated with a decrease in H3K9me3 (Bilen et al., 2020). It was possible to promote resilience to the behavioural effects of CSDS and limit epigenetic changes by treating mice with a precursor to a

methyl donor, methionine, during the defeat stress to restore methylation levels (Bilen et al., 2020). At this time, a number of studies discussing the involvement of histone methylation in the stress response, stress resilience and depression suggest that regulation of H3K9 methylation, and its associated gene repression, likely plays an important role in stress susceptibility and resilience albeit in a region-specific and cell-specific manner (Bilen et al., 2020; Hamilton et al., 2018; Kim et al., 2016; Mallei et al., 2019; Wilkinson et al., 2009).

H3K9 modifications have also been implicated in depressive-like behaviors by research focusing on a relatively new type of histone mark dependent on beta-hydroxybutyrate (Bhb) called beta-hydroxybutyrylation (H3K9bhb; Chen et al., 2017). Beta-hydroxybutyrate and H3K9bhb were reduced in hippocampus following chronic restraint stress and this could be ameliorated by chronic treatment with the antidepressant imipramine. Both ketogenic diets and exercise can increase Bhb in vivo (Freeman and Kossoff, 2010; Sumithran et al., 2013) suggesting that these environmental factors may be reducing depressive-like behaviours by reversing the impact of stress on H3K9bhb, although this link has yet to be proven. Social defeat stress also alters the regulation of a recently discovered histone modification called crotonylation (Kcr). Kcr is negatively regulated by chromodomain Y-like protein, a histone methyllysine reader that largely acts as a transcriptional repressor (Liu et al., 2019). CSDS reduced histone Kcr levels and increased chromodomain Y-like protein (Cdyl), in the medial PFC, but only for susceptible mice (Liu et al., 2018). Interestingly, a strong correlation was found between social avoidance behaviour of susceptible mice and *Cdyl* levels (Liu et al., 2018). It was further suggested that depressive-like behaviours resulting from CSDS caused a dysregulation in a pathway initiated by the increase in Cdyl, associated with a reduction in Kcr and H3K27me3 and the ultimate downregulation of *Vgf* and other genes. This study underlines the importance of the continued discovery of epigenetic marks and reminds us that we have likely only scratched the surface in terms of the complexity of epigenetic regulation and its response to stress.

As was shown in response to ELS, histone variant turnover/dynamics, specifically H3.3 dynamics in the nucleus accumbens, appears to have a critical role in susceptibility to depressive-like behaviors after exposure to CSDS (Lepack et al., 2016). Lepack et al. (2016) found that mice susceptible to the behavioural effects of CSDS had increased H3.3 turnover rates in the nucleus accumbens, and that viral-mediated inhibition of H3.3 turnover led to resilience to CSDS in young adult male mice. However, as pointed out by the authors, a limitation of this study was that it did not investigate differences in these histone dynamics between D1-and D2-MSNs in the nucleus accumbens (Lepack et al., 2016). It would be pertinent to differentially explore epigenetic mechanisms between D1-and D2-MSNs in the nucleus accumbens, seeing as they appear to play different roles in the stress response, with D1-MSN activation being associated with resilience and D2-MSN activation being associated with susceptibility (Chandra et al., 2017; Francis et al., 2015; Lobo et al., 2013; Hamilton et al., 2018; Kronman et al., 2021; Zhang et al., 2015).

Mecp2, a protein that reads DNA methylation to regulate gene expression, also appears to play an important role in the mechanisms determining stress resilience or susceptibility in adults. Mecp2 normally functions as a transcriptional repressor but has also been found to activate transcription in some cases (Chahrour et al., 2008). Male mice carrying a functional alteration in the Mecp2 protein that made it less active, were more susceptible to stress (Cosentino et al., 2019). These mice developed hypersensitivity, elevated corticosterone levels, altered gene expression, and other PTSD-like symptoms after exposure to high-intensity footshocks (Cosentino et al., 2019). More evidence for the involvement of Mecp2 in stress susceptibility comes from male BALB/c mice, a mouse strain that is more susceptible to chronic ultra-mild stress (CUMS) than male C57BL/6 mice (Uchida et al., 2011). BALB/c mice have differential histone modifications and DNA methylation in a promoter region of the glial-derived neurotrophic factor gene, *Gdnf*, and this is associated with differential Mecp2 and Hdac2 binding, ultimately leading to decreased H3 acetylation and *Gdnf* translation (Uchida et al., 2011). While both of these studies show a role for Mecp2 in susceptibility to stress, it should be noted that both studies only looked at males, highlighting the need for more research in females.

While much of the past research has focused on traditional epigenetic mechanisms like histone acetylation and DNA methylation, there have been increased numbers of studies focusing on the role of miRNAs in the long-term effects of stress and their association with depression. miRNAs provide a mechanism to quickly regulate gene transcription and protein translation, and they have been implicated in stress susceptibility (Allen and Dwivedi, 2020; Lopizzo et al., 2019; Torres-Berrío et al., 2017, 2021), the intergenerational transmission of stress (Gapp and Bohacek, 2018), as well as depression or depressive-like behaviors (Lou et al., 2019; Roy et al., 2017; Torres-Berrío et al., 2017, 2021; Wang et al., 2017; Xu et al., 2017). Here, we focus on two miRNAs that have been causally linked to the impact of stress and the development of depressive-like behaviours (miR-124, and miR-218), but there is evidence suggesting that many other miRNAs, including miR-16, miR-135, miR-182, miR-206, miR-223, and miR-451, are also differentially regulated in depression models (Bahi et al., 2014; Bai et al., 2012; Chang et al., 2020; Gu et al., 2019; Gururajan et al., 2016; Higuchi et al., 2016; Issler et al., 2014; Issler and Chen, 2015; Lepack et al., 2016; Lotan et al., 2018; Lou et al., 2019; Sillivan et al., 2020; Song et al., 2015; Tavakolizadeh et al., 2018; Torres-Berrío et al., 2017, 2020, 2021; Yang et al., 2020).

Multiple targets of miR-124 have been identified and implicated in depression via differential regulation in depression models, including Hdac4, Hdac5, glycogen synthase kinase 3 β (Gsk3β), glucocorticoid receptor (GR), Creb1 genes, and Bdnf genes (Liu et al., 2020; Xu et al., 2017; Yang et al., 2020). Hippocampal miR-124 has been shown to be critical for resilience or susceptibility to CUMS in adult male mice (Higuchi et al., 2016). The mice exposed to CUMS show an increase in depressive-like behaviours and a decrease in miR-124 expression in the hippocampus. However, overexpression or inhibition of miR-124 in non-stressed controls, through viral-mediated hippocampal overexpression and intrahippocampal infusion of an inhibitor, bi-directionally affected the depressive-like behaviours (Higuchi et al., 2016). The overexpression and inhibition of miR-124 led to behavioural resilience and susceptibility to the effects of a milder stress paradigm, respectively, suggesting a pivotal role for hippocampal miR-124 in stress resilience (Higuchi et al., 2016). The authors proposed a mechanism, where hippocampal miR-124 post-transcriptionally regulated *Hdac4*, *Hdac5*, and *Gsk3β* expression, thus affecting resilience since inhibition of these targets of miR-124 had antidepressant effects (Higuchi et al., 2016). Moreover, the resilience conferred by miR-124 overexpression was associated with reduced dentate gyrus granule neuron spine loss after stress exposure, and miR-124 inhibition was associated with spine loss after exposure to a milder stressor (Higuchi et al., 2016). This suggests that stress-induced changes in dendritic plasticity in the dentate gyrus may be modulated with miR-124 (Higuchi et al., 2016). In contrast, 21-days of exposure to social defeat stress led to an upregulation of miR-124 expression and a downregulation of Bdnf in the hippocampus of male rats, which was associated with an increase in depressive-like behaviors (Bahi et al., 2014); lentiviral inhibition of miR-124, and resultant reversal of the decreased Bdnf, resulted in an antidepressant effect. These findings are opposite to the findings from Higuchi et al. (2016), which could be the result of the difference in the severity of the stress treatment (mild versus severe) or different species (mouse versus rat). Altered synaptic plasticity, specifically impaired synaptic plasticity in the hippocampus and PFC, and enhanced synaptic plasticity in the amygdala, is consistently observed in major depressive disorder (MDD) and miRNAs are argued to play an important role in its regulation (Liu et al., 2017, 2020; Marsden, 2013).

Differential regulation of miR-218 has additionally emerged as a mediator of stress-induced depression in both adolescence and

adulthood (Torres-Berrío et al., 2017, 2020, 2021). In male mice, upregulation and downregulation of miR-218 in the medial PFC led to resilience and susceptibility to social defeat stress, respectively (Torres-Berrío et al., 2020). The mechanism for this is not clear, but miR-218 is known to downregulate *Dcc*, a netrin-1 guidance cue receptor gene that has been previously linked to MDD; miR-218 expression is typically decreased and *Dcc* expression increased in this disorder (Manitt et al., 2013; Torres-Berrío et al., 2021). Interestingly, a study by Torres-Berrío et al. (2017), conducted on male mice, suggested that miR-218 regulation of *Dcc* during adolescence may ultimately modulate resilience to stress in adulthood through the role of Dcc receptors in medial PFC maturation during adolescence. Furthermore, upregulation of miR-218 or downregulation of *Dcc* in the medial PFC of adult male mice prevented depressive-like behaviors after exposure to CSDS, whereas downregulation of miR-218 led to increased susceptibility to stress (Torres-Berrío et al., 2017). Similar to miR-124, the role of miR-218 in stress-induced depressive-like behaviors may be linked to its regulation of excitatory synaptic transmission (Torres-Berrío et al., 2020).

The importance of miRNA to depressive-like phenotypes has been further highlighted in a study using five weeks of chronic mild stress to produce depressive-like behaviours and a specific profile of sperm miRNAs and piRNAs that differ from control mice (Wang et al., 2021). The offspring of these mice also show similar depressive-like behaviours, but this behavioural transmission can be reversed by administering synthetic antisense strands to normalize miRNA expression in the zygote. These findings further suggest that abnormal miRNA expression are a causal element in the intergenerational transmission of adult stress-induced transmission of depressive-like behaviours (Wang et al., 2021).

6. Conclusion

Differential epigenetic regulation associated with behavioural changes that occur as a result of stress are evident at all periods of development (see Fig. 1 for a summary of findings discussed in this current review) and are subject to further environmental impact. For example, phenotypes can be rescued using exercise, and the intergenerational transmission of stress can be prevented in some cases through extinction of fear conditioning. Each period of stress has been shown to induce long-term and sometimes multigenerational behavioural changes that include depressive-, and anxiety-like behaviours, with prenatal stress also sometimes inducing a schizophrenia-like phenotype; the exact behavioural phenotype produced depends greatly on the type and duration of the stressor in addition to the developmental time period during which it is applied. It is also important to note that in addition to the negative impact of stress during development, certain stress treatments during development induce resilience to future stressors. There also does appear to be overlap with regards to the epigenetic impact of stress across different periods of development, including increases in *Hdac5* and *Dnmt3a* expression (Fig. 1). Upregulation of *Hdac5* mRNA expression in forebrain areas is observed after CUS exposure in adult rats (Li et al., 2017), and social housing can rescue the increased *Hdac5* expression in adult rats (Viana Borges et al., 2019). Additionally, a downregulation of *Hdac5* is observed in the PFC of adult resilient mice

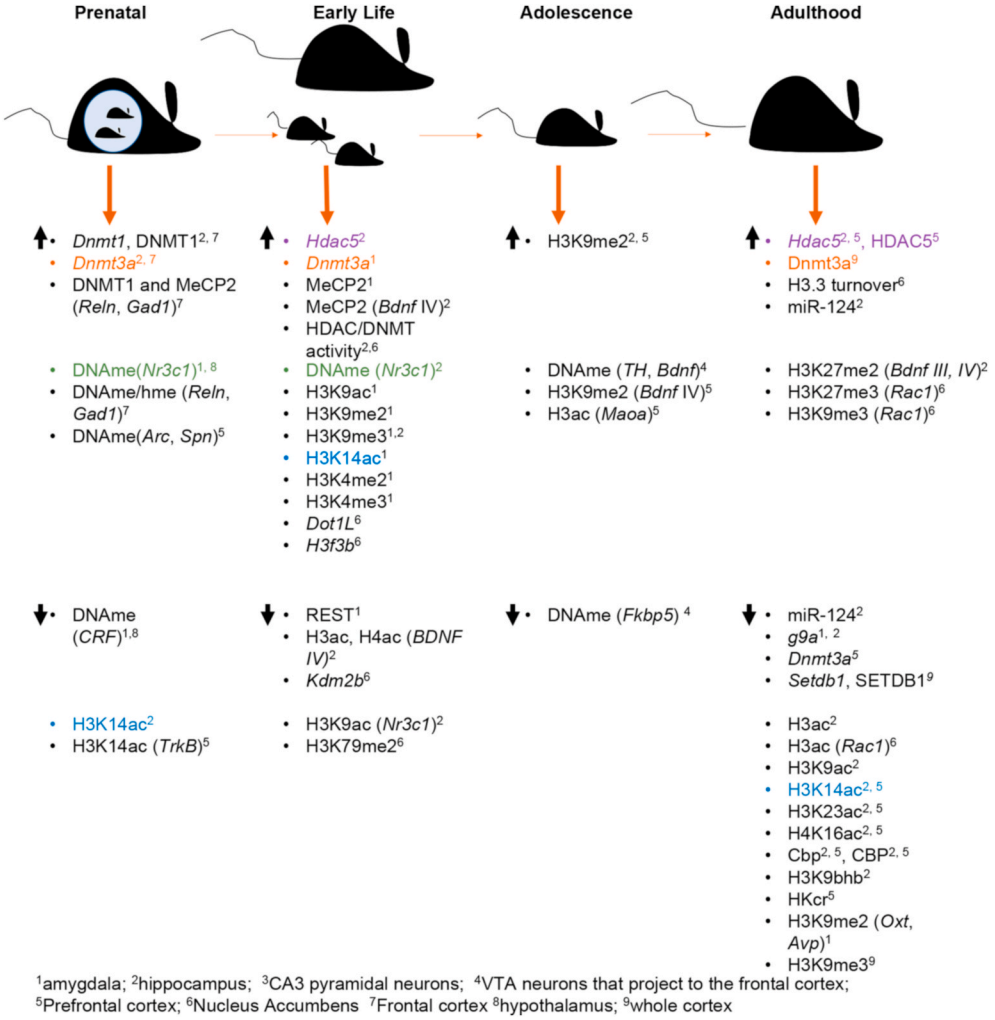

Fig. 1. Summary of epigenetic changes in male rodents occurring after chronic stress exposure during prenatal developmental, postnatal development, adolescence and adulthood, with similarities across developmental periods highlighted. Genes are included in brackets if the modification was linked to a specific gene. Arc, activity regulated cytoskeleton associated protein; DNAme, DNA methylation; DNAhme, DNA hydroxymethylation; Dnmt, DNA methyltransferase; Hdac, histone deacetylase; Mecp2, methyl CpG-binding protein 2; Spn, spinophilin.

(Mallei et al., 2019) and chronic tricyclic antidepressant treatment in young adult mice is associated with Hdac5 downregulation in rodents exposed to CSDS. An upregulation of *Hdac5* mRNA is also found in the hippocampus of male rats exposed to ELS through maternal separation and adult stress through restraint stress (Seo et al., 2016). This suggests that Hdac5 could play an important role in both the stress response and depression. This is further supported by the fact that Hdac5 is found to be a target of miR-124, which is intrinsically implicated in stress-induced depression and synaptic plasticity, thereby providing a possible mechanism through which Hdac5 is regulated after stress exposure (Higuchi et al., 2016). Similarly, stress experienced during prenatal or postnatal development, as well as in adulthood, has been found to increase Dnmt3a expression albeit in different brain areas. The extent to which these mechanisms also play a similar role in human brains is still unclear, but peripheral blood taken from individuals living with depression does have altered expression of histone deacetylases, including increased *Hdac5* (Hobara et al., 2010; Iga et al., 2007).These findings, in concert with those from animal models, may provide an epigenetic link between stress and increased risk of depression. Additional evidence that epigenetic mechanisms can be dysregulated in the human brain following stress is provided by *post mortem* hippocampus tissue taken from individuals that died by suicide, specifically with a history of childhood abuse, in which methylation of NR3C1 is increased, similar to rats with low licking/grooming mothers (McGowan et al., 2009).

We have only begun to understand the significance of epigenetic regulation to the behavioural impacts of stress and stress-related psychiatric disease, especially with the identification of new epigenetic marks with transcriptional implications. In particular, epigenetic research using rodents has suffered from a lack of tools available to specifically manipulate epigenetic marks and this has resulted in a paucity of causal data linking specific mechanisms and behavioural outcomes of stress across varying developmental periods. While some assumptions can be made based on correlative data, it has been difficult to draw firm conclusions about a direct impact of specific changes in epigenetic regulation and subsequent behaviour. It also seems that the effects of stress at every point of development can be transmitted to offspring across generations, with some evidence suggesting that epigenetic changes in the germline underlying transmission. Interestingly, there is some evidence for the effects of ELS on sperm miRNAs in humans, suggesting that epigenetic transmission of stress may occur via similar mechanisms in rodents and in humans (Dickson et al., 2018). However, animal studies of epigenetic inheritance have shown that traits are inherited differently depending on the generation and on sex, and it is difficult to differentiate between changes resulting from epigenetic inheritance and changes stemming from differences in maternal care due to stress treatments.

Lastly, a critical and significant gap in the rodent literature concerns sex differences and in particular the impact of stress on females. Despite evidence for the differential effects of stress in males and females, most of the literature includes only male subjects (Shansky and Murphy, 2021; Woitowich et al., 2020), and our knowledge of the impact of stress on females is limited. This has been further exacerbated by the widespread use of social defeat paradigms which are largely performed in males, highlighting the need for the development of new ethologically-valid models of chronic stress and depression.

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Declaration of competing interest

None to declare.

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This work was completed at Dalhousie University, which is located in Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2022.100434.

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