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Review

Post-translational histone modifications and their interaction with sex influence normal brain development and elaboration of neuropsychiatric disorders☆

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ABSTRACT

Sex differences in the risk for and expression of various brain disorders have been known for some time. Yet, the molecular underpinnings of these sex differences as well as how sex modifies normal brain development are still poorly understood. It has recently become known that epigenetic mechanisms play an essential role in establishing and maintaining sex differences in neurodevelopment and disease susceptibility. Epigenetic mechanisms such as post-translational modifications of histones (histone PTMs) integrate various hormonal and external environmental influences to affect genomic output, and this appears to occur in a sex-dependent manner. The present review aims to highlight current understanding of the role of histone PTMs in the sexual differentiation of the brain under normal conditions and how sex-specific modulation of histone PTMs may be involved in psychiatric conditions including autism spectrum disorder (ASD), schizophrenia, and major depressive disorder (MDD). The role of sex chromosome genes as sex-specific histone modifiers and their importance in sexually differentiating the brain will be discussed. Further, the contribution of sex-specific histone PTM marks in the placenta in programming the sexually dimorphic developmental course of the brain and susceptibility to diseases/disorders will be reviewed. Prenatal programming may have a long-lasting effect on the adult brain and behavior but due to the interaction of histone PTMs and its modifiers with fluctuating hormone levels and external influences over the lifespan, the process remains dynamic. Although a few studies indicate an association between sex and histone PTM-related mechanisms in ASD, schizophrenia, and MDD, more research is needed to fully appreciate the interactive effects of histone PTMs and sex in the development and manifestation of these disorders. Understanding the interactions between sex and histone PTMs will advance our understanding of psychiatric disorders and potentially guide development of future treatments tailored specifically to each sex.

1. Introduction

Epigenetics, defined as regulation of gene expression by introducing functional modifications in DNA without any alteration in the genomic sequence, has emerged as an integral component of brain development, aging and various central nervous system (CNS) disorders [1,2]. The epigenome, consisting of epigenetic marks such as DNA methylation and histone post-translational modifications (PTMs), mediates the influence of the environment on the genome and regulates the cascade of transcriptional programs crucial for both stability and plasticity of neuronal circuits [3]. Epigenetic plasticity at all stages of brain development and aging has important implications for the etiology and potential treatment of brain-related disorders [4–7]. Dysregulated epigenetic machinery during critical stages of prenatal and postnatal

Abbreviations: 5-HT, 5-hydroxytryptamine; ADP, adenosine diphosphate; ASD, autism spectrum disorder; E18 (or 12), embryonic day 18 (or 12); H3K, histone 3 lysine; HAT, histone acetyl transferase; HDAC, histone deacetylase; Histone PTMs, post-translational modifications of histones; HPA, hypothalamic pituitary adrenal axis; Kdm, lysine demethylase; Kmt, lysine methyltransferase; LPS, lipopolysaccharide; MDD, major depressive disorder; NAD, nicotinamide adenine dinucleotide; PND0, postnatal day 0; PND6, postnatal day 6; PND60, postnatal day 60; SET, Su(var)3–9, enhancer-of-zeste and trithorax

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development can reprogram key functional genes, altering the normal course of brain development, maturation and aging. The functional consequences of resulting aberrant gene function may increase the risk for psychiatric or neurodegenerative disorders [8–10]. Epigenetic modifications critical for normal brain development are also integral to organization and maintenance of sex differences in the brain [11]. Epigenetic mechanisms are linked to expression of sex differences in virtually every aspect of brain development [12–14] and thus, it is not surprising that males and females display differences in susceptibility, onset, pathogenesis, and severity of a variety of brain disorders. Unfortunately, our understanding of etiology of brain disorders and the origin of sex differences in expression of these disorders is far from clear. One reason for this is lack of complete understanding of the normal course of brain development and maturation in female brains as until recently, the majority of the developmental brain studies have used primarily male subjects. Even in studies where both sexes were used, sex has not been independently considered as a variable influencing various outcomes. In this review, we emphasize that the foundation for sex differences in risk of developing specific brain disorders may be laid during early development and further influenced by sex-specific epigenetic, hormonal signals and external environmental influences occurring throughout life. We will discuss how sex-specific expression of epigenetic machinery genes, particularly those involved in modifying the histone proteins, and the sex-specific deposition of histone marks in the developing fetal brain and placenta may create 'sex-specific epigenetic marks' that may play a role in programming sex-related expression of certain brain disorders. The majority of studies have focused on defining the sex-specific epigenetic profile for DNA methylation and relatively few have investigated the role of histone PTMs in sex-specific outcomes. Since histone PTMs are primary epigenetic modifications involved in regulating chromatin accessibility and transcriptional activity in the brain, this review highlights that more dedicated efforts are needed in the future to more fully understand the contribution of histone PTMs in the establishment and manifestation of sex-specific neurodevelopmental outcomes and development of CNS diseases/disorders.

More than a hundred type of modifications have been identified including variations of acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP-ribosylation, proline isomerization and biotinylation, and a considerable number of combinations of these modifications are possible [15]. The information contained in a single or combination of histone marks determines the functional state of the associated DNA, referred to as the histone code [16,17]. These various histone PTMs together determine the active and silenced (or repressive) chromatin states at both global and gene-specific levels (Fig. 1a and b). Enzymes that establish these modifications on histone tails are called writers or erasers and those recognizing these modifications are called readers which may stabilize the chromatin signature by recruiting other factors [18–20]. For example, histone acetyltransferases (HAT-a writer) acetylate the lysine residues of the histone tails, histone deacetylases (HDAC-an eraser) removes acetyl groups from histones and bromodomain (a reader) recognizes acetylated lysine residues. A specific stimulus or a combination of stimuli may result in the orchestration of histone PTMs at a particular gene, determining the transcriptional output of the associated gene.

Histone PTMs play a significant role throughout brain development, maturation, and aging and dysregulation of histone PTMs and genes/enzymes regulating these marks have been associated with alterations in the normal course of neurodevelopment and with a plethora of neurological and psychiatric diseases/disorders (Fig. 1c) [21–26]. For example, at the time of embryonic stem cell (ESCs) commitment to a neural precursor cell fate, the key developmental genes with bivalent domain containing H3K27Me3 and H3K4Me3, lose the H3K27Me3 mark and are committed to neural fate through upregulation of the demethylase *Kdm6b* and downregulation of the methyltransferase *Ezh2* (enhancer of Zeste 2 Polycomb Repressive Complex 2 Subunit) [27,28]. Reorganization of the histone landscape consisting of the H3K4Me3 mark in prefrontal cortical neurons was shown to occur during the transition from early infancy to later childhood in humans [29]. H3K4Me-associated methyltransferases, demethylases and reader proteins have been shown to be mutated in neurodevelopmental diseases including autism and schizophrenia [30,31]. Histone acetylation, methylation and phosphorylation have been shown to modulate synaptic plasticity and memory formation [32–34]. Histone modifiers have been proposed as potential therapeutic targets to treat age-associated cognitive decline [35,36]. Histone PTMs, through their interaction with the genome and hormonal milieu, have emerged as important players in sexually differentiating the developing brain and regulating the expression of complex behaviors in a sex-specific manner in adulthood [11,37,38]. In the following sections, we will discuss the evidence in support of the role of histone PTMs in shaping sex differences in the brain during early and later developmental stages of life. We will also highlight their potential contribution to sex differences in manifestation of various neurological disorders with a focus on incidence, onset, and progression of psychiatric disorders of autism spectrum disorder (ASD), schizophrenia, and major depressive disorder (MDD).

2. Sexual differentiation of brain and histone PTMs

2.1. Sex chromosome genes and histone PTMs

The primary sex determinants are encoded by the sex chromosomes -XX and XY. Various studies suggest that dynamic epigenetic regulation is important for appropriate temporal expression levels of sex-determining genes [39–41]. Although, fetal gonads either have XX or XY chromosome complements, they are initially bipotential, i.e., have the full ability to differentiate into ovaries or testes. Interestingly, the bipotential nature of gonads is reflected in the chromatin reorganization of key sex-determining genes during the transition to either male or female fate [42,43]. In mammals, the *Sry* (sex-determining region Y) gene, located on the Y chromosome, directs the differentiation of the bipotential fetal gonad towards the male fate versus female fate [44,45]. Several histone PTMs have been identified that activate the Sry gene leading to the development of testis and not ovary. Activation of *Sry* in mice has been associated with deposition of H3K27Ac by the CBP/p300 HATs, *Jmjd1a* (histone demethylase) dependent H3K9Me2 demethylation and enrichment of H3K4Me2, low H3K9Me3 and high levels of H3K4Me3 and H3Ac at its promoter [40,46–48]. *Sry* itself can act as an epigenetic regulator in fetal gonads by interacting with chromatin-modifying complexes. For example, SRY interaction with Kruppel-associated box only (KRAB-O) and Krab-associating protein 1 (KAP1) in fetal gonads at embryonic day 11.5 leads to recruitment of heterochromatin protein 1 (HP1), HDACs and H3K9 methyltransferase, resulting in an inactive chromatin state and repression of female fate-determining genes [42,49–52].

Brain sexual differentiation involves a surge in gonadal hormone, testosterone, during fetal development that results in permanent masculinization of the brain followed by a second surge in testosterone in males at early postnatal stage. Another spike in sex hormones during puberty, in both the sexes, further amplifies the sex differences setting the pathways for sex-dependent behaviors [53,54]. At these stages, the sex differences are the result of epigenetic changes induced by steroid hormones involving changes in histone PTMs that vary by brain region [55,56]. Apart from gonadal hormonal influences, genes on X and Y chromosomes also mediate sex-specific effects in the brain [57,58]. Brain development and function - related genes are highly concentrated on the X-chromosome, and X-linked genes are highly expressed in the brain which indicates that sex-linked genes induced sexual dimorphism in the brain can influence brain functioning to a great extent [57,59,60]. The *Sry* gene regulates brain sexual differentiation through direct or indirect influences via hormones. For example, the *Sry* gene in males (in both mice and humans) is involved in regulating

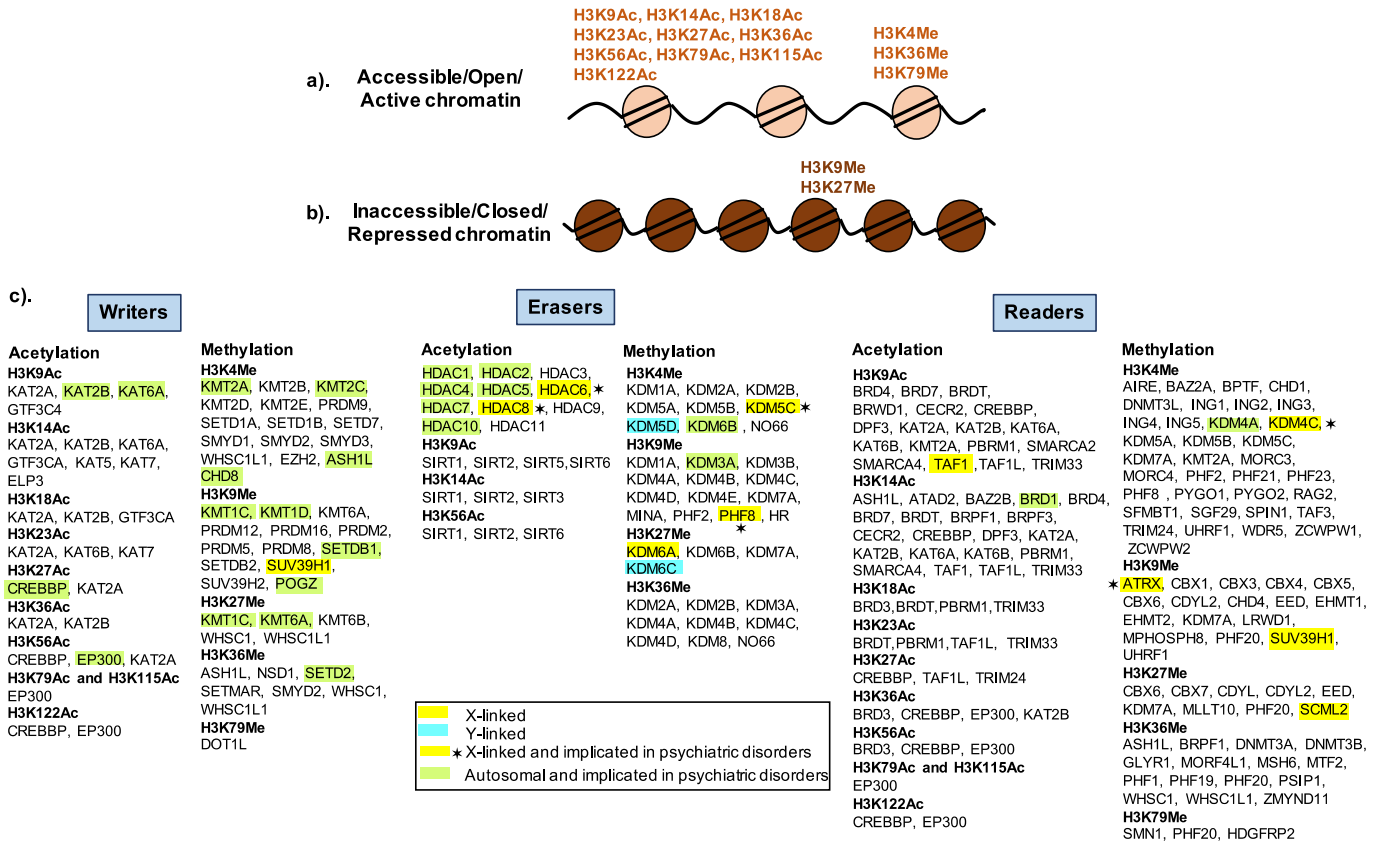

Fig. 1. Schematic diagram showing the role of histone (H3) PTMs (on lysine residue) in regulating chromatin accessibility. Top panel (a) shows post-translational modifications of histone, H3, that are associated with open chromatin structure and facilitate accessibility to transcription factors. Enrichment of these histone PTMs result in gene activation. Middle panel (b) shows post-translational modifications of histone, H3, that are associated with closed chromatin structure and inhibit accessibility to transcription factors. Enrichment of these latter histone PTMs and/or a decrease in PTMs shown in the top panel result in gene repression. Bottom panel (c) shows writers, erasers and readers for different types of histone (H3) acetylation and methylation modifications. X-linked and Y-linked histone modifiers are highlighted in yellow and blue boxes, respectively. X-linked factors or modifiers associated with psychiatric disorders are highlighted with a star. Histone modifiers located on autosomes and associated with psychiatric disorders are highlighted by green box. HDACs1–11 have ambiguous specificity and hence the lysine residues on which they act upon have not been specified here. Post-translational modifications on other amino acid residues like arginine are not shown here.

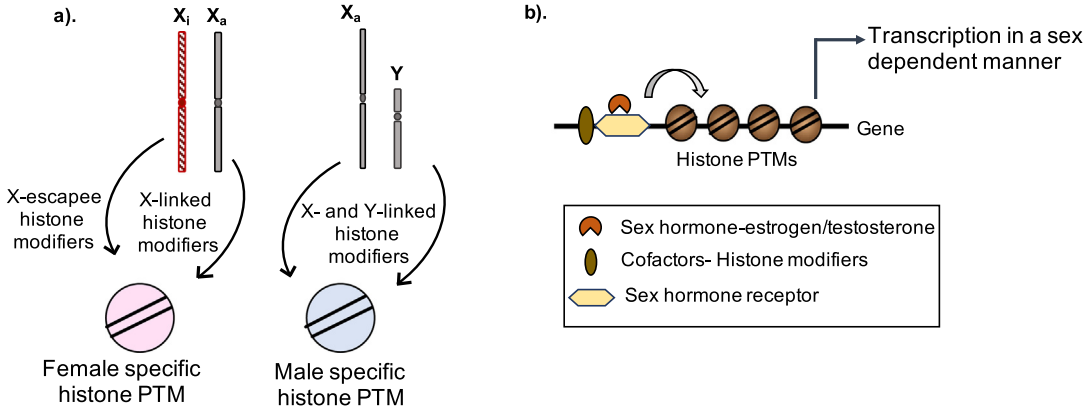

Fig. 2. Histone PTMs and sex. (a) X-linked genes including X-escapees (genes that escape X-inactivation) and Y-linked genes that act as histone modifying enzymes (or histone modifiers) might influence the gene-specific or genome-wide histone PTM landscape in the two sexes differently. X_i – inactive X chromosome, X_a – active X chromosome. (b) Interaction between sex hormones and the histone modifiers that bind to sex hormone receptors can influence the transcriptional output of genes in a sex dependent manner.

catecholaminergic pathways in the midbrain region [61–63]. It has been suggested that *Sry* expression in males may compensate for absence of female associated factor which is known to affect dopamine synthesis in females [62]. However, evidence to support the role of histone PTMs in regulating *Sry* expression in the male brain and disease phenotype are lacking. But as discussed above, histone PTMs do regulate *Sry* expression, and since *Sry* itself acts as an epigenetic regulator in gonads, it would not be surprising to see a similar effect of *Sry* as an epigenetic regulator in the brain. Many X-linked genes that escape X inactivation (X escapees) and Y-linked genes act as histone modifiers and play important roles in brain functioning in both mice and humans (Fig. 2a). *Jarid1c* (*Kdm5c*), an X escapee gene, encodes H3K4 specific

demethylase and is expressed at a higher level in XX than XY cells. Expression of its Y-linked homolog, *Jarid1d* (*Kdm5d*) in XY cells is incapable of compensating for the loss of *Jarid1c* and hence could potentially contribute to sex differences in brain function [57]. *Kdm5c* is highly expressed in brain regions important for cognitive function, and although the role of *Kdm5c* in neurodevelopment is still elusive, mutations in *Kdm5c* have been implicated in several disorders such as autism and intellectual disability [64], both of which are more prevalent in men. Another X-linked gene that escapes X inactivation is *Utx* (*Kdm6a*) and encodes H3K27me3 demethylase. *Utx* is expressed at higher levels during development and adulthood in females than in males in most brain regions, with the exception of the amygdala [57]. The *Utx* homolog on the Y chromosome, *Uty* (*Kdm6c*), appears to be functionally similar to *Utx* [42] but their expression levels and patterns differ in XX and XY brains, suggesting that they may mark genes in a sex-specific manner [57].

We suggest that sex chromosome-linked epigenetic regulators such as histone PTMs writers or erasers are exciting candidates to follow when investigating sex differences in neuronal development and disorders because of their ability to influence autosomal gene transcription regulation that could ultimately lead to sex-specific alterations in the transcriptome. Future studies focused on extensively investigating the roles of these genes in cellular processes critical for brain functioning, in a developmental stage and brain region-dependent manner, may further inform on the functional importance of histone PTMs in sculpting the sexually dimorphic brain.

2.2. Placental/brain axis: sex and histone PTMs

Emerging evidence has led to an appreciation of the role of the placenta in shaping fetal development, including neurodevelopment [65,66]. The placenta is capable of quickly adapting to a changing maternal milieu by regulating its gene expression through epigenetic mechanisms [67,68]. A recent report from Lester et al. [65] describing 17 studies of epigenetic modifications on placental genes and their relationships to human infant behavior supports the emerging concept that the placental epigenome can affect neurodevelopmental trajectories. Undoubtedly, epigenetic processes appear to be key to placental functioning as disruption of the placental epigenome has been associated with abnormal placental development and functioning [69]. Several studies demonstrate that histone PTMs play an important role in mediating normal gene expression and imprinting of genomic loci in the placenta, with effects on brain development [70,71]. For example, HDAC and histone acetyltransferase regulate the expression of a transcription factor, GCMA (glial cell missing homolog 1), which is crucial for regulating *Syncytin*, involved in mediating proper trophoblastic fusion in humans [72]. Histone methyltransferase *G9a* is also involved in placenta-specific imprinting [73]. Several epigenetic machinery genes, including those for histone-modifying enzymes, are expressed in a sex-specific manner during placental development. Expression of *Kdm5c*, an X-linked gene, is higher in female placenta, while expression of Y-linked genes *Kdm5d* and *Uty* is higher in male placenta [66,74,75]. Maternal high fat diet in mice significantly decreases the expression of histone methyltransferases *Kmt1a* and *Kmt2f* in female placenta and *Kmt1b* expression in male placenta in mice [76]. Maternal high fat diet has also been linked with mental illness and increased risk for behavioral disorders in offspring as well as with placental dysfunction in animal models [77], although sex-specific effects of a maternal high fat diet on the brains of offspring have not been consistently observed. The extent to which histone PTMs are involved in mediating the above-mentioned sex-specific effects by altering placental gene regulation in a sex-dependent manner needs to be more fully investigated. It is possible that sex differences in placental transcriptional output due to sex-specific histone PTM signatures at specific gene loci may be involved in regulating the developing brain transcriptome in a sex-specific manner. Despite the knowledge that histone PTMs are crucial for placental gene expression, the manner in which their misregulation in the placenta affects fetal brain development and programming of later life disease risk in a sex-specific manner remains poorly understood. In addition to sex-differences contributed by genes present on sex chromosomes, sexual dimorphism in autosomal gene expression between male and female placenta have been observed in rodents and humans under normal conditions as well as under conditions of altered in utero milieu [78–81]. Although the underlying mechanisms of sexually dimorphic expression of placental autosomal genes are still unknown, the influence of sex chromosomes on autosomal gene expression and sex-specific epigenetic marks on genes may be partly responsible for shaping sexually dimorphic placental gene expression patterns [79] and may have important implications for long-term neurodevelopmental programming.

It has also been proposed that the placenta of one sex might possess a greater ability to respond to *in utero* environmental changes than the other, ultimately affecting the course of neurodevelopment [82]. Supporting this, significant differences in epigenome, transcriptome, proteome, and steroid levels in the placenta, depending on the fetal sex, affect the placental and fetal adaptation to environmental factors such as prenatal stress (PS) [83–85]. Sex-specific differences in neurobehavioral outcomes resulting from PS are programmed by the placenta and placental genes linked to neurodevelopment and infant behavior such as *leptin* (LFP) are epigenetically regulated in a sex-specific manner [85,86], suggesting that the placenta may act as a programmable agent of sex-based disorders [83–88]. Results from several studies indicate that male fetuses have greater risk for later expression of neurodevelopmental disorders than female fetuses following exposure to environmental insults in utero (see [89]) and that the placenta plays a major role in determining this sex-specific vulnerability/resilience [87,90]. Research has begun to explore epigenetic mechanisms related to sex-specific placental programming of disease vulnerability/resilience. Higher levels of DNA methylation in the female placenta compared to male placenta have been proposed to protect the female fetus from dynamic alterations in gene expression due to environmental exposures such as prenatal stress [91]. Sex-specific chromosomal genes involved in creating sexually-dimorphic placentae can also determine prenatal vulnerability to neurodevelopmental risk. In the placental tissue of both mice and humans genes escaping X-inactivation are found with more number of X-escapee genes in humans (15–25%) as compared to mice (3%) [92]. For example, the *Ogt/OGT* (O-linked-*N*-acetylglucosamine transferase) gene, which plays an important role in regulating gene expression through chromatin changes, escapes X-inactivation both in rodents and humans and consequently females have higher expression of *Ogt/OGT* than in males. Bale and colleagues [93,94] found that deletion of *Ogt/OGT* in placental trophoblast cells dramatically affected hypothalamic gene expression, with genes involved in mitochondrial function and energy metabolism particularly affected, both in male neonates and adults. Results from these studies recapitulated the effects of their prenatal stress model where they first identified the placental *Ogt/OGT* gene as a candidate biomarker gene involved in transferring sex-specific effects of prenatal stress on the developing fetal brain [93]. They further proposed that crosstalk between OGT and EZH2 (an H3K27Me3 methyltransferase), which increases global levels of the H3K27Me3 mark [95], may contribute in sex-specific placental gene regulation [87]. Histone PTMs, being an integral component of the sex determining mechanism in gonads and brain, may play an important role in defining the molecularly and functionally distinct male and female placentas. *In utero*, this may have far-reaching consequences for fetal neurodevelopment in a sex-dependent manner. Indeed, recently Nugent et al. [96] showed that H3K27Me3 regulation by *Ogt* in placental trophoblasts is partly responsible for female resilience to prenatal stress in mice. They found increased H3K37Me3 levels in female mice at E12.5 and female human term placenta and genetic deletion of *Ogt* in female mice resulted in H3K27Me3 levels equivalent to male placenta, establishing that *Ogt*

regulates sex differences in H3K27Me3 levels in the placenta. Reduction of H3K27Me3 in female trophoblasts by genetic deletion of *Ezh2* in combination with prenatal stress promoted female vulnerability to prenatal stress and the hypothalamus from these E18.5 females revealed an altered transcriptome as compared to control females. This study demonstrates that an interaction between genotype and environment to alter epigenetic marks the in placenta plays an important role in regulating hypothalamic development in a sex-dependent manner and further supports the existence of placental/brain axis.

Thus, epigenetically regulated sex differences during gestation in developing fetal placenta and brain and an interaction between transplacental signals and brain may set the stage for occurrence, manifestation, and degree of severity of neurodevelopmental disorders in males and females. The maternal environment has the ability to directly or indirectly (through placenta) influence the temporal and spatial expression of genes involved in key developmental processes such as neural migration or synaptogenesis in the fetal brain [65,66,97,98]. In order to fully understand sex-related mechanisms of early programming of neurodevelopmental outcomes observed in adulthood, it appears to be important to consider the impact of the maternal environment on outcomes.

2.3. Age-related changes in the brain: influences of hormones, histone PTMs, and sex

Levels of both prenatal and postnatal hormones greatly influence the sexually dimorphic functioning of the brain and pre-existing sex differences during childhood become more apparent during adolescence due to a surge in hormonal levels at puberty [99]. Interestingly, pharmacological inhibition of histone deacetylation induces pubertal failure in rats by activating repressed genes in the hypothalamus that are normally expressed at a decreased level during puberty [100–102]. This suggests that histone PTMs may contribute to sex differences in the brain by regulating gene expression levels during the critical period of puberty. Although, sex chromosomes are responsible for the inherent different genetic content of male and female brains, the interaction of gonadal hormones with sex chromosome effects at embryonic and early postnatal stages, puberty, and adulthood together may play a crucial role in the manifestation and maintenance of sexually dimorphic brain characteristics. A recent study analyzing the human brain transcriptome by RNA-seq at the prenatal stage, early childhood, puberty, and adulthood in both sexes identified that a sex-specific pattern of gene expression is apparent early in brain development and further diversifies over time, with the greatest extent of sex-biased gene expression observed at puberty [103]. Interestingly, male-biased genes were enriched in genes associated with neurodevelopmental disorders while in females no such pattern was apparent at any developmental stage reflecting the known sex- biased expression of neurodevelopmental disorders in males.

The brain transcriptome is regulated in a spatiotemporal manner through epigenetic modifications [104,105] and hence biased enrichment of histone PTMs in male vs. females at different developmental stages, with or without hormonal influences, may be involved in regulation of expression of individual genes in a sex and age-specific manner. The first study comparing histone PTM levels of-H3K9/14Ac and H3K9Me3-in neonate male and female mice (at E18, PND0, and PND6) found no sex difference in the preoptic area (POA) and hypothalamus but higher levels of H3K9/14Ac in cortex and hippocampus of males than in females [55]. Two studies addressing the role of hormones and histone PTMs in creating the sexually dimorphic brain, anatomically and behaviorally, suggest that hormone-dependent reductions in histone acetylation accompany the masculinization of brain regions and behavior [56,106]. Murray et al. (2009) proposed that the effect of testosterone on brain sexual differentiation might require organized changes in histone acetylation. To test this, they injected an HDAC inhibitor, valproic acid (VPA), to neonate mice on the day of birth and examined BNSTp (the principal nucleus of the bed nucleus of the stria terminalis) volume and cell number at three weeks of age. They found inhibition of masculinization of the BNSTp as VPA treated -males and androgenized females-had female-like BNSTp volume and cell number supporting the hypothesis that testosterone regulates sexual differentiation of brain through histone acetylation. However, the target genes regulated by testosterone induced acetylation in BNSTp remain unknown. Sex steroid hormone receptors mediate the physiological effects of sex steroid hormones in the brain and histone PTMs might be involved in regulating their expression. Matsuda et al. (2011) found that in the POA, an important region for regulating male behavior, ERα (estrogen receptor) associated H4 acetylation at embryonic day 21 was higher than postnatal day 3 as compared to females. Knockdown of HDAC 2 and 4 in newborn male mice impaired male sexual behavior in adulthood implicating the crucial role of histone PTMs in brain masculinization. Genome-wide study of H3K4Me3 distribution found over 200 loci that showed > 1.2 fold and statistically significant sex difference in peak size with females in general showing larger peaks in forebrain structures-BNST (bed nucleus of the stria terminalis) and POA [107]. This study also reported greater H3K4Me3 levels in females on X escapee genes-*Kdm5c* and *Kdm6a* genes-indicating a role of H3K4Me3 in organizing the chromatin landscape of X-linked genes. Recently, we also reported that acetylated (H3K9Ac) and methylated (H3K4Me3, H3K9Me2 and H3K27Me3) global histone levels vary dynamically by sex-, age- (E18, PND0, PND6, and PND60), and brain region (frontal cortex and hippocampus) [108] in mice. One common observation across studies examining either gene expression or histone PTMs at various developmental stages is their dynamic regulation throughout development in a brain-region specific manner that is influenced by sex, suggesting an important role in sex-related brain functioning and a potentially important role in programming sex-related susceptibility or resilience to brain disorders. However, the changes at each developmental stage might not be dynamic to the same extent. One interesting observation has been that sex differences in H3K4Me3 levels did not associate very well with gene expression changes [107], emphasizing that sexually dimorphic changes in gene expression pattern are not simply related to changes in one specific histone PTM. Sexual dimorphism for a given epigenetic mark may be different from the sexual dimorphic gene expression which might involve other epigenetic influences. Alternatively, the marking of genomic regions with histone PTMs may not be reflective of current sex-specific gene expression changes but may have a significant role in regulating sexually dimorphic gene expression under a specific environmental context, i.e., they may be responsible for programming a gene response to a later life event.

Normal age-associated cellular changes occurring in the brain, when accelerated by a combination of genetic and environmental factors, may lead to increased risk for development of neurobehavioral and psychiatric disorders. Age-associated changes in level, activity, and function of enzymes that carry out addition and removal of histone PTMs, result in a dynamic alteration in histone marks across the genome. Class III histone deacetylases Sirtuins (Sirt), modulate the brain functioning not only during development by promoting neurite outgrowth, axon development, learning, and memory but have been linked to brain aging as well [109,110]. Expression of *Sirt1* which is a NAD^+-dependent deacetylase varies in a brain region-specific manner with aging, and its levels are also modified by sex [111]. As compared to 4-month-old mice, 12 and 24-month-old mice had decreased levels of *Sirt1* expression in the antero ventral thalamic nucleus (AV) and in the arcuate nucleus (ARC). An influence of sex on an age-associated change in *Sirt1* expression was seen in the subfornical organ (SFO) and the substantia nigra. Age-related differences in expression of *Sirt1* could be related to changes in sex hormone levels with aging as specific brain regions, such as SFO, are highly sensitive to endocrine effects [111]. Histone acetylation and methylation marks have been extensively studied in regard to aging but have not been fully explored in the context

of sex differences in brain aging. With aging, hypoacetylation at repetitive DNA elements occurs suggesting an association between genomic instability and aging [112]. In 16-month-old mice, age-associated memory impairment was linked with deregulation of H4K12 acetylation and gene expression in the hippocampus [113]. In rhesus macaque, H3K4me2 enrichment at promoters increases with age and, similar changes were found at enhancer regions as well as measured via ChIP-seq [114]. The results of most studies on histone PTMs and aging seem to suggest that with aging, a progressive opening of chromatin occurs accompanied by upregulation of activating marks and downregulation of repressive marks [115,116].

Sex-specific interactions of hormones with histone modification machinery may at least in part contribute to differences in susceptibility or resilience towards development of various brain disorders (Fig. 2b). Binding of sex steroids to their respective nuclear receptors results in recruitment of coactivator complexes, which through their histone acetylase activity, alter the transcriptional output of a gene [117]. For example, the nuclear receptor corepressor (NCoR) complex is associated with sex steroid hormone receptor activity and since one of the components of NCoR complex is HDAC, their recruitment to specific genomic loci can alter the chromatin landscape [41]. Moreover, NCoR levels during development differ in the developing amygdala and hypothalamus of males and females and might be dependent on estradiol [38] the level of which also varies with developmental stage and declines with aging [118–120]. Hence, differences in sex steroid hormone levels during development and aging as well as variation in distribution and expression of sex-steroid receptors in the brain [121] between the two sexes could result in sexually dimorphic epigenetic patterns in the brain over the lifespan. Since sex steroid hormones such as estrogens act through nuclear receptors and could potentially modify the chromatin organization and transcription factor assembly at a gene [122], it will be important going forward to investigate how varying levels of sex steroids during aging may affect brain-region specific gene expression differentially in males and females through alterations in specific epigenetic marks. Such studies could have important implications for human health and may advance our mechanistic understanding of sex biases in the development of certain brain disorders. Thus, sex differences in the brain begin *in utero* and an interplay among agents of sexual differentiation, i.e., sex chromosome genes and hormones and epigenetic marks such as histone PTMs across the lifespan, and agents of epigenetic change, i.e., environmental influences, appear to shape the genome in a sex- and brain region-specific manner (Fig. 3). The sex- and brain region-specific readout of the genome determines functional and behavioral outcomes, including the risk for vulnerability or resiliency for brain diseases/disorder. As this concept is significantly relevant to psychiatric disorders which show prevalent sex difference in etiology, this will be discussed in the following section.

3. Psychiatric disorders: sex differences and histone PTMs

3.1. Autism spectrum disorder (ASD)

ASD is four to five times more prevalent in males than in females [123,124]. Several theories have been proposed to explain the preponderance of ASD in males and factors including genetic, epigenetic and hormonal changes have been suggested as contributors (see [123]). Females diagnosed with ASD have more affective symptoms compared to their male counterparts who have a greater social impairment [124]. Disruption in placental gene regulation [125] especially in the serotonin system [126] has been proposed to be associated with the autistic phenotype. However, it remains to be determined if the placenta acts as a vehicle for sex-specific vulnerability to ASD. Interactions between genes, sex, and environment may underlie sex differences in ASD [123]. A recent study in mice showed that an interaction between sex (male), prenatal stress (PS), and specific genetic mutations predisposes males to develop autism [127]. Using *Cntnap2* (contactin-associated protein-like 2) mouse model for ASD, in males only, a significant decrease in hippocampal *Crhr1* (Corticotropin-releasing hormone receptor 1) mRNA levels and a decrease in levels of the activating mark H3K4Me3 at the *Crhr1* promoter, were observed in response to LPS-induced maternal immune activation. This suggests that a sex-specific alteration in the histone modification H3K4Me3 at specific genes may be involved in sex-specific vulnerability to ASD. Findings from a few studies indicate that females appear to require a larger genetic burden before they are diagnosed with ASD, suggesting that genetic variations for a gene to be a risk for ASD in females have to be present at a higher frequency in females as compared to males [123,128,129]. In a recent large-scale exome sequencing study of 3976 ASD subjects, several genes associated with histone modifying machinery were identified as ASD risk genes [130]. Mutations in five SET lysine methyltransferases (SUV420H1, MLL3, WHSC1, SETD5 and ASH1L), in four jumonji lysine demethylases (KDM3A, KDM5B and KDM6B) and in two readers (CHD8 and POGZ) were identified. POGZ, CHD8, SUV420H1, with a false discovery rate (FDR) < 0.1, showed female enrichment for de novo variation events, i.e., mutation in these genes, if present at a higher frequency leads to significantly more female ASD incidences compared to males. While ASH1L and SETD5 with an FDR between 0.1 and 0.3 showed less enrichment for female events consistent with their observation that de novo events in these genes have a modest impact on risk for ASD in females. An association between de novo mutation in genes CHD8, KDM6B, KDM5B and non-verbal IQ in autistic males was reported with a much weaker association in female subjects [131]. Shulha and colleagues reported altered H3K4Me3 peak densities at hundreds of gene loci in prefrontal cortical (PFC) neurons in a subset of autism cases and although both male and female subjects were included in the study due to a small number of female subjects compared to males did not allow for adequate examination of a potential sex-specific effect [132]. A mutation in an X-linked gene, *Kdm5c*, which demethylates di- and trimethylated H3K4 was reported in a single male ASD patient [133]. Genes under the regulation of *Kdm5c*, i.e., SCN2A, CACNA1H, BDNF and SLC18A1, have been associated with ASD [134–137]. These observations suggest that X-linked mutations in genes that function as epigenetic regulators (such as *Kdm5c*), may affect males more commonly and may adversely influence autosomal gene loci regulation leading to a sex-specific aberrant transcriptome and the pathology of ASD. Recently, a histone acetylome-wide association study (HAWAS) using H3K27Ac ChIP-seq was performed in three postmortem brain regions associated with ASD- prefrontal cortex, temporal cortex and cerebellum (individuals aged ≥ 10 years) from etiologically heterogenous ASD cases [138]. Although both sexes were included in the study, the data analysis was performed by controlling for sex. Despite etiological heterogeneity, > 5000 regulatory regions were associated with alteration in histone acetylation in cerebral cortex suggesting that different ASD cases may share common histone modification alterations that could be responsible for shared symptoms in ASD. Due to lack of power to reach statistical significance examining each sex separately, genome-wide studies generally pool the male and female subjects for analysis. However, in the future, sufficiently powered studies with appropriate statistical measures, will better inform about the potential shared and unique loci of epigenomic changes between male and female ASD patients. Characterizing the associated epigenomic changes in addition to genetic risks in a sex-specific manner could further help in understanding the etiology of ASD.

Thus, studies until now suggest that genes involved in writing, erasing and reading histone PTMs as well as genes that harbor changes in histone modification patterns are related to ASD etiology, however, additional studies are required to understand their contribution to the sex-specific molecular pathology of ASD. It was also suggested that sex hormones might modulate genes associated with ASD contributing to sex differences in ASD expression [123]. With an association between histone modifying enzymes and steroid receptors (discussed in the earlier section) it would not be surprising to find complex interactions

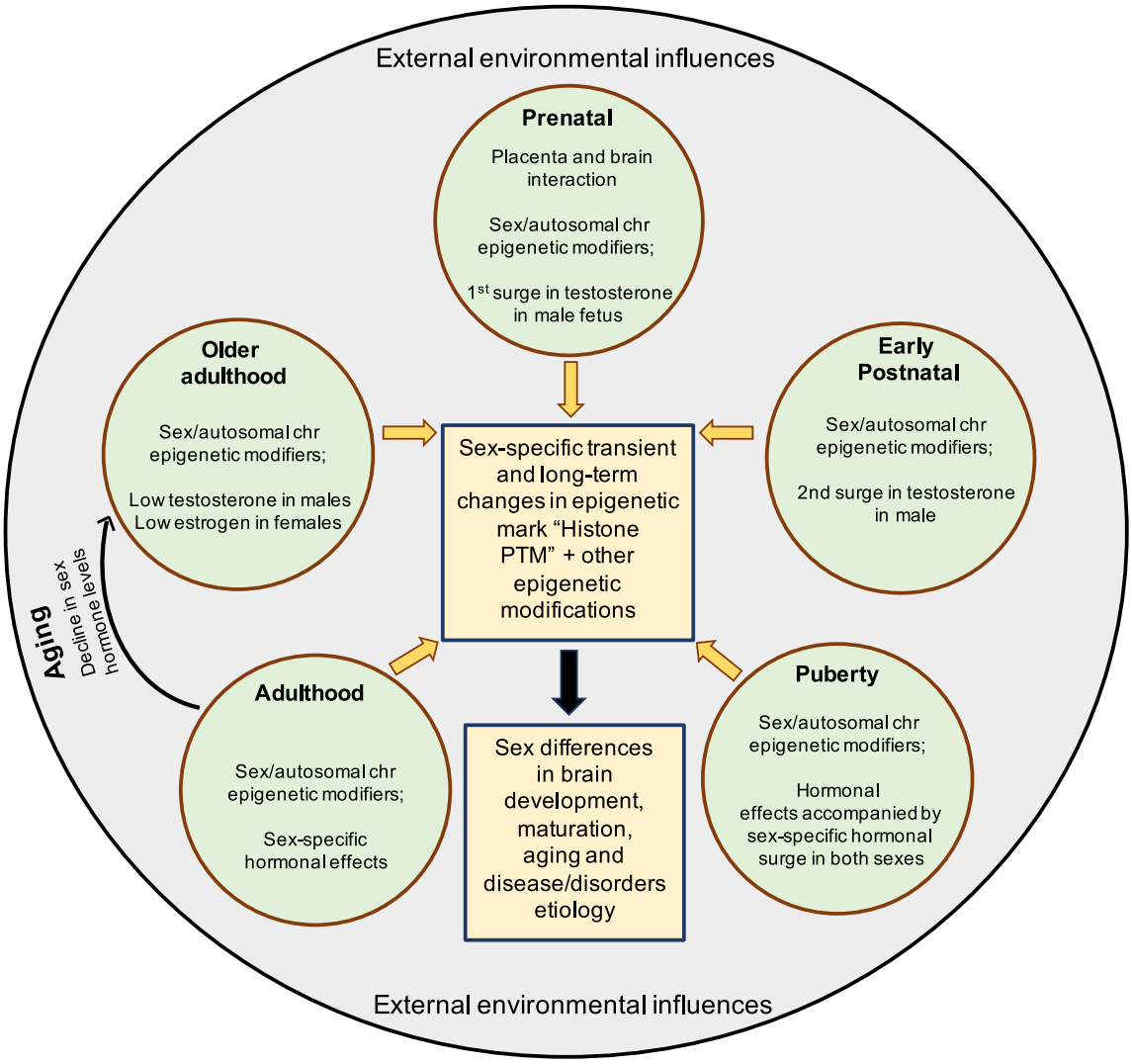

Fig. 3. Epigenetic modification through histone PTMs as a source of sex differences in brain development and risk of various disorders across the lifespan. Transient or stable changes occur in histone PTMs at a genomic region due to independent or interacting sex chromosome and hormonal effects at prenatal, early postnatal, puberty, or adulthood. Histone modifiers present on autosomes and their interaction with sex hormones/receptors may also lead to sex-specific deposition of histone PTMs. The foundation for sex differences in risk for developing specific brain disorders may be laid at the prenatal stage due to epigenetic effects mediated by histone PTMs (in concert with other epigenetic modifications) that may also involve an influence from the maternal environment perhaps mediated through the placenta. Although, early programming has enduring effects on the brain, sex differences in brain development, maturation and onset/progression of specific brain disorders may be further influenced by specific external environmental factors that induce epigenetic changes by interacting with unique hormonal profiles of each sex at specific points during the lifespan. Sex-specific epigenetic marking of the genome through histone modifications and other epigenetic mechanisms may ultimately determine sex differences during normal brain development and deviations from these normal trajectories leading to increased risk for developing certain brain disorders. chr - chromosome.

between histone modifiers and sex hormones or their receptors contributing to the sex-specific pathology of ASD. Although ASD is generally regarded as a psychiatric disorder with a developmental origin, a few cases have been reported where ASD onset was reported in late adulthood and as late as age 66–84 [139], including cases of failed diagnosis in early life as well as the late presentation of the disease itself. The biological basis for late-onset cases and any sex difference in onset remains to be determined. It is possible however that epigenetic drift in the aging brain may contribute to the late-onset of ASD, although this possibility has not yet been studied.

3.2. Schizophrenia

Schizophrenia is a complex psychiatric disorder that impacts cognitive, affective and social functioning [140,141]. Although the disorder affects both males and females, sex appears to modify the clinical outcomes and the disease trajectory. In women, schizophrenia is often less severe, with lower incidences, and a later age of onset compared to men [142,143]. Genetic, environmental or hormonal neurodevelopmental disruption during gestation, and/or environmental factors such as stress or trauma during the early and late postnatal period may individually or in combination contribute to expression of this disorder [142]. At molecular level schizophrenia has been mostly associated with a decrease in gene expression in more than one brain regions and this is supported by findings which indicate that repressive or restrictive chromatin is a characteristic of schizophrenia [144,145]. Histone PTMs which are the key determinant of restrictive versus permissive chromatin landscape have been implicated in the pathogenesis of schizophrenia, although little is known about the contribution of specific histone PTMs in schizophrenia in general and the potential sex differences in particular [146–148]. The first study investigating the role of histone PTMs in prefrontal dysfunction in schizophrenia

reported an association between high levels of global H3MeR17 (active chromatin mark) and reduced metabolic gene expression (*CRYM*, *OAT*, *CYTOC/CYC1* and *MDH*) in a subgroup of subjects [149]. Whether the increase in H3MeR17 level was reflective of an adaptive response to decreased metabolic gene expression specifically or altered the prefrontal transcriptome was unclear. The study included both male and female subjects, but results were not reported in a sex-specific manner. Other altered histone PTMs or alterations in histone modifying genes have been associated with schizophrenia but no sex-specific role has been described. A few such findings will be discussed here to highlight the link between histone PTMs and schizophrenia. Upregulation of HDAC1 (histone deacetylase 1) mRNA expression consistent with downregulated GAD_{67} expression in the stratum oriens (SO) of CA2/3 was observed in schizophrenic patients [150]. Correlation between reduced GAD1 mRNA expression and decreased H3K4Me3 levels at GAD1 gene locus was observed in the prefrontal cortex of schizophrenic patients [151]. In postmortem prefrontal cortex of schizophrenic patients, decreased H3K9Ac and H3K14Ac levels at several schizophrenia-related genes- GAD1, RGS4, HTR2C, PPM1E and UGT8 significantly correlated with their reduced expression level [152]. Another major finding from this study was significant hypoacetylation of H3K9 and H3K14 at *GAD*1, *UGT8*, *HTR2C* and *H1FNT* gene promoters consistent with decreased mRNA expression level, in younger patients with schizophrenia. This result was consistent with earlier demonstrated finding wherein common molecular changes in normal human aging and early-stage schizophrenia were observed [153]. De novo mutations in *SETD1A*, a component of histone methyltransferase complex, were implicated in the pathogenesis of schizophrenia and hence *SETD1A* has been identified as one of the risk genes for susceptibility to the disease [154,155]. Increase in both repressive histone modification, H3K9Me2, level and mRNA levels of enzymes which catalyze this modification, SETDB1, EHMT1 and EHMT2, was reported in postmortem brain samples of patients with schizophrenia [144].

Two studies have explored the sex-difference in schizophrenia in the context of histone modification alterations [143,156]. Sharma et al. (2008) reported that both male and female schizophrenia patients had increased levels of HDAC1 in the prefrontal cortex as compared to female control subjects, and female patients had around twice the amount of HDAC1 than male patients ($p < 0.003$). A limitation of this study was that only 3 females were included in the analysis compared to 13 males, and thus a clear sex-difference in outcomes is difficult to establish. This preliminary observation, however, suggests that in accordance with the theory that females require more genetic burden to express schizophrenia than males, a greater accumulation of epigenetic changes may also be needed in females compared to males to contribute to development of schizophrenia. In another study, *SETDB1*, *EHMT1* and *EHMT2* mRNA and the associated H3K9Me2 modification, were measured in the lymphocytes of both male and female schizophrenic patients [143]. Increased *SETDB1*, *EHMT1* and *EHMT2* mRNA and H3K9Me2 protein levels were found in men compared to women with schizophrenia. Furthermore, the increases in above-mentioned mRNA and protein levels showed male-specific correlations with the increased presentation of symptoms and poor quality of life. Women diagnosed with schizophrenia generally have less severe symptoms as compared to male patients [142], and further research is needed to investigate the interaction between histone enzymes and hormone receptors and the downstream effects on overall gene transcription cascades which may differentially affect vulnerability to schizophrenia in men and women.

Lastly, a recent study does not explore histone PTMs but offers potentially important insight into the sex bias in expression of schizophrenia [157]. In the context of increased susceptibility for schizophrenia due to the intra-uterine and perinatal environment, a subset of most significant genetic variants associated with schizophrenia was highly expressed in placenta and modified by stress, and most interestingly were more enriched in the male placenta compared to the female placenta. This suggests that the placenta may act as an important sex-specific mediator of the interaction between early environmental factors and genetic risk for schizophrenia. As we know that the placental epigenome is highly dynamic and is responsible for proper fetal neurodevelopment, it would be interesting to know how another layer of gene regulation, epigenetics and especially histone PTMs, in the placenta contribute to an increased schizophrenia risk in males.

3.3. Major depressive disorder (MDD)

MDD or major depression is a common multifactorial psychiatric disorder affecting 4.4% of the global population. According to recent WHO report, a number of affected individuals are increasing with each passing year as indicated by the increased rate of 18.4% between 2005 and 2015 [158]. Depression disorders are more common in females (5.1%) than males (3.6%), and although it can occur at any age in both sexes, MDD is more prevalent in older adulthood [158]. Despite a known sex bias in incidence and severity as well as sex differences in the manifestation of symptoms associated with MDD, the majority of MDD studies have only focused on males [159]. It is no surprise that the risk to develop MDD is closely tied with one's environmental context and especially stressful life experiences and their interaction with multiple susceptibility genes play a significant role in predisposing individuals to the development of illness [160,161]. Not only childhood or adulthood experiences but maternal pre-gestational and gestational exposure to traumatic events may also contribute to vulnerability to depression, as demonstrated in animal models and postmortem human brain studies [160,162–164]. Studies that have included both sexes in the analysis show numerous sex differences in behavioral outcomes and transcriptional regulation of specific genes as well as genome-wide level transcriptional changes [165–170]. For example, in postmortem brain samples, divergent transcriptional profiles across multiple brain regions (prefrontal cortex, anterior cingulate cortex and amygdala) were found in males vs. females with MDD, with almost no overlap in expression changes [166]. Markers of synaptic functions and neurons were reduced, and markers of microglia were increased in males with MDD while females with MDD had increased markers of synaptic functions and neurons and decreased markers of immune function. These results may suggest that MDD is associated with opposite transcriptional signatures in males and females with MDD and that developing therapeutic interventions based on only data from one sex may be ineffective in the other sex.

As environmental factors can modify the histone landscape through their influence on epigenetic machinery, it is likely that changes in gene expression observed in MDD might be partly related to histone PTMs changes. Indeed, various studies report correlated changes in gene expression and histone PTMs level in relation to MDD in both animal models and human postmortem brains. However, the extent to which histone PTMs may be involved in creating sex-specific phenotypes in MDD or in contributing to vulnerability or resilience to MDD has not been sufficiently explored. A recent study [171] explored the role of H3K9Ac modification in sex-specific depression-like behavior induced by prenatal stress (PS-restraint stress during late gestation day 14–20) at the tryptophan hydroxylase2 (*Tph2*) gene in juvenile rat hippocampus. *Tph2* is a rate-limiting enzyme for serotonin (5-HTergic) synthesis in the brain, and the 5-HTergic system plays an important role in pathophysiology and treatment of depression both in humans and animal models. PS-induced depression-like behavior (increased immobility in forced swim test) was found only in the juvenile male rats and not in the females and was associated with a decrease in *Tph2* mRNA, protein expression and H3K9Ac levels at promoter region in the hippocampus. Administration of trichostatin A (TSA), an HDAC inhibitor, reversed the PS induced effects in juvenile male rats including the level of H3K9Ac at the *Tph2* promoter. This study highlighted an important role of a histone PTM in the sex-specific occurrence of depression-like behavior in animal models and it may be important to investigate the origin of depression in adulthood as a consequence of

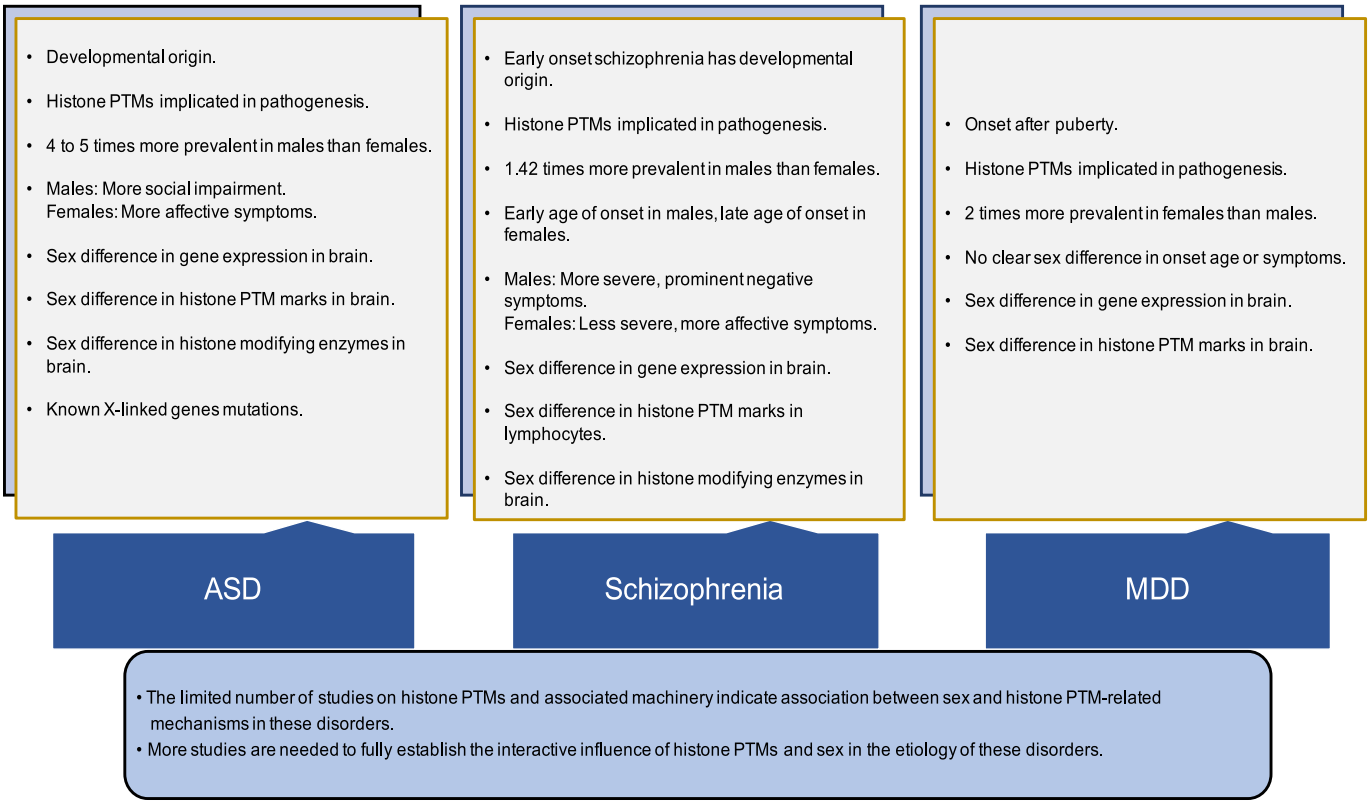

Fig. 4. Neuropsychiatric disorders with established sex differences in etiology and relationship to histone PTM-related mechanisms. Sex differences in prevalence, symptoms, onset, molecular changes including histone PTMs have been suggested for autism spectrum disorder (ASD), schizophrenia and major depressive disorder (MDD). More research is required to establish the link between histone PTMs and sex-based pathogenesis. See text for more details.

prenatal insults. For example, the placental serotonin system is the only source of 5-HT to the developing fetal forebrain in mice and humans, shaping the development of the fetal 5-HTergic system and neuronal connections [172]. Is it possible that PS could lead to sex-specific deposition of histone PTMs at 5-HTergic system genes resulting in differential transcriptional output and altering 5-HT levels in the placenta which subsequently alter the supply of 5-HT to developing prenatal brain in a sex-specific manner? It is not known the extent to which histone PTMs or histone modifying enzymes such as *Kdm5c/Kdm5d* or *Utx/Uty* in the placenta are involved in creating imprints of misregulated sex-specific neuronal connectome which could potentially set the pathway for development of depression later in life. What is the role of hormones during late gestation in modifying the susceptibility towards MDD in later life for each sex? To what extent does aging-associated decline in gonadal hormones and related changes in the histone PTM landscape put females at a greater risk to develop MDD? Histone deacetylase *Sirt1* involved in aging [173–175] and controlling sex hormone production via hypothalamic-pituitary-gonadal axis [110] regulation has also been linked with MDD [176] and may play an important role in development of MDD in early and late adulthood and should be investigated in context of sex-specific MDD etiology. The interaction between hormones and histone modifying enzymes may result in upregulation of key developmental genes at puberty and exposure to life adversities at this crucial stage may program these genes in a sex-specific manner increasing the risk for sex-specific susceptibility towards MDD. These key questions should be addressed in future studies. Other than 5HT-ergic system genes discussed above, HPA axis genes such as *Nr3c1* (glucocorticoid receptor) and *Crhr1* (corticotropin releasing hormone receptor) and brain neurotrophin, *Bdnf* (brain-derived neurotrophic factor), are regulated by histone PTMs and have been implicated in the pathogenesis of MDD [159,177–179] but sex-specific associations between these factors have not been explored. Due to the known complex interaction between hormones, hormone receptors, the HPA axis, brain neurotransmitter systems and their regulation via histone PTMs or associated enzymes, it is plausible that disruption at any of these levels may promote the sex bias in expression of MDD.

4. Conclusion

Despite recent interest in understanding sex differences in several physiological and behavioral processes, there remains a paucity of information related to how an individual's brain development is sculpted based on sex. Among known epigenetic mechanisms, histone PTMs and the enzymes involved in modifying histones, have emerged as important regulators of brain development, behavior, and related disorders as well as in sexually differentiating the brain. A few studies addressing the prevalence of sex differences in psychiatric disorders indicate that histone PTMs might be associated with sex-specific outcomes, but more research is needed to better understand whether they are actually causative factors leading to the sex differences in occurrence and manifestation of disease (Fig. 4). Environmental factors influence histone PTMs and hormone interactions throughout the lifespan from early development to aging and integration of these mechanisms with the brain genome in a sex-specific manner may influence the vulnerability and resiliency to psychiatric disorders. Understanding how these mechanisms interact and contribute to disease etiology has the potential to inform about development of novel interventions. Clearly, sex matters in brain development and in expression of brain disorders. The challenges for future research, however, are many due to poor understanding of (1) similarities and differences between male and brain female brains at functional, anatomical, and molecular levels; (2) molecular and functional correlates that may vary by brain region and cell type within each sex; (3) how individual experiences and

responses to different types of environmental exposures across the lifespan shape the epigenome and hence the genome in a context-dependent manner; (4) the functional consequences of subtle differences at molecular level between sexes and (5) lack of proper statistical methods/design to validate the significance of such biological effects. As we move forward, it will be important to start addressing these issues.

It is clear that incorporating both sexes into study designs, whether using animal models or human subjects, is critical. Even though a disease in focus may have a male or female bias, including both sexes will inform about factors that may confer vulnerability or resiliency to one sex or the other. A better understanding of the nature of epigenetic changes, including histone PTMs and crosstalk among different histone PTMs and with other epigenetic marks, induced by sex chromosome effects and hormone interactions, within the context of different environmental factors, will be important for defining the basis of sex differences in normal and abnormal brain development and function.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Transparency document

The Transparency document associated with this article can be found, in online version.

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