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Gene regulatory mechanisms underlying sex differences in brain development and psychiatric disease

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Abstract

The sexual differentiation of the mammalian nervous requires the precise coordination of the temporal and spatial regulation of gene expression in diverse cell types. Sex hormones act at multiple developmental time points to specify sex-typical differentiation during embryonic and early development and to coordinate subsequent responses to gonadal hormones later in life by establishing sex-typical patterns of epigenetic modifications across the genome. Thus, mutations associated with neuropsychiatric conditions may result in sexually dimorphic symptoms by acting on different neural substrates or chromatin landscapes in males and females. Finally, as stress hormone signaling may directly alter the molecular machinery that interacts with sex hormone receptors to regulate gene expression, the contribution of chronic stress to the pathogenesis or presentation of mental illness may be additionally different between the sexes. Here, we review the mechanisms that contribute to sexual differentiation in the mammalian nervous system and consider some of the implications of these processes for sex differences in neuropsychiatric conditions.

Keywords

epigenetic mechanisms; sex differences; steroid hormones; development; neuropsychiatric illness

Many psychiatric conditions display a sex bias in incidence, onset, or symptoms; however, the underlying mechanisms that lead to these sex differences are still obscure. Here, we consider some of the levels of development and mechanisms of gene regulation in which sex-specific processes may contribute to sexual dimorphisms observed in mental illness, with a focus on gene regulation and epigenetic mechanisms. We first describe early behavioral sex differences in humans, focusing on two early-presenting disorders that are diagnosed more frequently in males: autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). We next consider the developmental events that give rise to sex differences in the brain and discuss gene regulatory mechanisms that may underlie the

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persistent effects of these processes on brain function. We then explore how similar genetic risks for ASD and schizophrenia could be invoked in either early life or adolescence, resulting in the distinct trajectories seen in these two conditions. We propose that the intersection between the gene programs that regulate sex-specific development and function in the brain and those that are disrupted in the context of psychiatric illness can significantly influence the pathogenesis and presentation of most neuropsychiatric conditions.

Sex differences in human behavior and neurodevelopmental disorders

Before considering the molecular mechanisms through which pathways for sexual differentiation may intersect with genetic and environmental factors that contribute to psychiatric illness, we first consider a few examples in which early sexual differentiation of the nervous system manifests in early differences in behavior between boys and girls. Not surprisingly, these differences appear in the context of both normal development and in the early presentation of neuropsychiatric conditions.

Little debate exists as to the effects of cultural influences on the early aspects of sex-typical behavior in children. Indeed, the dichotomy of nature versus nurture and their distinct contributions to sex-typical development and behavior is generally acknowledged as false, and human sex-typical behaviors are considered to be the result of dynamic interactions between pre- and postnatural biological factors as well as a child's social milieu (reviewed in Refs. 1–3). At the earliest stages of life, consistent differences in behavior and neurologic development appear between boys and girls. Infant girls appear to have more intense and expressive reactions to painful stimuli.[1,2] Male infants appear to track objects more consistently in an event-mapping task.[2,3] Intriguingly, while both infant boys and girls attend more to female faces, no significant difference in eye-tracking of social stimuli appears between in the sexes in healthy infants.[3–5] Such differences reflect only a few of the likely innate differences in neural function between infant boys and girls. Nevertheless, they illustrate the perhaps intuitive conclusion that, like other mammals, embryonic and early developmental programs regulated by sex hormones result in innate differences between the sexes that are present at the earliest stages of life.

While the consequences of such differences for normal development remain unknown, though actively explored, they likely contribute to differences in presentation seen in pediatric neuropsychiatric conditions. Two examples serve to illustrate how, in addition to likely sex differences in the molecular pathogenesis of such disorders (discussed below), innate sex differences in behavior likely also contribute to the differences in symptoms observed between boys and girls. ASD is diagnosed nearly four times more often in boys than in girls.[6–9] In addition to this overall sex difference, the presentation of ASD also differs between boys and girls. While many studies have documented a higher incidence of intellectual impairment in girls with ASD compared with boys, some debate exists as to whether the overall severity of ASD differs between them.[10] Differences between the presentation of boys and girls with ASD reflect biological differences in symptoms, which may also contribute to biases in reporting and attention. Externalizing behaviors, such as aggression, repetitive behaviors, restricted interests, reduced prosocial behavior, and hyperactivity tend to occur more prominently in males, while females with ASD have more

internalizing symptoms, including anxiety, depression, and self-oriented emotional disruption, that are often only reported by parents.[10–12] As a consequence of these potential differences in presentation, ASD in boys is more likely to come to attention due to disruptive behaviors in school or at home, thereby skewing the bias in prevalence even further. Sex differences in innate responses to stimuli or patterns of emotional expressivity likely contribute to distinct presentation of these disorders. Indeed, sex differences in patterns of cognition, in particular specific dimensions of social cognition and abstract reasoning associated with identifying rules and patterns within systems, led to the hypothesis that domains of autistic symptoms may arise from an extreme masculinization of the brain in autistic patients.[13] Nevertheless, despite many efforts to determine if prenatal exposure to increased levels of androgens is associated with ASD, no causal mechanisms have been established linking sex hormone signaling to ASD.[14,15] However, it is worth noting that such a relationship has been repeatedly supported, linking elevated levels of umbilical cord testosterone to language delays in children, suggesting that, in specific contexts likely determined by diverse genes affecting sensitive aspects of CNS development, sex differences in developmental pathways may contribute to patterns of symptoms that children present.[16] Additional mechanisms may mediate sex differences in the sensitivity to genomic disruption or the consequences of ASD mutations for neural development.

Given the innate differences between the sexes in the presentation or pathogenesis of most if not all psychiatric conditions, it is worth considering whether a re-evaluation of the criteria for those particularly diagnosed in childhood may be warranted. For example, in ASD, aside from specific core deficits in social cognition and emotion processing, other patterns of symptoms used to establish diagnostic criteria may vary between the sexes. Further investigation of sexual dimorphisms in phenotypes resulting from disease-associated mutations will be central to such refinements in clinical criteria.

Extreme sex biases in the diagnosis of ADHD have been observed, such that boys can outnumber girls by up to 10:1, though meta-analyses and population-based studies suggest that this ratio is likely closer to 4:1.[17–19] Intriguingly, sex differences in the prevalence of ADHD appear highest during childhood and become significantly less pronounced later in life.[20,21] As with ASD, given that the pattern of symptoms of ADHD manifested by boys more strongly correlates with conduct disorder and disruptive behaviors, parents or teachers are more likely to bring these cases to attention. Consistent with a model in which females are more likely to manifest comorbid distress or disorders with internalizing symptoms, girls are typically diagnosed later in childhood than their male counterparts.[22] However, in addition to sex differences in overall prevalence rate, the distribution of subtypes or patterns of associated phenotypes also appears to differ between the sexes, with a larger percentage of females (45–60%) presenting as inattentive compared with males (35–50%).[17,23] Thus, innate sex differences in the circuits regulating attention or behavioral inhibition may underlie the presentation of ADHD, as well as other neuropsychiatric conditions. Indeed, it has been observed that boys with ADHD exhibit deficits in behavioral inhibition, while girls tend to display impairments in planning.[24] Given that the extent and pattern of sex differences in ADHD-associated symptoms appear to decrease with age into adulthood, it is interesting to speculate that, despite innate differences in neural circuits underlying attention and behavioral inhibition, the developmental pathways activated during adolescence

(discussed below) normalize these differences and restructure such circuits to participate in behavioral processes common to both sexes in adults, while distinct pathways elaborate the sexual dimorphisms in behavior and pathology seen in later in development.

Independent of the societal factors that likely skew the diagnoses of these two syndromes, the male bias of ASD and ADHD prevalence and the distinct patterns in which boys versus girls present with these disorders suggest that innate sex differences in the brain are likely programmed during the earliest stages of development and contribute to sex differences in the symptoms observed. We now turn to the molecular mechanisms that mediate the sexual differentiation of the mammalian nervous system and discuss how these pathways may be altered to give rise to sex differences in the pathogenesis of neuropsychiatric conditions.

Sexual differentiation of the brain is regulated by gonadal hormones

Much of our knowledge about the cellular and molecular differences between the sexes in the mammalian brain has been obtained through studies of the hormonal regulation of the differentiation and function of neural circuits underlying innate, sex-typical behaviors and physiology in rodents, particularly sexual behavior and territorial aggression. The neural circuitry that controls these behaviors develops under the control of gonadal hormones.[25–29] Male mice undergo a surge of testosterone at birth that subsides within hours.[30,31] This circulating testosterone is directly converted to estradiol in the brain by aromatase.[32,33] Estradiol is the primary endogenous estrogen, although estrone and estriol also bind estrogen receptors; here, we primarily use the general term estrogen for simplicity. Pharmacological and genetic experiments have demonstrated that this brain-derived perinatal estrogen is the primary driver of sexual differentiation of the brain and permanently establishes sex-typical differences in the structure and function of the neural circuitry that mediates sex-specific behaviors in the adult.[28,34–36] Females given estradiol at birth display male-typical fighting behavior as adults with no additional hormone supplementation.[37] This sensitivity to estradiol is lost by the second postnatal week.[38–40] Although sex differences in neural circuitry are specified during this postnatal critical period, sex-typical behaviors are not displayed until puberty, when the male testes produce testosterone and female ovaries make estrogens and progesterone. These hormones are acutely required in adult life: gonadectomy abolishes mating and aggression, but the circuit structure remains intact and behaviors can be restored by exogenous hormones. Although testosterone is the primary driver of adult male-typical behaviors, estradiol alone can restore some mating and territorial behaviors.[41–44] Therefore, estrogen acts to both modulate postnatal male-typical circuit development and to “activate” circuits for sex-typical behaviors in adulthood.

In addition to its masculinizing effects on behavior, perinatal estrogen is known to give rise to anatomic and molecular sex differences. Many excellent reviews have summarized findings on cellular and neuroanatomic sex differences, including cell number, neural projections, and spine number.[27,34,45–48] Sex differences in gene expression in the brain have also been described in both rodents and humans.[49–56] Although estrogen is the primary driver of sexual differentiation in rodents, both estrogen and testosterone signaling are required for full masculinization of adult behaviors. Male mice mutant for androgen receptor (AR), the receptor for testosterone, show decreased spatial memory, increased anxiety,

decreased play fighting, and reduced sexual and territorial behaviors.[57,58] Loss of estrogen signaling, either through gonadectomy or mutation of estrogen receptors, increases anxiety in mice.[59,60]

In humans, however, it appears that brain masculinization occurs largely through testosterone signaling, rather than estrogen. Human males with mutations in *CYP19A1*, the gene for aromatase, cannot synthesize estrogen, yet present as normal males. Men with aromatase deficiency experience sustained linear growth rather than a pubertal growth spurt and epiphyseal closure, demonstrating that estrogen is required in males for proper skeletal maturation.[61] In contrast, AR function is essential for phenotypic and behavioral masculinization of human males. Patients with an XY karyotype and a complete loss of AR function have complete androgen insensitivity syndrome (CAIS), present as women, and have female-typical brain morphology.[62] Humans also experience developmental testosterone surges; though consistent with the scaling of natal development, they are much more prolonged than those in rodents. The testes begin to secrete testosterone around week 7 of gestation, with maximal levels between weeks 8 and 24.[63,64] Human brain at mid-gestation is similar to mouse brain at birth with regard to staging of cortical development.[65,66] The timing of developmental hormone surges is thus somewhat conserved between rodents and humans: the mid-gestation testosterone surge in humans is concordant with the perinatal surge in mice and rats. Human males also experience an additional surge in infancy that peaks between months 1 and 3.[67,68] Female ovaries are also known to be active during infancy, but the levels of estradiol are variable, and the time course of its secretion has not been well described.[68–70] The timing of these increases in gonadal hormone levels intersects with neural development so that male and female brains have very different internal states during neurogenesis, neuronal migration and synaptogenesis (Fig. 1). Consequently, it is not surprising that, like the myriad dimorphisms observed in rodents due to the postnatal testosterone surge, humans also demonstrate innate differences during fetal and infant development between the sexes.[71,72]

Sex chromosomes and brain development

Sex chromosomes also contribute to sexual differentiation of the brain, both directly through their own genetic content and indirectly through regulation of gonadal development (reviewed in Refs. [73–76]). Sex chromosome aneuploidies are some of the most common genetic disorders in humans, affecting nearly 1/400 live births.[77] These disorders are associated with cognitive and behavioral symptoms, particularly social skills and motor abilities.[78] Notably, language and spatial abilities appear to correlate with sex chromosome dosage; females with X monosomy show normal or increased verbal and lexical abilities and visuospatial deficits, while individuals with sex chromosome polysomy have language impairments that increase with the number of chromosomes, while spatial skills are often enhanced.[77–79] Brain imaging studies have identified a relationship between sex chromosome dosage and brain volume[77] and highlight specific chromosomal effects in cortical[80] and subcortical[81,82] brain areas. Mouse models of sex chromosome aneuploidies have been used to discern the effects of sex chromosomes on specific behaviors, including social behaviors, anxiety, feeding, and nociception.[74] The most widely used model is that of the “four core genotypes.” This system employs two modified alleles of the testis-

determining Sry gene; one where *Sry* has been deleted from the Y chromosome, resulting in genetic males that resemble females, and another where *Sry* has been inserted on an autosome to generate XX animals that develop testes.[83] Comparison of these mutants with wild-type XX and XY animals thereby permits the dissociation of sex chromosome complement and gonadal development.

Similar to *Sry*, the few other genes on the Y chromosome are primarily specialized for testis determination and spermatogenesis.[84] Gene products such as DDX3Y, UTY, and KDM5D are abundant in the brain, but their neural functions have not been elucidated.[51,85–87] In contrast, the X chromosome is enriched for genes that control brain function; 40% of the genes on the X are expressed in the brain, and X-linked gene expression is higher in the brain of both sexes compared with other tissues.[88–91] As the X chromosome is also the most rapidly evolving mammalian chromosome, it has been suggested that this enrichment of neural-expressed genes is a consequence of natural selection for increased cognitive abilities.[88,92–94] Consequently, X-linked mutations are a leading cause of intellectual disability, a condition that is more prevalent in boys than girls.[89,93,94] As female cells achieve dosage compensation through stochastic inactivation of one X chromosome (XCI), females are buffered from the effects of deleterious X mutations.[95,96] A recent analysis of XCI in diverse human cell types and tissues established that the extent of X inactivation varies within and between individuals and is often incomplete.[97] In brain, excitatory and inhibitory neurons show different patterns of clonal XCI mosaicism within a cortical column owing to their different developmental migration patterns. Excitatory neuron XCI is heterogeneous with high variance within and between individuals, while inhibitory neurons show equal, fine-grained inactivation patterns, suggesting that any heterozygosity for an X-linked gene would affect excitatory circuitry only in specific clonal areas, but all inhibitory circuits would be affected equally.[98]

What genes on the X or Y chromosomes are contributing to sex differences in brain development and function? Histone lysine demethylases are intriguing candidates, as they can induce broad, persistent effects on gene expression. *Kdm6a/Utx* and *Kdm5c/SMCX* are known escapers of X-inactivation, resulting in increased expression of these epigenetic regulators in the brains of females. Mutations in *KDM5C* have been implicated in a variety of neurodevelopmental disorders, including intellectual disability, ASD, and cerebral palsy.[99,100] Mice lacking *Kdm5c* display increased aggression, decreased anxiety, impaired motor coordination, and decreased dendritic arborization in the amygdala, although these phenotypes are dramatically reduced with a forebrain-specific deletion in adulthood.[100,101] This finding provides evidence that these enzymes have distinct genomic targets in specific cellular or developmental contexts. In the next section, we will explore current questions and approaches regarding regulation of gene expression in the brain.

Gene regulation in the brain: unique strategies and new methodologies

From a general perspective, epigenetic regulation refers to mechanisms that mediate persistent changes in gene expression in response to transient events, such as developmental programs, experience, or environmental cues, although the stringency of this definition is much debated.[102–105] Thus, the activity of a specific gene or sets of genes across the genome

is regulated by changes in chromatin structure that occur via interactions with the gene's local environment (*cis*) or other regions in the genome (*trans*) and changes in nuclear structure. Such chromatin remodeling involves dynamic processes that include the movement of histones along DNA, covalent modifications to histone proteins (including acetylation, methylation, and phosphorylation), the binding of transcription factors to regulatory regions and the subsequent recruitment of coactivators and corepressors that may be responsible for such modifications, or the covalent modification of DNA itself. These processes work to integrate developmental and environmental signals over time to determine levels and patterns of gene expression.

Several recent reviews discuss general principles of epigenetics and gene regulation in neurons.[104,106–111] While the details of the mechanisms regulating neural gene expression are beyond the scope of this review, we wish to emphasize the unique developmental trajectory of chromatin state in neurons and to highlight recent insights obtained from high-throughput sequencing approaches. Chromatin structure is known to reorganize during the peak of synaptogenesis in postnatal life. This was first observed through analysis of chromatin repeat length, which reflects the length of the linker DNA between nucleosomes and is a proxy for the density of chromatin packing.[112] Chromatin repeat length in cortical neurons is shorter than that of neighboring glia or other cell types,[113] which suggests a unique pattern of higher-order chromatin organization in neurons. Furthermore, shortening of repeat length coincides with region-specific dynamics of neuronal maturation, suggesting that regions undergo chromatin reorganization in response to neural activity and circuit formation.[114–116] Epigenomic analyses are now elaborating on these pioneering findings, particularly through studies on higher-order chromatin organization and DNA methylation.[117–122]

The extraordinary heterogeneity of the mammalian nervous system raises challenges in dissecting the role of a given factor or genetic variant in precise spatial and developmental contexts. The advent of single-cell sequencing has made it possible to identify and classify neurons from their transcriptomes in addition to morphological or electrophysiological characteristics.[123–127] The *cis*-regulatory elements that coordinate the specification and function of discrete neuronal types are being revealed through technological refinements in chromatin immunoprecipitation sequencing (ChIP-seq) and ATAC-seq (assay for transposase-accessible chromatin using sequencing) methods.[125,128–131] Future studies will describe the dynamics of these elements across development or in disease. In postnatal development, experience-dependent neural activity induces transcriptional programs that sculpt neural circuits by regulating synapse development and plasticity.[132,133] The complex dialogue between the synapse and the nucleus involves diverse adhesion molecules, scaffolding proteins, and chromatin regulators, many of which have been implicated in neurodevelopmental disorders, such as ASD.[134–136] Thus, perturbation of the mechanisms that regulate gene expression at a genomic level may affect the development of the nervous system during the earliest stages, causing global disruption in neuronal differentiation and wiring or, at later time-points, causing abnormalities in synaptic function or activity-dependent processes that underlie learning or more complex aspects of information processing in the developed brain.

Epigenetic mechanisms can define developmental trajectories

Gonadal hormones, such as estrogen and testosterone, bind steroid hormone receptors (SRs): nuclear receptor transcription factors that can recruit chromatin remodeling machinery to activate or repress gene expression. Accordingly, it has been proposed that developmental exposure to hormones organizes sexual differentiation of the brain in part through long-term effects on gene expression.[137–141] Differential exposure to hormones in males and females during a neurodevelopmental critical period is likely to result in sex-specific patterns of gene expression by SRs that can lead to persistent sexually dimorphic chromatin patterning (Fig. 2). Consequently, when the gonads begin to secrete hormones at puberty, the same SR-expressing neurons would possess a differential capacity to respond to the same hormone stimulus, as a consequence of the previously established chromatin landscape. However, it has proven difficult to test this hypothesis, as sex differences in gene expression are subtle—even key drivers of sex differences, such as estrogen receptor α (ERα) and AR vary by only a few folds in expression levels and are rarely detected in genome-wide screens for sex differences. Identifying sites of hormone action and the mechanisms by which hormones regulate gene expression in the brain is essential for understanding which neural processes are likely to differ between the sexes. Given the dynamics of sex hormone levels throughout development, it becomes apparent that disruptions in specific neurodevelopmental programs may intersect with sex-specific gene regulation at various points in development or adulthood to cause differences in the symptoms experienced by males and females.

Regulation of gene expression by steroid hormone receptors

Studies on sex differences in SR function in the brain have focused primarily on the fundamental differences in circulating ligands: female ovaries primarily produce estrogen and progesterone, while male testes release testosterone that can be converted into local estradiol in the brain. However, there are many additional factors that can fine-tune specificity in hormone-regulated gene expression, such as neural production of diverse steroid hormones (neurosteroids), transcription co-factor expression, and local chromatin context. Extensive details of SR mechanisms have been elucidated over the past 20 years; however, the role of these receptors in regulating gene expression in distinct, behaviorally relevant populations of neurons remains poorly characterized. This is largely due to the technical challenges of isolating and purifying sufficient numbers of the sparse populations that express hormone receptors. Here, we discuss mechanisms of gene regulation by SRs, emphasizing insights obtained from biochemical and genomic approaches in non-neural systems, to better understand how SR signaling can give rise to sex differences in gene expression in the brain. We then discuss regions of the mammalian brain in which steroid hormones are known to mediate sex-specific differentiations.

In the classic description of gene activation by SRs, circulating steroid hormones diffuse through the cell membrane and bind to receptors, which then undergo a ligand-dependent conformational change, dimerization, and association with cognate recognition sequences on DNA.[142,143] Estrogen receptor β (ERβ) is highly homologous to ERα, with 95% homology in the DNA-binding domain and 55% homology in the ligand-binding domain and similar ligand-binding affinity for physiological estrogens.[144] ERα and ERβ bind the same

recognition sequence and can heterodimerize.[145] As these receptors are co-expressed in many brain regions, they therefore have the potential to both cooperate and compete with one another. In addition to sex differences in levels of hormones and their receptors, sexually dimorphic transcription programs can emerge from over 350 transcriptional cofactors that provide contextual specificity and tuning of gene expression.[146,147] Nuclear receptor coactivators are large multi-unit complexes that link sequence-specific hormone receptors to the general transcription machinery, as well as enzymatic factors that can covalently modify histone tails or invoke ATP-dependent chromatin remodeling machinery.[148] Corepressors generally bind unliganded receptors and recruit histone deacetylase (HDAC)-containing enzymatic complexes that maintain a repressive chromatin state.[147] Of note, nuclear receptor corepressor 1 (NCoR) interacts with MeCP2[149] and is also an ASD risk gene.[150] Co-expression analysis of Allen Brain Atlas data recently identified the SR cofactors, including NCoR, that are likely to play key roles in the mouse brain.[151] It will be interesting to determine whether these factors contribute to sex differences in gene expression or to disease susceptibility. Characterization of neuron-specific or cell-type specific SR co-regulators could lead to the development of neural selective estrogen receptor modulators (SERMs) that potentiate or attenuate ERα/β transcriptional output in a defined population of neurons to provide neuroprotective or mood benefits.

Steroid hormones are also known to produce rapid changes in neuronal function or behavior that occur on the order of minutes, rather than hours or days.[152–154] Notably, many of these non-genomic effects may in fact converge at the level of gene regulation. Studies in diverse tissues and cell types have demonstrated that estrogen and testosterone can act through intracellular signaling cascades to mobilize calcium stores, causing CREB phosphorylation.[155] Phospho-CREB can then activate a number of immediate early genes, including *FOS*, and this cascade is required for estrogen-dependent dendritic spine formation.[156,157] An additional level of cross talk can occur at the level of signaling through Fos itself. Fos protein heterodimerizes with Jun to form the AP-1 transcription factor, which directly binds ERα and recruits it to DNA via a tethering mechanism.[158,159] Thus, steroid hormones can regulate gene expression both through their own consensus DNA-binding sites and through the actions of phospho-CREB and immediate early genes. Such cross talk may explain why social experience can enhance or replace the effects of gonadal hormones on innate behaviors in rodents, as seen in maternal behaviors demonstrated by reproductively naive females exposed to pups.[160–162]

SR expression patterns in the brains of rodents and humans

All four gonadal hormone receptors (AR/PR/ERα/ERβ) are expressed most abundantly in limbic and hypothalamic areas that regulate innate reproductive behaviors, including the bed nucleus of the stria terminalis (BNST), the medial preoptic hypothalamus (MPOA), the medial amygdala (MeA), and the ventrolateral nucleus of the ventromedial hypothalamus.[151,163–168] All but ERβ are expressed in the arcuate nucleus, which regulates homeostasis including feeding and energy balance.[169] Extensive analysis of ERα, ERβ, and PR expression describes signal throughout the cortex and in midbrain areas, such as the ventral tegmental area (VTA), substantia nigra (SNc), periaqueductal gray (PAG), and raphe.[163,164,170–173] Thus, sex differences in reward processing and reward-seeking behavior may

be controlled by the effects of SR function in VTA- and SNc-associated dopaminergic pathways, while expression in the PAG may underlie sex differences in pain processing and analgesia. Similarly, serotonergic projections from raphe nuclei have ramifications throughout the brain, and widespread effects of such neuromodulation may underlie sex differences in fear and anxiety behaviors, as well as stress-sensitivity and the activation of the hypothalamic–pituitary–adrenal axis.[174] AR is also expressed in the cortex, particularly in the primary visual cortex and prefrontal cortex.[175] These four receptors are present in the suprachiasmatic nucleus of the hypothalamus, which regulates circadian rhythm, allowing gonadal hormones to directly influence daily fluctuations in the adrenal output, sleep and mood.[176] Finally, ERα, ERβ, and AR are found in astrocytes and endothelial cells,[176,177] while ERβ has anti-inflammatory effects in microglia.[178] There are still few studies quantifying the co-expression of these receptors or detailing the ontogeny of their expression. RNA-seq experiments and fluorescent double *in situ* hybridization will provide further insight into the shared sites of action of SRs, pinpoint novel hormone-responsive populations, and classify the cell types that express gonadal hormone receptors.

In humans and monkeys, ERα and ERβ are expressed in similar areas as in mice, including high levels in the hypothalamus and amygdala and lower expression in the hippocampus and cortex, particularly the temporal cortex.[179] ERβ is more prominent in the cortex compared to the hypothalamus, with significantly higher levels of expression in the deep layers of the temporal and entorhinal cortex, suggesting that ERβ is the principal modulator of estrogen effects on cognition in humans.[180] AR is similarly expressed in the hypothalamus, amygdala, and temporal cortex, as well as the diagonal band of Broca.[181]

Sex differences in SR expression and the onset of SR expression during brain development have not been well described in humans,[182] and indeed these receptors are only minimally detected in human brain transcriptome studies. Focused gene expression analyses in subcortical areas rich in SRs may therefore identify downstream genes regulated by hormone receptors that show a sex bias in expression. One such region, the accessory basal nucleus of the amygdala, is larger in primates compared with rodents and sends projections to the hippocampus and entorhinal cortex.[179] At a more general level, sex-specific processes in the neural circuits underlying dimorphic behavior can arise from the differentiation of these pathways at different points[183] (Fig. 3). Better understanding of where hormone receptors are expressed in humans, when expression is initiated during development, and the connectivity of these regions is necessary to understand how gonadal hormones can specify unique developmental trajectories in males and females.

As discussed above, surges in testosterone during early development mediate male-specific aspects of early brain development and differentiation. Lasting changes in gene expression programmed by such developmental hormone surges or perturbations during hormone-mediated sexual differentiation of the brain may therefore contribute to the male bias observed in some neuropsychiatric disorders. Despite limited knowledge of the extent of SR expression in the human brain, sex differences in specific syndromes may be linked to hypothalamic dysfunction stemming from abnormal activity or development in individual nuclei. For example, sex differences in impulsivity in the form of aggression and hypersexual behavior seen in neurodevelopmental conditions such as ASD are thought to

arise, in part, as a consequence of SR-regulated sex dimorphisms in hypothalamic nuclei that control reproductive drive and contribute to affective state.[184] Similarly, it has been well documented that males and females differ in patterns of activation in the amygdala in response to acute stress, and sex differences in the sensitivity of the amygdala to chronic stress, as well as in the connectivity and function of corticoamygadlar pathways, is thought to underlie aspects of the dramatic sex differences in the incidence and presentation of depression and anxiety.[185–187] In addition, sex differences in the function and connectivity of serotonergic projections from the raphe nuclei throughout the brain also likely contribute to the dimorphisms seen in mood and anxiety disorders, as well as the response to medications that act on these pathways.[188–190] Finally, the dense interconnectivity of reward pathways with frontal cortical circuitry is involved in attention, planning, and other aspects of cognition and may contribute to sex differences in the incidence and presentation of ADHD, as well as schizophrenia.[191–193] In a similar manner, it is likely that sex differences in midbrain dopaminergic signaling underlies some of the sex differences in patterns of drug abuse and addiction, as well as the difference between the sexes in their response to antipsychotic medications.[194–196]

Integrating patient sequencing studies and patient symptoms to link genes to pathology

As the list of syndromic neuropsychiatric disorders—those caused by mutations in specific genes—continues to grow, deep phenotypic analyses of the discrete patterns of deficits caused by disruption of individual genes will help to elucidate the developmental and molecular programs that underlie specific and shared neural processes. Most neuropsychiatric conditions are thought to occur as a consequence of the interactions of environmental risk factors with genetically specified developmental sensitivity. The advent of high-throughput sequencing led to an explosion of patient-sequencing studies that provided fundamental insight into the developmental origins of psychiatric disorders. We will now examine the findings in ASD and schizophrenia to discuss the possible mechanisms by which epigenetic regulation of neural development may interact with pathways for sexual differentiation in the nervous system.

Using a wide range of techniques to examine patterns of mutations associated with neuropsychiatric conditions, culminating recently with whole-exome sequencing of patients and their parents and siblings to identify *de novo* and rare coding mutations, many studies have led to the identification of genes whose mutation correlates with the occurrence of ASD and schizophrenia, as well as depression and bipolar disorder (reviewed in Refs. [197–201]). Whole-genome sequencing is now extending this work to identify noncoding mutations associated with disease.[202,203] These studies are likely to identify regulatory elements that direct specific aspects of brain development and function and may provide insight into the majority of disease cases, which have no currently known genetic origin. With regards to ASD in particular, in addition to implicating neural specific processes, including synaptic structure and neuronal excitability, these studies revealed a critical role for genes implicated in chromatin and transcriptional regulation in the pathogenesis of these disorders[66,197,200,204] (Fig. 4). Integrating patient genome–sequencing studies with human

gene expression and epigenomic data has identified key regulatory nodes and pathways highlighting the importance of chromatin regulation in brain development and function.[66,197,200,204–213]

ASD and schizophrenia: shared genes but distinct trajectories?

Recent evidence suggests an overlap in the genetic risks for ASD and schizophrenia with regard to rare copy number variants and *de novo* mutation events, particularly for genes involved in synaptic function and immune regulation, though the contribution of shared common genetic risk between these disorders is less clear.[214–216] Like ASD, the incidence and presentation of schizophrenia shows a significant difference between males and females.[217] Males typically present earlier in adolescence with more severe symptoms and poorer outcomes, suggesting that fundamental sex differences in the developing brain contribute to the onset and pattern of deficits. However, despite some overlap in the mechanisms contributing to ASD and schizophrenia and aspects of the behavioral and cognitive deficits with which they present, the dramatic difference in their trajectories illustrates the central role of distinct developmental periods.

As discussed above, ASD is typically diagnosed early in childhood, suggesting disruptions of early developmental programs in the brain that result in deficits at the earliest stages of life. Consistent with this hypothesis and the identification of multiple genes involved in chromatin regulation and structure as risk alleles, recent work has identified genome-wide alterations in the regulation of noncoding RNAs, patterns of histone modification, and higher-order chromatin structure in tissue from patients with ASD.[211,213,218,219] In contrast, the majority of symptoms in schizophrenia evolve during adolescence, suggesting that distinct developmental programs or mechanisms that are activated by the onset of puberty may play roles in the pathogenesis.[220] The initiation of developmental programs following the onset of puberty occurs via SR-dependent and SR-independent pathways, both of which contribute to the restructuring and development of the nervous system for adult and sexually dimorphic behaviors. A hallmark of these processes that occurs following the initiation of these pathways at the onset of puberty is, for example, the elimination of synapses in regions, including the prefrontal cortex, that continues throughout adolescence and into early adulthood.[221,222] Consistent with these observations at the cellular level, functional studies demonstrate that cortical gray matter volume peaks before adolescence and then slowly declines until reaching its adult volume.[223] Such synaptic pruning is thought to achieve the balance of excitatory and inhibitory activity in adult cortical regions, with adult patterns of inhibitory activity in prefrontal cortical regions implicated as an essential part of network dynamics and synchronized activity thought to underlie cognition and cortical processing.[224,225] An intriguing additional mechanism for sex differences in the incidence and presentation of psychiatric illnesses during adolescence is the role of microglia in the maturation and pruning that occurs during this adolescent period and the sex differences in gene expression that suggest additional dimorphisms downstream of their activity.[226,227] Thus, the developmental programs initiated by the onset of puberty that persist throughout adolescence and into early adulthood represent fundamental programs of reorganization that may unmask or create new substrates for the neuropathology that underlies adult presentations of psychiatric illnesses.[228]

Intriguingly, recent work suggests shared common genetic overlap in social communication difficulties and both ASD and schizophrenia but distinct patterns in the relationship between genetic traits and each disorder, largely consistent with the onset of clinical symptoms.[216] Thus, while the sex differences in ASD may be a consequence of the early sex differentiation of the brain during embryonic and perinatal development, those observed in schizophrenia are likely a consequence of the regulatory epigenetic landscape established during this period but only activated by the onset of puberty. In this context, sex differences observed in the onset and presentation of schizophrenia could arise either from the direct activation of genes in a sexually dimorphic manner by gonadal hormones or through signals in adolescence common to both sexes acting on poised sexually dimorphic programs established early in development (Fig. 2).

Consistent with both models, sequencing studies of sex-biased gene expression in regions of the human brain at distinct developmental time points reveals limited overlap between sex-biased genes early in development and in adolescence and an enrichment for genes implicated in neuropsychiatric illness in those with a male expression bias.[229] Future studies will undoubtedly reveal whether additional sets of mutations associated with schizophrenia are enriched in regulatory regions that mediate aspects of gene regulation specifically during adolescence, thus contributing to the developmental window during which symptoms and sex differences manifest.[202,230–235]

Sex differences and stress: intersection at the level of DNA

As a final example of how such regional regulation of sexually dimorphic differentiation of the nervous system may contribute to sex differences in neuropsychiatric illness, we consider role of early life stress in the later onset of depression. Women have twice the lifetime risk of developing depression compared with men and appear to experience symptoms that are more severe and diverse.[236,237] Like many other major neuropsychiatric conditions, major depressive disorder typically evolves during early adolescence, with an earlier and distinct presentation in girls compared with boys.[238,239] This suggests that sex-specific pathways that regulate mood are activated by the onset of puberty and may intersect with stress response pathways to contribute to gender-specific symptoms.[240,241]

Increasing evidence supports a role for epigenetic changes in the pathogenesis of depression, particularly in response to early-life stress. The interactions with stress signaling and the pathways for sex differentiation suggest a mechanism by which the activation of stress pathways may act sex-specifically to control the response to chronic stress.[184,239,242] These findings are supported at the gene regulatory level by recent studies on cross talk between SRs and glucocorticoid receptor (GR). In response to stress, the adrenal glands release glucocorticoid hormones: cortisol in humans and corticosterone (CORT) in rodents. In the brain, CORT binds to both glucocorticoid (GR) and mineralocorticoid (MR) receptors. MR and GR have a highly homologous DNA-binding domain but possess different affinities for CORT: MR has a very high affinity of 0.5 nM, while GR affinity is about 10-fold lower.[243] Thus, MR is thought to respond to the onset of stress, while GR responds to increasing levels of CORT to end the stress reaction and promote memory consolidation,[244] although a recent *in vivo* study found that these receptors heterodimerize in response to acute stress.[245]

Both receptors are expressed in the hippocampus and lateral septum, while GR is found in many other areas, including the central amygdala, paraventricular hypothalamus, and prefrontal cortex.[246,247]

The DNA-binding domains of GR and MR are homologous to those of AR and PR; therefore, all four of these receptors can bind the same recognition sequences.[143] ChIP-seq data from castration-resistant prostate cancer (CRPC) has shown that half of AR occupancy sites are bound by GR in dexamethasone-treated cells and that GR can substitute for AR to regulate a subset of AR transcriptional programs.[248] These observations reveal a mechanism by which stress can alter sexual differentiation of the brain. For example, FK506-binding protein 5 (FKBP5) is a GR target gene and co-factor that that has been implicated in depression, posttraumatic stress disorder (PTSD), and anxiety.[249] AR directly increases FKBP expression in the prostate through multiple distal and intronic enhancers,[250,251] but regulation of FKBP5 by testosterone signaling in the brain has not yet been explored. GR recruitment can also modify chromatin to facilitate binding by other transcription factors in a process known as *assisted loading*.[252] ChIP-seq studies have demonstrated that GR increases chromatin accessibility to modulate ERα binding to DNA through AP-1 sites.[253,254] This could potentially lead to new estrogen-responsive gene programs after a period of stress. Taken together, these studies suggest that stress can directly alter regulation of gene expression by gonadal hormones in the brain (Fig. 5).

Intriguingly, hypermethylation of the GR locus has been observed in hippocampal tissues from males with a history of abuse who completed suicide.[255,256] Both sexes show changes in DNA methylation in immune-related genes in the context of PTSD, while some sex differences are observed in non-neuronal cell types in the setting of depression,[257,258] highlighting a role for epigenetic changes in mediating long-term pathology via cell type–specific mechanisms. Indeed, multiple studies have already identified heterogeneity in patterns of methylation across neuronal populations.[259,260] Thus, pathways induced by chronic stress are likely to interact both with mechanisms that mediate long term, sex-specific patterns of gene regulation across the genome, as well as direct activation of targets of sex hormone regulation to mediate the pathogenesis of depression and PTSD.

Conclusions

In summary, epigenetic mechanisms likely mediate sex-specific differentiation in the nervous system at every stage of development. As these pathways elaborate, the impact of genetic and environmental factors that contribute to psychiatric illness can thus have distinct effects in either sex, contributing to sex differences in the time of presentation, pattern of symptoms, or severity of illness. As we continue to understand the specific developmental programs and neural process that mediate sex-specific differentiation and function in the brain at particular developmental time-points, we will gain deeper insights into how specific mutations sensitize individuals to distinct neuropsychiatric conditions. Although we are not yet capable of developing treatments that target specific epigenetic mechanisms or sex-specific developmental processes to ameliorate the symptoms of any psychiatric illness, understanding how these mechanisms contribute to these conditions in both sexes is critical to the future of treatment in mental health.

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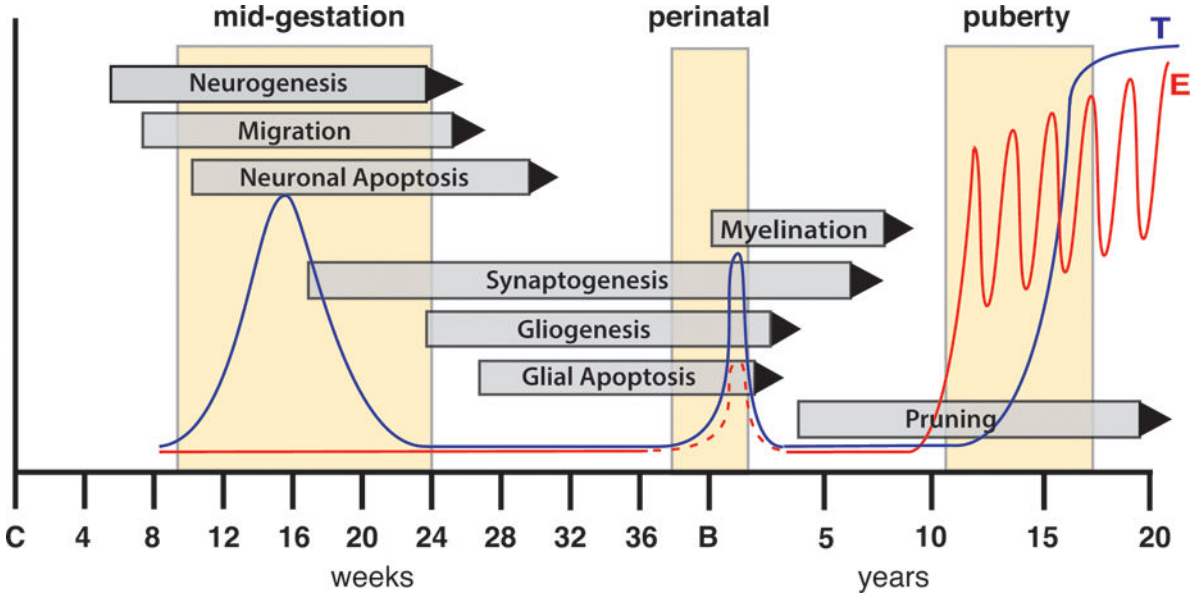

Figure 1.

Intersection of hormone surges with stages of brain development and maturation. Major events in neural development are depicted during human gestation (weeks) and into adulthood (years). Fluctuations in hormone levels intersect with these events in a sex-specific fashion; critical periods for sexual differentiation of the brain are boxed in orange. Male testosterone levels (blue line) begin to rise during the eighth week of gestation as the testes mature, peak around week 16, and decline after week 24. Testosterone levels spike again in infancy with a peak around 1–3 months and then remain flat until the onset of puberty. In contrast, in females, the ovaries are largely inactive during gestation and begin to secrete estradiol (red line) and progesterone during puberty. There is also evidence of estradiol secretion in female infants, but the exact levels and duration are not well described.

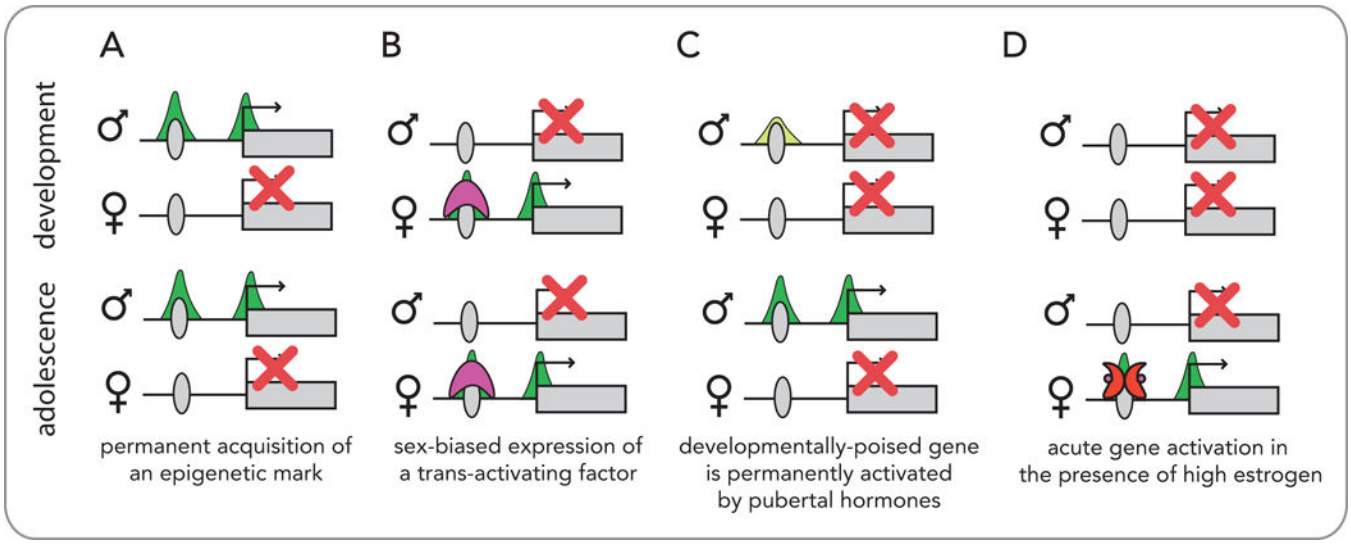

Figure 2.

Gene regulatory strategies for achieving sex-biased gene expression. Sex differences in gene expression can be patterned by differential exposure to gonadal hormones during early life or puberty. Such differences can arise either from epigenetic events where lasting changes in chromatin state are established by transient exposure to hormone or through the induction of a *trans*-acting factor. (A) During developmental hormone exposure (mid-gestation or perinatal), ligand-bound steroid hormone receptors induce an active chromatin state (green peak) on an enhancer (grey oval), thereby causing a gene to be expressed more highly in males. (B) Alternatively, a chromatin modifier, co-regulator, or transcription factor may be present in one sex or the other; here, this scenario is depicted in females. The effects of early hormone signaling may not become apparent until puberty. (C) Male hormones prime a gene for later expression during adolescence (yellow peak indicates poised enhancer). (D) Cycling hormones in adolescent and adult females regulate gene expression acutely in the presence of estradiol or progesterone. A ligand-bound ERα homodimer is depicted in red.

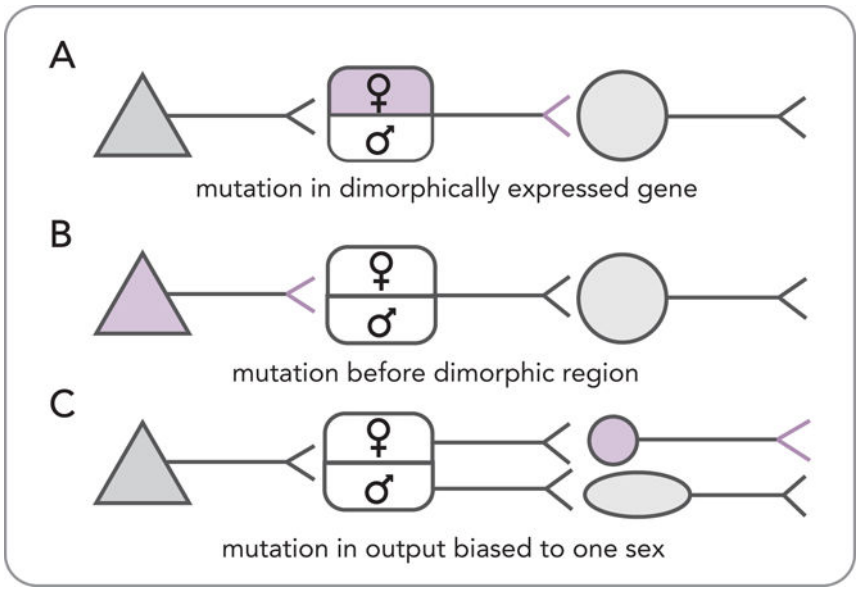

Figure 3.

Sex-specific function in neural circuits and effects of mutations. Sex-specific differentiation in the nervous system may occur at different points in neural circuits to produce gender-typical behaviors. (A) A mutation may therefore alter expression of a gene that is expressed in a sex-specific manner in a brain region, thereby changing its output to cause phenotypes in only one sex. (B) Alternatively, a mutation may produce different effects in the two sexes non-cell autonomously by affecting the function of a region functionally upstream of sex-specific circuitry to cause distinct phenotypes in each sex. (C) Finally, functional disruption of a downstream behavioral output region that receives sexually dimorphic input can also produce a different effect in the two sexes; here, the mutation changes the response of neurons that receive more input in females compared with males.

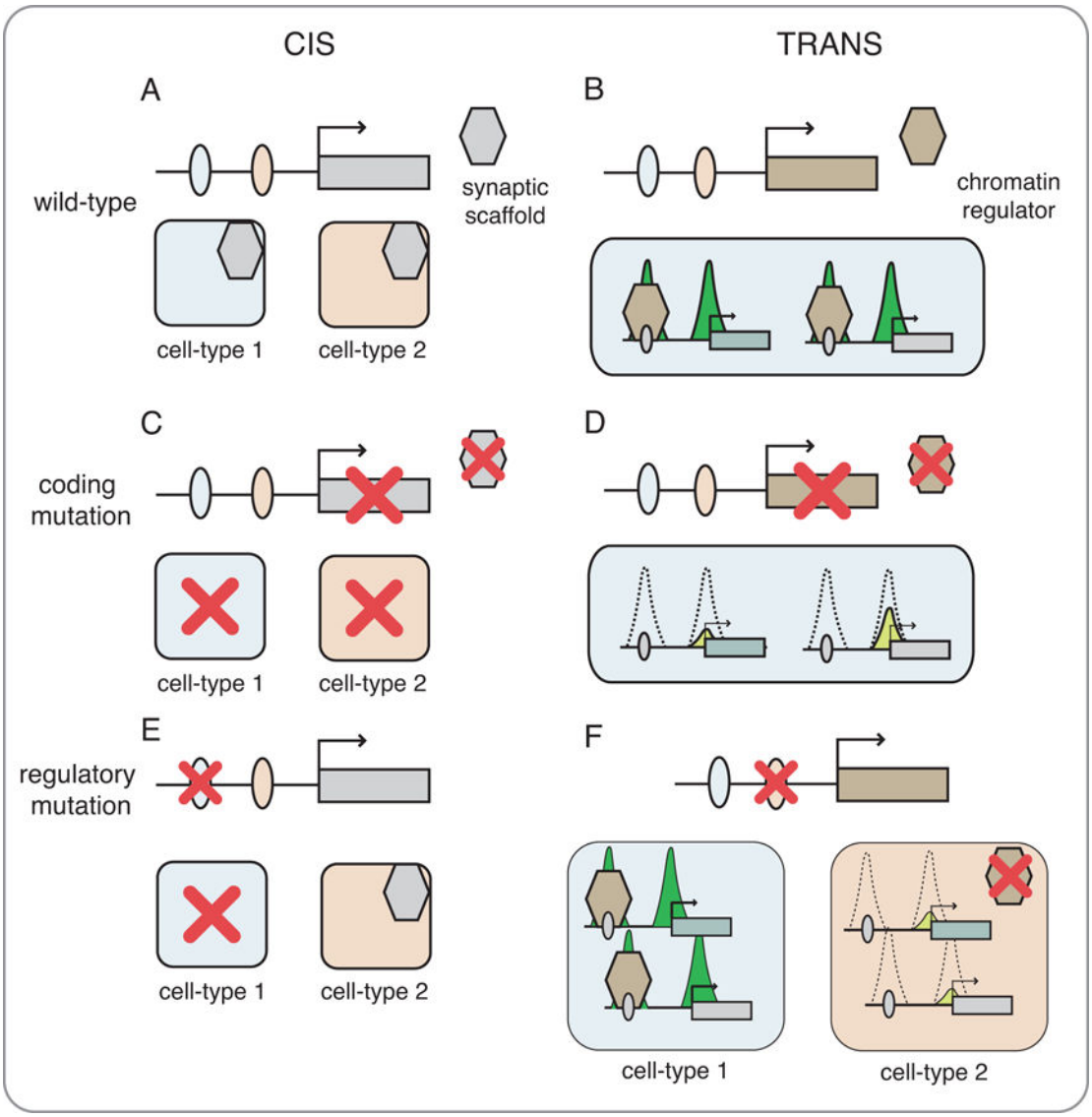

Figure 4.

Mechanisms of gene regulation and effects of disease-associated mutations. Genes implicated in cell-specific neuronal function may (A) encode proteins that are expressed in distinct cell types or (B) regulate chromatin structure to control patterns of the expression of many genes in specify distinct cell types . (C) Profound phenotypes may arise from a loss-of-function mutation (LoF) in a coding sequence of a broadly expressed gene. (D) Mutations in a chromatin regulatory factor affect gene expression in trans by changing chromatin state at multiple target genes, thereby resulting in dysregulation of gene expression but not complete LoF. (E) Alternatively, a mutation in a regulatory element could alter spatial or temporal aspects of gene expression, effectively causing a LoF in a specific context, such as a distinct cell type. Active chromatin states are depicted in green in wild-type individuals and attenuated to a yellow-green when the chromatin regulator is not functional. (F) Finally, a mutation in an enhancer of a chromatin regulator can lead to aberrant chromatin patterning

in only a subset of neurons or developmental stages, resulting in a comparatively mild phenotype.

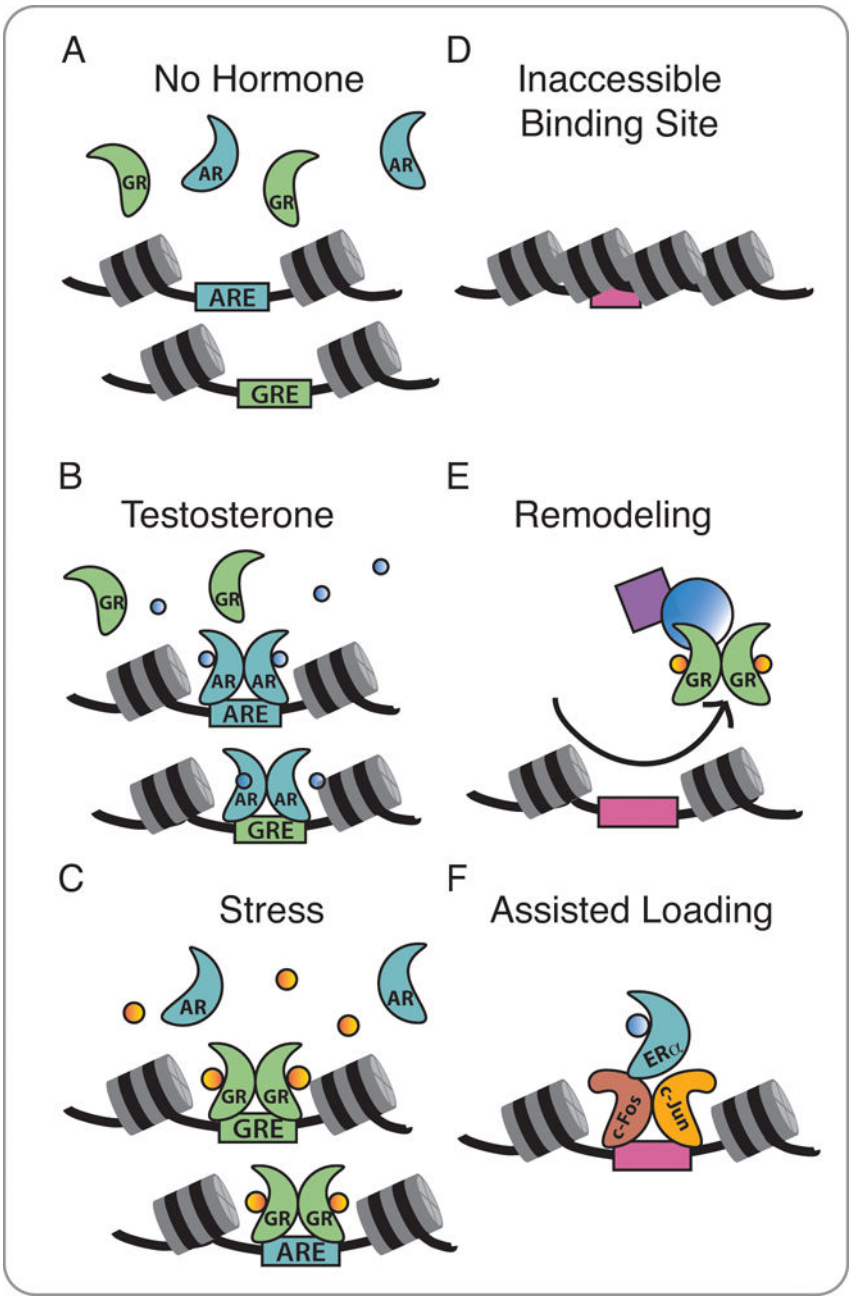

Figure 5.

Cross talk between gonadal hormone signaling and stress response. (A) In the classical model of nuclear receptor action, there is no binding of AR to its consensus androgen response elements (ARE) in the absence of ligand. (B) When testosterone is present, AR homodimerizes and binds AREs, but can also bind glucocorticoid response elements (GREs) that are typically responsive to CORT. (C) Conversely, in the presence of CORT, GR can both activate its own GRE targets and bind AREs to activate testosterone-responsive genes. GR can also open (inaccessible chromatin (D) through transient binding to non-consensus

sites, and € recruitment of chromatin-remodeling machinery. (F) This action reveals additional binding sites that can later be bound by ERα tethered to AP-1.