Sex Differences in Neurodevelopment and Its Disorders

11

Richard E. Brown

Learning Objectives

- The role of genes in sex determination.
- The role of hormones in sexual differentiation.
- That sex differences develop during critical periods of development.
- That genes and hormones are involved in the sexual differentiation of the brain
- That there is a sexual differentiation of glial cells (astrocytes and microglia) and that these cells are involved in the sex differentiation of the brain and neuroendocrine system.
- That there are sex differences in brain structure, function and neurochemical pathways that underlie sex differences in NDD.
- That the sexual differentiation of the hypothalamic-pituitary (neuroendocrine) system results in sex differences in the secretion and actions of hormones throughout the body.
- That hormones may underlie the sex differences in NDD disorders.
- That puberty is a critical period for the reorganization of brain and neuroendocrine systems during the transition from childhood to adulthood.
- That neurotoxins and endocrine-disrupting chemicals in the environment can disrupt sexual differentiation during critical periods of development.

Highlights

- Sex differences depend on the XX and XY chromosomes.
- Sex differences depend on the gonadal steroid hormones, estrogen, and testosterone.
- Sex differences depend on the sexual differentiation of neurons and neurotransmitter pathways in the hypothalamus and related brain areas: the amygdala, hippocampus, and arcuate nucleus.
- Sex differences depend on glial cells and gliotransmitters.

Introduction to Sex Differences in Neurodevelopmental Disorders

Anatomical, physiological, and cognitive-behavioral systems in mammalian development all show some form of sexual dimorphism [1–3]. Sex differences also occur in susceptibility to disease [4], and among neurological diseases, "virtually every neurodegenerative and neuropsychiatric disease shows some variation, often striking, between males and females" ([5], page 2). Zagni, et al. [6] noted that NDDs occur more often in males, while adult-onset neurological disorders have a higher frequency in females. Neuroendocrine abnormalities may underlie a number of NDDs [7, 8] and this chapter examines the genetic, epigenetic, and neurochemical factors that underlie sex differences in NDDs.

Table 11.1 lists some NDDs, giving estimates of their frequency of occurrence per 100 children [9] and the sex ratio of children with each disorder [10, 11]. In many NDD, the sex ratio may not differ, but the neural and behavioral manifestations of the disorder show sex differences [12, 13]. This chapter describes the process of sex determination and then examines the role of genes, hormones, glial cells, and neuroimmune interactions in sexual differentiation of the brain and nervous system and how these mechanisms regulate sex

R. E. Brown (✉)
Department of Psychology and Neuroscience, Department of Physiology and Biophysics, Dalhousie University, Life Sciences Centre, Halifax, NS, Canada
e-mail: rebrown@dal.ca

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Table 11.1 List of NDD, prevalence, and sex ratios

Disorder	Prevalence per 100 (%)	Sex Difference (M:F)	Reference
ADHD	5.0	2.1–3.0:1.0 (M>F)	[11, 365, 366]
Angelman Syndrome	0.0040	1.0: 1.0 (M=F)	[367]
Asperger syndrome	0.005	4-6:1 (M>F)	[366]
Autism Spectrum Disorder	0.65	4.0:1.0 (M>F)	[11, 365, 366]
CDKL5		1.0:5.0 (F>M)	[367]
Cerebral Palsy	0.15	1.0:1.0 (M=F)	[10]
Cornella de Lange Syndrome	0.0014	?	[10]
Cri du Chat Syndrome	0.0020	(F>M)	[10]
Depression & Anxiety		1.0:2.0 (F>M)	[11]
Developmental coordination disorder	6.5		[368]
Developmental dyscalculia	3.0	?	
Developmental dyslexia	6.0	?	
Developmental intellectual disability	0.004-0.0300	1.0:1.0 (M=F)	[366]
Down syndrome	0.1667		[10]
Duchenne muscular dystrophy	0.0143		[10]
Fetal Alcohol syndrome	0.1000	1.3:1,0 (M>F)	[10, 369]
Fragile X syndrome	0.0615	2.0:1.0 (M>F)	[10]
Galactosemia	0.0020	?	[10]
Intellectual disability	5.5	1.6:1.0 (M>F)	[365]
Klinefelter syndrome (XXY)	0.086	Only males	[10]
Language disorders		M>F	[370]
Lesch-Nyhan syndrome	0.0005		[10]
Lowe syndrome	0.0005		[10]
Marfan syndrome	0.0067	M=F	[10, 367]
Motor disorders	3-6%		[365]
Multiple sclerosis		1.0:2.0–3.0 (F>M)	
Neurofibromatosis Type 1	0.0308		[10]
Noonan syndrome	0.0571	M>F	[10, 367]
Phenylketonuria	0.0100	?	[10]
Prader-Willi Syndrome	0.0067	M=F	[10, 367]
Rett Syndrome	0.0080	Only F	[10, 367]
Rubinstein-Taybi Syndrome	0.0008		[10]
Specific language impairment	7.4	M>F	[370]
Specific Learning Disorder	5–15	2.1–3.1/1.0 (M>F)	[365]
Tic disorders	.3%	2.1–4:1.0 (M>F)	[365]
Tourette Syndrome	0.5000	M & F differ in Symptoms	[10, 371]
Tuberous sclerosis	0.0167	M=F	[10, 367]
Turner Syndrome (45XO)	0.0400	F only	[10]
Trisomy 18	0.0250		[10]
Chromosome 22q11.2 Deletion Syndrome			
Velocardiofacial syndrome	0.0250		[10]
Williams Syndrome	0.0044	M=F	[10, 367]
XYY syndrome	0.0545	Only males	[10, 367]
Trisomy X(XXX)	0.0550	Only females	[10, 367]

differences in the development of NDD. The chapter concludes with a discussion of sex differences in NDD at puberty and a discussion of the theories about the causes of sex differences in NDDs.

Sex Determination and Sexual Differentiation

In mammals, sex determination depends on the genes on the sex chromosomes, while sexual differentiation depends on the action of gonadal hormones and other chemical signals, which activate gene expression differentially in each sex. Females have two X chromosomes (46 XX in humans; 40 XX in mice), while males have an X and a Y chromosome (46XY in humans; 40XY in mice). Most of the research has been done on rodents and the ability to make genetically modified mice has enabled sex differences determined by genes and those determined by hormones to be dissociated [3, 14–19].

Masculinization depends on the *SRY* ("sex-determining region Y") genes on the TDF (testis-determining factor) locus on the Y chromosome [20–25]. Early in embryonic development, the gonads are undifferentiated and are identi-

cal in males and females, having bipotential precursor cells which can develop either into testis or ovaries. The differentiation of the bipotential gonad into a testes is determined by the *SRY* genes on the Y chromosome and is controlled by a cascade of gene expression which is regulated by transcription factors. The differentiation of these precursor cells into testes is induced by the expression of the *SRY* gene in somatic cells that differentiate into Leydig (Androgen producing) and Sertoli (sperm producing) cells.

If there is no Y chromosome or if the *SRY* gene is missing, the bipotential precursor cells of the gonad develop into ovarian follicular cells and, under female-specific gene expression, oocytes develop. If there is a Y chromosome or if an X chromosome has *SRY* gene, testes develop. At the beginning of embryonic development, embryos of the two sexes differ only by their sex chromosomes, but once the Sertoli cells begin to secrete androgens, sexual differentiation begins. The *DMRT1* gene is essential for maintaining the differentiated testes and for preventing ovarian development in postnatal mouse testes [21, 26]. The Y chromosome may therefore act independently of sex hormones to regulate sex differences in growth and metabolism, cardiovascular diseases, immune system physiology, and autoimmune and infectious diseases [16, 27]. The testes-determining gene *SRY* is also expressed in the hypothalamus, midbrain, and cortex and masculinizes these neurons. *SRY* is particularly expressed in the Tyrosine hydroxylase (TH) containing dopaminergic neurons of the Substantia nigra pars compacta (SNpc) that project to the striatum and masculinizes these neurons which are involved in motor behavior [28]. Downregulation of *SRY* in these TH neurons in the substantia nigra (SN) results in deficits in DA and in sensori-motor function (as occurs in Parkinson's disease, which occurs more often in males than females) [28].

There is no single ovary-determining gene in females that is analogous to *SRY* in males, but there are a number of genes and transcription factors that activate ovarian development in the absence of *SRY*. Throughout the development of the ovary, the *FOXL2* gene is required to suppress *DMRT1* expression and prevent the masculinization of granulosa and theca cells into testicular Sertoli and Leydig cells [21, 26]. The granulosa cells of the ovary produce the female sex steroid hormones, estrogen and progesterone, and the follicular cells produce the oocytes [20, 25, 29].

Although females have two X chromosomes, one is inactivated in each cell during development, so that females are mosaics, with some cells having a maternal X chromosome (Xm) and some cells having a paternal (Xp) chromosome [3]. Thus there is a sex difference in X chromosome "dosage": females have two X chromosomes and males only one [30]. There are three X chromosome effects that influence sexual differentiation: (1) The X chromosome that is inactivated can be from the mother (Xm) or from the father (Xp) resulting in "*parental imprinting*" or parent of origin effects as the active X chromosome expresses the trait of the parent from which it was derived ("you have your mother's eyes, but your father's nose"); (2) Some genes *escape from X inactivation* and are expressed on both X chromosomes in females; and (3) Some genes are "dosage dependent" and cells with two X chromosomes may express more of these genes than cells with one X chromosome [30]. Genes on the X chromosomes appear to influence sex differentiation of females, but the expression of genes on the X chromosomes is a complex phenomenon.

Genetic and Epigenetic Disorders of Sex Determination

A number of NDDs are due to abnormalities in sex chromosomes and sex determination [31] (Table 11.2). These disorders are the result of abnormalities in gene transcription during the differentiation of the bipotential gonad into testes or ovaries [32, 33]. In Turner's syndrome, a female has only one X chromosome (45X0) and is incompletely feminized, with gonadal dysgenesis, premature loss of oocytes, and infertility. In Klinefelter's syndrome, the most common disorder of male sex determination, a male has one or more

Table 11.2 Disorders of sex determination and sex differentiation and the five sexes [26, 34, 296]

A. Disorders of sexual determination: Genetic disorders	
46XX	Normal female
45X0	Turner's syndrome (female) 1:2000 girls
47XXX	Trisomy X (female) 1:1000 girls
$46XX^{Y}$	Masculinized female or XX male syndrome (male) 1:25,000 males
47XXY	Klinefelter Syndrome (males) 1:600 births
48XXYY	48 XXYY syndrome (male) 1: 18,000 males
47XYY	XYY syndrome (male) 1:1000 males
46XY	Normal male
B. Disorders of Sexual differentiation: Hormonal disorders	
Female: Ovaries and vagina	
Masculinized females: Congenital adrenal hyperplasia: Ovaries and Penis	
Hermaphrodite: Ovaries & testes; Penis and vagina	
Feminized male: Congenital androgen insensitivity syndrome: testes and vagina	
Kallmann syndrome: Failure of the development on the GnRH neurons: hypogonadotropic hypogonadism (HH) with anosmia	
Females that are masculinized at puberty: 5alpha-reductase 2 deficiency: testes	
Male: testes and penis.	
C. The Five sexes	
Male	
Male pseudohermaphrodite	
True hermaphrodite	
Female pseudohermaphrodite	
Female	

extra X chromosomes (47XXY; 48XXXY) and is partially feminized, resulting in small testes, infertility, and the possibility of ambiguous external genitalia at birth [26, 34, 31]. Trisomy X (47XXX) is the most common female chromosomal abnormality and has little effect on sexual differentiation [35]. If the *SRY* gene is displaced from the Y to the X chromosome, then a person with a $46XX^{SRY}$ phenotype is masculinized and develops male genitals. Because there is a "normal" male phenotype, this disorder is often not discovered until puberty is delayed or men are found to be infertile or develop gynecomastia. However, the testes may be small and there may be incomplete masculinization of the external genitals at birth [36]. Males with 47XYY syndrome have a normal male phenotype but may have reduced fertility [37]. In 48XXYY syndrome males have both an extra Y and an extra X chromosome, resulting in hypogonadism and reduced fertility [38]. In the majority of these sex chromosome disorders, there are neurobehavioral developmental disorders, which are described in the references cited.

The differentiation of the bipotential gonad into testes or ovaries requires epigenetic mechanisms that regulate the temporally organized sequence of gene expression for both sex determination and sexual differentiation [39]. DNA methylation is essential for X chromosome inactivation and for genomic imprinting and epigenitic dysfunction can disrupt these processes in developing females. Disorders of DNA methylation may also disrupt the ability of the *SRY* gene to masculinize males [40]. Likewise, disruption of histone methylation and noncoding RNA functions can disrupt sex determination [39]. Environmental stimuli, including nutrients and endocrine disruptors, can also disrupt sex determination and sexual differentiation [41].

The Neurobiology of X-Linked Intellectual Disabilities and Infectious Diseases

Over 140 genes on the X chromosome may contribute to X-linked intellectual disabilities [42] and other X-linked genes contribute to immune system function and susceptibility to infectious diseases [43]. Because males have only one X chromosome, many X-linked intellectual disorders affect males more than females; however, some of these, such as fragile X syndrome, affect both sexes. Others, such as Rett syndrome (RTT) and CDKL5 syndrome, occur almost exclusively in females [44, 45] but do occur in some males [46–48]. Sex hormones interact with genetic and epigenetic factors in determining sex differences in NDD and this interaction will be discussed in Section "Genetic and epigenetic factors in brain sexual differentiation". Mutations in X-linked genes involve loss of neuronal function by altering dendritic spine size, shape, and density, resulting in the impairment of both excitatory and inhibitory neurotransmission [49]. The synaptic pathologies related to Fragile X syndrome are caused by mutations in the Fmr1 gene; RTT, caused by Mecp2 gene mutations; and "atypical Rett syndrome," caused by CDKL5 mutations [49]. X-linked NDD can also be caused by mutations in Rgo GTPase genes and genes coding for cell adhesion proteins, such as L1CAM and the Neuroligins, all of which affect synapse function [49].

Human females have a stronger innate and humoral immune response than males and are, therefore, less susceptible to many infectious diseases (bacterial, fungal, parasitic, and viral infections) but more prone to autoimmune disorders [43, 50, 51]. These sex differences in immune responses (Fig. 11.1) may be due to X chromosome-linked genes and to X chromosome inactivation as the noncoding micro RNAs on the X chromosome can influence the sex bias in disease frequency [43, 51]. As a result of sex differences in the immune system, there are also sex differences in responses to vaccines, with females showing not only greater antibody responses to vaccines than males but also more adverse side effects [52]. Because females with Turner's syndrome (45 X0) have only one X chromosome, their immune responses are impaired compared to 46XX females, while males with Klinefelter's syndrome (47XXY) have one X chromosome inactivated and they have a feminized immune response [43, 50].

Since the androgen receptor is also coded for by genes on the X chromosome, sex differences due to the actions of testosterone are regulated by genes on the X chromosome [43]. Since testosterone inhibits immune system activity by upregulating inflammatory cytokines, such as IL-10, and estrogen enhances immune system responses by upregulating pro-inflammatory cytokines, such as TNFa, the genes on the X chromosome modulate sex differences in susceptibility to infectious diseases [43, 50]. While some of the sex differences in disease susceptibility are only evident after puberty, sex differences in immune responses also occur in infancy and old age, suggesting that genes on the sex chromosomes and the sex hormones may have independent effects on sex differences in immune responses [43, 50, 51, 53].

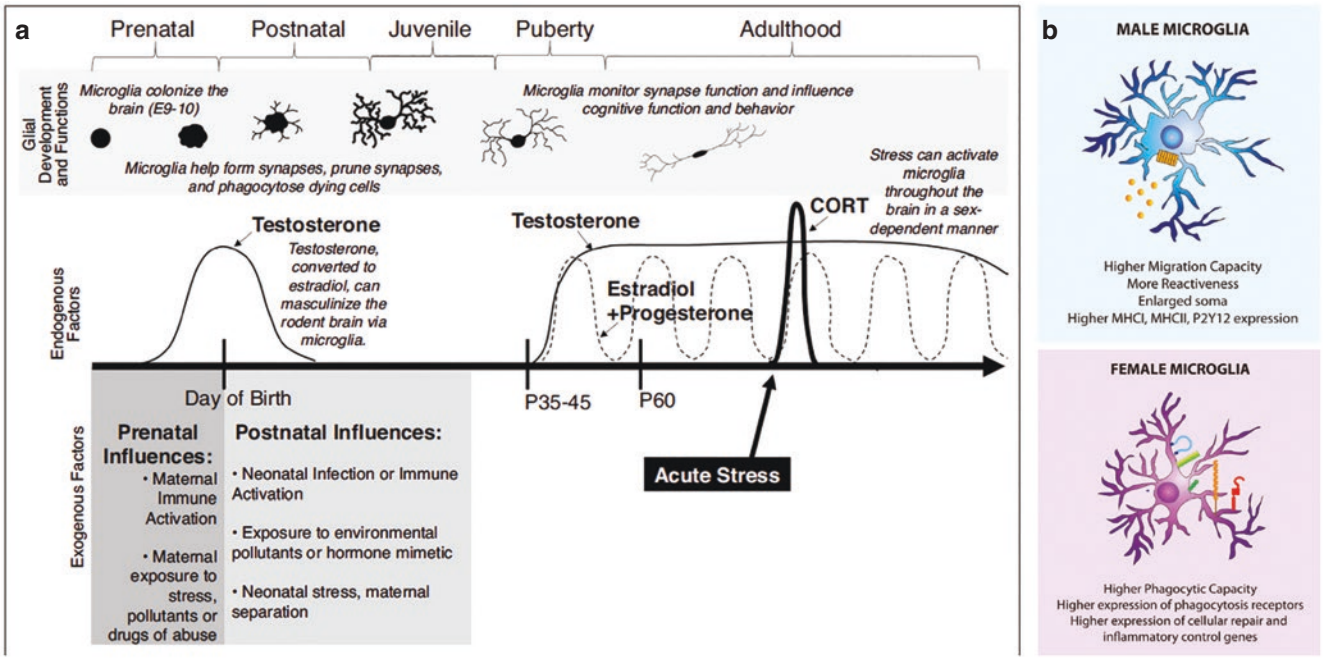

Fig. 11.1 Microglia, hormones, and sexual differentiation during critical periods in the developing brain. (**a**) Microglia and the development of sex differences in the brain. Microglia regulate synapse development and function in the brain, and the development of microglia is regulated by the sex hormones and by environmental stimuli, such as infections, pollutants, endocrine-disrupting chemicals, and stress. Microglia colonize the brain early in development (embryonic day (E) 9–10 in rodents) and regulate the development and function of synapses by initiating synapse formation, pruning aberrant synapses, and phagocytosing naturally dying cells. During the perinatal critical period testosterone masculinizes microglia in males, resulting is male and female microglia. Sexually differentiated microglia influence many neurodevelopmental processes. There are also many perinatal events that can program the function of microglia and later life behavior in a sex-dependent manner. In general, males are more vulnerable to early life insults, including immune activation or stress. Later in life, microglia continue to have an important role in monitoring synapse function and formation, and thereby influencing cognitive function and behavior. During this time, microglia can be influenced by circulating sex steroid hormones, either testosterone in males or estradiol and progesterone in females. Acute stress can also induce the activation of microglia in the brain via glucocorticoid secretion (CORT), in a sex-dependent manner. [**From:** Osborne BF, Turano A, Schwarz. 2018. Sex differences in the neuroimmune system. Current Opinion in Behavioural Sciences. 23: 118-123. Figure 1]. (**b**) Physiological sex differences in male and female microglia. Male microglia have an enlarged soma and more reactiveness in physiological conditions than female microglia. Male microglia also have more pro-inflammatory responses, higher migration capacity, and enhanced Major Histocompatibility Complex, type 1 and 2 (MHCI & MHCII), and adenosine diphosphate receptor P2Y12 gene expression compared to female microglia. Female microglia have a higher phagocytic capacity and higher gene expression of cell repair and inflammatory control genes than male microglia. [**From:** Yanguas-Casas N. 2020. Physiological sex differences in microglia and their relevance in neurological disorders. Neuroimmunology and Neuroinflammation 7: 13–22. Figure 1 [290]]

Sexual Differentiation of the Brain

As discussed in Chap. 1, sexual differentiation occurs during three critical (sensitive) periods (Fig. 11.1): (1) a prenatal critical period during which androgens masculinize males; (2) a postnatal sensitive during which estrogens feminize females; and (3) a pubertal sensitive period during which secondary sex characteristics develop and sex differences in the brain and neuroendocrine system become activated [15, 54–59]. Sexual differentiation during these critical periods involves interactions between genes, sex hormones, the neuroimmune system, and environmental stimuli (Fig. 11.1). At puberty, the surge in gonadal hormones activates the cells that were sexually differentiated during the pre- and postnatal organizational periods. However, puberty is also a critical organizational period for sexual differentiation [60, 61]. The sexual differentiation of the brain during these critical periods determines the organization of sensory, motor, cognitive, and socio-sexual behavior throughout the lifespan [62–65].

There are androgen and estrogen receptors in the brain, each with different spatial distributions (Fig. 11.2). During the critical period of sexual differentiation, testosterone is aromatized to estradiol and binds to E2 receptors to masculinize the brain [55, 66, 67]. The aromatize enzyme is located primarily in those areas of the brain which regulate reproductive behaviors: the hypothalamus and amygdala; however, there are neurons containing aromatase in the hippocampus, cerebral cortex, cerebellum, and spinal cord. Aromatase has also been detected in radial glial cells and astrocytes [68]. Aromatase levels in the preoptic area and

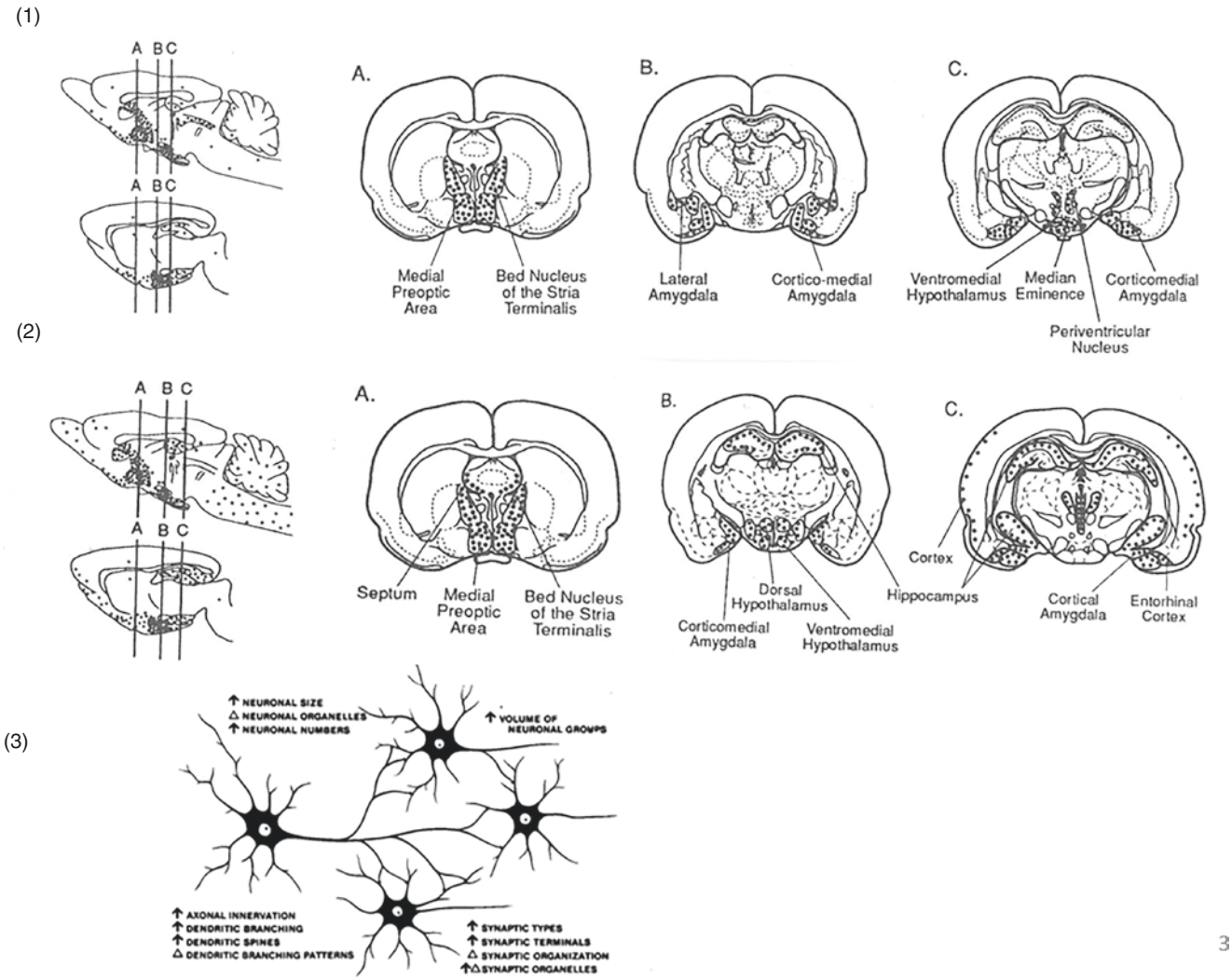

Fig. 11.2 The distribution of estrogen and androgen receptors in the rodent brain. Steroid hormone receptors in the brain. Three coronal (frontal) sections showing the locations of (1) radioactive testosterone and (2) radioactive estrogen uptake in the mouse brain. The lines (A, B, and C) indicate where the sections were cut with respect to testosterone and estrogen receptors shown in sagittal section. [**From**: Brown 1994. An Introduction to Neuroendocrinology. Cambridge University Press, Figures 9.4 and 9.5, [362]]. (3) A drawing of a neural circuit to indicate the ways that steroid hormones can result in sexual dimorphism in the CNS. Neural responses to steroid hormones can result in differences in the growth and development of target axons and dendrites and in the organization and stability of their synapses, thus enhancing neuronal survival and resulting in sex-specific neural circuits with sexually dimorphic neural connections. [**From:** Toran-Allerand CD. 1984. On the genesis of sexual differentiation of the Central Nervous System: Morphogenetic consequences of steroidal exposure and possible role of a-fetoprotein. Progress in Brain Research, 61: 63–98. Figure 5.]

hypothalamus peak during the critical period of sexual differentiation by testosterone, but the timing of aromatase mRNA expression varies in different brain areas, suggesting a range of functions [67, 68].

The aromatization theory indicates that testosterone is aromatized to estrogen which masculinizes the male brain. But the female ovary produces estrogens, so why do not these estrogens masculinize the female? The answer is that alpha-fetoprotein (AFP), which is produced by the fetal liver, binds to circulating estrogens and prevents them from masculinizing and defeminizing females [66, 69]. Excessive estrogens during the prenatal critical period can masculinize the female fetus, producing a number of disorders of female sexual differentiation [55, 70]. While estrogen masculinizes the brains of rodents, androgens binding to androgen receptors appear to masculinize the brains of humans and other primates [71]. However, this is a controversial issue as there is a debate whether it is androgen or estrogen that masculinizes the brains of primates [72, 73]. AFP does, however, have a number of functions during development, including the

regulation of growth, apoptosis, and regulation of the immune system [70]. While estrogens during the prenatal critical period of sexual differentiation will masculinize female rodents, there is a second postnatal critical period (Fig. 11.1), in which estrogens are necessary for feminization [55]. This critical period for estrogens to feminize female rodents appears to be from 15 to 25 days postnatal age. During the early postnatal period (PND 1–15) it appears that estrogens continue to masculinize the female brain but after day 15, they feminize the female brain [74].

Genetic and Epigenetic Factors in Brain Sexual Differentiation

Sex differences in the brain may be due to the expression of the *SRY* gene in the cortex, midbrain, hypothalamus, and SN [75]. Since *SRY* acts as a transcriptional activator and as an activator of epigenetic processes, such as DNA methylation, histone acetylation or methylation, and posttranscriptional regulation of noncoding RNA (ncRNA) or microRNA (mRNA), it can modulate the sexual differentiation of neurons and glial cells [22]. *SRY* gene expression can also modulate the actions of the enzymes TH and monoamine oxidase A (MAO-A) in catecholamine and dopaminergic pathways in the midbrain, resulting in sex differences in these neurotransmitter systems [75]. Sex differences in brain development are modulated by DNA methylation [76]. Masculinization of the brain requires androgens to suppress DNA methylation, while brain feminization is promoted by DNA methylation. Numerous environmental factors, including poor nutrition, drugs, and physical and mental stressors, can alter the epigenetic gene regulation of neural development, resulting in a number of different NDDs [77]. However, unlike gene mutations, which are permanent, epigenetic mechanisms are reversible; thus, NDDs that are caused by epigenetic mechanisms could also be "repaired" by epigenetic reversibility of the environmental stimuli that caused them in the first place: "epigenetic therapeutics": drugs, behavior therapy nutrition, or stress reduction ([77–79]).

Genes, Hormones, and Microglia Interact in the Sexual Differentiation of the Brain

Although the sexual differentiation of the brain is testosterone dependent [80], the sex chromosomes, transcription factors, and microglia are all involved in the sexual differentiation of the brain [16, 19]. Based on the four core genotypes model in which the effects of an XX versus XY genotype without gonadal hormones can be tested, it was found that genes on the Y chromosome coded for an increase in the number of dopaminergic (TH positive) cells in the mesencephalon on embryonic mice [81]. Gonadal steroid hormones activate their receptors in specific brain areas by binding to nuclear transcription factors to active gene transcription and protein synthesis, and the development of sexually dimorphic neural pathways (Fig. 11.2) is modulated by microglia as well as other chemical signals during critical periods [82]. It is hypothesized that microglial cells are sexually differentiated by gonadal steroids during the embryonic organizational period and that they are then involved in modulating the sexual differentiation of particular brain areas [83]. Microglia clear debris from the brain and regulate synaptic communication in adults, but in the developing brain they may eliminate redundant or apoptopic (dead) neurons, modulate synaptogenesis, and regulate the development of neural circuits (See Chap. 1).

Sexual Differentiation of Glial Cells: Astrocytes and Microglia

As noted in Chap. 1, glial cells play an important role in brain development and are intricately involved with synapses, forming a "Tripartite synapse" with the pre-and postsynaptic neurons [84, 85, 86]. Glial cells show sex differences in adults and this differentiation occurs during critical periods of development. However, glial cells also regulate the sexual differentiation of neurons; thus, glial cells are both the targets and promoters of sexual differentiation in the brain [87, 88]. Astrocytes and microglia (Fig. 11.1) are sexually differentiated [89, 90]. Microglia show sex differences in cell number, morphology, and function, which develop during critical organizational periods [83]. There are also sex differences in the number of astrocytes in the medial amygdala in mice and rats [91].

There are three stages of microglial cell development in the brain of rats: the early embryonic period (E10.5–14), the perinatal period (E14–P9), and adolescence (P28 and later) [92]. Humans have two embryonic phases of microglia development; one at four–five weeks into gestation and a second at 10–13 weeks of gestation [92]. There are age-related sex differences in microglia in the amygdala, hippocampus, and nucleus accumbens (NAc) in rats [92] (Fig. 11.1) and microglia are differentially expressed in the cerebral cortex, hippocampus, striatum, and cerebellum of male and female mice [92]. During the embryonic critical period for masculinization of the mPOA, males have twice as many microglia as females and a more activated morphological profile. During the first few days after birth in rats, males have more microglia than females in the sexually dimorphic medial preoptic area of the hypothalamus as well as the amygdala and hippocampus [90]. On the other hand, females have more activated microglia as juveniles and adults (P30–60). The sex differences in the development of microglia at

different ages suggests that during the organizational period there might develop sex differences in the innate immune system which could result in lifelong sex differences in disease susceptibility [92].

There are three mechanisms through which microglia can be sexually differentiated: sex chromosomes, gonadal steroid hormones, and neural environment. Since all glial cells have male or female sex chromosomes, direct expression of the genes on these chromosomes may lead to sexual differentiation of the glial cells. Testosterone may masculinize glial cells during the prenatal critical period by aromatization to estrogen and sex differences in microglia are responsive to the neural environment in which they function [87, 92]. The sex differences in microglia differ in different brain regions; thus, there is not a unitary sex difference: The local activity of growth factors, cytokines, NT, NP, and hormones shapes the maturation of the microglia in each brain area. Sex differences in microglia formed during the prenatal organizational period may persist for a lifetime due to epigenetic programming. Histone acetylation or methylation or DNA methylation may be "imprinted" during the organizational period so that microglia retain the male or female phenotype for life [87] (Fig. 11.1). Finally, environmental stimuli, such as high fat diets, pollutants, stress, infection, or environmental toxins, may disrupt the sexual differentiation of glia and/or disrupt the role of microglia in sexual differentiation [87, 93].

Sex Differences in the Brain

Since every brain cell in males has an X and a Y chromosome and every brain cell in females has two X chromosomes, every brain cell shows a genetic sex difference, and since many brain cells have androgen and/or estrogen receptors, many neural circuits are sexually differentiated [94]. There are many types of sex differences in the brain. Some neurons only develop in one sex, while others are larger in one sex. Sex differences in the brain can be examined in terms of (1) neuroanatomy, (2) neural circuits, (3) neurochemistry, and (4) neuroendocrinology. This has led to the "**mosaic hypothesis**" which proposes that some brain areas are masculinized, while others are feminized [95]. Another way of looking at sex differences in the brain is to distinguish morphological differences in neuron size, shape, or number (**sexual dimorphism**) from biochemical, physiological or pharmacological sex differences in cell function (**sexual diergism**) as defined by Rhodes and Rubin [96]. It has been proposed that neuroinflammatory signals are the "primary drivers of the masculinization of specific brain regions" while steroid hormones modulate the neuroimmune signaling [16, 82]. Sexual dimorphism in neural and glial cells gives rise to neuromorphological cell phenotypes, while sexual diergism in neurochemistry and neurophysiology gives rise to neurochemical phenotypes (see [62]). Both sexual dimorphism and sexual diergism result in sex differences in cognition, emotion, and behavior.

Neuroanatomy

In the human brain, there are sex differences in total brain morphology, with males having larger volumes than females, as well as regional sex differences in gray matter volume and density [97]. Males also have larger amygdala and thalamus volumes than females as well as larger NAc, putamen, and hippocampus [98, 99]. There are sex differences in the size or volume of brain cells in the cortex and cerebellum of humans, as well as in subcortical structures: the thalamus, amygdala, hippocampus, hypothalamus, and many other areas (see [97–101]). However, the distributions of measures of brain parameters for males and females have significant overlap (Joel et al 2019; [99]). There are very few nuclei which have very large sex differences. These include the bed nucleus of the stria terminalis (BNST), the interstitial nucleus of the anterior hypothalamus (INAH1), which is also called the sexually dimorphic nucleus of the preoptic area, the INAH3, and the infundibular nucleus (Joel et al., 2019; [100]). The use of a deep learning technique found sex differences in whole brain measures as well as a number of specific brain areas in the cortex, thalamus, cerebellum, and limbic system of men and women [102]. However, some sex differences in neuroanatomy, particularly in the limbic system, may be influenced by social-emotional factors during development and thus environmental epigenetic stimuli may facilitate brain plasticity during development, resulting in significant individual differences in neuroanatomy within and between sexes [103]. Likewise, there are sex differences in the neuroanatomy in many areas of the rodent brain, including the cortex, hippocampus, olfactory bulb, amygdala, septum, thalamus, and hypothalamus [101, 104, 105].

Neural Circuits

As well as the size of particular brain regions, there are sex differences in the extent of dendritic arborization, the density and pattern of synaptic connections, the size, number, and phenotype of neurons in a particular region and glial cell morphology. All of these structural differences are believed to underlie adult sex differences in behavior. It is not possible to discuss all of the sexually dimorphic and sexually diergic areas of the brain, so I will focus on some of the sex differences in (1) the olfactory pathways, (2) the hypothalamus, (3) the hippocampus, (4) amygdala, and the (5) locus coeruleus (Fig. 11.4) [106–110].

(1) The neurons of the olfactory bulb and the olfactory connections to the medial amygdala, BNST, mPOA, AVPV, and VMH which regulate socio-sexual behavior of mice are sexually differentiated by androgens during the prenatal organizational period (Fig. 11.3) [106–110].
(2) Several hypothalamic nuclei show sexual differentiation during embryonic and pubertal development [100, 105] (Fig. 11.3). These include (1) the sexually dimorphic nucleus (SDN) of the medial preoptic area (mPOA) which is larger in males than females [111–113]. (2) The central region of the BNST is masculinized by androgens and is larger in males [114, 115], while the anterior BNST (the oval nucleus of the BNST) and the ventral BNST (vBNST) are feminized by estrogens and are larger in females than males [116, 117]. (3) The anteroventral periventricular nucleus of the preoptic region (AVPV) of the hypothalamus is larger and contains more neurons in females than in males [111, 118, 119]. (4) There are numerous pathways in the ventromedial nucleus of the hypothalamus (VMH), which are sexually dimorphic regulate sex differences in metabolism and energy expenditure as well as sexual behavior and aggression [120–122].
(3) A number of nuclei in the hippocampus are sexually differentiated by androgens during the prenatal critical period [123], and there are sex differences in synapse formation and dendritic arborization of hippocampal neurons. Males show more CA1 pyramidal neuron dendritic arborizations than females, while females show more primary dendrites in the CA3 area [124, 125]. As in the hypothalamus, the sex differences in the CA1 area may be localized into male-specific and female-

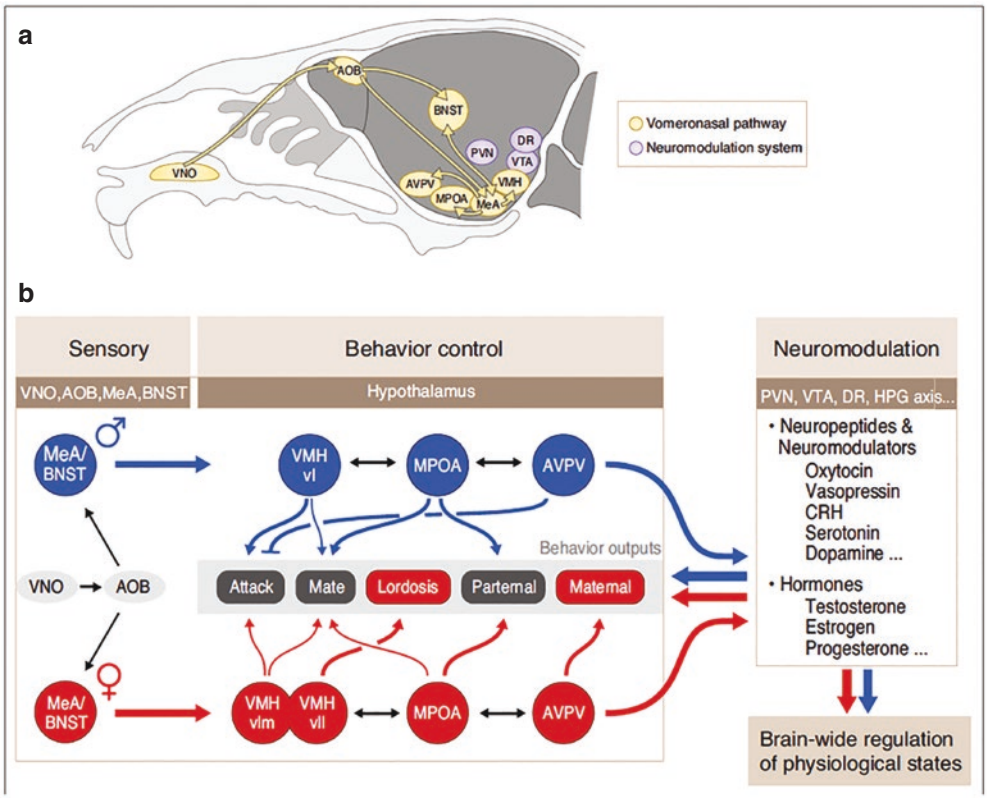

Fig. 11.3 Sex-specific neural pathways in mouse brain. Sexually dimorphic neural circuits involved in the processing of sex-specific social cues in mice. (**a**) Schematic representation of brain regions involved in the processing of sex-specific social cues and in the regulation of social behaviors. (**b**) Control of social behaviors in male (blue) and female (red) mice. Social behaviors, such as aggression, sexual behavior, and parental care, are controlled by different hypothalamic nuclei. Some of these nuclei, such as the ventrolateral part of the ventral medial hypothalamus (VMHvl) and the medial preoptic area (MPOA), drive similar social behaviors in males and females. Others, such as the female lateral part of the VMHvl (VMHvll) and the anteroventral periventricular nucleus (AVPV), are involved in eliciting different behavioral responses in both sexes. Specific hypothalamic nuclei, such as the medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST), receive inputs from the vomeronasal pathway and are regulated by different neuromodulators (hormones and neuropeptides) in a sex-specific manner. *AOB* accessory olfactory bulb, *DR* dorsal raphe nucleus, *PVN* paraventricular nucleus, *VMHvl* ventrolateral part of the ventral medial hypothalamus, *VMHvll* lateral part of the VMHvl, *VMHvlm* medial part of the VMHvl, *VNO* vomeronasal organ, *VTA* ventral tegmental area. [**From:** Li Y and Dulac C. 2018. Neural coding of sex-specific social information in the mouse brain. Current Opinion in Neurobiology. 53: 120–130. Figure 1 [363]]

specific pathways, but these differences may be labile and depend on the activational effects of hormones at puberty and on epigenetic activation of gene expression in particular neurons [126, 127]. Bundy et al. [128] found over 60 genes that were differentially expressed in the hippocampus of male and female mice, suggesting that many sex differences have yet been described. The hippocampus functions in cognitive and emotional behavior [129, 130] and sex differences in cognitive function, depression, and NDDs involve the hippocampus [125, 127, 131].

(4) The medial amygdala is responsive to changes in androgen levels in adulthood and shows morphological plasticity with circadian, annual, and socially modulated androgen levels [132]. Sex differences have been shown in the anatomy of the amygdala [97, 133, 134], with some nuclei being masculinized and some feminized. The medial amygdala is intricately associated with olfactory pathways (see Fig. 11.3) and olfactory stimuli from conspecifics (Pheromones) activate different sexually dimorphic neurons in the medial amygdala in males and females [106, 135].

(5) The Locus coeruleus of females has a larger volume and a greater number of neurons than in males and it appears that the number of such cells is reduced by apoptosis postnatally in males, while estrogen modulates the survival of these neurons in females [136–138]. The locus coeruleus (LC) of females has more noradrenergic neurons than males and these have larger and more complex dendrites than those of the male LC [136].

Neurochemistry

As noted by Nieuwenhuys [139], the chemical signaling pathways of the brain transect its neuroanatomical regions. Many neurons have steroid hormone receptors and these steroid hormone target neurons are susceptible to sexual differentiation (Figs. 11.2). Thus, although the neuroanatomical regions of the brain, such as the medial preoptic area, ventral hypothalamus, hippocampus, and amygdala, can be defined morphologically, these anatomical regions may contain a plethora of neurochemically differentiated neurons which use different neurochemicals and have been sexually differentiated by androgens or estrogens during critical periods [122, 140–142]. There are sex differences in a number of neurochemical systems in the brain. These examples of ***sexual diergism*** mean that there can be functional differences in chemical signaling and intracellular communication that are not measurable in terms of brain morphology [96]. These include the locus coeruleus noradrenergic system [136]; the cholinergic system [143, 144]; and sex differences in GABA release in the neurons of the BNST [145, 146]. There are also sex differences in neuropeptide signaling systems, including enkephalin, CCK, and beta endorphin (See [147]).

There are many different patterns of sex differences in neural signaling pathways.

(1) The neurons in one sex can be eliminated by apoptosis, while those in the other sex are rescued by neurohormone actions. Such apoptotic processes may involve steroid hormone activation of glial cells, immune cells, and epigenetic activation of genes regulating either cell death or cell survival pathways. (2) There is a larger number of neurons in a particular neuroanatomical area in one sex than in the other. (3) There are more dendritic spines and/or synapses on neurons in one sex than in the other. (4) There are sex differences in the pattern of neurochemical signals in the neurons of each sex. (5) There is differential activation of intracellular biochemical pathways in each sex resulting in differences in gene expression. (6) There are sex differences in epigenetic responses of neurons to the same neurochemical stimulation resulting in sex differences in gene expression. (7) The responses of neurons to sex hormones is plastic, depending on the environment so that the same neuron may under some circumstances express a female pattern and under other circumstances express a male pattern. (8) There are sex differences in the actions of glial cells. (9) There are sex differences in the actions of immune-related cells and the release of cytokines. The end result is that a cascade of neurochemical signals results in a sexually dimorphic **pattern of gene expression** in a cell which regulates sex differences in physiology, metabolism, and behavior (Fig. 11.4) [140, 142, 148].

Summary: Sex Differences in Brain Structure, Function, and Neurochemical Pathways

The study of sex differences in the brain and their relationship to NDDs is undergoing a paradigm shift based on the availability of more and more sensitive molecular and genetic technologies. Whereas the initial studies focused on morphological differences in particular neuroanatomical regions, the newer studies focus on gene expression and molecular differences in specific neurons. For example, Labonte et al. [149] identified sex-specific gene expression patterns in six brain regions associated with sex differences in major depressive disorders (MDD) in humans [the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex, dorsolateral PFC, anterior insula (aINS), NAc, and ventral subiculum (vSUB)]. This seems to be the future of studies on sex differences in the brain underlying neurodevelopmental and neurodegenerative disorders. The key breakthrough, however, will involve understanding how sex differences in gene expression and molecular biology lead to sex differences in neurochemical communication and synaptic function, because synaptic damage seems to underlie all neurodevelopmental

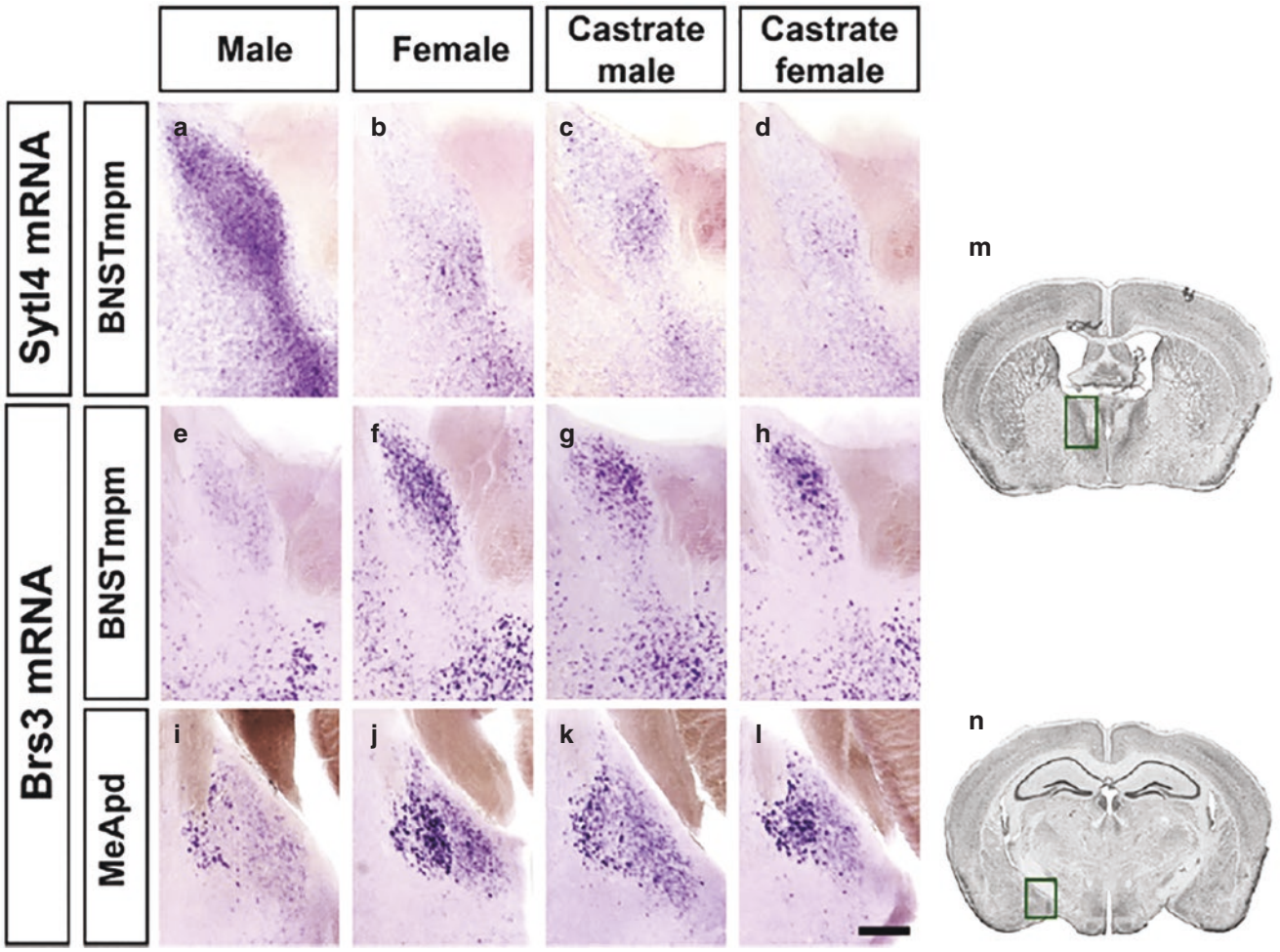

Fig. 11.4 Sex differences in gene expression patterns in the brain. Sex differences in gene expression patterns in mice are regulated by gonadal hormones. Sexually dimorphic mRNA expression of Synaptotagmin Like 4 (**Sytl4**) and Bombesin Receptor Subtype 3 (**Brs3**) genes in coronal sections from the brains of male and female, castrated male and castrated (ovariectomized) female mice. There is more Sytl4 mRNA in the posteromedial area of the medial bed nucleus of the stria terminalis (BNSTmpm) in males than females (**a**–**d**), but there is more Brs3 mRNA in the BNSTmpm (**e**–**h**) and posterodorsal Medial Amygdala (MeApd) (**i**–**h**) of female mice than males. The boxed areas of the Nissl stained brain sections (M and N) show the BNST (**m**) and MeA (**n**) regions shown in sections **a**–**h** and **i**–**l**, respectively. The scale bar (**a**–**l**) represents 100 mm. [**From:** Xu X, Coats JK, Yang CF, Wang A, Ahmed OM, Alvarado M, Izumi T, Shah NM. 2012. Modular genetic control of sexually dimorphic behaviours. Cell. 148: 596–607. Figure 2 [142]]

and neurodegenerative disorders [150–152]. Synaptic organization underlies neural development during critical periods [153] and both pre- and postsynaptic molecules are involved in NDDs [152, 154–157]. Sex differences have been found in almost all neurochemical systems, including those underlying neurodevelopmental and neurodegenerative disorders and sex differences in these neurotransmitter and neuropeptide pathways occur throughout the brain [147, 158, 159]. Sex differences at synapses (Fig. 11.2) can occur in the release of neurotransmitters from pre-synaptic nerve terminals or in their receptors at pre- and postsynaptic nerve terminals [160], or in the excitatory/inhibitory synapse ratio [161, 162]. As noted below, sex differences may also occur in the contribution of glial cells to "tripartite synapses," the neuro-immune system or even the communications between the gut microbiome and the brain [163].

The Role of Glial Cells in the Sexual Differentiation of the Brain

Astrocytes are involved in synapse development and function and microglia regulate neuron cell number during development and facilitate cell proliferation and differentiation and may play a role in the sexual differentiation of brain areas by regulating apoptosis (See Chap. 1). Microglia also regulate axon outgrowth and synaptogenesis; modulating activity-dependent synapse formation by eliminat-

ing weak synapses and promoting the growth of new ones [88]. Microglia play different roles at different times during development, but at each developmental period, they are involved in the sexual differentiation of the nervous system (Fig. 11.5). During embryonic development, microglia have organizational effects through the promotion of neural proliferation and cell survival by secreting cytokines which facilitate neural development and neural circuit development and abnormalities during this period have lifelong effects. During this embryonic critical period, testosterone masculinizes the POA by stimulating microglia to facilitate the development of synaptic spines [164]. In females, microglia appear to function postnatally to feminize the brain by facilitating synapse development during the first few postnatal weeks [165]. Later microglia prune superfluous cells by inducing apoptosis and facilitate axonal

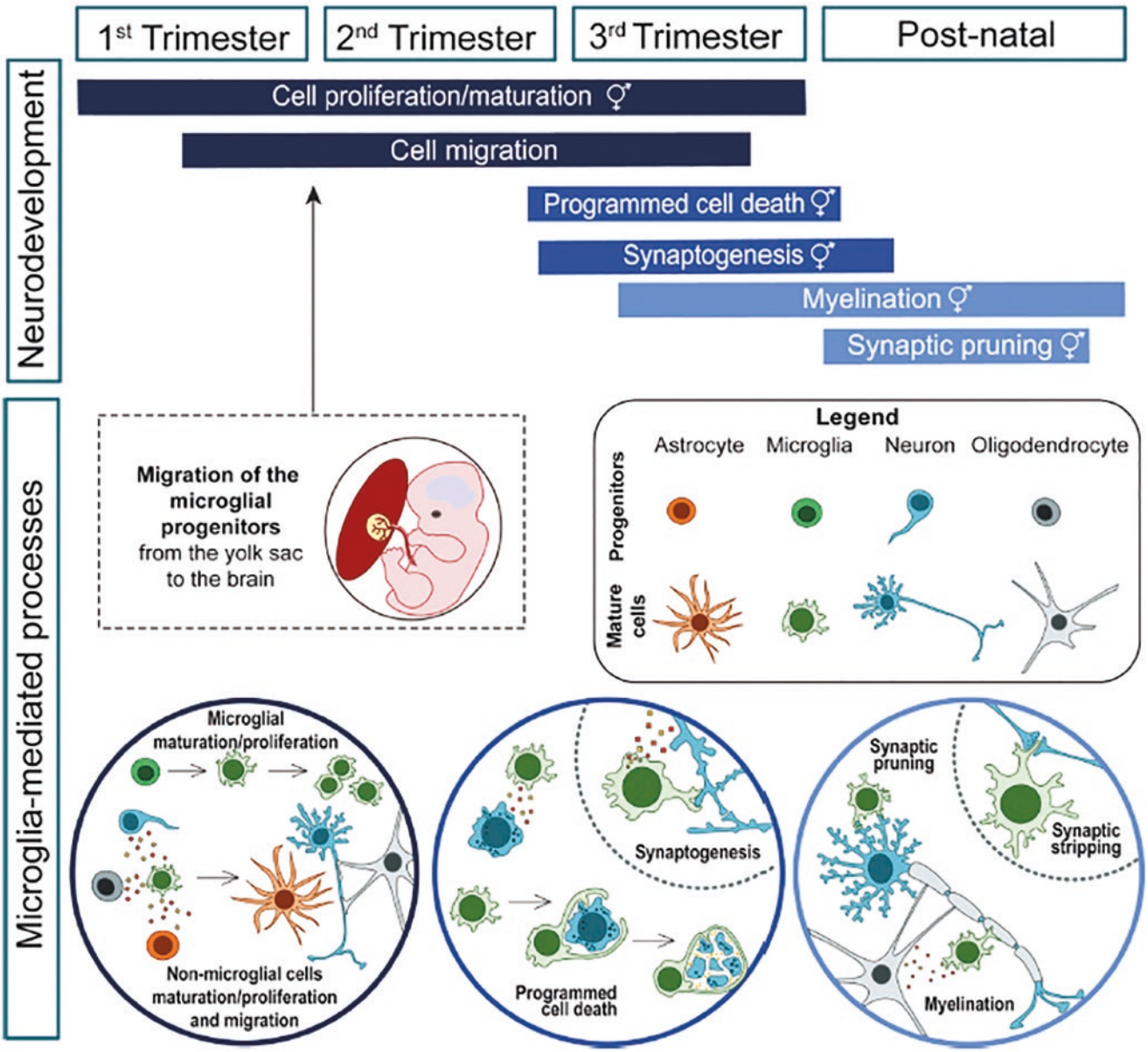

Fig. 11.5 Microglia and sexual differentiation of the brain. A timeline showing the influence of microglia on neural development. After microglial progenitors migrate into the brain from the embryonic yolk sac, microglia proliferate and participate in the neurodevelopmental processes involving astrocytes, neurons, and oligodendrocytes, including programmed cell death, synaptogenesis, myelination, synaptic pruning, and synaptic stripping. Astrocytes, microglia, neurons, and oligodendrocytes are, respectively, represented in orange, green, teal, and gray, where the microglial progenitors possess a rounded shape compared to mature cells. Sexually dimorphic processes of neurodevelopment are indicated by the symbol o. [From: Bordeleau M, Carrier M, Luheshi GN, Tremblay M-E. 2019. Microglia along sex lines: From brain colonization, maturation and function, to implication in neurodevelopmental disorders. Seminars in Cell & Developmental Biology. 94: 152–163. Figure 1 [169]]

outgrowth and synaptic connectivity by promoting synaptogenesis and pruning excess synapses [87]. In adulthood, microglia facilitate experience-dependent synaptic remodeling by regulating the interface between environmental (epigenetic) stimuli and synaptic changes in neural circuits [88]. These effects are more like activational effects, but they are susceptible to disruption by environmental stressors or endocrine disruptors.

The Role of Glial Cells in Sex Differences in NDD

Given the complex interactions between astrocytes, microglia, and neurons in the sexual differentiation of the brain, it is no surprise that glial cells may be involved in the sex differences in NDDs [166, 167]. Astrocytes are essential for synapse formation and synaptic function and sex differences in gliotransmission may be involved in the sex differences found in NDD [84, 156]. Thus, the role of astrocytes in sex differences in NDD may be in their role in the tripartite synapse and the modulation of synaptic activity, possibly by regulating the E/I ration of synapses [168]. Neuroinflammation is an important component of a number of neurodevelopmental and neurodegenerative diseases and microglia may mediate sex differences in NDD by regulating neuroimmune responses during early development as well as in adulthood and aging [11, 169]. This could occur through sex differences in the elimination of synapses by microglia during synaptic pruning, or through sex differences in the neuroimmune responses of microglia to external (environmental) stimuli (Fig. 11.5). Since microglia are involved in sexual differentiation, they may be involved in X-linked NDDs. Finally, the sex hormones, estrogen and testosterone, may have differential effects on microglia [170], being neuroprotective or neurotoxic, depending on the neural environment. For example, chronic stress has differential effects on astrocytes and microglia in males and females and this difference may be mediated by the sex hormones [171]. Likewise, during a state of low oxidative stress, sex hormones may be neuroprotective, but during high oxidative stress they may be neurotoxic [172]. Nevertheless, it is becoming increasingly clear that microglia are involved in the sexual differentiation of the brain, in sex differences in neuroimmune activation and in the development of sex differences in neural dysfunction in infancy, adulthood, and aging [169, 173].

Gut Microflora, the Immune System, Glial Cells, and Sex Differences in NDD

As if things were not too complex already, the role of gut bacteria, the microbiome, adds yet another factor in the causal chain of sex differences in NDD. The microbiome and microglia communicate with one another through a number of chemical signals, including neurotransmitters (serotonin, noradrenaline, or dopamine), short-chain fatty acids (such as propionic acid (PPA), acetic acid (AA), and butyric acid (BA)), cytokines, and microbial-associated molecules (such as bacterial lipoproteins, double stranded RNA and lipopolysaccharides) [174]. Secondly, the microbiome may act as an epigenetic regulator of microglial phenotypes, thus influence microglial function during development [175]. Thirdly, through their communication with the microglia and other immune functions, the microbiome can influence the development of NDD [176]. Finally, there are sex differences in the gut–brain axis [177], which can contribute to the sex differences in the onset of NDD [178]. A microbial imbalance in the gastrointestinal tract (gut dysbiosis) seems to be one of the major causes of sex differences in NDD. It has been proposed that sex differences in gut microflora may underlie sex differences in metabolic disorders [179]; major depressive disorder [180]; autism spectrum disorder [178]; and other neuropsychiatric disorders (see [181]). The microbiome–immune–microglia interactions can be activated by environmental stressors (early life adversity) and affect the functioning of the autonomic nervous system in a sex-dependent manner [182], resulting in sex differences in stress-related behavior and sympathetic nervous system activation, which underlies neurovascular disorders, such as hypertension [183]. The gut microbiome may modulate sex differences in neural development through communication with the immune system via microglia [169, 174, 184] and led to sex differences in neural development and in a wide range of NDD and other neural disorders [177]. Figure 11.6 presents an overview of the complex interactions between the gut microflora, immune system, neuroendocrine system, genes, and environmental stimulation in the sexual differentiation of the CNS.

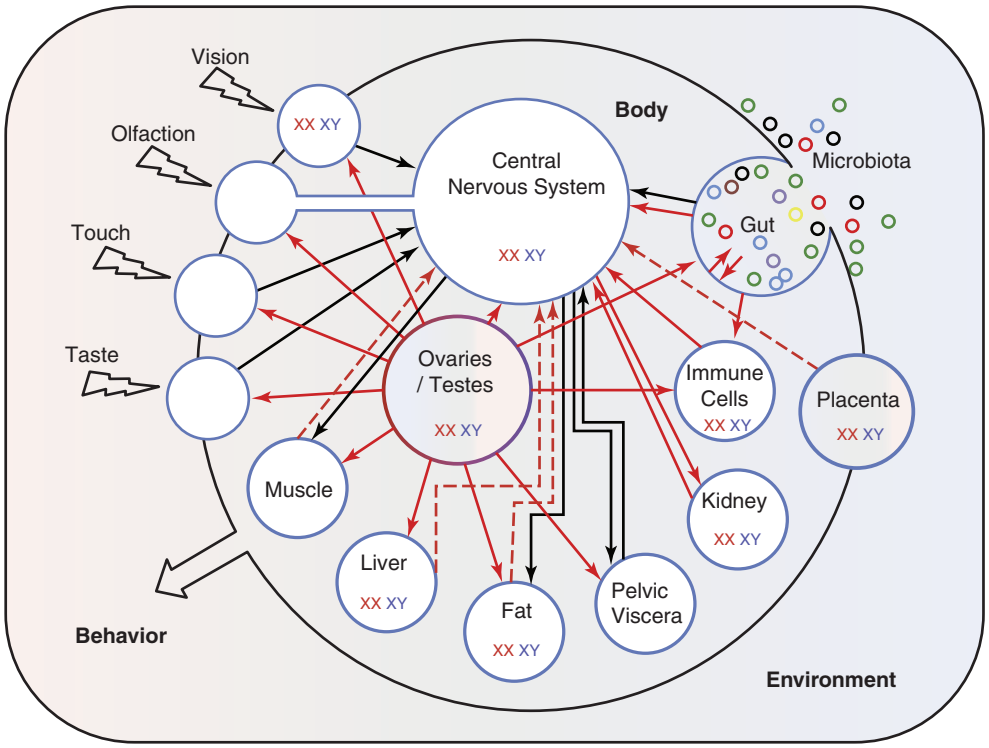

Fig. 11.6 Complex interactions in the sexual differentiation of the CNS. A diagram summarizing the factors influencing sex differences in the central nervous system. The central nervous system is embedded in a sexually differentiated body. Solid arrows indicate a sex influence from one organ on another. Dashed arrows indicate an influence inferred from circumstantial evidence. Black arrows indicate neural communications; red arrows indicate humoral communication. "XX XY" indicates organs in which sex chromosome complement has a demonstrated effect, either directly within that organ or indirectly via effects on other organs. The body is embedded in an environment that affects the individual in a sex-dependent manner. The small colored circles in the upper right are the many species of microorganisms (microbiota) living commensally in our gut or on our skin. On the left, vision, olfaction, touch, and taste may all be processed differently in males and females. [From: De Vries, G.J., Forger, N.G., 2015. Sex differences in the brain: a whole body perspective. Biol. Sex Differ. 6, 15. Figure 1 [364].]

Sexual Differentiation of the Hypothalamic-Pituitary (Neuroendocrine) System

The pituitary gland has two distinct parts: the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary), each of which is connected to the hypothalamus [185, 186, 187]. The posterior pituitary (neurohypophysis) is formed from neural tissue, while the anterior pituitary (adenohypophysis) is a true endocrine gland. During development the two parts of the pituitary gland become intertwined through a complex series of genetic, epigenetic, and hormonal interactions [185, 188–194]. The hypothalamic-pituitary system is sexually differentiated in a number of complex ways. The neurohypophyseal system consists of the neuroendocrine cells of the Supraoptic nucleus (SON) and the Paraventricular nucleus (PVN) of the hypothalamus which synthesize the neurohormones oxytocin and vasopressin, and which send their axons down the hypophyseal stalk (Infundibulum) to the Pars nervosa or posterior pituitary gland where these hormones are released into the bloodstream [195, 186]. In addition to their hormonal function in the bloodstream, oxytocin and vasopressin are also released into neural pathways in the brain where they act as neuromodulators [196–198].

The adenohypophysis (anterior pituitary) contains five types of endocrine cells which secrete growth hormone, prolactin, LH and FSH, ACTH, and TRH as well as cells in the pars intermedia which secrete MSH [186]. Synthesis and secretion of the hormones of the adenohypophysis is regulated by the hypothalamic hypophyseal hormones, which are secreted from the parvocellular neurons of the PVN, ventromedial nucleus, and other nuclei of the hypothalamus and released into the bloodstream in the median eminence of the hypothalamus, from which they travel down the hypophyseal portal veins of the pars tuberalis in the pituitary stalk to the adenohypophysis. As with the neurohypophyseal hormones, the hormones of the adenohypophysis also act as neuromodulators in the brain

Neurohypophyseal Hormones and Sex Differences in NDD

Both vasopressin and oxytocin may mediate sex differences in NDD involving social behavior and anxiety-related behavior. The lateral septum AVP system is involved in sex differences in social recognition, social play, and anxiety-related behavior in rats, while the mPFC-OXY system is involved in socio-sexual motivation in female mice and anxiety-related behavior in mice [199]. It appears that OXY and AVP have some neuromodulatory effects on sex differences in NDD, but the effects are quite complex and their effect may be to shift the excitatory/inhibitory NT balance in subtle ways to influence both vulnerability and resilience to the development of NDD. Oxytocin and vasopressin systems have been implicated in Autism spectrum disorder, Prader-Willi syndrome, Williams syndrome, and Fragile X syndrome; however, the exact role of these neuromodulators in these disorders is unclear [200]. Given the importance of oxytocin in social and sexual behavior, there has been considerable attention to its role in Autism Spectrum Disorder [201]. The amount of oxytocin released, the number of oxytocin receptors, and the function of glycoprotein CD38, which is present on the surface of many immune cells (including $CD4^+$, $CD8^+$, B lymphocytes and natural killer cells) and also functions in cell adhesion, signal transduction, and calcium signaling, have all been implicated in ASD. However, the use of oxytocin analogues to treat ASD has met with little success [202, 203]. On the other hand, the social behavior and oxytocin abnormalities in ASD may be the result of dysfunctions in synaptic proteins, such as Neuroligan3 (NLGN3 gene) [204], a sex-linked gene found in the X chromosome [205]. In addition, genetic polymorphism and epigenetic modulation of oxytocin receptors have been implicated in ASD [206–208]

Adenohypophyseal Hormones, Sex Differences, and NDD

A complex spatio-temporal sequence of neurochemical and genetic events are involved in the sexual differentiation of the neuroendocrine hypothalamus during the fetal organizational period [209, 210]. The GnRH neurons are born in the olfactory placode and must migrate to the preoptic area of the hypothalamus. This is under the control of a number of genes, growth factors, cell adhesion molecules, and other chemical signals. Once the hypothalamic GnRH neurons develop, they begin to secrete GnRH which activates the pituitary and gonads. GnRH release is pulsatile and the "pulse generator" differs in males and females [211]. In males, androgens from the testes provide negative feedback, resulting in small regular pulses of GnRH. In females on the other hand, estrogen provides positive feedback, resulting in surges of GnRH secretion once every reproductive cycle (estrus cycle in rats, menstrual cycle in humans). However, the sex difference in the HPG feedback system is not regulated directly by the GnRH neurons themselves, which are not sexually dimorphic, but indirectly by a complex system of neurotransmitters and neuropeptides [212, 213], of which the kisspeptin neurons are the most important. The kisspeptin neurons are located in the MPOA/AVPV and in the Arcuate nucleus (ARC) and are sexually differentiated by gonadal steroids during prenatal critical periods [214]. Prenatal androgens promote the development of kisspeptin neurons in the ARC but not in the AVPV in males, while postnatal estrogen facilitates kisspeptin neuron development in the AVPV in females [214].

As well as kisspeptin, other neuropeptides and neurotransmitters are involved in the regulation of GnRH secretion. These include the neurotransmitters Glutamate, GABA, dopamine and noradrenaline, and the neuropeptides leptin, NPY, VIP, neurokinin B, and dynorphin as well as GnRI, gonadotropin inhibitory hormone [186, 210, 212, 215]. In mice, AVP and VIP stimulate kisspeptin neurons in the ARC more in females than in males, but Neurokinin B stimulates kisspeptin release equally in males and females [216]. The ability of neurotransmitters and neuropeptides to regulate GnRH secretion means that any epigenetic (environmental) factors that alter these neurochemical signaling pathways can affect the kisspeptin-GnRH release [212], thus providing a neural pathway for endocrine disruptors of many types to influence the hypothalamic-pituitary hormone systems. As if all these were not enough, the glucocorticoid hormones of the HPA system and the thyroid hormones of the HPT system also modulate GnRH release in a sex-specific manner through their effects on Kisspeptin, GnRH, and GnRI [212, 215].

HPG System

Failure of the HPG system to develop normally affects sexual differentiation, puberty, physical development, and reproduction. Mutations of kisspeptin or the KISS1R lead to disorders associated with pubertal development, such as precocious puberty and idiopathic hypogonadotropic hypogonadism. Failure of the GnRH neurons to develop normally can result in hypogonadotropic hypogonadism or in Kallmann syndrome or hypogonadotropic hypogonadism with anosmia (Table 11.2). In this case the GnRH neurons fail to migrate from their origin on the olfactory bulb to the hypothalamus and the olfactory neurons also fail to develop [217]. In this condition, there is no GnRH secretion, so puberty is delayed, and people are infertile. It is treated with gonadal hormone replacement therapy [218]. Males with GnRH dysfunction who have hypogonadotropic hypogonadism have abnormal kisspeptin – Kiss-R1 receptor development [219]. On the other hand, early activation of the

Kisspeptin-GnRh system can result in precocious puberty in both girls (under age 8) and boys (under age 9) [217].

HPA System

The general consensus [220] is that females are more vulnerable to the long-term effects of early life stressors than males. Sex differences in the HPA system are most evident in responses to stress, which is associated with several psychiatric disorders that occur more frequently in women than men, including panic attacks, anxiety disorders, posttraumatic stress disorder (PTSD), and depression [221]. The stress response involves the activation of the HPA system and for some disorders, such as depression, women seem to have a stronger HPA activation than males; however, the evidence is controversial and sex differences in the HPA response to stress may differ between rodent models and humans [222]. Studies in rodent models indicate that females have a greater HPA response to stress than males, with a greater release of CRF, ACTH, and corticosterone [221, 223, 224]; however, in humans the sex difference in the cortisol response to stress depends upon the stressor [225]. After an extensive review of the literature, [220], concluded that there was evidence of increased HPA axis reactivity to stressors in human females compared with males, but this depends on a number of developmental and environmental factors and on the nature of the stressors. The HPA system in human males is activated more by cognitive and verbal stressors, while the HPA system of females is activated more by social stressors [225]. In addition, females have a greater HPA response in depression than males. Thus, it is clear that sex differences in the HPA system and the response to stress are very complicated.

Two results of the increased sensitivity of girls to HPA axis activation are the stress-related inhibition of puberty and the increase in major depressive disorder in females [226]. These sex differences in stress-related disorders may involve sex differences in the functions of the hypothalamic CRH which acts as a neuropeptide through its receptors in the brain, as well as a hormone acting at the adenohypophysis [222, 227, 228]. Sex differences in the HPA response to stress and the **development of emotional disorders** may be the result of early life stressors which affect the "developmental programming" of the HPA axis during critical periods of development [229, 230]. Early life stressors of many types (maternal stress, maternal deprivation, maternal nutrition, social stress, environmental stressors, inflammation) can act as epigenetic factors to shape sex differences in HPA responses to stress [228]. These epigenetic effects can occur through the neural pathways or through the involvement of the immune system and glial cells, such as astrocytes which modulate the development of the HPG neuroendocrine system [231–233]. Early life stress can alter the development of serotonin receptors (Htr2a and Htr1a) in the amygdala and the effects of stress on these receptors differs in male and female rats [234]. Early life stress increases the number of presynaptic Htr1a receptors and decreases the number of postsynaptic Htr2a receptors in females, but has little effect on males, thus indicating an epigenetic mechanism for the sexually dimorphic effects of early life stress on anxiety-related behavior, at least in rodents in this study. Sex differences in the effects of prenatal stress on the HPA system may be the result of sex differences in the responses of DNA methylation to early life stressors. In rats, for example, chronic restraint stress of pregnant females results in sexually dimorphic differences in the HPA axis [235], and in DNA methylation in the GR gene, resulting in sex differences in stress-related behaviors in adulthood [236]. Early life stressors induce sex-specific developmental changes in the neural connections between the PFC, amygdala, and hippocampus in rodents [237] and these connections may mediate sex differences in behavioral and HPA responses to stressors. Such epigenetic changes in neural pathways following early life stressors during development may be the cause of sex differences in major depression and other emotional disorders related to the HPA axis [238].

The HPT System

Congenital hypothyroidism is the most common endocrine disorder in newborn children and is the leading cause of preventable mental retardation [239]. Hypothyroidism (congenital, autoimmune) is sexually dimorphic [240, 241] with three times as many girls affected as boys (3:1 sex ratio) [242]. Females are also more prone than males to develop autoimmune thyroid disorders during puberty [240, 243] and since these disorders are caused by anti-thyroid antibodies produced by immune system, there is a neuro-endocrine-immune interaction in the sex differences in the development of thyroid disorders [244]. There are three other aspects of sex differences in HPT system that are related to NDD disorders: (1) metabolism and the growth spurt during puberty and obesity, (2) the sex difference in depression, and (3) epigenetic effects from environmental pollutants.

The HPT system is essential for thermoregulation and regulates energy balance by controlling energy expenditure, heat production, and metabolism [245]. Hypothyroidism results in lowered metabolic rate and hypothermia as well as delayed physical and mental growth. Since thyroid hormones stimulate bone growth and maturation, hypothyroidism is also associated with short stature. Thyroid hormones play an important role in the pubertal growth spurt and sex differences in body weight [246]. At puberty there is a surge in thyroid gland growth in both males and females, and after menarche, females have larger thyroid glands than males [246]. While GH and IGF1 may drive the increase in thyroid hormone growth at puberty, the sex difference may be the result of estrogen acting on the thyroid gland [246, 247]. Females are diagnosed with thyroid disorders, both hypo- and hyperthyroidism and are more likely to have thyroid autoim-

mune disorders than males [243, 248]. Sex differences in body weight control involve the regulation of energy homeostasis by the HPT system [249] and obesity related to hypothyroidism and autoimmune disorders is more common in women than men (see [250]). Sex differences in body fat distribution are related to sex differences in levels of circulating leptin and other adipokines [251]. Leptin levels rise at puberty and may be responsible for sex differences in fat mass after puberty: Girls gained more fat mass than boys, whereas boys gained more fat-free mass [252]. Leptin and other adipokines stimulate the immune system and since females have higher levels of leptin than males, this may be one underlying cause of sex differences in autoimmunity in general and in thyroid autoimmune disorders in particular [244]. Thus, the sex differences in body composition that occur during puberty reflect differential activity of the HPG system, the HPT system as well as leptin and other adipokines.

In addition to cognitive impairment, hypothyroidism may result in anxiety, depression or bipolar disorder, restlessness, psychomotor retardation, decreased appetite, fatigue, lethargy, and impaired concentration [248]. Women have a higher frequency of mood disorders than men, including unipolar depression and bipolar disorder which may be related to thyroid dysfunction [248]. Among patients hospitalized for depressive disorder and other neuropsychiatric disorders, females are more likely than males to have hypothyroidism [253, 254]. Low levels of TSH during development have also been associated with higher levels of ADHD in girls, but not boys [255].

Environmental toxins which disrupt the development of the HPT system (Thyroid-disrupting chemicals) have widespread effects on brain development [256]. Many of the same chemicals that disrupt the HPT system also disrupt the HPG system and thus may result in sexually dimorphic abnormalities in neural development [256, 257]. There are many endocrine-disrupting chemicals, and Bisphenol A (BPA) can be used as an example of a chemical which disrupts multiple neuroendocrine systems, including the HPT and HPG systems [258]. **BPA** is both an estrogen disruptor and a thyroid hormone disruptor, as it can interact with ER, AR, and thyroid hormone receptors (TRs) as well as other nuclear hormone receptors [259]. BPA inhibits thyroid hormone secretion and blocks TRs while stimulating estrogen receptors. It has been implicated in the increase in ADHD and related behavioral deficits in boys and in a reduction in cognitive function, but it also affects the immune system, insulin, and glucose metabolism and adipose tissue [256, 258, 260, 261]. There are sex-specific effects of prenatal BPA on NDD, suggesting that the interaction of the endocrine-disrupting effects of BPA on the sex hormones and thyroid hormones results in different NDD in boys and girls [262, 263]. Endocrine disruptors, such as BPA alter DNA methylation, by modulating the DNA methyltransferase enzymes (DNMT1 and DNMT3A) in estrogen receptors in the prefrontal cortex and hypothalamus differentially in males and females [264]. By altering DNA methylation and histone acetylation, BPA can cause widespread disruption of reproductive development, particularly in males [265]. Likewise BPA disrupts DNA methylation and histone modifications on androgen receptors and other hormone receptors [266]. Finally, early life anesthesia can result in neurodevelopmental abnormalities which differ between males and females [267]. General anesthetics can cause neural death (apoptosis) and thus act as neurotoxins during early brain development. Since anesthetics target GABA and NMDA receptors, they affect the development of the cortex, hippocampus, and hypothalamus through altering DNA methylation and histone proteins [267]. General anesthetics may also act as endocrine disruptors to alter the development of the HPT and immune systems [268].

GH and Prolactin

Short stature has been associated with a number of NDD, and this may be related to abnormalities in the HPT or GH/IGF1 systems [269]. The GH/IGF1 system has significant effects on brain development and synaptic function and abnormalities in the development of this system may underlie the development of certain NDD, such as Autism and RTT [270–272]. Abnormal synapse formation in Autism may be related to abnormalities in IGF1 levels, in the hippocampus and cerebellum [271]. The fact that the GH/IGF1 system is sexually dimorphic with increased activity in males, suggests that a dysfunction in this system during development may underlie the preponderance of males in autism and related NDD. There have been attempts to correlate elevated prolactin levels with the onset of psychoses in men and women [273], but although women had higher PRL levels than men, the results showed no relationship between prolactin levels and sex differences in psychoses. On the other hand, Labad [274] proposed that sex differences in the HPA system and PRL response to stressors may underlie the onset of schizophrenia.

Summary and a Caveat

Section "Puberty: The Organization of the Adult Brain and the Integration of Sex Differences in the Neuroendocrine, Neuroimmune, and Energy Homeostasis Systems" examines sex differences in the hypothalamic-pituitary hormone systems and suggested ways in which these could underlie sex differences in NDD. However, there is a significant difficulty in the study of sex differences in the neuroendocrine system underlying NDD in that everything depends on everything else, and the causal chain is a circle. For example, the HPG system is sexually dimorphic and sex hormones masculinize

or feminize certain brain regions, leading to sex differences in the hypothalamic-pituitary release of hormones and then these hormones bind to their receptors in the brain, in a sexually dimorphic manner. So what came first: the sexual differentiation of neurons causing sexually different hypothalamic-pituitary hormone release OR the sexually different hormone release causing sex differences in neural development? One might argue that both are true at different developmental periods. During the perinatal organizational phase the gonadal hormones cause sexual differentiation of brain areas and then during the pubertal-adult activational phase, the sexually differentiated brain areas cause sex differences in hormone secretion. However, brain damage – abnormal neurogenesis and synaptogenesis – may cause both NDD and neurohormone abnormalities. The development of the brain and the neuroendocrine system, not to mention the neuroimmune system, are intricately linked and almost impossible to dissociate.

Puberty: The Organization of the Adult Brain and the Integration of Sex Differences in the Neuroendocrine, Neuroimmune, and Energy Homeostasis Systems

Puberty defines the border between childhood and adulthood. It involves the maturation of sex differences in the brain and the initiation of reproductive function. Puberty is both a period of activation of the sexually dimorphic neural pathways that were organized during the perinatal critical period and also a period of the adult organization of the sexually dimorphic neuroendocrine pathways. During puberty there is the maturation of the gonads, the development of secondary sexual characteristics, accelerated growth, changes in brain and behavior, and the attainment of reproductive fertility [61, 275, 276]. Puberty involves sex differences in gene expression underlying the reorganization and activation of many neurochemical systems, including the HPG, HPA, HPT, GH/IGF1, and leptin-related metabolic systems. Puberty also involves the sexual differentiation of the neuroimmune system. Because puberty is a critical period for the development of adult sex differences, the neuroendocrine changes during this time are susceptible to alteration by endocrine disruptors and other epigenetic mechanisms that can result in puberty-related NDD, including disorders of metabolism; early (precocious) of delayed puberty; disorders of sexual differentiation; psychiatric disorders; and disorders of gender identity and role.

Puberty-Related Neural and Neuroendocrine Reorganization

The primary activator of puberty is the change in negative feedback sensitivity of the HPG system which allows the increased release of GnRH, LH, and FSH, stimulating and increased release of gonadal hormones. This is regulated by leptin and kisspeptin [277]. The kisspeptin neurons in the ARC are "masculinized" by androgens (or high levels of estrogens via the aromatization of androgens during critical period of prenatal development) and regulate to pulsatile release of GnRH in males [214, 278]. At puberty, there is a critical period of sexual differentiation of neural development which leads to sex differences in cognition, behavior, emotionality, social behavior, and the onset of adolescent NDD [60, 279–282]. This involves the reorganization of a number or neural circuits in the hypothalamus, hippocampus, amygdala, and cortex [59, 60, 283, 284]. Sex differences in this "brain remodeling" involve (1) masculinization of the brain by androgens and an increase in neurogenesis in the sexually dimorphic neurons of the stria terminalis and mPOA-SDN of the hypothalamus which is not shown in females [57, 285], and (2) feminization of the locus coeruleus and the hypothalamic neurons that control the LH surge during ovulation [138, 286]. The medial posterior region of the BNST and the LC thus show opposite patterns of sexual dimorphism. The BNST in males is greater in volume and number of neurons than in females (male > female), while in the LC, the opposite is true (female > male) [287].

After puberty, there is a decrease in the number of neurons, dendrites and synapses in the prefrontal cortex while myelination in the white matter increases, and these changes are more marked in female rats than males [279]. A detailed description of the organization of sex differences in the brain at puberty is given by Peper et al. [288]. Ovarian hormones shape cell number and cell group volume female brains during puberty [59]. The increase in estrogen levels at puberty has been correlated with increases in gray matter in the left middle temporal gyrus and with decreases in gray matter in the superior- and inferior prefrontal, orbitofrontal, parietal, as well as temporal cortices. It is noteworthy that numerous changes in gray and white matter in the cortex were correlated with changes in levels of estrogen throughout the lifespans of human females [289]

Sex Differences in Microglia at Puberty

Glial cells play an important role in the sexual differentiation of the brain during the perinatal organizational period and a sex-specific role in the reorganization of the brain during puberty [290]. In adulthood, male microglia have an enlarged soma and have more pro-inflammatory responses than female microglia, while female microglia have a higher phagocytic capacity and higher capacity than male microglia for cell repair and inflammatory control (Fig. 11.7). These sex differences in microglia at puberty may influence the sex differences in the lifespan development of neurodegenerative diseases during later adulthood as well as NDDs [11]. Thus,

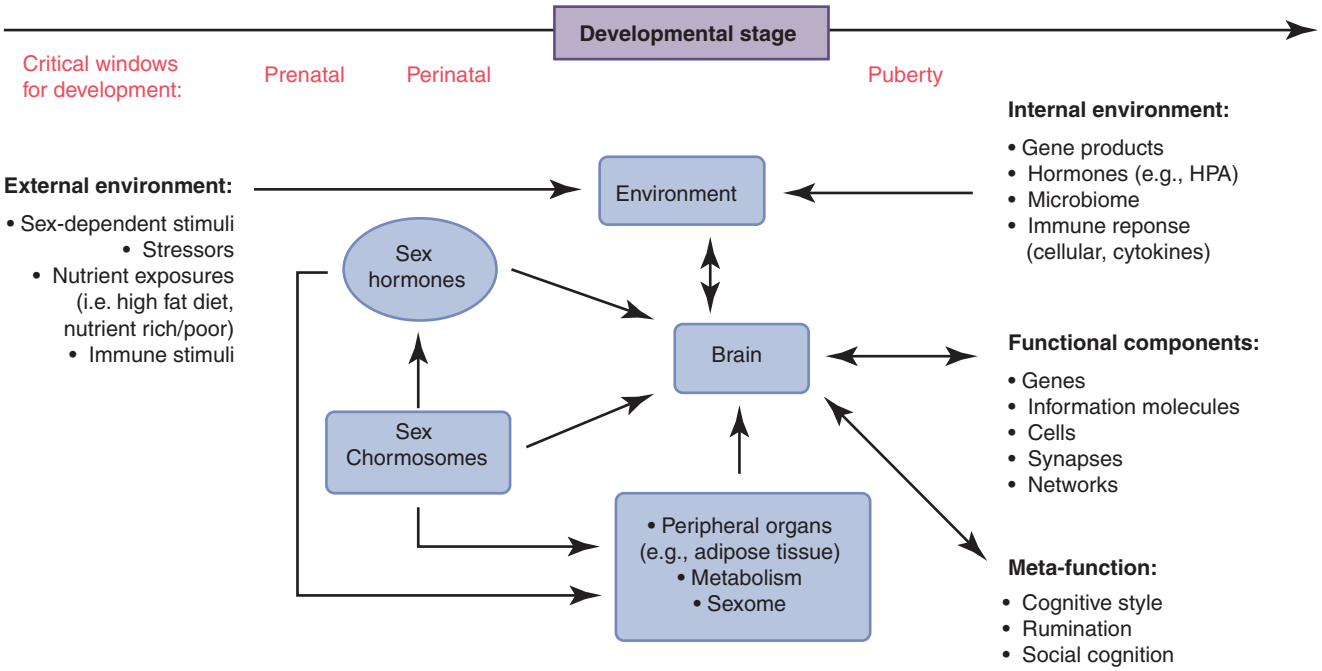

Fig. 11.7 Sex differences in microglia at puberty. A schematic depiction of the multiple levels at which sex influences brain function. The organizational and activational effects of the sex chromosomes and gonadal sex hormones during critical periods of development produce sex differences in brain organization and function. Sex influences the internal environment in which brain function occurs (e.g., differential exposure to stress or immune soluble molecules) as well as modulating the impact of the external environment (e.g., diet or stressors, particularly in the prenatal environment, or even social responses from others based on sex). Sex chromosomes impact brain development directly, may impact physiology through differences in exposure to gene products (e.g., sex-linked genes or differences in gene dosage), and alter brain function developmentally and activationally through sex-determined gonadal function and differential exposure to sex hormones. Sex differences in peripheral organs (e.g., adipose, liver) lead to differential exposure of the brain to hormones as well as medications (through effects on metabolism). The "sexome" refers to the cumulative array of sex-related modulatory effects on intracellular molecular interactions. Sex differences appear at all levels of neural organization, from cell to circuit. Finally, reported sex differences in metacognitions may influence perception and processing of environmental stimuli, thus influencing affective generation and regulation. [From: Rubinow and Schmidt 2019. Sex differences in the neurobiology of affective disorders. Neuropsychopharmacology. 44: 111–128. Figure 1 [228]]

some of the neuroprotective effects of estrogen may involve female microglia. For example, in mice, males show a greater inflammatory response than females to brain injury, while microglia from adult females reduce the damage caused by cerebral ischemia [291]. Microglia have been found to shape sex differences in dopamine pathways at puberty and thus influence sex differences in reward pathways. Microglia and immune-mediated phagocytic activity reduce the number of D1 receptors in the NAc of male but not female rats at puberty [292]. Interactions between glial cells, gliotransmitters, and neurons and neurotransmitters may be essential for the neuroendocrine changes in the hypothalamic-pituitary system at puberty, regulating both the HPT and HPG systems and modulating both metabolism and reproduction [293].

Sex Differences in Gene Expression at Puberty: Epigenetic Effects of Gonadal Hormones

The surges in gonadal hormones during the perinatal and pubertal critical periods are responsible for activating genes that regulate the sex differences in neuroendocrine and neurophysiological activity. In this way, the gonadal hormones act as epigenetic signals to regulate gene expression and this epigenetic modulation of gene expression can be permanent or transitory and can fluctuate across the estrus/menstrual cycle in females [294, 295]. Thus, sex differences in neural activity as the result of gene activation by gonadal hormones can fluctuate over time. This may be one of the many reasons why there is so much variability in measures of sex differences in neuron structure and function: as gonadal hormone levels fluctuate, so does gene expression and neural activity.

Sex differences in gene expression occur during specific critical periods and may be related to sex differences in neuropsychiatric disorders [296]. While DNA methylation at some sites showed sex differences in expression during the critical organizational period, others, which occurred during the perinatal organizational period, were not evident until after puberty [297]. Two genes were of particular interest for their consistent sex-specific expression at different ages: GPR37 (G protein-coupled receptor associated with Parkinson's disease) in females and APLNR (the APELIN G protein-coupled receptor associated with control of the cardiovascular system) in males. Sexually dimorphic genes

involved in synapse formation are also expressed at puberty. Finally, a number of sex-biased genes were shown to be related to NDD. In males these included genes related to autism, bipolar disorder, schizophrenia, Alzheimer's disease, and Parkinson's disease. Female-biased genes were related to OCD, schizophrenia, epilepsy, and AD. Finally, there are sex differences in the activation of gene expression in the PFC, NAc, and VTA of mice in response to stress and cocaine treatment [298]. This indicates a sex differences in gene expression in reward pathways (see below).

Summary

Puberty is both a time when the sex differences in the brain are activated with the rise in gonadal hormones and also a time when a second phase of brain reorganization occurs. While both of these changes depend on gonadal hormones, they involve a number of neurotransmitters and neuropeptides, along with the gonadal steroid hormones, all of which act to regulate gene expression and neuroendocrine development via epigenetic mechanisms of DNA methylation and histone modifications [297]. It is clear that the changes in reproductive function that occur at puberty are accompanied by changes in metabolism, growth, and the functions of the HPA and HPT systems. Puberty is thus a period of neuroendocrine system-wide readjustment which shifts the body from childhood to adulthood. Endocrine disruptors seem to have a more potent effect on puberty in females than in males, but more research has been conducted on puberty in females than males. What is clear is that a wide range of changes in neurochemicals and their receptors occur in the brain at puberty. While kisspeptin seems to regulate the changes in the HPG system at puberty, there are also changes in reward pathways and stress pathways which appear to be sexually dimorphic. All of these changes can result in puberty-related NDDs.

Puberty-Related Neurodevelopmental Disorders

Puberty is associated with a collection of NDDs. These can be divided (arbitrarily) into disorders of puberty timing, eating disorders and addictions, neuropsychiatric disorders, and disorders of sexual development (DSD).

Disorders of Puberty Timing

The most outstanding physiological and physical changes at puberty concern the sexually dimorphic development of secondary sex characteristics. As noted in Table 11.2, there are a number of disorders of sexual differentiation that become obvious at puberty that are due to genetic disorders of sex determination or perinatal hormone disorders of sexual differentiation [299]. The disorders of puberty timing involve precocious puberty or delayed puberty [300, 301]. While these disorders have traditionally been thought of as disorders of the HPG system, it is now clear that disruption of the Kisspeptin system (the Kiss1 gene or the Kisspeptin receptor) is involved in both precocial and delayed puberty as it regulates the release of GnRH [217, 302, 303].

Precocious puberty can be caused by premature activation of the hypothalamic-pituitary gonadal axis (true precocious puberty); by increased estrogen or androgen secretion due to steroid-secreting tumors, or to external steroid hormones in food or vis endocrine-disrupting chemicals (precocious pseudopuberty or Gonadotropin-independent puberty); or to the secretion of gonadal steroids from the adrenal gland (congenital adrenal hyperplasia). The result is that a child goes through puberty at an early age (as young as seven years old in girls or nine years old in boys). Precocious puberty is a sexually dimorphic disorder, being five to ten times more common in girls than boys [300, 301]. Delayed puberty is caused by the failure of the HPG system to develop (hypogonadotropic hypogonadism). In delayed puberty, there is no development of the secondary sexual characteristics. All of the hormones of the HPG system are at low levels, females do not ovulate or show a menstrual cycle and sperm production does not occur in males. Delayed puberty is more common in boys than girls [300, 301, 304].

Sex Differences in the Activation of Reward Pathways at Puberty: Eating Disorders and Addictions

After puberty there are sex differences in addictive disorders, including eating disorders, drug addiction, and other addictions [305] which may be the result of sex differences in neural reward pathways [306].

Reward Pathways The reward pathways in the brain involve dopamine and the opioids and sex differences in these pathways in the NAc and VTA and their pathways to the PFC and the amygdala may mediate sex differences in obesity and addictions [306–308]. Although both men and women show addictive behaviors, women become addicted faster than men, experience more difficulties getting rid of their addictions, and relapse more often than men, and this may be due to the interaction of estrogen and androgens with the dopaminergic and opioid reward pathways [306, 307]. Exactly how sex differences in these reward pathways manifest in addictions is unknown (See long discussion by [306]).

Eating Disorders and Obesity Puberty is one of the most common risk periods for the development of eating disorders, primarily anorexia nervosa and bulimia nervosa, which are more common in girls than boys [309, 310]. In girls the mean age for the onset of eating disorders is between 15 and 19 years of age, but for boys, there are fewer studies and the relationship with puberty is mixed (see [310]). It is possible that perinatal androgens which masculinize the brain reduce the likelihood of the development of eating disorders at puberty in males [309]. There are two ways of looking at sex differences in eating disorders and obesity related to puberty: (1) the close ties between metabolism and body weight with puberty and reproduction in females and (2) the general issue of eating as an addiction related to brain reward circuits. As discussed above, the timing of puberty and the initiation of reproduction in females is closely tied to metabolism and body weight. The development of female reproductive behavior at puberty in rats requires estrogen [74]. The rise in estrogen levels at puberty activates neural reorganization; the female brain is "shaped" by a cascade of hormones and neuropeptides that regulate metabolism and reproduction [289, 311, 312]. The key is the maturation and "rewiring" of hypothalamic neural circuits during puberty. Metabolic signals involving leptin, ghrelin, and insulin regulate the activity of kisspeptin and other neuropeptides regulating the hypothalamic control on GnRH. Thus, any disruption of the metabolic reproductive axis may result in eating disorders [311]. In boys, metabolism and the timing of puberty are less closely intertwined and so eating disorders may be independent of puberty in males.

On the other hand, the conception of eating disorders as addictions focuses on the role of reward circuits in the brain [306, 308, 313]. From this point of view, eating disorders are the result of disrupted dopamine and opioid systems in sexually dimorphic areas of the brain. Because so many components of the reproductive, feeding, and reward systems in the brain are activated at puberty, it is difficult to determine what exactly the term "sex difference" means. It can relate to the sex chromosomes, perinatal organizational period of gonadal sex differentiation, or to the many areas of the brain and neural pathways that are sexually dimorphic (See [314]). In addition, microglia in the medial basal hypothalamus regulate metabolic physiology and may be involved in both metabolic disorders and involvement of metabolism in the timing of puberty [315, 316].

Drug Addiction Drug addiction usually begins between 12 and 17 years of age and although more men use drugs, women are at a greater risk of addiction [305, 317]. Drug use at puberty has been related to sensation seeking and impulsivity in both girls and boys [318] and in women, substance abuse varied over the menstrual cycle [317]. This leads to two hypotheses about sex differences in drug addictions: (1) sexual differentiation of the brain during the neonatal organizational period [317] and (2) the activation/ organization of sex differences in the dopaminergic and opioid reward systems at puberty [319]. Since sex differences in the DA system are due to the effects of gonadal hormones during the perinatal organizational period and the activational period at puberty, the DA hypothesis is a subset of the sexual differentiation hypothesis.

Other Addictions There are many addictions beyond food and drug addiction: sex, gambling, and internet addictions being more common in men, and exercise addiction being more common in women. However, gambling addiction in women may be associated with depression and other psychiatric problems, while in men it is associated with impulsivity, sensation seeking, and risk taking (See [305]). Sex differences in these behaviors may be due to sex differences in reward pathways in the brain or to the activational effects of sex hormones. Other addictions, such as compulsive shopping for clothes (mainly by women) or tools and electronic equipment (mainly by men) and pyromania (mainly by men) may also be related to anxiety, depression, and other psychiatric problems [305], which are also sexually dimorphic (See below).

Sex Differences in Neuropsychiatric Disorders, Anxiety, and Depression at Puberty

Puberty has been associated with a wide range of psychopathologies and neuropsychiatric syndromes in both boys and girls [320, 321]. Twice as many women as men develop anxiety and depression after puberty and it has been proposed that this is the result of the activation of sex differences in the HPA and serotonergic systems at puberty [322]. It is noteworthy that sex differences in cortisol metabolism begin around 11 years of age and increase as puberty advances, after which men secrete more cortisol metabolites than women [323]. However, it has been suggested that the sexual differentiation of the HPG pathway during the perinatal organizational period sets the stage for the activation of sex differences in responses to stress at puberty [324] as there is a close association between the HPG and HPA pathways as discussed above. The sex differences in the development of anxiety, depression and other disorders may be the result of the interaction of stressful stimuli on the sexually dimorphic HPA system [220]. Puberty can also result in the onset of adolescent NDDs, such as schizophrenia [59, 282, 325–327]. Because there is significant synaptic remodeling at puberty, there is the "window of vulnerability" for the development of synaptopathies and for disruption of excitatory: inhibitory signaling ratios. Since the neuroendocrine changes that occur at puberty are all regulated by chemical signaling pathways,

there is the opportunity for environmental epigenetic mechanisms to disrupt the neuroendocrine system during this critical period of brain development [280, 328].

Pediatric Infection-Triggered Neuropsychiatric Disorder Although not particularly associated with puberty, there is a subtype of obsessive-compulsive disorder and/or tics (Tourette's syndrome) which is caused by an infection or neuro-immune activation [320, 329]. This disorder occurs more often in males than females (65:35 ratio) and can begin before or after puberty, with a median age of 11 years old. It has been associated with Group A streptococcal (GAS) infections and the onset is abrupt (e.g., Overnight). As well as OCD it can result in anxiety and/or depression, and sensorimotor disabilities (see [329]). I include it here because of the role of the immune system in neural development and in sexual differentiation in perinatal and pubertal development.

Disorders/Differences of Sexual Development

At one time it was believed that there were only two sexes, male and female, but there can be five sexes or more [330, 331] (Table 11.2). The root causes of the differences in sexual development are a mismatch between sex chromosomes, gonadal hormones, and anatomical features [26, 332, 333]. A true hermaphrodite (Ovotesticular disorder) has both XX and XY chromosomes, both testes and ovaries, a penis and a vagina, and can secrete both androgens and estrogens. A male pseudohermaphrodite (46, XY DSD) has XY chromosomes and testes but a feminized body, with a vagina and breast development due to a lack of androgens or androgen receptors. A female pseudohermaphrodite (46, XX DSD) has XX chromosomes and ovaries but a masculinized body with a penis due to excessive androgen secretion, primarily from the adrenal cortex [332, 333]. There can also be XX males (46, XX testicular DSD) and XY sex reversal (46, XY complete gonadal dysgenesis) (see [334, 335]). These disorders of sexual differentiation are usually detected neonatally. The decision to give surgical or hormonal correction and rear these children as boys or girls is usually made shortly after birth and involves many complex issues (see [334, 335]). What concerns us here are the issues raised at puberty with respect to **gender identity** (whether a person feels that they are male or female), **gender role** (whether a person behaves as a male or female, as defined by their culture), and **sexual orientation** (a person's attraction to the same or opposite sex, or both: heterosexual, bisexual, homosexual). Disorders of gender identity and role fall under the heading of "gender dysphoria."

Gender dysphoria refers to males who identify as females and females who identify as males. Although gender of rearing is the best predictor of gender identity and role in most people with DSD [336] gender dysphoria affects up to 20% of people with DSD [337, 338]. As discussed in Sects. "Sex Determination and Sexual Differentiation" and "Sex Differences in the Brain" on sexual determination and sexual differentiation, females who are exposed to androgens neonatally are masculinized (e.g., congenital adrenal hyperplasia) and males with mutations in androgen synthesis or androgen receptors are feminized [333–335]. Females with CAH have XX chromosomes and are generally reared as female and that works well if the levels of prenatal androgen are low, but if there are high levels of androgens prenatally, the "girl" may decide that she is a boy and wish to have sex reassignment at puberty (See [339]). One procedure to "treat" gender dysphoria in both males and females is to suppress puberty using GnRH analogues, along with psychological support, followed by hormone therapy and gender reassignment surgery. This seems to be successful [340, 341].

Adolescent-onset gender dysphoria is increasing in frequency and is sexually dimorphic, with male-to-female gender dysphoria (transsexualism) having a rate of 6.8/100,000 and female-to-male transsexualism at 2.8/100,000 [342]. Other surveys find that more female than male adolescents report gender dysphoria, with sex ratios of up to 7.5:1 [343]. The "Dutch model" for treating adolescent gender dysphoria is to use puberty suppression around 12 years of age, hormone treatment at 16 years of age, and surgery after 18 years of age [342]. Adolescents with gender dysphoria often have anxiety and depressive disorders, but some are in danger of committing suicide [343]. The phenomenon of "rapid onset gender dysphoria" occurs in adolescents around 16 years of age in more than 80% are female [344, 345]. This is a controversial topic and seems to be a socio-cultural phenomenon rather than a neuroendocrine phenomenon [343, 346]. Time will tell.

Theories of gender dysphoria and the desire for sex change surgery focus on chromosomal sex determination, and hormonal sex differentiation during the neonatal critical period for brain organization. The focus has been on the sexual differentiation of the brain and whether gender dysphoria is the result of abnormal neuroendocrine organization of sexually dimorphic neural circuits in the brain that are activated at puberty. There is considerable evidence that perinatal sexual differentiation of the hypothalamic areas (the BNST and the third interstitial nucleus of the anterior hypothalamus (INAH-3) are two areas which underlie gender dysphoria in males. If they are not sufficiently masculinized by androgens during development, it appears that men may fail to develop a masculine gender identity and role [347–351]. Gender dysphoria is most likely the result of abnormalities in the organizational

effects of sex chromosomes and gonadal hormones during the perinatal organizational period (see [352–354]). Kisspeptin neurons may also be involved in the regulation of sexual differentiation, and the development of gender identity and role and thus dysfunction of the kisspeptin system may underlie gender dysphoria [355]. In addition, the glial cells, which regulate sexual differentiation, metabolism, and the development of the HPG system, may also be involved in gender dysphoria [293, 338, 349, 356].

Summary: Theories About the Causes of Sex Differences in Neurodevelopmental Disorders: Genetic, Hormonal, Immune, and Environmental (epigenetic) Mechanisms

In this chapter I have tried to dissect all of the information on the causes of sex differences in NDDs. From the studies examined, it is clear that (1) sex differences depend on the XX and XY chromosomes; (2) sex differences depend on the gonadal steroid hormones, estrogen, and testosterone; (3) sex differences depend on the sexual differentiation of neurons and neurotransmitter pathways in the hypothalamus and related brain areas: the amygdala, hippocampus, and arcuate nucleus; and (4) sex differences depend on glial cells and gliotransmitters. There is a critical perinatal organizational period for sexual differentiation with masculinization by gonadal androgens occurring before feminization by estrogens. During this critical period many cells in the body are sexually differentiated. Finally, at puberty there is a surge in gonadal steroids regulated by the hypothalamus which activates the sex differences determined perinatally and reorganizes many neuroendocrine brain circuits. Since hormones, neurotransmitters, and neuropeptides act via epigenetic mechanisms to regulate gene transcription in a sexually dimorphic fashion, endocrine-disrupting chemicals in the environment can modulate these same pathways and alter the normal patterns of sexual differentiation during perinatal critical periods.

Finally, it must be remembered that there is the potential for sex differences in gene expression in virtually every cell in the body, including the liver, adipose tissue, muscle, and brain [357, 358]. "Male biased" genes are expressed more highly in males and "female-biased" genes are expressed more highly in females. Most sexually dimorphic genes are located on the sex chromosomes, with more female-biased genes on the X chromosome and more male-biased genes on the Y chromosome, but many autosomes also contain sexually dimorphic gene expression in a tissue-specific fashion [358]. The sex difference in gene expression may be due to the actions of the gonadal hormones as transcription factors. Sex differences in gene expression profiles in brain tissues may underlie the sex differences in neurodevelopmental and neurodegenerative disorders [295, 359]. Likewise, sex differences in gene expression profiles in nongonadal tissues in the body may be associated with sex differences in the incidence of cancer, atherosclerosis, obesity, and responses to drugs [358, 360, 361]. Thus, it is not surprising that there are sex differences in the incidence of NDDs, but it is difficult to pinpoint the causes of such sex differences in individuals. Every patient is their own experiment.

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Multiple-Choice Questions

1. If a person has XXY sex chromosomes, they have the disorder A and will have the physical features of B
   (a) Turner's syndrome; female
   (b) **Klinefelter syndrome; male**
   (c) Klinefelter syndrome; female
   (d) Congenital adrenal hyperplasia; female
   (e) Kallman syndrome; male
2. During the prenatal critical period of development, the hormone A has the effect of B of the brain.
   (a) **Testosterone; masculinization**
   (b) Prolactin; masculinization
   (c) Testosterone; feminization
   (d) Progesterone; feminization
   (e) Corticosterone; masculinization
3. The neuropeptide A regulates the secretion of the hypothalamic hormone B to regulate the sexual differentiation.
   (a) Substance P; GnRH
   (b) Galanin; CRH
   (c) CCK; TRH
   (d) **Kisspeptin; GnRH**
   (e) Kisspeptin; Oxytocin
4. The area of the brain that regulates hormone secretion from the pituitary gland is
   (a) the prefrontal cortex
   (b) the amygdala
   (c) the hippocampus
   (d) the cerebellum
   (e) **the hypothalamus**
5. Bisphenol A is a
   (a) neurotransmitter
   (b) neuropeptide
   (c) **endocrine disruptor**
   (d) hypothalamic hormone
   (e) anterior pituitary hormone

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