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Review article

Genes and sex hormones interaction in neurodevelopmental disorders

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ABSTRACT

The prevalence, age of onset and symptomatology of many neurodevelopmental disorders strongly differ between genders. This review examines sex biases in human neurodevelopmental disorders and in validated animal models. A focus is made on disorders of well-established genetic origin, such as Rett syndrome, CDKL5-associated disorders, Fragile X and Down syndrome. Autism is also addressed, given its paradigmatic role as a sex-biased neurodevelopmental disorder. Reviewed literature confirms that a complex interaction between genetic factors and sex hormones may underlie the differential susceptibility of genders and may impact the severity of symptoms in most of the analyzed neurodevelopmental disorders. Even though further studies addressing the advantages and disadvantages conferred by biological sex in this class of disorders are needed to disentangle the underlying mechanisms, present findings suggest that modulation of sex steroid-related pathways may represent an innovative approach for these diseases. Much effort is now expected to unravel the potential therapeutic efficacy of drugs targeting sex hormones-related signaling pathways in neurodevelopmental disorders of well-established genetic origin.

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Contents

1. Introduction

Neurodevelopmental disorders (NDDs) represent a wide, clinically heterogeneous group of psychiatric illnesses, caused by aberrant development of the central nervous system. Affected domains include motor function, cognitive abilities, language and affective states. Among most common NDDs, there are autism spectrum disorders, social communication disorders, syndromic and

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non-syndromic intellectual disabilities and attention deficit hyperactivity disorder (APA, 2013).

The prevalence, age of onset, pathophysiology, and symptomatology of many neurodevelopmental disorders strongly differ between genders. The increased vulnerability of males to mutations of X-linked genes is an obvious source of sex differences in diseases (Arnold, 2004). However, it seems apparent that sex dimorphism within this class of neuropsychiatric disorders extends beyond the obvious X-linked pathologies (Baron-Cohen et al., 2011 and Section 3.1). Marked sex differences in terms of incidence and clinical symptoms are in fact evident in disorders of multi-factorial origin characterized by abnormal neurodevelopment, such as schizophrenia and autism (Hill et al., 2004; Kokras and Dalla, 2014; Mottron et al., 2015), thus suggesting that steroid hormones of gonadal origin and neurosteroids can either mask/unmask an underlying vulnerability for behavioral disorders or ameliorate/aggravate the severity of related symptoms (Keller and Ruta, 2010; Knickmeyer and Baron-Cohen, 2006). A better understanding of the mechanisms underlying risk and resilience to disease between the sexes may be of fundamental importance to identify innovative therapeutic targets and pharmacological approaches for these diseases. In this line, promising results are emerging on the potential use of sex steroid hormones and selective estrogen receptor modulators as adjunctive treatments for some of these disorders (Huerta-Ramos et al., 2014; Kulkarni et al., 2014; Weickert et al., 2015). For preclinical research in this framework, see (Biamonte et al., 2009; Macri et al., 2010).

2. Genes and sex hormones interaction in sexually dimorphic brain development

Nowadays it is generally agreed that the brain is a sexually dimorphic organ that can be shaped by sex-specific selection pressures. The classic view of sex dimorphism of the brain postulates that sex-specific differences specifically arise from differential development of the gonads and differential exposure to gonadally-secreted steroid hormones (Miller, 1988; Mottron et al., 2015; Robel and Baulieu, 1994). Once produced, these gonad-derived hormones are released into the systemic circulation to exert their biological activity in a wide variety of reproductive and non-reproductive tissues, including the central nervous system. In particular, in rodent brains, the dominant driver of most sex differences is estradiol, which is locally produced by the portion of circulating testosterone which gains access to the brain (Wu et al., 2009). See Fig. 1 for an overview of the developmental expression of the major hormone synthesizing enzymes and hormone receptors in the brain.

The organizational/activational hypothesis of steroid hormone action on the brain was first proposed by Phoenix et al. (1959), in a seminal paper which revealed that the exposure to androgens during the early developmental period is essential for the presentation of androgen-induced male-specific behaviors at adulthood. These data obtained in Guinea pigs provided the first evidence that gonadal hormones exert a permanent/organizational effect during a critical period, corresponding to fetal and neonatal development (Knickmeyer and Baron-Cohen, 2006).

Another major breakthrough in steroid hormone research field has been represented by the demonstration that *de novo* steroid synthesis contributes to the establishment and maintenance of sex dimorphisms within the nervous system in both sexes, particularly in brain sites unrelated to reproduction (McCarthy et al., 2008; Schwarz and McCarthy, 2008). This pioneering discovery came from the observation that blood levels of steroid hormones do not necessarily overlap with their brain concentrations (Schumacher et al., 2003). Nowadays, extensive evidence, in a variety of species, supports this notion and steroids synthesized in the brain are commonly referred to as neurosteroids.

While overwhelming consensus has been reached on the contribution made by gonadally-produced sex steroids and neurosteroids to brain gender differences, it has become clear that not all sex differences can be explained by gonadal hormonal effects (Arnold, 2009; McCarthy and Arnold, 2011). Several studies conducted to identify other factors underlying, and contributing to, brain sex differences, point to differential neural expression of genes specifically located on the X and Y sex chromosomes as other major actors in the differentiation of male and female brains (Arnold, 2009; Davies and Wilkinson, 2006; Wolstenholme et al., 2013). To further complicate the topic, increasing evidence demonstrates that steroid hormones exert epigenetic effects on the developing nervous system to dictate adult sex differences in brain and behavior (Matsuda et al., 2012). These include modifications in DNA methylation, histone modification, genomic imprinting and microRNAs (McCarthy and Nugent, 2015). Moreover, it seems apparent that specific brain areas rely on different mechanisms to attain sex dimorphism (Brandt et al., 2013; Dean and McCarthy, 2008; McCarthy and Konkle, 2005), thus further corroborating the potential involvement of epigenetic regulation of steroid action in the brain.

3. Sexual dimorphism in abnormal brain development: exploring the role of genes and sex hormones interaction in human neurodevelopmental disorders

As discussed above, increasing evidence demonstrates a complex interaction between sex hormones and genetic and epigenetic factors in the establishment of sex differences in brain and behavior. The widespread differential susceptibility to pathology of males and females affected by neuropsychiatric diseases suggests a potential involvement of an abnormal genes and sex hormones interplay during brain development in this class of disorders (Hill et al., 2004; Kokras and Dalla, 2014; Mottron et al., 2015).

To shed light on this topic, this review will examine sex biases in human neurodevelopmental disorders from a clinical point of view, particularly focusing on those of well-established genetic origin, such as Rett syndrome, CDKL5-associated disorders, Fragile X and Down syndrome. Autism will be also addressed, given its paradigmatic role as a sex-biased neurodevelopmental disorder (Lai et al., 2015b). Current knowledge about sex differences in validated animal models for these disorders will be also explored. Given the increasing number of mouse models carrying mutations in genes relevant for this class of diseases, we will exploit this valuable tool to address the potential interplay between genes and sex hormones at the preclinical level.

3.1. Autism

Autism is a neurodevelopmental disorder characterized by restricted and repetitive patterns of behavior, interests, or activities, and deficits in social communication and interaction (APA, 2013). Males are diagnosed with this disease three to four times more commonly than females and a number of gender differences has been reported in this disorder, starting as early as the postnatal period (Baron-Cohen et al., 2011; Fombonne, 2005; Schaafsma and Pfaff, 2014; Werling and Geschwind, 2013) Such differences span from the onset and severity of symptoms, with females being more severely affected, to sex/gender differences in neuroanatomical and physiological endpoints (Lai et al., 2013; Mottron et al., 2015). Discoveries on this issue have been recently summarized in a special issue by *Molecular Autism*, 2015 (Lai et al., 2015a).

The “extreme male brain theory” of autism proposed by Baron-Cohen postulates that individuals suffering from disorders related

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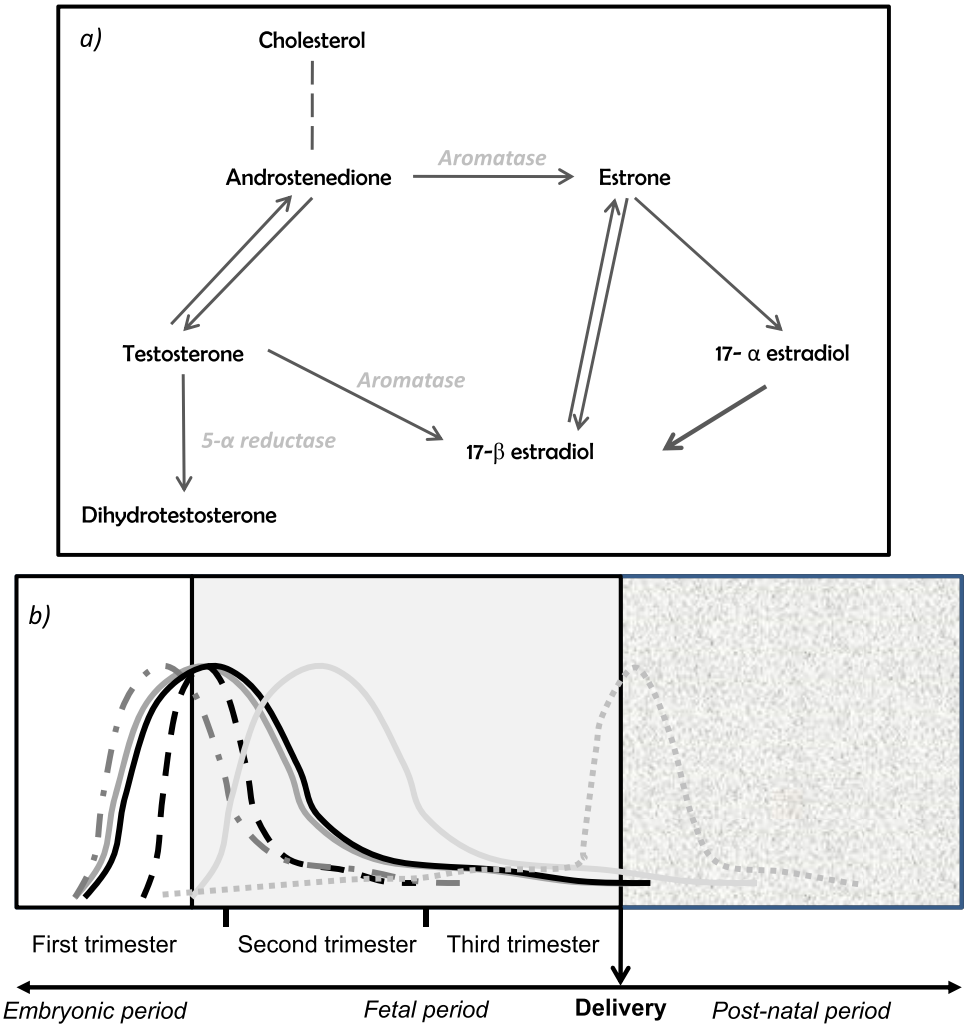

Fig. 1. (a) Biosynthetic pathways of neuroactive steroids. Major hormone synthesizing enzymes are shown in grey. (b) Diagram summarizing the developmental expression of the major hormone synthesizing enzymes and hormone receptors in the brain. Aromatase in black: continuous line for humans (peak of expression between the embryonic and the fetal period); dashed line for rodents (peak of expression between embryonic day E15 and E19). 5-α reductasi in dark gray: continuous line for humans (peak of expression between the embryonic and the fetal period); dashed line for rodents (peak of expression between E14 and E16). Estrogen receptor α in light gray: continuous line for humans (peak of expression during the fetal period); dashed line for rodents (peak of expression post-natal days 4 and 6).

to autism show a pattern of functions typical of the extreme male brain, a brain best suited to understand and predict the functioning of a law-driven system (Baron-Cohen, 2002). According to this theory, identifying, understanding, and reacting correctly to the thoughts and emotions of others are characteristics of the female brains, which would not be well represented in autistic patients.

These considerations, together with the observation that plasma and salivary testosterone levels are elevated in autistic male patients (Geier and Geier, 2007; Kelemenova et al., 2010), possibly as a consequence of reduced expression of the enzyme aromatase (Crider et al., 2014; Sarachana et al., 2011; see Fig. 1), and that autistic females are more likely than non-autistic females to develop steroid-related conditions, such as polycystic ovary syndrome (Palomba et al., 2012), suggest that exposure to abnormal levels of androgens is associated with autism. In particular, it was proposed that both the male bias in autism and the masculinized phenotype of patients might be attributed to the effect of an abnormal exposure to testosterone during pregnancy (Baron-Cohen et al., 2011). Support to this hypothesis has been recently provided by a study which found that the levels of fetal testosterone in amniotic fluid correlated positively with a number of autistic traits and inversely with social skills and levels of empathy in children at 4 years of age (Baron-Cohen et al., 2015; Knickmeyer et al., 2005; Knickmeyer and Baron-Cohen, 2006).

It must however be noted that, according to a recent meta-analysis, the results on this topic still appear inconsistent (Gore et al., 2014). The elevated levels of fetal testosterone may thus effectively contribute to increase susceptibility of males for this disorder only when other predisposing factors, such as genetic susceptibility, occur. A recent interesting candidate gene for such increased susceptibility to autism is the *RORA* gene, the expression of which is low in the frontal cortex of autistic individuals and oppositely regulated by male and female hormones (Hu et al., 2015). Even though, further studies are needed to verify these hypotheses, these data confirm the paradigmatic role of autism in the study of sex and gene interplay in health and disease and stresses the need for systematic investigations in available animal models of this complex and promising interaction.

3.1.1. *Sex differences in mouse models of autism*

Since the etiopathogenesis of autism has not been clearly elucidated so far, the diagnosis of this disorder is mainly based on presentation of three core symptoms: profound alterations in social interaction, communication deficits and stereotyped behaviors (i.e.

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Table 1
Sex-dependent behavioral differences in a selection of rodent models of autism.

Rodent models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Females	
		Genetic mutations		
BTBR T+ tf/J	Motor performances	Locomotor activity (open field) ↔	Not investigated	Defensor et al. (2011),
		Exploratory behavior ↔	Not investigated	Kokras & Dalla (2014),
		Repetitive behaviors ↑	Not investigated	McFarlane et al. (2008),
	Cognitive abilities	Learning ↔	Not investigated	Scattoni et al. (2011),
	Sensory gating	ASR, PPI ↔	Not investigated	Silverman et al. (2010),
	Social behavior	**Sociability ↓**	**Sociability ↔or↓ (contradictory results)**	Yang et al. (2012)
		Social interaction ↓	Social interaction ↓	
		Juvenile play ↓	Not investigated	
		Unusual repertoire of USVs	Unusual repertoire of USVs	
	Anxiety-like behavior	Anxiety-like behaviour ↔	Not investigated	
NL-3 KO	Motor performances	Locomotor activity (open field) ↑	Not investigated	Radyushkin et al. (2009), Tabuchi et al. (2007)
		Motor coordination ↔	Not investigated	
		Exploratory behavior ↑	Not investigated	
	Cognitive abilities	Abnormal learning and memory (slightly superior)	Not investigated	
		Social novelty preference ↓	Not investigated	
	Sensory gating	PPI ↔	Not investigated	
	Social behavior	USVs ↓	Not investigated	
		Sociability ↔	Not investigated	
		Social interaction ↔	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
	Depressive-like behavior	Sucrose preference ↔	Not investigated	
	Seizures	Seizure susceptibility ↔	Not investigated	
En2 KO	Motor performances	Locomotor activity (activity chamber) ↔	Locomotor activity (activity chamber) ↔	Cheh et al. (2006)
		Motor coordination ↓	Not investigated	
		Exploratory behavior ↓	Not investigated	
		Repetitive behaviors ↑	Not investigated	
	Social behavior	Juvenile play ↓	Juvenile play ↓	
		Social interaction ↔	Not investigated	
		Territorial aggression ↓	Not investigated	
Gabrb3 KO	Motor performances	Locomotor activity (three chamber apparatus)↑	Not investigated	DeLorey et al. (2008)
		Exploratory behavior ↓	Not investigated	
		Nest building ↓	Not investigated	
	Cognitive abilities	Attention ↓	Not investigated	
	Social behavior	Sociability ↓	Not investigated	
	Seizures	Seizure susceptibility ↑	Not investigated	
CAPS2 KO	Motor performances	Locomotor activity (home cage) ↑	Not investigated	Sadakata and Furuichi (2010), Sadakata et al. (2007)
		Exploratory behavior ↓	Not investigated	
	Behavioral rhythms	Abnormal sleep–wake rhythm	Not investigated	
	Cognitive abilities	Learning and memory ↓	Not investigated	
	Anxiety-like behavior	Anxiety ↑	Not investigated	
	Social behavior	Absent	Maternal behavior ↓	
		Social interaction ↓	Not investigated	
glut3 +/-		Sex not specified		Zhao et al. (2010)
	Motor performances	Locomotor activity (activity chamber) ↓		
		Motor coordination ↔		
		Repetitive behaviors ↑		
	Cognitive abilities	Social novelty preference ↓		
		Learning and memory ↓		
		Reversal learning ↓		
	Social behavior	Sociability ↓		
		USVs ↓		
GAP43 +/−	Motor performances	Repetitive behaviors ↔	Repetitive behaviors ↔	Zaccaria et al. (2010)
	Cognitive abilities	Reversal learning ↓	Reversal learning ↓	
	Anxiety-like behavior	Anxiety-like behavior ↑	Anxiety-like behavior ↑	
		Escape oriented behavior ↓	**Escape oriented behavior ↔**	
Mthfr +/−	Motor performances	**Locomotor activity (open field) ↑**	**Locomotor activity (open field) ↔**	Levav-Rabkin et al. (2011)
	Cognitive abilities	Recognition memory ↓	Recognition memory ↓	
V1aR KO	Motor performances	Swim performance ↔	Not investigated	Bielsky et al. (2004)
	Sensory gating	ASR, PPI ↔	Not investigated	
	Social behavior	Social recognition ↓	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↓	Not investigated	

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Table 1 (*Continued*)

Rodent models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Females	
Emht1 +/-	Motor performances	Locomotor activity (home cage) ↓	Locomotor activity (home cage) ↓	Balemans et al. (2010), Kokras and Dalla (2014)
		Motor coordination ↔	Motor coordination ↔	
		Exploratory behavior ↓	Exploratory behavior ↓	
	Cognitive abilities	**Social novelty preference** ⟵	**Social novelty preference** ↓	
	Social behavior	**Juvenile play** ↓	**Juvenile play** ↔	
		Sociability ↑	Sociability ↑	
	Anxiety-like behavior	Anxiety-like behavior ↑	Anxiety-like behavior ↑	
Dvl1-deficient	Sensory gating	PPI ↓	PPI ↓	Lijam et al. (1997)
	Social behavior	Social interaction ↓	Social interaction ↓	
		Nest building ↓	Nest building ↓	
		Gene-environment interactions		
patDp/+		Sex not specified		Nakatani et al. (2009)
	Cognitive abilities	Spatial learning ↔		
		Reversal learning ↓		
		Social novelty preference ↓		
	Anxiety-like behavior	Anxiety-like behavior ↑		
		Generalized fear		
	Social behavior	Sociability ↓		
		USVs ↓	Not investigated	
NL-4 KO	Motor performances	Locomotor activity (open field) ↔	Not investigated	Jamain et al. (2008)
		Motor coordination ↔	Not investigated	
		Exploratory behavior ↔	Not investigated	
	Cognitive abilities	Learning and memory ↔	Not investigated	
		Social novelty preference ↓	Not investigated	
	Sensory gating	PPI ↔	Not investigated	
	Social behavior	USVs ↓	Not investigated	
		Sociability ↓	Not investigated	
		Social Interaction ↓	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
	Seizures	Seizure susceptibility ↔	Not investigated	
MALTT	Motor performances	Locomotor activity (open field) ↑	Locomotor activity (open field) ↑	Hamilton et al. (2011)
		Circling stereotypy	**No circling stereotypy**	
	Sensory gating	PPI ↑/ASR ↓	PPI ↑/ASR ↓	
	Social behavior	Sociability ↓	Not investigated	
		Social interaction ↓	Not investigated	
	Seizures	Seizure susceptibility ↑	Seizure susceptibility ↑	
Exposure (*E14-E17*) to *B(a)P* in *Cpr*$^{lox/lox}$ mice		Sex not specified		Sheng et al. (2010)
	Cognitive abilities	Attention, learning and memory ↓		
Exposure (*P14*) to *VPA* in *GSTM1*-/- mice	Social behavior	Play behavior ↓	Play behavior ↓	Yochum et al. (2010)
Neonatal exposure to *GVG* in *Mthfr* +/− mice	Motor performances	Locomotor activity (open field) ↑	Locomotor activity (open field) ↑	Levav-Rabkin et al. (2011)
	Cognitive abilities	Recognition memory ↓	Recognition memory ↓	
Reln^{rl-orl}	Motor performances	Motor coordination ↓	Not investigated	Lalonde et al. (2004)
		Exploratory behavior↓	Not investigated	
	Cognitive abilities	Spontaneous novelty preference ↓	Not investigated	
		Spatial learning ↓	Not investigated	
Reelin $^{rl/+}$	Motor performances	Motor coordination ↔	Not investigated	Laviola et al. (2009), Macri et al. (2010), Ognibene et al. (2007)
	Cognitive abilities	Reversal learning ↓	Not investigated	
	Social behavior	Sociability ↔	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↓	Anxiety-like behavior ↓	
		Motor impulsivity ↑	Motor impulsivity ↑	
Neonatal thimerosal in SJL Mice	Motor performances	Motor coordination ↔	Motor coordination ↔	Berman et al. (2008)
	Cognitive abilities	Social novelty preference ↔	Social novelty preference ↔	
	Sensory gating	ASR, PPI ↔	ASR, PPI ↔	
	Social behavior	Sociability ↔	Sociability ↔	
	Anxiety-like behavior	Anxiety-like behavior ↔	Anxiety-like behavior ↔	
		Environmental factors		
Exposure in utero (*E0-E20*) to letrozole	Social behavior	**Juvenile social interaction** ↔	**Juvenile social interaction** ↓	Xu et al. (2015)
		Adult social interaction ↔	Adult social interaction ↔	
		Not investigated	Eterosexual social interactions during estrous phases ↓	

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Table 1 (*Continued*)

Rodent models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Females	
Exposure (*E12,5*) to *VPA*	Motor performances Social behavior Anxiety-like behavior	Repetitive behaviors ↑ **Social interaction ↓** **Anxiety-like behavior ↑**	Repetitive behaviors ↑ **Social interaction ↔** **Anxiety-like behavior ↔**	Kokras and Dalla (2014), Schneider et al. (2008)
		Brain lesions		
5,7-DHT (*P0*)	Motor performances Anxiety-like behavior	**Exploratory behavior ↓** **Anxiety-like behavior ↑**	**Exploratory behavior ↔** **Anxiety-like behavior ↔**	Hohmann et al. (2007)

↔: unaltered; ↓: reduced; ↑: increased; ↘: tend to be reduced; ⟵: delayed. Sex-dependent differences are highlighted in bold. *Abbreviations: KO:* knockout*; +/−:* heterozygous*; PPI:* prepulse inhibition*; ASR:* acustic startle response*; BTBR:* inbred mouse strain; *NL-3*: neuroligin-3, *En2*:engrailed-2; *Gabrb3:* gene, which encodes the β3 subunit of the GABAA receptor; *CAPS2*: Ca2+-dependent activator protein for secretion 2*; glut3:* Neuronal glucose transporter isoform 3*; GAP43:* growth-associated protein-43*; Mthfr*: methylenetetrahydrofolate reductase gene*;V1aR:* Vasopressin receptor Via; *Emht1*: euchromatin histone methyltransferase 1; *Dvl1:* Dishevelled, *patD*: paternally inherited duplication of 6.3 Mb of mouse chromosome 7 (mirroring human chromosome 15q11-13 duplication); *NL-4:* neuroligin-4; *MALTT:* multiple autistic-like transgenic traits; *VPA:* valproic acid; *B(a)P:* benzo(a) pyrene*; Cpr:* Cytochrome p450 reductase; *GSTM1:* glutathione-S-transferaseM1; Thimerosal (sodium ethylmercury thiosalicylate) is an antimicrobial preservative used in numerous vaccines; *GVG:* vigabatrin*; Rl:* reelin gene; *letrozole*: potent aromatase inhibitor; *5,7-DHT*: 5,7-exposure to dihydroxytryptamine on postnatal day 0.

repetitive behaviors and restricted interests). Different approaches have therefore been adopted to model these pathologies in rodents, ranging from neonatal environmental challenges to reproduce the early environmental factors that may have an etiological role in autism (Dufour-Rainfray et al., 2010; Krause et al., 2002; Patterson, 2002; Shi et al., 2003; Torres, 2003; Vojdani et al., 2003), to targeted gene mutations in loci relevant for autism susceptibility identified by association or linkage studies in human populations (Berkel et al., 2010; Jamain et al., 2003; Kim et al., 2008; Laumonnier et al., 2004; Laviola et al., 2009; Lintas and Persico, 2009; Moessner et al., 2007). Table 1 provides a summary of current knowledge about sex differences at the behavioral level and a schematic view of available mouse models of autism.

As shown in Table 1, because of the prevalence of male affected individuals for this disorder, only a few studies have systematically explored the sex effects in mouse models of autism, thus making difficult the drawing of any conclusion. It seems, however evident, that the few sex differences highlighted so far concern the time devoted to exploratory behavior and the occurrence of spontaneous stereotyped behaviors, which appear affected specifically in males (Hamilton et al., 2011; Hohmann et al., 2007; Levav-Rabkin et al., 2011; Zaccaria et al., 2010). Further studies aimed at understanding the relevance of these preliminary observations in mouse models to the repetitive patterns of behavior, interests and activities which characterize autistic patients are however needed. Recent data do in fact suggest that girls with autism compared to affected males present less severe repetitive/restricted behaviors, but comparable deficits in the social and communication domains (Supekar and Menon, 2015). Interestingly, this behavioral difference was accompanied by sex-dependent differences in morphometry in relevant motor regions (Supekar and Menon, 2015).

Another domain which seems to be highly affected by the hormonal milieu in the mouse models of autism is the sociability (Table 1). The direction of the results is however highly variable, thus rendering very hard the possibility to draw any conclusion. Interestingly, similar results are reported in disorders of genetic origin (see e.g. Section 3.2.1 and Table 2) as well as in response to early hormonal challenges (see below), thus suggesting that this behavioral domain may be controlled by a complex interaction among sex, genes and epigenetic mechanisms.

Of particular interest to the aims of this review is a recent preclinical study addressing the long-term behavioral effects of the exposure to elevated levels of testosterone during pregnancy on rat offsprings (Xu et al., 2015). Interestingly, the exposure to similar hormone levels in males and females during pregnancy exerted long-term sexually dimorphic consequences, thus providing a possible framework for the biased sex ratio in autism prevalence. Specifically, this early hormonal challenge affected social behaviors specifically on female offspring, which spent less time interacting with a conspecific in adolescence and exhibited impaired heterosexual interactions as adults. The neonatal vocalization behavior of rat pups of both sexes was also affected. As a whole, however, the consequences of the prenatal hormonal challenge appear mild and transient, thus questioning the crucial role attributed to abnormal sex hormonal environment in the susceptibility to autism. These data, together with those obtained at the clinical level (see Section 3.1), argue for a complex interaction between genes and sex hormone interplay during critical windows of susceptibility as a major source of autism. In this line, a mitigation of symptoms' severity was found when a hormonal challenge based on neonatal estradiol administration into the cisterna magna was applied on a substrate of genetic susceptibility to autism, namely in males carrying a spontaneous mutation in the *Reelin* gene, one of the molecules that are under examination as a risk factor for autism (Biamonte et al., 2009; Macri et al., 2010). A single estradiol treatment on postnatal day 5, the age at which a peak in the expression of estradiol receptors can be observed in mouse brain (see Fig. 1), did in fact mitigate the social and cognitive phenotype of heterozygous reeler mice in adulthood and rescued the neuroanatomical abnormalities specifically in the amygdala. These results suggest the importance of studies aimed at assessing the organizational effects of neuroactive hormones on genetic models of autism for a better understanding of the interactions between hormones and genes in the physiopathology of this disorder.

3.2. Rett syndrome

Rett syndrome (RTT) is a rare and pervasive developmental disorder, primarily affecting girls with a prevalence of 1 in every 10,000 births (Hagberg, 2002); it represents the second most common cause of intellectual disability in females (Hagberg et al., 1983; Rett, 1966). RTT patients undergo an "apparently" normal prenatal and perinatal development until about 6–18 months of age (Hagberg, 2002). A regression period then occurs, characterized by a profound loss of acquired developmental skills in the areas of communication and hand use as well as by head growth deceleration, also leading to microcephaly (Hagberg, 2002). At the end of this period, development reaches a plateau associated with a wide variety of specific symptoms: stereotyped hand movements, major breathing abnormalities, bloating, EEG irregularities, sleep problems, gait dispraxia, back deformities, feeding abnormalities as well as autistic-like behaviors (Chahrour and Zoghbi, 2007; Hagberg, 2002; Mount et al., 2001).

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Table 2
Sex-dependent behavioral differences in mouse models of Rett syndrome and CDKL5-disorders.

Mouse models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Females	
MeCP2 KO	Motor performances	Motor coordination ↓ Spontaneous activity in the dark phase ↓ Locomotor activity (open field) (**3–4 weeks**) ↓ Grip strength ↓ Swim performance ↓	Motor coordination ↓ Spontaneous activity in the dark phase↓ Locomotor activity (open field) (**17 weeks**) ↓ Grip strength ↓ Swim performance ↓	Guy et al. (2011), Ricceri et al. (2008), Samaco et al. (2013), Santos et al. (2007), Stearns et al. (2007)
	Cognitive abilities	Learning and memory↓ **(worse than females)**	Learning and memory↓	
	Sensory gating	Not investigated	PPI ↑	
	Social behavior	Not investigated	ASR ↓ Sociability ↓	
	Anxiety-like behavior	Anxiety-like behavior ↓	Anxiety-like behavior ↓	
MeCP2 truncated	Motor performances	Motor coordination ↓ Locomotor activity (home cage)↓ Exploratory behavior ↓ Not investigated Not investigated Nest building ↓	Motor coordination ↓ Locomotor activity (home cage)↓ Exploratory behavior ↓ Drinking/eating ↑ Coordinated use of mouth and forepaws ↓ Nest building ↓	McGill et al. (2006), Moretti et al. (2005), De Filippis et al. (2010, 2012, 2015a, 2015b, 2015c), Ricceri et al. (2008), Shahbazian et al. (2002), Woods et al. (2012)
	Cognitive abilities	Learning and memory ↓ **Social novelty preference (2–3 months)** ↔	Learning and memory ↓ **Social novelty preference (2–3 months)** ↓	
	Social behavior	**Sociability (1–2 months)** ↓ Social interaction ↓	**Sociability (1–2 months)** ↔ Social interaction ↓	
	Anxiety-like behavior	Anxiety-like behavior ↑	Not investigated	
CDKL5	Motor performances	Locomotor activity (home cage) ↑or↓ (contradictory results) Motor coordination ↓ Nest building ↓	Locomotor activity (home cage ↘) (open field ↔) Not investigated Not investigated	Amendola et al. (2014), Wang et al. (2012)
	Cognitive abilities	Learning and memory ↓ Motor learning ↔	Not investigated Not investigated	
	Social behavior	Sociability ↓ Social interaction ↓	Not investigated Not investigated	
	Anxiety-like behavior	Anxiety-like behavior↓	Not investigated	

↔: unaltered; ↓: reduced; ↑: increased; ↘: tend to be reduced. Sex-dependent differences are highlighted in bold. *Abbreviations: KO:* knockout; *PPI:* prepulse inhibition; *ASR:* acustic startle response; *MeCP2*: methyl – CpG – binding protein 2; *CDKL5*: Cyclin-dependent kinase-like 5.

RTT was originally described by the Austrian paediatrician, Andreas Rett in 1966 (Rett, 1966) and in 1999 mutations in the X-linked gene encoding methyl–CpG-binding protein 2 (*MECP2*) were identified as clear etiological factors for more than 90% of classical RTT cases (Amir, 1999; Chahrour and Zoghbi, 2007). The *MECP2* gene encodes two closely related proteins which selectively bind to methylated CpGs, sequences of the DNA (Jones et al., 1998). Although initially MeCP2 was thought to act primarily as a transcriptional repressor, subsequent studies have clearly showed that MeCP2 can both activate and repress transcription (Chahrour et al., 2008) and can also induce a global chromatin remodeling (Cohen et al., 2011). To elucidate the physiological role of MECP2, several target genes have been identified [for an overview: (Chadwick and Wade, 2007)].

RTT affects almost exclusively girls (Renieri et al., 2003). The frequency of disease-causing *MECP2* mutations in mentally retarded male patients is between 1.3% and 1.7% (Villard, 2007). Males have classical RTT when mutation arises as somatic mosaicism or when they have an extra X chromosome. In all other cases, males with *MECP2* mutations show diverse phenotypes, from severe congenital encephalopathy, mental retardation with various neurological symptoms, to mild mental retardation only (Bourdon et al., 2003; Moog et al., 2003; Renieri et al., 2003; Villard, 2007). Interestingly, *de novo* mutations in sporadic RTT occur almost exclusively on the paternally derived X chromosome, thus providing additional support to the high female:male ratio observed in sporadic cases with RTT (Zhu et al., 2009).

Consistent with the X-linked nature of the disorder (Arnold, 2004), sex differences in symptomatology mainly concern the severity of the disorders with males being more affected in several domains.

3.2.1. Sex differences in mouse models of Rett syndrome

Following the identification of *MECP2* gene mutations as clear etiological factors in about 90% of classical RTT cases, strategies employing gene targeting have been used to generate several lines of mice carrying endogenous *MeCP2* mutations (Ricceri et al., 2008, 2013). These mutant mice are, at the moment, regarded as good models of RTT for their high construct validity [i.e. the extent to which a model reproduces the etiology and pathophysiology of a disorder (McKinney, 1984)]. Moreover, indications are available suggesting a high face validity for these models [i.e. the degree to which a model resembles the symptoms of a disorder], as MeCP2 mutant mice have been reported to recapitulate many RTT symptoms.

Table 2 summarizes the current knowledge about sex-dependent differences derived from behavioral analyses so far carried out in major MeCP2 mouse models of RTT. Given the prevalence of the disorder among female patients, the RTT research community has increasingly focussed its attention on this sex in recent years (Katz et al., 2012).

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Taken together the results presented in Table 2 provide evidence of the validity as a RTT model of *MeCP2*-mutated females, the sex which is generally neglected in preclinical research due to the confounding effects of the oestrus cycle on behavioral parameters (Prendergast et al., 2014).

The comparison of available preclinical investigations also highlights the presence of subtle sex behavioral differences in RTT mouse models, particularly in the social domain (see Table 2). This is consistent with evidence demonstrating that *MeCP2* is differentially expressed in male and female brains during development (for an overview on the developmental expression of *MeCP2*, see Kurian et al., 2007). In this framework, a transient reduction in *MeCP2* expression in the rat amygdala (30–65%), induced by a treatment with small interfering RNA during a sensitive period of brain sexual differentiation (postnatal days 0–2), disrupts the organization of sex differences in juvenile social play behavior (Kurian et al., 2008). In particular, male juvenile social play decreased to female-typical levels, whereas no changes were observed in females. Interestingly, such a behavioral effect was accompanied by a transient impact on androgen receptor expression in male mouse brain, which returned to normal levels at two weeks of age, and a lasting impact on arginine vasopressin (AVP) expression, a neuropeptide known to be crucially involved in the expression of social behaviors and responses to stress (Forbes-Lorman et al., 2012).

Given that neonatal androgen exposure is known to regulate juvenile social play behavior (Hotchkiss et al., 2002), and that testosterone signalling has been implicated in the regulation of methylation status of the AVP promoter and in the expression of AVP mRNA (Auger et al., 2011), a complex interaction between sex hormones and MeCP2 is likely to occur in the early programming of sex differences. Unfortunately, however, no one has so far investigated the levels of sex hormones in different brain areas and at different developmental ages in RTT mouse models. Gaining knowledge on this topic may be fundamental for a better understanding of the differential role played by MeCP2 in the developing male versus female brain.

More recently, it was demonstrated that reduction in *MeCP2* expression increased the expression and protein levels of the astrocytic marker GFAP in the female, but not the male developing amygdala (Forbes-Lorman et al., 2014), suggesting that the relevance of MeCP2 in the organization of lasting sex differences may extend beyond social behavior. As a whole, these data suggest that the *MeCP2* gene may play a crucial role at the interface between sex, genes and epigenetic mechanisms.

3.3. CDKL5-associated disorders

Mutations in Cyclin-dependent kinase-like 5 (*CDKL5*) gene, located on Xp22, have been reported in patients characterized by various neurologic disorders, including the X-linked infantile spasms syndrome, or West syndrome, early infantile epileptic encephalopathy, and Angelman syndrome or Angelman-like phenotype (Russo et al., 2009), with the most common being the Hanefeld variant of RTT (Scala et al., 2005).

CDKL5 encodes a serine/threonine kinase expressed in various tissues, with the brain presenting the highest levels of expression (Rusconi et al., 2008). Available data point to a crucial role for CDKL5 in fundamental neurodevelopmental processes such as neuronal morphogenesis and plasticity (Kilstrup-Nielsen et al., 2012): down-regulation of CDKL5 in cultured neurons inhibits neurite growth, reduces dendritic arborization and impacts dendritic spine structure and synapse activity (Chen et al., 2010; Ricciardi et al., 2012).

The common features in all CDKL5-associated disorders are the onset of seizures in the first months of life, severe global developmental delay resulting in intellectual disability, poor motor control and the presence of RTT-like features such as hand stereotypies (Kilstrup-Nielsen et al., 2012). CDKL5 disorders affect primarily females with a ratio of 12:1 males. In general, males have a more severe epileptic encephalopathy and a worse outcome compared to female patients, which is in agreement with the location of the *CDKL5* gene on the X chromosome (Bahi-Buisson and Bienvenu, 2012). Actually no cure exists for these severely affected patients.

3.3.1. Sex differences in mouse models of CDKL5-associated disorders

The absence of robust preclinical models has long hampered a deep understanding of the physiological roles played by CDKL5. This limitation has been overcome in the past years with the establishment of two mouse models carrying inactivating mutations in the catalytic domain of Cdkl5 (Amendola et al., 2014; Wang et al., 2012).

The recent generation of these knockout mice (KO) has allowed a first characterization of the *in vivo* consequences of the loss of function of this protein. Although the behavioral phenotyping of these mutant mice is at the moment quite far from complete, indications are available suggesting a high face validity, with mutant mice showing abnormal locomotor activity, defective cognitive performance and autistic-like behavioral abnormalities, such as reduced sociability (Amendola et al., 2014; Wang et al., 2012).

Importantly, only one of these two recent studies has compared the phenotype of males and females carrying the inactivating mutation in the *Cdkl5* gene (see Table 2). Results demonstrate that the impairments in a small group of functions, namely hindlimb clasping, home cage locomotor activity and eye tracking, are of comparable magnitude and direction in *Cdkl5* hemizygous males and homozygous females compared to sex-matched wild-type controls, with heterozygous females showing an intermediate phenotype (Amendola et al., 2014). These results provide support to the hypothesis that sex-dependent differences in patients with CDKL5 disorders might be entirely explained by the compensation that occurs in heterozygous females due to the presence of a second, non-affected, X chromosome. It will be interesting in the future to assess whether similar sex-dependent differences can be observed in other relevant domains which have not been investigated so far, such as cognitive function and sociability (see Table 2).

It is worth mentioning that the recent development of these mouse models has represented a major breakthrough for a better understanding of the role played by CDKL5 in health and disease. Key, unanticipated findings may thus be expected within this research field in the next future.

3.4. Down syndrome

Down syndrome (DS) is the most common genetic cause of intellectual disability, with a prevalence of 1 in every 700 births (http://www.agpd.it/ctg/sindrome-di-down/). DS is caused by trisomy of human chromosome 21 (Hsa21). Approximately 0.45% of human conceptions are trisomic for Hsa21 (Hassold et al., 1996). In general, a prevalence of males is found in children with all trisomy 21 variants (sex ratio: 1.24), except the cases with mosaicism, in which females appear more affected (sex ratio: 0.88) (Kovaleva et al., 2001).

The most prominent feature of DS is the learning and memory defect that affects 100% of patients. The disease also presents an array of other abnormal behavioral phenotypes, including the incomplete and delayed acquisition of motor, linguistic and visual-spatial abilities and neurobehavioral disorders. In general, it has been reported that DS males, even though they present a significantly greater life expectancy than females (Glasson et al., 2003), have major behavioral problems, including attention deficit hyperactivity-like behaviors in childhood and depression at adulthood (Maatta et al., 2006).

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Other phenotypes characterizing DS patients include cardiovascular, breathing and skeletal alterations. Sex differences in these domains are also apparent and include a skewed ratio in atrioventricular septal defects, with males being affected twice more than females (Freeman et al., 2008), a higher prevalence of sleep-disordered breathing in DS boys (64.7%) than in girls (38.5%) (de Miguel-Diez et al., 2003) and a lower bone mineral apparent density in DS females (Gonzalez-Aguero et al., 2011).

Interestingly, DS patients have been reported to present an increased risk of developing Alzheimer-like dementia (AD) by the age of 40, with DS women having a particularly increased risk compared to the general population (Lai et al., 1999). As in the general population, women who have low baseline levels of estradiol are four times more likely to develop AD (Schupf et al., 2006), these data suggested a link between this increased incidence of AD in DS female patients and the alterations in hormonal function between DS patients and normal controls (Schupf et al., 1998). In fact, women with DS may present hyperandrogenism (Bagatin et al., 2010) and are twice more likely to undergo early menopause (Patel et al., 2001). In this line, levels of estradiol were found to correlate with onset of cognitive decline in DS female patients (Granholm et al., 2003).

Abnormal hormonal serum levels have been also reported in DS male patients, who present elevated levels of estradiol, luteinizing hormone and follicle-stimulating hormone and slightly decreased levels of testosterone compared to controls (Suzuki, 2010). Prolactin is also greater in DS patients, both over the entire sample and in the subgroup of men with Down's syndrome (Hestnes et al., 1991).

As a whole, the hormonal status of DS patients appears highly affected, thus highliting the need for preclinical studies aimed at understanding the mechanisms underlying the genes and sex hormones interplay in this disorder.

3.4.1. Sex differences in mouse models of Down syndrome

DS is caused by trisomy of the human chromosome Hsa21.To model the increased expression of genes located on this additional chromosome, several mouse models that are trisomic for different sets of genes that are orthologous to those expressed on the human Hsa21 have been generated (Rueda et al., 2012). In fact, in the mouse, the genomic regions orthologous to Hsa21 are located on chromosomes 10, 16, and 17, with the largest genetic region located on chromosome 16 (Belichenko et al., 2015). Available models span from mice with the triplication of a region of chromosome 16, such as the Ts1Cje mouse which presents a trisomy of 81 genes (Belichenko et al., 2015; Fernandez and Garner, 2007; Sago et al., 1998), to a mouse model in which the entire human Hsa21 has been triplicated, the Tc1 (Belichenko et al., 2015; Galante et al., 2009; Morice et al., 2008; Witton et al., 2015).

The most commonly used and best characterized model of DS is the Ts65Dn mouse (Costa et al., 1999; Faizi et al., 2011; Sago et al., 2000; Zampieri, 2014). This model bears a partial trisomy of a segment of the chromosome 16 and contains approximately 92 genes orthologous to the human Hsa21 genes (Sultan et al., 2007). Despite only a set of genes triplicated in DS are in trisomy in this model, the Ts65Dn model present good face validity (Rueda et al., 2012).

Recently, advances in chromosomal engineering have been used to create a mouse model containing all of the mouse homologues of Hsa21 genes, the triple trisomic (TTS) model of DS (Yu et al., 2010).

Table 3 summarizes the behavioral analyses so far carried out in four exemplificative DS models. As shown in the table, only a few studies have explored sex-dependent behavioral differences in available mouse models (Faizi et al., 2011; Sago et al., 2000; Stewart et al., 2007). Moreover, contrary to what reported in the clinical setting (see Section 3.4), current preclinical models were not able to reproduce differences between DS male and female mice.

Importantly, however, Ts65Dn male and female mice have been reported to differentially respond to an environmental challenge with respect to their sex-matched controls (Martinez-Cue et al., 2002). In particular, DS female mice after 7 weeks of exposure to an enriched environment showed a normalization of general motor activity along the 24 h and an improved cognitive profile. By contrast, the same environmental enrichment impaired the performance of DS male mice. These results suggest that the endogenous hormonal milieu may play a significant modulatory role on DS symptoms presentation and that modulation of these hormonal levels may constitute an innovative strategy for DS.

In this line, prolonged estrogen treatment improved cognitive deficits in Ts65Dn female mice and restored the deficits in brain cholinergic system function (Granholm et al., 2002; Granholm et al., 2003). This phenotypic improvement was associated with a normalization of the serum levels of estrogen, which were reduced in DS female mutant mice. These studies based their rationale on the reported increased susceptibility of DS females to develop AD (Schupf et al., 1998; see Section 3.4) and on previous findings demonstrating that the female hormone estrogen may play a key role in delaying the onset and severity of dementia in women with AD (Kulkarni et al., 2013; Simpkins et al., 2009). Importantly, however, no changes were evident in Ts65Dn male mice receiving a comparable estradiol treatment (Hunter et al., 2004). Whether an abnormal baseline levels of sex hormones in this mouse model may have contributed to the lack of beneficial effects of the hormonal stimulation in DS male mice remains to be established. In fact, no data are available about the central and peripheral steroid levels in Ts65Dn male mice.

Taken together, these results highlight the importance of evaluating the potential efficacy of novel therapeutic strategies in both genders at the preclinical level, to exclude the possibility that differences in the sex hormonal milieu may impact the ability of responding to therapeutic challenges.

3.5. Fragile X syndrome

Fragile X syndrome (FXS) is the most common monogenetic cause of inherited developmental disability, occurring in 1:4000 males and 1:7000 females (Loesch et al., 2004; Schaefer et al., 2015). Common characteristics of individuals with FXS include intellectual impairment, increased anxiety, hyperarousal to stimuli and unusual physical features (*e.g.*, an elongated face, flat feet and hyperextendable finger joints). Obsessive compulsive disorder-like behavior, attention-deficit/hyperactivity disorder symptoms, increased risk for seizures, self-injurious behavior, perseverative language, sleep issues and aggression also occur (Garber et al., 2008).

FXS results from an expansion of unstable cytosine guanine guanine (CGG) trinucleotide repeats within the promoter of the fragile X mental retardation 1 gene (*FMR1*), which resides on the X chromosome. This gene encodes for FMRP, an mRNA binding protein that has been shown to regulate the expression of hundreds of mRNAs in the central nervous system (Santos et al., 2014). The trinucleotide repeat expansion within the *FMR1* promoter is usually inherited from a maternal carrier whose gene undergoes a further expansion which leads to the silencing of the *FMR1* gene and the consequent appearance of FXS symptomatology (Schaefer et al., 2015).

In individuals carrying the full mutation, the severity of the physical and behavioral phenotypes correlates with lower levels of FMRP. Due to the X-linked nature of its inheritance, however, FXS phenotypes are highly heterogeneous and vary considerably between males and females. In general, females typically display

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Table 3
Sex-dependent behavioral differences in a selection of mouse models of Down syndrome.

Mouse models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Females	
Ts65Dn	Motor performances	Locomotor activity ↑ (activity chamber/home cage)	Locomotor activity ↑ (activity chamber/home cage) **(more than males)**	Belichenko et al. (2015), Costa et al. (1999), Das et al. (2013), Faizi et al. (2011), Heller et al. (2014), Kleschevnikov et al. (2012), Sago et al. (2000), Stewart et al. (2007), Zampieri (2014)
		Motor coordination ↓	Not investigated	
		Exploratory behavior ↑	Exploratory behavior ↑	
		Grip strength ↓	Not investigated	
		Swim performance ↓	Not investigated	
		Repetitive behaviors ↑	Not investigated	
		Nest building ↓	Not investigated	
	Cognitive abilities	Learning and memory (short- and long-term) ↓	Learning and memory (short and long-term) ↓	
		Spontaneous novelty preference ↓ **(lower than females/significantly lower than chance level)**	Spontaneous novelty preference ↓	
		Social novelty preference ↔	Social novelty preference ↔	
	Sensory gating	ASR ↔	ASR ↔	
	Social behavior	USVs: altered quality (lower frequencies, longer syllables)	Not investigated	
		Sociability ↔	Sociability ↔	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
		Thigmotaxis ↔or↑ (contradictory results)	Not investigated	
Tc1	Motor performances	Locomotor activity (open field) ↑	Not investigated	Belichenko et al. (2015), Galante et al. (2009), Morice et al. (2008), Witton et al. (2015)
		Motor coordination ↓	Not investigated	
		Grip strength ↔	Not investigated	
		Lateralization ↔	Not investigated	
		Repetitive behaviors ↑	Not investigated	
	Cognitive abilities	Short-term memory ↓	Not investigated	
		Long-term memory ↔	Not investigated	
		Motor learning ↓	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
		Thigmotaxis ↓	Not investigated	
Ts1Cje	Motor performances	Locomotor activity (home cage) ↓	Locomotor activity (home cage) ↓	Belichenko et al. (2015), Fernandez and Garner (2007), Sago et al. (1998, 2000)
		Exploratory behavior ↓	Not investigated	
	Cognitive abilities	Spatial learning ↓	Spatial learning ↓	
		Reversal learning ↓	Reversal learning ↓	
		Sex not specified		
		Long- and short-term memory ↔		
		Spontaneous novelty preference ↓		
Ts1Rhr	Motor performances	Locomotor activity (open field/activity chamber) ↔	Not investigated	Belichenko et al. (2009, 2015)
	Cognitive abilities	Learning and memory ↓	Not investigated	
		Spontaneous novelty preference ↓	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
		Thigmotaxis ↑	Not investigated	
TTS	Motor performances	Locomotor activity (activity chamber) ↑	Not investigated	Belichenko et al. (2015)
		Grip strength ↓	Not investigated	
		Repetitive behaviors ↓	Not investigated	
	Cognitive abilities	Spontaneous novelty preference ↓	Not investigated	
		Long-term memory ↓	Not investigated	
	Anxiety-like behavior	Anxiety-like behavior ↔	Not investigated	
		Thigmotaxis ↔	Not investigated	

↔: unaltered; ↓: reduced; ↑: increased; ↘: tend to be reduced. Sex-dependent differences are highlighted in bold. *Abbreviations: KO:* knockout*; PPI:* prepulse inhibition*; ASR:* acustic startle response; *Ts1Cje:* mouse which presents a trisomy of 81 genes of chromosome 16; *Tc1:* mouse model in which the entire human Hsa21 has been triplicated; *Ts65Dn:* this model bears a partial trisomy of a segment of the chromosome 16*; TTS:* triple trisomic model of DS.

milder symptoms than males due to compensation by the second non-affected X chromosome (Kazdoba et al., 2014). However, in addition to the different severity level, other differences in symptomatology have been observed. Most FRX males show a peculiar phenotype characterized by mental retardation and a greater likelihood of displaying autistic-like behaviors than would be expected on the basis of mental disability alone (Reiss and Freund, 1990; Reiss et al., 1988). These include hyperactivity and a short attention span (Hagerman and Sobesky, 1989). Moreover, FXS males often exhibit extreme eye gaze avoidance and hyperarousal when they encounter stressful social situations (Hall et al., 2012). These observations are particularly interesting, given that autism is more frequent in males than in females (see Section 3.1).

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Table 4
Sex-dependent behavioral differences in mouse models of Fragile X syndrome.

Mouse models	Behavioral domain	Behavioral alterations (compared to wt mice)		References
		Males	Female	
Fmr1 KO	Motor performances	Locomotor activity (open field) ↑	Locomotor activity (open field) ↑	Ding et al. (2014), Qin et al. (2005), Rotschafer et al. (2012), Spencer et al. (2005, 2011), Veeraragavan et al. (2014)
		Motor coordination ↓	Not investigated	
		Exploratory behavior ↑	Not investigated	
		Repetitive behaviors ↑	Not investigated	
	Cognitive abilities	Learning and memory ↓	Learning and memory ↓	
	Sensory gating	PPI ↑ ASR ↓	PPI ↑ ASR ↓	
	Social behavior	USVs ↓	Not investigated	
		Social interest and recognition ↔	Not investigated	
		Social anxiety ↑	Not investigated	
		Social interactions: active behavior↑/passive behavior↓	Not investigated	
	Anxiety-like behavior	**Anxiety-like behavior** ↓	**Anxiety-like behavior** ↔	
	Seizures	Seizure susceptibility ↑	Seizure susceptibility ↑	

↔: unaltered; ↓: reduced; ↑: increased; ↘: tend to be reduced. Sex-dependent differences are highlighted in bold. *Abbreviations: KO:* knockout; *PPI:* prepulse inhibition; *ASR:* acustic startle response; *Fmr1*: fragile X mental retardation 1 gene.

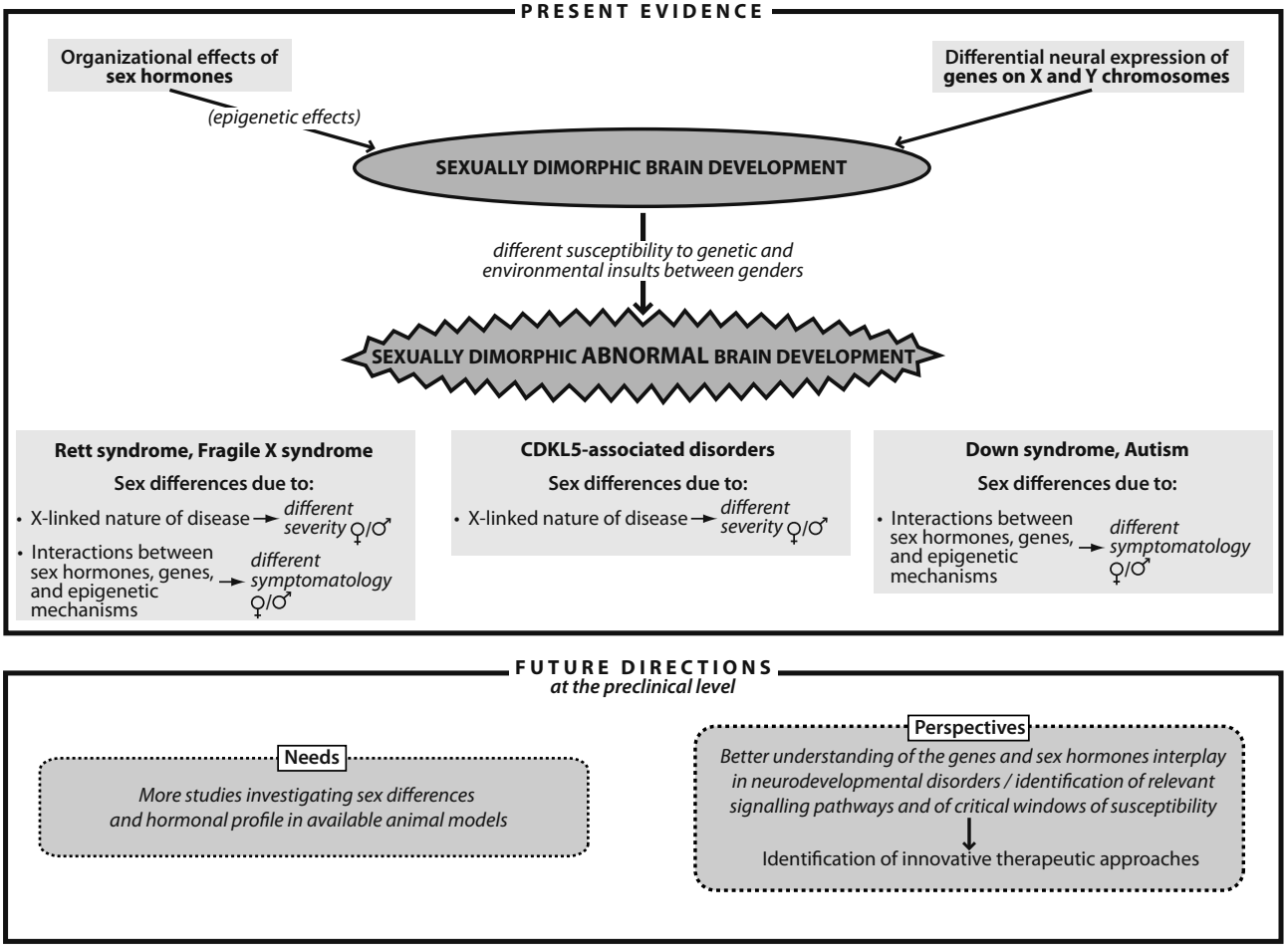

Fig. 2. Overview of gender differences in susceptibility to neurodevelopmental disorders. The factors influencing the establishment of male to female differences in brain during development are supposed to be the same that determine different susceptibility to pathologies between genders. For any of the neurodevelopmental diseases examined in the review, the nature of gender differences – either in severity or quality of symptoms – and the potential origin are here summarized. Future needs and perspectives to better understand gender influences on disease onset, progression and on potential therapies are also outlined.

A different profile can be observed in FRX females. Extreme shyness and low self esteem are the most commonly reported features in this gender. Intellective capacity is generally normal in 40% of those affected by complete mutation (Ferrando Lucas et al., 2004). However, although the majority is of normal intelligence, females with fragile X syndrome have an increased rate of schizophrenia spectrum disorders (Reiss et al., 1988). Moreover, they show dysfunctions in social interaction, thought processes, and affective regulation (Hagerman and Sobesky, 1989; Reiss and Freund, 1990). These results suggest that the compensation by the second non-affected X chromosome that occurs in FRX females may not be sufficient by itself to explain all sex-dependent differences in FRX patients.

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Recent data in fact suggest a complex regulation of *Fmr1* gene expression by sex hormones. In particular, 17beta-estradiol has been found to regulate *Fmr1* gene expression by lowering the methylation of its promoter in the brain of both male and female mice in an age-dependent manner (Singh and Prasad, 2008a). Moreover, testosterone down-regulates *Fmr1* gene expression in the cerebral cortex of gonadectomized old male mice (Prasad and Singh, 2014). More recently, alterations in estradiol-mediated facilitation of long-term potentiation, synaptic architecture and fear memory have been also observed in *Fmr1* KO neurons (Yang et al., 2015), thus further supporting a complex interaction between FMRP and sex hormones.

Taken together, reviewed literature suggests that a better understanding of the mechanisms underlying sex-dependent differences in FRX may be of crucial importance for the identification of innovative therapeutic strategies for this disorder.

3.5.1. Sex differences in mouse models of Fragile X syndrome

Animal models of FXS have been developed in various species, such as the Drosophila fruit fly, zebrafish, mouse, and rat (Hamilton et al., 2014; McBride et al., 2005; McBride et al., 2012; Tucker et al., 2004). *Fmr1* KO mice are the most used and best characterized model of FRX. This mouse model was generated in 1994 by gene targeting procedures that blocked the expression of the *Fmr1* gene on a C57BL/6J genetic background (Bakker et al., 1994). Even though these mice do not have an expanded CGG repeat domain, they recapitulate the human full-mutation. Available data demonstrate that *Fmr1* KO mice present many of the morphologic, behavioral, electrophysiologic, and physical phenotypes that are present in FXS patients (Santos et al., 2014).

Despite the widespread evidence of sex-dependent differences in the presentation of symptoms in FRX patients (see Section 3.5), however, so far only few studies have investigated sex differences in the *Fmr1* mouse model (Baker et al., 2010; Ding et al., 2014; Qin et al., 2005). Table 4 summarizes available data on this topic.

As shown, data so far collected are consistent with FRX females showing a milder phenotype compared to affected males. In particular, anxiety-like behaviors appeared impaired in *Fmr1* male mice only (Qin et al., 2005).

The few studies exploring the phenotype of *Fmr1* KO females do not allow drawing any definitive conclusion about the possibility that the sex-dependent differences reported in FRX patients may be the results of a complex interaction between the abnormal genotype of these animals and their sex hormonal milieu. Moreover, no data are so far available concerning the peripheral and central hormonal profile in male and female *Fmr1* KO mice and no studies have addressed the potential therapeutic value of the pharmacological modulation of the brain sex hormone levels in this mouse model. Given the increasing evidence demonstrating a complex interplay between the *Fmr1* gene and sex hormones under physiological conditions (Prasad and Singh, 2014; Singh and Prasad, 2008b; Yang et al., 2015; Section 3.5), understanding the contribution of these mechanisms to the presentation of FRX-related symptomatology has the potential to provide a better understanding of the differential vulnerability of males and females to FRX and to be highly informative in the search for a cure for this devastating disorder.

4. Conclusions

Taken together, the literature reviewed so far confirms that a complex interaction between genetic factors and sex hormones may underlie the differential susceptibility of a given gender, and may impact the severity of symptoms, in most of the analyzed neurodevelopmental disorders (see Fig. 2). In line with recent preclinical data (Biamonte et al., 2009; Huerta-Ramos et al., 2014; Kulkarni et al., 2014; Macri et al., 2010; Weickert et al., 2015), this evidence suggests that pharmacological modulation of sex steroid-related pathways may represent promising innovative pharmacological approaches for at least some of the neurodevelopmental diseases under investigation.

In particular, recent data highlight a potential role for *MeCP2* and *Fmr1*, the genes responsible for RTT and FRX, respectively, in the organization and maintenance of sex differences, and suggest their involvement at the interface between sex, genes and epigenetic mechanisms during critical periods of brain development (see Sections 3.2 and 3.5).

The interplay between Trisomy 21 and sex hormones appears more complex, with clinical sex differences in symptomatology not being replicated at the preclinical level (see Section 3.4). The recent development of a novel mouse model with higher construct validity (Yu et al., 2010) will hopefully shed light on this issue. Literature on Down syndrome also provided a paradigmatic example of the importance of evaluating the potential efficacy of novel therapeutic strategies in both genders at the preclinical level. Alterations in the sex hormonal profile during critical periods of brain development may in fact permanently impact the ability of responding to therapeutic challenges at later stages (see Section 3.4).

Contrary to the other disorders of genetic origin under investigation, in CDKL5-disorders clinical and preclinical data suggest that sex differences might be entirely explained by the X-linked nature of the disease, with the compensation due to the presence of a second, non-affected, X chromosome being responsible for the milder phenotype of heterozygous females (see Section 3.3).

In general, the revision of the literature we have carried out strongly argues for the need of further studies aimed at the evaluation of the advantages and disadvantages conferred by biological sex under pathological conditions of neurodevelopmental origin, for a better understanding of the underlying mechanisms. There are in fact still a small number of studies addressing the central and peripheral hormonal profile and the status of brain sex steroid-related pathways in validated animal models of genetic neurodevelopmental disorders. Moreover, testing the organizational effects of neuroactive hormones on genetic models of neurodevelopmental disorders may be extremely informative for a better understanding of the interactions between sex hormones and genetic vulnerability in the development of a given disorder and in the search for a cure for these devastating syndromes. In this framework, a paradigmatic example is represented by autism, a sex- biased neurodevelopmental disorder of multifactorial origin (see Section 3.1). Even though further studies are needed, the major efforts of the autism research community have allowed a better understanding of the contribution made by sex hormones to the disease and their potential therapeutic value (see Section 3.1). Much effort is now expected to unravel the potential therapeutic efficacy of drugs targeting sex hormones-related signaling pathways in neurodevelopmental disorders of well-established genetic origin. A better understanding of the mechanisms underlying risk and resilience to disease between the sexes may be of fundamental importance to identify innovative therapeutic targets and pharmacological approaches for these diseases. In this line, promising results are emerging on the potential use of sex steroid hormones and selective estrogen receptor modulators as adjunctive treatments for some of these disorders.

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References

A.P.A., 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 5th edition).
Amendola, E., Zhan, Y., Mattucci, C., Castroflorio, E., Calcagno, E., Fuchs, C., Lonetti, G., Silingardi, D., Vyssotski, A.L., Farley, D., Ciani, E., Pizzorusso, T., Giustetto, M., Gross, C.T., 2014. Mapping pathological phenotypes in a mouse model of CDKL5 disorder. PLoS One 9, e91613.
Amir, R.E., Van den Veyver, I.B., Wan, M., Tran, C.Q., Francke, U., Zoghbi, H.Y., 1999. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat. Genet. 23, 185–188.
Arnold, A.P., 2004. Sex chromosomes and brain gender. Nat. Rev. Neurosci. 5, 701–708.
Arnold, A.P., 2009. The organizational–activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm. Behav. 55, 570–578.
Auger, C.J., Coss, D., Auger, A.P., Forbes-Lorman, R.M., 2011. Epigenetic control of vasopressin expression is maintained by steroid hormones in the adult male rat brain. Proc. Natl. Acad. Sci. U. S. A. 108, 4242–4247.
Bagatin, E., Kamamoto, C.S., Guadanhim, L.R., Sanudo, A., Dias, M.C., Barraviera, I.M., Colombo, F.C., 2010. Prevalence of acne vulgaris in patients with Down syndrome. Dermatology 220, 333–339.
Bahi-Buisson, N., Bienvenu, T., 2012. CDKL5-related disorders: from clinical description to molecular genetics. Mol. Syndromol. 2, 137–152.
Baker, K.B., Wray, S.P., Ritter, R., Mason, S., Lanthorn, T.H., Savelieva, K.V., 2010. Male and female Fmr1 knockout mice on C57 albino background exhibit spatial learning and memory impairments. Genes Brain Behav. 9, 562–574.
Bakker, C.E., Verheij, C., Willemsen, R., van der Helm, R., Oerlemans, F., Vermey, M., Bygrave, A., Hoogeveen, A.T., Oostra, B.A.O., 1994. Fmr1 knockout mice: a model to study Fragile X mental retardation. The Dutch–Belgian Fragile X Consortium. Cell 78, 23–33.
Balemans, M.C., Huibers, M.M., Eikelenboom, N.W., Kuipers, A.J., van Summeren, R.C., Pijpers, M.M., Tachibana, M., Shinkai, Y., van Bokhoven, H., Van der Zee, C.E., 2010. Reduced exploration, increased anxiety, and altered social behavior: autistic-like features of euchromatin histone methyltransferase 1 heterozygous knockout mice. Behav. Brain Res. 208, 47–55.
Baron-Cohen, S., 2002. The extreme male brain theory of autism. Trends Cogn. Sci. 6, 248–254.
Baron-Cohen, S., Auyeung, B., Norgaard-Pedersen, B., Hougaard, D.M., Abdallah, M.W., Melgaard, L., Cohen, A.S., Chakrabarti, B., Ruta, L., Lombardo, M.V., 2015. Elevated fetal steroidogenic activity in autism. Mol. Psychiatry 20, 369–376.
Baron-Cohen, S., Lombardo, M.V., Auyeung, B., Ashwin, E., Chakrabarti, B., Knickmeyer, R., 2011. Why are autism spectrum conditions more prevalent in males? PLoS Biol. 9, e1001081.
Belichenko, N.P., Belichenko, P.V., Mobley, W.C., 2009. Evidence for both neuronal cell autonomous and nonautonomous effects of methyl-CpG-binding protein 2 in the cerebral cortex of female mice with Mecp2 mutation. Neurobiol. Dis. 34, 71–77.
Belichenko, P.V., Kleschevnikov, A.M., Becker, A., Wagner, G.E., Lysenko, L.V., Yu, Y.E., Mobley, W.C., 2015. Down syndrome cognitive phenotypes modeled in mice trisomic for all HSA 21homologues. PLoS One 10, e0134861.
Berkel, S., Marshall, C.R., Weiss, B., Howe, J., Roeth, R., Moog, U., Endris, V., Roberts, W., Szatmari, P., Pinto, D., Bonin, M., Riess, A., Engels, H., Sprengel, R., Scherer, S.W., Rappold, G.A., 2010. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat. Genet. 42, 489–491.
Berman, R.F., Pessah, I.N., Mouton, P.R., Mav, D., Harry, J., 2008. Low-level neonatal thimerosal exposure: further evaluation of altered neurotoxic potential in SJL mice. Toxicol. Sci. 101, 294–309.
Biamonte, F., Assenza, G., Marino, R., D'Amelio, M., Panteri, R., Caruso, D., Scurati, S., Yague, J.G., Garcia-Segura, L.M., Cesa, R., Strata, P., Melcangi, R.C., Keller, F., 2009. Interactions between neuroactive steroids and reelin haploinsufficiency in Purkinje cell survival. Neurobiol. Dis. 36, 103–115.
Bielsky, I.F., Hu, S.B., Szegda, K.L., Westphal, H., Young, L.J., 2004. Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. Neuropsychopharmacology 29, 483–493.
Bourdon, V., Philippe, C., Martin, D., Verloes, A., Grandemenge, A., Jonveaux, P., 2003. MECP2 mutations or polymorphisms in mentally retarded boys: diagnostic implications. Mol. Diagn. 7, 3–7.
Brandt, N., Vierk, R., Rune, G.M., 2013. Sexual dimorphism in estrogen-induced synaptogenesis in the adult hippocampus. Int. J. Dev. Biol. 57, 351–356.
Chadwick, L.H., Wade, P.A., 2007. MeCP2 in Rett syndrome: transcriptional repressor or chromatin architectural protein? Curr. Opin. Genet. Dev. 17, 121–125.
Chahrour, M., Jung, S.Y., Shaw, C., Zhou, X., Wong, S.T., Qin, J., Zoghbi, H.Y., 2008. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 320, 1224–1229.
Chahrour, M., Zoghbi, H.Y., 2007. The story of Rett syndrome: from clinic to neurobiology. Neuron 56, 422–437.
Cheh, M.A., Millonig, J.H., Roselli, L.M., Ming, X., Jacobsen, E., Kamdar, S., Wagner, G.C., 2006. En2 knockout mice display neurobehavioral and neurochemical alterations relevant to autism spectrum disorder. Brain Res. 1116, 166–176.
Chen, Q., Zhu, Y.C., Yu, J., Miao, S., Zheng, J., Xu, L., Zhou, Y., Li, D., Zhang, C., Tao, J., Xiong, Z.Q., 2010. CDKL5, a protein associated with rett syndrome, regulates neuronal morphogenesis via Rac1 signaling. J. Neurosci. 30, 12777–12786.
Cohen, S., Gabel, H.W., Hemberg, M., Hutchinson, A.N., Sadacca, L.A., Ebert, D.H., Harmin, D.A., Greenberg, R.S., Verdine, V.K., Zhou, Z., Wetsel, W.C., West, A.E., Greenberg, M.E., 2011. Genome-wide activity-dependent MeCP2 phosphorylation regulates nervous system development and function. Neuron 72, 72–85.
Costa, A.C., Walsh, K., Davisson, M.T., 1999. Motor dysfunction in a mouse model for Down syndrome. Physiol. Behav. 68, 211–220.
Crider, A., Thakkar, R., Ahmed, A.O., Pillai, A., 2014. Dysregulation of estrogen receptor beta (ERbeta), aromatase (CYP19A1), and ER co-activators in the middle frontal gyrus of autism spectrum disorder subjects. Mol. Autism 5, 46.
Das, I., Park, J.M., Shin, J.H., Jeon, S.K., Lorenzi, H., Linden, D.J., Worley, P.F., Reeves, R.H., 2013. Hedgehog agonist therapy corrects structural and cognitive deficits in a Down syndrome mouse model. Sci. Trans. Med. 5, 201ra120.
Davies, W., Wilkinson, L.S., 2006. It is not all hormones: alternative explanations for sexual differentiation of the brain. Brain Res. 1126, 36–45.
De Filippis, B., Chiodi, V., Adriani, W., Lacivita, E., Mallozzi, C., Leopoldo, M., Domenici, M.R., Fuso, A., Laviola, G., 2015a. Long-lasting beneficial effects of central serotonin receptor 7 stimulation in female mice modeling Rett syndrome. Front. Behav. Neurosci. 9, 86.
De Filippis, B., Fabbri, A., Simone, D., Canese, R., Ricceri, L., Malchiodi-Albedi, F., Laviola, G., Fiorentini, C., 2012. Modulation of RhoGTPases improves the behavioral phenotype and reverses astrocytic deficits in a mouse model of Rett syndrome. Neuropsychopharmacology 37, 1152–1163.
De Filippis, B., Fabbri, A., Simone, D., Canese, R., Ricceri, L., Malchiodi, F., Fiorentini, C., Laviola, G., 2010. Improvement of behavioral phenotype and astrocytic function in a mouse model of Rett syndrome: Effects of the Rho GTPase-modulating protein CNF1. In: 2nd European Rett Syndrome Conference, Edimburgh, UK, pp. 213–223.
De Filippis, B., Musto, M., Altabella, L., Romano, E., Canese, R., Laviola, G., 2015b. Deficient purposeful use of forepaws in female mice modelling Rett syndrome. Neural Plast., 326184.
De Filippis, B., Valenti, D., Chiodi, V., Ferrante, A., de Bari, L., Fiorentini, C., Domenici, M.R., Ricceri, L., Vacca, R.A., Fabbri, A., Laviola, G., 2015c. Modulation of Rho GTPases rescues brain mitochondrial dysfunction, cognitive deficits and aberrant synaptic plasticity in female mice modeling Rett syndrome. Eur. Neuropsychopharmacol. 25, 889–901.
de Miguel-Diez, J., Villa-Asensi, J.R., Alvarez-Sala, J.L., 2003. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. Sleep 26, 1006–1009.
Dean, S.L., McCarthy, M.M., 2008. Steroids, sex and the cerebellar cortex: implications for human disease. Cerebellum 7, 38–47.
Defensor, E.B., Pearson, B.L., Pobbe, R.L., Bolivar, V.J., Blanchard, D.C., Blanchard, R.J., 2011. A novel social proximity test suggests patterns of social avoidance and gaze aversion-like behavior in BTBR T+ tf/J mice. Behav. Brain Res. 217, 302–308.
DeLorey, T.M., Sahbaie, P., Hashemi, E., Homanics, G.E., Clark, J.D., 2008. Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: a potential model of autism spectrum disorder. Behav. Brain Res. 187, 207–220.
Ding, Q., Sethna, F., Wang, H., 2014. Behavioral analysis of male and female Fmr1 knockout mice on C57BL/6 background. Behav. Brain Res. 271, 72–78.
Dufour-Rainfray, D., Vourc'h, P., Tourlet, S., Guilloteau, D., Chalon, S., Andres, C.R., 2010. Fetal exposure to teratogens: evidence of genes involved in autism. Neurosci. Biobehav. Rev. 35, 1254–1265.
Faizi, M., Bader, P.L., Tun, C., Encarnacion, A., Kleschevnikov, A., Belichenko, P., Saw, N., Priestley, M., Tsien, R.W., Mobley, W.C., Shamloo, M., 2011. Comprehensive behavioral phenotyping of Ts65Dn mouse model of Down syndrome: activation of beta1-adrenergic receptor by xamoterol as a potential cognitive enhancer. Neurobiol. Dis. 43, 397–413.
Fernandez, F., Garner, C.C., 2007. Object recognition memory is conserved in Ts1Cje, a mouse model of Down syndrome. Neurosci. Lett. 421, 137–141.
Ferrando Lucas, M.T., Banus Gomez, P., Lopez Perez, G., 2004. Cognitive aspects in girls with fragile X syndrome. Rev. Neurol. 38 (Suppl 1), S53–S57.
Fombonne, E., 2005. Epidemiology of autistic disorder and other pervasive developmental disorders. J. Clin. Psychiatry 66 (Suppl. 10), 3–8.
Forbes-Lorman, R.M., Kurian, J.R., Auger, A.P., 2014. MeCP2 regulates GFAP expression within the developing brain. Brain Res. 1543, 151–158.
Forbes-Lorman, R.M., Rautio, J.J., Kurian, J.R., Auger, A.P., Auger, C.J., 2012. Neonatal MeCP2 is important for the organization of sex differences in vasopressin expression. Epigenetics 7, 230–238.
Freeman, S.B., Bean, L.H., Allen, E.G., Tinker, S.W., Locke, A.E., Druschel, C., Hobbs, C.A., Romitti, P.A., Royle, M.H., Torfs, C.P., Dooley, K.J., Sherman, S.L., 2008. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genet. Med. 10, 173–180.
Galante, M., Jani, H., Vanes, L., Daniel, H., Fisher, E.M., Tybulewicz, V.L., Bliss, T.V., Morice, E., 2009. Impairments in motor coordination without major changes in cerebellar plasticity in the Tc1 mouse model of Down syndrome. Hum. Mol. Genet. 18, 1449–1463.
Garber, K.B., Visootsak, J., Warren, S.T., 2008. Fragile X syndrome. Eur. J. Hum. Genet. 16, 666–672.
Geier, D.A., Geier, M.R., 2007. A prospective assessment of androgen levels in patients with autistic spectrum disorders: biochemical underpinnings and suggested therapies. Neuroendocrinol. Lett. 28, 565–573.
Glasson, E.J., Sullivan, S.G., Hussain, R., Petterson, B.A., Montgomery, P.D., Bittles, A.H., 2003. Comparative survival advantage of males with Down syndrome. Am. J. Hum. Biol. 15, 192–195.

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Gonzalez-Aguero, A., Vicente-Rodriguez, G., Moreno, L.A., Casajus, J.A., 2011. Bone mass in male and female children and adolescents with Down syndrome. Osteoporos. Int. 22, 2151–2157.
Gore, A.C., Martien, K.M., Gagnidze, K., Pfaff, D., 2014. Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. Endocr. Rev. 35, 961–991.
Granholm, A.C., Ford, K.A., Hyde, L.A., Bimonte, H.A., Hunter, C.L., Nelson, M., Albeck, D., Sanders, L.A., Mufson, E.J., Crnic, L.S., 2002. Estrogen restores cognition and cholinergic phenotype in an animal model of Down syndrome. Physiol. Behav. 77, 371–385.
Granholm, A.C., Sanders, L., Seo, H., Lin, L., Ford, K., Isacson, O., 2003. Estrogen alters amyloid precursor protein as well as dendritic and cholinergic markers in a mouse model of Down syndrome. Hippocampus 13, 905–914.
Guy, J., Cheval, H., Selfridge, J., Bird, A., 2011. The role of MeCP2 in the brain. Annu. Rev. Cell Dev. Biol. 27, 631–652.
Hagberg, B., 2002. Clinical manifestations and stages of Rett syndrome. Ment. Retard. Dev. Disabil. Res. Rev. 8, 61–65.
Hagberg, B., Aicardi, J., Dias, K., Ramos, O., 1983. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. Ann. Neurol. 14, 471–479.
Hagerman, R.J., Sobesky, W.E., 1989. Psychopathology in fragile X syndrome. Am. J. Orthopsychiatry 59, 142–152.
Hall, S.S., Lightbody, A.A., McCarthy, B.E., Parker, K.J., Reiss, A.L., 2012. Effects of intranasal oxytocin on social anxiety in males with fragile X syndrome. Psychoneuroendocrinology 37, 509–518.
Hamilton, S.M., Green, J.R., Veeraragavan, S., Yuva, L., McCoy, A., Wu, Y., Warren, J., Little, L., Ji, D., Cui, X., Weinstein, E., Paylor, R., 2014. Fmr1 and Nlgn3 knockout rats: novel tools for investigating autism spectrum disorders. Behav. Neurosci. 128, 103–109.
Hamilton, S.M., Spencer, C.M., Harrison, W.R., Yuva-Paylor, L.A., Graham, D.F., Daza, R.A., Hevner, R.F., Overbeek, P.A., Paylor, R., 2011. Multiple autism-like behaviors in a novel transgenic mouse model. Behav. Brain Res. 218, 29–41.
Hassold, T., Abruzzo, M., Adkins, K., Griffin, D., Merrill, M., Millie, E., Saker, D., Shen, J., Zaragoza, M., 1996. Human aneuploidy: incidence, origin, and etiology. Environ. Mol. Mutagen. 28, 167–175.
Heller, H.C., Salehi, A., Chuluun, B., Das, D., Lin, B., Moghadam, S., Garner, C.C., Colas, D., 2014. Nest building is impaired in the Ts65Dn mouse model of Down syndrome and rescued by blocking 5HT2a receptors. Neurobiol. Learn. Mem. 116, 162–171.
Hestnes, A., Stovner, L.J., Husoy, O., Folling, I., Fougner, K.J., Sjaastad, O., 1991. Hormonal and biochemical disturbances in Down's syndrome. J. Ment. Defic. Res. 35 (Pt 3), 179–193.
Hill, S.K., Beers, S.R., Kmiec, J.A., Keshavan, M.S., Sweeney, J.A., 2004. Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. Schizophr. Res. 68, 127–136.
Hohmann, C.F., Walker, E.M., Boylan, C.B., Blue, M.E., 2007. Neonatal serotonin depletion alters behavioral responses to spatial change and novelty. Brain Res. 1139, 163–177.
Hotchkiss, A.K., Ostby, J.S., Vandenburgh, J.G., Gray Jr., L.E., 2002. Androgens and environmental antiandrogens affect reproductive development and play behavior in the Sprague–Dawley rat. Environ. Health Perspect. 110 (Suppl 3), 435–439.
Hu, V.W., Sarachana, T., Sherrard, R.M., Kocher, K.M., 2015. Investigation of sex differences in the expression of RORA and its transcriptional targets in the brain as a potential contributor to the sex bias in autism. Mol. Autism 6, 6.
Huerta-Ramos, E., Iniesta, R., Ochoa, S., Cobo, J., Miquel, E., Roca, M., Serrano-Blanco, A., Teba, F., Usall, J., 2014. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur. Neuropsychopharmacol. 24, 223–231.
Hunter, C.L., Bimonte-Nelson, H.A., Nelson, M., Eckman, C.B., Granholm, A.C., 2004. Behavioral and neurobiological markers of Alzheimer's disease in Ts65Dn mice: effects of estrogen. Neurobiol. Aging 25, 873–884.
Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I.C., Soderstrom, H., Giros, B., Leboyer, M., Gillberg, C., Bourgeron, T., 2003. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nat. Genet. 34, 27–29.
Jamain, S., Radyushkin, K., Hammerschmidt, K., Granon, S., Boretius, S., Varoqueaux, F., Ramanantsoa, N., Gallego, J., Ronnenberg, A., Winter, D., Frahm, J., Fischer, J., Bourgeron, T., Ehrenreich, H., Brose, N., 2008. Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. Proc. Natl. Acad. Sci. U. S. A. 105, 1710–1715.
Jones, P.L., Veenstra, G.J., Wade, P.A., Vermaak, D., Kass, S.U., Landsberger, N., Strouboulis, J., Wolffe, A.P., 1998. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat. Genet. 19, 187–191.
Katz, D.M., Berger-Sweeney, J.E., Eubanks, J.H., Justice, M.J., Neul, J.L., Pozzo-Miller, L., Blue, M.E., Christian, D., Crawley, J.N., Giustetto, M., Guy, J., Howell, C.J., Kron, M., Nelson, S.B., Samaco, R.C., Schaevitz, L.R., St Hillaire-Clarke, C., Young, J.L., Zoghbi, H.Y., Mamounas, L.A., 2012. Preclinical research in Rett syndrome: setting the foundation for translational success. Dis. Models Mech. 5, 733–745.
Kazdoba, T.M., Leach, P.T., Silverman, J.L., Crawley, J.N., 2014. Modeling fragile X syndrome in the Fmr1 knockout mouse. Intractable Rare Dis. Res. 3, 118–133.
Kelemenova, S., Schmidtova, E., Ficek, A., Celec, P., Kubranska, A., Ostatnikova, D., 2010. Polymorphisms of candidate genes in Slovak autistic patients. Psychiatr. Genet. 20, 137–139.
Keller, F., Ruta, L., 2010. The malep revalence in autism spectrum disorders: hypotheses on its neurobiological basis. In: Blatt, G.J. (Ed.), The Neurochemical Basis of Autism. Springer, Verlag.
Kilstrup-Nielsen, C., Rusconi, L., La Montanara, P., Ciceri, D., Bergo, A., Bedogni, F., Landsberger, N., 2012. What we know and would like to know about CDKL5 and its involvement in epileptic encephalopathy. Neural Plast., 728267.
Kim, H.G., Kishikawa, S., Higgins, A.W., Seong, I.S., Donovan, D.J., Shen, Y., Lally, E., Weiss, L.A., Najm, J., Kutsche, K., Descartes, M., Holt, L., Braddock, S., Troxell, R., Kaplan, L., Volkmar, F., Klin, A., Tsatsanis, K., Harris, D.J., Noens, I., Pauls, D.L., Daly, M.J., MacDonald, M.E., Morton, C.C., Quade, B.J., Gusella, J.F., 2008. Disruption of neurexin 1 associated with autism spectrum disorder. Am. J. Hum. Genet. 82, 199–207.
Kleschevnikov, A.M., Belichenko, P.V., Faizi, M., Jacobs, L.F., Htun, K., Shamloo, M., Mobley, W.C., 2012. Deficits in cognition and synaptic plasticity in a mouse model of Down syndrome ameliorated by GABAB receptor antagonists. J. Neurosci. 32, 9217–9227.
Knickmeyer, R., Baron-Cohen, S., Raggatt, P., Taylor, K., 2005. Foetal testosterone, social relationships, and restricted interests in children. J. Child Psychol. Psychiatry 46, 198–210.
Knickmeyer, R.C., Baron-Cohen, S., 2006. Fetal testosterone and sex differences in typical social development and in autism. J. Child Neurol. 21, 825–845.
Kokras, N., Dalla, C., 2014. Sex differences in animal models of psychiatric disorders. Br. J. Pharmacol. 171, 4595–4619.
Kovaleva, N.V., Butomo, I.V., Korblein, A., 2001. Sex ratio in Down syndrome: Studies in patients with confirmed trisomy 21. Tsitol. Genet. 35, 43–49.
Krause, I., He, X.S., Gershwin, M.E., Shoenfeld, Y., 2002. Brief report: immune factors in autism: a critical review. J. Autism Dev. Disord. 32, 337–345.
Kulkarni, J., Berk, M., Wang, W., Mu, L., Scarr, E., Van Rheenen, T.E., Worsley, R., Gurvich, C., Gavrilidis, E., de Castella, A., Fitzgerald, P., Davis, S.R., 2014. A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. Psychoneuroendocrinology 43, 52–61.
Kulkarni, J., Gavrilidis, E., Worsley, R., Van Rheenen, T., Hayes, E., 2013. The role of estrogen in the treatment of men with schizophrenia. Int. J. Endocrinol. Metab. 11, 129–136.
Kurian, J.R., Bychowski, M.E., Forbes-Lorman, R.M., Auger, C.J., Auger, A.P., 2008. Mecp2 organizes juvenile social behavior in a sex-specific manner. J. Neurosci. 28, 7137–7142.
Kurian, J.R., Forbes-Lorman, R.M., Auger, A.P., 2007. Sex difference in mecp2 expression during a critical period of rat brain development. Epigenetics 2, 173–178.
Lai, F., Kammann, E., Rebeck, G.W., Anderson, A., Chen, Y., Nixon, R.A., 1999. APOE genotype and gender effects on Alzheimer disease in 100 adults with Down syndrome. Neurology 53, 331–336.
Lai, M.C., Baron-Cohen, S., Buxbaum, J.D., 2015a. Understanding autism in the light of sex/gender. Mol Autism 6, 24.
Lai, M.C., Lombardo, M.V., Auyeung, B., Chakrabarti, B., Baron-Cohen, S., 2015b. Sex/gender differences and autism: setting the scene for future research. J. Am. Acad. Child Adolesc. Psychiatry 54, 11–24.
Lai, M.C., Lombardo, M.V., Suckling, J., Ruigrok, A.N., Chakrabarti, B., Ecker, C., Deoni, S.C., Craig, M.C., Murphy, D.G., Bullmore, E.T., Baron-Cohen, S., 2013. Biological sex affects the neurobiology of autism. Brain 136, 2799–2815.
Lalonde, R., Hayzoun, K., Derer, M., Mariani, J., Strazielle, C., 2004. Neurobehavioral evaluation of Reln-rl-orl mutant mice and correlations with cytochrome oxidase activity. Neurosci. Res. 49 (3), 297–305.
Laumonnier, F., Bonnet-Brilhault, F., Gomot, M., Blanc, R., David, A., Moizard, M.P., Raynaud, M., Ronce, N., Lemonnier, E., Calvas, P., Laudier, B., Chelly, J., Fryns, J.P., Ropers, H.H., Hamel, B.C., Andres, C., Barthelemy, C., Moraine, C., Briault, S., 2004. X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. Am. J. Hum. Genet. 74, 552–557.
Laviola, G., Ognibene, E., Romano, E., Adriani, W., Keller, F., 2009. Gene-environment interaction during early development in the heterozygous reeler mouse: clues for modelling of major neurobehavioral syndromes. Neurosci. Biobehav. Rev. 33, 560–572.
Levav-Rabkin, T., Blumkin, E., Galron, D., Golan, H.M., 2011. Sex-dependent behavioral effects of Mthfr deficiency and neonatal GABA potentiation in mice. Behav. Brain Res. 216, 505–513.
Lijam, N., Paylor, R., McDonald, M.P., Crawley, J.N., Deng, C.X., Herrup, K., Stevens, K.E., Maccaferri, G., McBain, C.J., Sussman, D.J., Wynshaw-Boris, A., 1997. Social interaction and sensorimotor gating abnormalities in mice lacking Dvl1. Cell 90, 895–905.
Lintas, C., Persico, A.M., 2009. Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist. J. Med. Genet. 46, 1–8.
Loesch, D.Z., Huggins, R.M., Hagerman, R.J., 2004. Phenotypic variation and FMRP levels in fragile X. Ment. Retard. Dev. Disabil. Res. Rev. 10, 31–41.
Maatta, T., Tervo-Maatta, T., Taanila, A., Kaski, M., Iivanainen, M., 2006. Mental health, behaviour and intellectual abilities of people with Down syndrome. Downs Syndr. Res. Pract. 11, 37–43.
Macri, S., Biamonte, F., Romano, E., Marino, R., Keller, F., Laviola, G., 2010. Perseverative responding and neuroanatomical alterations in adult heterozygous reeler mice are mitigated by neonatal estrogen administration. Psychoneuroendocrinology 35, 1374–1387.
Martinez-Cue, C., Baamonde, C., Lumbreras, M., Paz, J., Davisson, M.T., Schmidt, C., Dierssen, M., Florez, J., 2002. Differential effects of environmental enrichment on behavior and learning of male and female Ts65Dn mice, a model for Down syndrome. Behav. Brain Res. 134, 185–200.

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Matsuda, K.I., Mori, H., Kawata, M., 2012. Epigenetic mechanisms are involved in sexual differentiation of the brain. Rev. Endocr. Metab. Disord. 13, 163–171.
McBride, S.M., Choi, C.H., Wang, Y., Liebelt, D., Braunstein, E., Ferreiro, D., Sehgal, A., Siwicki, K.K., Dockendorff, T.C., Nguyen, H.T., McDonald, T.V., Jongens, T.A., 2005. Pharmacological rescue of synaptic plasticity, courtship behavior, and mushroom body defects in a Drosophila model of fragile X syndrome. Neuron 45, 753–764.
McBride, S.M., Holloway, S.L., Jongens, T.A., 2012. Using as a tool to identify Pharmacological Therapies for Fragile X Syndrome. Drug Discov. Today Technol. 10, e129–e136.
McCarthy, M.M., Arnold, A.P., 2011. Reframing sexual differentiation of the brain. Nat. Neurosci. 14, 677–683.
McCarthy, M.M., Konkle, A.T., 2005. When is a sex difference not a sex difference? Front. Neuroendocrinol. 26, 85–102.
McCarthy, M.M., Nugent, B.M., 2015. At the frontier of epigenetics of brain sex differences. Front. Behav. Neurosci. 9, 221.
McCarthy, M.M., Schwarz, J.M., Wright, C.L., Dean, S.L., 2008. Mechanisms mediating oestradiol modulation of the developing brain. J. Neuroendocrinol. 20, 777–783.
McFarlane, H.G., Kusek, G.K., Yang, M., Phoenix, J.L., Bolivar, V.J., Crawley, J.N., 2008. Autism-like behavioral phenotypes in BTBR T+tf/J mice. Genes Brain Behav. 7, 152–163.
McGill, B.E., Bundle, S.F., Yaylaoglu, M.B., Carson, J.P., Thaller, C., Zoghbi, H.Y., 2006. Enhanced anxiety and stress-induced corticosterone release are associated with increased Crh expression in a mouse model of Rett syndrome. Proc. Natl. Acad. Sci. U. S. A. 103, 18267–18272.
McKinney, W.T., 1984. Animal models of depression: an overview. Psychiatr. Dev. 2, 77–96.
Miller, W.L., 1988. Molecular biology of steroid hormone synthesis. Endocr. Rev. 9, 295–318.
Moessner, R., Marshall, C.R., Sutcliffe, J.S., Skaug, J., Pinto, D., Vincent, J., Zwaigenbaum, L., Fernandez, B., Roberts, W., Szatmari, P., Scherer, S.W., 2007. Contribution of SHANK3 mutations to autism spectrum disorder. Am. J. Hum. Genet. 81, 1289–1297.
Moog, U., Smeets, E.E., van Roozendaal, K.E., Schoenmakers, S., Herbergs, J., Schoonbrood-Lenssen, A.M., Schrander-Stumpel, C.T., 2003. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2). Eur. J. Paediatr. Neurol. 7, 5–12.
Moretti, P., Bouwknecht, J.A., Teague, R., Paylor, R., Zoghbi, H.Y., 2005. Abnormalities of social interactions and home-cage behavior in a mouse model of Rett syndrome. Hum. Mol. Genet. 14, 205–220.
Morice, E., Andreae, L.C., Cooke, S.F., Vanes, L., Fisher, E.M., Tybulewicz, V.L., Bliss, T.V., 2008. Preservation of long-term memory and synaptic plasticity despite short-term impairments in the Tc1 mouse model of Down syndrome. Learn. Mem. 15, 492–500.
Mottron, L., Duret, P., Mueller, S., Moore, R.D., Forgeot d'Arc, B., Jacquemont, S., Xiong, L., 2015. Sex differences in brain plasticity: a new hypothesis for sex ratio bias in autism. Mol. Autism 6, 33.
Mount, R.H., Hastings, R.P., Reilly, S., Cass, H., Charman, T., 2001. Behavioural and emotional features in Rett syndrome. Disabil. Rehabil. 23, 129–138.
Nakatani, J., Tamada, K., Hatanaka, F., Ise, S., Ohta, H., Inoue, K., Tomonaga, S., Watanabe, Y., Chung, Y.J., Banerjee, R., Iwamoto, K., Kato, T., Okazawa, M., Yamauchi, K., Tanda, K., Takao, K., Miyakawa, T., Bradley, A., Takumi, T., 2009. Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism. Cell 137, 1235–1246.
Ognibene, E., Adriani, W., Granstrem, O., Pieretti, S., Laviola, G., 2007. Impulsivity-anxiety-related behavior and profiles of morphine-induced analgesia in heterozygous reeler mice. Brain Res. 1131, 173–180.
Palomba, S., Marotta, R., Di Cello, A., Russo, T., Falbo, A., Orio, F., Tolino, A., Zullo, F., Esposito, R., La Sala, G.B., 2012. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. Clin. Endocrinol. (Oxf.) 77, 898–904.
Patel, B.N., Seltzer, G.B., Wu, H.S., Schupf, N., 2001. Effect of menopause on cognitive performance in women with Down syndrome. Neuroreport 12, 2659–2662.
Patterson, P.H., 2002. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. Curr. Opin. Neurobiol. 12, 115–118.
Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369–382.
Prasad, S., Singh, K., 2014. Testosterone down regulates the expression of Fmr-1 gene in the cerebral cortex of gonadectomized old male mice. Biogerontology 15, 503–515.
Prendergast, B.J., Onishi, K.G., Zucker, I., 2014. Female mice liberated for inclusion in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 40, 1–5.
Qin, M., Kang, J., Smith, C.B., 2005. A null mutation for Fmr1 in female mice: effects on regional cerebral metabolic rate for glucose and relationship to behavior. Neuroscience 135, 999–1009.
Radyushkin, K., Hammerschmidt, K., Boretius, S., Varoqueaux, F., El-Kordi, A., Ronnenberg, A., Winter, D., Frahm, J., Fischer, J., Brose, N., Ehrenreich, H., 2009. Neuroligin-3-deficient mice: model of a monogenic heritable form of autism with an olfactory deficit. Genes Brain Behav. 8, 416–425.
Reiss, A.L., Freund, L., 1990. Fragile X syndrome. Biol. Psychiatry 27, 223–240.
Reiss, A.L., Hagerman, R.J., Vinogradov, S., Abrams, M., King, R.J., 1988. Psychiatric disability in female carriers of the fragile X chromosome. Arch. Gen. Psychiatry 45, 25–30.
Renieri, A., Meloni, I., Longo, I., Ariani, F., Mari, F., Pescucci, C., Cambi, F., 2003. Rett syndrome: the complex nature of a monogenic disease. J. Mol. Med. (Berl.) 81, 346–354.
Rett, A., 1966. On a unusual brain atrophy syndrome in hyperammonemia in childhood. Wien. Med. Wochenschr. 116, 723–726.
Ricceri, L., De Filippis, B., Laviola, G., 2008. Mouse models of Rett syndrome: from behavioural phenotyping to preclinical evaluation of new therapeutic approaches. Behav. Pharmacol. 19, 501–517.
Ricceri, L., De Filippis, B., Laviola, G., 2013. Rett syndrome treatment in mouse models: searching for effective targets and strategies. Neuropharmacology 68, 106–115.
Ricciardi, S., Ungaro, F., Hambrock, M., Rademacher, N., Stefanelli, G., Brambilla, D., Sessa, A., Magagnotti, C., Bachi, A., Giarda, E., Verpelli, C., Kilstrup-Nielsen, C., Sala, C., Kalscheuer, V.M., Broccoli, V., 2012. CDKL5 ensures excitatory synapse stability by reinforcing NGL-1-PSD95 interaction in the postsynaptic compartment and is impaired in patient iPSC-derived neurons. Nat. Cell Biol. 14, 911–923.
Robel, P., Baulieu, E.E., 1994. Neurosteroids biosynthesis and function. Trends Endocrinol. Metab. 5, 1–8.
Rotschafer, S.E., Trujillo, M.S., Dansie, L.E., Ethell, I.M., Razak, K.A., 2012. Minocycline treatment reverses ultrasonic vocalization production deficit in a mouse model of Fragile X Syndrome. Brain Res. 1439, 7–14.
Rueda, N., Florez, J., Martinez-Cue, C., 2012. Mouse models of Down syndrome as a tool to unravel the causes of mental disabilities. Neural Plast., 584071.
Rusconi, L., Salvatoni, L., Giudici, L., Bertani, I., Kilstrup-Nielsen, C., Broccoli, V., Landsberger, N., 2008. CDKL5 expression is modulated during neuronal development and its subcellular distribution is tightly regulated by the C-terminal tail. J. Biol. Chem. 283, 30101–30111.
Russo, S., Marchi, M., Cogliati, F., Bonati, M.T., Pintaudi, M., Veneselli, E., Saletti, V., Balestrini, M., Ben-Zeev, B., Larizza, L., 2009. Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. Neurogenetics 10, 241–250.
Sadakata, T., Furuichi, T., 2010. Ca^{2+}-dependent activator protein for secretion 2 and autistic-like phenotypes. Neurosci. Res. 67, 197–202.
Sadakata, T., Washida, M., Iwayama, Y., Shoji, S., Sato, Y., Ohkura, T., Katoh-Semba, R., Nakajima, M., Sekine, Y., Tanaka, M., Nakamura, K., Iwata, Y., Tsuchiya, K.J., Mori, N., Detera-Wadleigh, S.D., Ichikawa, H., Itohara, S., Yoshikawa, T., Furuichi, T., 2007. Autistic-like phenotypes in Cadps2-knockout mice and aberrant CADPS2 splicing in autistic patients. J. Clin. Invest. 117, 931–943.
Sago, H., Carlson, E.J., Smith, D.J., Kilbridge, J., Rubin, E.M., Mobley, W.C., Epstein, C.J., Huang, T.T., 1998. Ts1Cje, a partial trisomy 16 mouse model for Down syndrome, exhibits learning and behavioral abnormalities. Proc. Natl. Acad. Sci. U. S. A. 95, 6256–6261.
Sago, H., Carlson, E.J., Smith, D.J., Rubin, E.M., Crnic, L.S., Huang, T.T., Epstein, C.J., 2000. Genetic dissection of region associated with behavioral abnormalities in mouse models for Down syndrome. Pediatr. Res. 48, 606–613.
Samaco, R.C., McGraw, C.M., Ward, C.S., Sun, Y., Neul, J.L., Zoghbi, H.Y., 2013. Female Mecp2(+/−) mice display robust behavioral deficits on two different genetic backgrounds providing a framework for pre-clinical studies. Hum. Mol. Genet. 22, 96–109.
Santos, A.R., Kanellopoulos, A.K., Bagni, C., 2014. Learning and behavioral deficits associated with the absence of the fragile X mental retardation protein: what a fly and mouse model can teach us. Learn. Mem. 21, 543–555.
Santos, M., Silva-Fernandes, A., Oliveira, P., Sousa, N., Maciel, P., 2007. Evidence for abnormal early development in a mouse model of Rett syndrome. Genes Brain Behav. 6, 277–286.
Sarachana, T., Xu, M., Wu, R.C., Hu, V.W., 2011. Sex hormones in autism: androgens and estrogens differentially and reciprocally regulate RORA, a novel candidate gene for autism. PLoS One 6, e17116.
Scala, E., Ariani, F., Mari, F., Caselli, R., Pescucci, C., Longo, I., Meloni, I., Giachino, D., Bruttini, M., Hayek, G., Zappella, M., Renieri, A., 2005. CDKL5/STK9 is mutated in Rett syndrome variant with infantile spasms. J. Med. Genet. 42, 103–107.
Scattoni, M.L., Ricceri, L., Crawley, J.N., 2011. Unusual repertoire of vocalizations in adult BTBR T+tf/J mice during three types of social encounters. Genes Brain Behav. 10, 44–56.
Schaafsma, S.M., Pfaff, D.W., 2014. Etiologies underlying sex differences in Autism Spectrum Disorders. Front. Neuroendocrinol. 35, 255–271.
Schaefer, T.L., Davenport, M.H., Erickson, C.A., 2015. Emerging pharmacologic treatment options for fragile X syndrome. Appl. Clin. Genet. 8, 75–93.
Schneider, T., Roman, A., Basta-Kaim, A., Kubera, M., Budziszewska, B., Schneider, K., Przewlocki, R., 2008. Gender-specific behavioral and immunological alterations in an animal model of autism induced by prenatal exposure to valproic acid. Psychoneuroendocrinology 33, 728–740.
Schumacher, M., Weill-Engerer, S., Liere, P., Robert, F., Franklin, R.J., Garcia-Segura, L.M., Lambert, J.J., Mayo, W., Melcangi, R.C., Parducz, A., Suter, U., Carelli, C., Baulieu, E.E., Akwa, Y., 2003. Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. Prog. Neurobiol. 71, 3–29.
Schupf, N., Kapell, D., Nightingale, B., Rodriguez, A., Tycko, B., Mayeux, R., 1998. Earlier onset of Alzheimer's disease in men with Down syndrome. Neurology 50, 991–995.
Schupf, N., Winsten, S., Patel, B., Pang, D., Ferin, M., Zigman, W.B., Silverman, W., Mayeux, R., 2006. Bioavailable estradiol and age at onset of Alzheimer's disease in postmenopausal women with Down syndrome. Neurosci. Lett. 406, 298–302.
Schwarz, J.M., McCarthy, M.M., 2008. Cellular mechanisms of estradiol-mediated masculinization of the brain. J. Steroid Biochem. Mol. Biol. 109, 300–306.

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Shahbazian, M.D., Antalffy, B., Armstrong, D.L., Zoghbi, H.Y., 2002. Insight into Rett syndrome: MeCP2 levels display tissue- and cell-specific differences and correlate with neuronal maturation. Hum. Mol. Genet. 11, 115–124.
Sheng, L., Ding, X., Ferguson, M., McCallister, M., Rhoades, R., Maguire, M., Ramesh, A., Aschner, M., Campbell, D., Levitt, P., Hood, D.B., 2010. Prenatal polycyclic aromatic hydrocarbon exposure leads to behavioral deficits and downregulation of receptor tyrosine kinase, MET. Toxicol. Sci. 118, 625–634.
Shi, L., Fatemi, S.H., Sidwell, R.W., Patterson, P.H., 2003. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J. Neurosci. 23, 297–302.
Silverman, J.L., Yang, M., Lord, C., Crawley, J.N., 2010. Behavioural phenotyping assays for mouse models of autism. Nat. Rev. Neurosci. 11, 490–502.
Simpkins, J.W., Perez, E., Wang, X., Yang, S., Wen, Y., Singh, M., 2009. The potential for estrogens in preventing Alzheimer's disease and vascular dementia. Ther. Adv. Neurol. Disord. 2, 31–49.
Singh, K., Prasad, S., 2008a. Age- and sex-related analysis of methylation of 5'-upstream sequences of Fmr-1 gene in mouse brain and modulation by sex steroid hormones. Biogerontology 9, 455–465.
Singh, K., Prasad, S., 2008b. Differential expression of Fmr-1 mRNA and FMRP in female mice brain during aging. Mol. Biol. Rep. 35, 677–684.
Spencer, C.M., Alekseyenko, O., Hamilton, S.M., Thomas, A.M., Serysheva, E., Yuva-Paylor, L.A., Paylor, R., 2011. Modifying behavioral phenotypes in Fmr1KO mice: genetic background differences reveal autistic-like responses. Autism Res. 4, 40–56.
Spencer, C.M., Alekseyenko, O., Serysheva, E., Yuva-Paylor, L.A., Paylor, R., 2005. Altered anxiety-related and social behaviors in the Fmr1 knockout mouse model of fragile X syndrome. Genes Brain Behav. 4, 420–430.
Stearns, N.A., Schaevitz, L.R., Bowling, H., Nag, N., Berger, U.V., Berger-Sweeney, J., 2007. Behavioral and anatomical abnormalities in Mecp2 mutant mice: a model for Rett syndrome. Neuroscience 146, 907–921.
Stewart, L.S., Persinger, M.A., Cortez, M.A., Snead 3rd, O.C., 2007. Chronobiometry of behavioral activity in the Ts65Dn model of Down syndrome. Behav. Genet. 37, 388–398.
Sultan, M., Piccini, I., Balzereit, D., Herwig, R., Saran, N.G., Lehrach, H., Reeves, R.H., Yaspo, M.L., 2007. Gene expression variation in Down's syndrome mice allows prioritization of candidate genes. Genome Biol. 8, R91.
Supekar, K., Menon, V., 2015. Sex differences in structural organization of motor systems and their dissociable links with repetitive/restricted behaviors in children with autism. Mol. Autism 6, 50.
Suzuki, K., Nakajima, K., Kamimura, S., Takasugi, K., Suzuki, Y., Sekine, H., Ishii, N., 2010. Eight case reports on sex-hormone profiles in sexually mature male Down syndrome. Int. J. Urol. 17, 1008–1010.
Tabuchi, K., Blundell, J., Etherton, M.R., Hammer, R.E., Liu, X., Powell, C.M., Sudhof, T.C., 2007. A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science 318, 71–76.
Torres, A.R., 2003. Is fever suppression involved in the etiology of autism and neurodevelopmental disorders? BMC Pediatr. 3, 9.
Tucker, B., Richards, R., Lardelli, M., 2004. Expression of three zebrafish orthologs of human FMR1-related genes and their phylogenetic relationships. Dev. Genes Evol. 214, 567–574.
Veeraragavan, S., Bui, N., Perkins, J.R., Yuva-Paylor, L.A., Carpenter, R.L., Paylor, R., 2014. Modulation of behavioral phenotypes by a muscarinic M1 antagonist in a mouse model of fragile X syndrome. Psychopharmacol. (Berl.) 217, 143–151.
Villard, L., 2007. MECP2 mutations in males. J. Med. Genet. 44, 417–423.
Vojdani, A., Pangborn, J.B., Vojdani, E., Cooper, E.L., 2003. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int. J. Immunopathol. Pharmacol. 16, 189–199.
Wang, I.T., Allen, M., Goffin, D., Zhu, X., Fairless, A.H., Brodkin, E.S., Siegel, S.J., Marsh, E.D., Blendy, J.A., Zhou, Z., 2012. Loss of CDKL5 disrupts kinome profile and event-related potentials leading to autistic-like phenotypes in mice. Proc. Natl. Acad. Sci. U. S. A. 109, 20516–21521.
Weickert, T.W., Weinberg, D., Lenroot, R., Catts, S.V., Wells, R., Vercammen, A., O'Donnell, M., Galletly, C., Liu, D., Balzan, R., Short, B., Pellen, D., Curtis, J., Carr, V.J., Kulkarni, J., Schofield, P.R., Weickert, C.S., 2015. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. Mol. Psychiatry 20, 685–694.
Werling, D.M., Geschwind, D.H., 2013. Sex differences in autism spectrum disorders. Curr. Opin. Neurol. 26, 146–153.
Witton, J., Padmashri, R., Zinyuk, L.E., Popov, V.I., Kraev, I., Line, S.J., Jensen, T.P., Tedoldi, A., Cummings, D.M., Tybulewicz, V.L., Fisher, E.M., Bannerman, D.M., Randall, A.D., Brown, J.T., Edwards, F.A., Rusakov, D.A., Stewart, M.G., Jones, M.W., 2015. Hippocampal circuit dysfunction in the Tc1 mouse model of Down syndrome. Nat. Neurosci. 18, 1291–1298.
Wolstenholme, J.T., Rissman, E.F., Bekiranov, S., 2013. Sexual differentiation in the developing mouse brain: contributions of sex chromosome genes. Genes Brain Behav. 12, 166–180.
Woods, R., Vallero, R.O., Golub, M.S., Suarez, J.K., Ta, T.A., Yasui, D.H., Chi, L.H., Kostyniak, P.J., Pessah, I.N., Berman, R.F., LaSalle, J.M., 2012. Long-lived epigenetic interactions between perinatal PBDE exposure and Mecp2308 mutation. Hum. Mol. Genet. 21, 2399–2411.
Wu, M.V., Manoli, D.S., Fraser, E.J., Coats, J.K., Tollkuhn, J., Honda, S., Harada, N., Shah, N.M., 2009. Estrogen masculinizes neural pathways and sex-specific behaviors. Cell 139, 61–72.
Xu, X.J., Zhang, H.F., Shou, X.J., Li, J., Jing, W.L., Zhou, Y., Qian, Y., Han, S.P., Zhang, R., Han, J.S., 2015. Prenatal hyperandrogenic environment induced autistic-like behavior in rat offspring. Physiol. Behav. 138, 13–20.
Yang, M., Abrams, D.N., Zhang, J.Y., Weber, M.D., Katz, A.M., Clarke, A.M., Silverman, J.L., Crawley, J.N., 2012. Low sociability in BTBR T + tf/J mice is independent of partner strain. Physiol. Behav. 107, 649–662.
Yang, Q., Yang, L., Zhang, K., Guo, Y.Y., Liu, S.B., Wu, Y.M., Li, X.Q., Song, Q., Zhuo, M., Zhao, M.G., 2015. Increased coupling of caveolin-1 and estrogen receptor alpha contributes to the fragile X syndrome. Ann. Neurol. 77, 618–636.
Yochum, C.L., Bhattacharya, P., Patti, L., Mirochnitchenko, O., Wagner, G.C., 2010. Animal model of autism using GSTM1 knockout mice and early post-natal sodium valproate treatment. Behav. Brain Res. 210, 202–210.
Yu, T., Liu, C., Belichenko, P., Clapcote, S.J., Li, S., Pao, A., Kleschevnikov, A., Bechard, A.R., Asrar, S., Chen, R., Fan, N., Zhou, Z., Jia, Z., Chen, C., Roder, J.C., Liu, B., Baldini, A., Mobley, W.C., Yu, Y.E., 2010. Effects of individual segmental trisomies of human chromosome 21 syntenic regions on hippocampal long-term potentiation and cognitive behaviors in mice. Brain Res. 1366, 162–171.
Zaccaria, K.J., Lagace, D.C., Eisch, A.J., McCasland, J.S., 2010. Resistance to change and vulnerability to stress: autistic-like features of GAP43-deficient mice. Genes Brain Behav. 9, 985–996.
Zampieri, B.L., Fernandez, F., Pearson, J.N., Stasko, M.R., Costa, A.C., 2014. Ultrasonic vocalizations during male-female interaction in the mouse model of Down syndrome Ts65Dn. Physiol. Behav. 128, 119–125.
Zhao, Y., Fung, C., Shin, D., Shin, B.C., Thamotharan, S., Sankar, R., Ehninger, D., Silva, A., Devaskar, S.U., 2010. Neuronal glucose transporter isoform 3 deficient mice demonstrate features of autism spectrum disorders. Mol. Psychiatry. 15, 286–299.
Zhu, X.W., Pan, H., Li, M.R., Bao, X.H., Zhang, J.J., Wu, X.R., 2009. Analysis of the parental origin of de novo MECP2 mutations and X chromosome inactivation in fifteen sporadic cases with Rett syndrome. Zhonghua Er Ke Za Zhi 47, 565–569.

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