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REVIEW

Sex differences in animal models of psychiatric disorders

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Psychiatric disorders are characterized by sex differences in their prevalence, symptomatology and treatment response. Animal models have been widely employed for the investigation of the neurobiology of such disorders and the discovery of new treatments. However, mostly male animals have been used in preclinical pharmacological studies. In this review, we highlight the need for the inclusion of both male and female animals in experimental studies aiming at gender-oriented prevention, diagnosis and treatment of psychiatric disorders. We present behavioural findings on sex differences from animal models of depression, anxiety, post-traumatic stress disorder, substance-related disorders, obsessive–compulsive disorder, schizophrenia, bipolar disorder and autism. Moreover, when available, we include studies conducted across different stages of the oestrous cycle. By inspection of the relevant literature, it is obvious that robust sex differences exist in models of all psychiatric disorders. However, many times results are conflicting, and no clear conclusion regarding the direction of sex differences and the effect of the oestrous cycle is drawn. Moreover, there is a lack of considerable amount of studies using psychiatric drugs in both male and female animals, in order to evaluate the differential response between the two sexes. Notably, while in most cases animal models successfully mimic drug response in both sexes, test parameters and treatment-sensitive behavioural indices are not always the same for male and female rodents. Thus, there is an increasing need to validate animal models for both sexes and use standard procedures across different laboratories.

LINKED ARTICLES

This article is part of a themed section on Animal Models in Psychiatry Research. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-20

Abbreviations

5-HTT, 5-HT transporter; 8-OH-DPAT, 7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol; Akt1, V-akt murine thymoma viral oncogene homologue 1; BDNF, brain-derived neurotrophic factor; BTBR, BTBR T + tf/J; CMS, chronic mild stress; COMT, catechol-O-methyltransferase-deficient mice; CR, conditioned response; CRF, corticotrophin-releasing factor; CS, conditioned stimulus; D_1 receptor, dopamine 1 receptor; D_2 receptor, dopamine 2 receptor; *DISC1*, disrupted-in-schizophrenia 1; Ehmt1, euchromatin histone methyltransferase 1; FBGRKO, forebrain glucocorticoid type II receptor (NR3C1) knockout; FSL, flinders sensitive rat line; FST, forced swim test; GSK3, glycogen synthase kinase 3; HAB, high anxiety-related behaviour rats; ICSS, intracranial self-stimulation; LAB, low anxiety-related behaviour rats; LI, latent inhibition; *Mthfr*, methylenetetrahydrofolate reductase; OCD, obsessive–compulsive disorder; PPI, prepulse inhibition; PTSD, post-traumatic stress disorder; SSRI, selective 5-HT re-uptake inhibitors; US, unconditioned stimulus; WKY, Wistar Kyoto

Introduction

The total disease burden for neuropsychiatric disorders in the European Union has been recently calculated as 30.1% in women and 23.4% in men (Wittchen *et al.*, 2011). Many of these disorders are characterized by substantial sex differences in their prevalence, symptomatology and treatment response. Specifically, women are more susceptible than men to develop dementia, panic disorder, post-traumatic stress disorder (PTSD) and major depression (Kessler, 2007; Wittchen *et al.*, 2011). However, it was not until the 1990s that the U.S. National Institutes of Health, the U.S. Food and Drug Administration, and later the European Union recommended and supported by relevant laws the inclusion of women in clinical studies for the investigation of new drugs (Merkatz *et al.*, 1993).

Animal models are widely used to study the neurobiology of psychiatric disorders and the mechanism of action of current and novel psychotropics (Nestler *et al.*, 2002; Desbonnet *et al.*, 2012). Animal models allowed neuroscience to gain invaluable knowledge, although they have limitations and only simulate specific domains instead of accurately and fully modelling psychiatric syndromes (Neumann *et al.*, 2011; Stephens *et al.*, 2013). However, male animals are routinely used in such preclinical pharmacological studies, as models have been mainly developed and validated for male animals (Beery and Zucker, 2011). Female behaviour is mistakenly assumed to be similar to male behaviour, but more variable. Therefore, female animals are usually not included, as researchers fear that the oestrous cycle may confound the expected results (Becker *et al.*, 2005). Additionally, as noted elsewhere (Cryan and Mombereau, 2004), it is not known at what point in the evolutionary history these sex differences that render sexes more or less vulnerable to certain psychiatric disorders emerged. Given that female animals are less well studied in psychopharmacology, it remains open to debate whether rodents are indeed a good model for studying sex differences in psychiatry. Nevertheless, the need for inclusion of both male and female animals in experimental pharmacological studies has been consistently stressed (Hughes, 2007). It has been argued that using both sexes will enhance the validity of animal models and contribute to gender-oriented prevention, diagnosis and treatment of psychiatric disorders. Notably, research on novel psychiatric molecules should take into consideration potential sex differences, because otherwise important information and discoveries could be lost (Dalla *et al.*, 2010; Wald and Wu, 2010).

Nowadays, more and more experimental studies include both male and female animals and substantial findings on sex differences in models of psychiatric disorders and drug response are being discovered. In this review, we discuss those findings from animal models regarding psychiatric disorders, such as depression, anxiety, PTSD, substance-related disorders, obsessive–compulsive disorder (OCD), schizophrenia, bipolar disorder and autism (Table 1). We focus on behavioural comparisons between adult male and female rodents as these are most frequently used and on sex differences in psychotropic drug response. Moreover, when available, we discuss behavioural differences across different stages of the oestrous cycle. However, we do not discuss, because of space limitations, studies on gonadectomised animals with or without hormonal replacement, because although valuable and informative, they mimic specific human conditions, such as surgical menopause or human endocrinological diseases.

Sex differences in animal models of depression

Depression is twice as common in women than in men, and women present different symptom severity (Wittchen *et al.*, 2011). Depressed women make a greater number of suicide attempts, show more somatization, anger and hostility, and display increased appetite and weight gain. In fact, although melancholic depression occurs equally in both sexes, the anxious and atypical forms of depression are more commonly found in women (Frank *et al.*, 1988; Marcus *et al.*, 2005; 2008). It is now well established that oestrogens influence depressive symptoms, including irritability, insomnia, appetite and general physical well-being (Kornstein *et al.*, 2010; Young and Korszun, 2010). Together, these observations suggest the potential importance of considering the role of sex and the ovarian steroid milieu in evaluating the efficacy of antidepressant therapy. Indeed, several studies have reported that women respond better to selective 5-HT re-uptake inhibitors (SSRI) than men (Kornstein *et al.*, 2000; Joyce *et al.*, 2003; Khan *et al.*, 2005). Animal models of depression are usually based on the reproduction of one or a few depressive symptoms (e.g. despair, anhedonia). Some of the most popular models are the forced swim test (FST), the learned helplessness model and the chronic mild stress (CMS). Additionally several genetic models of depression, with or without co-morbid anxiety, have been proposed (Dalla *et al.*, 2010) (Table 2).

FST is a widely used test for the screening of new molecules with antidepressant potential and for the assessment of depressive behaviour in rats and mice (Porsolt, 1979; Cryan *et al.*, 2005). Mice are exposed to one swim session of 5–6 min in a cylinder filled with water. Rats are usually forced to swim for 15 min and 24 h later they are placed again in the same cylinder to swim for 5 min. During FST exposure, rodents exhibit passive behaviours, such as immobility or floating, which have been equated with symptoms of despair or helplessness in depressed humans (Kirby and Lucki, 1997; Cryan *et al.*, 2002). Importantly, antidepressant treatment enhances the duration of active behaviours in the FST and decreases the duration of passive behaviours (Cryan *et al.*, 2002; 2005). Sex differences have been observed in the FST, but the direction of the sex difference differs among studies. In our laboratory, we have consistently shown that female rats display higher levels of immobility during the second FST session than male rats and this is suggestive of enhanced depressive behaviour in female rats (Drossopoulou *et al.*, 2004; Dalla *et al.*, 2008; Pitychoutis *et al.*, 2009; 2011; Kokras *et al.*, 2012). However, other studies show opposite results regarding immobility levels (Alonso *et al.*, 1991; Barros and Ferigolo, 1998; Brotto *et al.*, 2000; Brummelte *et al.*, 2006; Martinez-Mota *et al.*, 2011) or find no sex differences (Poltyrev *et al.*, 2005; Andrade *et al.*, 2007; Alves *et al.*, 2008). Also, another behaviour that shows significant sex differences in the FST is the frequency of head swinging, with female rats exhibiting lower numbers than male rats (Barros and Ferigolo, 1998; Drossopoulou *et al.*, 2004; Kokras *et al.*, 2009a). Most probably, the reason for the

Table 1

Animal models where behavioural sex differences have been studied

Psychiatric disorder	Depression	Anxiety	PTSD	Substance-related disorders	OCD	Schizophrenia	Bipolar disorder	Autism
Environmental and pharmacological models	FST	Open field, hole board, social interaction	Predator stress and anxiety/fear tests	Self-administration	Compulsive lever pressing	Administration of psychostimulants (e.g. amphetamine)	Administration of psychostimulants (e.g. amphetamine)	
	Learned helplessness	Elevated plus maze, T-maze and light/dark	Footshock and anxiety/fear tests	ICSS	Disruption of spontaneous alternation by 8-OH-DPAT	Administration of NMDA antagonists (e.g. PCP, MK-801)	Sleep deprivation	Perinatal antiepileptic exposure (e.g. valproate)
	CMS	Novelty suppressed feeding	Fear conditioning and extinction	Conditioned place preference	Marble burying	PPI in the acoustic startle response	Resident-intruder model	
		Passive avoidance, vogel-punished drinking	Tailshock and eyeblink or startle	Aversive conditioning	Stereotypic behaviours in deer mice	LI in associative learning		
		Light-enhanced startle	Fear-potentiated startle					
Selective breeding and genetic models	FSL rats	HAB/LAB rats			ArKO	D1 and D2 knockouts	*CLOCK* mutant mice	Glutathione-S-transferase-M1 knockouts
	5-HTT$^{-/-}$ rats	WKY rats				Akt1- knockouts	*DISC1* transgenics	
	5-HT1A and 5-HT1B	5-HTT$^{-/-}$ rats				Y2 knockouts	GSK3b knockouts	Ehmt1$^{+/-}$
	Knockouts							*Mthfr*$^{+/-}$
	5-HT3 knockouts	BDNF-5-HTT double knockouts				ArKO	*CACNA1c* knockouts	BTBR T + tf/J
	BDNF-5-HTT double knockouts	BDNF conditional knockouts					Dopamine transporter knockouts	
	BDNF conditional knockouts	5-HT3 knockouts						
	CRF1-CRF2 double knockouts	CRF1-CRF2 double knockouts						
	Urocortin 2 knockouts	COMT knockouts						
	FBGRKO							

Table 2

Sex differences in models of depression

Models of depression	Main behavioural index	Male/female vulnerability	Strength of evidence
FST	Immobility (FST)	Conflicting findings	****
Learned helplessness	Escape behaviour	Males > females	***
CMS	Sucrose preference	Conflicting findings	***
FSL rats	Immobility (FST)	Depends on behavioural index	*
5-HTT$^{-/-}$ rats	Immobility/sucrose preference	No differences	**
5-HT$_{1A}$ knockout	Immobility/sucrose preference	Males > females	**
5-HT$_{1A}$ overexpress	Immobility (FST)	Males > females	*
5-HT$_{1B}$ knockout	Immobility (FST)	Males > females	*
5-HT$_3$ knockout	Immobility (FST)	Females > males	*
BDNF knockout	Immobility (FST)	Females > males	**
FBGRKO	Immobility (FST)	Males > females	*
Urocortin-2 knockout	Immobility (FST)	Males > females	*

Animal models of depression reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes low strength of evidence in the literature.
***Denotes medium strength of evidence in the literature.
****Denotes high strength of evidence in the literature.

discrepancies in the FST is the different methodologies used in various laboratories (i.e. differences in tank dimensions, temperature, water depth, number of sessions etc.). This problem could be addressed by the use of standard and validated FST procedures already described for male rodents (Slattery and Cryan, 2012). Regarding the oestrous cycle, most studies show that the phase of the oestrous cycle does not influence basal female FST behavioural performance in a significant way (Alonso *et al.*, 1991; Bravo and Maswood, 2006; Jans *et al.*, 2007; Tonelli *et al.*, 2008; Andrade *et al.*, 2010; Craft *et al.*, 2010; Allen *et al.*, 2012; Kokras *et al.*, 2012; Flores-Serrano *et al.*, 2013). However, the oestrous cycle could play a role in antidepressant response, but the studies using standard antidepressants in intact female rats during different phases of the cycle are limited (Marvan *et al.*, 1996; Barros and Ferigolo, 1998; Contreras *et al.*, 1998; Consoli *et al.*, 2005; Allen *et al.*, 2012; Dalla *et al.*, 2012; Flores-Serrano *et al.*, 2013). For example, administration of the SSRI sertraline at a low dose (10 mg·kg^{-1}) in female rats during the transition from dioestrous to prooestrous results in no antidepressant effect. However, a higher dose (40 mg·kg^{-1}) exerts an antidepressant effect in all phases of the oestrous cycle (C. Dalla *et al.*, unpubl. data). Nevertheless, the effectiveness of antidepressants in reducing immobility and enhancing active behaviours in male and female animals depends on the compound and the selected dosage scheme (Barros and Ferigolo, 1998; Contreras *et al.*, 1998; Consoli *et al.*, 2005; West and Weiss, 2005; Kokras *et al.*, 2009a; Pitychoutis *et al.*, 2011; Allen *et al.*, 2012; Dalla *et al.*, 2012; Flores-Serrano *et al.*, 2013). For instance, with the use of the modified FST, sertraline enhances swimming duration in both sexes (Dalla *et al.*, 2012), and this has been linked with changes in 5-hydroxytryptaminergic activity (Detke *et al.*, 1995; Detke and Lucki, 1996; Mikail *et al.*, 2012). In contrast, selective noradrenergic re-uptake inhibitors, which increase noradrenergic activity, enhance mainly climbing duration in the FST (Detke *et al.*, 1995).

Learned helplessness is one of the oldest animal models of depression and anxiety (Seligman *et al.*, 1975; Maier, 1984). In this model, animals are exposed to either controllable or uncontrollable stress, such as tailshock or footshock. During training, female rats escape the shock faster than male rats, and extinction of the avoidance behaviour occurs more slowly in female than in male rats (van Haaren *et al.*, 1990; Heinsbroek *et al.*, 1991; Shors *et al.*, 2007; Dalla *et al.*, 2008; Dalla and Shors, 2009). With regards to the oestrous cycle, it has been shown that avoidance/escape behaviour is facilitated during prooestrous (Sfikakis *et al.*, 1978). Opposite effects have also been observed, with avoidance behaviour being facilitated in dioestrous 2, decreased in prooestrous and further decreased in oestrous and dioestrous 1 (Diaz-Veliz *et al.*, 1989). In order to assess learned helplessness behaviour, animals are subsequently tested in more complex tasks where they must press a lever or pass through a gateway twice in order to escape the shock (Hunziker and Dos Santos, 2007). Male animals previously exposed to uncontrollable stress do not learn to escape, and this has been equated with 'helplessness' expressed in depressed humans (Seligman *et al.*, 1975; Maier, 1984). On the contrary, most female rats promptly learn to escape the shock and thus do not express the learned helplessness observed in male rats (Shors *et al.*, 2007; Dalla *et al.*, 2008; Padilla *et al.*, 2009). This is probably related to the fact that female rats generally outperform male rats during operant conditioning tasks (Beatty and Beatty, 1970; Scouten *et al.*, 1975; van Haaren *et al.*, 1990; Steenbergen *et al.*, 1990;

Shors *et al.*, 2007; Dalla *et al.*, 2008). Although female rats could fail to escape and thus express learned helplessness should the task be more difficult, as in jumping through a window in order to terminate the footshock (Hunziker and Dos Santos, 2007). Regarding the effect of the oestrous cycle on helplessness behaviour, Jenkins *et al.* reported that stressed female rats in dioestrous required more time to escape in comparison with unstressed dioestrous female rats and to oestrous female rats (Jenkins *et al.*, 2001). However, other studies have reported no effects of the oestrous cycle in learned helplessness behaviour (Setnik *et al.*, 2004; Dalla *et al.*, 2008).

CMS is another well-validated animal model of depression based on the application of mild stressors (food and water deprivation, changes in lights, white noise, changes of cage mates, etc.) alternating for a period of 4–7 weeks (Willner *et al.*, 1987; Willner, 1997; 2005). Animals are trained to drink a palatable sucrose solution and present a reduction in sucrose intake or sucrose preference over water after a few weeks of stress exposure. This phenomenon is equated with the core depressive symptom of anhedonia (loss of pleasure for hedonic stimuli). Other symptoms of depression, such as decreased sexual behaviour and self-care, changes in sleep architecture and locomotor activity have been reported as well, thus increasing the validity of this model (Willner, 1997; 2005). Following CMS, there is a reduction in both sexes in sucrose intake, when assessed with 1 h tests once weekly, but the effect is more robust in male rats, in comparison with female rats (Dalla *et al.*, 2005a; 2008; Grippo *et al.*, 2005; Kamper *et al.*, 2009). It is possible that sucrose intake in 1 h tests is not an appropriate behavioural index for female rats, because there is a trend for female rats to drink more sucrose than male rats and to show a more erratic increase in their consumption (Dalla *et al.*, 2005a). However, when sucrose intake is measured during 24 h periods a gradual reduction of sucrose consumption is observed in female rats, but not in male rats subjected to CMS (Konkle *et al.*, 2003). Accordingly, in a recent study, sucrose preference was also assessed for 24 h and was found to be decreased in both sexes, but the decrease was more pronounced in female rats. Treatment with the antidepressant venlafaxine enhanced sucrose preference, but did not eliminate the sex difference (Xing *et al.*, 2013).

Another approach used to overcome difficulties with the sucrose preference test could be the newly developed sucrose drive test. This test integrates food preference measurement with ultrasonic vocalization recordings. Female and male rats exposed to CMS both showed a marked decrease of preference in this test (Mateus-Pinheiro *et al.*, 2014). In the past, ahnedonia was also assessed with the brain stimulation reward paradigm by implanting electrodes in the ventral tegmental area, but there was no CMS effect in both sexes (Baker *et al.*, 2006). CMS had also an effect on exploratory behaviour, with female rats exhibiting fewer rearings and total locomotor activity than male rats in the open field (Dalla *et al.*, 2005a; Xing *et al.*, 2013), but in another study, CMS male and female rats had no differences in locomotor activity and male rats showed signs of enhanced anxiety (Duncko *et al.*, 2001). The oestrous cycle in female rats cannot be taken into consideration, because CMS is a chronic model and thus female rats are exposed during all phases of the cycle to various stressors. Additionally, the oestrous cycle is disrupted in a high percentage of female rats exposed to CMS and thus, it cannot be studied in this model (Dalla *et al.*, 2005a; Baker and Bielajew, 2007).

Moreover, several models of depression are based on selective breeding and/or genetic manipulations. One widely used model is the flinders sensitive line (FSL) of rats, which are derived from Sprague-Dawley rats selectively bred for cholinergic hypersensitivity (Overstreet *et al.*, 1979; Overstreet and Wegener, 2013). The FSL rats have considerable validity because the cholinergic system has been found to be disrupted in mood disorders (Janowsky and Overstreet, 1990). FSL rats express a wide range of depressive-like symptoms, which are reversed by chronic antidepressant treatment (Overstreet *et al.*, 2005). Sex differences have been observed in FSL rats, with male rats being less active and more anxious in the open field and the elevated plus maze tests, in comparison with Sprague-Dawley controls, whereas there are no differences in female rats. Treatment with the SSRI citalopram decreased anxiety levels in both sexes (Kokras *et al.*, 2011b). In the FST, both male and female FSL rats show enhanced depressive symptomatology, but different behavioural parameters are affected. Specifically, FSL male rats exhibit high immobility levels, whereas female rats present a decreased latency to become immobile. Behavioural deficits were reversed by antidepressant treatment in both sexes in a sex-dependent manner (Kokras *et al.*, 2009a,b). Another genetic model of depression is based on mutant rats devoid of the 5-HT transporter (5-HTT$^{-/-}$ rats) (Homberg *et al.*, 2007). These rats present enhanced depressive symptomatology, as indicated by their enhanced immobility in the FST and decreased sucrose preference (Olivier *et al.*, 2008). However, no major sex differences are observed between male and female 5-HTT$^{-/-}$ rats in depression tests (Olivier *et al.*, 2008).

Several 5-HT receptor genes have been targeted in models of depression and antidepressant potential. Knockout male and female mice lacking 5-HT$_{1A}$ receptors (for nomenclature see Alexander *et al.*, 2013a) exhibit reduced immobility, but only female mice exhibit enhanced preference for sucrose (Jones and Lucki, 2005; Castagne *et al.*, 2011). Male mice overexpressing specifically post-synaptic 5-HT$_{1A}$ receptors also exhibit reduced depressive-like behaviours, but this is not observed in their female counterparts. Interestingly, antidepressant treatment reduces immobility in both sexes (Gunther *et al.*, 2011). In contrast, female mice lacking 5-HT$_{1B}$ receptors exhibit reduced depressive behaviour, whereas male mice are similar to wild-type controls. Again, antidepressant treatment decreases immobility in both male and female 5-HT$_{1B}$ knockout mice (Jones and Lucki, 2005). Finally, female but not male 5-HT$_3$ knockouts show depressive behaviour with enhanced immobility and decreased swimming levels during a second FST session (Bhatnagar *et al.*, 2004). Moving away from 5-HT receptors, the brain-derived neurotrophic factor (BDNF) has also been implicated in the pathophysiology of depression. Conditional BDNF knockout mice are used as a model of depression and show marked sex differences. Male rats exhibit enhanced locomotor activity, but normal levels of depressive behaviour (Monteggia *et al.*, 2007). In contrast, female rats show depressive behaviour with increased immobility in the FST and decreased sucrose preference, which is exaggerated following chronic stress expo-

sure (Monteggia *et al.*, 2007; Autry *et al.*, 2009). Interestingly, in both sexes of the conditional BDNF knockout mice, the antidepressant desipramine failed to exert an antidepressant effect in the FST, demonstrating BDNF's importance in antidepressant drug response for both sexes (Monteggia *et al.*, 2007). Finally, it has been recently shown that male mice lacking the forebrain type II glucocorticoid receptor NR3C1 (see Alexander *et al.*, 2013b) (FBGRKO) exhibit enhanced depressive behaviour in the FST and sucrose preference test, whereas female mice do not (Solomon *et al.*, 2012). Lastly, female but not male mice lacking urocortine 2, which is a member of the corticotrophin-releasing factor (CRF) family of peptides, show decreased immobility levels in the FST and the tail suspension test (Chen *et al.*, 2006).

By inspection of the studies mentioned earlier, it is obvious that robust sex differences exist in models of depression, sometimes at baseline or after stress or drug exposure (Dalla *et al.*, 2011). Notably, testing conditions and behavioural parameters sensitive to treatment often differ between the two sexes. Thus, the differential response of the two sexes should be taken into consideration and models should be adjusted in a way that they work in validity in both male and female animals. Finally, genetic models will contribute to the elucidation of the role of specific genes or systems on the appearance of sex differences, which could ultimately lead to gender-based treatment targets (Valentino *et al.*, 2013).

Sex differences in tests of anxiety

Most anxiety disorders, including panic disorder, agoraphobia, social phobia, generalized anxiety disorder and specific phobias, are twice as common in women than in men (Wittchen *et al.*, 2011). Several experimental models using rodents have been developed in order to study the neurobiology of fear and anxiety, as well as the pharmacology of anxiolytics (Cryan and Sweeney, 2011). Some of these tests induce a conflict between the rodent's drive to explore for potential rewards and its instinct of avoiding potentially dangerous situations, such as illuminated or exposed spaces. Other anxiety tests instead provoke a fearful response via an aversive or anticipated event (Graham *et al.*, 2011). Interestingly, in most models of anxiety, female mice present with lower anxiety levels in comparison with male mice, as previously reviewed (Johnston and File, 1991; Donner and Lowry, 2013) (Table 3).

Specifically, in the open field test, female mice exhibit less anxiety than male mice when examining thigmotaxis and avoidance of illuminated space (Zimmerberg and Farley, 1993; Ramos *et al.*, 1998; Roman and Arborelius, 2009; An *et al.*, 2011). Interestingly, female mice in prooestrous display less anxiety in comparison with male mice (Frye *et al.*, 2000). Furthermore, in the open field test and with the use of running wheels, female mice have been consistently shown

Table 3

Sex differences in models/tests of anxiety

Models/tests of anxiety	Main behavioural index	Male/female vulnerability	Strength of evidence
Open field	Thigmotaxis	Males > females	***
Plus or T-maze	Aversion to open space	Males > females	****
Holeboard	Exploration	Males > females	*
Light/dark	Aversion to light	Males > females	***
Passive avoidance	Escape behaviour	Males > females	****
Vogel punished drinking	Aversion	Females > males	**
Social interaction	Interaction	Conflicting findings	***
Light-enhanced startle	Acoustic startle response	Females > males	**
Maternal separation	Aversion to open space	Males > females	**
Restraint stress	Thigmotaxis	Females > males	*
HAB/LAB rats	Aversion to open space	Conflicting findings	*
WKY rats	Immobility in FST/aversion to open space	Females > males	*
5-HTT$^{-/-}$ rats	Novelty suppressed feeding	Males > females	**
5-HT$_3$ knockouts	Defensive withdrawal	Males > females	*
BDNF/5-HTT$^{-/-}$ double knockouts	Aversion to open space	Males > females	*
CRF$_1$/CRF$_2$ knockouts	Aversion to open space	Males > females	*
COMT knockouts	Aversion to light	Females > males	*

Animal models of anxiety reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability (i.e. enhanced anxiety) to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes low strength of evidence in the literature.
***Denotes medium strength of evidence in the literature.
****Denotes high strength of evidence in the literature.

to be more active than male mice (Dawson *et al.*, 1975; Beatty and Fessler, 1976; Slob *et al.*, 1981; Hyde and Jerussi, 1983). In the elevated plus maze, another widely used test of anxiety, female mice consistently display lower levels of anxiety, as indicated by their increased exploration of the open, exposed arms of the plus maze (Imhof *et al.*, 1993; Rodgers and Cole, 1993; Frye *et al.*, 2000; Ramos *et al.*, 2002; Estanislau and Morato, 2006; Walf *et al.*, 2008). Furthermore, female mice in dioestrous are more anxious than female mice in other phases of the oestrous cycle and male rodents (Marcondes *et al.*, 2001; Dominguez *et al.*, 2003). In support of this finding, Walf and colleagues showed that young female mice of reproductive age were less anxious than older senescent ones (Walf *et al.*, 2009). Similarly, in the elevated T-maze female mice showed less anxiety than male ones (Almeida *et al.*, 1996; Ramos *et al.*, 2002) and female mice in dioestrous were more anxious than male mice (Gouveia *et al.*, 2004). The same result, of females in dioestrous being more anxious was also found in the novelty suppressed feeding (Mora *et al.*, 1996). In the hole board, female mice displayed fewer boli, spent less time near the wall, more time in the centre, and they were active for longer times than male mice (Adamec *et al.*, 2006). In the light/dark paradigm, female mice showed a longer latency to enter the dark chamber, suggesting reduced anxiety levels than male mice (Voikar *et al.*, 2001; Adamec *et al.*, 2006; Reimer *et al.*, 2012). Also, when ultrasonic vocalization is measured, young male mice present as more anxious (Naito and Tonoue, 1987; Hahn *et al.*, 1998). Regarding the anxiolytic diazepam, Nomikos and Spyraki in 1988 reported that in the elevated plus maze, its anxiolytic effect was evident in oestrous and dioestrous 1 female mice, but not in dioestrous 2 and prooestrous female mice (Nomikos and Spyraki, 1988). In contrast, Stock *et al.* reported no effect of the female hormonal status following chronic or acute diazepam treatment (Stock *et al.*, 2000).

Moreover, in passive avoidance studies, female mice again appear less anxious. In this test, animals receive a footshock in one compartment of a testing box and 1 h later the latency to step through the compartment where they got shocked is measured. Female mice enter the compartment that they got shocked faster than male mice (van Haaren *et al.*, 1990). Also, retention of passive avoidance behaviour is higher in female mice in dioestrous, whereas it is inhibited in oestrous and proestrous phases of the cycle (Mora *et al.*, 1996). Sex differences in avoidance behaviour have been attributed to the fact that female mice respond to the shock more actively than male mice, which react mainly with freezing (Beatty and Beatty, 1970; Kirk and Blampied, 1985; van Haaren *et al.*, 1990; Steenbergen *et al.*, 1990; Dalla *et al.*, 2008; Dalla and Shors, 2009). In general, male and female rats seem to develop different strategies in response to aversive stimuli, such as shock. Sex differences have also been reported in electrical resistance and reactivity and this could influence reaction to shock exposure (Levine and Broadhurst, 1963; Beatty and Beatty, 1970; van Haaren *et al.*, 1990). At the same time, sex differences in nociception and stress-induced analgesia might also play a role (Beatty and Fessler, 1977; Romero *et al.*, 1987; Vendruscolo *et al.*, 2004; Aloisi and Bonifazi, 2006). When comparing male and female mice, such issues could be avoided by measuring activity levels and by including the observation of other behaviours during shock exposure, such us jumps and vocalization.

As it is obvious from the tests presented earlier, a possible confounding factor in many anxiety tests is locomotion and its correct distinction from anxiety. Female mice are generally more active in the open field and in anxiety tests. In fact, testing female rodents in anxiety tests often proves problematic (Imhof *et al.*, 1993) as some behavioural tests may not have the power to discriminate between anxiety and arousal states (Fernandes *et al.*, 1999; Doremus *et al.*, 2006). Given that locomotion is the driving force behind the behaviour scored in most conflict tests (e.g. light/dark, elevated plus maze, etc.), such distinction may at times be impossible. Several studies indicate that female rats are more active or aroused than male rats (Valle and Gorzalka, 1980; Kelly *et al.*, 1999; Brotto *et al.*, 2000; Romero and Chen, 2004; Dalla *et al.*, 2005a), possibly because of the effects of gonadal hormone and the distinct female coping strategy in conflict tests (Palanza, 2001; Lightfoot, 2008).

In fact, tests that depend less on the general locomotion, such as the Vogel punished drinking and the social interaction test, show instead higher levels of anxiety in female rats. Indeed, female rats are more anxious in the Vogel punished drinking (Johnston and File, 1991; Walf *et al.*, 2009). In the social interaction test, female rats interact less than male rats, suggesting that female rats are more anxious in this test (Johnston and File, 1991; Reeb and Tang, 2005; Stack *et al.*, 2010; Viviani *et al.*, 2012), although in mice the opposite has been reported (An *et al.*, 2011) and other studies were inconclusive (Johnston and File, 1991). Again, the social interaction test seems to be dependent on gonadal hormones as female Long Evans rats in prooestrous exhibit more interaction, in comparison with female rats in other stages of the oestrous cycle and male rats (Frye *et al.*, 2000). Interestingly, female Sprague-Dawley rats in prooestrous show less interaction, and thus appear more anxious, than female rats in dioestrous and male rats (Stack *et al.*, 2010) (Blanchard *et al.*, 1991), suggesting that rodent strain may also be a confounding factor when studying sex differences in anxiety. Another anxiety paradigm, in which female rats show an enhanced response and thus appear more anxious, in comparison with males, is the light-enhanced startle paradigm. In this paradigm rats are exposed to a bright light for 5–20 min, and later an enhanced acoustic startle response is observed (Walker and Davis, 1997; Toufexis *et al.*, 2005; Toufexis, 2007).

Apart from models that induce or simulate induced anxiety, chronic anxiety state is of interest as well. This can be achieved by maternal separation that appears to affect more male than female offspring (Wigger and Neumann, 1999; Romeo *et al.*, 2003; Viveros *et al.*, 2009). Other gestational stressors present a varying degree of sex differences according to the stressor applied. Restraint stress in mothers increases anxiety in the open field in female rats (Bowman *et al.*, 2004), whereas unpredictable stress results in sex-specific alterations in anxiety in male and female offspring (Schulz *et al.*, 2011). Male rats following CMS display reduced exploration in an open field, whereas female rats display increased exploratory activity (Ter Horst *et al.*, 2009). Using the same chronic stress paradigm for male and female rats, Ter Horst *et al.* (2009) suggested that male rats readily adopt the 'fight or flight' behavioural response, whereas female rats show a distinct

behaviour, which is in line with the 'tend and befriend' hypothesis (Taylor *et al.*, 2000). Models of innate anxiety, with or without co-morbid depression, are also based on selective breeds of rats (Wegener *et al.*, 2012). Such selective breeding of Wistar rats for anxiety-related behaviour on the elevated plus maze has resulted in high (HAB) and low (LAB) anxiety-related behaviour rats, but potential sex differences in this model are as yet unclear. Selective breeding for more FST immobility of the Wistar Kyoto (WKY) rats resulted in male rats presenting low anxiety behaviours from early adolescence, whereas adult female rats showed both elevated depression and anxiety, but only after adolescence (Mehta *et al.*, 2013).

Several genetic models are also used to elucidate the neurobiology of anxiety and its treatment. Many genetic models share impairments implicated in depression and anxiety, and as described earlier present significant sex differences. In most genetic models, male rats appear more anxious than female rats. Indeed, male but not female 5-HTT$^{-/-}$ rats exhibit increased anxiety in the novelty suppressed feeding and impaired fear extinction, indicating a greater sensitivity to aversive stimuli (Olivier *et al.*, 2008; Kalueff *et al.*, 2010). Similarly, male 5-HT$_3$ receptor knockouts display enhanced anxiety levels in the defensive withdrawal test, whereas in female rats an opposite effect is observed (Bhatnagar *et al.*, 2004). Male double BDNF/5-HTT knockout mice exhibit enhanced anxiety levels in the elevated plus maze, whereas there is no difference in female mice (Ren-Patterson *et al.*, 2006). Moreover, female double CRF$_1$/CRF$_2$ knockout mice display less anxiety in comparison with male and with wild-type female mice (Bale *et al.*, 2002). Instead COMT-deficient female mice appear more anxious in the light/dark box, whereas male mice are similar to wild-type mice (Gogos *et al.*, 1998).

In summary, rodent models of anxiety share a high degree of predictive validity with regards to anxiolytic treatments, but do not necessarily simulate well the female vulnerability found in humans. Sex differences in general locomotor activity, induced in part by gonadal hormones, heavily modulate the anxiety-related behavioural outcome in anxiety tests that depend mainly on locomotor activity. Furthermore, differences in coping strategies between male and female rodents (Taylor *et al.*, 2000; Dalla *et al.*, 2010) may significantly interfere with the direct comparison of behavioural indices of anxiety between sexes. As a result, female rodents appear less anxious in many tests, and furthermore, dioestrous female rodents display increased anxiety levels, in comparison with female rodents in other stages of the oestrous cycle. In cases where anxiety tests are less dependent on locomotor activity, they are deemed more suitable for the study of sex differences in anxiety. In general, it seems necessary to use more than one test and evaluate the anxiety-related behavioural outcomes using elaborated techniques, such as principal component analyses, z-scoring computation or ANCOVA with general locomotor activity as a covariate. Using a similar analysis File *et al.* showed that male behaviour is driven by anxiety and female by activity (File, 2001). Thus, care should be given so that results are not masked by anxiety-irrelevant behaviours or the animal's physiology and will properly address and quantify potential sex differences in rodent anxiety models.

Sex differences in animal models of PTSD

PTSD consistently emerges as one of the most sex-differentiated psychiatric disorders, with women being at considerably higher risk, although both sexes show similar recovery rates. Several investigators have attempted to explain this difference, and suggestions are that women perceive stronger eventual threats and present more peritraumatic dissociation than men. In fact, it is challenging to explore sex differences in PTSD because men and women perceive similar trauma exposure differently. Additionally, in explaining sex differences in PTSD, socio-cultural factors are often presented as confounding factors. In this context, animal models can assist in studying sex differences in PTSD (Olff *et al.*, 2007; Zohar *et al.*, 2008; Cohen and Yehuda, 2011; Cohen *et al.*, 2012). PTSD models are based on exposure to an acute stressor, usually shock exposure and on subsequent conditioning paradigms, such as fear conditioning and extinction of fear (Table 4). Sex differences do exist in acute stress responses, as well as in associative learning and

Table 4

Sex differences in models of PTSD

Models of PTSD	Main behavioural index	Male/female vulnerability	Strength of evidence
Cat predator stress	Startle/aversion	Females > males	**
Fear conditioning	Freezing	Males > females	**
One footshock exposure	Aversion/freezing	No differences	*
Tailshock exposure	Conditioned eyeblink/startle	Females > males	***
Fear potentiated startle	Startle	Females > males	*

Animal models of PTSD reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes medium strength of evidence in the literature.
***Denotes high strength of evidence in the literature.

extinction of aversive conditioned responses (CR; Dalla and Shors, 2009).

In 2006, Adamec *et al*. showed that female mice exposed to cat predator stress are more vulnerable than male mice, as this is shown by greater ratio average startle amplitude in the startle acoustic paradigm (Adamec *et al*., 2006). Other researchers have applied a PTSD model that is based on individual behavioural responses assessed with the elevated plus maze and the acoustic startle response paradigms. Again rats are subjected to predator stress and cut-off criteria are applied in order to select those rats that are more affected by stress. Interestingly, the prevalence rates of severely affected male and female rats are the same. However, males and females respond in a different way, probably because baseline stress levels are higher in females and the magnitude of response is lower (Mazor *et al*., 2009; Cohen and Yehuda, 2011; Cohen *et al*., 2012).

Sex differences are also present in the fear-conditioning paradigm, in which animals are trained to associate a conditioned stimulus (CS), such as a cue (e.g. tone) or a context with an unconditioned stimulus (US) of aversive nature, such as a footshock. During testing, animals are exposed again to the same CS and they show a CR, such as freezing or enhanced startle reflex. In contextual fear conditioning, female rats show less learned freezing behaviour than male rats (Maren *et al*., 1994; Pryce *et al*., 1999). In cue fear conditioning, male rats again exhibit more conditioned fear than female rats, either when freezing or when ultrasonic vocalizations are used as a CR (Maren *et al*., 1994; Pryce *et al*., 1999; Kosten *et al*., 2005).

It has been proposed that PTSD patients show reduced extinction of the fear induced by the traumatic experience (Milad *et al*., 2006; 2008; Rauch *et al*., 2006). In animals, extinction can be assessed by exposing them repeatedly to the CS without the US and observe the reduction of the CR. Extinction in female rats differs across the phases of the oestrous cycle (Milad *et al*., 2009). Female rats that extinguish the learned response during prooestrous exhibit lower freezing during a recall test, suggesting facilitation of extinction. In the same study no sex differences in extinction were observed between male and female rats, but female rats that extinguish fear during the dioestrous phase of the cycle show higher freezing during the recall test, in comparison with male and female rats in prooestrous (Milad *et al*., 2009). Subsequent studies from the same laboratory showed that when the SSRI fluoxetine is administered in an acute way, it increases fear responses during extinction in both sexes. However, when rats are pretreated with fluoxetine for 2 weeks, fear during extinction learning is reduced only in female rats that are in dioestrous, when oestrogens are low. Dioestrous is also the phase of the cycle when female rats show exaggerated fear during extinction learning, suggesting that the treatment is more effective when fear responses are high (Lebron-Milad *et al*., 2013).

In another PTSD model with one footshock exposure male and female rats are similarly affected when tested in the elevated plus maze and the dark–light anxiety tests. When stress-induced sensitization is assessed by measurement of freezing in a silence period following a white noise, both male and female rats exhibit enhanced fear responses. However, there are sex differences in basal levels with male rats reacting more than female rats to sudden silence, independently of previous shock exposure (Gogos *et al*., 2008).

Moreover, in studies from Shors laboratory, tailshock is used as an acute stressor and 24 h later classical conditioning with the use of the eyeblink paradigm is assessed (Dalla and Shors, 2009; Bangasser and Shors, 2010). With the use of this paradigm, learning is enhanced in male rats whereas it is impaired in female rats when they are stressed in dioestrous 2 and trained in prooestrous. Prooestrous is also the phase of the cycle when female rats show enhanced learning (Shors *et al*., 1998). Interestingly, when rats are pretreated with fluoxetine chronically before application of the stressor, the stress effects on learning are prevented in both sexes and sex differences in learning are alleviated (Leuner *et al*., 2004). In response to acute tailshock, female rats also show enhanced startle sensitivity to a stimulus of low intensity when they are stressed and tested in dioestrous. In contrast, startle responsivity is suppressed when female rats are stressed and tested in oestrous (Harvey *et al*., 2005).

Finally, another paradigm used in PTSD research is the fear-potentiated startle where rats associate a cue, such as a light with a footshock. When they are later exposed to the light without the footshock, they show enhanced startle reflex, in response to a sudden noise (Davis, 2001). In this paradigm, intact female rats show a greater potentiation of startle than male rats (de Jongh *et al*., 2005).

Overall, it seems that sex differences in the various PTSD paradigms depend on the testing conditions and the behavioural responses that are assessed. In general, male rats show higher freezing responses, whereas female rats are more vulnerable to acute stressors and show enhanced fear and startle responses, as well as decreased extinction when oestrogen levels are low (i.e. in dioestrous).

Sex differences in animal models of substance-related disorders

Substance-related and addictive disorders are now viewed as a continuum from milder to more severe states, moving away from the traditional clinical distinction between abuse and dependence and acknowledging that substances as well as other stimuli, such as gambling, activate the brain reward system in a similar manner (American Psychiatric Association, 2013). Men are significantly more likely to have an addiction disorder than women, although it is not clear yet whether this sex difference reflects gender differences in opportunity and availability or increased men's vulnerability to addiction. In fact, women escalate intake of addictive substances more rapidly and find it more difficult to quit than men. Substantial basic research supports the argument of robust sex differences in the neurobiology of addiction (Carroll and Anker, 2010). Animal models are well-validated for studying the addiction cycle components (compulsive use, withdrawal, craving). These models broadly rely on self-administration, intracranial self-stimulation, the conditioned place preference and aversion paradigms. In this section we focus on those commonly used models from the point of behavioural pharmacology and we highlight notable sex differences (Table 5).

In the self-administration paradigm, animals are trained to bar-press or nose poke in order to receive access to a drug, usually by i.v. infusion. The animal's pattern of drug taking

Table 5

Sex differences in models of substance-related disorders

Models of substance-related disorders	Main behavioural index	Male/female vulnerability	Strength of evidence
Self-administration	Bar press/nose pokes	Females > males	***
ICSS	Lever pressings	Inconclusive	***
Conditioned place preference paradigm	Preference	Females > males	**
Aversive conditioning	Avoidance	Females > males	*
Locomotor sensitization	Locomotion	Females > males	***

Animal models of substance-related disorders reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes low strength of evidence in the literature.
***Denotes medium strength of evidence in the literature.

can be studied during acquisition, maintenance and relapse. Female rats acquire self-administration of low doses of addictive substances faster than male rats and at higher percentages, while oestradiol enhances such acquisition (Lynch and Carroll, 1999; Carroll *et al.*, 2002; Hu *et al.*, 2004; Roth *et al.*, 2004). During maintenance conditions, female rats in oestrus preferred higher doses of cocaine compared with female rats in other phases of the oestrous cycle or male rats (Lynch *et al.*, 2000). Also, female rats appear more motivated to obtain cocaine in oestrus compared with the other stages of the oestrous cycle (Sell *et al.*, 2005). Finally, it has been suggested that female rats are more sensitive than male rats to cocaine's reinforcing effects and interestingly, it has been shown that progesterone suppresses the reinstatement of cocaine seeking (Roberts *et al.*, 1989; Anker *et al.*, 2007).

Another model used is the intracranial self-stimulation (ICSS) paradigm, which assesses the brain reward system and has also been used in bipolar and depression research as a measure of dysregulated motivation. With the use of the ICSS paradigm and by activation of the medial forebrain bundle, basal reinforcement thresholds do not differ between male and female rats and there were no differences across the female oestrous cycle (Stratmann and Craft, 1997). For ICSS of the lateral hypothalamus it has been reported that male rats have higher response rates than female rats aged 15–45 days (Velley and Cardo, 1977). However, when older rats are used (2–10 months), female rats display higher response rates than male rats (Cohen and Lieblich, 1981). In other studies, no sex differences with the use of intra-ventral tegmental area ICSS have been reported (Rao and Desiraju, 1990). With regards to the oestrous cycle, many studies find no differences of ICSS response rate across the phases of the oestrous cycle (Hitt and Gerall, 1969; Drewett and Herberg, 1975; Rao and Desiraju, 1990). However, it has been found that the response rate is highest during oestrus and this is not due to enhanced activity levels (Prescott, 1966). Also, peak ICSS response with stimulation of the pars compacta of the substantia nigra has been observed in the night of prooestrous to oestrus (Steiner *et al.*, 1981).

Finally, another commonly used model is based on the conditioned preference or avoidance of a place that has been associated with an addictive substance (Randall-Thompson and Riley, 2003; Busse *et al.*, 2005; Jones *et al.*, 2006; Rinker *et al.*, 2008). In the conditioned place preference paradigm, with the use of cocaine, female rats exhibit place preference in fewer trials than male rats (Russo *et al.*, 2003a,b). In the conditioned place aversion, when amphetamine at low doses is used as the aversive stimulus, female rats acquire stronger aversions than males and extinguish it more slowly (Roma *et al.*, 2008). Lastly, in studies examining sex differences in locomotor sensitization, female rats are more sensitive than male rats to drug-induced locomotor sensitization (Festa and Quinones-Jenab, 2004a; Festa *et al.*, 2004b; Nazarian *et al.*, 2004; Carroll *et al.*, 2007).

In summary, addiction is perhaps one of the fields in behavioural pharmacology that has advanced substantially in studying sex differences and several excellent reviews provide a more in-depth view of such progress (Lynch, 2006; Becker and Hu, 2008; Fattore *et al.*, 2008; Carroll and Anker, 2010).

Sex differences in animal models of schizophrenia

Schizophrenia, a severe psychiatric disorder with chronic course and a variable complex set of symptoms, presents interesting sex differences. Men have an overall 40% greater chance of developing schizophrenia and the mean age of onset is 3–4 years earlier, in comparison with women (Häfner, 2003). Instead, women have a less severe illness course with shorter hospitalizations, fewer relapses and superior functioning (Abel *et al.*, 2010). Possible explanations include the protective role of oestrogens (Kulkarni *et al.*, 2013) and the greater response of women to antipsychotic treatment. However, women experience more antipsychotic-related side effects than men (Seeman, 2010). Additionally, negative symptoms are more common in men, whereas women tend to have more affective symptoms and fluctuation of their psychopathology across the menstrual cycle, with symptoms deteriorating when oestrogens are low (Riecher-Rossler and Hafner, 2000; Agius *et al.*, 2009; Pregelj, 2009; Markham, 2012). Schizophrenia is a complex disease that cannot be fully modelled in rodents, as is usually the case for animal models. Instead positive, negative and cognitive symptoms

Table 6

Sex differences in models of schizophrenia

Models of schizophrenia	Main behavioural index	Male/female vulnerability	Strength of evidence
Administration of NMDA antagonists	Many indices	Females > males	****
LI	Conditioning	Conflicting findings	***
PPI	Acoustic startle	No differences	**
D2 knockouts	LI	No differences	*
D1 knockouts	LI	Females > males	*
Akt1- knockouts	PPI	Females > males	*
Y2 knockouts	Many indices	Males < females	*

Animal models of schizophrenia reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes low strength of evidence in the literature.
***Denotes medium strength of evidence in the literature.
****Denotes high strength of evidence in the literature.

are simulated through pharmacological and developmental/genetic models (Desbonnet *et al.*, 2012; Hida *et al.*, 2013; Wu *et al.*, 2013) (Table 6).

A classical model of schizophrenia's positive symptoms is treatment of rodents with amphetamine, which is also considered a model of mania and will be discussed in the appropriate section. Additionally, negative and cognitive symptoms of schizophrenia can be modelled by treating rodents with NMDA antagonists, such as phencyclidine (PCP), ketamine and MK-801 (Carlsson and Carlsson, 1990; Krystal *et al.*, 2000). Following MK-801, intact female rats show significantly greater behavioural sensitivity than male rats with enhanced scores of locomotion, stereotyped sniffing and ataxia (Andine *et al.*, 1999). Female rats are also more sensitive to PCP than male rats, as assessed by hyperactivity, stereotyped behaviours, motor incoordination, tremor, ataxia, suppression of operant responses for food and extra-dimensional shift stage of the attentional set-shifting task (Nabeshima *et al.*, 1984; Wessinger, 1995; Snigdha *et al.*, 2011). However, female rats display less anxiety following PCP withdrawal, whereas the opposite effect is evident in male rats (Turgeon *et al.*, 2010; 2011). Notably, 17β-oestradiol reverses the PCP-induced deficits of intact female rats in the novel object-recognition test (Sutcliffe *et al.*, 2008). Interestingly, it seems that sex differences, in response to acute administration of NMDA antagonists, are due to pharmacokinetic differences between male and female rats and specifically because of the lower metabolism of NMDA antagonists and thus higher plasma and brain levels (Nabeshima *et al.*, 1984; Andine *et al.*, 1999; Shelnutt *et al.*, 1999).

In addition to the behavioural parameters mentioned earlier, latent inhibition (LI) is extensively studied in models of schizophrenia (Weiner, 2003; Weiner and Arad, 2009). LI refers to a phenomenon of retarded conditioning, closely related to dopaminergic activity, disrupted in schizophrenia and restored by typical and atypical antipsychotics (Weiner, 2003; Weiner and Arad, 2009) (Mackintosh, 1975). Specifically, when a stimulus (e.g. a tone) is repeatedly presented in an unpaired way and signals no consequence, then subsequent associative learning is diminished when later the same stimulus is presented in a paired/conditioned way. LI is used for screening of antipsychotic activity, as both typical and atypical antipsychotics restore reduced LI in amphetamine-treated rats. Also, persistent LI induced by NMDA antagonists is prevented by atypical, but not typical antipsychotics (Harvey *et al.*, 2005; Heresco-Levy, 2005; Arad and Weiner, 2008). With regards to sex differences in LI, conflicting results have been reported. Specifically, in mice, there is a clear sex difference in the occurrence of LI, with female rats showing reduced LI in comparison with male rats (Bay-Richter *et al.*, 2009), which is in line with similar observations in men and women (Lubow and De la Casa, 2002). Instead, female rats exhibit greater LI than male rats (Bethus *et al.*, 2005), whereas other researchers have not found marked sex differences in LI (Arad and Weiner, 2010). Regarding the oestrous cycle, female rats tested during prooestrous, when oestrogen levels are high, exhibit a marked attenuation of LI, in comparison with female rats in oestrous or dioestrous, when oestrogen levels are lower (Quinlan *et al.*, 2010). In another study, female rats in oestrous during the pre-exposure phase and in dioestrous during the conditioning phase (oestrous–dioestrous group) displayed a normal LI as did male rats, whereas LI was absent in female rats at other stages of the oestrous cycle (Arad and Weiner, 2008). Interestingly, haloperidol and clozapine restored LI in prooestrous–oestrous females, whereas only clozapine and not haloperidol restored LI in dioestrous–prooestrous and dioestrous 1–dioestrous 2 female rats (Arad and Weiner, 2008). Additionally, high doses of 17β-oestradiol administered to intact female and male rats result in a typical antipsychotic pattern on LI, whereas low doses have the opposite effect and disrupt LI. Finally, MK-801-induced persistent LI is ameliorated by 17β-oestradiol in male but not in female rats, suggesting that 17β-oestradiol could act as an atypical antipsychotic in male rats (Arad and Weiner, 2008).

Another paradigm that is often used in schizophrenia research is the acoustic startle response that occurs in

response to a sudden loud noise and its attenuation by a preceding prestimulus (Hoffman and Ison, 1980). This phenomenon is called prepulse inhibition (PPI) and is used as an index of sensorimotor gating deficits often observed in schizophrenic patients and in animal models of schizophrenia (Braff *et al.*, 2001). In women, PPI depends on the menstrual cycle, and women are less inhibited by weak prepulses than men (Plappert *et al.*, 2005; Kinkead *et al.*, 2008). However in 1998, Koch found no difference in PPI between male and female rats, but PPI was reduced in female rats during prooestrous, in comparison with oestrous and dioestrous phases of the cycle (Koch, 1998). Other researchers have found opposite results, such as higher PPI in male and female rats in prooestrous, in comparison with female rats in dioestrous (Kinkead *et al.*, 2008) or no differences across the oestrous cycle (Adams *et al.*, 2008). These discrepancies have been attributed to different testing conditions, such as stimulus intensity and testing during the light or dark phase.

With regard to genetic models of schizophrenia, several mutant mouse models have been studied in combination with environmental factors (Desbonnet *et al.*, 2012; Hida *et al.*, 2013). For example, LI has been found to be enhanced in both male and female dopamine receptor 2 (D_2-receptor) knockout mice. In contrast, only female D_1 receptor knockout mice exhibit enhanced LI and not male mice, suggesting a sex-differentiated involvement of the dopaminergic system in this phenomenon (Bay-Richter *et al.*, 2009). V-Akt murine thymoma viral oncogene homologue 1 (*Akt1*) knockout female, but not male mice, exhibit enhanced immobility in the tail suspension test, indicating enhanced depressive symptomatology, and PPI deficits that are not alleviated by the antipsychotic drugs raclopride or clozapine. However, PPI deficits are partially normalized by glycogen synthase kinase 3 (GSK3) inhibitors (Chen and Lai, 2011). Moreover, male mice deficient for the neuropeptide Y, Y_2 receptor, exhibit enhanced activity levels and social interaction, whereas they have no learning and memory deficits. Male Y_2 receptor-knockout mice also show improved PPI of the acoustic startle response, which shows normal response to the psychotropic drugs dexamphetamine and MK-801. In contrast, female Y_2 receptor-knockout mice exhibit normal levels of social interaction, working memory abilities and PPI (Karl *et al.*, 2010).

Overall, behavioural indices in schizophrenia models are highly sensitive to fluctuation of sex hormones, and this should be taken into consideration. Moreover, paradigms based on the interaction of genes with environmental factors need to be validated for both male and female animals. Finally, more studies comparing antipsychotic activity in both sexes are required.

Sex differences in models of bipolar disorder

In contrast to anxiety disorders and unipolar mood disorder, bipolar disorder does not differ in its incidence between men and women. However, significant sex differences exist in the presentation and its course. Women are at increased risk of bipolar type II, hypomanic, rapid cycling and mixed episodes. Additionally, the onset of bipolar occurs later in women and they are more susceptible to the seasonal pattern of mood disturbance. Important differences also exist in patterns of co-morbidity with women suffering more often from anxiety, and men presenting substance-related disorders. There are no data on sex differences in response to mood stabilizers, but treatment of bipolar disorder is challenging in women during pregnancy, lactation and post-partum period (Arnold, 2003; Diflorio and Jones, 2010). Bipolar disorder is difficult to model in animals and the lack of suitable animal models is hindering our understanding of potential sex differences in the neurobiology of bipolar disorder (Machado-Vieira *et al.*, 2004b; Gould and Einat, 2007).

Limited animal models typically simulate either mania or depression (Table 7). Hyperactivity is most frequently used as the primary outcome to assess the validity of many animal models of mania. Interestingly the increasing recognition of the multifaceted nature of mania has revealed a need for relevant animal models, which simulate other symptoms as well. However, the validation of such models remains

Table 7

Sex differences in models of bipolar disorder

Models of bipolar disorder	Main behavioural index	Male/female mania vulnerability	Strength of evidence
Amphetamine-induced hyperactivity	Locomotion	Females > males	**
Sleep deprivation	Insomnia/locomotion	No differences	*
Resident–intruder	Aggression	No differences	*
Dopamine transporter knockouts	PPI/locomotion	No differences	*
GSK3b knockouts	Many indices	No differences	*
DISC1 transgenics	Many indices	Females > males	*
CLOCK mutant mice	Activity	Females > males	*
CACNA1c knockouts	Many indices	Females > males	*

Animal models of bipolar disorder reviewed herein are presented and the main behavioural index assessed is noted. Male and/or female vulnerability to the model (mania) is mentioned.
*Denotes scarce evidence in the literature.
**Denotes high strength of evidence in the literature.

limited. Thus, amphetamine-induced hyperactivity is still considered to be the most validated and widely used rodent model of mania (Young *et al.*, 2011). Female rats exhibit a greater initial behavioural response to amphetamine or cocaine and show an even greater sensitization than male rats, that is a greater absolute increase in psychomotor behaviour to subsequent treatments (Becker *et al.*, 2001). Although the effects of amphetamine sensitization are confounded by sex differences in amphetamine metabolism, sex differences persist even when males are given higher doses of amphetamine in order to produce comparable brain amphetamine concentrations (Robinson *et al.*, 1982; Robinson, 1984; Camp and Robinson, 1988a,b; Forgie and Stewart, 1994; Fattore *et al.*, 2008). Moreover, oestrogen-treated rats or rats in oestrous display a heightened amphetamine-induced locomotor activity (Becker and Beer, 1986; Becker, 1990; Becker *et al.*, 2001). Accordingly, female aromatase knockout (ArKO) mice, which lack oestrogens, display lower amphetamine-induced hyperlocomotion in comparison with wild-type controls. A reduction in the effect of amphetamine is also evident in male ArKO mice, but the genotype difference is smaller (Chavez *et al.*, 2009). In summary, amphetamine-induced locomotor hyperactivity is highly dependent on oestrogens, and thus female rats appear far more sensitive to amphetamine's behavioural effects.

More recently, researchers have highlighted the need to develop animal models of mania that assess more than just levels of activity (Einat, 2006). Several models have been proposed, but most of them have limited validation (Machado-Vieira *et al.*, 2004a; Einat, 2007). In the rat sleep deprivation model of mania, at the end of the sleep deprivation period, rats present insomnia, hyperactivity and irritability. Those symptoms simulate mania and are controlled by antipsychotics and lithium. In this model there is a lack of specific studies with regards to sex differences (Gessa *et al.*, 1995). However, evidence from sleep deprivation studies in other areas of neuroscience raises a strong suspicion that this model presents significant sex differences (Koehl *et al.*, 2006; Hajali *et al.*, 2012). Similarly, another proposed model of mania is the resident–intruder mice model. In this test, an intruding mouse is placed in a cage along with resident mice and aggressive behaviours are scored. These behaviours are then controlled by mood stabilizers; hence, this model has been proposed as a model of mania. This model lacks specific studies on potential sex differences as well. However, its use in other areas of neuroscience suggests important sex differences as well (Pinna *et al.*, 2004; Clipperton Allen *et al.*, 2010; Clipperton-Allen *et al.*, 2011).

Finally, several genetic models of mania have been proposed, mainly based on findings from human association studies and our knowledge regarding the pharmacological action of known mood stabilizers. One such putative model of mania is the dopamine transporter knockout mouse, as the gene of this transporter emerges from several genetic linkage studies to be implicated in mania. However, a previous study failed to show sex differences in this mouse model (Ralph-Williams *et al.*, 2003). Another gene putatively, although not consistently, linked to mania is GSK3. This gene attracts attention as the mood stabilizers lithium and valproate possibly act via GSK3. Again, an earlier study failed to reveal sex differences in GSK3b knockout mice (Prickaerts *et al.*, 2006). Disrupted-in-schizophrenia 1 (*DISC1*) is another gene implicated in schizophrenia and bipolar disorder (Hodgkinson *et al.*, 2004). Kuroda *et al.*, in 2004 showed that female mice lacking exons 2 and 3 of the *DISC1* gene, exhibit enhanced methamphetamine hyperactivity, in comparison with control mice and have decreased PPI. Both male and female mice exhibit reduced anxiety in the elevated plus maze test, whereas other behaviours (e.g. LI, depressive) appear normal (Kuroda *et al.*, 2011). Transgenic mice with inducible expression of mutant human *DISC1* (*hDISC1*) also show sex-dependent behavioural abnormalities. Male rats display enhanced spontaneous locomotor activity and alterations in social behaviours, whereas female rats show impairment in spatial reference memory in the Morris water maze task (Pletnikov *et al.*, 2008). Another candidate genetic model of mania employs the *CLOCK* gene, which is involved in the regulation of circadian rhythm and implicated in the mechanism of action of mood stabilizers. Female mutant *CLOCK* mice display enhanced activity and exploration in response to a novel environment (enhanced rearing and entries in the open field test), whereas in male rats the changes in the open field test are less robust. In the FST, only female *CLOCK* mutant mice exhibit lower immobility levels than controls (van den Buuse and Gogos, 2007). In another proposed model of bipolar disorder, the *CACNA1c* knockout mouse, female mice exhibit more robust attenuation of amphetamine-induced hyper-locomotion than male mice. Moreover, female, unlike male mice, display an attenuated acoustic startle response and reduced expression of learned helplessness, along with phenotypes of increased anxiety or decreased risk taking (Dao *et al.*, 2010).

In summary, several models of bipolar disorder have been proposed and used, but none of them convincingly simulates the alternating states of human mania and depression. Instead, separate paradigms are traditionally used for mania and depression. Thus, there is a strong need for developing and validating better models of bipolar disorder. In most models of mania, limited evidence indicates sex differences, which deserve further investigation. In contrast, in depression, sex differences have been studied more thoroughly and are described in the first section of this review.

Sex differences in models of OCD

Regarding gender and OCD, evidence shows a male preponderance in underaged populations, and an almost equal gender ratio in adulthood. OCD has an earlier onset in male rats and associates more frequently with tic and attention deficit hyperactivity disorder. By contrast, women present more contamination obsessions and cleaning rituals, whereas sexual obsessions are more common among men. Generally OCD in men has a greater impact on several domains of functioning affecting social adjustment and interpersonal relationships more than in women (Mathis *et al.*, 2011). Several genetic, pharmacological and behavioural models exist for OCD, but most of them have not been validated for female animals (Joel, 2006; Albelda and Joel, 2012a,b) (Table 8).

Compulsive lever pressing is an animal model of OCD where both male and female animals have been studied. In a paradigm that the rats learn to associate the pressing of a lever with a tone, a light and a food reward, no sex differences

Table 8

Sex differences in models of OCD and autism

	Main behavioural index	Male/female vulnerability	Strength of evidence
Models of OCD			
Compulsive lever pressing	Lever pressings	No differences	*
8-OH-DPAT disruption of spontaneous alternation	Alternation	Undetermined	*
Marble burying	Burying	Undetermined	*
Deer mice	Stereotypy	No differences	*
ArKO mice	Grooming/locomotion	Males > females	*
Models of autism			
Prenatal valproic acid	Many indices	Males > females	*
Mthfr$^{+/-}$	Hyperactivity	Males > females	*
Ehmt1$^{+/-}$	Social behaviour	Males > females	*
BTBR T + tf/J	Social behaviour	Males > females	**

Animal models of OCD and autism and the main behavioural index assessed is noted. Male and/or female vulnerability to the model is mentioned.
*Denotes scarce evidence in the literature.
**Denotes low strength of evidence in the literature.

are observed. However, oestrous cycle influences the extinction that occurs when lever-pressing is followed by the tone and the light, but not the food reinforcement. Extinction is highest during dioestrous and lowest during the oestrous phase of the oestrous cycle (Flaisher-Grinberg *et al.*, 2009). In another OCD model, spontaneous alternation at a T-maze is disrupted by administration of the 5-HT$_{1A}$ agonist 7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (8-OH-DPAT). Female animals show preservation behaviour for one arm of the maze, which is highest at late dioestrous and prooestrous and lowest at the oestrous phase (Agrati *et al.*, 2005). Also, fluoxetine treatment reduces 8-OH-DPAT-induced perseveration during dioestrous and prooestrous, but not during oestrous (Fernandez-Guasti *et al.*, 2006).

Marble burying behaviour has also been studied in OCD research, and it is sensitive to fluctuations in the sex hormones along the oestrous cycle. Thirty percent of female rats bury more marbles in dioestrous, in comparison with prooestrous, and this is attenuated by acute treatment with the antidepressants fluoxetine, nomifensine and the anxiolytic diazepam (Schneider and Popik, 2007). Accordingly, female rats spend more time burying in dioestrous than in prooestrous (Llaneza and Frye, 2009). However, others have found that in this test, female rats in prooestrous are more sensitive to diazepam, than male and female rats in dioestrous (Fernandez-Guasti and Picazo, 1990). Finally, in a study where the marble burying test was used as an anxiety model, female rats tended to bury fewer objects than male rats (Goel and Bale, 2008).

In another model of OCD, the deer mice, which are characterized by stereotypical behaviours, mice of both sexes have been used but no sex differences have been reported to date (Korff *et al.*, 2008). With regard to genetic models, male ArKO mice, which lack oestrogens, show enhanced OCD-like behaviours, such as grooming and wheel running, whereas females do not (Hill *et al.*, 2007). Also, ArKO male mice 12–18 months of age, but not female rats, show decreased PPI in comparison with wild-type mice, whereas in female ArKO mice, the effects of apomorphine and amphetamine on PPI are reduced (van den Buuse *et al.*, 2003; Chavez *et al.*, 2009). In contrast, female mice, but not male aromatase knockout mice show enhanced depressive behaviour in the FST (Dalla *et al.*, 2004; 2005b).

It is obvious that OCD models need to be validated for both sexes, but there is a lack of relevant studies. The findings gathered so far show that gonadal hormones exert a role in OCD-like behaviours and thus the phases of the oestrous cycle and reproductive state should be taken into consideration.

Sex differences in animal models of autism

Autism is a severe neurodevelopmental disorder characterized by stereotyped behaviours, severe impairments in social behaviour and in verbal and non-verbal communication. These patients frequently present other symptoms, such as anxiety, aberrant sensitivity to sensory stimulation and immunological disorders. Autism is much higher in boys than in girls with a ratio of 4:1 (Fombonne, 2003).

In basic research, few animal models for autism are available, and most studies include only male animals, as the disorder is more prevalent in males (Bolivar *et al.*, 2007; McFarlane *et al.*, 2008; Karvat and Kimchi, 2012; Oddi *et al.*, 2013) (Table 8). One such model is based on the prenatal exposure of rats to the antiepileptic drug valproic acid. This exposure produces a range of behavioural and immunological alterations, which are most evident in male offspring. In particular, male rats exposed prenatally to valproic acid presented lower sensitivity to pain, increased repetitive/stereotypic-like activity, elevated anxiety and decreased social behaviours compared with control male rats, whereas female

rats only showed enhanced repetitive/stereotypic-like movements (Schneider *et al.*, 2008).

In another study, valproic acid was administered postnatally in male and female mice lacking the glutathione-S-transferaseM1 gene, which has been associated with autism. In play behaviour trials, female knockout animals exhibited lower alo-groom behaviours than wild-type female mice, whereas this was not evident in male mice. Valproic acid decreased social behaviour, only in knockout mice, but no sex differences were observed (Yochum *et al.*, 2010).

Male heterozygous mice for the methylenetetrahydrofolate reductase (*Mthfr*) gene, which has been associated with autism, are hyperactive, whereas this is not evident in female mice. Post-natal exposure of *Mthfr* male and female heterozygous mice to the antiepileptic drug vigabatrin resulted in hyperactivity and memory impairments in both sexes (Levav-Rabkin *et al.*, 2011).

Other knockout studies include male and female heterozygous mice for the euchromatin histone methyltransferase 1 $(Ehmt1)^{+/-}$, which models a mental retardation syndrome with autistic features. All $Ehmt1^{+/-}$ mice appeared less active than wild-type mice, and they exhibited decreased explorative and social behaviours, as well as increased anxiety. In particular, $Ehmt1^{+/-}$ juvenile male mice showed a higher decrease in social play compared with the wild-type mice, which was not evident in female mice (Balemans *et al.*, 2010).

Finally, the inbred BTBR T + tf/J (BTBR) mice that display social deficits and repetitive behaviours similar to autistic symptoms display sex differences. In particular, male BTBR mice show social deficits that are not evident in female BTBR mice (Defensor *et al.*, 2011). However, both male and female juvenile and adult BTBR mice exhibited deficits in social interactions when paired with novel partners of different strains. (Yang *et al.*, 2012). Finally, no sex differences were observed in adult BTBR mice when complex vocalizations emitted during same-sex interactions were assessed (Scattoni *et al.*, 2011). Overall, it seems that in the few models that both sexes have been studied for autistic behaviours, male animals are more sensitive.

Conclusions

In this review, we aimed to present a descriptive panorama of sex differences that characterize the majority of rodent models of psychiatric disorders. These sex differences are, more often than rarely, overlooked or it is assumed that they are not relevant to the study of disease neurobiology and treatment response. This assumption might be a crucial factor explaining why animal models in psychiatry occasionally fall short in advancing new treatments.

Sex differences in several animal models based on the application of environmental factors (e.g. stress) or pharmacological treatments have been presented. Also, some genetic models in which both sexes have been studied are included. However, because of space limitations, an exhaustive list of animal models of psychiatric disorders that have included both male and female animals was not possible. In particular, there are many models employed during development of the brain, early life, puberty or particular stages of reproduction (e.g. *post-partum*) that are of great importance in the investigation of sex differences in psychiatric disorders (Galea *et al.*, 2008; Goel and Bale, 2009; Brummelte and Galea, 2010; Glover and Hill, 2012; Pawluski *et al.*, 2012; McCormick and Green, 2013).

One conclusion that could be drawn from exploring the field is that consensus on sex differences in behavioural pharmacology is more often the exception than the rule. A combination of relatively fewer research groups consistently studying sex differences and scattered studies that incidentally perform between-sex comparisons has not yet produced a clear understanding of the male and female behavioural phenotype in most rodent models. As a result, in many cases, findings from animal models do not match or explain the sex differences in different aspects of psychiatric diseases in humans.

From the data reviewed here, it will hopefully be obvious that preclinical psychiatric research should be sex-aware. It is evident that all (both current and new) models and tests for psychiatric disorders/symptoms need careful validation for male and female animals. In some cases, the fluctuation of sex hormones across the oestrous cycle is of importance and should be taken into consideration. However, in other cases as in chronic models, the female oestrous cycle cannot be considered. Thus, it is important to standardize experimental procedures for models and tests, in order to use them as screening tools for new treatments. For this, there are several excellent review papers that give guidelines on how to address sex differences in animal models (Becker *et al.*, 2005; McCarthy *et al.*, 2012; McLean *et al.*, 2012).

Furthermore, it should be taken into consideration that many times, while most animal models successfully mimic drug response in both sexes, treatment-sensitive behavioural indices are not always the same in male and female rodents. Also, often, treatment response is affected by sex-dependent differences in baseline behaviour, whereas the response to psychotropic drugs masks sex differences post-treatment. Importantly, sex differences in response to psychotropic drugs, are often related to pharmacokinetic sex differences and this should be taken into account when results from animal and human studies are interpreted (Nabeshima *et al.*, 1984; Andine *et al.*, 1999; Shelnutt *et al.*, 1999; Hodes *et al.*, 2010; Kokras *et al.*, 2011a).

Behavioural sex differences usually result from sex differences in neural underpinnings and/or are linked with sex differences in brain structure, neurochemistry, neuroendocrinology and neurobiology (Cahill, 2006; Cosgrove *et al.*, 2007; Solomon and Herman, 2009). Sex differences result from chromosome effects, organizational effects of sex hormones during development of the brain and/or activational effects of sex hormones (McCarthy *et al.*, 2012). Apart from genetic factors, epigenetic mechanisms across the lifespan should also be taken into consideration, as it seems that these play an important role in sex differences in behaviour and drug response (Shepard *et al.*, 2009; Hodes, 2013).

In fact, this constellation of behavioural differences between males and females presented here, along with many interesting studies on the sex-differentiated neurobiological substrate raises a significant doubt as to whether many excellent studies on male rodents will ever be replicated in female rodents. From our studies (Dalla *et al.*, 2005a; Kokras *et al.*,

2009a,b; 2011b), we have repeatedly observed in models of anxiety and depression that the male and female neurobiology at times diverges and/or converges following stress or treatment. Furthermore, the mere existence of a sex difference at the behavioural level does not necessarily imply that the neurobiology is sex-differentiated. Inversely, the absence of a sex difference at the behavioural response following manipulations or specifically pharmacological treatments often involves a heavily sex-differentiated neurobiological adaptation. Therefore, all this significant knowledge in neuroscience gained by experiments in male rodents should perhaps carefully be revisited. In support of this notion is also the view that animal models in females may perhaps be more representative of many psychiatric disorders in humans.

Conclusively, male and female animals should be included in all studies, if possible, in order to understand the frequency and pattern of sex-dependent manifestations of psychiatric disorders and to search for effective and safe sex-orientated treatments.

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Conflict of interest

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