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The underestimated sex: A review on female animal models of depression

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ABSTRACT

Major depression (MD) is the most common psychiatric disorder, predicted to affect around 264 million people worldwide. Although the etiology of depression remains elusive, the interplay between genetics and environmental factors, such as early life events, stress, exposure to drugs and health problems appears to underlie its development. Whereas depression is twice more prevalent in women than in men, most preclinical studies are performed in male rodents. In fact, females' physiology and reproductive experience are associated with changes to brain, behavior and endocrine profiles that may influence both stress, an important precipitating factor for depression, and response to treatment. These specificities emphasize the need to choose the most suitable models and readouts in order to better understand the pathophysiological mechanisms of depression in females.

With this review, we aim to provide an overview of female animal models of depression highlighting the major differences between models, regarding behavioral, physiological, and molecular readouts, but also the major gaps in research, attending to the role of etiological factors, protocol variability and sex.

1. Introduction

Major depression (MD) is the most common psychiatric disorder predicted to affect more than 260 million people worldwide (GBD, 2017). The symptoms of depression, as stated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5: Psycom.net - Mental Health Treatment Resource Since, 1986), include, depressed mood, markedly diminished pleasure or interest in activities (anhedonia), significant weight gain or weight loss, excessive guilt, loss of energy and diminished capacity to think or concentrate (DSM-5, 2013). To be diagnosed with MD, the individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either depressed mood or anhedonia (DSM-5: Psycom.net - Mental Health Treatment Resource Since, 1986). Moreover, depression can significantly increase the risk of other causes of mortality (Gilman et al., 2017).

Although the etiology of depression remains unclear, the interplay between genetics and environmental factors, such as early life events, exposure to stress and/or drugs and other health problems appear to underlie its development (Bembnowska and Jośko-Ochojska, 2015). People whose first-degree relatives suffer from MD are estimated to be 1.5–3 times more probable to develop depression. However, heritability alone cannot justify the development of MD, as 60 % of the factors involved in its etiology are explained by other factors (Flint and Kendler, 2014). Additionally, there is evidence of a bidirectional correlation between depression and other disorders, including diabetes, drug or alcohol addiction and cancer, as each condition seems to impact negatively on the other (Katon, 2003).

Before puberty, depression is rare and develops at about the same frequency in girls and boys. However, with the onset of adolescence, the risk of developing MD increases in women (Fig. 1; Adapted from Albert, 2015; Breslau et al., 2017). In adulthood, MD is twice more prevalent in women than in men (Albert, 2015). Reproductive hormones, genetics, environmental variables and socio-economic context, which may be unique to women's life experience, seem to be contributing factors for this disparity (Table 1; adapted from Stegenga et al., 2012 and Martin et al., 2013). As sequencing methods continue to advance, there may be fundamental sex differences that allow the brain to function similarly in male and female individuals despite their very different peripheral environments. However, knowledge of basic and disease-related sex

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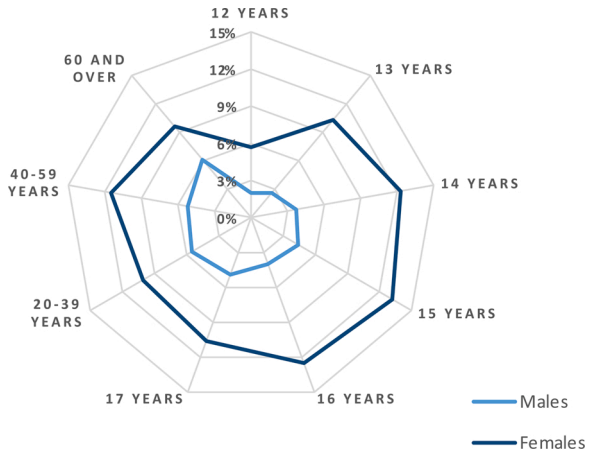

Fig. 1. Schematic representation of the occurrence of first-onset depression among adolescents and adults, by age and sex (Data source - National Survey on Drug Use and Health, 2016; Breslau et al., 2017).

differences is becoming more complicated, underscoring the importance of distinguishing between pathologically relevant sex differences and changes attributable to typical sexual differentiation (Rainville et al., 2021).

A previous study has identified risk factors for MD in patients of a cohort study - PredictD (Stegenga et al., 2012). Risk differences for the onset of MD in male and female were assessed for 35 risk factors from 7101 participants, of both genders, without MD at baseline (Stegenga et al., 2012). Twenty-eight risk factors (80.0 %) had a stronger impact in women than in men (Stegenga et al., 2012). Risk factors such as non-European ethnicity, lower levels of education, religious or spiritual beliefs, lifetime alcohol problem, two or more recent negative life events, a neighborhood perceived as not being safe, financial strain and problems with someone close, had a significantly stronger impact in women. Regarding symptom profiles, women with MD have been associated with increased incidence of hypersomnia, fatigue, psychomotor retardation and suicidal attempts, suggesting a higher occurrence of atypical symptoms (Kim et al., 2015a, b).

Other studies have proposed that the increased incidence of MD in women is linked with hormonal changes, mainly throughout puberty, before menstruation, after pregnancy and at perimenopause (Halbreich, 2000). This disease-incidence correlation implies that female hormonal

Table 1
Compilation of the main risk factors for depression in women versus men (adapted from Stegenga et al., 2012; Martin et al., 2013; Seney et al., 2018; Halbreich, 2000).

	Women	Men
Sociodemographic	Lower Education	None
Psychiatric comorbidity/function	Alcohol problem	None
	Other anxiety problem	None
Adverse experiences/life events	Two or more negative life event	None
Work, living and environment	Neighborhood perceived not safe	Nonprofessional occupation
	Financial strain	Living alone
Family and friends	Problems with someone close	None
Genetic factors	Increase in synapse-related genes	Decrease in synapse-related genes
	Decrease in oligodendrocyte- and microglia-specific genes	Increase in oligodendrocyte- and microglia-specific genes
	Immune-related gene reduction	
Gonadal hormones	Low estrogen	Low testosterone
	Hormone changes during puberty	
	Premenstrual problems	Altered testosterone/oestradiol ratios
	Sudden drop in high levels of hormones shortly after birth	

fluctuations could also be a trigger for MD (Albert, 2015). Given that hormones have been hypothesized to interfere in modulation of endocrine, immune and neurotransmitter systems, it can be hypothesized that female prevalence of atypical depression is associated with the action of those hormones (Antonijevic, 2006; Angst et al., 2002; Silverstein, 2002).

As one of the major components of the stress response, through the coordination of neuroendocrine and autonomic mechanisms, the hypothalamic-pituitary-adrenal (HPA) axis is critical for maintaining mental and physical health, as its hyper- and hypoactivity have been linked to disease states. Research has also revealed sex differences in numerous components of the HPA axis and its responses, which may partially form the basis for sex disparities namely in psychiatric disease (Goel et al., 2014; Heck and Handa, 2019; Rao and Androulakis, 2017). For instance, sex differences in the HPA axis response to acute stress have been reported in rodent studies. In response to physical and psychological stressors, females secrete higher absolute concentrations of corticosterone than males and present a higher reactivity to stress. The mechanisms causing this sexual dichotomy involve a confluence of neural and peripheral circuitries, which seem to be primed to lead to greater glucocorticoid release in females (Goel et al., 2014).

The serotonergic system is also controlled by female gonadal steroid hormones. These hormones can modify density and function of pre- and post-synaptic serotonin receptors and transporters (Klink et al., 2002). Remarkably, compared to men, women have increased somatodendritic 5-HT1A receptor binding (Parsey et al., 2002). Serotonin 5-HT1A heteroreceptors also influence neuroplasticity in the dorsal raphe 5-HT nerve cells and in the hippocampus (Borroto-Escuela et al., 2018). Estrogen stimulates GABAergic transmission, suggesting that females, particularly during the pre-menopausal years, are at a bigger risk for decreased serotonergic neurotransmission (Herbison and Fenelon, 1995). This sequentially might benefit HPA hypoactivity and a bigger risk to develop atypical depression (Antonijevic, 2006).

The molecular signature of MD is also different between men and women (Seney et al., 2018). Gene expression was found to be regulated differently in men and women in 52 genes; men with MD had decreased synapse-related genes, while women displayed gene expression increases in this pathway (Seney et al., 2018). Cell type analysis also showed that men with MD exhibited increased expression of microglia- and oligodendrocyte-related genes, whereas women had decreased expression of these cell types (Seney et al., 2018).

Given the limitations of studying the pathophysiology of MD in humans, most of the constructs for therapeutic development come from animal models, namely rodent models. Considering the numerous environmental, biological and social risk factors for depression, preclinical research implies the use of multivariable models that integrate these factors. The validity of an animal model may be attained by the evaluation of four major criteria: predictive validity, face validity, construct validity and etiological validity (Belzung and Lemoine, 2011; Abelaira et al., 2013). Briefly, animal models of depression should mimic the human condition in the following aspects, including, 1) improvement or reduction of behavioral signs by clinical effective antidepressant therapies (predictive validity); 2) resemblance between the clinical-symptom profile and the behavioral phenotype (face validity), 3) similarity between neurobiological substrates (construct validity) and 4) triggering of the disease in the same manner as the human disorder (etiological validity) (Abelaira et al., 2013). The more criteria an animal model fulfills, the more precise and consistent is the data it produces (Belzung and Lemoine, 2011; Abelaira et al., 2013). Though fully recapitulating the complexity of the human disease is not possible, specific symptoms or a subset of symptoms can be successfully modeled in animals. Moreover, animal models of depression can be developed by exposure to known etiological factors of depression, such as chronic stress, selective breeding, genetic manipulations and pharmacological administration (Wang et al., 2017). The most widely used animal models of MD generally rely on exposure to stressful stimuli and aversive psychosocial experiences, for example, neglect, interpersonal violence, or separation, that induce behavioral or physiological changes, similar to those of the human disease (Berton et al., 2012).

Neurodevelopmental determinants, as well as reproductive maturation and experience, are also important mediators of changes in neural plasticity, circuitry and behavior that may influence both stress and treatment response in females (Halbreich, 2000; Pooley et al., 2018). For this reason, studies in female animal models of depression should be prioritized for a better understanding of the disease pathophysiology.

Previous literature reviews have discussed the existing models and suggested the need to better define clinically relevant symptoms based on sex disparities, clinically relevant risk factors and improved the translation and design of clinical trials (Harro, 2018; Rygula et al., 2018; Wang et al., 2017; Yin et al., 2016; Planchez et al., 2019). Because animal models have, on numerous occasions, been unsuccessful in modeling depression and ineffective in predicting response to therapy, reviewing female animal models of depression may lead to a more comprehensive understanding of the field (Greek and Menache, 2013) and to the identification of possible gaps that need to be filled. In this review, we sought to critically present the published female preclinical animal models of depression highlighting their major hallmarks and differences, attending to factors such as etiological factors, protocol variability, age and species. In this analysis, male models have been used as comparators.

2. Materials and methods

PubMed and Cochrane Library databases were used to identify relevant studies describing female animal models of depression, published before February 2021. Potentially pertinent papers were primarily identified through title and abstract searches, the full text and reference list of the selected articles was then assessed. Two search strategies were used: 1) Combination of MeSH Major Topic "animal disease models" and Mesh Major Topic “depressi*", filtering the results to only females and other-animals; 2) Combination of Mesh term "Animal models" and search terms "depressive-like AND females", filtering the results to only females and other-animals (Fig. 2). The inclusion criteria were: 1) Studies regarding only females or in which females and males were analyzed separately; 2) Studies in which depression or anxiety was validated by behavioral outcomes. Different species were found across studies and included, *Phodopus sungorus* (hamster), *Microtus ochrogaster* (prairie vole), *Macaca mulatta* (Rhesus monkey), *Rattus norvegicus* (rat) *and Mus musculus* (mouse).

The exclusion criteria were: 1) ovariectomized rodents; 2) articles which made no distinction between males and females on the behavioral outcomes.

Data was extracted using a multistep process of study selection centered on search strategy, abstract screening, full-text article screening and eligibility of the studies based on the defined inclusion and exclusion criteria. The following data was extracted from each study: animal model, method of induction, animal-related variables (species, strain, age and diet), sample size, protocol duration and outcome measures.

3. Results

Forty-three studies focusing on female animal models of depression were included in this review (Fig. 2). Because behavioral and physiological traits of major depression can be induced by different paradigms, female animal models of depression were divided in four main classes based on the nature of the etiological factor used (Table 2):

1 Stress-based animal models:
   i) Maternal separation animal models;
   ii) Social stress animal models;
   iii) Acute and chronic stress animal models;

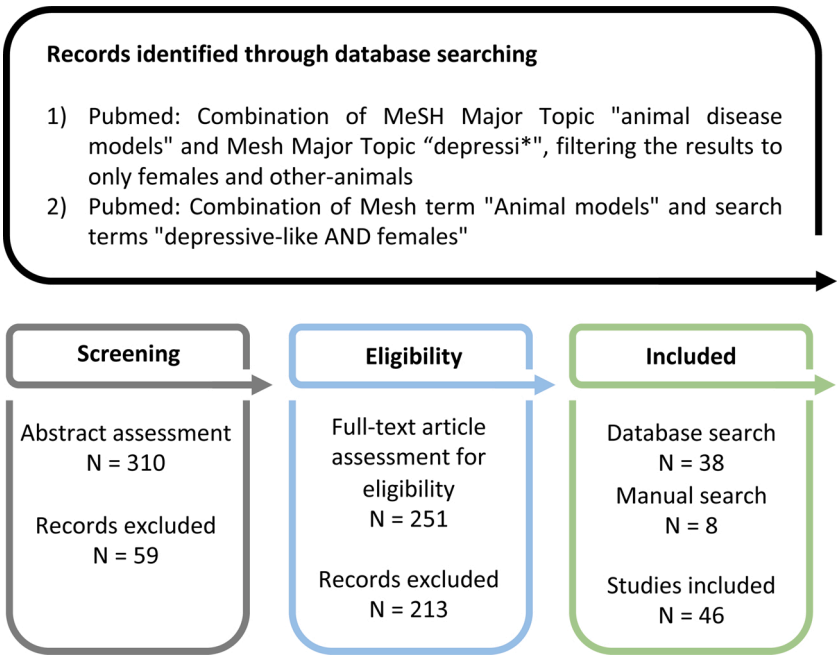

Fig. 2. Flow diagram, depicting the flow of information through the different phases of a systematic review. Data was extracted using a multistep process of study selection centered on search strategy, abstract screening, full-text article screening and eligibility of the studies based on the defined inclusion and exclusion criteria.

2 Pharmacologically-induced animal models;
3 Pathology-induced animal models;
4 Genetic animal models.

Thirty-one studies reporting stress-based animal models in females were found, of which twenty-one (21) were social stress animal models, five (5) maternal separation models and five (5) acute and chronic stress animal models. Pharmacologically-induced female animal models were reported in five (5) studies, pathology-induced animal models in two (2) studies and genetic animal models in five (5) studies.

4. Behavioral outcomes in animal models of depression

Establishing an animal model of such a complex disorder may be a challenging task, given that animal models are not able to display the complex cognitive and emotional traits that characterize the disease, even because some of these are presumably limited to humans. Notwithstanding, preclinical models display some of the core behavioral and physiological traits of depression, referred to as endophenotypes (Gould and Gottesman, 2006), including anhedonia, appetite and sleep disturbances, behavioral despair and anxiety-like behaviors (Krishnan and Nestler, 2011). Moreover, a large variety of behavioral tests can be used to evaluate such traits (Krishnan and Nestler, 2011). One of the core symptoms of depression, anhedonia, or the diminished capacity to experience pleasure, is usually assessed in preclinical models using the state-of-the-art sucrose consumption test (SCT) but also other novel and multi-parametric approaches such as the sweet drive test (SDT) or the cookie test (Mateus-Pinheiro et al., 2013; Surget et al., 2011). In these tests, anhedonic behavior is measured as a decrease in sucrose consumption compared to a baseline (SCT), or as a decreased preference for sweet food (SDT and cookie test) and decreased number of 50 kHz USVs in the SDT. These tests are frequently accompanied by measures of depressive-like behavior, which in rodents can be attained through the forced swim (FST), tail suspension (TST) and open-space swim (OSST) tests; Though this concept has been highly disputed, immobility time in these tests is assumed as a proxy measure of depressive-like behavior (Belovicova et al., 2017), as animal models of depression typically exhibit longer periods of immobility during the FST, TST or OSST and antidepressants are able to reverse this behavior. Anxiety, a highly prevalent comorbidity of depression is evaluated through behavior tests that rely on the conflict between the natural willingness to explore novel environments and potential threat they may pose (Belovicova et al., 2017); these include the novelty suppressed feeding test (NSF), the elevated plus maze (EPM) test, the open field (OF) test, the light-dark box test (LDB) and the marble burying test (MBT). Increased latency to feed in the NSF test is used as an anxiety-like behavior measurement. Due to the exploratory activity of rodents, increased time spent in the periphery (OF) or closed arms (EPM) can be used as an indication of anxiety-like behavior. An increased exploratory behavior of the illuminated compartment (LDB) or increased number of buried marbles (MBT) can also be a predictor of anxiolytic-like or anxiogenic-like activity.

Memory and learning deficits are also found in depressed individuals and these have been shown to play a significant role in the risk of relapse and therapeutic response, suggesting a correlation between these changes and the pathophysiology of MD (Castaneda et al., 2008). In animal models of depression, this cognitive component is measured using cognitive tasks to assess different types of memory and behavioral flexibility (Bushnell, 1999). For example, long-term memory and object location memory can be assessed using the novel object recognition test (NOR). Animals explore the novel object as their natural propensity to the novelty and therefore the recognition measure is calculated by the interval between time spent with novel object and time spent with sample object (object presented during familiarization).

At last, because MD can significantly change the hierarchy in human social groups, sociability and social novelty are also behavioral determinants that can be studied in animal models of depression (Ellenbroek and Youn, 2016). The Three-Chamber test for example assesses cognition in the form of general sociability and interest in social novelty. Rodents normally prefer to spend more time with another rodent and will investigate a novel intruder more than a familiar one. Based on these, the Three-Chamber Test can help identify rodents with sociability deficits.

4.1. *Stress-based animal models*

Stress is one of the most widely used etiological factors in rodent

Table 2
Relevant studies published before February 2021 describing the results from female animal models of depression. Data was extracted using a multistep process of study selection centered on search strategy, abstract screening, full-text article screening and eligibility of the studies based on the defined inclusion and exclusion criteria. The following information was extracted from each study independently: animal model, method of induction, animal-related variables (species, strain, age and diet), study sample size, protocol duration and outcome measurements.

		Animal Variables			Protocol details			
	Reference	Specie	Strain	Age (Beginning of protocol)	Duration	Age (Behavioral testing)	Outcome measurements	Stressor impact
Maternal separation animal models	Maternal separation animal models							
	Dimatelis et al., 2016	*Rattus norvegicus*	Sprague Dawley	2 days	12 days	65 days	ultrasonic vocalizations (USVs)	↓ 22 kHz vocalizations
							open field test	↓ time in center
							forced swim test	↓ immobility
							protein content	↓ phospho-ERK levels in ventral hippocampus
	Donmez et al., 2016	*Rattus norvegicus*	Wistar Han	8 days	13 days	62 days	home cage activity	↓ time grooming
							elevated plus maze test	↑ time in open arms
							novel object recognition test	no impact
	Leuss et al., 2012	*Rattus norvegicus*	Sprague Dawley	2 days	18 days	36 days	forced swim test	↓ immobility
							USVs	no impact
							BDNF protein levels	no impact
							Fear conditioning with escapable and inescapable shock	↑ latency to escape
							protein content	no effect
							cell survival	no effect
	Malki et al., 2014	*Mus musculus*	129S1/SvImJ, C57LB/6 J, DBA/2 J and FVB/NJ	9 days	24h	10 days	gene expression	347 dysregulated genes
	Mourlon et al., 2010	*Rattus norvegicus*	Long-Evans	0 days	22 days	23 days	forced swim test	no effect
							repeated open space swim test (OSST)	↓ swimming activity
							sucrose consumption test	no effect
							novel object recognition test	no effect
Social stress animal models	Chronic social instablity stress							
	Baranyi et al., 2005	*Rattus norvegicus*	Wistar Han	Adult	15 days	*NA*	weight gain	↓ weight gain
							social interaction test	↓ social interaction ↑ agonistic interaction
							elevated plus maze test	No impact
	Breach et al., 2019	*Rattus norvegicus*	Sprague Dawley	Adolescence (30 days)	15 days	70 days	body weight gain	No impact
							adrenal glands weight	No impact
							dendrites in prelimbic cortex	↓ branch number ↓ apical branch length
							spine density	No impact
	Dadomo et al., 2018	*Mus musculus*	CD1	70 days old	28 days	70–98 days	body weight gain	↓ weight
							food intake	↓ intake
							sucrose consumption test	No impact
							adrenal glands weight	No impact
							corticosterone levels	No impact
							plasma ACTH levels	No impact
							estrous cycle	Animals not cycling
	Herzog et al., 2009	*Rattus norvegicus*	Wistar Han	Adult	28 days	*NA*	weight gain	No impact
							food intake	↓ intake
							adrenal glands weight	↑ weight
							corticosterone levels	↑ levels
							prolactine levels	↑ levels
							luteinizing hormone levels	↑ levels
								↑ temperature

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Table 2 (*continued*)

Reference	Animal Variables			Protocol details		Outcome measurements	Stressor impact
	Specie	Strain	Age (Beginning of protocol)	Duration	Age (Behavioral testing)		
						core body temperature	
						sucrose consumption test	No impact
						forced swim test	No impact
						NGF and BDNF levels in hippocampus	No impact
						body weight gain	No effect
Jarcho et al., 2015	*Mus musculus*	CD1	Adult	35 days	*NA*	corticosterone levels	↑ levels
						rearing frequency	No effect
						forced swim test	↑ climbing activity
						sucrose consumption test	↓ consumption
						food intake	No impact
						weight gain	No impact
						mRNA expression in the hippocampus	↓ GR and IL-10 expression
Labaka et al., 2017	*Mus musculus*	CD1 mice	56 days	28 days	56–87 days	corticosterone levels	↑ levels
						estradiol levels	No impact
						estrous cycle	↑ time estrous cycle phases
						whiskers length	↓ length whiskers
						monoamines levels in Hippocampus	↓ 5HT, DA and DOPAC ↑ d 5HIAA
McCormick et al., 2010	*Rattus norvegicus*	Long Evans	Adolescence (30 days)	15 days	47–48 and 72–73 days	BrdU cell count	↓ cell count
						Ki-67 cell count	No impact
						spatial location test	↓ short-term memory
McCormick et al., 2013	*Rattus norvegicus*	Long Evans	22 or 62 days	15 days	46–51 or 70–75 days	vocalizations	↑ number
						contextual fear condition test	Higher sensitivity to stress
						body weight	No impact
Nowacka et al., 2014	*Rattus norvegicus*	Sprague Dawley	56 days	28 days	84 days	adrenal glands weight	↑ weight
						corticosterone levels	No impact
						BDNF expression	No impact
Nowacka-Chmielewska et., 2017a	*Rattus norvegicus*	Sprague Dawley	63 days	28 days	91 days	BDNF expression	No effect
						protein content	No effect
						sucrose consumption test	↑ consumption
						open field test	↓ rearing time
						adrenal weight	↑ weight
Nowacka-Chmielewska et., 2017b	*Rattus norvegicus*	Sprague Dawley	63 days	28 days	91 days	corticosterone levels	No effect
						plasma ACTH levels	No effect
						VEGF expression	↑ levels in hippocampus, amygdala and hypothalamus
						serum VEGF levels	↓ levels
						open field test	↓ rearing and grooming
						elevated plus maze test	↓ time open arms
						weight gain	No impact
Nowacka-Chmielewska et., 2017c	*Rattus norvegicus*	Sprague Dawley	60–63 days	28 days	88–94 days	estrous cycle	No impact
						ACTH/ Corticosterone ratio	↑ ratio
						gene expression	Alterations in the hippocampus, amygdala, prefrontal cortex and hypothalamus
						social interaction test	↓ aggression
Pittet et al., 2017	*Rattus norvegicus*	Sprague Dawley	60–70 days	28 days	95 days	grooming behavior	No effect
						maternal care	No effect
		NA	Adult	49 days	*NA*		↓ time open arms

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Table 2 (*continued*)

	Reference	Animal Variables			Protocol details		Outcome measurements	Stressor impact
		Specie	Strain	Age (Beginning of protocol)	Duration	Age (Behavioral testing)		
							elevated plus maze test	
	Saavedra-Rodríguez and Feig, 2013	*Mus musculus*					social interaction test	↓ interaction
							social Novelty test	↓ interaction
							corticosterone levels	↑ levels
							open field test	↓ time in center
							elevated plus maze test	No impact
	Yohn et al., 2019	*Mus musculus*	C57BL/6J	56 days	49 days	105 days	forced swim test	No impact
							novelty suppressed feeding test	↑ latency to feed
							corticosterone levels	↑ levels
							Dcx cell count	↓ cell count
	Social isolation							
							sucrose consumption test	↓ consumption
	Grippo Angela et al., 2008	*Microtus ochrogaster*	*NA*	60–90 days	28 days	88 days	elevated plus maze test	↓ time open arms
							forced swim test	↑ immobility
							pup exposure	↑ aggression
							body weight	No impact
							Social interaction test	↓ encounters with unfamiliar hamster
	Jacqueline, 1984	*Phodopus sungorus*	*NA*	42 days	21 days	63 days	body weight	No impact
							monoamine levels	↑ Norepinephrine levels
	Kim and Kirkpatrick, 1996	*Microtus ochrogaster*	*NA*	36–38 days	24h	39 days	body weight	No impact
							corticosterone levels	No impact
							forced swim test	No effect
							elevated plus maze test	↓ time open arms
	Leussis and Andersen (2008)	*Rattus norvegicus*	Sprague Dawley	30 days	5 days	36 days	Fear conditioning with escapable and inescapable shock	↑ latency to escape
							protein content	↓ spinophilin in prefrontal cortex
							light/dark box test	No effect
							forced swim test	↑ immobility
							tail suspension test	↑ bouts of immobility
	Martin and Brown (2010)	*Mus musculus*	C57BL/6J	23 weeks (161 days)	35 days	168–196 days	cued and context fear conditioning	No effect
							weight gain	↑ weight gain
							corticosterone levels	↑ levels
	Pisu et al., 2016	*Rattus norvegicus*	Sprague Dawley	Adolescence (30 days)	30 days	60 days	sucrose consumption test	No impact
	Chronic Juvenile Stress							
							sucrose consumption test	↓ consumption
							elevated plus maze test	No effect
	Eiland et al., 2012	*Rattus norvegicus*	Sprague Dawley	20 days	21 days	43 days	forced swim test	↓ immobility
							corticosterone levels	↑ levels
							neuronal morphology	↓ length
Acute or chronic stress animal models	Unpredictable Chronic Mild Stress							
	Malki et al., 2014	*Mus musculus*	129S1/SvImJ, C57BL/6 J, DBA/2 J and FVB/NJ	70 days	14 days	84 days	gene expression (whole-genome oligonucleotide arrays)	350 dysregulated genes
							hole board test	no effect
							sucrose consumption test	no effect
	Marco et al., 2017	*Rattus norvegicus*	Wistar Han	56 days	42 days	98 days	forced swim test	↑ immobility
							two bottle choice test	↑ preference alcohol

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Table 2 (*continued*)

	Reference	Animal Variables			Protocol details		Outcome measurements	Stressor impact
		Specie	Strain	Age (Beginning of protocol)	Duration	Age (Behavioral testing)		
							food intake	no effect
							weight gain	no effect
							protein content	↑ GFAP and CB1R levels ↓ CB2R and NCAM-140KDa
							corticosterone levels	no effect
							open field test	↓ time in center
							elevated plus maze test	↓ time open arms
	Zhu et al., 2014	*Mus musculus*	C57BL/6 mice	56 days	28 days	84 days	novelty suppressed feeding test	↑ latency to feed
							forced swim test	↑ immobility
							sucrose consumption test	↓ consumption
	Photoperiod Manipulation							
							sucrose consumption test	↓ consumption
	Qin et al., 2015	*Macaca mulatta*	*NA*	11–14 years	*NA*	*NA*	Active Behavior	↓ behavior
							locomotion	↓ locomotion
							body weight	↓ body weight
							cortisol levels	↑ cortisol levels
	Corticosterone administration							
							open field test	no impact
							forced swim test	↑ immobility
	Kott et al., 2016	*Rattus norvegicus*	Sprague Dawley	77–84 days	23 days	96 days	estrous cycle	no impact
							body weight	↓ weight
							cell density	no impact
							elevated plus maze test	no impact
							open field test	↓ time in center
							novelty suppressed feeding test	↑ latency
	Mekiri et al., 2017	*Mus musculus*	C57BL6/ Ntac mice	56–70 days	28 days	84–98 days	splash test	↓ grooming
							weight gain	↓ weight
							fur coat state	Altered
							cell proliferation, survival and maturation	no impact
	Lipopolysaccharide administration							
Pharmacologically-induced animal models							sucrose consumption test	↓ consumption
							food and water intake	↓ intake
	Kubera et al., 2013	*Mus musculus*	C57BL/6 mice	90 days	120 days	230 days	cytokine levels	no impact
							corticosterone levels	↑ level
							spleen cells proliferation	↓ proliferation
							spleen and thymus weight	↓ thymus weight
	Pegylated interferon-alpha (IFN-a) administration							
							locomotor activity	no impact
							forced swim test	no impact
	Loftis et al., 2006	*Rattus norvegicus*	Lewis rats	adult	21 days	*NA*	body weight	no impact
							protein content and phosphorylation	no impact
	TNF-alpha administration							
							tail suspension test	↑ immobility
	Manosso et al., 2013	*Mus musculus*	swiss mice	45–55 days old	3 days	48–58 days	open field test	no impact
							protein content and phosphorylation	no impact
	Diabetes induced depression							
							forced swim test	↑ immobility
Pathologically induced animal models	Aswar et al., 2016	*Rattus norvegicus*	Wistar rat	adult	21 days	*NA*	open field test	↓ ambulation, rearing and grooming activities
							elevated plus maze test	↓ time in open arms
							cortisol levels	↑ levels
	Cancer induced depression							

(*continued on next page*)

Table 2 (*continued*)

	Reference	Animal Variables			Protocol details		Outcome measurements	Stressor impact
		Specie	Strain	Age (Beginning of protocol)	Duration	Age (Behavioral testing)		
Genetic animal models	Nashed et al., 2015	*Mus musculus*	BALB/c mice	28–42 days	28 days	56–70 days	sucrose consumption test forced swim test tail suspension test dendritic morphology in the prefrontal cortex	↓ consumption ↑ immobility ↓ immobility ↓ complexity
	Kim et al., 2014	*Mus musculus*	C57BL6/J	10–16 weeks (70–112 days)	20 days	90–132 days	sucrose consumption test C-fos expression corticosterone	↓ consumption ↑ c-fos expression in PFC, Striatum, Nac, hypothalamus ↑ levels
	Meylan et al., 2016	*Mus musculus*	*NA*	35 days	21 days	56 days	forced swim test protein content gene expression Agmat-expressing cells	↑ immobility Agmat upregulation in the prefrontal cortex and hippocampus Agmat upregulation in the cortex ↑ number of Agmat-expressing cells
	Popa et al., 2005	*Mus musculus*	CD1	2–3 months	60 days	2–5 months	locomotor activity sleep disturbances corticosterone body temperature	↓ basal locomotor activity ↑ Slow Wave Sleep 2 ↓ REM sleep Dysregulation of sleep and wakefulness across the estrous cycle ↑ levels no effect
	Will et al., 2003	*Rattus norvegicus*	Wistar Kyoto	70 days	28 days	70–98 days	EEG spectra wakefulness monitoring open field test defensive burying test genetic heterogeneity	↓ power density in the delta frequency range (0.5–4.99 Hz) ↓ levels of wakefulness hypoactivity no effect Reduced variability
	Yacoubi et al., 2013	*Mus musculus*	CD1	3–4 months	28 days	3–4 months	forced swim test elevated plus maze open field test sucrose preference test light/dark box test	↑ immobility ↓ time open arms ↓ time in center ↓ consumption ↓ time light compartment

models of depression (Kessler, 1997). Stress-based models use very different types of stress and use environmental challenges that rodents meet, including social defeat and unpredictable stressors over a long time period (Koolhaas et al., 2017). The severity, duration and unpredictability of the applied stressors are essential parameters to consider in these models (Koolhaas et al., 2017). Herein, we will review stress protocols that are currently validated for females, namely social isolation (SI), chronic social instability stress (CSIS), unpredictable chronic mild stress (uCMS), photoperiod manipulation (PM), single prolonged stress (SPS), chronic juvenile stress (CJS), and maternal separation (MS).

4.1.1. Maternal separation (MS)

In animal models of depression, the timing of stress exposure throughout the rodent's lifetime seems to be one of the most relevant factors for the development of the maladaptive responses leading to dysfunction and behavioral alterations akin to depression (Novais et al., 2017). Prolonged periods of MS induce high levels of stress in the offspring (Lehmann and Ferdon, 2000). The consequences of maternal separation are expressed in adulthood and persist for life, and include, among others, an hyperreactivity of the HPA axis.

Female rats exposed to MS immediately after birth showed decreased swimming activity during the OSST, yet no significant differences during the FST (Mourlon et al., 2010). However, at 36 days old, females that had been previously exposed to MS at birth, reported increased depressive-like behavior in the learned helplessness paradigm (Leussis et al., 2012). Behavioral tests were also performed 62–67 days following MS at birth and these female rats revealed decreased anxiety and depressive-like behavior in the EPM and FST, respectively (Dimatelis et al., 2016; Donmez et al., 2016).

In a different protocol, MS for 24 h in 9 days-old male and female mice led to changes in expression of about 347 genes (Malki et al., 2014). Pathway analysis of these genes revealed a gene network which

included Ppm1a, Ywhaz, Nkfb and Mapk. All four genes have been implicated in both the etiology of MD and the response to treatment and may, therefore, represent a final common pathway to the disorder.

These results suggest that MS causes molecular and behavioral alterations in female animals up to 36 days after stress exposure, but at 62 days old the animals reveal no deficits.

4.1.2. Social stress animal models

Chronic social stress is possibly the most common etiological factor of depressive disorders in humans (Kessler, 1997). In preclinical studies, social defeat is a frequently used social stress in male rodents (Miczek, 1979). This model, based on a resident-intruder paradigm, where male rodents interact aggressively to establish dominance (Miczek, 1979), is not suitable to induce stress in female rodents since they do not exhibit territorial hostility (Haller et al., 1999). Though female rodents establish consistent social structures, their hierarchies seem less steep and despotic when compared to male hierarchies (Williamson et al., 2019). Due to this, preclinical models of depression based on social stress in females mostly rely on social isolation and chronic social instability (Goñi-Balentziaga et al., 2018). Social isolation (SI) consists in the total isolation of an animal in regular home cages with access to water and food *ad libitum*. SI results in neurochemical and neuroendocrine changes, as well as anatomical, physiological and behavioral alterations in both animal and humans (Goñi-Balentziaga et al., 2018). Praire voles (*Microtus ochrogaster*) socially isolated for 28 days developed anhedonia measured with the SCT, increased aggression, as well as depressive- and anxiety-like behavior using the FST and EPM, respectively (Grippo Angela et al., 2008). Contrarily, female rats (*Rattus norvegicus*) isolated for only 5 days already developed anxiety-like behavior that was accompanied by decreased levels of Spinophilin in the prefrontal cortex, a protein important for the regulation of the synaptic cytoskeleton and increased helplessness, often considered as a proxy of depressive-like behavior, following inescapable shock (Allen et al., 1997; Leussis and Andersen, 2008). When isolated for 30 days they developed high corticosterone levels and deficiency of glucocorticoid receptor (GR) and Corticotropin Releasing Hormone Receptor 1 (CRHR1) (Pisu et al., 2016). Female mice (*Mus musculus*) also showed increased depressive-like behavior during the FST when isolated for 35 days (Martin and Brown, 2010). Russian dwarf hamsters (*Phodopus sungorus*) isolated for 21 days revealed decreased sociability during the social interaction test along with increased norepinephrine levels in the diencephalon (Jacqueline, 1984). While other physiological parameters, such as food intake and body weight, were not affected by these SI paradigms, none of these studies evaluated cognitive performance. In comparison, male rats exposed to SI, demonstrated increased behavioral excitability compared with group-housed rats. Increased food consumption and a decrease in plasma leptin levels was observed in isolated male rats (Nikolaienko et al., 2020).

Altogether, chronic SI appears to be an effective stressor across rodent species in females causing deficits akin to human depression (Nikolaienko et al., 2020).

Yet, another commonly used social stress protocol is the chronic social instability stress (CSIS), which includes periods of isolation interspersed with overcrowding. This paradigm has been shown to induce HPA axis activation and anxiety-like behavior in females (Haller et al., 1999). At least two different protocols have been described in rats, a 15- and a 28-day long protocol, with impacts in terms of behavioral and other physiological outcomes.

Adult female rats exposed to CSIS for 15 days revealed decreased social interaction (Baranyi et al., 2005; McCormick et al., 2013) along with neuronal atrophy (Breach et al., 2019). A similar study using adolescent female rats, showed decreased neurogenesis and decreased short-term memory measured with the spatial location test (McCormick et al., 2010). Females exposed to a 15-day protocol did not present anxiety-like deficits in these studies.

Likewise, female rats exposed to a 28 days CSIS protocol presented decreased food intake in 2 studies (Dadomo et al., 2018; Herzog et al., 2009) along with increased body temperature and a dysregulated estrous cycle (Herzog et al., 2009; Labaka et al., 2017). Nowacka-Chmielewska alongside Labaka and Herzog also reported increased corticosterone levels, increased adrenal gland weight, increased anxiety in the EPM test and decreased number of rearings in the OF test (Herzog et al., 2009; Labaka et al., 2017; Nowacka et al., 2014; Nowacka-Chmielewska et al., 2017b, c). At last, decreased aggression in the social interaction test was only reported by one study from Pittet (Pittet et al., 2017) as well as increased anhedonia using the SCT reported from Labaka (Labaka et al., 2017).

Moreover, while BDNF and NGF expression in the amygdala and hippocampus was not affected (Herzog et al., 2009; Nowacka et al., 2014; Nowacka-Chmielewska et al., 2017a), VEGF expression in the amygdala, hippocampus and hypothalamus was reported to be increased in one report (Nowacka-Chmielewska et al., 2017b). VEGF has been shown to impact synaptic transmission and serve as a neurotrophic factor in hippocampal neurogenesis (Jin et al., 2002; McCloskey, 2005), while also influencing memory and learning (Cao et al., 2004). Labaka et al. also observed that GR expression in the hypothalamus and IL-10 expression in the hippocampus were reduced (Labaka et al., 2017). The increased plasma corticosterone and the lower hypothalamic GR expression are suggestive of an HPA axis hyperactivity, which is also a common feature of human depression. Interestingly, and similar to rats, this study also showed that the estrous cycle was dysregulated (Labaka et al., 2017).

At last, female mice, exposed to CSIS protocols with duration ranges from 35 to 49 days, were shown to develop increased anxiety and decreased sociability accompanied by increased levels of plasma corticosterone and decreased hippocampal neurogenesis (Saavedra-Rodríguez and Feig, 2013; Jarcho et al., 2015; Labaka et al., 2017; Yohn et al., 2019).

In males, CSIS induced anhedonic and anxiety-like behaviors, evidenced by a decrease in sucrose consumption and an increase in the number of buried marbles (Perić et al., 2017). Moreover, CSIS in males compromised redox homeostasis, targeting enzymes such as GPx, CAT, GST (Perić et al., 2017). Both males and females presented consistent anxiety-like behavior, however anhedonia is more consistent in males since females were only shown to present anhedonic behavior in one study. The possibility that females are not as sensitive to the SCT paradigm, which was initially developed in males, cannot be ruled out.

Weight gain changes were inconsistent between studies. Females, when exposed to a 15-day protocol, showed decreased weight gain (Baranyi et al., 2005) or no impact (Breach et al., 2019). When exposed to a 28–35 days protocol revealed no changes in 8 out of 9 studies (Herzog et al., 2009; Nowacka et al., 2014; Labaka et al., 2017; Nowacka-Chmielewska et al., 2017a, b; Nowacka-Chmielewska et al., 2017c; Pittet et al., 2017; Jarch et al., 2015), only one study in this range revealed decreased weight gain (Dadomo et al., 2018).

Together, these results suggest that the duration of the CSIS protocol is determinant for the development and installation of anxiety-like behavior, as well as other physiological alterations that were only observed when longer protocol periods were applied. This is in line with other studies showing that, not only the type but also the duration of stress exposure, is a major factor; it's only when stress exceeds a certain duration or intensity that it starts eliciting maladaptive responses thus triggering the development of neuropathological scenarios (Sousa, 2016; Sousa and Almeida, 2012).

Moreover, SI and CSIS, though being both social-based stressors, produce different phenotypes in female rodents, suggesting an impact on distinct neural substrates. While SI did not affect physiological measures, it induced anhedonia, a decrease in sociability, depressive- and anxiety-like behavior. On the other hand, CSIS induced anxiety-like behavior and estrous cycle dysregulation, increased temperature and corticosterone levels, decreased neurogenesis and short-term memory, but did not induce depressive-like behavior.

4.1.3. Acute or chronic stress animal models

Apart from socially induced stress, other stressful experiences have been also shown to be critical to the pathogenesis and development of numerous psychiatric disorders, namely MD, schizophrenia, and anxiety (Heim and Nemeroff, 1999).

Animal models induced by stress exposure vary in the nature of the stressors and their duration (Campos et al., 2013). Here, we gathered data from both acute and chronic stress models, namely unpredictable chronic mild stress (uCMS), photoperiod manipulation (PM), single prolonged stress (SPS) and chronic juvenile stress (CJS).

The unpredictable chronic mild stress (uCMS) is one of the most widely used models to study the neurobiological underpinnings of depression, however, mostly described in male rodents (Frisbee et al., 2015). Amongst the collected studies, uCMS protocols performed in female mice were applied during 14, 28 or 42 days. UCMS induced the dysregulation of 350 genes after 14 days and anhedonia, anxiety- and depressive-like behavior after 28 days (Malki et al., 2014; Zhu et al., 2014). Interestingly, amongst the dysregulated genes, gene pathway analysis showed functional networks associated with neurodevelopmental disorders, cell stress response and cell-signaling. Female rats exposed to uCMS for 42 days also developed depressive-like behavior using the FST, increased GFAP and CB1R protein expression, as well as a decrease of CB2R (Marco et al., 2017). However, no changes in anhedonia, measured in the SCT, following uCMS were detected. Nevertheless, sexual hormones may represent an important confounding factor when evaluating anhedonia as sucrose consumption seems to be influenced by the estrous cycle (Liang et al., 2008).

PM is another protocol capable of inducing depression-related symptoms (Qin et al., 2015), as the length of the lighting period per day is considered as one of the main etiological factors of a subtype of depression – the seasonal affective disorder (SAD) (Shelton et al., 2002). In fact, changes in circadian rhythm have been shown to strongly impact on the individual's psychological and physical homeostasis (Shelton et al., 2002). Though it is a good protocol for the induction of short-term stress responses, chronic exposure can lead to adaptation. One study where manipulation of the photoperiod was performed in *Macaca mulatta* females revealed the development of anhedonia measured in the SCT, decreased active behavior and body weight, as well as increased cortisol levels, which matches clinical reports of SAD (Qin et al., 2015). In males, altered daily activity was observed, such as rest pattern, reduced sleep, and induced depressive-like responses (decreased eating and self-grooming, self-mutilation, and reduced novel object exploration) (Taufique et al., 2018).

The timing of stress exposure is also an important factor to be considered in animal models of depression, as adverse experiences during neural developmental phases can negatively impact adult health (Chang et al., 2019). CJS, mainly through exposure to chronic restraint stress, can mimic this condition in female rats unraveling immediate and lasting effects in adulthood that include increased corticosterone levels, anhedonia (using the SCT) and neuronal atrophy (Eiland et al., 2012). Interestingly enough, this protocol did not induce depressive- or anxiety-like behavior tested in the FST and EPM, respectively (Eiland et al., 2012). In males, chronic repeated restraint stress was shown to induce cognitive dysfunction mediated through impaired dendritic plasticity in SD rats (Sun et al., 2020).

The three different types of stress protocols presented in this section were shown to induce at least some deficits related to human depression, though important differences were observed in outcomes and between species. The deficits shown in animals exposed to uCMS demonstrated that depressive and anxiety-like behaviors were present across studies, however, behavioral findings also show that sucrose intake was inconsistent in female rats exposed to uCMS. Contrarily, CJS did not induce depressive- or anxiety-like behavior in female or male rats, so it might not be accurate to consider it a model of depression. Moreover, still a very small number of studies are available for each protocol in females, reinforcing the need to replicate these findings.

4.2. Pharmacologically induced animal models

Pharmacologically induced models of depression are based on the direct application of clinical observations, namely on hormonal changes in HPA axis, monoamine depletion and dysregulation of the immune system (Krishnan and Nestler, 2011).

Four different types of drug-induced models are presented in this review, including administration of lipopolysaccharides (LPS), Pegylated interferon-alpha, TNF-alpha and corticosterone.

Multiple intermittent LPS administration in female mice was shown to induce anhedonia in the SCT, increase corticosterone levels and decrease spleen cells proliferation and spleen weight (Kubera et al., 2013). The etiological basis of this animal model of depression comes from observations that changes in immune-inflammatory pathways may play a significant role in the pathophysiology of MD (Leonard and Maes, 2012), and might be a suitable animal model of depression also in females. LPS administration can induce neurobehavioral and neuroimmune changes, including increased superoxide production by macrophages in females, but not males. It has been demonstrated that LPS reduces estrogen levels, hence it may be speculated that the increased levels of stimulated superoxide production in LPS-treated female mice is associated with a decrease in the estrogen-induced activation of the complex machinery of antioxidant compounds and enzymes (Kubera et al., 2013). On the other hand, LPS injections do not induce a chronic state of depression in male mice according to the work of Kubera and colleagues (Kubera et al., 2013).

Other studies have also shown the association between inflammation and depression to impact on the levels of tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) (Dowlati et al., 2010). The potential of TNF-α to induce depressive-like symptoms was also evaluated in females, with a reported depressive-like phenotype in the TST (Manosso et al., 2013). In comparison, Yamada et al. (2000) showed that male TNF-α knockout mice display a mild antidepressant phenotype supporting the results in females (Yamada et al., 2000). Along these same lines, administration of the TNF-α inhibitor infliximab during chronic mild stress exposure to male rats significantly decreased immobility time in the FST, increased sucrose consumption during the SCT, and decreased anxiety-like behavior in the EPM (Karson et al., 2013).

On the other hand, chronic administration of pegylated IFN-α, which can lead to the development of depressive disorders in hepatitis C patients (Loftis and Houser, 2004), was not able to induce depressive-like symptoms in female rodents (Loftis et al., 2006).

Stress and depressive-like behaviors are widely recognized to be linked to changes in the HPA axis leading to corticosterone hypersecretion in response to stress (Bao and Swaab, 2019). Interestingly, and for the sake of etiological validity, changes in the HPA axis, namely the hypersecretion of cortisol, also holds true for around half of depressive patients. At least two studies have reported the development of anxiety- and depressive-like behavior in female rats and mice upon chronic administration of corticosterone (Mekiri et al., 2017; Kott et al., 2016), while not affecting neurogenesis (Mekiri et al., 2017), attesting at least a partial validation of this model. Notably, the effect of CORT treatment on males was not so marked because animals did not develop depressive-like behavior (Berger et al., 2019).

4.3. Pathology-induced models

MD that is secondary to other medical conditions, such as cancer and stroke, can be clinically indistinguishable from primary depression (Kang et al., 2015). Depression is, for instance, a common comorbid condition in many cancer cases, affecting more than 10 % of patients (Young and Singh, 2018). Moreover, there is substantial clinical evidence that psychological alterations related to MD precede the diagnosis of cancer (Passik and Roth, 1999), with more than 25 % of women displaying symptoms of depression prior to being informed of their cancer diagnosis (Van Esch et al., 2012). Though yet to be defined,

mechanisms such as inflammation, HPA axis dysregulation and glutamate excitotoxicity may play a role in the onset of MD in the context of cancer (Young and Singh, 2018).

The first successfully validated cancer induced depression (CID) model, developed by injecting 4T1 mammary carcinoma cells in female rodents, has shown to induce the development of anhedonia, measured in the SCT, and depressive-like behavior (using the FST, but not the TST), as well as dendritic atrophy in the prefrontal cortex (Nashed et al., 2015).

MD occurrence is also increased in diabetic patients (Eker, 2018). This link may be explained by the activation of the brain's renin angiotensin system (RAS), brain inflammatory events and HPA axis dysregulation (Aswar et al., 2016). Persistent hyperglycemia in both female and male rats was shown to induce depressive- and anxiety-like behavior as observed by increased immobility in the FST and reduced exploration of the open arms in the EPM test, respectively (Aswar et al., 2016).

These pathology-induced models highlight a strong correlation between the development of MD, inflammation and HPA axis regulation in the context of other medical conditions. This suggests that many other disorders involving these mechanisms are a potential target in the context of MD development and should be further studied as they have crucial implications for disease management, namely in female subjects.

4.4. Genetic models

There is a significant influence of genetic factors in the pathogenesis of depression (Shi et al., 2011). Even though it is largely acknowledged that genetic and environmental factors are key to depression pathophysiology, there is still limited understanding, namely on how robust the genetic predisposition is, and on how genetics shapes adult depression and regulates the susceptibility to stressors (Will et al., 2003).

Many transgenic mouse lines have been developed to target genes of pathways traditionally associated to the pathophysiology of MD (Planchez et al., 2019). Genetic models also include selectively bred mouse and rat lines, selected according to stress sensitivity based on the manifestation of depressive-like behavior in specific tests (Will et al., 2013). Though genetic models alone have small etiological validity as depression models, when combined with a second stimuli they may reflect important genetic vulnerabilities occurring in the human disease.

4.4.1. Selective breeding

Helpless female mice have shown high levels of corticosterone (Popa et al., 2005), anhedonia, anxiety- and depressive-like behavior (Yacoubi et al., 2013). Moreover, they present changes in sleep patterns, including decreased levels of wakefulness, basal locomotor activity, and Rapid Eye Movement (REM) sleep, as well as decreased power density of delta frequencies (Popa et al., 2005). Sleep alterations are also common in depressed patients and include, sleep fragmentation, sleep onset insomnia and disturbances of the REM sleep (Adrien, 2002).

In addition, selectively bred female and male rats show hypoactivity in the OF test and decreased genetic variability. However, it is dubious that this hypoactivity shows increased fear/anxiety since there were no significant differences in the defensive burying test (Will et al., 2003).

4.4.2. Transgenic lines

Concerning transgenic lines, at least two have been assessed as animal models of depression in females, namely Crtc1-/- and Pitx3-/- mice (Meylan et al., 2016; Kim et al., 2014). CREB-regulated transcription coactivator 1 (CRTC1) has an association with behavioral and molecular depressive-like endophenotypes (Meylan et al., 2016). Female mice lacking CRTC1 present a depressive-like phenotype in the FST along with an upregulation of agmatine-degrading enzyme (AGMAT) (Meylan et al., 2016). Agmatine has been previously shown to have antidepressant potential in animal models of depression and has been implicated in mood regulation (Meylan et al., 2016). Pituitary homeobox 3 (*Pitx3*) is a transcription factor with a crucial role in survival and development of midbrain dopaminergic neurons in mammals (Smith et al., 2008; Chung et al., 2005). Behavioral, biochemical and pharmacological data validate parkinsonism phenotypes in Pitx3-deficient mice (Hwang et al., 2003; Nunes et al., 2003). Because nearly 40–50 % of Parkinson's disease (PD) patients display depressive symptoms (Lemke, 2008), Pit3x-deficient mice have been used to evaluate acute stress responses and depressive-like behaviors (Kim et al., 2014). Pit3x deficient female mice showed increased anhedonia measured in the SCT, increased c-fos expression in the prefrontal cortex, striatum, Nac and hypothalamus, and high corticosterone levels in accordance with a depressive-like phenotype (Kim et al., 2014).

5. Discussion and perspectives

Literature has consistently reported that women are at a higher risk of developing MD compared to men, but also that they report more frequently the disorder (Kuehner, 2003). Moreover, the manifestation of MD appears to differ between men and women, though not meaning that this condition could be divided into two distinct forms. Also, important differences in the brains of depressed individuals as well as in treatment response occur between males and females (Eid et al., 2019).

Because non-human animal models cannot capture the human cultural, educational and socio-economic factors, they can be useful constructs to isolate the "biological sex" component, thus eliciting a better understanding of the role of hormones and sexually dimorphic systems. However, there is still an underrepresentation of female animal models of depression in the literature, that likely compromises an accurate comprehension of the disease pathophysiology and treatment in women. This underrepresentation of female rodents in the preclinical investigation of MD can be, at least partly, explained as an attempt to avoid oestrous cycle-related inter-subject variability, as some evidence reveals that the stage of the oestrous cycle can affect behavior and response to drugs (Wang et al., 2017; Halbreich, 2000). Yet, others have shown that female rodents tested anytime within the oestrous cycle are not more variable than males on a broad array of biological traits (Docherty et al., 2019; Prendergast et al., 2014) . Either way, the potential problems that may arise from studying only males, when the purpose is to extrapolate these preclinical findings to the human population, are striking (Docherty et al., 2019; Prendergast et al., 2014).

Over the years, animal models have also shown to be sex-specific for depressive-like behaviors. Dysregulation of the serotonergic signaling system has been implicated in the pathology of mood disorders such as depression in recent years and various rodent models display depression-related behavioral phenotypes. In fact, Pang et al. (2008) and Du et al. (2012), have reported that females present sex-specific phenotypes that could explain the tendency of HD female mice to present more severe depressive-like behaviors than HD male mice (Pang et al., 2008; Renoir et al., 2012; Du et al., 2012). However little work has been done in this area.

Another underestimated topic is the fact that widely applied tests to assess behaviors that are used as proxies of human depression have been designed for male subjects. Adjustments and validation of more adequate behavioral tests that can fully capture putatively different phenotypic presentations, should be carefully considered specifically in this research field. Common anxiety- and depressive-like behavioral tests, such as the FST and EPM, were developed using male rodents only. These classical behavioral paradigms should be re-evaluated and refined or, in addition, the field should consider the development of specific tests for females, which take into account nuances of female physiology and behavior that may influence the final readout. For instance, it has been suggested that sucrose intake might not be as appropriate for female rats, because unstressed females tend to drink more sucrose than males and show a more erratic increase in their consumption (Dalla et al., 2010). As such, novel paradigms to assess such an important phenotype as anhedonia, which are better suited for females, should be

investigated and tested.

As preclinical and clinical research moves toward personalized treatments, it must be considered that the mechanisms contributing to the disease state may vary not only according to sex but also age and developmental stage (Hodes and Epperson, 2019; Palanza, 2001). For instance, susceptibility and resilience to stress depend on 1) the timing of exposure in relation to development, 2) the point across the lifespan at which effects are measured, and 3) the behavioral or biological phenotype under consideration (Hodes and Epperson, 2019). Stress exposure during puberty for example has stronger proximal effects on females, including increased risk of developing mood- and stress-related disorders such as depression, anxiety, and post-traumatic stress disorder. Furthermore, hormonal changes during menopause and andropause affect the processes of memory and emotion in both women and men, with women at higher risk for dementia (Hodes and Epson, 2019). In this review, we focused on 4 different major types of models, mostly based on the etiological factors pertaining depression, including stress-based, pharmacologically- and pathology-induced and genetic models (Fig. 3). Whereas most of these models fulfill at least one of the validity criteria, there are fundamental differences between them, including in the degree of manifestation of the depressive-like signs, namely the core behavioral deficits of anhedonia and depressive-like behavior, but also on additional physiological parameters, that are well-known symptoms of human depression (Fig. 3).

Among the female animal models discussed in this review, SI, uCMS, injection of corticosterone, hyperglycemia and models of selective breeding, all presented both depressive and anxiety-like behavior. Of notice, part of these animal models of depression, such as SI and CORT treatment models, were shown to induce opposite phenotypes in females and males, underlining the need for more insightful understanding of sex-differences in the development and treatment of psychiatric diseases. CSIS and cancer-induced depression appear to only promote the development of anxiety-like phenotype in females and, at last, animals exposed to maternal separation or TNF-a, as well as *Pitx3* mice and *Crtc1* mice only develop depressive-like behaviors.

When observing depression animal models in females as a whole, pathologically-induced animal models and genetic animal models, in contrast to other factors, appear to have very consistent and clear results. Nevertheless, animal models such as social stress have a wider number of studies in females as well as a wider number of protocols and variables that may diffuse the results due to the inconsistencies amongst protocols leading to a somewhat incomplete interpretation. Additionally, their construct validity may be higher when compared to the previous ones. Specific behaviors also stood out after exposure of females to stress for being consistently affected when reported, namely social interaction. However, it appears to face the same validity problem since this type of behavior was evaluated in a short amount of studies.

Protocol standardization arose as a major concern when evaluating these models, as many inconsistencies were found between laboratories with repercussions on reproducibility. For instance, differences in stressors duration, in outcome measurements and the lack of data reporting (e.g. oestrous cycle phase at the time of behavioral testing) were some of the problems we identified. These differences and inconsistencies precluded us from taking further conclusions. Though this problem is not exclusive to female models, it compels the field to measure and report additional measures when studying females, namely hormonal fluctuations and the reproductive experience. Additionally, our analysis unveiled the still very small number of studies using female models of depression, which necessarily leads to an incomplete understanding of the etiology, symptomatology and treatment of psychiatric disorders in women. A few initiatives have been taken to address this gap, such as the Sex as a Biological Variable (SABV) mandate introduced by the U.S. National Institutes of Health (NIH) in 2016, as part of a broader initiative to improve the rigor and reproducibility of research (Shansky and Murphy, 2021). Because at present, the success of this and other initiatives depends entirely on the cooperation of researchers, there is an urgent need to implement standard procedures and good practices for the field to support replication across laboratories. In order to determine mechanisms for stress risk and resilience, establishing rigorous and widely reproducible models of chronic stress in female models is critical to advance research on the biological basis of sex differences and sex-specific mechanisms of stress vulnerability (Lopez and Bagot, 2021).

The study of more suitable etiological factors for animal models of depression, the refinement of testing and readouts interpretation specifically for females will certainly improve research in the depression

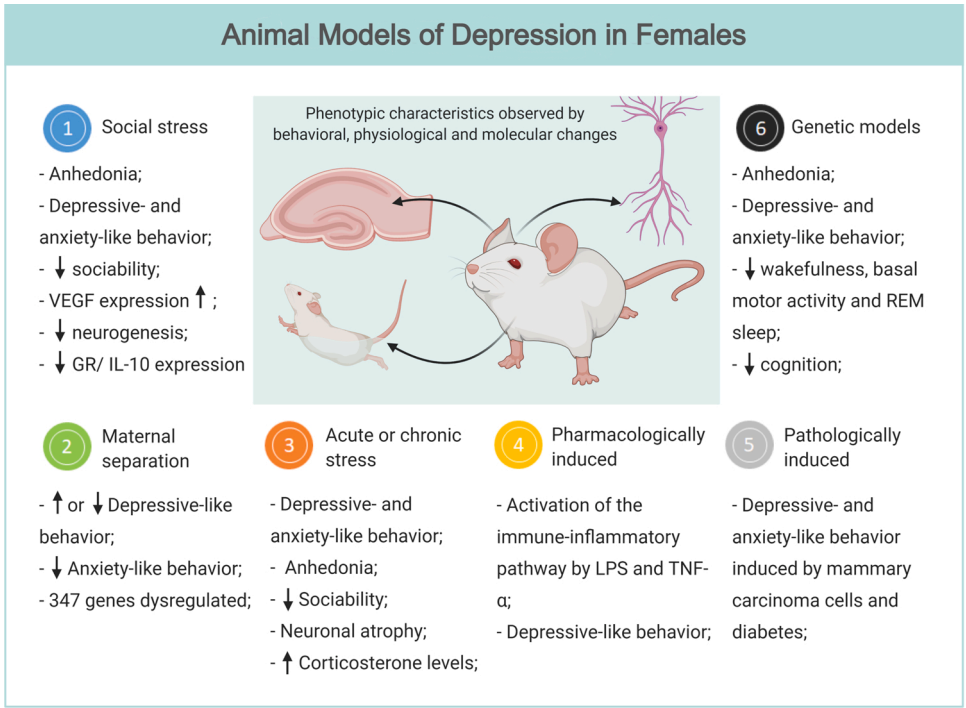

Fig. 3. Overview of the identified animal models of depression performed in females and corresponding phenotypic characteristics. Among the female animal models discussed in this review, SI, uCMS, injection of corticosterone, hyperglycemia and models of selective breeding, all presented both depressive and anxiety-like behavior. On the other hand, CSIS and cancer-induced depression develop an anxious phenotype. At last, animals exposed to maternal separation or TNF-a, as well as pitx3 mice and crtc1 mice only develop depressive-like behaviors.

field. Also, the inclusion of female animals in all preclinical basic and translational studies, as well as data replication and improved reporting are required to validate the models and study methodologies. Together, these will certainly improve the understanding of the disease pathophysiology and the development of better therapies.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors report no declarations of interest.

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