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Review

Stress-based animal models of depression: Do we actually know what we are doing?

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ABSTRACT

Depression is one of the leading causes of disability and a significant health-concern worldwide. Much of our current understanding on the pathogenesis of depression and the pharmacology of antidepressant drugs is based on pre-clinical models. Three of the most popular stress-based rodent models are the forced swimming test, the chronic mild stress paradigm and the learned helplessness model. Despite their recognizable advantages and limitations, they are associated with an immense variability due to the high number of design parameters that define them. Only few studies have reported how minor modifications of these parameters affect the model phenotype. Thus, the existing variability in how these models are used has been a strong barrier for drug development as well as benchmark and evaluation of these pre-clinical models of depression. It also has been the source of confusing variability in the experimental outcomes between research groups using the same models. In this review, we summarize the known variability in the experimental protocols, identify the main and relevant parameters for each model and describe the variable values using characteristic examples. Our view of depression and our efforts to discover novel and effective antidepressants is largely based on our detailed knowledge of these testing paradigms, and requires a sound understanding around the importance of individual parameters to optimize and improve these pre-clinical models.

1. Depression: a silent epidemic

Major depressive disorder (MDD), also known as clinical depression, is a serious mood disorder with a high prevalence in all developed countries. In 2007, a study from the World Health Organization (WHO) estimated that depression affected health more profoundly compared to many other chronic diseases (Moussavi et al., 2007). As depression is often comorbid with other health conditions, there is an urgency to both improve its treatment and reduce its burden. Although clinical symptoms of depression vary, patients generally struggle to cope with their daily personal and social lives. They experience loss of self-worth, disturbed sleep, reduced pleasure and concentration, increased fatigue and irritability (Paris, 2014). At its worst, depression is an important risk factor of suicide (Angst et al., 1999). In 2012 alone, depression caused a million deaths worldwide and contributed to 12.5% of all suicide cases caused by mental disorders (Marcus et al., 2012; WHO, 2012), representing a serious public health concern till today. The complexity of depression is reflected from the variety of known causal factors of this disorder, such as genetic/epigenetic, environmental, medications and secondary to other neuropsychological conditions. Although the genetic factors are thought to contribute up to 50% of depression cases (Fava and Kendler, 2000), recent advances in the epigenetics of depression suggest that regulation of certain genes but not their actual sequence may contribute to the high heritable component of depression (Krishnan and Nestler, 2008; Krishnan and Nestler, 2010).

It is widely known that chronic stress is associated with the onset of depression. There is significant evidence proving that most of the depression episodes are likely consequence of prolonged stressful life (Dumont and Provost, 1999; Frazer and Morilak, 2005; Hammen, 2005; Salavecz et al., 2014). Chronic or lifetime stress is a strong predictor for the development of depressive symptoms (Gutman and Nemeroff, 2011), associated with pathophysiological changes in brain function and structure. For instance, it has been shown that stressful

Abbreviations: MDD, major depressive disorder; WHO, The World Health Organization; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; FST, forced swimming test; TST, tail suspension test; LH, learned helplessness; HPA, hypothalamic-pituitary-adrenal; CMS, chronic mild stress; NS, non-shock; IS, inescapable shock; ES, escapable shock; SIA, stress-induced analgesia

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Table 1
Classification of current animal models of depression and description of their main pros and cons as described in the literature.

Main Classes	Models	Stressor	Main Advantages	Main Disadvantages	Example references
Acute and sub-chronic stress-induced	FST	Inescapable forced swimming	Fast induction and drug-screening, cheap & easy setting	Unspecific response to non-antidepressants, weak validities, present single symptom	(Chourbaji et al., 2005; Cryan et al., 2005a; Slattery and Cryan, 2012)
	TST	Tail suspension			
	LH	Inescapable electric shocks	Strong validation, variety of behaviors and symptoms	Comprehensive protocol & equipment, strong stressors	(Chourbaji et al., 2005)
Chronic stress-induced	CSI	Prolonged-chronic isolation	Strong validity, variety of depressive symptoms	Long experimental duration, complex setting, anxiety symptoms	(Hill et al., 2012)
	CSD	Repeated bouts of social subordination			
	CMS	Chronic expose to alternate and variable stressors	Strong validity, long lasting symptoms	Long experimental duration, anxiety symptoms	
Models of secondary depression	HPA axis dysregulation	Administration of corticosterone	Correlation with pathophysiological and molecular mechanisms of depression, present various depressive symptoms	Questionable correlation with depression	(O'Reilly et al., 2008; Pariante and Lightman, 2008; Udina et al., 2014; Van Winkel et al., 2008)
	Retinoic acid model	Prolong use of retinoic acid			
	Immune system dysregulation	Administration of pro-inflammatory cytokines			
Immutable models	Olfactory bulbectomy	Surgical removal of olfactory bulb	Variety of symptoms, specificity in studies of particular pathways	Indistinguishable adaptation mechanisms	(Kelly et al., 1997; Overstreet and Wegener, 2013)
	Genetically modified models	Genetically selected for hypersensitivity to drugs, receptor knockouts etc.			

FST: Forced swimming test, TST: tail-suspension test, LH: learned helplessness, CSI: chronic social isolation, CSD: chronic social defeat, CMS: chronic (unpredicted) mild stress.

situations over an extended period of time can lead to reduced hippocampal size, a brain area that regulates mood in both animals and humans (Czéh et al., 2001). This strong link between stress and depressive symptoms have been used as a cornerstone of creating animal models of depression, which are vital for the study of this disorder as well as for research in novel antidepressant medications.

1.1. Antidepressants

The molecular pathology of depression is still not very well understood and current pharmacological treatments rely heavily on the monoamine theory of depression, which postulates that reduced levels of serotonin, dopamine and noradrenaline in the brain are linked to the manifestation of depressive symptoms (Koch et al., 2002). Current antidepressants used in the clinic are largely based on this theory and aim to increase levels of monoaminergic neurotransmitters in the synaptic cleft through inhibiting reuptake or the reduction of metabolism, ultimately increasing the activity of hypothalamic-pituitary-adrenal (HPA) axis (Frazer and Morilak, 2005; Pariante, 2003). These drugs include selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). While the development of SSRIs in the 1980s significantly improved the tolerability of antidepressant therapy compared to TCAs, the pharmacological antidepressants still remains largely suboptimal and challenging. It is important to note that conventional antidepressants exhibit varying effects in different animal models of depression. Furthermore, differences have even been observed in the same model across tests and laboratories. In the FST, imipramine (15 mg/kg/day, i.p.) reduced depressive-like symptoms by 82.4%, (Vitale et al., 2009a), which was nearly twice the effect seen in the LH model (54.4%) using the same dose and treatment duration (Joca et al., 2003). In contrast, desipramine decreased the depression-like symptoms by 45.5% in the LH paradigm (Reed et al., 2009), whereas twice of the dose had to be applied in the FST to achieve the same effect (Carr et al., 2010). It is worth noting that even the same class of drugs showed inconsistent effects in the same model. For example, the MAO-inhibitor, tranylcypromine, significantly decreased the symptoms in the FST whereas another MAO-inhibitor, phenelzine, showed no effect at the same dose (Bourin et al., 2002). However, phenelzine used by another group did reduce behavioral despair in the rat FST (Khursheed et al., 2014). Since the pharmacological effects of antidepressants also heavily depend on the experimental design, the differences of model parameters could be one of the major reasons that directly affect the inconsistency of test results. Therefore, in addition to the development of new, improved therapies, it is essential to develop and improve animal models of depression in parallel that are associated with consistent results across studies and labs, as well as increased accuracy. Although current animal models were crucial to develop and evaluate current antidepressant therapies over the last two decades, a number of limitations have to be addressed, to maximize our efficiency to discover effective, new antidepressant drugs.

1.2. Current animal models of depression

A number of pre-clinical models are currently used to evaluate the pharmacological effects of potential antidepressants (Krishnan and Nestler, 2008). These models have been evaluated on the basis of three major criteria, or 'validities': construct validity (the experimental conditions of the animal model replicate the cause of disease in patients), face validity (the symptoms observed in the animal model replicate clinical features of the disease), and predictive validity (the animal response to the drugs can predict the potential drug activities in patients) (Willner and Mitchell, 2002). The more valid a particular animal model is, the more accurate and reliable are the data it produces. Current animal models of depression can be generally

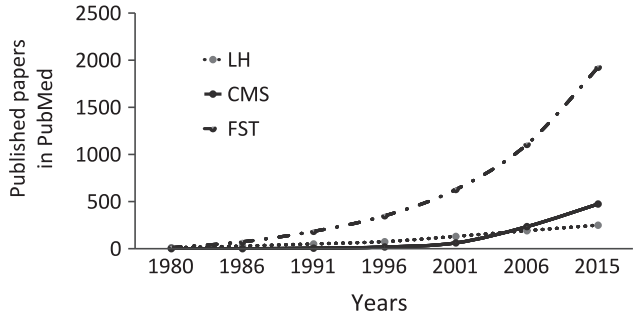

Fig. 1. Cumulative number of original research articles published from 1/1/1980 to 31/12/2015 listed in PubMed that used the forced swimming test (FST), the learned helplessness (LH) or the chronic mild stress (CMS) as primary models of depression.

classified in four main classes based on the nature of their induction phase, as shown in Table 1.

The first class is based on the application of acute or sub-chronic stressors for the induction of depressive-like symptoms. It includes behavioral models such as the forced swimming test (FST) and the tail suspension test (TST), which are also called as despair-based models. They are frequently used in fast drug-screening studies of novel antidepressants, because of their easy and cheap set-up, as well as their acceptable face and predictive validities (Borsini and Meli, 1988; Chourbaji et al., 2005; Frazer and Morilak, 2005). However, these models lack the essential construct validity and only produce limited short-lasting depressive-like symptoms. The learned helplessness model (LH) of this class is probably the only one that stands out since it offers stronger validation and medium-term lasting behavioral and related cognitive symptoms. Nevertheless, the electrical shocks that used in this model and the comprehensive equipment that required establishing this model limit the use of this model. The second class is based on long-term exposure to various stressors as triggering mechanism for the manifestation of depressive-like symptoms such as anhedonic-like behavior, aversion of activity and changes in appetite etc. It includes three main animal models of depression, the chronic mild stress (CMS), the chronic social defeat (CSD) and the chronic social isolation (CSI) models. The CMS model demonstrates particularly strong validities, in term of generating anhedonic-like symptoms in stressed animals (Wiborg, 2013). However, anhedonic-like behavior, a crucial index of depressive mood in this type of models, is not only specific to depression but also seen in schizophrenia and substance withdrawal (Der-Avakian and Markou, 2012; Nestler and Hyman, 2010; Strauss and Gold, 2012). The third class of depression models applies various biochemical and pharmacological concepts to mimic clinical observations. The models in this class are named according to the pathophysiological and molecular pathways of depression that they manipulate. They manifest either potential molecular sources of the depressive symptoms, or adaptive/responsive mechanisms of depression, for example, the function of HPA axis (Dinan, 1994; Johnson et al., 2006; Pariante and Lightman, 2008), to induce hippocampus inhibition by administration of retinoids (Bremner and McCaffery,

Table 2
Examples of antidepressant effects in three stress-based models of depression using different animal species and strains. The reductions of depressive-like symptoms in experiment group were presented as percentages from stressed-saline group. There are obvious variations in the observed response between studies using the same model, same treatment and in similar species or strains. Methodological differences in a model's protocol parameters are believed to play an important role in these variations. (n/a: no significant changes from controls)

Model	Recorded behaviors	Animal species and strains	Tested antidepressants	Dose (mg/kg/day)	% reduction of depressive-like symptoms in experiment group	Reference
FST	Immobilization during monitoring phase	Wistar rat	desipramine	30, i.p.	−76.8%	(Gavioli et al., 2004)
		Wistar rat	imipramine	15, i.p., 22 days	−82.4%	(Vitale et al., 2009b)
		Wistar rat	imipramine	15, i.p.	−25.0%	(Porsolt et al., 1978)
		Wistar rat	imipramine	15, i.p.	n/a	(Khursheed et al., 2014)
			phenelzine	10, i.p.	−62.5%	
		NIH Swiss mouse	imipramine	10, i.p.	−43.3%	(Li et al., 2006)
		NIH Swiss mouse	desipramine	20, i.p.	−60.0%	(Lucki et al., 2001)
		C57/BL6 mouse	desipramine	20, i.p.	−15.4%	
		Swiss mouse	tranylcypromine	4, i.p.	−13.0%	(Bourin et al., 2002)
			phenelzine	4, i.p.	+4.0%	
	Immobilization counts	Sprague Dawley rat	fluoxetine	10, i.p.	−31.3%	(Brenes and Fornaguera, 2009)
		Sprague Dawley rat	fluoxetine	10, i.p.	−31.3%	(Page et al., 1999)
		Sprague Dawley rat	desipramine	20, i.p.	−45.5%	(Carr et al., 2010)
		Wistar-Kyoto rat	desipramine	20, i.p.	−34.9%	
LH	Escape failures	Wistar rat	imipramine	15, i.p., 22 days	−45.5%	(Joca et al., 2003)
		Wistar rat	imipramine	32, i.p.	n/a	(Petty et al., 1992)
		ICR mouse	desipramine	10, p.o.	−52.9%	(Tohda and Mingmalairak, 2013)
		CD rat	fluoxetine	50, p.o.	n/a	(Greenwood et al., 2007; Ji et al., 2016)
			imipramine	50, p.o.	−68.2%	
	Escape latency	Sprague Dawley rat	escitalopram	10, i.p.	−40.9%	(Reed et al., 2009)
			desipramine	10, i.p.	−45.5%	
		Swiss mouse	fluoxetine	30, i.p.	−43.5%	(Holanda et al., 2016)
CMS	Amount of sucrose consumption	Wistar rat	imipramine	10, i.p.	−46.2%	(Papp et al., 1996)
		Wistar rat	imipramine	10, p.o.	−54.5%	(Papp et al., 2016)
		SD rat	fluoxetine	10, i.p.	−60.0%	(Lee et al., 2015)
		Wistar rat	imipramine	10, i.p.	−57.8%	(Duda et al., 2016)
	Preference of sucrose solution to plain water	Wistar rat	imipramine	10, i.p.	−24.7%	(Bessa et al., 2009)
			fluoxetine	10, i.p	−21.9%	
		Wistar rat	fluoxetine	10, i.p.	−10.8 %	(Melo et al., 2015)
		C57BL/6 mouse	imipramine	20, i.p.	−12.4%	(Zhang et al., 2016)
		C57BL/6 mouse	imipramine	30, p.o.	−30.0 %	(Yan et al., 2015)

2008) and to change immune function by administration of specific cytokines (Dunn et al., 2005; Gold and Irwin, 2006). This class is not only designed to generate depressive symptoms, but also as a tool of studying the pathophysiology of depression and involvement of particular molecular pathways. However, the major limitation of this type of models is that it is associated with a wide range of behavioral abnormalities, which may be not specific to depression (Patterson, 2011; Sartori et al., 2012).

The fourth class of animal models of depression involves the application of genetic and surgical techniques, which can permanently change animal's phenotypes and behaviors. Those models include olfactory bulbectomized rodents (Kelly et al., 1997; Mucignat-Caretta and Caretta, 2004), genetically modified strains such as the stress-sensitive Flinders rat (Overstreet, 1993) and specific receptor-knockout murine that have been observed to manifest depressive-like symptoms (for a thorough review on genetically modified mice strains used as animal models of depression refer to Cryan and Mombereau's study (Cryan and Mombereau, 2004)). Since only about 10–50% of rodents successfully develop depressive-like symptoms (Overstreet, 1993), the use of strains that are vulnerable to stress could increase the face validity of animal models of depression. Although these animal models are particularly useful when studying specific aspect of the pathophysiology and pharmacology, they offer very poor construct validity compared to other classes. Generally, models of secondary depression and the immutable models of depression are not only able to produce various stress-induced symptoms, but also can be used to study depression-induced cognitive changes by combining them with models of learning and memory (Hozumi et al., 2003). In addition, these pre-clinical models can be used via combining with other rodent models of depression, such as the FST (Nowak et al., 2003). Such combination can help to investigate the onset mechanisms of depression without inducing additional physical stimuli. Nevertheless, the present review concentrates only on acute stress- and chronic stress-based models that will be discussed in details.

The three most popular and widely used pre-clinical models of depression are the FST, the LH and the CMS model. Bibliometric data produced from analytical searches using the PubMed database between 1980 and 2015 reveal a trend of fast increasing number of publications using these models, at varying grades (Fig. 1).

The FST model appears to be the most 'popular' model in pre-clinical research for depression (72.7% of the total published papers using animal models of depression) and shows the steepest increase in published articles among the three models, probably due to its low set-up cost, simplicity and short experimental duration. On the other hand, the powerful validity and the manifestation of long-lasting symptomatology using the CMS are probably its strong points that bring it the second in popularity. Finally, the number of articles using the LH model have shown a substantial increase in publications about five times during these 20 years of its use. Clear advantages and disadvantages exist for all these three models, which will be discussed further in this review along with the technical variability that exist in these models.

Although it generally accepted that the documented variation of face validity in these models could be explained based on their conceptual and methodological differences, it appears that substantial differences in behavioral responses are also observed between studies that use the same animal model, as shown in Table 2. For example, the use of specific strains, such as the stress-sensitive Flinders rats, can be beneficial to obtain better readouts and reduce variance for selected behavioral paradigms. Nevertheless, differing results are also reported for studies using the same animal strain. In addition, small alterations of methodological protocols contribute to the divergent observed animal responses in different studies. Due to the highly technical nature of these behavioral models, research groups tend to tailor the technical parameters of their experiments (such as time length of induction, intensity and duration of stressors, types of observational arenas, modes of measurement etc.), according to their particular research needs and experimental observations. As a result, there is a huge number of protocols produced, which amplifies various variations in animal behavioral responses. In this review we provide a methodological "bird's eye view" of these three most-frequently used animal models of depression (namely the FST, the LH, and the CMS models), in an effort to highlight the role of protocol variability in animal model tuning and validation.

2. Three frequently used animal models of depression

2.1. Forced Swimming Test (FST)

The forced swimming test was originally described as "a new method for inducing in rats a behavioral state resembling depression" (Porsolt et al., 1977a). This model is described to induce a low-mood state, so-called "behavior despair", in rodents in a fairly short period of time. Because only limited time is needed for induction of depressive-like symptoms in this models, contrary to the development time of clinic depression in patients, the FST is now only seen as a quick tool to screen for potential antidepressants (Browne, 1979a; Lucki, 1997). Nevertheless, at present, it has become the most widely used pre-clinical model to assess antidepressant activity, due to its ease of use and its ability to predict a broad range of antidepressant activities (Cryan et al., 2005b). In this model, the rodents are placed into a cylinder with cold water and are forced to swim to survive from an inescapable situation. The term of immobility is used to define the floating of the animal when in the water, without efforts of swimming but only necessary minor movements required to keep the head above the water. Immobility is used as the predominant index of the level of behavioral despair and, therefore, increased duration of immobility or counts of immobile activity are the characteristic of depressive-like behavior.

The original description of the rat FST procedure contained two phases (Porsolt et al., 1977a), with rats initially receiving a 15-minute forced swimming training, preceding a six-minute testing session at 24 hours after training (Fig. 2). A mouse FST model was modified by using only a single 15-min session for testing the efficacy of potential antidepressant drugs to reduce immobility levels (Porsolt et al., 1977b).

Because of its simplicity, this paradigm is considered the most suitable for high-throughput screening of antidepressant compounds in rodents. On the other hand, the FST can also be used after chronic stress exposure (Garcia-Marquez and Armario, 1987; Strekalova et al., 2004), as a follow-up method to measure the development of depressive-like symptoms in a chronic-stress-based model and to quickly evaluate drug activity (Luo et al., 2008). This feature promotes the use of the FST not only as a model *per se* to predict antidepressants activity, but also as an assessment of depressive-like symptoms that have been induced by other depression paradigms. Recent modifica-

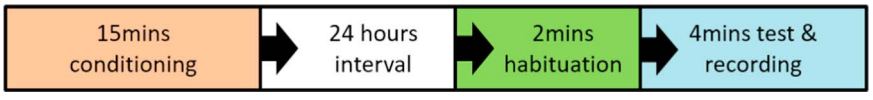

Fig. 2. Overall protocol of the forced swimming test. Animal training (conditioning to the circumstances) is followed by a single day interval before re-exposure to the experimental setting, where after habituation behavior is recorded. Main behavioral measurements include immobility times and counts of specific time-blocks of continuous activity (i.e. climbing, swimming).

tions were introduced based on different observed activities, as well as differences in the behavioral pharmacology among drugs. Active swimming, such as diving, climbing and swimming are now also routinely measured individually (Detke et al., 1995). In addition, it has been shown that serotonergic and noradrenergic antidepressants differentially influence the swimming and climbing behavior in this model. The serotonergic system is shown to mediate the swimming motion, whereas noradrenergic antidepressants enhance the climbing behavior (active movements with forepaws in and out of water, usually against the cylinder wall) (Detke et al., 1995), which suggests that it might be important to distinguish the monitoring of these behaviors when using this model. Both tricyclic antidepressants (TCA) (Barros and Ferigolo, 1998) and serotonin–norepinephrine reuptake inhibitors (SNRIs) (Rénéric et al., 2002; Xue et al., 2013) increase both climbing and swimming activities. Due to the fact that increases in locomotion can be confused with decreased immobility as an index of behavioral despair, most studies that use the FST model combine it with data from the open field arena (e.g. open space that records movement) to assess potential hyperactivity. All clinically used antidepressants show efficiency in the FST without affecting locomotion in the open field test, compared to the immobility scores and locomotion of non-treated controls (Saitoh and Yamada, 2012), which indicates that the swimming, climbing and diving behaviors in the FST can be increased without inducing hyperactivity.

Although the FST is used for nearly three decades, the strength of the validity of the FST is still disputed (Su et al., 2013). Recent modifications to this model are implemented either to increase sensitivity and specificity to the treatment, or to improve the consistency of results between studies or research groups. Table 3 summarizes the main parameters that differentiate among studies using the FST as a model in depression. Even simple model parameters such as the cylinder diameter, the depth of water and the water temperature are sensitive enough to lead to variations in measured responses (Castagné et al., 2011). For example, a smaller cylinder diameter has been accused of generating more false positive responses due to the animals' rotatory locomotor activity (Sunal et al., 1994), which is another argument for the inter-validation of the FST measurements with a locomotion test like the open field. On the other hand, water depth is one of the predominant differences among studies. In the rat model of the FST, a water depth of 30 cm was reported to produce more "behavioral despair" (Borsini et al., 1986), compared to a depth of 15 cm that was used in the original protocol (Porsolt et al. 1977a). The depth of the water should be sufficient to lead to non-supporting swimming in relation to the rats' size and full leg extension. Finally, both high and low water temperatures have been shown to result in short-lasting immobility and false-positive results, suggesting that water temperature should be ambient for optimal results (Arai et al., 2000; Taltavull et al., 2003).

The specificity of the FST for screening antidepressant-like agents has been widely questioned (Petit-Demouliere et al., 2005), since a large variety of non-antidepressant drugs in the clinic have been shown to exhibit antidepressant-like effects in this model, in comparison to conventional antidepressants (Betin et al., 1982; Górka and Janus, 1985; Nagatani et al., 1984). One of the earliest studies in the FST showed that the anticholinergic scopolamine and the antipsychotic clozapine significantly reduced the "behavioral despair" observed in the FST (Browne, 1979b). In addition, injections of antidepressants immediately decrease duration of immobility in this model, which conflicts with the clinical onset of conventional therapies, which usually takes 2 to 3 weeks (Artigas, 2001). What's more, this model has been questioned regarding its appropriateness to use "immobility" as a behavioral index of psychological despair, without factoring the "energy saving strategy". This strategy is used as a natural response of rodents to increase their chance to survive in an environment where they are forced to swim but cannot escape (Nishimura et al., 1988a). This immobilization behavior is even equal to freezing response that seen in rodents when experiencing fear (Borsini et al., 1986). However, it was proposed that immobilization should be considered as a natural product of learning and memory after exposure to the stress of acute forced-swimming, instead of "behavioral despair" or depressive-like symptoms (de Kloet and Molendijk, 2016). According to this hypothesis, stress exposure is suggested to increase the production of stress

Table 3
Characteristic examples of variability in major methodological parameters in the forced swimming test protocol. Studies in mice show higher degree of variability in the protocol parameters used than rat studies. Training session duration and testing duration show the largest variability. Up to date, there are no meta-analysis data that document an advantage of a particular parameter value over another in terms of model validation.

Training duration (min)	Animal species	Cylinder size		Water level (cm)	Water temp. (°C)	Testing duration (min)	Main measurements of recorded behavior	Example references
		Height (cm)	*Diameter* (cm)					
0	CD mouse ddY mouse C57/BL6 mouse	16–25	10	6–15	21–23	6	Total duration of immobility during the last 4 min	(Porsolt et al., 1977b) (Baamonde et al., 1992) (Redrobe et al., 2002) (Kita et al., 1997) (Nieto et al., 2005)
15	C57BI/6J mouse	*Nd*	*Nd*	*Nd*	~30	4 trials×6 mins +7min inter-trial interval		(Reindl et al., 2008)
2 trials x10 min +24 h inter-trial interval	ICR mouse	*Nd*	*Nd*	15	~23	6		(Saitoh et al., 2004)
15	Swiss mouse	18.5	12.5	13.5	25 ± 1	5	Total duration of immobility	(Gavioli et al., 2003) (Vergura et al., 2006)
0	SD rat	46	20	30	25 ± 1	15	Counts of immobility, swimming and climbing	(Jutkiewicz et al., 2004; Jutkiewicz et al., 2005; Torregrossa et al., 2005; Torregrossa et al., 2006; Zhang et al., 2007)
15	SD rat	40–46	18–20	30	25 ± 1	5	Total duration of immobility	(Porsolt et al., 1977a) (Vergura et al., 2008)
15	Wistar Kyoto rat Wistar rat	46	20	30	24–26	5	Total duration of immobility, swimming and climbing	(Carr et al., 2009) (Rizzi et al., 2011)

Nd: Not described in the study.

hormones, which lead to the acquisition of immobility memory. This hypothesis is supported by the observation that inhibition of the glucocorticoid receptor decreases the duration of immobilization in the testing phase of the FST (Veldhuis et al., 1985). The switch from active (i.e., swimming, diving and climbing) to passive coping (immobility and floating) in this model would illustrate a successful adaptive strategy for rodents to prolong their survival chances under inescapable circumstances. As such, learning and memory is seen to heavily determine this behavioral change (West, 1990). In line with this notion, it was suggested that the effect of antidepressants such as imipramine in the FST was more likely to prevent the acquisition of immobilization memory, rather than to reverse the "behavioral despair" (De Pablo et al., 1989), which could well explain the rapid results of antidepressants observed in this model. Although these arguments are the basis for the weak validity associated with the FST, it is still unknown whether protocol parameters such as number of training sessions, testing duration and equipment dimensions affect the strength of this model's validities in any other ways. Comparative studies are needed to address this question, by testing a range of different parameters in the same laboratory settings and looking at the effects of these parameters on swimming activities.

2.2. Chronic mild stress (CMS)

The chronic mild stress model (CMS) was developed as a preclinical model of depression more than two decades ago (Katz, 1982). Since then, different groups have developed different versions of protocols in an effort to improve its efficiency and tailor it to the particular needs of their research (Fedotova, 2012; Feng et al., 2012; Nikseresht et al., 2012; Salehi-Sadaghiani et al., 2012; Willner, 1986). The CMS is mainly designed to produce the anhedonic-like behavior and general loss of interest towards rewards, as seen in most depressive patients. In this animal model, the behavioral deficits are induced over a period of 3–9 weeks by imposing a variety of stressors in a semi-random manner intermitted by various intervals (Fig. 3), thus hindering the potential development of adaptation mechanisms that are usually seen with continuous application of a single stressor (Frisbee et al., 2014).

The natural preference of rodents to sweetened water is considered to parallel human behavior towards reward. At the same time, a loss of interest towards reward is one of the clinical characteristics of patients with depression (Forbes et al., 2010). Therefore, the amount of sweetened versus plain water consumed before and after exposure to stressors is used as index of depressive-like symptoms in the CMS model (Grønli et al., 2004). Different stress stimuli are used between measurements, such as water and food deprivation and cage tilting, which reduces the intake of sweetened water compared to non-stressed control animals (Muscat and Willner, 1992). Other behaviors, such as, grooming frequency, reduced sexual activity, aggression and reduced locomotion can also be measured as indicators of depressive-like behavior (Mutlu et al., 2009, 2012).

The nature of the protocol allows a combination of a large variety of stressors, with different number/length of intervals and the measurement of different behaviors as a response to rewards (Table 4). Grouped housing, overnight illumination, restraintstress, and day-night cycle disturbance and flashing light are only a few stressors in a long list of interchangeable stimuli, which are applied to the animal over a certain period of time, intermitted by a variety of intervals (i.e. 1–2 stressors per day with random intervals, 1 stressor per day with 10 intervals etc.). Measurements of sucrose consumption during the experiment and preference of sucrose solution over water are examples of recorded behaviors in this model. In addition, the total length of these tests that varies among the CMS studies from 3 weeks to 9 weeks, contributes significantly to the large diversity in the experimental protocols of the CMS model. Until today, no study has focused on the effect of these variations of the CMS protocol to the validity or the efficiency of the model. Usually research groups choose a particular combination of stressors and timing based on previous practical experience and/or the particular needs of their experiments. Thorough analysis of these studies is needed to assess the contribution of these variations to the efficiency of the model in order to improve it further.

Even with this extensive variability in the CMS model, the general principle remains the same: chronic application of varied stressors creates depressive-like symptoms of aversion to reward. The advantage of the CMS over other models is its strong validity, which relates well with the time course of the condition and treatment in the clinic. The time course of the induction of this model reflects the manifestation of long-term depressive symptomatology, which is thought to be the major advantage over shorter-length models such as the FST and the LH. Compared to acute- and sub-chronic stress-based models, the CMS is superior to induce anhedonic-like symptoms. Importantly, these symptoms can be reversed by chronic antidepressant treatment over 4–6 weeks, which mirrors much closer the activity of antidepressants used in the clinic. (Chan et al., 2009; Mutlu et al., 2012; Stein et al., 2009). In addition, the use of stress-sensitive rodent strains, such as the stress-sensitive Flinders rat, in the CMS could further enhance the anhedonic-like symptoms, compared to the use of normal strains (Pucilowski et al., 1992). In terms of measurable responses, the CMS model presents behavioral impairments in sucrose consumption (Borsini and Meli, 1988; Crema et al., 2013; Willner, 1986), preference of sweetened solution over water (Hales et al., 2011; Koch et al., 2002; Moussavi et al., 2007) and grooming frequency (Bair et al., 2003; Carter and Sullivan, 2002; Mutlu et al., 2009, 2012), which are observable and quantifiable in this model. What is more, the CMS model is associated with changes to neurotransmitter levels and signaling, which further disturb mood and rewarding behavior. This feature makes the CMS model align with the monoamine theory of depression (Al-Hasani et al., 2013; Frazer and Morilak, 2005; Jang et al., 2004; Li et al., 2009; Vancassel et al., 2008).

Nevertheless, the CMS model is not without its limitations. Prolonged stress exposure typically creates a barrier for animal ethics approvals, compared to other models of depression due of the variety and duration of exposure to the stressors included in this protocol (de Felipe et al., 1989). The lack of standardized guidelines or supportive bibliography of using prolonged stress exposure amplifies this limitation of the CMS. In terms of operational limitations, one of the biggest drawbacks of the CMS paradigm is the difficulty to replicate results. It is thought to arise from objective difficulties to repeat accurate procedures reliably for a long period. This creates large variations in data produced by different laboratories that follow the same protocol (Darko et al., 1992; Djurovic et al., 1999). Compared to the FST and the LH models, the CMS paradigm is highly labor-intense, involves long experimental time-periods and various stressor procedures, which all makes this model's efficiency highly susceptible to the effect of environmental factors. Finally, it has to be noted that repeated exposure to chronic stress may increase the risk to induce resilient phenotypes, which can show a similar response to the non-stressed

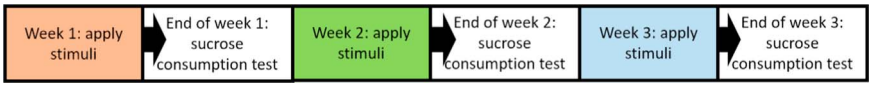

Fig. 3. General structure of the chronic mild stress model. Different stressors (stimuli) are applied weekly and are transiently followed by a test-period of monitored sucrose consumption, to quantify the depressive-like symptoms.

Table 4
Variability of different protocols exist today in the chronic mild stress model. Variable stressors are applied once or twice a day randomly to induce the depressive-like symptoms, which can be measured by a number of different ways, during a variety of experimental length.

Procedure (weeks)	Animal Species	Stressors applied	Stressor intervals	Main measurement	Example references
3	Wistar rat	● food or water deprivation ● cage tilting ● intermittent illumination damp sawdust ● grouped housing ● low-intensity stroboscopic illumination	Stressors applied individually and continuously with 10–14 intervals	Amount of consumption of 1% sucrose solution	(Christiansen et al., 2012; Jayatissa et al., 2006; Sanchez et al., 2003; y Palacios et al., 2011)
3	SD rat	● food or water deprivation ● cage titling and wet cage ● continuous overnight illumination ● grouped housing ● low-intensity stroboscopic illumination	1 or 2 stressors per day and randomized intervals		(Grønli et al., 2004; Segev et al., 2014)
4	SD rat	● food or water deprivation ● continuous overnight illumination ● cage titling ● grouped housing ● damp sawdust ● stroboscopic illumination	Stressors applied individually and continuously	Test of preference of 1% sucrose solution to plain water	(Li et al., 2012)
4	C57BL/6 mouse	● restraint stress ● cage titling ● grouped housing ● white noise ● day-night cycle disturbance	Stressor applied individually for 1 h per day		(Zhu et al., 2014)
4	Lister hooded rat	● food or water deprivation ● cage tilting ● intermittent or overnight illumination ● grouped housing ● low-intensity stroboscopic illumination ● white noise	First 2 weeks: two stressors per day during daylight Last 2 weeks: two stressors per day during night	Amount of consumption of 0.7% sucrose solution	(Monleon et al., 1995)
5	Wistar rat	● food or water deprivation ● cage titling ● intermittent or stroboscopic illumination ● soiled cage ● paired housing	Stressor applied individually and continuously with 10–14 intervals	Amount of consumption of 1% sucrose solution	(Pochwat et al., 2014)
5	SD rat	● grouped housing ● cage titling and wet cage ● food or water deprivation ● stroboscopic illumination ● white noise ● continuous overnight illumination	1 stressor per day, with or without repetition	Amount of consumption of 1% sucrose solution	(First et al., 2013)
6	BALB/c mouse	● grouped housing ● noise ● damp or remove sawdust ● cage changing & tilting ● cold water swim ● low-intensity stroboscopic	1 or 2 stressors per day at different time each day	Measured body weight, coat state and grooming frequency	(Yalcin et al., 2007)

(continued on next page)

Table 4 *(continued)*

Procedure (weeks)	Animal Species	Stressors applied	Stressor intervals	Main measurement	Example references
		illumination • day-night cycle disturbance			
6	Wistar rat	• food or water deprivation • restraint stress • forced swimming • flashing light • isolation	One stressor per day at different times each day; repeated at random	Sweet food consumption	(Réus et al., 2012)
8	BALB/c mouse	• cage change & tilting • grouped housing • damp or remove sawdust • restraint stress • noise • day-night cycle disturbance	2 stressors per day with randomized combinations and 1–2 h interval	Amount of consumption of 1% sucrose solution	(Nollet et al., 2013)
8	Wistar rat	• restraint stress • cage titling • paired housing • nip tail • day-night cycle disturbance	1 stressor per day and each stressor repeated 6–7 times across the procedure	Test of preference of 20% sucrose solution to plain water	(Karson et al., 2013)
9	Wistar rat	• food or water deprivation • cage tilting • intermittent illumination • soiled cage • grouped housing • low intensity stroboscopic illumination	Stressor applied individually and continuously with 10–14 intervals	Amount of consumption of 1% sucrose solution	(Papp et al., 2003)

control group (Bergström et al., 2007). This phenomenon challenges the face validity of the CMS model and questions its translation to the clinic (Pryce and Seifritz, 2011; Scharf and Schmidt, 2012).

2.3. Learned helplessness (LH)

One of the core symptoms of clinical depression is the feeling of helplessness, which manifests in the form of losing any meaning in life and giving up trying to escape from their stressful situation, as a result of exposure to uncontrollable events (Abramson et al., 1978). The features of learned helplessness are highly translational from mammals and even non-mammal species to humans (Vollmayr and Gass, 2013). The first learned helplessness paradigm was described in dogs (Seligman et al., 1968), where a series of unconditioned stimuli, namely mild electric shocks, were used to induce depressive-like symptoms. Clinically, learned helplessness refers to a mental state in patients that 1) fail to control unpleasant stimuli, and 2) lose the willingness or ability to avoid future stressful events (Peterson, 1993). Problem solving is a typical example to explain this behavior. When people fail to fulfill specific tasks, they believe that they are not capable to solve similar tasks and consequently they generate negative expectations regarding any future attempts in a similar task. This passive state of mind contributes to poor performance, and leads to the manifestation of learned helplessness (Abramson et al., 1978; Dweck, 1975).

Similarly, rodents exhibit changes in their emotional and cognitive status, as well as significant performance deficits in behavioral tests (Vollmayr and Henn, 2001). Taking advantage of rodents' adaptive ability to avoid stressors and danger, inescapable shocks are used in this model to produce the "helplessness" symptoms. After learning the uselessness of their positive avoidance response to the stimulus, a negative coping strategy, called escape failures, is generated in the following test phases (Boice, 1972). The LH protocol as a depression model includes three phases, the induction of depressive-like symptoms, the recovery and the test phase (Fig. 4). In the induction phase, LH symptoms are induced by delivering inescapable electric foot-shocks (Chourbaji et al., 2005; Hajszan et al., 2009) or tail-shocks (Drugan et al., 1997; Grahn et al., 2000). The induction is typically composed of 60 trials that each includes a stressor-delivery period and an interval period. After a recovery period of at least 24 h (to allow memory consolidation), the animal enters the final phase (testing) where they are presented with escapable electric shocks. In this scenario, the animals are allowed to exit through an opening to a neighboring safe chamber. The shocks are delivered acutely (~3 s) followed by a half-minute interval, with this trial cycle repeated 30 times per day, for 3 consecutive days. Non-induced animals will immediately seek the available exit when presented with mild electric shocks, in an effort to avert the stressor (active avoidance). Learned helplessness-induced animals though will not seek to exit but rather accept the "inevitable" stressor (a behavior called "escape failure"). The measurable response in the LH model is the number of escape failures during the test phase, in each of the 3 days. In order to differentiate the active avoidance responses of the animal (exit during shocks) with passive avoidance responses that account for anticipation, the model includes the use of a short unconditioned stimulus immediately prior to the shock delivery during the test trials (usually a tone or light). Measurements of the number of escape failures, passive avoidance responses and number of escapes during the inter-trial interval time, are used by the model as surrogate markers of depression, instrumental learning and locomotor activity respectively (Besson et al., 1996; Seligman and Maier, 1967).

Unlike the FST and the CMS models, only a limited number of studies have looked at the impact of protocol variability on the efficiency of the LH model. It has been suggested, that the parameters that define the electric foot-shocks (i.e. intensity, duration, delivery pattern etc.), are most vital for a successful induction phase (Amat et al., 2005; Maier and Watkins, 2005). Table 5 exhibits the variances of main parameters that used among different LH protocols. Apart from the definition of the electric shocks (intensity and duration), there are a number of numerical parameters that describe the number of sessions, the number of trials, the length of intervals, as well as the use of conditioned and unconditioned stimulus during the test phase. Although there are not many studies that have particularly focused on the effect of these parameters in the efficiency and validity of this model, it is important to note that the nature of the LH model is such that provides the ability to use specific internal controls to demonstrate the effect of some parameters in the measurable response. For example, an animal group that receives escapable shocks (ES) during the induction phase, instead of inescapable shocks (IS) provides the internal benchmarking for determining the effect of IS on the model (Amat et al., 2010; Maier and Seligman, 1976). Nevertheless, new studies that can provide insight on the nature of the link between these LH parameters and the manifestation of depressive-like symptoms are urgently needed in order to assess the LH model and improve it further.

Apart from the strong validation profile of the LH model and the variety of depressive symptoms it offers, a number of other advantages render it as one of the most efficient animal models for the study of depression and antidepressants. For example, in contrast to the quick onset of effects produced after administration of antidepressants in the FST model, most of the tested antidepressants in the LH model require multiple administrations over 3–5 days to reverse the stress-induced learned helplessness (Takamori et al., 2001). In addition, the specificity of antidepressant therapy versus anxiolytic therapy is also an advantage of this model. Unlike anxiolytics (i.e. diazepam) or neuroleptics (i.e. chlorpromazine), only repeated administrated antidepressants were observed to significantly reduce depressive-like symptoms in the LH model (Sherman et al., 1982).

Even though the escape deficits produced by electric shocks appears similar to the immobility in the FST (e.g. inhibition of response), the inescapable foot-shocks are thought to induce longer-lasting depressive-like symptoms than the FST. It is mainly due to the intensity of the stressor involved (Anisman et al., 1983), which could explain the selectivity of antidepressant therapy over anxiolytics in the LH, compared to the FST. Moreover, the randomization of IS eliminates the possibility of predictability for "safe" periods by the animal during the induction session and increases the possibility to establish chronic depressive-like symptoms (Price and Geer, 1972; Seligman, 1968). Finally, in the LH paradigm the combination of Pavlovian conditioning in phase one and instrumental learning in phase three, provides an efficient tool for understanding not only the therapeutic effect of administered drugs but also the complex neuropsychopathology of depression (Vollmayr et al., 2007). Nevertheless, the LH paradigm is associated with some limitations that are largely based on its complex

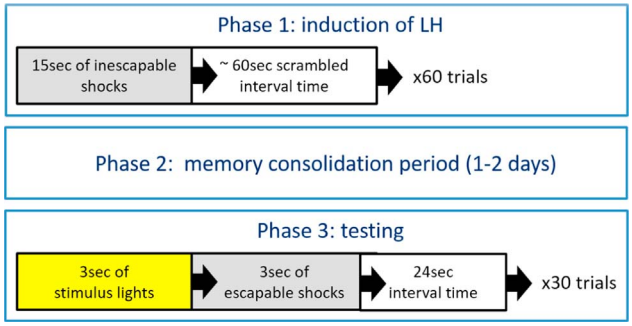

Fig. 4. Structure of the most frequently used protocol for the learned helplessness model, which is divided in three phases. Phase 1 (induction) provides repetitive trials of inescapable shock periods intervened by a short recovery period. Phase 2 offers a long rest period for memory consolidation, whereas Phase 3 is the testing phase which involves repetitive escapable shock trials intervened by short recovery periods. The escape failures of the animals are recorded as surrogate marker of depressive like symptoms.

Table 5
Different protocols used in the induction phase and testing phase of learned helplessness model. Key influence factors, namely number of sessions of each phase, number of each session, intensity and duration of shocks and the duration of intertribal interval are listed as index of per protocol.

	Training sessions	*Trials per session*	*Shock intensity (mA)*	*Shock duration (s)*	*Intertrial interval (s)*	Interphase interval	*Testing sessions*	*Trials per session*	*Trial type*	*Trial duration*	*Shock intensity (mA)*	*Intertrial interval (s)*	Reference
Wistar rat	1	60	0.8	15	60	2	3	30	CS/US	3s light+3 s shock	0.8	24	(Besson et al., 1996; Gibert-Rahola et al., 1990; Tejedor-Real et al., 1998)
Wistar rat	1	60	1.0	2	30	1	1	40	US only	Maximum 30 s shock	1.0	Average 60	(Steenbergen et al., 1990)
SD rat	2	90	2.0	9.9	2, 5 or 10	2	2	50	CS/US	5 s light and tone+5s shock	2.0	30	(Hudzik et al., 2011)
SD rat	2	60	0.65	30	20–40	1	2	30	CS/US	3 s tone+6 s shock	0.65	Average 30	(Shirayama et al., 2004)
Swiss-Webster mouse	1	14	0.28	10 s light +20 s shock	20	1	1	10	US only	2 s shock	0.28	60	(Schulteis and Martinez, 1990)
Balb/c mouse	2	30	0.3	10s light+20 s shock	25–35	1	3	30	CS/US	10 s light+20 s shock	0.3	Average 30	(Aguilar et al., 1998)
FVB/N mouse	2	180	0.15	1–3	1–15	1	1	30	CS/US	5s light+max 10 s shocks	0.15	30	(Schmidt et al., 2016)

protocol and specialized equipment needed to perform the experiments and accurately record the variations in produced behavior. For example, a technical limitation of the LH model is that changes to the emotional and cognitive status during the interphase interval are difficult to examine experimentally due to the nature of the experimental protocol (Moscarello and LeDoux, 2013). Finally, contrary to what we see in the LH paradigm, the inescapable stress in humans only induces short-term depressive-like symptoms that do not characterize clinical depression (Maier, 2001). Nevertheless, all these limitations create a challenge for future modifications in this protocol, which should aim to improve the correlation of observed animal behavioral symptoms with the symptomatology seen in clinical depression, in order to better optimize the application of this model

3. Conclusion

The extensive use of pre-clinical animal models over the last 30 years has provided valuable experience and useful insights into the possible neuro-psychopathological causes of clinical depression, as well as a vital tool for assessing novel drugs for antidepressant efficacy (Nestler and Hyman, 2010). Nevertheless, one of the biggest challenge of animal models of depression today is the technical benchmarking across a range of methodological parameters for each protocol. Only a small number of studies to date have highlighted the importance of "tuning" these parameters (Cryan et al., 2002; Lucki, 1997; Vollmayr and Henn, 2001), and more studies are needed to optimize these models and to understand the pathology of depression-like symptoms. Currently, these three most popular animal models of depression offer very distinct advantages and limitations, which although can be recognized and described, we have not been able to thoroughly assess to date. It is widely accepted that each model predominantly assesses one particular behavioral symptom of depression compared to the other models; despair in the FST (Nishimura et al., 1988b), aversion towards rewards in the CMS (Willner et al., 1992) and helplessness in the LH (Maier, 1984). Therefore, the use of one model can often complement other models to get to a deeper understanding of the results. Over the last years, these models have been refined by many groups worldwide. There is some evidence that some of those models can be simplified without losing their predictive value. These developments not only benefit the researchers, since shorter paradigms will directly reduce costs but also represent a major improvement with regards to animal welfare and husbandry.

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