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REVIEW

Modelling depression in animals: at the interface of reward and stress pathways

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Abstract
Rationale Despite substantial research efforts the aetiology of major depressive disorder (MDD) remains poorly understood, which is due in part to the heterogeneity of the disorder and the complexity of designing appropriate animal models. However, in the last few decades, a focus on the development of novel stress-based paradigms and a focus on using hedonic/anhedonic behaviour have led to renewed optimism in the use of animal models to assess aspects of MDD.
Objectives Therefore, in this review article, *dedicated to Athina Markou*, we summarise the use of stress-based animal models for studying MDD in rodents and how reward-related readouts can be used to validate/assess the model and/or treatment.
Results We reveal the use and limitations of chronic stress paradigms, which we split into non-social (i.e. chronic mild stress), social (i.e. chronic social defeat) and drug-withdrawal paradigms for studying MDD and detail numerous reward-related readouts that are employed in preclinical research. Finally, we finish with a section regarding important factors to consider when using animal models.
Conclusions One of the most consistent findings following chronic stress exposure in rodents is a disruption of the brain reward system, which can be easily assessed using sucrose, social interaction, food, drug of abuse or intracranial self-stimulation as a readout. Probing the underlying causes of such alterations is providing a greater understanding of the potential systems and processes that are disrupted in MDD.

Keywords Drug withdrawal · Anhedonia · Stress · Microbiome · ICSS · Susceptible · Sucrose

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Introduction

Major depressive disorder (MDD) is a heterogeneous and multi-faceted disorder, which has a lifetime prevalence of approximately 10–15% and is more frequent in woman than in men (Kessler 2003; McGrath et al. 2016). In Europe, the 12-month prevalence of MDD is around 6.9% (approximately 30 million people) making it the psychiatric disorder with the largest burden on society (Wittchen et al. 2011). Although the Greek physician Hippocrates provided a biological description of melancholia over 2000 years ago, it was through serendipity that the original antidepressants, iproniazid and imipramine, were discovered. Despite this, as well as the introduction of defined diagnostic criteria, there is still a poor understanding of the biological basis and underpinnings of MDD. Moreover, one third of patients do not respond to current treatment options, and there is a delayed onset of therapeutic benefit (2–4 weeks) in patients for whom antidepressants are effective. Another major issue is that the effect size of antidepressants relative to placebo is small. Therefore, a great deal of emphasis has been placed on obtaining a better understanding of the aetiology of MDD with which to design and develop more efficacious and faster-acting antidepressants.

There are many reasons for the high-profile failures of numerous compounds with novel mechanisms of action including the heterogeneity of the disorder, the high placebo response, the irrelevance of the proposed mechanisms of action, the use of a diagnostic criteria and the lack of appropriate

animal models of the disorder. While animal models are unable to replicate such complex disorders in their entirety, the last few years have seen a shift in the way such models are both perceived and used. This has been aided by the introduction of the Research Domain Criteria (RDoC) approach to studying disorders by the National Institutes of Health (NIH; see the "Research domain criteria" section below). Furthermore, the lack of understanding of why patients develop MDD has hindered the development of animal models based on similar inducing factors as in patients. However, one of the most reliable and consistent findings to emerge is that exposure to repeated, or chronic, adverse life events increases the risk of a person developing MDD (Kendler et al. 1999). Therefore, there has been a recent emphasis on using chronic stress models to gain a better understanding of the biological alterations that occur upon stress exposure, as it is believed that this will better reflect the human situation (Langgartner et al. 2015; Slattery and Cryan 2014; Slattery et al. 2007).

In addition to an inducing factor, animal models of MDD require suitable functional readouts to assess the effect of the chosen manipulation. Given that anhedonia—the loss of interest, or pleasure, in previously rewarding stimuli—is a core symptom of MDD and can be readily assessed in rodents, the majority of researchers use reward-related readouts as essential readouts of animal models of depression. This is because a wide variety of stimuli, such as sucrose, drugs of abuse, social interaction and sexual pheromones, display high hedonic value for rodents (and humans) and they will actively work to gain their access. Importantly, in the context of the present review, repeated/chronic stress-based paradigms have been repeatedly shown to lead to a reduction in the consumption and seeking of such rewarding stimuli. It is important to point out that the loss of interest and loss of pleasure are distinct processes that differ in their underlying neurobiology, which we address in the following section.

The neurobiology of stress and reward

The brain reward circuitry has been extremely well characterised and is known to be affected at numerous levels in patients with MDD. Moreover, much of the brain reward circuitry is highly conserved between rodents and humans, which is reflected in the fact that many of the stimuli that we derive pleasure from, such as palatable food, sugary drinks, drugs of abuse, social interaction and sex, are able to elicit similar responses in rodents. As it is beyond the scope of the current review article to describe the brain reward circuitry in detail, we only provide a brief overview here and direct readers wishing more information to the following articles (Barnes et al. 2014; Geyer and Markou 1995b; Markou et al. 2009; Markou et al. 1998; Russo et al. 2012; Wise 2002).

Several researchers have highlighted the fact that the anhedonia is a general term, which can relate to many different situations (Der-Avakian and Markou 2012; Markou et al. 2013; Rizvi et al. 2016). This is because anhedonia has traditionally been considered to reflect a loss of pleasure in something that is rewarding, e.g. consummatory enjoyment of palatable food. However, there are a number of reward processes that might be affected in MDD patients. A stimulus first has to show hedonic value for it to be associated as rewarding, which then leads to anticipation and interest in receiving the stimuli/reward, as well as motivation and effort to obtain the stimuli/reward. These different reward facets are governed, at least in part, by different regions of the brain reward circuitry, as well as different neurotransmitter systems (for reviews see, Der-Avakian and Markou 2012; Rizvi et al. 2016; Volkow and Morales 2015). Dopamine has been traditionally associated as the main player within the brain reward circuitry, but growing evidence supports a role of 5-HT, GABA, glutamate, opioids, neuropeptides and endocannabinoids in various aspects of reward. The network of structures comprising the brain reward circuit includes the ventral tegmental area (VTA), ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, amygdala, hippocampus, nucleus accumbens, ventral pallidum and associated structures (for reviews see, Der-Avakian and Markou 2012; Rizvi et al. 2016; Volkow and Morales 2015).

Arguably, the most studied component of the brain reward circuitry is the dopaminergic mesolimbic system, which projects from the VTA to the nucleus accumbens and upon activation, e.g. by administration of drugs of abuse or a rewarding stimuli such as food, results in a release of dopamine within the nucleus accumbens. This pathway is involved in processing and motivational aspects of reward-related stimuli. VTA neurons can fire tonically (1–8 Hz) or phasically (>15 Hz) with increased dopamine release observed when neurons are phasically active (Schultz 2016). Novel or unexpected rewards, as well as reward-related cues, increase dopaminergic neuron activity supporting its role in prediction, anticipation and motivational aspects of reward. However, if an expected reward (e.g. after presentation of reward-related cues) is not received, dopaminergic firing is suppressed (Schultz 2016). While all drugs of abuse (acutely) increase dopamine release within the nucleus accumbens, VTA neurons also project to other regions and form the brain reward circuitry, such as the hippocampus, prefrontal cortex, habenula and amygdala. In addition to drugs of abuse, administration of cholinergic agents in to the ventral tegmental area has been shown to activate this pathway and is believed to underlie the rewarding properties of intracranial self-stimulation (see below) (Barnes et al. 2014; Geyer and Markou 1995b; Markou et al. 2009; Markou et al. 1998; Russo et al. 2012; Wise 2002).

However, there is converging clinical evidence that many of the alterations seen in brain activity in MDD patients could act in concert to reduce the activity of the reward circuitry,

such as decreased activation and/or volume of the nucleus accumbens, the orbital frontal cortex, hippocampus and regions of the amygdala (Bredt et al. 2015; Drevets et al. 2008; Savitz and Drevets 2013). Furthermore, overactivation of the VTA to nucleus accumbens pathway, for example in drug addiction, eventually leads to a reduced activity of the reward circuitry, which is hypothesised to be one reason for the link between drug withdrawal and MDD (see "Drug-withdrawal paradigms" section). Interestingly, a similar picture appears in rodent studies whereby exposure to chronic stress or withdrawal from drugs of abuse lead to a host of central changes. These alterations, induced by stress hormones such as glucocorticoids and adrenaline, include changes in volume, dendritic architecture, hippocampal neurogenesis, as well as anhedonic-like behaviour.

Importantly, many of these changes occur within the brain reward circuitry, revealing a great deal of intersection between the stress and reward pathways. For example, numerous chronic stress paradigms have been shown to cause atrophy of neurons within the prefrontal cortex and hippocampus, as well as profound changes to the mesolimbic dopaminergic system. Additionally, increased brain-derived neurotrophic factor (BDNF) signalling within the nucleus accumbens has been shown to reflect susceptibility to chronic stress, whereas increased delta fosB signalling within this region conveys resilience to chronic stress exposure (Berton et al. 2006; Krishnan et al. 2007; Russo et al. 2012; Vialou et al. 2010). Interestingly, many of the changes are also observed in models of drug addiction, illustrating the overlap between the consequences of stress exposure and drug addiction. Further, stress exposure increases drug seeking and/or intake in animal models and can also reinstate drug intake following drug extinction (Jonkman and Kenny 2013; Kenny 2011; Kenny and Markou 2004; Koob and Volkow 2016; Picciotto and Kenny 2013; Volkow et al. 2016).

Therefore, in this review, *dedicated to the memory of Athina Markou*, who spent much of her career focusing on modelling aspects of reward in the context of depression and other psychiatric disorders, we focus on animal models that employ stress as an inducing factor and reward as a readout. We will describe these models in terms of their function and the readouts that have been used to characterise them, as well as important considerations to define prior to the establishment/setup of such models.

Criteria for successful animal models

Many researchers have outlined that their ideas of criteria animal models should fulfil in order for them to be translational and relevant. These relate to different facets of the disorder being studied and state that they must be similar/identical in the animal model to the human situation (Belzung 2014; Berton et al. 2012; Chadman et al. 2009; Cryan et al. 2002; Cryan et al. 2005; Cryan and Slattery 2007; Cryan and Slattery 2010; Frazer and Morilak 2005; Fuchs 2005; Gould and Einat 2007; Neumann et al. 2011; O'Leary and Cryan 2013; Pryce and Seifritz 2011; Schmidt et al. 2008; Slattery and Cryan 2011; Willner 1984).

Therefore, a perfect animal model for MDD is unattainable based on the principle that such a model would need to show identical etiological, face, predictive and construct validity to the disorder being studied. The reasons for this are two-fold; from the preclinical side, it is impossible to mimic some MDD symptoms in rodents (e.g. thoughts of guilt and suicide), and from the clinical side, the causes and biological correlates of MDD are incompletely understood.

However, animal models can be used to study certain facets of MDD, and it was postulated by McKinny and Bunney in the late 1960s that appropriate animal models only require to be "reasonably analogous" to the human disorder, have a behavioural change that can be monitored and reversed by treatments that are effective in patients and be reproducible between laboratories (McKinney and Bunney 1969). It was Paul Willner who first suggested, *in this Journal*, that animal models should fulfil the criteria outlined above (Willner 1984). In 1995, Geyer and Markou further refined the criteria that are necessary and sufficient, at least for initial use of an animal model, to predictive validity and reliability (Geyer and Markou 1995a). More recently, we and others, based on the concepts of Gottesman and colleagues (Gottesman and Gould 2003), have suggested that animal models should use an endophenotype-based approach, whereby an endophenotype can be specific symptoms, biological markers or risk factors of the disorder being studied. This serves to reduce the complexity of psychiatric disorders, such as MDD, to more translatable aspects, such as anhedonia, which can be studied in both rodents and humans (Gould and Einat 2007; Gould and Gottesman 2006; Hasler et al. 2004; Hasler et al. 2005; Hasler and Northoff 2011; Slattery and Cryan 2014; Slattery et al. 2007).

It should also be pointed out that due to a lack of correlation between the primary mechanisms of action of current antidepressant drugs and their onset of therapeutic benefit, designing novel models using predictive validity may not lead to better compounds. Moreover, it may even lead to a "Catch 22" situation, whereby the novel models are only responsive to monoaminergic manipulation. For a comprehensive review discussing the various facets of criteria of animal models, together with a historical perspective and outlook, we refer the interested reader to the following review (Belzung and Lemoine 2011) and to the seminal papers of Geyer and Markou (Geyer and Markou 1995a; Geyer and Markou 1995b; Markou et al. 2009; Markou et al. 1998).

Research domain criteria

The endophenotype-style approach has been taken a step further, with the recent introduction of RDoC in 2009 by the NIH

(Casey et al. 2013; Cuthbert and Insel 2013). RDoC stemmed from the fact that the diagnostic systems that are currently utilised for diagnosing someone with a psychiatric disorder do not consider the underlying neurobiology, but merely symptoms and feelings via questionnaires. As discussed above, such diagnostic criteria make it difficult to study altered behavioural states in both humans and animals. Therefore, the basic concept of RDoC is to categorise specific functional dimensions of behaviour, such as negative valence systems, arousal and systems for social processes (see https://www.nimh.nih.gov/research-priorities/rdoc/development-and-definitions-of-the-rdoc-domains-and-constructs.shtml). It is believed that such an approach will lead to findings relevant for a wide range of psychiatric disorders and lead to better defined neurobiological systems and targets that are involved in specific behavioural dimensions (Casey et al. 2013; Cuthbert and Insel 2013). Indeed, a recent clinical study by Drysdale et al. (2017), using such an approach, demonstrated that four neurophysiological subtypes of depression, which overlapped at the clinical symptomology level, could be characterised by distinct resting-state connectivity patterns. This suggests novel approaches for the design of animal models, whereby discrete manipulation of brain circuitry, based on the findings of Drysdale, could be assessed for their relevance to different aspects of depression. Similarly, such manipulations could also be employed to determine whether they may prevent (or exacerbate) the effect of stress or drug-withdrawal on reward-related readouts.

Animal tests and models of MDD

The difference between a model and a test is often confused and sometimes understandably conflated; thus, we will give a short definition of the two here. While an animal model requires both a manipulation (i.e. chronic stress exposure or withdrawal from drugs of abuse [see below for further details]) and a readout (i.e. sucrose preference), a test merely refers to a readout (i.e. sucrose preference; see Fig. 1). The majority of tests that have been utilised for the study of MDD can more accurately be referred to as animal tests of antidepressant-like efficacy/activity since they have all been established based on the ability of current antidepressant drugs to cause a particular effect (Cryan and Slattery 2007; Slattery and Cryan 2014). We, and others, have dedicated numerous reviews to describing such tests, including the forced swim test (FST), tail suspension test (TST), sucrose preference test (SPT) and the more recently employed female urine sniffing test, as well as animal models of MDD such as the olfactory bulbectomy and learned helplessness paradigm amongst others and the reader is directed to them (Cryan and Holmes 2005; Cryan et al. 2002; Cryan et al. 2005; Cryan and Slattery 2010; Geyer and Markou 1995b; Gould and Einat 2007; Henn and Vollmayr 2005; Kelly et al. 1997; Lucki 1997; McArthur and Borsini 2006; Nestler and Hyman 2010; Neumann et al. 2011; O'Leary and Cryan 2013; Pryce et al. 2011; Slattery and Cryan 2011, 2014; Song and Leonard 2005; Tanti and Belzung 2010). Thus, here, we will focus on drug-withdrawal and stress-related models and reward-related readouts.

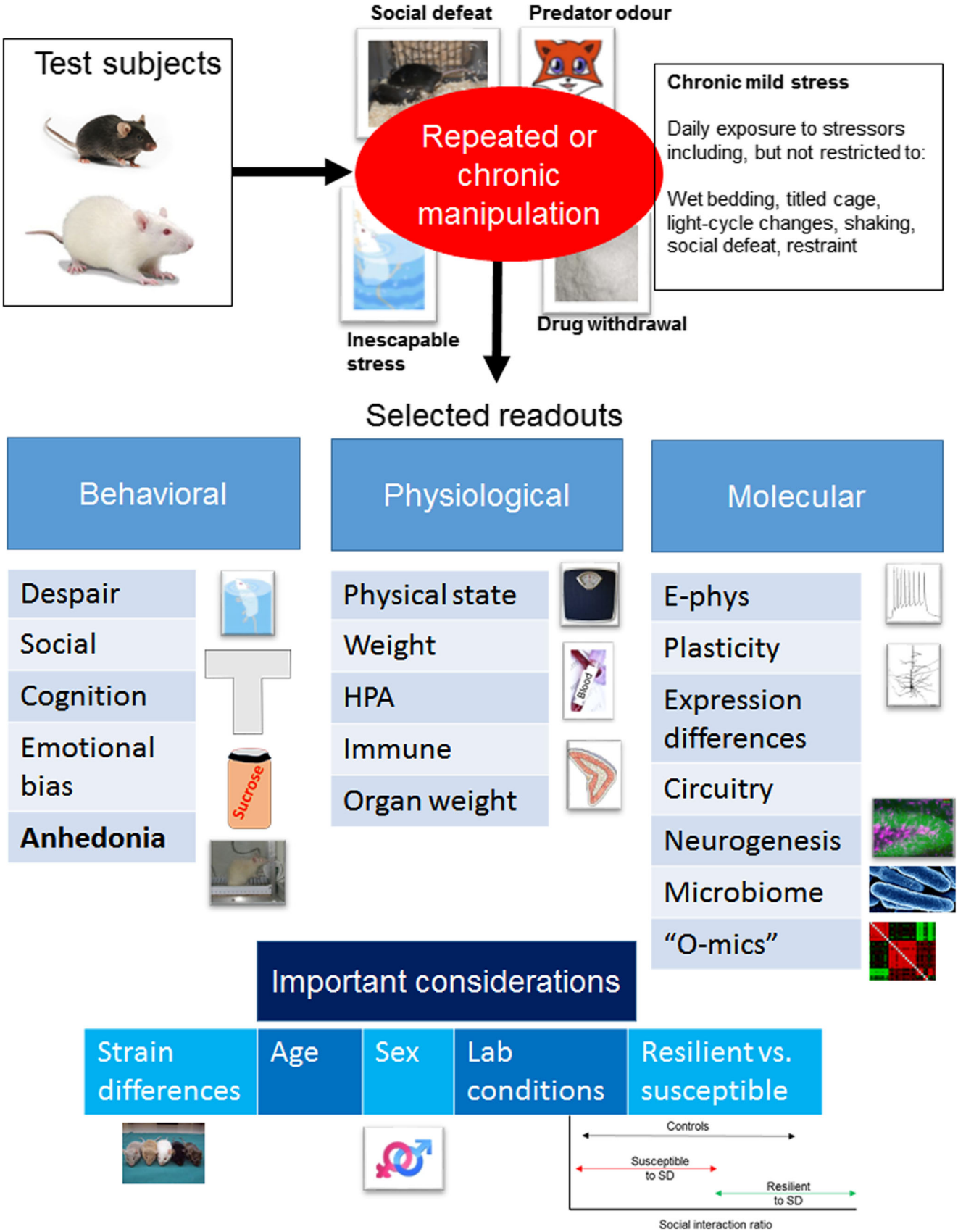
Fig. 1 Schematic representation of manipulations and commonly used readouts described in the article to study major depressive disorder in rodents together with important variables to consider. While the focus of this review is on reward-related readouts to assess the hedonic state of the animal, numerous others are also employed at the behavioural, molecular or physiological levels, including those highlighted in the figure

Drug-withdrawal paradigms

Epidemiological studies show that a high-comorbidity between drug-use/abuse (e.g. alcohol, smoking) and MDD exists. Many people, including Markou and colleagues, hold the belief that in many cases, such drug use/abuse may, at least at the beginning, be an attempt to "self-medicate" (Markou et al. 1998). This is also supported by empirical data showing that many neurobiological correlates of drug addiction and MDD overlap and the fact that withdrawal from such drugs (e.g. amphetamine or phencyclidine) in humans can lead to MDD (Markou et al. 1998). These observations lead to the employment of drug-withdrawal paradigms to study the aetiology and potential treatments of MDD, as well as drug addiction and schizophrenia (Young and Markou 2015). It is believed that such models fulfil many of the criteria outlined above regarding the use of translationally relevant animal models (Geyer and Markou 1995a). Numerous studies have revealed that withdrawal from repeated or continuous drugs of abuse, such as amphetamine, leads to an anhedonic state, as assessed using a variety of readouts, such as progressive ratio break-point, sexual behaviour and intra-cranial self-stimulation (ICSS) thresholds (see the "Reward-related readouts" section for more details). Moreover, it has recently been demonstrated that even the withdrawal from a single acute administration of amphetamine can lead to increased immobility (in the FST) and deficits in dopamine neuron activity in the VTA, supporting an anhedonic-like state (Belujon et al. 2016).

Chronic stress paradigms

Given that chronic stress has repeatedly been linked with a wide variety of disorders including MDD, numerous paradigms employing a wide range of different stressors, both social and non-social, have been employed. The first such paradigm to study MDD was that established by Richard Katz (1981), who subjected male Sprague-Dawley rats to a 21-day battery of different severe stressors such as 1 h of


Test subjects
Social defeat
Predator odour
Repeated or chronic manipulation
Chronic mild stress
Daily exposure to stressors including, but not restricted to:
Wet bedding, titled cage, light-cycle changes, shaking, social defeat, restraint
Inescapable stress
Drug withdrawal
Selected readouts
Behavioral
Despair
Social
Cognition
Emotional bias
Anhedonia
Sucrose
Physiological
Physical state
Weight
HPA
Immune
Organ weight
Blood
Molecular
E-phys
Plasticity
Expression differences
Circuitry
Neurogenesis
Microbiome
"O-mics"
Important considerations
Strain differences
Age
Sex
Lab conditions
Resilient vs. susceptible
Controls
Susceptible to SD
Resilient to SD
Social interaction ratio

unpredictable shock, 40-h food deprivation, cold (4 °C) swim stress and a reversed day-night cycle. Rats exposed to the stressors displayed alterations in behaviour (open field) and corticosterone levels, which were reversed by ECT (Katz 1981). The severity of the stressors used in this study cannot be used today, but a number of groups established what are termed either chronic mild stress (CMS) or chronic unpredictable mild stress (CUMS) models based on these original findings. While some of these models, which are effective in both rats and mice, include social components (i.e. social instability), below, we will separate chronic stress paradigms into those that are purely social versus those that also employ non-social components.

CUMS and CMS models

Paul Willner and colleagues were the first to adapt the Katz model. They revealed that subjecting rats to mild unpredictable stressors, without footshock, was sufficient to reduce sucrose preference, indicative of anhedonic-like behaviour. Moreover, the reduction was prevented by administration of chronic desipramine supporting the predictive validity of the model (Willner et al. 1987). This reduced preference was not related to body weight loss or the calorific content of sucrose, as replacing it with saccharin achieved the same reduction in sweet-solution following CUMS or CMS exposure. Numerous laboratories have developed their own versions of CUMS/CMS, which differ in the duration of stress exposure and the stressors employed. Typical stressors include wet-bedding, cage-tilt, altered light-dark cycles, forced swim stress and social defeat, which are given in an unpredictable manner in order to increase their impact (for a review of CUMS/CMS models, see Willner (2005)). It should be pointed out that the complexity of such paradigms, i.e. the number of different variables used as stressors, as well as other important factors such as laboratory conditions (see "Important considerations when designing/using animal models" section), mean that CUMS and CMS paradigms can be difficult to replicate in other laboratories. However, the paradigms continue to be widely utilised and are accepted as valid animal models of MDD, especially as they lead to deficits in other reward-related domains, such as conditioned place preference and intracranial self-stimulation responding and chronic antidepressant administration is required to reverse these behavioural alterations (Hill et al. 2012).

Repeated/chronic social stress paradigms

The difficulty for some laboratories to gain ethical approval for CMS/CUMS models has in part lead to a shift towards chronic social stress paradigms, which has also been driven by the accumulating evidence showing psychosocial stress to be a risk factor for MDD. In general, social stress paradigms can be separated into separation paradigms (e.g. early-life maternal deprivation or adult social isolation), hierarchy-based paradigms (e.g. resident-intruder encounters, chronic subordination paradigms) or social instability paradigms, which are particularly effective in female rodents (Baranyi et al. 2005; Brown and Grunberg 1995; Dalla et al. 2010, 2011; Hillerer et al. 2012; Kokras and Dalla 2014; Kokras et al. 2011; Perani and Slattery 2014; Schmidt et al. 2010).

Maternal separation/deprivation-based models have been repeatedly used, in rodents and non-human primates given the evidence showing that early adverse life events are a strong risk factor for the development of MDD (O'Mahony et al. 2009; Pryce et al. 2005). Probably the most widely used early-life separation paradigm involves removing the pups from their home-cage for 3 h per day between post-natal day (PND) 2 to 12; although a wide range of others are employed. Such separation has repeatedly been shown to result in a wide range of behavioural, molecular and physiological deficits in adulthood. In contrast, a short handling period of 15 min across the same time-frame has actually been shown to have beneficial effects for the rodent (for review see, Pryce et al. (2005)). This ties in with the mismatch theory of stress, that organisms never exposed to stressful events cope worse when later exposed to a stressor or that animals growing up in stressful environments cope less well when all stressors are removed, for which there is a growing body of supporting evidence (Bateson et al. 2014; Brockhurst et al. 2015; Buwalda et al. 2013; Daskalakis et al. 2013; Nederhof and Schmidt 2012; Santarelli et al. 2014; Schmidt 2011).

With respect to hierarchy-based paradigms, Fuchs and colleagues have repeatedly shown that chronic subordination in tree shrews results in multiple behavioural and molecular alterations that have relevance for MDD (for reviews, see Czeh et al. (2016) and Fuchs (2005)). However, in the last decade or so, the predominant model used to assess social stress is the chronic social defeat stress model (Berton et al. 2012; Chaouloff 2013; Cryan and Slattery 2007; Nestler and Hyman 2010; Reber 2012). In this paradigm, individual experimental mice are introduced into the home-cage of a larger resident mouse and subjected to physical social defeat followed by 24-h sensory contact with the resident. This is repeated for 10 days, and then, the effectiveness of the stressor is typically shown as social avoidance behaviour. Such chronic social defeat has been shown to alter other anhedonia-type readouts, such as cocaine and sucrose preference, but interestingly not to alter behaviour in traditional tests such as the FST and tail suspension test (Krishnan et al. 2007). This highlights the need in preclinical models to assess multiple behavioural readouts. A similar social defeat stress paradigm in rats has also been shown to increase the ICSS thresholds from those at baseline, from the first defeat to the last defeat 21 days later (Der-Avakian et al. 2014). The molecular underpinnings of these defeat-induced behavioural deficits have been

extensively studied and reveal that multiple systems are involved. Moreover, it has been shown that approximately 35% of mice subjected to the defeat do not show the social avoidance behaviour, which enables researchers to study the neurobiological underpinnings of the different outcome to the same stress exposure (see "Resilient vs susceptible animals and breeding for extremes in behaviour" section). Finally, it should be pointed out that variation in the extent of physical injuries that are tolerated in the course of the social defeat sessions across different laboratories strongly influences the behavioural and molecular readouts. For example, biting that breaks the skin leads to a strong activation of the immune system, which would interact with the psychosocial stress component in the model (Fuertig et al. 2016; Pryce and Fuchs, 2017).

Reward-related readouts

As mentioned throughout the manuscript, numerous behavioural reward-related readouts can be employed during, or following, stress exposure to establish whether the stress has affected the individual's hedonic state. Next, we give details about the most widely employed tests and readouts and their use. For an overview of brain regions that are known to play a role in these readouts, we refer the reader to the following reviews (Barnes et al. 2014; Der-Avakian and Markou 2012).

Saccharin/sucrose preference

When rodents are given a free choice between drinking water or a weak sucrose solution (usually 1–2%), they exhibit a preference for the sweet sucrose solution. This is believed to reflect a rewarding aspect to consuming the sucrose solution and thus, give a measurement of the hedonic state of the animal. Typically, sucrose preference testing is performed by providing singly housed rodents with two bottles and the amount of sucrose vs total (sucrose plus water) consumption calculated to provide an overall preference. It has been shown that this test can be performed repeatedly, usually once a week, throughout the stress procedure and that stress-induced reductions in sucrose preference are reversible/preventable by chronic antidepressant administration.

Food reward

In addition to sucrose, palatable food is often used to assess the hedonic status of rodents following chronic stress paradigms. The foods that are used range from sweet cereals to chocolate or high-fat diets and, like sucrose, animals will prefer these foods over their normal chow. Researchers can also take advantage of the fact that rodents will reduce their food intake and/or take longer to approach the rewarding food in novel environments. Tests that utilise this fact, termed novelty-suppressed hyponeophagia, assess the conflict between the rodent's desire for the palatable food or liquid and their anxiety of the novel environment. With this test, it has been shown that prior exposure to chronic stress will increase the latency to approach the reward and decrease the overall consumption of the food or liquid: both measures being reversible by chronic antidepressant administration (Cryan and Sweeney 2011; Dulawa and Hen 2005).

Drug reward

In addition to using drug withdrawal as a stressor, it is obviously possible to employ (self-) administration of drugs of abuse to assess the brain reward circuitry following stress exposure. The high hedonic value of drugs like cocaine and amphetamine make animals work to receive them in tests such as self-administration via fixed- or progressive-ratio responding or to return to places associated with the drug intake such as conditioned place preference (see sections directly below).

Female urine sniffing test

The female urine sniffing test has recently test for assessing reward-related behaviour in rodents. It was developed in the laboratory of Manji and colleagues (Malkesman et al. 2010) and takes advantage of the fact that male rodents find pheromones in the urine of females in oestrous attractive/rewarding. In the test, males, of a variety of strains, were shown to spend a longer time sniffing a cotton-bud coated in female urine than a water-coated bud. Moreover, this test is sensitive to stress exposure, as subjection to either footshock or the learned helplessness paradigm reduced the time spent sniffing the female urine. The anhedonic effect of learned helplessness could also be prevented by chronic treatment with citalopram showing that the test can be modulated bi-directionally (Malkesman et al. 2010).

Conditioned place preference

This test takes advantage of the rewarding properties of food or drugs of abuse and usually consists of either two or three chambers that differ in context (i.e. different floor textures and visual cues on the walls). In one chamber, which is inescapable during the initial phase, animals are repeatedly given an injection of a drug, such as nicotine, amphetamine or cocaine, or food, which makes the animal associate that chamber with the hedonic properties of the drug or food. The animal is placed in the other chamber following a vehicle injection, and on the test day, the animal is placed in the apparatus and freely allowed to explore. Typically, the animal will spend longer in the chamber that was associated with the hedonic properties of the food, i.e. high-fat food (Figlewicz et al. 2004) or drug of abuse (Lhuillier et al. 2007; Mombereau et al.

2007). In the three chamber version, there a neutral chamber is included, which the animal has not been conditioned in.

Fixed and progressive-ratio responding

Due to the hedonic value of sucrose, food or drugs of abuse, animals will actively work in gaining access to them. This fact is taken advantage of in the fixed and progressive ratio responding tests, in which animals are trained to nose-poke or press a lever to receive access to a small reward, typically sucrose or self-administration of a drug of abuse. In the fixed ratio version, animals are first trained to press the lever, or nose-poke, once in order to obtain the sucrose pellet or drug infusion, and once they reach criterion, researchers can increase the number of lever presses required to obtain the reward and determine the number of rewards obtained in a fixed time period. In the progressive ratio schedule of reinforcement, the number of lever presses or nose-pokes is increased by an exponentially increasing amount between each successful trial. In this version, the animal will eventually reach a break-point at which point the amount of effort needed to receive the reward outweighs the hedonic value of the reward. Stress exposure and withdrawal from drugs of abuse have been shown to reduce the break-point in rodents (see Barnes et al. (2014) and Young and Markou (2015) for reviews).

Intracranial self-stimulation

This technique stems from the finding of Olds and Milner that rats returned to an area of the cage where they had previously received intracranial electrical stimulation. From this observation, they proceeded to reveal that rats would actively lever-press to stimulate themselves, particularly when the electrode was implanted in the septal region, and would even forgo food in order to receive more stimuli (Olds and Milner 1954). The high reward value suggests that ICSS directly activates the brain reward system and is typically performed with electrodes implanted in the lateral hypothalamus or medial forebrain bundle (Phillips et al. 1989; Wise 2002). Typically, after surgery, animals are trained to either nose-poke, turn a wheel or press a lever inside a chamber to receive electrical stimulation via the implanted electrode. A major advantage of ICSS compared with many other reward-related paradigms is that there is no satiation, tolerance or sensitisation to the rewarding stimulation and each individual maintains a stable baseline reward threshold following training. Generally, two methods are employed in ICSS studies, the discrete-trial current-intensity procedure and the rate-frequency curve-shift procedure. In the former, animals are trained to turn the manipulandum following presentation of a stimulation in order to receive the same stimulation again. At each intensity, there are three presentations, and the current is then decreased incrementally until the animal stops responding and then increased again until the stimulation becomes rewarding for the animal. This is repeated, and the average reward threshold is calculated based on when the animal stops and starts responding in each series. In the other procedure, animals are presented with a stimulus, and then, the animal is given a set response window during which it can receive further presentations by turning the wheel or pressing the lever. As in the discrete-trial procedure, the intensity is then reduced, and the process repeated until the animal responds below a pre-determined rate (see Barnes et al. (2014) for a review).

Since the individual reward thresholds remain stable under baseline conditions, it is possible to determine the effect of manipulations on the hedonic state of the animal. In keeping, all drugs of abuse lower ICSS reward thresholds, which is believed to reflect the fact that they activate the brain reward system. In contrast, it has been shown that withdrawal from amphetamine administration (Cryan et al. 2003), olfactory bulbectomy (Slattery et al. 2007), social defeat (Der-Avakian et al. 2014) and CMS (Moreau et al. 1995) elevates reward thresholds. These findings suggest that the brain reward system requires higher intensity stimuli to be perceived as rewarding by the animal.

Future directions

While this review has mainly focussed on animal models utilising stress and reward-related readouts, there are many other directions that lend themselves for modelling MDD in rodents. These include examining other facets of MDD following chronic stress or drug-withdrawal paradigms, such as cognitive aspects of depression, the molecular underpinnings of the behavioural outcomes and circuits that are affected by the model (see Fig. 1). Moreover, reward-related readouts are sensitive to punishment or biases. While less studied, researchers have developed translational models based on tasks used in humans, some of which are discussed here:

Probabilistic reversal learning task

The probabilistic reversal learning task is a cognitive-emotional task in which subjects are presented with two stimuli, one given a high probability of being rewarded and the other a low probability. Subjects are told to continue selecting the high probability stimulus, but that these probabilities may be reversed at any given time, and that they should then switch too. MDD patients show increased sensitivity to negative feedback and are more likely to switch following a non-rewarded trial. Pryce and colleagues have developed a similar paradigm for use in mice, which may provide mechanistic insights into such sensitivity to negative feedback in MDD patients (Ineichen et al. 2012).

Affective bias test

Another model that has been used to assess positive and negative biases in rodents is the affective bias test (Stuart et al. 2013). In this test, during discrimination, learning animals learn to associate food reward with two specific digging substrates and are then presented with a preference test between the two reward-paired substrates. Animals are presented with drugs known to lead to positive bias in humans (e.g. antidepressants) or negative bias (e.g. rimonabant) that showed the same affective bias (Stuart et al. 2013).

Response bias probabilistic reward task

This task is based on the observation that humans when presented with two ambiguous stimuli will develop a preference/response bias for the one that is more frequently rewarded. Typically, the stimuli that are briefly presented are short or long mouths on a cartoon face with one being rewarded three times more often than the other (Pizzagalli et al. 2005). However, MDD patients do not develop such a response bias, which is believed to reflect reduced reward responsivity (Pizzagalli et al. 2005). Recently, Markou and co-workers developed a rat version of this task, replacing mouth length with differing tone durations, but maintaining as many other parameters as possible. In the task, rats are first trained to discriminate between two tones that vary in duration (0.5 or 2 s) and to press the correct lever to obtain a food reward. After reaching response criteria (>70% accuracy), rats are trained to expect only partial reinforcement before being presented with more ambiguous tones (0.9 and 1.6 s) with correct identification of the tone being rewarded three times more frequently for one stimuli than the other. As with humans, rats develop a response bias, which can be bi-directionally altered via pharmacological intervention. Thus, acute administration of the D2/D3 receptor agonist, pramipexole, blunted response bias, as had been shown in healthy human subjects (Pizzagalli et al. 2008), whereas amphetamine administration increased response bias (Der-Avakian et al. 2013). Thus, while more studies are required to validate this task, the PRT represents a translationally relevant reward-related readout to employ in animal models of MDD (see Markou et al. (2013) for review).

Such models assessing negative bias or valence show great translational promise and can complement the models and readouts discussed in this review (for review see Robinson and Roiser (2016)).

Important considerations when designing/using animal models

In addition to the factors we have described above, there are a number of important considerations that researchers must consider when using animal models of MDD that may influence their findings. We will discuss some of these below, and it is also important to remember that some of the factors described below can actually be incorporated into the design of the model/study.

Strain differences

It has been repeatedly shown that a *mouse* is not a *mouse* and a *rat* is not a *rat*. For example, substantial strain differences have been demonstrated in both the TST and FST for baseline behaviour and response to antidepressant administration (Crowley et al. 2005; Lucki et al. 2001). These data, along with many others (for review, see Jacobson and Cryan (2007)), reveal that the appropriate choice of background strain is important. For example, strains that already show high levels of depressive-like behaviour (e.g. BALB/cJ) may not be a good starting point for chronic stress paradigms as there may be a ceiling effect in place. Similarly, given strain differences in the response to drug administration, such as the tricyclic antidepressant desipramine (Lucki et al. 2001) and the $GABA_B$ receptor agonist baclofen (Jacobson and Cryan 2005), consideration should be given to the neurobiological readout and/or substance that you intend to study when choosing the strain to perform your experiments in.

However, strain differences can also be utilised in order to study the neurobiological underpinnings of MDD. This has been repeatedly demonstrated with the Wistar Kyoto rat line (WKY), which show numerous behavioural and neurobiological qualities that render them a "depressed line" compared with their control line (Sprague Dawley). Thus, WKY rats have been shown in numerous depression-related behaviour tests to show a depressive-like phenotype, which is reversible by antidepressant administration (Malkesman and Weller 2009; Willner and Belzung 2015). Moreover, they also show changes in plasticity that have been observed in MDD patients, such as reduced GFAP expression in cortico-limbic regions of the brain (Gosselin et al. 2009). Similar studies have been performed using mice lines that differ in their behaviour in depression-related tests in order to assess potential mechanisms and systems that may underlie the differences in behaviour (see Jacobson and Cryan (2007) for a review). Further study of the biological substrates that underlie such strain differences will provide important information regarding the aetiology of traits relevant to MDD.

Resilient vs susceptible animals and breeding for extremes in behaviour

Before it became more common in the literature due to the separation of mice subjected to social defeat in to "susceptible" and "resilient" groups, a number of models had been generated due to differences in behavioural

responding to specific tests. For example, since only approximately 70% of rodents, given an inescapable shock, develop learned helplessness, lines were bred for learned helplessness (cLH) or resistance to learned helplessness (cNLH). Although bred based on their response in one test, cLH rats show anhedonic-like behaviour, as well as an impaired response to antidepressant administration (Henn and Vollmayr 2005). This is a common occurrence in other breeding lines that have been established based on the behavioural responding in a particular task, such as the non-helpless NH/Rouen mouse line and the helpless H/Rouen line, which were initially bred for extremes in behaviour in the tail suspension test (El Yacoubi et al. 2013), the Flinders Sensitive Line, bred for susceptibility to anticholinesterase agents and the high-anxiety-related behaviour (HAB) rats and mice, bred for extremes in behaviour on the elevated plus maze (Landgraf et al. 2007; Neumann et al. 2011; Sah et al. 2012). In all instances, these lines have been shown to have structural or plasticity changes that may be relevant for MDD, such as differences in the number of excitatory synapses in the infralimbic cortex of cLH rats (Seese et al. 2013), differences in metabotropic glutamate receptor expression in NH and H/Rouen mice (O'Connor et al. 2013), mitochondrial morphology and number in the hippocampus of FSL rats (Chen et al. 2013) and hippocampal neurogenesis in HAB rats and mice (Lucassen et al. 2009; Sah et al. 2012).

As mentioned at the start of the section, in the last decade or so, it has repeatedly been demonstrated that it is also possible to separate individuals based on their susceptibility or resilience to chronic social defeat (Friedman et al. 2016; Friedman et al. 2014; Krishnan et al. 2007). This has led to substantial research into what differs between two subgroups that are subjected to the same quality of stressor. The usual measure at the end of the stress procedure is to assess social avoidance behaviour, and it has been repeatedly demonstrated that approximately 35% of mice subjected to the defeat paradigm will not display social avoidance (Krishnan et al. 2007; Russo et al. 2012). Perhaps in contrast to initial beliefs, the studies assessing the molecular alterations between the susceptible and resilient groups of mice have shown that resilient mice actually display a greater array of alterations than susceptible mice (for review, see Russo et al. (2012)). However, strain differences can play a role in this model as well, since not all laboratories have been able to replicate the social-defeat induced avoidance in C57/BL6 mice, but only in the more stress-reactive BALB/c line (Razzoli et al. 2011; Savignac et al. 2011). Recently, it has also been shown that removal of the actual physical defeat from this model can also lead to reduced stress responsivity, depression- and anxiety-related behaviour in mice (Brockhurst et al. 2015). In this case, the authors argue that this "stress inoculation training" leads to a variety of learning processes that may reflect similar interventions used in humans to build stress resilience (Brockhurst et al. 2015). These findings of stress inoculation and resilience resonate with Han Selye's statement that "*It is not stress that kills us, but our reaction to it*" and also opens a newer approach to the study of MDD, namely resilience mechanisms in addition to mechanisms that convey vulnerability.

Age and sex

As is evident from the review thus far, rodent models of depression are typically performed in adult male mice and rats (at the time of testing/assessment). However, MDD is twice as prevalent in women, and there is an increasing awareness of both adolescent and old-age depression in patients. The former group has recently been addressed by the NIH who now ask for both males and females to be studied in proposals. However, many considerations need to be addressed when assessing males and females. For example, there are numerous differences in basal parameters that are typically studied in depression models and tests of antidepressant efficacy, such as corticosterone levels, behaviour in the FST, neurogenesis and drug metabolism/response (Bale and Epperson 2016; Dalla et al. 2010, 2011; Galea et al. 2016; Gobinath et al. 2014; Hillerer et al. 2013; Kokras and Dalla 2014; Kokras et al. 2011; Slattery and Hillerer 2016). Other issues that need to be addressed are the oestrous cycle, which can also affect both brain and behaviour, as well as the fact that male and female rodents display differences in aggressive behaviour making comparison of social defeat models, which are believed to be more relevant to the human situation, difficult to compare. Therefore, it is clear that much more research effort in to the establishment of appropriate models with which to study MDD in female rodents is warranted.

The same situation is true for old-age depression, with the majority of studies using older rodents focussing on neurodegenerative disorders. As with females, there are a number of problems that need to be overcome in order to study depressive-like behaviour in old-age, one of the most striking being that the majority of tests rely on locomotor activity. Like stated above for females, there is also evidence that elderly patients respond differentially to antidepressants (Calati et al. 2013), as it is also true in rodents (Couillard-Despres et al. 2009). Therefore, both age and sex of the rodents that are studied in models for depression will have important implication for the behavioural and neurobiological outcomes that are reported.

Onset of action and treatment resistance

Two clear requirements that need to be improved in the treatment of MDD are the delayed onset of action of current drugs in patients and the high level of treatment resistance, which is in part related to the high placebo response. These issues can be readily assessed in preclinical models, for example by

splitting groups into treatment responders and non-responders. Then, as detailed above for susceptible and resilience mice, the molecular differences between the two subgroups can be assessed to ascertain factors that may underlie the different response outcomes. Onset of action of treatment can be harder to determine in animal models as often the behavioural readout can only be performed once. However, there are a number of tests outlined in this review that can be used repeatedly, such as ICSS and sucrose preference, which can be used to determine when the treatment restores response or intake to control levels, as well as performing a battery of different tests.

Laboratory conditions

As addressed in the section regarding the criteria that are required to fulfil when attempted to model depression in rodent, inter-laboratory replication is an important factor. This is often neglected but is pertinent since many findings can be related to conditions at the study centre, as elegantly outlined by Crabbe and colleagues (Crabbe et al. 1999). In more recent studies, it has been demonstrated that the gender of the experimenter performing behavioural tests can influence the result. For example, mice and rats were shown to produce enhanced stress responses to male, in comparison with female, experimenters, as well as stress-induced analgesia, decreased pain-related behaviour and increased anxiety-related behaviour (Sorge et al. 2014). Furthermore, as legal requirements for providing animals with environmental enrichment in their housing differ across countries/laboratories, this factor can also influence the outcome of experiments. Indeed, environmental enrichment has been shown to counteract the effect of stress (Crofton et al. 2015). Moreover, we could also reveal by subjecting mice to repeated social defeats across 19 days in either the active or inactive phase that the time of stressor exposure is also critical (Bartlang et al. 2012). Other factors that have been recently shown to affect results from different laboratories include the gut microbiome. We have reported on the potential role for commensal gut bacteria such as lactobacillus rhamnosus as mediators of stress resilience, consistent with the concept of the gut microbiome having a significant influence on behaviour (Sherwin et al. 2016a; Sherwin et al. 2016b). In turn, it has been recently shown that chronic psychosocial stress only in the presence of certain gut pathobionts causes spontaneous colitis (Langgartner et al. 2016b) and that the presence of microorganisms with immunoregulatory properties prevents negative stress consequences even in the presence of these gut pathobionts (Reber et al. 2016 PNAS). This growing emphasis on the relationship between the gut microbiota and behaviour means that it is another variable to take into account when cross-comparing studies and laboratories.

There are likely to be more factors to consider that need to be systematically studied in order to reveal their relevance such as light conditions and acidified water vs normal tap water (Langgartner et al. 2016a) and food supply. These findings highlight the fact that different stress paradigms lead to varying outcomes and have to choose with care if being established in a new laboratory. Indeed, some of these issues were recently covered in news articles by Nature (http://www.nature.com/news/a-mouse-s-house-may-ruin-experiments-1.19335) and Science (http://www.sciencemag.org/news/2016/08/mouse-microbes-may-make-scientific-studies-harder-replicate).

Conclusions

At the beginning of a recent review article, the late Athina Markou quoted another Greek. *Epicurus (341–270 B.C.)* "*For it is then that we have need of pleasure, when we feel pain owing to the absence of pleasure*", which very appropriately reflects the theme of this review article. Indeed, as outlined above, one of the most common findings following chronic stress exposure in rodents is a reduction in interest or consumption of reward-related stimuli, such as palatable food/drink and drugs of abuse. Thus, continued understanding of the changes that occur via convergence between the stress and reward pathways will enable us to gain greater insight into stress-induced anhedonia. Furthermore, determining factors underlying stress susceptibility/resilience, sex-, age- and laboratory-based differences may aid us to understand other aspects of the clinical landscape, such as gender differences and the role of other environmental factors, such as the microbiome, in MDD.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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