Abstract

The wide spectrum of disruptions that characterizes major depressive disorder (MDD) and bipolar disorder (BD) highlights the difficulties researchers are posed with as they try to mimic these disorders in the laboratory. Nonetheless, numerous attempts have been made to create rodent models of mood disorders or at least models of the symptoms of MDD and BD. Present antidepressants are all descendants of the serendipitous findings in the 1950s that the monoamine oxidase inhibitor iproniazid and the tricyclic antidepressant imipramine were effective antidepressants. Thus, the need for improved animal models to provide insights into the neuropathology underlying the disease is critical. Such information is in turn crucial for identifying new antidepressants and mood stabilisers. Currently, there is a shift away from traditional animal models to more focused research dealing with an endophenotype-style approach, genetic models, and incorporation of new findings from human neuroimaging and genetic studies. Such approaches are opening up more tractable avenues for understanding the neurobiological and genetic bases of these disorders. Further, such models promise to yield better translational animal models and hence more fruitful therapeutic targets. This overview focuses on such animal models and tests and how they can be used to assess MDD and BD in rodents.

Key Words: depression; cognition; animal model; stress; bipolar disorder

Introduction

Psychiatric disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are multifaceted, heterogeneous diseases and are among the leading medical and social problems in society. Indeed, MDD affects more than 340 million people worldwide and is predicted to become the leading cause of global disease burden by 2030 (Michaud et al. 2001), while a recent study conducted by the World Health Organization encompassing 24 different countries revealed that after neurological disorders, BD was associated with the greatest loss in work days per year (Alonso et al. 2011). Although there are a number of effective treatment options, they all work with a delayed onset of action and approximately 30–40% of patients do not respond to any therapy. Therefore, there is an urgent need for more efficacious and novel-acting treatments. However, although numerous potential antidepressants, and to a lesser extent mood stabilisers, have been identified in preclinical research, the vast majority have failed to show clinical efficacy (Cryan and Slattery 2007). A number of reasons for this failure rate have been identified, including high placebo response, the lack of objective diagnostic criteria (see Frazer and Morilak 2005 for a review), and the translatability of animal models (see Belzung 2014). In keeping with this, the more traditional paradigms are better referred to as tests of antidepressant activity (Cryan and Holmes 2005; Cryan et al. 2005; Cryan and Slattery 2007, 2010; Geyer and Markou 1995). Although these approaches have undoubtedly advanced our understanding of mood disorders, recent research focus has attempted to design better models, with the ultimate aim to make the findings more translational. However, given that MDD and BD are multifaceted, heterogeneous diseases with multiple symptoms as set out in the current diagnostic manuals (DSM-V and ICD-10; see Cryan and Holmes 2005 and www.dsm5.org for a list of diagnostic criteria), this goal remains challenging. This is compounded by our limited knowledge of the underlying factors that predispose to mood disorders. However, it is clear that genetics and stressful life events are clear players (Wong et al. 2012; Wong and Licinio 2001). In the following review, we discuss animal approaches to study these disorders and highlight their benefits and drawbacks.

What Are the Differences Between a Model and a Test?

The distinction between a model and a test is not always made clear and as a result, sometimes a test is called a model.
A model comprises both an independent variable, known as the inducing manipulation, and a dependent variable that is behavioural/neurochemical readout, whereas a test simply comprises the latter variable (Geyer and Markou 1995). As the underlying pathophysiology of MDD and BD is poorly understood, this has had a knock-on effect in choosing independent variables. In recent years, increased clinical experimental evidence has, however, provided preclinical researchers with more information to design the independent variables and, therefore, garner more information about the underlying aetiology of mood disorders. This approach has also been aided by the relatively recent focus on an endophenotype-based approach to study psychiatric disorders. In more detail, this more focused approach attempts to assess only one symptom, or marker, of the disease, thereby using characteristic endophenotypes of diseases and then modelling them independently rather than the whole syndrome (Cryan and Slattery 2007; Hasler et al. 2004, 2005; Slattery and Cryan 2011). This has the benefit of simplifying complex disorders, such as MDD and BD, into individual behaviours, which are more easily measurable in both patients and laboratory animals. Moreover, this approach is akin to preclinical testing, in which only one variable is generally measured and is likely to involve fewer genes (Gottesman and Gould 2003; Gould and Gottesman 2006). However, a number of symptoms of MDD and BD are clearly not measurable in preclinical paradigms, such as recurrent thoughts of death or suicide or excessive thoughts of guilt (see Slattery and Cryan 2011 for more details).

Criteria to Consider When Using/Creating Animal Models of Mood Disorders

In a perfect situation, any animal model reflecting a disease would have identical causative factors (construct validity), symptomology (face validity), and treatment modalities (predictive validity) (Geyer and Markou 1995). However, because the underlying aetiology and causative factors of MDD and BD are poorly understood, it is not feasible to base animal models of mood disorders solely on aetiology (Cryan et al. 2002). Thus, three general strategies to develop animal models have been used: (1) genetic manipulation, (2) selective breeding for behavioural extremes, and (3) environmental, physical, or pharmacological manipulations or a combination of the above (Neumann et al. 2011). Another issue when using animal models is the requirement for repeatability between laboratories, which implies strictly controlling all possible elements of the test. However, even if all factors within different laboratories are controlled as tightly as possible, the results can often be divergent (Crabbe et al. 1999). Additionally, as was shown with the recent modifications introduced to the traditional forced swim test (FST; see below), which provide greater reliability and information, a degree of flexibility is required to allow refinement (Cryan et al. 2002; Lucki 1997).

Traditional Animal Models and Tests of Depression

Despite the difficulties outlined above, a number of diverse animal models of depression have been widely utilized and many show substantial predictive validity (i.e. antidepressant administration reverses the behavioural parameters assessed). These animal models are often referred to as tests of antidepressant-like activity given that they have all been validated since the introduction of clinically approved medications (Markou et al. 2009). Numerous reviews have been dedicated to these models and their construct validity, which will only be briefly discussed here; thus, the interested reader is directed to these comprehensive articles (Belzung 2014; Berton et al. 2012; Chen et al. 2010; Cryan and Holmes 2005; Cryan and Slattery 2007, 2010; Cryan et al. 2005; Geyer and Markou 1995; Gould and Einaid 2007; Hales et al. 2014; Harro 2013; Henry et al. 2010; Joel and Yanelevitch-Yahav 2014; Kokras and Dalla 2014; Kronenberg et al. 2014; McArthur and Borsini 2006; Nestler and Hyman 2010; Perani and Slattery 2014; Pollak et al. 2010; Tanti and Belzung 2010).

FST and Tail Suspension Test (TST)

These tests represent the most widely utilized preclinical tests employed in basic research of depression. They are based on the observation that when mice or rats are subjected to an inescapable situation (i.e. cylinder filled with water or suspended by their tail) after initial escape-directed behaviour, the animals quickly adopt an immobile posture (Cryan et al. 2005; Petit-Demouliere et al. 2005). This change to immobility is believed to reflect behavioural despair; either a failure to persist with escape-directed behavior or a passive behavior to cease active forms of coping to the stressful stimuli (Cryan et al. 2002; Cryan and Slattery 2007; Slattery and Cryan 2006). It has been repeatedly demonstrated that clinically effective antidepressants, usually given acutely, increase the time that rodents spend in escape-directed behavior (see Cryan et al. 2005; Cryan and Slattery 2007; Petit-Demouliere et al. 2005). However, caution is required when employing these tests, because the readout, immobility, can be easily influenced by interventions that alter locomotor activity, which may lead to false positive or negative findings (Slattery and Cryan 2012). Moreover, the appropriate choice of mouse or rat strain must be employed, because they vary widely in their baseline activity in the FST (Crowley et al. 2005; Slattery and Cryan 2012). A major criticism that has been directed at these two tests is that they do not appear to reflect the clinical situation. However, recent studies have begun to shed light on the underlying circuitries/brain regions that are recruited in the test. Thus, recent data indicate that the hippocampus, infralimbic cortex, and ventral tegmental area to nucleus accumbens pathway and central dopamine signalling are crucial for FST-induced effects (Airan et al. 2007; Chaudhuri et al. 2013; Slattery et al. 2011; Tye et al. 2013; Warden et al. 2012).
Although the FST and TST appear to be similar in construct, it has been shown that different neurobiological substrates underlie them (Cryan and Holmes 2005; Cryan and Slattery 2007). For example, GABA<sub>B</sub> receptor antagonists and knockout mice have been shown to have antidepressant-like properties in the FST but not TST (Slattery and Cryan 2006). Therefore, studies such as the aforementioned that assess the circuitry and systems that underlie the behavioral and pharmacological correlates of these tests will help to improve their validity and employment. Finally, the recent landmark finding that inactivation of Brodmann Area 25 using deep brain stimulation could alleviate depressive symptoms in treatment-resistant patients (Mayberg et al. 2005) gave rise to the possibility of examining the effects of a similar treatment in an animal model of antidepressant activity. Analogous to the human situation, inactivation of the infralimbic cortex, the rodent correlate of Brodmann Area 25, resulted in an antidepressant-like phenotype in normal rats. More pertinently, this finding could be replicated in rats with an innate high level of depression-related behavior, analogous to the findings in treatment-resistant patients (Slattery et al. 2011). These results show that it is possible to replicate findings from a clinical trial in rodents, and with the development of more sophisticated clinical studies, such reverse translational studies will become more common and informative.

**Learned Helplessness**

This model also takes advantage of placing animals in to inescapable situation. However, in this instance rodents are subjected to inescapable shocks and then reintroduced to the same environment, but this time with escape possible. In contrast, the control animals are subjected to escapable shocks each time. A subset of animals will exhibit a reduced number of escape attempts and such a deficit is considered to be indicative of a depressive-like phenotype, which is not related to the shock per se. This can enable comparison of non-helpless and helpless cohorts at a variety of levels (e.g. behavioral, neuronal, and molecular) to assess potential differences underlying their phenotype. Unlike the FST and TST, pharmacological reversal of helpless behavior requires at least 3 to 5 days of antidepressant administration (see Pryce et al. 2011 for more details).

**Olfactory Bullectomy**

Unlike humans, the olfactory bulbs constitute a large percentage of the rodent brain and their removal results in multiple long-term alterations in behavior, immune, endocrine, and neurochemical functions (Cryan et al. 2002; Song and Leonard 2005). Importantly, the primary reason for these alterations is not the loss of smell, as administration of zinc sulphate to induce anosmia does not lead to the same phenotype (Song and Leonard 2005). The most consistent behavioral alterations caused by bulbectomy are hyperactivity in a novel, brightly lit, open field arena and deficits in passive avoidance learning, both of which are responsive to chronic, but not acute, antidepressant administration (Cryan et al. 1998, 1999; Kelly et al. 1997; Song and Leonard 2005). Moreover, a number of the neurochemical adaptations, such as 5-HT hyper-innervation (van der Stelt et al. 2005) and disinhibition of the amygdala are also reversed by chronic antidepressant treatment (Song and Leonard 2005; van der Stelt et al. 2005). Thus, this time frame is more akin to that observed in the clinical situation, which makes bulbectomy an attractive model. More recently, it was shown that peripheral administration of 5-HT<sub>2C</sub> receptor antagonists for 5 days, but not citalopram, reversed the behavioral phenotype of olfactory bulbectomy, suggesting it may be a suitable model to look for fast-onset of action drugs (Opal et al. 2013). Other serotonergic agents have also been shown to rapidly reverse the bulbectomy-induced phenotype, such as 7 days with 5-HT<sub>7</sub> receptor antagonists (Mnie-Filali et al. 2011) and 3 days with a 5-HT<sub>4</sub> receptor antagonist (Lucas et al. 2007). Therefore, it would be of great interest to determine whether ketamine would display its fast-acting antidepressant action in this model. However, the fast-acting augmentation of pindolol onto SSRI treatments does not work in this model (Cryan et al. 1998). Moreover, it is performed in only a few laboratories, and it is becoming increasing difficult in a number of countries to receive ethical approval for such an invasive procedure.

**Chronic Stress Procedures (Nonsocial)**

Chronic stress exposure is a well-documented risk factor for MDD and has resulted in the use of a number of chronic mild stress (CMS) paradigms based on the initial discovery by Katz that exposure to severe predictable stressors led to an anhedonic phenotype in rats (Katz 1981). Reducing the severity of the stressors (e.g. social instability, 24-hour light exposure, restraint, food and water deprivation) but prolonging their duration and making them unpredictable resulted in the CMS paradigm. These models are attractive as the depressive-like phenotype provoked by the stress procedure, usually assessed by sucrose preference, can only be reversed by chronic antidepressant treatment (for a comprehensive review of CMS, see Nollet et al. 2013). A potential confound of such studies should be considered, as the sucrose’s calorific content may lead to increased consumption to offset the effect of stress. However, this implies that decreased consumption is reflective of anhedonia, because animals would be more inclined to intake sucrose to gain the increased energy. It is also possible to avoid such a confound by using saccharin instead, because animals prefer it over water and it has no calorific benefit. Finally, due to their complexity and increased number of variables, such protocols are difficult to standardize and can often lead to inconsistent behavioral and physiological, and hence molecular and neuronal, phenotypes.

**Assessing Specific Endophenotypes/Symptoms**

The majority of the tests and models described above, although showing strong predictive validity, do not, at least on the
surface, possess strong face validity (i.e. similar symptoms to the human situation). However, the fact that several symptoms, or symptom clusters, can be modelled in both rodents (and humans) has resulted in a number of newer approaches to study mood disorders in basic research. Thus, rather than attempting to model the whole syndrome, recent approaches have focussed on studying a specific symptom or endophenotype of the disorder. In this case, an endophenotype relates to specific genetic factor, biological substrate, and symptomology (Beltzung 2014; Hasler and Northoff 2011). This symptom- or endophenotype-based, approach has both advantages and disadvantages. Thus, it simplifies the study of multifaceted disorders to its individual components, which are likely to be controlled by fewer genes and more reliable across laboratories but may lead to findings that do not translate to the clinical situation (Cryan et al. 2002; Hasler et al. 2004). However, with regard to this latter potential problem, such an approach may increase our understanding of the aetiology and treatment of specific symptoms such as those that follow that may be beneficial in numerous psychiatric disorders. Alternatively, it is possible that the findings are too specific to a certain symptom and therefore translate to novel treatments that are not effective for MDD/BD. As mentioned above regarding the design of animal models, a number of considerations should be adhered to when following such an approach. Thus, the chosen endophenotype or symptom should be inherently relevant to the disease of interest, and its heritability and centrality to the disorder should also be considered (Cryan and Slattery 2007; Hasler et al. 2004; Slattery and Cryan 2011). Below, we discuss anhedonia and cognitive processing which have been studied in this fashion in relation to MDD. For a more comprehensive review, including other endophenotypes and symptoms, we refer the reader to other reviews (Cryan and Holmes 2005; Cryan and Slattery 2007, 2010).

Anhedonia

Anhedonia has been used as a behavioral end point for a number of the existing animal models of depression, such as CMS and maternal separation, where sucrose preference is often measured (Slattery et al. 2007). A more recent approach to study anhedonia in rodents is the female urine sniffing test. In this test, males are allowed to freely explore a novel environment where sawdust containing female urine has been placed in one section of the arena. Under normal circumstances, male rodents will spend the majority of the time in the arena investigating the section with the female urine as a sexually motivated-driven behavior. It has been demonstrated that animals that have been subjected to stress will spend less time investigating the female urine and that this can be reversed by antidepressant treatment or exposure to a high-fat diet (Finger et al. 2011; Malkesman et al. 2010).

Moreover, it is possible to study anhedonia following particular manipulations, genetic or environmental, utilizing paradigms that were initially used in the field of drug addiction, for example, progressive ratio responding or intracranial self-stimulation (ICSS). Numerous researchers have used such readouts to assess the effect that stress exposure or withdrawal from drugs of abuse (Cryan et al. 2003) has on this endophenotype of depression. Moreover, two recent studies have combined the olfactory bulbectomy model with ICSS. Although we could show that anhedonia was observed immediately after bulbectomy, this lasted only 7 days (Slattery et al. 2007). However, conflicting results were observed in relation to the ability of cocaine and amphetamine to reduce the ICSS response threshold (Romeas et al. 2009; Slattery et al. 2007), which may be due to the different psychostimulants employed. Early-life stress, which has been used to study MDD and anxiety disorders in preclinical research, has recently been shown to affect ICSS responding following social defeat. Thus, rats that underwent maternal separation in early life display an anhedonic phenotype to repeated social defeat and increased reward enhancing effect to acute amphetamine 1 week after stress termination (Der-Avakian and Markou 2010). Although the use of this model is time and labor intensive, ICSS has the advantage that it can be repeatedly performed in the same animal without habituation or sensitization (such as occurs in other MDD tests). Therefore, it is theoretically possible to use ICSS with animal models that lead to long-lasting anhedonic phenotype to determine not only the dose range of “antidepressants” that are required to alleviate the anhedonia but also whether different drug concentrations have differential temporal time frames. Indeed, it has recently been shown that chronic social defeat stress in both rats (Der-Avakian et al. 2014) and mice (Donahue et al. 2014) leads to a persistent anhedonic phenotype as assessed by ICSS responding. Such information at present is not attainable in other MDD models/tests without resorting to truly large experimental numbers. Thus, more extensive use of the ICSS procedure in preclinical research would provide invaluable insights into the time course of alterations to the brain reward system and anhedonic-like behavior.

Studies have also shown that the reward system appears to be hypersensitive in severely depressed patients (Eshel and Roiser 2010; Naranjo et al. 2001; Tremblay et al. 2002, 2005). The hypersensitivity was associated with decreased activity of a number of regions of the reward circuitry as well as cortical regions following drug administration. These findings resemble the findings from recent animal studies revealing increased cocaine preference following chronic stress exposure (Krishnan et al. 2007). Interestingly, in this study, increased brain-derived neurotrophic factor signalling in the ventral tegmental area-nucleus accumbens pathway was found to underlie, at least in part, the depressed phenotype. Taken together, these studies reveal converging evidence from rodent and human studies supporting an alteration in the brain reward system in the aetiology of rodent and human models.

Cognitive Processes

Another endophenotype that has more recently been studied in relation to MDD is cognitive dysfunction. It has been repeatedly demonstrated that patients can have difficulty in concentrating and display more attention and processing of
negative stimuli than controls, which is believed to consolidate and prolong the depressive episode (Disner et al. 2011; Elliott et al. 1998, 2004). Although negative bias has not been as widely studied in animal models as other endophenotypes, there is growing evidence that rodents subjected to stress, for example the learned helpless paradigm, show similar negative bias (Enkel et al. 2010; Pryce et al. 2011, 2012; Pryce and Seifritz 2011; Richter et al. 2012). More recently, Robinson and co-workers have developed a model in rats to study affective bias (Stuart et al. 2013). This work is based on the fact that acute, not only chronic, antidepressant treatment can lead to a positive shift in emotion processing in humans (Browning et al. 2010), making it an attractive symptom to study. In this paradigm, rats are given two separate positive experiences of equal absolute value on different days under either neutral conditions or during pharmacological or affective state manipulations. Affective bias is then assessed using a preference test where both positively rewarded substrates are presented together. Using this test, the authors could show that acute antidepressant treatment leads to a positive bias towards the substrate paired with administration, whereas drugs associated with negative bias in humans also lead to a similar phenotype in the rats. Finally, opposite effects of acute social stress and environment enrichment were also shown, suggesting that this model is responsive to both pharmacological and environmental manipulation (Stuart et al. 2013). Another recent study that assessed the role of cognitive processing in depression focused on the beneficial effects of learned safety (Pollak et al. 2008). The authors define learned safety as “the learning and memory resulting from a conditioned inhibition training procedure,” and it is established using a fear conditioning paradigm in which the conditioned stimulus and the shock are not paired. When mice were then subjected to the FST or a CMS paradigm in the presence of the conditioned stimulus, the observed depressed-like behavior was decreased, findings that required intact hippocampal neurogenesis (Pollak et al. 2008). Thus, it appears that safety signals have antidepressant properties, perhaps by reducing the stressful situation for the individual. Therefore, such studies show that assessment of cognitive (dys)-function in rodent models of depression is possible and that more such studies are required to gain a greater insight into the biological substrates underlying this symptom.

**Social-Stress Based Models**

Given the evidence purporting social stress to be a risk factor for the development, not only of cardiovascular diseases but also of MDD in vulnerable individuals, recent attempts have focused on the development of social stress paradigms (Berton et al. 2006; Finger et al. 2011; Krishnan et al. 2007; Peters et al. 2013; Reber et al. 2006, 2007). Such paradigms are believed to be more relevant to the human situation than non-social stress paradigms (e.g. repeated restraint; Cryan and Slattery 2007; Reber 2012). Social defeat (Berton et al. 2006), chronic subordinate colony housing in mice (Reber et al. 2007), social defeat overcrowding (Fi...
be preceded by stress, whereas in the majority of cases such stress does not lead to the development of depression (Kendler et al. 1999). Similar variation to stressors has also been shown in preclinical studies, with some animals displaying high or low behavioral responses. For example, approximately 70% of rats exposed to inescapable stressors subsequently display helpless behavior (Henn and Vollmayr 2005). These observations have formed the basis of a number of selective breeding programs, such as the Flinders Sensitive Line rats and High- versus Low- anxiety-related behavior rodents, which have been extensively reviewed elsewhere (Bunck et al. 2009; Landgraf et al. 2007; Neumann et al. 2011). Such breeding programs have revealed the importance of selectively bred lines for studying the underlying aetiology of a disease, such as depression and anxiety, and also potential novel therapeutic strategies to test in the clinic. Moreover, they show the importance of combining a genetic model with stress exposure, as this is likely to translate to the human situation more accurately.

Sex Differences in Modelling MDD

Women exhibit a higher susceptibility to stress-related illnesses, such as mood and anxiety disorders, than men in general (Kessler 2003), which is particularly true during their reproductive years (Gutierrez-Lobos et al. 2002). Furthermore, it is apparent that there are sex differences in drug metabolism, which may relate to different effective doses of novel antidepressants between males and females (Kokras et al. 2011). Despite this, most basic studies assessing MDD and BD are performed in males. This is due, in part, to the complexity of studying females given the differences in a number of factors that are observed across the oestrus cycle, for example OXT-R expression (Bale et al. 1995) and HPA axis activity (Atkinson and Waddell 1997). Although traditional tests have been employed to study MDD in females (e.g. FST, TST, sucrose preference test), many other tests are not appropriate (e.g. female urine sniffing test). In light of this, it is important to note that forms of stress that are effective in males may not be in females and vice versa (see Hillerer et al. 2012; Perani and Slattery 2014 for reviews). Moreover, corticotropin-releasing factor overexpression, mimicking chronic stress exposure, can lead to a lengthening of the oestrus cycle (Keen-Rhinehart et al. 2009), complicating the choice of appropriate controls. Female rodents tend to exhibit greater HPA axis responses to stress and display less habituation to repeated stress compared with males (see O’Leary and Cryan 2013 for review). Such findings would appear to be in keeping with those in humans showing that women are more susceptible to stress-related illnesses. Indeed, in one of the few studies that have compared males and females, females showed exaggerated FST immobility and differential response to antidepressants (Dalla et al. 2010, 2011), although the phenotype induced by the learned helpless paradigm between the sexes is less clear (Chourbaji et al. 2010; Dalla et al. 2011). There have also been studies that employ the sucrose preference test to assess anhedonia in females following stress exposure, but these have been relatively few (for review see Kokras and Dalla 2014). Therefore, many more studies are required before a clearer picture regarding the utility of such tests for assessing MDD in females is feasible. Furthermore, one of the periods of highest risk for women to develop psychiatric disorders is during the peripartum period such as postpartum depression, which affects 15–20% of mothers (O’Hara and McCabe 2013; Perani and Slattery 2014). A number of risk factors have been identified that may increase the risk of postpartum depression, including the dramatic fluctuation in sex steroids and stress exposure (Bloch et al. 2000, 2005; Brummelte and Galea 2010; Hillerer et al. 2012). Although it is unlikely that a specific rodent model of postpartum depression can be achieved, a number approaches have been utilized to provide a better understanding of its etiology (see Brummelte and Galea 2010; Perani and Slattery 2014 for reviews).

Modelling Treatment-Resistant Depression

As stated above, many patients do not respond to any antidepressant therapy currently available, and many responders stop taking the medication due to a number of reasons, particularly because of the side effects of the treatment. Therefore, it is feasible to conceive of animal models that could be utilized to assess the neurobiology and novel treatment options of treatment-resistant depression. We have already mentioned above one such study, where findings from a human study were reverse-translated in to animals (see FST section above) (Slattery et al. 2011). Indeed, similar findings were also observed when rodents received deep brain stimulation in the rodent correlate, the infralimbic cortex, of Broadmann Area 25 that was targeted in the human study (Hamani et al. 2010). Another approach that has been taken is to separate antidepressant responders and nonresponders in a CMS paradigm and assess the molecular characteristics that differ between the groups (Bisgaard et al. 2012; Christensen et al. 2011). Similarly, while many strain differences are observed in FST behavior, it can also be stated that many strains do not respond to antidepressant treatment (Crowley et al. 2005; O’Leary and Cryan 2013). Therefore, such strains can be assessed to determine if alternative or augmentative treatments may restore the antidepressant efficacy of the currently available therapeutics (see O’Leary and Cryan 2013 for review). Finally, in recent years, there has been substantial interest in ketamine, as it has been shown to have rapid antidepressant effects in humans that can last up to 1 week (Niciu et al. 2014; Zarate et al. 2006, 2013a, 2013b), which has been recapitulated in animal models (Beurel et al. 2011; Duman and Aghajanian 2012; Li et al. 2010). By further exploring the mechanism of action of ketamine, novel targets may be uncovered that may be more effective in treatment-resistant patients (Cryan and O’Leary 2010; Naughton et al. 2014; O’Connor et al. 2013).

Modelling Depression in Old Age

Similar to the statement above regarding the predilection to perform MDD studies in males, the vast majority of studies
<table>
<thead>
<tr>
<th>Animal model/test</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>FST</td>
<td>Rodents placed in an inescapable container of water swim more following antidepressant administration</td>
<td>Ease of use, high throughput, responsive to AD, inter-laboratory reliability, but responsive to acute drug administration, reliant on motor function, and not always responsive to SSRIs</td>
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<tr>
<td>Modified FST</td>
<td>Same as above but swimming and climbing behaviors are separated and increased with serotonergic or catecholaminergic antidepressants, respectively</td>
<td>Ease of use, high throughput, responsive to AD (including SSRIs), inter-laboratory reliability, but responsive to acute drug administration and reliant on motor function</td>
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<tr>
<td>TST</td>
<td>Rodents, chiefly mice, when hung from the tail will adopt an immobile posture. Antidepressant treatment increases the time animals spend in active behaviors</td>
<td>Ease of use, high throughput, inter-laboratory reliability, responsive to antidepressants, but may differ from FST results, responsive to acute drug administration, and reliant on motor function</td>
</tr>
<tr>
<td>CMS</td>
<td>Animals are subjected to a variety of unpredictable stressors, which leads to a constellation of symptoms that are reversed by antidepressant treatment</td>
<td>Stress exposure increases depressive symptoms in susceptible rodents, requires chronic antidepressant, but has low reliability and throughput</td>
</tr>
<tr>
<td>DRL-72</td>
<td>Reinforcement of voluntary responses (e.g. lever presses) with inter-responses longer than 72 s and punishment for incorrect responding. Antidepressant administration improves the number of reinforced trials</td>
<td>Models cognitive aspect of depression, sensitive to TCAs and SSRIs, but not widely utilized, time-consuming, and may not detect novel antidepressants</td>
</tr>
<tr>
<td>Drug-withdrawal paradigms</td>
<td>When animals are withdrawn from drugs of abuse, they display numerous characteristics that resemble those observed in depression</td>
<td>Face validity, responsive to AD, model core symptom of depression, but low throughput and expensive</td>
</tr>
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<td>Learned helplessness</td>
<td>Animals exposed to inescapable shocks subsequently fail to escape when able to. Antidepressant treatment increases the number of escapes; not all animals develop this helpless behavior</td>
<td>Responds to some AD, causes depression-like symptoms, not all animals become helpless, which can enable comparison between helpless and nonhelpless cohorts, but requires foot-shock</td>
</tr>
<tr>
<td>Maternal deprivation</td>
<td>When animals are separated from the mother during early postnatal life, they can develop a number of depression- and anxiety like behavioral characteristics. These behaviors are not present in all animals subjected to this treatment</td>
<td>Early-life stress increase MDD likelihood in humans, deficits in reward, but has low reliability and throughput</td>
</tr>
<tr>
<td>Olfactory bulbectomy</td>
<td>Removal of the olfactory bulbs causes a constellation of behavioral and neurochemical alterations, which are only reversed by chronic antidepressant treatment</td>
<td>Requires chronic AD, translational neurochemical and structural changes, but not utilized and mainly reliant on motor function</td>
</tr>
<tr>
<td>Reward paradigms</td>
<td>It is possible to study anhedonia in animals following other manipulations by utilizing paradigms that were initially used in the field of drug addiction, for example, progressive ratio responding or ICSS</td>
<td>Respond to some antidepressants, analogous to core symptom of depression, but not well-validated and low throughput</td>
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are also performed in young adults. However, the incidence of MDD in adolescence and old age has increased substantially in recent years and, although there is a great body of work assessing the effect of early-life stress and depression (see McClelland et al. 2011; Murgatroyd and Spengler 2011; Pryce and Feldon 2003 for reviews), the field of aged depression has not received as much study. It has been shown, for example, that antidepressants are less effective in older patients (Nelson et al. 1995; Roose et al. 1994). Hippocampal neurogenesis, often implicated in both the pathophysiology of depression and antidepressant efficacy (Santarelli et al. 2003; Snyder et al. 2011) has been shown to both decrease with age and become less sensitive to antidepressant treatment in aged rats (Couillard-Despres et al. 2009; Villeda et al. 2011). Therefore, it is possible to envisage that hippocampal neurogenesis may play a role in depression in old age; although studies are required to reveal a causal link. The traditional tests of depression highlighted above may be of less use to study depression in aged rodents given their reliance on motor activity, but some of the novel approaches, such as assessing affective bias (Stuart et al. 2013), learned safety (Pollak et al. 2008), or social-stress based models may provide a starting point to improve our understanding of the neurobiology of MDD in old age. Another interesting approach in this field is the fact that both aged humans and rodents have elevated immune activation (Kinsey et al. 2008; Shaw et al. 2013) and given the immune hypotheses of MDD (Leonard and Maes 2012; Maes 2008; Miller et al. 2009), immune challenge paradigms may represent a novel approach to study the pathophysiology of old-age MDD. Such studies have important translational value as treatment modalities that are effective in aged animals are likely to reflect the situation in elderly patients to a greater degree. However, there are also challenges to developing such models, including adequately separating the normal cognitive decline due to ageing versus an induced deficit.

### Animal Approaches to Study BD

There have also been a number of models and tests employed to gain a better understanding of BD, which affects about 1% of the population and is characterized by a cycling between depressive episodes and mania. Mania reflects periods of irritable mood, elation, and overactivity as set out in the diagnostic manuals (DSM-IV and ICD-10) that last for >1 week (see Table 2). These symptoms may be concurrent with other alterations such as decreased need for sleep, aggressiveness, and poor judgement. There are a number of drugs available for the treatment/prophylaxis of BD, with the mood stabilizers such as lithium, carbamazepine, valproate, and newer options, including lamotrigine and atypical antipsychotics being used. Thus, as for MDD, the lack of definitive biological changes and understanding of the aetiology of BD, as well as its heterogeneity, has hindered preclinical research attempts to investigate this disorder (Chen et al. 2010; Cryan and Slattery 2007; Tanti and Belzung 2010; Young et al. 2011). Therefore,
scientists again have tended to use an endophenotype-based approach to study BD by focussing on several key symptoms associated with BD.

The first attempts to model mania in basic research centered around the fact that psychostimulant administration causes hyperactivity in rodents. For example, it has repeatedly been shown that acute lithium administration can reverse amphetamine-induced hyperactivity in rodents, although there are a number of caveats that can affect this behavior, including environmental novelty, circadian rhythm, and chronicity of drug administration. A number of other drugs that lead to hyperactivity have also been employed, such as the adenosine triphosphatase inhibitor ouabain and the dopaminergic agent quinpirole (see Herman et al. 2007; Young et al. 2011 for reviews). Although helpful, assessment of purely locomotor activity can provide only limited information regarding the aetiology of a complex disorder such as BD. Therefore, a number of manipulations have been studied in relation to mania, including sleep deprivation (Szabo et al. 2009) and social defeat stress (Einat 2007b). Such manipulations, while causing hyperactivity, also lead to other symptoms such as increased aggression and changes in sexual activity, as well as molecular alterations in systems that are affected by mood stabilizers such as the glycogen synthase kinase-3 gene (for reviews see Young et al. 2011). As with MDD, genetic studies have been performed to assess mania (Chen et al. 2010; Einat 2007a; Malkesman et al. 2009; Saul et al. 2012), many of which take the form of assessing strain differences or disruptions in circadian rhythms (Roybal et al. 2007). Ultimately, as with MDD, utilization of a variety of approaches will be required to gain a better insight into the underlying pathophysiology of BD.

Conclusions and Outlook

Taken together, the findings outlined above and summarized in Tables 1 and 2 reveal the necessity of a multidisciplinary approach to study MDD and BD and show that novel approaches both in the paradigm employed and the readouts are required in basic research. Moreover, they show that at an individual systems level, drug manipulation may give different outcomes in relation to depressive symptomology and therefore, employing numerous models/tests is necessary to reach a conclusive answer. Ultimately, replication of such preclinical findings in a clinical setting is required to validate the findings from basic research.

Acknowledgments

The work by D.A.S. was supported in part by the Deutsche Forschungsgemeinschaft (DFG SL141/4-1). The work by J.F.C. was supported in part by Science Foundation Ireland in the form of a center grant (Alimentary Pharmabiotic Centre) under grant number SFI/12/RC/2273 and an Investigator Programme grant (SFI/12/IA/1537), by the Health Research Board of Ireland (grant number no. HRA_POR/2012/32), and by the European Community’s Seventh Framework Programme (grant no. FP7/2007-2013) under grant agreement no. 278948 (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndrome).

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