Affective biases in humans and animals

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Abstract

Depression is one of the most common but poorly understood psychiatric conditions. Although drug treatments and psychological therapies are effective in some patients, many do not achieve full remission and some patients receive no apparent benefit. Developing new improved treatments requires a better understanding of the aetiology of symptoms and evaluation of novel therapeutic targets in pre-clinical studies. Recent developments in our understanding of the basic cognitive processes that may contribute to the development of depression and its treatment offer new opportunities for both clinical and pre-clinical research. This chapter discusses the clinical evidence supporting a cognitive neuropsychological model of depression and antidepressant efficacy, and how this information may be usefully translated to pre-clinical investigation. Studies using neuropsychological tests in depressed patients and at risk populations have revealed basic negative emotional biases and disrupted reward and punishment processing, which may also impact on non-affective cognition. These affective biases are sensitive to antidepressant treatments with early onset effects observed, suggesting an important role in recovery. This clinical work into affective biases has also facilitated back-translation to animals and the development of assays to study affective biases in rodents. These animal studies suggest that, similar to humans, rodents in putative negative affective states exhibit negative affective biases on decision-making and memory tasks. Antidepressant treatments also induce positive biases in these rodent tasks, supporting the translational validity of this approach. Although still in the early stages of development and validation, affective biases in depression have the potential to offer new insights into the clinical condition, as well as facilitating the development of more translational approaches for pre-clinical studies.

Keywords: emotion, reward, rodents, animal model, major depressive disorder, antidepressants

Introduction

Depression is a debilitating condition that affects hundreds of millions of people worldwide. Its associated economic and social costs are enormous. For example, depression has been estimated to cost the EU economy £77 billion annually (Wittchen et al. 2011), much of which comprises reduced productivity and out-of-work benefits; and in the UK twice as many people die specifically as a result of suicide in depression than are killed on its roads each year (UK Office for National Statistics), representing a profound degree of personal tragedy for patients and their families.

At first glance, these statistics may seem at odds with the fact that depression is highly treatable, with robust evidence supporting both antidepressant medications and psychological therapies from large randomised controlled trials. However, effect sizes in these trials are generally small to medium relative to control conditions (Fournier et al. 2010), and when averaged across individuals represent just a few points on standard depression scales. In fact, such aggregate results mask great variability, as revealed by studies such as the STAR*D (Trivedi et al. 2006); which found that only around one-third of patients recovered fully on the first antidepressant they were prescribed, with another third subsequently recovering with either an alternate medication or psychotherapy. However, a third of patients remained unwell even following several courses of medication, representing months if not years of unsuccessful treatment.

Therefore, despite the existence of dozens of approved medications for depression, developing novel, better treatments remains a priority. In order to achieve this, pharmaceutical companies require valid animal models on which to test potential new treatments during early development. However, over the past decade this endeavour has been largely unsuccessful in identifying compounds that succeed in human trials (Agid et al. 2007), a major reason for the large-scale withdrawal of the pharmaceutical industry from research and development in psychiatry.

While there were several factors that precipitated this troubling development, a commonly cited issue is the relatively weak ability of animal models to recapitulate human psychiatric diagnoses. The latter are defined solely descriptively, on the basis of symptom clusters, because the pathological mechanisms that drive these symptoms in humans remain largely unknown. Instead, as discussed below and in the previous chapter, pre-clinical scientists working in psychiatry drug development often employed variants of stress exposure models developed from the 1960s onwards (e.g. learned helplessness, proposed by Seligman and colleagues), because these models demonstrated sensitivity to (serendipitously discovered) early antidepressants (McArthur and Borsini 2006). However, an important corollary of this approach is that the drugs it yielded (often SSRIs or SNRIs) largely converged around the same mechanism of action, specifically to increase monoamine transmission in the projection sites of these systems either through reuptake blockade or inhibiting metabolism. As discussed above, a substantial proportion of depressed patients do not respond to these classes of drugs, likely reflecting the heterogeneity in mechanisms driving depressive symptoms. New approaches to translation are therefore required in order to drive the development of novel treatments targeted at specific mechanisms, suited to specific subgroups of patients.

Classic animal models of depression derived from exposure to uncontrollable stress were considered to have strong face validity because (1) stress is known to precipitate depression in humans and (2) the behavioural features (“read-outs”) induced in rodents were superficially similar to certain symptoms in humans. For example the “behavioural despair” (giving up) evoked by the forced swim test (and other variants of learned helplessness) seemed to mimic depressive hopelessness and passivity; while reduced preference for sucrose bears a superficial similarity with anhedonia (Vollmayr et al. 2004). However, this approach could potentially be misleading, because different

cognitive and neural processes could potentially give rise to the same apparent symptoms. Moreover, different individuals (rodent or human) may respond to stress in very different ways. Indeed, the high degree of individual variability elicited by uncontrollably stressful situations in human experiments, and the descriptions of the attendant thought processes that participants reported, provided the rationale for Seligman and colleagues to move away from using ideas inspired by animal learned helplessness to explain depression (Abramson et al. 1978), towards high-level psychological descriptions of attributional style. Since such high-level constructs can only be accessed through introspection, and measured through verbal report or written questionnaires, impossible in animals, this marked a watershed parting of ways between "biological" and "psychological" explanations of depression, which to a large extent remains to this day.

In this paper we intend to show how this gap can be re-bridged. Though the conceptual distance between classic cognitive and animal models of depression is great, modern research has demonstrated that there exist several types of disrupted basic cognitive processes in depression. Importantly, unlike high-level psychological constructs such as attributional style or dysfunctional negative schemata, these processes can be measured in animals, allowing back-translation in a much more straightforward manner. Contemporary theoretical accounts of depression, which are consistent with extensive neurocognitive and psychopharmacological data in depressed patients, propose that basic cognitive processes in depression play a causal role in the development of both high-level psychological constructs and symptoms (Harmer et al. 2009a; Roiser et al. 2012); and, at least in some patients, are critically related to effective treatment.

We initially provide an overview of disrupted basic cognitive processes in depression, including both "hot" (emotionally-laden) and "cold" (emotionally-independent) cognition, emphasising the existence of negative processing biases in both reward and emotional processing. We then review psychopharmacological data that suggest that altered monoamine neurotransmission may have a critical role to play in driving these biases, and outline the cognitive neuropsychological model of depression, which incorporates both high-level psychological constructs and basic cognitive processes. Moving onto work in animals, we briefly review the limitations of current methods used to study depression-like behaviour, before explaining how basic cognitive processes derived from the human depression literature can be assessed in animals. We illustrate this concept with several examples, in particular focusing on interpretational bias and reinforcement learning. Importantly, we explain how such basic cognitive processes in animals are altered through psychopharmacological manipulations in a manner consistent with that observed in humans, paving the way for a translational approach to drug development grounded in cognitive neuroscience, with high potential for developing personalised treatment.

Disrupted "hot" and "cold" processing in depression

Demonstrations of negative processing biases in depression have a long history, going back to early cognitive theorists. Beck, among others, noted that depressed patients have a tendency to focus on current and past negative events (Beck 1967), which he ascribed to "negative schemata"; in other words, biased models of the environment, instantiated through early experience, which colour the processing of external sensory inputs. This idea of a "top-down" bias – that depressed individuals focus on negative stimuli because these accord with their expectations – forms an important part of traditional cognitive approach to understanding and treating depression. However, as explained in more detail below, recent cognitive models of depression incorporate the additional possibility that these processing biases are "bottom-up" in nature; that is, the inputs themselves are negatively biased.

Whether caused by “top-down” or “bottom-up” processing, or some combination of the two, the existence of mood-congruent negative processing biases on “hot” (i.e. emotionally-laden) cognitive tasks in depression is well established (reviewed in Roiser et al. 2012). By contrast, a consistent finding in never-depressed individuals is the presence of a small positive processing bias. Negatively biased processing in depressed groups, relative to controls, has been reported on tests of perception (e.g. face categorisation), memory (e.g. autobiographical narrative and free recall), attention (e.g. go/no-go or dot-probe tasks) and working memory (e.g. maintaining representations on-line in the face of distractors) (Erickson et al. 2005; Joormann and Gotlib 2006; 2008; Matt et al. 1992; Murphy et al. 1999). For example, one common approach is to present faces expressing positive or negative emotion (perhaps using morphing software to create gradations of intensity), and instructing participants to categorise them according to the six basic emotions: happy, sad, fearful, angry, disgusted and surprised. Depressed individuals exhibit a negative bias, miscategorising happy faces as negative, especially at lower intensity levels when emotion is more ambiguous (reviewed in Gotlib and Joormann 2010). Although beyond the scope of this article, it is worth noting that individuals suffering from anxiety (which is highly comorbid with depression) also exhibit negative processing biases, particularly during the early stages of stimulus processing (Teachman et al. 2012).

Another aspect of “hot” processing that is disrupted in depression is reinforcement processing. This encompasses tasks on which participants may gain or lose money, points or more basic reinforcers such as food, water or pain. These kinds of measures are highly relevant to symptoms such as anhedonia and difficulty in decision-making (Eshel and Roiser 2010; Huys et al. 2015). Although this literature is more recent, and therefore less extensive than that on emotion processing, a consistent pattern of results has emerged. While basic hedonic responses (i.e. ratings of reward pleasantness) appear to be intact in depression (Treadway and Zald 2011), a wealth of data supports the notion that depressed patients are hypo-sensitive to rewards (positive reinforcers) and hyper-sensitive to punishments (negative reinforcers) in terms of their influence on behaviour.

For example, several studies report that depressed individuals fail to adapt response patterns during a difficult, asymmetrically rewarded, perceptual decision task (Henriques and Davidson 2000; Henriques et al. 1994; Pizzagalli et al. 2008b) (such failure is also associated with poor outcome following treatment: Vrieze et al. 2013), and that they are unwilling to exert physical effort to obtain rewards (Treadway et al. 2012). Other studies reported reduced learning about stimuli associated with rewards in depression (Chase et al. 2010), especially in individuals with marked anhedonic symptoms. Finally, there have been several reports of impaired reward-related decision-making in depression, using tasks in which learning is not required. A consistent finding is that depressed individuals are relatively unwilling to place high bets on their decisions when they are very likely to win (Murphy et al. 2001; Roiser et al. 2009). Interestingly, reward processing abnormalities are also present in non-depressed individuals at high risk of developing symptoms, either because they have previously been depressed (Pizzagalli et al. 2008a) or are closely related to a depressed person (Rawal et al. 2013), underscoring the likely causal nature of these reinforcement processing abnormalities in the development of symptoms.

Fewer studies have focused specifically on punishment processing in depression. Early studies on this topic explored the hypothesis that the reliable “cold” (i.e. non-emotion dependent) cognitive impairment in depressed groups relative to matched controls, equivalent to approximately half of one standard deviation on most neuropsychological tests (Rock et al. 2013; Snyder 2012), could be related to a “catastrophic response to perceived negative feedback” (Beats et al. 1996). These studies examined the pattern of responding across trials, finding that on tests during which participants received feedback, depressed individuals were far more likely to make an error if they

had received an error on the previous trial (Elliott et al. 1997; Elliott et al. 1996). Therefore it may be that an ostensibly "cold" cognitive impairment is partly driven by exaggerated punishment processing, leading patients simply to give up when they make a mistake. An additional possibility may be that low motivation contributes to poor performance, though the extant data do not support this hypothesis unequivocally (see Austin et al. 2001 for a detailed discussion). Supporting the notion of exaggerated responses to punishment, probabilistic reversal learning tasks, on which misleading negative feedback is occasionally provided when the correct stimulus is selected, have revealed an exaggerated tendency to switch to the less frequently rewarded stimulus immediately following negative feedback in depressed individuals (Murphy et al. 2003; Taylor Tavares et al. 2008). However, disrupted reward and punishment processing cannot completely account for "cold" cognitive impairments in depression, for two reasons: 1) cognitive impairments remain even after symptoms have remitted (Rock et al. 2013), suggesting that they are not driven solely by current symptoms such as low motivation; 2) impairments are often observed on tests that do not feature explicit feedback.

Pharmacological effects on "hot" processing in depression

As discussed above, "hot" processing biases in depression have usually been ascribed to "top-down" influences, such as dysfunctional negative schemata. However, over the past decade a wealth of data has emerged from human experimental psychopharmacology studies suggesting that this explanation is likely to be incomplete. Specifically, this literature shows that manipulations that either boost or dampen transmission in the monoamine systems (dopamine, noradrenaline and serotonin) can shift "hot" processing biases over timescales on the order of hours, in both depressed patients and healthy volunteers. Since dysfunctional negative schemata are proposed to be stable, inflexible representations of the environment, which take months if not years to change, and are not thought to be directly affected by pharmacological manipulations, traditional cognitive models of depression cannot easily account for these effects. Instead, a new cognitive neuropsychological model of depression has been proposed, in which "bottom-up" biases, driven by disrupted monoamine transmission, play a critical role in the development of schemata, symptoms, and their treatment (Harmer et al. 2009a; Roiser et al. 2012).

The first direct support for the hypothesis that monoamine transmission may play a role in depressive symptoms (other than the mood effects of antidepressant drugs themselves, which was the original basis for the monoamine hypothesis) was derived from studies using the acute tryptophan depletion (ATD) method (Ruhe et al. 2007). This dietary manipulation, which acutely restricts the supply of the precursor of serotonin to the brain, was used in a series of experiments that identified a temporary recurrence of some depressive symptoms in remitted patients during the low tryptophan period (lasting a few hours), which were resolved following resumption of a normal diet (Delgado et al. 1990; Smith et al. 1997). However, later work suggested that pronounced effects on mood were mainly observed in patients maintained on serotonergic antidepressant medication (Ruhe et al. 2007) leading to the criticism that ATD may simply have reversed a treatment effect. Interestingly, mood effects of ATD were rarely observed in healthy volunteers. Around the same time, complementary research using positron emission tomography (PET) to measure serotonin receptors reported substantial alterations in depressed patients, particularly decreased 5-HT1A receptors, which were elevated following a variety of antidepressant treatments (Savitz et al. 2009).

The above investigations did not measure basic cognitive processing, but instead focused on symptoms. However, from the early 2000s onwards several studies in healthy subjects reported that ATD, as well as similar methods that deplete dopamine or noradrenaline, could elicit negative processing biases on "hot" processing tests, including emotional and reinforcement processing

(Cools et al. 2005; Firk and Markus 2008; Hasler et al. 2009; McLean et al. 2004; Murphy et al. 2002; Robinson et al. 2011; Rogers et al. 2003; Roiser et al. 2006; Roiser et al. 2008); importantly, mood was generally unaffected. Studies in remitted depressed individuals showed broadly similar results (Booij et al. 2005; Hayward et al. 2005; Munafo et al. 2006; Roiser et al. 2005), and in some cases the negative biases observed appeared remarkably similar to those observed in currently depressed patients, independent of any changes in mood. Complementing these findings, a series of studies taking the opposite approach, inducing a short-term boost in monoamine transmission with either antidepressant medication or tryptophan supplementation, found that emotional biases could also be shifted positively, in both healthy volunteers (Harmer et al. 2003; Harmer et al. 2004; Murphy et al. 2006) and depressed individuals (Bhagwagar et al. 2004; Harmer et al. 2009b), again, usually in the absence of mood changes (reviewed in Harmer 2008). In some cases, early enhancement of positive emotional processing during antidepressant treatment preceded and predicted later symptomatic relief in depressed individuals (Tranter et al. 2009).

A cognitive neuropsychological model of depression and its treatment

The above studies have motivated a reconsideration and extension of traditional cognitive models of depression in order to incorporate pharmacological effects (Harmer et al. 2009a; Roiser et al. 2012). While "top-down" biases, such as dysfunctional negative schemata, are still considered to play a critical role in the development and particularly the maintenance of depression, this new account additionally emphasises the contribution of biased "bottom-up" processing. In particular, it provides a cognitive framework for understanding how antidepressant drug exert their effects, and a mechanistic explanation for the genesis of negative schemata.

In the cognitive neuropsychological model "bottom-up" negative biases, which may be distally caused by either genetic or environmental influences that alter monoamine transmission (in particular psychosocial stress, which is thought to affect serotonin through its effects on cortisol: Dinan 1994), form a basis for the development of "top-down" biases. In other words, prolonged and consistent exposure to negatively-biased inputs ("bottom-up" processing biases) causes the brain to develop negatively-biased expectations ("top-down" processing biases). Since negative inputs accord with negative expectations, this state of combined "top-down" and "bottom-up" bias can become extremely stable. If it is experienced over a long period dysfunctional negative schemata will become entrenched, eliciting high-level negative cognitions and low mood.

In the cognitive neuropsychological model different treatment modalities (pharmacological and psychological) are proposed target the different mechanisms driving symptoms ("bottom-up" and "top-down", respectively), providing a theoretical basis for prescribing different treatments to different patients. Antidepressant medications are proposed to target "bottom-up" biases, and should be effective when "top-down" biases are weaker, since less fixed schemata are more likely to resolve spontaneously (i.e. without the assistance of a therapist) when negative inputs are removed. For example, the model would predict better response to medication in patients with shorter episodes and fewer dysfunctional attitudes, which is consistent with clinical data (Kohler et al. 2015; Riedel et al. 2011). By contrast, psychotherapy, for example CBT, is proposed to target "top-down" biases directly, and should be effective when "bottom-up" biases are weaker, since the absence of negatively biased inputs should enable schemata to resolve more easily. Indeed, there are some preliminary data supporting this prediction (see Figure 2 in Roiser et al. 2012). Finally, combining pharmacological and psychological treatment modalities should be more effective on average than either alone, for two reasons: 1) both "bottom-up" and "top-down" biases may operate simultaneously in some patients, meaning that both mechanisms need to be targeted for treatment to be effective; 2) in patients for whom either "top-down" or "bottom-up" biases are strong,

combining treatment modalities provides the best chance that the relevant mechanism will be targeted. Again, this prediction is consistent with clinical data, at least in severely depressed individuals (Hollon et al. 2014).

In summary, the cognitive neuropsychological model of depression provides a useful theoretical framework for understanding how basic negative processing biases drive the development and maintenance of symptoms, as well as a cognitive account of how antidepressant drugs exert their effects. As outlined in the following sections, the discovery that basic affective biases can be directly modulated by pharmacological treatments in humans (both positively and negatively) has inspired pre-clinical researchers to develop novel models of emotional disturbance in depression. In a departure from previous approaches, these are focused not on symptoms themselves, but instead on the affective biases thought to underpin them.

Limitations associated with standard animal models of depression

Recapitulating in animals the symptoms associated with psychiatric disorders is challenging and potentially an impossible task, particularly when the major species used for basic research are rodents. The human condition of depression is characterised by a heterogeneous range of symptoms, often assessed via self-report. In order to relate these symptoms to measurements in animals, a degree of anthropomorphism is inevitable. Methods used in animals to study depression-related behaviours have been strongly criticised; although perhaps it is not the methods which warrant criticism, but rather the way researchers have used the approaches and interpreted the resulting data.

Studies in animals provide researchers with the opportunity to test hypotheses about the cause and treatment of illness and are a key component in studies to understand the aetiology of depression and the development of new treatments. Patients' symptoms and associated psychopathology and neuropathology are often complex and further complicated by prolonged periods of illness. Unravelling the cause versus consequence of symptoms is therefore challenging. Animals offer a 'blank canvas' in which specific hypotheses can be tested. However, these studies depend on the use of translatable endpoints and quantification of affective biases in animals may provide one methodological step needed to achieve this goal.

Animal models used in depression research are considered in detail in the preceding chapter. Therefore, this section focuses on the assays used to quantify depression-related behaviours in rodents (Table 1). When considering animal models of depression, the term 'model' is often used to describe both the methods to induce a depression-like phenotype and those methods used to assay depression-like behaviour. The two key areas tested in depression-related studies are behavioural despair/hopelessness and anhedonia (Table 1). Neither of these behaviours directly translate to measures made in humans, but a degree of validity has been achieved through studies using known antidepressant treatments (predictive validity) and stress-related manipulations (face validity) (Geyer and Markou, 1995; Cryan and Slattery, 2007). Behavioural despair, quantified using either the forced swim test (FST) or tail suspension test (TST), was initially developed as an assay to detect novel monoaminergic antidepressants (Porsolt et al. 1977) although it is now widely used in fundamental research and aetiological studies. Despite its high predictive validity for monoaminergic agents, the FST/TST is thought to have limited translational validity (see Nestler and Hyman, 2010; Pollak et al. 2010; Berton et al. 2012; O'Leary and Cryan, 2013 for further discussion). Its efficacy for the acute vs delayed effects of treatment, as well as its lack of sensitivity to non-monoaminergic manipulations has been highly criticized. Learned helplessness also measures a form of behavioural despair, where exposure to an inescapable stressor (usually footshock) induces a specific deficit in

escape behaviour during subsequent presentations in an escapable environment (Overmier and Seligman, 1967; Seligman and Beagley, 1975; G Maier, 1984). The induction of learned helplessness not only produces a specific behavioural deficit which can be quantified, but also results in changes in neurobiology, suggesting it provides a phenotypic model (Pryce et al. 2011). Interestingly, not all animals treated in this paradigm develop learned helplessness, which has underpinned the development of the congenital learned helpless and non-learned helpless strains used as models of depression and resistance to depression (Henn and Vollmayr, 2005; Pryce et al. 2011).

As discussed above, changes in reward processing are also commonly observed mood disorders (for a review see Eshel and Roiser, 2010), and anhedonia has been widely used as a measure of depression-related behaviour in animals (Table 1). The approaches used in animals are usually based on consummatory tests such as the sucrose preference test (Willner et al. 1987). An alternative approach has been to look at reward threshold using intracerebral self-stimulation (ICSS) of reward centres in the brain (Vogel et al. 1986; Zacharko and Anisman, 1991). Although these anhedonia tasks have better translational validity in principle, the measures used in patients are still largely based on self-report and the subjective experience of pleasure (Treadway and Zald, 2011). Recent data from neuropsychological tests of reward processing may, however, provide a closer link between animal and human work, as discussed in more detail in the subsequent sections.

Measuring affective biases in pre-clinical depression research

Back translating human neuropsychological tests, used to measure affective biases in depression, requires the modification of the task to species-appropriate cues and behaviours (Paul et al. 2005). In almost all human studies affective biases are investigated using emotional processing or interpretation tasks, which feature stimuli that are either language-dependent or facial expressions. Although animals are unable to perform tasks build around these cues, the principles that underlie such tasks can be developed for use in animals (Paul et al. 2005). Cues can be presented as either tones, lights or spatial locations, and one of the most useful set-ups to achieve this an operant chamber (as shown in Fig 2). The presentation of the cues, the animal's responses and resulting outcomes are all fully automated, enabling efficient and consistent methods to be used across laboratories. An alternative method for presenting animals with distinct cues is the bowl digging set-up (shown in Fig 2). Here the animals are trained to associate a particular cue, for example the digging substrate or odour, with the presence of a hidden reward. More recently, touch-screen equipment has been developed for rodents offering the potential to also develop tasks using visual cues (Bussey et al. 2012).

Ambiguous cue interpretation/judgement bias task

The first empirical data to suggest that animals exhibit affective biases, similar to those observed in humans, was published by Harding and colleagues in 2004. Their experiment was designed to investigate whether animals in a putative negative affective state would exhibit pessimistic behaviours similar to those seen in human disorders such as depression. Building on the observations that patients with depression were more likely to anticipate negative outcomes when presented with neutral or ambiguous cues (Wright and Bower, 1992), the group developed a rodent task which would enable similar ambiguous cue interpretations to be quantified in non-humans. In this pre-clinical 'cognitive bias task', animals were initial trained to make an approach behaviour and press a lever to obtain a food reward, or to refrain from lever pressing to avoid a punishment. Each behaviour was trained using a specific tone frequency and animals were trained until they could distinguish the two cues. When these same animals were exposed to chronic mild stress and then presented with intermediate ambiguous tone frequencies, the animals in the putative negative affective state made fewer reward approach responses and were slower to respond. These data

were interpreted as indicative of a 'pessimistic' phenotype resulting from the negative affective state. A detailed discussion of the theoretical framework that underpins this task and how different behavioural response profiles may map onto human emotions is provided in Mendl et al. (2010).

The concepts from this original work have developed over the last decade and a number of different variations to the original 'cognitive bias task' have been reported (for review see Hales et al. 2014). The format of the task can involve either active choice, where the animal is required to make a response to either obtain reward or avoid punishment, or a go/no-go where only the reward response requires a response and avoidance of punishment is achieved by refraining from making a response. To investigate the underlying decision-making behaviour leading to either an optimistic or pessimistic choice, a go/go format is preferred over a go/no-go format, in which a reduction in approach behaviour could arise from either changes in reward-related motivation or enhanced anticipation of punishment. Hypothetical data illustrating either a positive or negative affective bias in an active choice task are shown in Fig 2. Studies may use a mid-point only cue or multiple intermediate cues to include a near positive and near negative. By using multiple intermediate ambiguous cues it may also be possible to dissociate further between affective biases associated with reduced anticipation of reward versus increased anticipation of punishment, though further work is needed in this area. The majority of studies that have used this task to study depression-related neurobiology have used active choice formats with a footshock used as the punisher (Enkel et al. 2010; Papciak et al. 2013; Anderson et al. 2013). This does introduce a further potential confound, however, as animal are exposed to multiple footshocks over the course of training and testing, which may impact on affective state. The active choice tasks also have a long training period of ~ 3 months.

The original task utilised auditory cues where the animals were trained to associate distinct tone frequencies with either reward or avoidance of punishment (white noise) (Harding et al. 2004). Subsequent studies have also tested whether the same concept can be tested using spatial cues (Burman et al. 2008; Richter et al. 2012)). In the spatial task, animals are trained to associate a specific location with obtaining a reward and a second location with either a lower value or aversive reward e.g. quinine flavoured pellet. The animals are trained until they show differential latencies between to two locations and are either slower to approach to low value location or do not approach it at all. Judgement bias is then tested by placing goal posts in intermediate locations between the high-value reward and low-value locations. A more pessimistic judgement is reflected in a slower latency to approach the intermediate location. However, while this format is much easier to train, it may not engage the same neural processes as an active choice task which measures anticipation of reward and punishment avoidance (for further discussion see Hales et al. 2014).

Validation of interpretation/judgment task as model of affective biases in depression

The initial work undertaken with these tasks primarily focussed on animal welfare through validation of an objective measure of affective state. The number of studies where pharmacological manipulations have been used to test the validity of the judgement bias task methodology is limited. Overall, the studies where acute drug treatments have been used are not consistent with their predicted antidepressant or pro-depressant profile in man (Anderson et al. 2013; Rygula et al. 2014). Interestingly, treatment with a noradrenaline reuptake inhibitor, either with or without co-administration of corticosterone, has been reported to produce a negative bias by three different research groups (Enkel et al. 2010; Anderson et al. 2013; Rygula et al. 2014). The SSRIs appear to have mixed or no effect whilst one study has found that amphetamine, which is not an antidepressant, induces a positive bias (Anderson et al. 2013; Rygula et al. 2014). One possible explanation for the lack of positive bias effects seen with acute antidepressant treatments may relate to the apparent delayed onset of clinical efficacy. In the one study where fluoxetine was

administered chronically, a tendency for a positive shift was observed, although this effect was not statistically robust (Anderson et al. 2013). Studies in animal models of depression include those in congenitally helpless rats, which were shown to exhibit a pessimistic phenotype (Enkel et al. 2010). The effect of chronic stress in normal animals has also been investigated, with one study reporting that chronic stress increases negative bias, an effect that was associated with baseline vulnerability (Rygula et al. 2013). A subsequent study from the same group showed a comparable finding in relation to chronic social defeat stress (Papciak et al. 2013).

Together, the data published for the judgement bias tasks suggest that the method offers a novel and translational approach to investigate affective biases associated with decision-making in rodents. Potential confounds relating to motivation and hedonic changes need to be taken into consideration in the design and interpretation of the experiments and further work is needed to gain a broader insight into the task's validity for depression research. The ability to use the task design in many different species, including honey bees (Bateson et al. 2011) is particularly appealing as it could facilitate studies in species such as drosophila where more complex genetic analysis are more achievable.

Reward processing tests in rodent depression models

Disrupted processing of reward information may be an additional important contributory factor to several symptoms of depression, including core features such as anhedonia and fatigue. In animals, anhedonia is a widely used endpoint for depression research (Table 1). Translation of this work to human studies is complicated by the fact that animal studies generally use primary rewards (food or electrical stimulation of reward pathways) whereas human studies use either hypothetical rewards (assessed via questionnaire) or secondary rewards (money). Additionally, studies in depressed patients suggest that reinforcement processing impairments may involve higher order cognitive processes, such as learning and value-based choice, as opposed to simple consummatory responses (Eshel and Roiser, 2012; Elliott et al. 2011; Roiser et al. 2012, 2013). Evidence to support this hypothesis includes data showing that patients with depression do not show altered hedonic responses to a primary reward in tests akin to the sucrose preference test (Dichter et al, 2010; McCabe et al, 2009; although also see Berlin et al, 1998).

Few animal studies have directly investigated reward learning and motivation in the context of depression models. These have generally quantified acquisition of a response-reward association such as a lever press task and/or motivation to respond for reward using a progressive ratio schedule, in which the effort required to obtain reward increases with each trial. In animals where a putative depression-like phenotype has been induced, reduced motivation for reward and/or impaired learning has been observed (Olausson et al. 2013; Leventopoulos et al. 2009; Gourley et al. 2008; Rüedi-Bettschen et al. 2005). In the congenitally helpless rat, reduced motivation for reward was detected using a progressive ratio task, with the same animals shown to have no deficits in learning in a non-food motivated task, the Morris Water Maze (Vollymar et al. 2004). These changes may relate directly to the hedonic value of the reward and reflect similar neurobiological deficits as those observed using the sucrose preference test. It is, however, also possible that these changes involve a more complex process where affective biases influence learning and memory and, in turn, the subsequent recall of those associations, thereby directing and modifying subsequent behavioural responses.

An interesting translational task which may also provide a valuable approach to understanding the processing of both positive and negative information is the probabilistic reversal learning task (Dickstein et al. 2010; Hasler et al. 2009; Eshel and Roiser, 2010). Again, only a small number of studies have been carried out in animals but the potential value in studying behavioural responses

following both positive and negative feedback is appealing. An initial pharmacological characterisation of the task found effects associated with the serotonergic system including treatments with antidepressants (Bari et al. 2010). A role for serotonin was further supported by a subsequent study in mice (Ineichen et al. 2012). More recently, impairments in performance in animals exposed to isolation rearing have also been reported (Amita et al. 2014).

The rodent affective bias test

The rodent affective bias test (ABT: Stuart et al. 2013; Stuart et al. 2015) was developed to investigate the hypothesis that the cognitive processes associated with reward-related learning and memory may be modified by affective states. These affective biases then influence the animal's subsequent choice when the reward-associated cues are re-encountered. The ABT uses a discrimination learning phase where animals learn the association between a specific cue (a digging substrate) with a positive outcome (finding a food reward) (Fig. 2). The animals acquire these two independent experiences on different days with one learned during control conditions and the other during treatment. Affective bias is then quantified using a preference test where both the rewarded substrates are presented together and the animal's choices recorded. A bias score is then calculated from the number of choices made for the treatment-paired substrate versus choice for the control-paired substrate. An increase in choices for the treatment-paired substrate is interpreted as a positive bias, and a decrease as a negative bias (hypothetical data illustrated in Fig 2). The value of the experience is kept constant and all factors are counter-balanced so that any arising bias can be attributed to a relative shift in the perceived value of the memory of that experience. This task builds on clinical data which has shown that depression is strongly associated with both disrupted reward processing and affective biases associated with memory retrieval (Mathews and MacLeod, 2005; Clark et al. 2009; Gotlib and Joormann, 2010; Pringle et al. 2011; Roiser et al. 2012).

The ABT is limited to acute drug or affective state manipulations as it requires a within-subject study design, together with alternate presentations of each of the treatment-substrate-reward associations (Stuart et al. 2013). However, initial validation data revealed both antidepressant and pro-depressant drug treatments induce affective biases in this task that are consistent with similar treatments in healthy human volunteers performing emotional processing tasks (Stuart et al. 2013; Pringle et al. 2011). Antidepressant drugs from both the re-uptake inhibitor classes and receptor-blocking agents have been shown to induce positive biases, whilst drugs thought to have pro-depressants effects in man induce negative biases on this task (Stuart et al. 2013). Using a highly enriched social environment as a manipulation induced a positive bias towards experiences encountered during this enriched period (Stuart et al. 2013). Although still in the early stages of validation, the ABT appears to exhibit a high degree of translational validity in terms of pharmacological, physiological and psychological manipulations of affective state (Stuart et al. 2013).

In a recent study, the rates of onsets of conventional antidepressants versus the NMDA antagonist ketamine were compared using the ABT. The results suggest that the rapid onset of action of ketamine may be related to its ability to modify previously learned biases, whereas the conventional antidepressant venlafaxine only modified new learning (Stuart et al. 2015). One potentially interesting idea arising from the observation that affective states appear to bias memories associated with rewarding experiences is the potential impact this may have on subsequent behaviour and motivation. The animals' choices are biased by their affective states *at the time the information was learned*. In the ABT, the animal makes a decision about which of the two experiences it encountered it prefers. In the context of a more naturalistic setting, these biases may influence motivation i.e. negative biases leading to reduced motivation to re-engage in the associated behaviours.

Conclusions

Affective biases in depression provide an important opportunity for translational studies. The ability to quantify these biases using objective rather than subjective measures means a more direct comparison between human and animal studies can be made. In animals, judgement biases can be tested through the presentation of ambiguous information. These have been reported for a range of species and some degree of validation in the context of human depression has been demonstrated, for example through biases in processing mildly emotional faces. Negative judgement biases have been observed following chronic manipulations that are thought to induce negative affective states, but pharmacological studies using either acute or chronic administration have produced less clear results. The rodent ABT focuses on biases associated with reward learning and memory in rodents. This task does not have a direct human equivalent but initial studies suggest a reasonable degree of face validity and good predictive and translational validity. The task is also sensitive to stress manipulations, suggesting a degree of construct validity. Taken together with findings of basic affective processing biases in depression that motivated the cognitive neuropsychological model, which appear to be directly modified by antidepressant treatment, these novel pre-clinical approaches raise great promise for the development of a truly translational novel paradigm for drug discovery.

Acknowledgments and disclosures

ESJR currently holds research funding from the MRC, BBSRC, Wellcome Trust and Eli Lilly. Previous support which has contributed to the development of this work includes funding from RCUK and the British Pharmacological Society Integrative Pharmacology Fund. JPR is funded by the Wellcome Trust and previously received support from the Medical Research Council.

JPR is a consultant for Cambridge Cognition.

References

Abramson LY, Seligman ME, Teasdale JD (1978) Learned helplessness in humans: critique and reformulation. J Abnorm Psychol 87: 49-74

Agid Y, Buzsaki G, Diamond DM, Frackowiak R, Giedd J, Girault JA, Grace A, Lambert JJ, Manji H, Mayberg H, Popoli M, Prochiantz A, Richter-Levin G, Somogyi P, Spedding M, Svenningsson P, Weinberger D (2007) How can drug discovery for psychiatric disorders be improved? Nat Rev Drug Discov 6: 189-201

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Amitai N, Young J, Higa K, Sharp R, Geyer M, Powell S (2013). Isolation rearing effects on probabilistic learning and cognitive flexibility in rats. Cognitive, Affective, & Behavioral Neuroscience: 1-19.

Anderson MH, Munafò M, Robinson EJ (2013). Investigating the psychopharmacology of cognitive affective bias in rats using an affective tone discrimination task. Psychopharmacology 226: 601-613.

Austin MP, Mitchell P, Goodwin GM (2001) Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 178: 200-6

Bari A, Theobald DE, Caprioli D, Mar AC, Aidoo-Micah A, Dalley JW, et al. (2010). Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. Neuropsychopharmacology 35: 1290-1301.

Bateson M, Desire S, Gartside SE, Wright GA (2011). Agitated honeybees exhibit pessimistic cognitive biases. Current Biology 21: 1070-1073.

Beats BC, Sahakian BJ, Levy R (1996) Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med 26: 591-603.

Beck AT (1967) Depression: Clinical, experimental and theoretical aspects. Harper & Row, New York

Berlin I., Givry-Steiner L., Lecrubier Y., Puech AJ. (1998). Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. Eur. J Psychaitry, 13:303–309.
Berton O, Hahn CG, Thase ME (2012). Are we getting closer to valid translational models for major depression? Science 338: 75-79.
Bhagwagar Z, Cowen PJ, Goodwin GM, Harmer CJ (2004) Normalization of enhanced fear recognition by acute SSRI treatment in subjects with a previous history of depression. Am J Psychiatry 161: 166-8
Booij L, Van der Does AJ, Haffmans PM, Riedel WJ, Fekkes D, Blom MJ (2005) The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. J Psychopharmacol 19: 267-75
Burman OHP, Parker R, Paul ES, Mendl M (2008). A spatial judgement task to determine background emotional state in laboratory rats, Rattus norvegicus. Animal Behaviour 76: 801-809.
Bussey TJ, Holmes A, Lyon L, Mar AC, McAllister KA, Nithianantharajah J, Oomen CA, Saksida LM. (2012) New translational assays for pre-clinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. Neuropharmacology. 62(3):1191-203.
Clark L, Chamberlain SR, Sahakian BJ (2009). Neurocognitive Mechanisms in Depression: Implications for Treatment. Annual Review of Neuroscience 32: 57-74.
Chase HW, Frank MJ, Michael A, Bullmore ET, Sahakian BJ, Robbins TW (2010) Approach and avoidance learning in patients with major depression and healthy controls: relation to anhedonia. Psychol Med 40: 433-40
Cools R, Blackwell A, Clark L, Menzies L, Cox S, Robbins TW (2005) Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. Neuropsychopharmacology 30: 1362-73
Cryan JF, Slattery DA (2007). Animal models of mood disorders: Recent developments. Curr Opin Psychiatry 20: 1-7.
Cryan JF, Mombereau C, Vassout A (2005). The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 29: 571-625.
Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR (1990) Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 47: 411-8
Detke MJ, Rickels M, Lucki I (1995). Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology 121: 66-72.
Dichter GS, Smoski MJ, Kampov-Polevoy AB, Gallop R, Garbutt JC. (2012). Unipolar depression does not moderate responses to the Sweet Taste Test. Depress Anxiety. 27:859-63.
Dickstein DP, Finger EC, Brotman MA, Rich BA, Pine DS, Blair JR, Leibenluft E. (2009). Impaired probabilistic reversal learning in youths with mood and anxiety disorders. Psychol Med. 40(7):1089-100.
Dinan TG (1994) Glucocorticoids and the genesis of depressive illness. A psychobiological model. Br J Psychiatry 164: 365-71
Elliott R, Sahakian BJ, Herrod JJ, Robbins TW, Paykel ES (1997) Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. J Neurol Neurosurg Psychiatry 63: 74-82.
Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES (1996) Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. Psychol Med 26: 975-89.
Elliott R, Zahn R, Deakin JF, Anderson IM (2011). Affective cognition and its disruption in mood disorders. Neuropsychopharmacology 36: 153-182.
Enkel T, Gholizadeh D, von Bohlen Und Halbach O, Sanchis-Segura C, Hurlemann R, Spanagel R, et al. (2010). Ambiguous-cue interpretation is biased under stress- and depression-like states in rats. Neuropsychopharmacology 35: 1008-1015.

Erickson K, Drevets WC, Clark L, Cannon DM, Bain EE, Zarate CA, Jr., Charney DS, Sahakian BJ (2005) Mood-congruent bias in affective go/no-go performance of unmedicated patients with major depressive disorder. American Journal of Psychiatry 162: 2171-3
Eshel N, Roiser JP. (2010). Reward and punishment processing in depression. Biol Psychiatry. 68(2):118-24.
Firk C, Markus CR (2008) Effects of acute tryptophan depletion on affective processing in first-degree relatives of depressive patients and controls after exposure to uncontrollable stress. Psychopharmacology (Berl) 199: 151-60
Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J (2010) Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 303: 47-53
Geyer, M., Markou, A. (1995). Animal Models of psychiatric disorders. In: Bloom F, Kupfer D, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press; pp. 787–798.
Gorwood P. (2008) Neurobiological mechanisms of anhedonia. Dialogues Clin Neurosci. 10(3):291-9.
Gotlib IH, Joormann J (2010). Cognition and Depression: Current Status and Future Directions. Annual Review of Clinical Psychology 6: 285-312.
Gourley SL, Kiraly DD, Howell JL, Olausson P, Taylor JR. (2008). Acute hippocampal brain-derived neurotrophic factor restores motivational and forced swim performance after corticosterone. Biol Psychiatry. 64(10):884-90.
Hales CA, Stuart SA, Anderson MH, Robinson ES. (2014). Modelling cognitive affective biases in major depressive disorder using rodents. Br J Pharmacol. 171(20):4524-38.
Harding EJ, Paul ES, Mendl M (2004). Animal behaviour: Cognitive bias and affective state. Nature, 427: 312-312.
Harmer CJ (2008) Serotonin and emotional processing: does it help explain antidepressant drug action? Neuropharmacology 55: 1023-8
Harmer CJ, Goodwin GM, Cowen PJ (2009a) Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. British Journal of Psychiatry 195: 102-8
Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM (2003) Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. Am J Psychiatry 160: 990-2
Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM, Cowen PJ (2009b) Effect of acute antidepressant administration on negative affective bias in depressed patients. Am J Psychiatry 166: 1178-84
Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004) Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am J Psychiatry 161: 1256-63
Hasler G, Luckenbaugh DA, Snow J, Meyers N, Waldeck T, Geraci M, Roiser J, Knutson B, Charney DS, Drevets WC (2009) Reward processing after catecholamine depletion in unmedicated, remitted subjects with major depressive disorder. Biol Psychiatry 66: 201-5
Hasler G, Mondillo K, Drevets WC, Blair JR. (2009). Impairments of probabilistic response reversal and passive avoidance following catecholamine depletion. Neuropsychopharmacology. 34(13):2691-8.
Hayward G, Goodwin GM, Cowen PJ, Harmer CJ (2005) Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. Biol Psychiatry 57: 517-24
Henn FA, Vollmayr B. (2005). Stress models of depression: forming genetically vulnerable strains. Neurosci Biobehav Rev. 29(4-5):799-804.
Henriques JB, Davidson RJ (2000) Decreased responsiveness to reward in depression. Cognition and Emotion 14: 711-24
Henriques JB, Glowacki JM, Davidson RJ (1994) Reward fails to alter response bias in depression. J Abnorm Psychol 103: 460-6

Hollon SD, DeRubeis RJ, Fawcett J, Amsterdam JD, Shelton RC, Zajecka J, Young PR, Gallop R (2014) Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. JAMA Psychiatry 71: 1157-64
Huys QJ, Daw ND, Dayan P (2015) Depression: A Decision-Theoretic Analysis. Annu Rev Neurosci
Ineichen C, Sigrist H, Spinelli S, Lesch KP, Sautter E, Seifritz E, Pryce CR. (2012). Establishing a probabilistic reversal learning test in mice: evidence for the processes mediating reward-stay and punishment-shift behaviour and for their modulation by serotonin. Neuropharmacology. 63(6):1012-21.
Joormann J, Gotlib IH (2006) Is this happiness I see? Biases in the identification of emotional facial expressions in depression and social phobia. J Abnorm Psychol 115: 705-14
Joormann J, Gotlib IH (2008) Updating the contents of working memory in depression: interference from irrelevant negative material. J Abnorm Psychol 117: 182-92
Kohler S, Unger T, Hoffmann S, Mackert A, Ross B, Fydrich T (2015) Dysfunctional cognitions of depressive inpatients and their relationship with treatment outcome. Compr Psychiatry 58: 50-6
Leventopoulos M, Russig H, Feldon J, Pryce CR, Opacka-Juffry J. (2009). Early deprivation leads to long-term reductions in motivation for reward and 5-HT1A binding and both effects are reversed by fluoxetine. Neuropharmacology. 56(3):692-701.
Maier SF. (1984). Learned helplessness and animal models of depression. Prog Neuropsychopharmacol Biol Psychiatry. 8(3):435-46.
Mathews A, MacLeod C (2005). Cognitive Vulnerability to Emotional Disorders. Annual Review of Clinical Psychology 1: 167-195.
Matt GE, Vazquez C, Campbell WK (1992) Mood-Congruent Recall of Affectively Toned Stimuli - a Meta- Analytic Review. Clinical Psychology Review 12: 227-255
McArthur R, Borsini F (2006) Animal models of depression in drug discovery: a historical perspective. Pharmacol Biochem Behav 84: 436-52
McCabe C, Cowen PJ, Harmer CJ. (2009). Neural representation of reward in recovered depressed patients. Psychopharmacology (Berl). 205:667-77.
McLean A, Rubinsztein JS, Robbins TW, Sahakian BJ (2004) The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. Psychopharmacology (Berl) 171: 286-97
McGuire PS, Seiden LS. (1980) Differential effects of imipramine in rats as a function of DRL schedule value. Pharmacol Biochem Behav. 13(5):691-4.
Mendl M, Burman OHP, Paul ES (2010b). An integrative and functional framework for the study of animal emotion and mood. Proceedings of the Royal Society B: Biological Sciences 277: 2895-2904.
Mendl M, Paul ES, Chittka L (2011). Animal behaviour: emotion in invertebrates? Curr Biol 21: R463-465.
Munafo MR, Hayward G, Harmer C (2006) Selective processing of social threat cues following acute tryptophan depletion. J Psychopharmacol 20: 33-9
Murphy FC, Michael A, Robbins TW, Sahakian BJ (2003) Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. Psychol Med 33: 455-67
Murphy FC, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, Paykel ES, Sahakian BJ (2001) Decision-making cognition in mania and depression. Psychological Medicine 31: 679-93.
Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, Paykel ES (1999) Emotional bias and inhibitory control processes in mania and depression. Psychological Medicine 29: 1307-21.
Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ (2002) The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. Psychopharmacology (Berl) 163: 42-53

Murphy SE, Longhitano C, Ayres RE, Cowen PJ, Harmer CJ (2006) Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers. Psychopharmacology (Berl) 187: 121-30
Nestler EJ, Hyman SE (2010). Animal models of neuropsychiatric disorders. Nat Neurosci 13: 1161-1169.
O'Leary OF, Cryan JF (2013). Towards translational rodent models of depression. Cell Tissue Res 354: 141-153.
Olausson P, Kiraly DD, Gourley SL, Taylor JR. (2013) Persistent effects of prior chronic exposure to corticosterone on reward-related learning and motivation in rodents. Psychopharmacology (Berl). 225(3):569-77.
Overmier JB, Seligman ME: (1967). Effects of inescapable shock upon subsequent escape and avoidance responding. J Comp Physiol Psychol. 63:28-33.
Papciak J, Popik P, Fuchs E, Rygula R (2013). Chronic psychosocial stress makes rats more 'pessimistic' in the ambiguous-cue interpretation paradigm. Behavioural Brain Research 256: 305-310.
Paul ES, Harding EJ, Mendl M (2005). Measuring emotional processes in animals: the utility of a cognitive approach. Neuroscience & Biobehavioral Reviews 29: 469-491.
Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH (2008a) Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. Biol Psychiatry 64: 162-8
Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M (2008b) Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. J Psychiatr Res 43: 76-87
Pollak DD, Rey CE, Monje FJ (2010). Rodent models in depression research: classical strategies and new directions. Ann Med 42: 252-264.
Porsolt RD, Le Pichon M, Jalfre M (1977). Depression: a new animal model sensitive to antidepressant treatments. Nature 266: 730-732.
Pringle A, Browning M, Cowen PJ, Harmer CJ (2011). A cognitive neuropsychological model of antidepressant drug action. Prog Neuropsychopharmacol Biol Psychiatry 35: 1586-1592.
Pryce CR, Azzinnari D, Spinelli S, Seifritz E, Tegethoff M, Meinlschmidt G. (2011) Helplessness: a systematic translational review of theory and evidence for its relevance to understanding and treating depression. Pharmacol Ther. 132(3):242-67.
Rawal A, Collishaw S, Thapar A, Rice F (2013) 'The risks of playing it safe': a prospective longitudinal study of response to reward in the adolescent offspring of depressed parents. Psychol Med 43: 27-38
Richter SH, Schick A, Hoyer C, Lankisch K, Gass P, Vollmayr B (2012). A glass full of optimism: enrichment effects on cognitive bias in a rat model of depression. Cogn Affect Behav Neurosci 12: 527-542.
Riedel M, Moller HJ, Obermeier M, Adli M, Bauer M, Kronmuller K, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Schennach-Wolff R, Henkel V, Seemuller F (2011) Clinical predictors of response and remission in inpatients with depressive syndromes. J Affect Disord 133: 137-49
Robinson OJ, Cools R, Sahakian BJ (2011) Tryptophan depletion disinhibits punishment but not reward prediction: implications for resilience. Psychopharmacology (Berl)
Rock PL, Roiser JP, Riedel WJ, Blackwell AD (2013) Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med: 1-12
Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS (2003) Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. Neuropsychopharmacology 28: 153-62
Roiser JP, Blackwell AD, Cools R, Clark L, Rubinsztein DC, Robbins TW, Sahakian BJ (2006) Serotonin transporter polymorphism mediates vulnerability to loss of incentive motivation following acute tryptophan depletion. Neuropsychopharmacology 31: 2264-72

Roiser JP, Cannon DM, Gandhi SK, Tavares JT, Erickson K, Wood S, Klaver JM, Clark L, Zarate CA, Jr., Sahakian BJ, Drevets WC (2009) Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. Bipolar Disord 11: 178-89
Roiser JP, Elliott R, Sahakian BJ (2012) Cognitive mechanisms of treatment in depression. Neuropsychopharmacology 37: 117-36
Roiser JP, Levy J, Fromm SJ, Wang H, Hasler G, Sahakian BJ, Drevets WC (2008) The effect of acute tryptophan depletion on the neural correlates of emotional processing in healthy volunteers. Neuropsychopharmacology 33: 1992-2006
Roiser JP, McLean A, Ogilvie AD, Blackwell AD, Bamber DJ, Goodyer I, Jones PB, Sahakian BJ (2005) The subjective and cognitive effects of acute phenylalanine and tyrosine depletion in patients recovered from depression. Neuropsychopharmacology 30: 775-85
Roiser JP, Sahakian BJ (2013). Hot and cold cognition in depression. CNS Spectr 18: 139-149.
Rüedi-Bettschen D, Pedersen EM, Feldon J, Pryce CR. (2005). Early deprivation under specific conditions leads to reduced interest in reward in adulthood in Wistar rats. Behav Brain Res. 156(2):297-310.
Ruhe HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Molecular Psychiatry 12: 331-59
Rygula R, Papciak J, Popik P (2013). Trait pessimism predicts vulnerability to stress-induced anhedonia in rats. Neuropsychopharmacology 38: 2188-2196.
Rygula R, Papciak J, Popik P. (2014). The effects of acute pharmacological stimulation of the 5-HT, NA and DA systems on the cognitive judgement bias of rats in the ambiguous-cue interpretation paradigm. Eur Neuropsychopharmacol. 24(7):1103-11.
Savitz J, Lucki I, Drevets WC (2009) 5-HT(1A) receptor function in major depressive disorder. Prog Neurobiol 88: 17-31
Seiden LS, Dahms JL, Shaughnessy RA. (1985). Behavioral screen for antidepressants: the effects of drugs and electroconvulsive shock on performance under a differential-reinforcement-of-low-rate schedule. Psychopharmacology (Berl). 86(1-2):55-60.
Seligman ME, Beagley G. (1975). Learned helplessness in the rat. J Comp Physiol Psychol. 88(2):534-41.
Smith KA, Fairburn CG, Cowen PJ (1997) Relapse of depression after rapid depletion of tryptophan. Lancet 349: 915-9.
Snyder HR (2012) Major Depressive Disorder Is Associated With Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. Psychol Bull
Steru L, Chermat R, Thierry B, Simo, P (1985). The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl), 85: 367-370.
Stuart SA, Butler P, Munafò MR, Nutt DJ, Robinson ESJ (2013). A Translational Rodent Assay of Affective Biases in Depression and Antidepressant Therapy. Neuropsychopharmacology 38: 1625–1635.
Stuart SA, Butler P, Munafò MR, Nutt DJ, Robinson ESJ (2015). Distinct Neuropsychological Mechanisms May Explain Delayed- Versus Rapid-Onset Antidepressant Efficacy. Neuropsychopharmacology. doi: 10.1038/npp.2015.59.
Taylor Tavares JV, Clark L, Furey ML, Williams GB, Sahakian BJ, Drevets WC (2008) Neural basis of abnormal response to negative feedback in unmedicated mood disorders. Neuroimage 42: 1118-26
Teachman BA, Joormann J, Steinman SA, Gotlib IH (2012) Automaticity in anxiety disorders and major depressive disorder. Clin Psychol Rev 32: 575-603
Tranter R, Bell D, Gutting P, Harmer C, Healy D, Anderson IM (2009) The effect of serotonergic and noradrenergic antidepressants on face emotion processing in depressed patients. J Affect Disord 118: 87-93
Treadway MT, Bossaller NA, Shelton RC, Zald DH (2012) Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. J Abnorm Psychol 121: 553-8

Treadway MT, Zald DH. (2011). Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 35:537-55.
Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 163: 28-40
Vogel, G.W., Minter, K., Woolwine, B. (1986). Effects of chronically administered antidepressant drugs on animal behavior. Physiol Behav, 36, 659-666.
Vollmayr B, Bachteler D, Vengeliene V, Gass P, Spanagel R, Henn F. (2004). Rats with congenital learned helplessness respond less to sucrose but show no deficits in activity or learning. Behav Brain Res. 150(1-2):217-21.
Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, Schmidt M, Claes S (2013) Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry 73: 639-45
Willner, P., Towell, A., Sampson, D., Sophokleous, S., Muscat, R. (1987). Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology,93, 358-364.
Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol 21: 655-79
Wright, W.F., Bower, G.H. (1992). Mood effects on subjective probability assessment. Organizational Behavior and Human Decision Processes, 52, 276-291.
Zacharko RM, Anisman H (1991). Stressor-induced anhedonia in the mesocorticolimbic system. Neurosci Biobehav Rev 15: 391-405.

Table 1: Assays used to quantify depression-related behaviour in rodents

Animal behavioural assay	Proposed relationship to clinical condition	Key references
Forced swim test (FST) – rat and mouse or Tail suspension test (TST) - mouse	Hopelessness/ despair	Porsolt et al., 1979 Detke et al., 1995 Steru et al., 1985; Cryan et al., 2005
Learned helplessness	Hopelessness/ despair	Maier, 1984
Sucrose preference test	Anhedonia	Willner et al., 1987
Intracerebral self stimulation (ICSS)	Anhedonia	Vogel et al., 1986; Zacharko and Anisman, 1991
Differential reinforcement of low-rate 72 seconds (DRL-72)	Undefined but predictive of antidepressant efficacy	McQuire and Seiden, 1980; Seiden et al., 1985

*also see Markou and Pizzigalli, Depression models, this edition, for discussion about methods used to induce a depression-like phenotype.

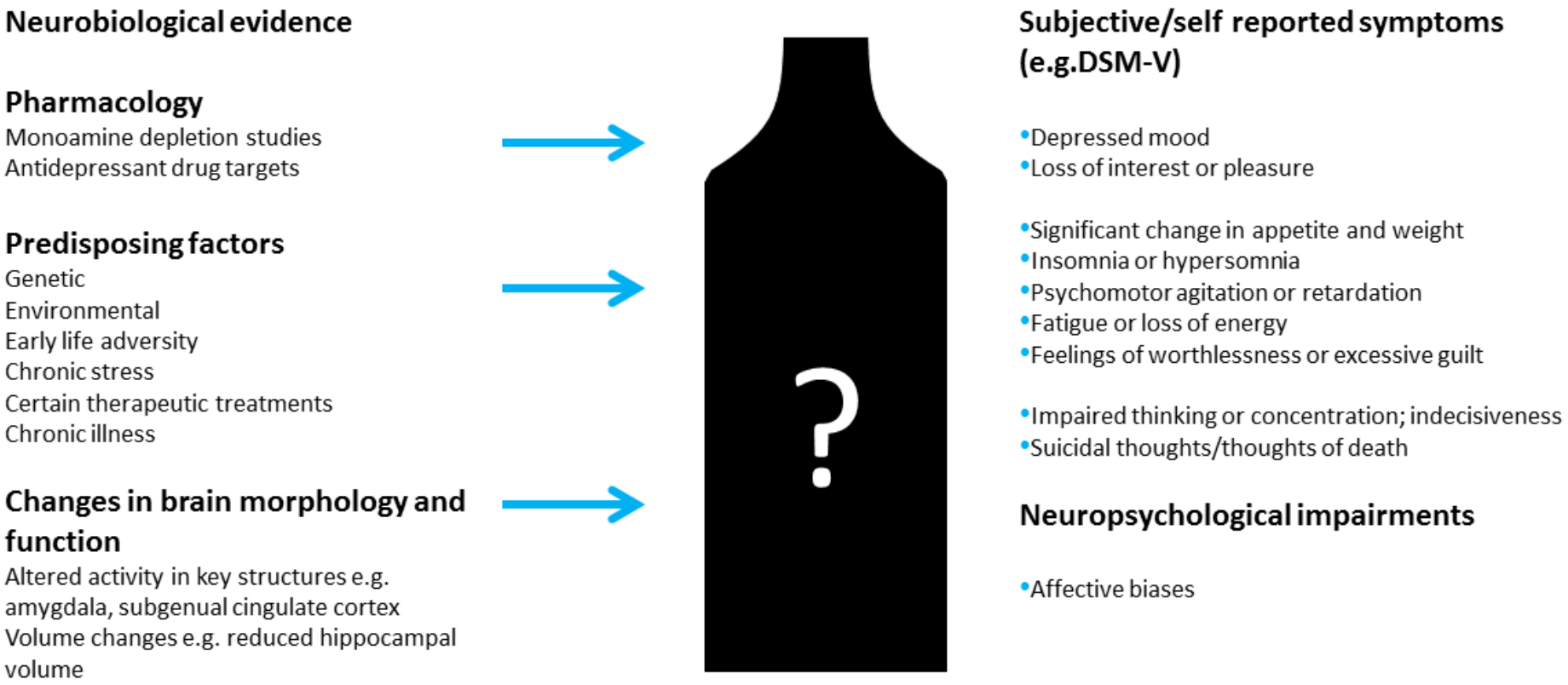
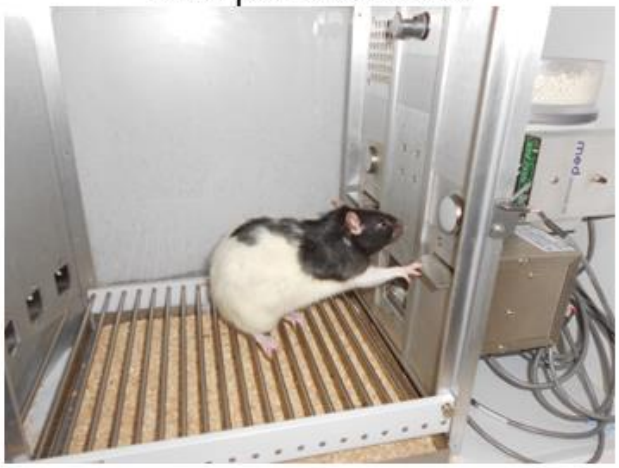
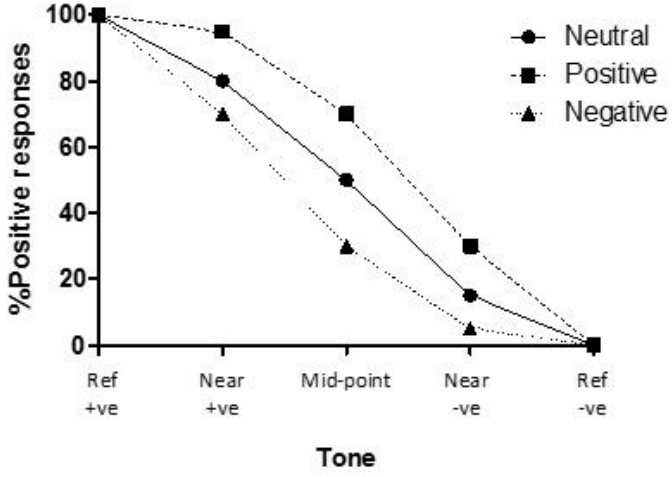


Figure 1: Limitations in the ability to translate neurobiological data to clinical symptoms in depression has led to a bottleneck and lack of development of novel treatments. Self-report of symptoms is the most common approach used in diagnosis of depression and evaluation of clinical outcomes during clinical trials. These subjective symptoms cannot be directly translated to animal studies, which severely limits our understanding of how neurobiological changes linked to depression relate to symptoms, and how this knowledge can be utilised to develop new treatments. Methods used to quantify objective changes in neuropsychological processes such as affective biases in depression may provide the translational, objective measures needed to facilitate new understanding of the neurobiological processes underlying symptoms and the development of novel treatments.

Judgement bias/Ambiguous cue interpretation task





Affective bias test

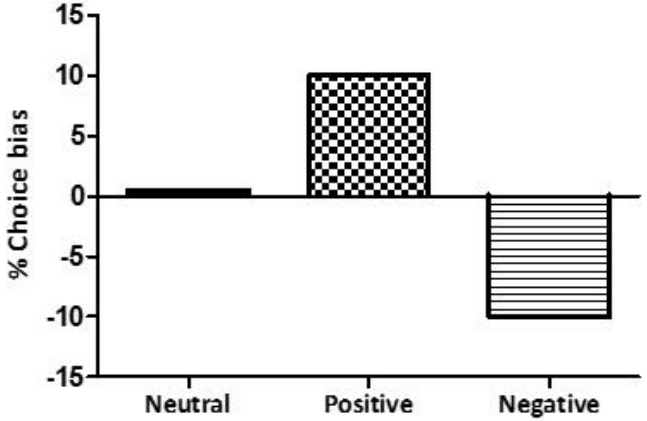


Figure 2: Examples of two different approaches used to quantify affective biases in animals and hypothetical data illustrating the impact of different affective states. The judgement bias/ambiguous cue interpretation tasks (left panels) are the most widely used method to assess affective biases in animals. The tasks are hypothesised to quantify behavioural changes induced by different affective states, which reflect similar interpretational biases to those observed in humans with anxiety and/or depression (see Mendl 2005 for review and discussion). Animals are trained to associated two distinct cues with a positive and a negative outcome. Animals are then presented with intermediate, ambiguous cues (near positive, midpoint, near negative) and their response selection is used to assess judgement bias. Positive biases are reflected in an upward shift in the graph with an increase in the number of responses in anticipation of positive events whilst negative biases are reflected in a reduced number of responses during ambiguous cue presentation. The affective bias test (right panel) is designed to measure affective biases associated with the learning and recall of positive experiences (the association of a food reward with a specific digging medium). In this task, animals learn to associate one digging medium with finding a food reward under neutral conditions and a second digging medium during an affective state or drug manipulation. Using a choice test, the animal's subsequent preference for one of the substrates over the other is tested. If both experiences are encountered during a neutral affective state, no bias is observed; but both positive and negative affective state manipulations induce a choice bias during the preference test, reflected in an increase or decrease in the number of times the reward-paired substrate is chosen, respectively (lower right panel).