"Nevertheless the difference in mind between man
and the higher animals, great as it is, certainly is one of
degree and not of kind. We have seen that the senses
and intuitions, the various emotions and faculties,
such as love, memory, attention, curiosity, imitation,
reason, etc., of which man boasts, may be found in
an incipient, or even sometimes in a well-developed
condition, in the lower animals."

Charles Darwin, The Descent of Man, page 86 (1871).

Darwin’s thesis, while emphasizing that “the difference
between the mind of the lowest man and that of the
highest animal is immense”, provided a foundation
ideology for the development of the modern scientific
fields of ethology and comparative psychology, in which
behaviour in animals is studied to gain insight into the
neural processes underlying behaviour in humans. The
emergence of these two divergent disciplines, champ-
ioned by Lorenz (ethology) and Skinner (comparative
psychology), has spawned manifold attempts to develop
tractable animal models of human behaviour and,
subsequently, aberrant forms of behaviour found in
pathological neuropsychiatric disease states. Coincident
with these advances in the study of animal behaviour,
the medical model became dominant in psychiatry and
through this model the first modern psychotherapeutic
drugs, such as lithium, chlorpromazine, imipramine
and chlordiazepoxide, emerged (the medical model
regards psychiatric illness as the result of abnor-
malities in brain function that can be identified using the
modern techniques of neuroscience and successfully
treated with pharmacological medicines). But despite
these advances, psychiatry as a field has proven to be
among the least penetrable clinical discipline for pro-
ductively amalgamating knowledge of human pathol-
gy with animal behaviour to develop satisfactory
in vivo animal models for evaluating novel treatment
approaches. Here, we describe how the burgeoning use
of genetically modified mice in drug discovery for other
disorders highlights the pressing need for developments
in this field. In addition, we explore the current use of
animal models of depression and anxiety disorders, and
the scope for future progress.

Affective disease: an emerging pandemic
Depression and anxiety disorders represent some of
the most common and proliferating health problems
worldwide. The World Health Organization predicts
that unipolar depression will be the second most preva-
lent cause of illness-induced disability by 2020 (REF 3).
**REVIEWS**

**Table 1 | Modelling symptoms of major depression* in mice**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>How might symptom be modelled in mice?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markedly diminished interest or pleasure in everyday activities (anhedonia)</td>
<td>Reduced intracranial self-stimulation, progressive ratio responding for positive reward (for example, sucrose) and social withdrawal</td>
</tr>
<tr>
<td>Large changes in appetite or weight gain</td>
<td>Abnormal loss in body weight after exposure to chronic stressors</td>
</tr>
<tr>
<td>Insomnia or excessive sleeping</td>
<td>Abnormal sleep architecture (measured using electroencephalography)</td>
</tr>
<tr>
<td>Psychomotor agitation or slowness of movement</td>
<td>Difficulty in handling and alterations in various measures of locomotor activity and motor function</td>
</tr>
<tr>
<td>Fatigue or loss of energy</td>
<td>Reduced activity in home cage, treadmill/running-wheel activity, nest building and active waking electroencephalogram</td>
</tr>
<tr>
<td>Indecisiveness or diminished ability to think or concentrate</td>
<td>Deficits in working and spatial memory and impaired sustained attention</td>
</tr>
<tr>
<td>Difficulty performing even minor tasks, leading to poor personal hygiene</td>
<td>Poor coat condition during chronic mild stress</td>
</tr>
<tr>
<td>Recurrent thoughts of death or suicide</td>
<td>Cannot be modelled</td>
</tr>
<tr>
<td>Feelings of worthlessness or excessive or inappropriate guilt</td>
<td>Cannot be modelled</td>
</tr>
</tbody>
</table>

*Symptoms used in the Diagnostic and Statistical Manual-IV/ diagnosis of major depression.*

Recently published data suggest that the current lifetime prevalence for depression is as high as 16.2% in the adult population of the United States, with a financial burden of US$80 billion per year. Likewise, anxiety disorders are serious medical illnesses that affect approximately 19 million North American adults (according to the National Institute of Mental Health government statistics; see Further information). The burden on health systems around the world from depression and anxiety is hard to overstate. Individuals suffering from these disorders are not only faced with considerable disruption to their psychological well-being, but are at considerably greater risk for various somatic conditions such as heart disease and obesity, Alarmingly, suicide, which is invariably associated with emotional disturbance, is now the third largest cause of death among young adults in Western countries. Abnormal emotion is also frequently seen in other neuropsychiatric and neurological diagnoses, ranging from Alzheimer’s disease to substance abuse, and can frequently precipitate symptoms in these conditions. Current treatments for this emerging pandemic of depression and anxiety disorders are of limited efficacy in a considerable proportion of patients, and are associated with a troublesome side-effect burden that reduces compliance in many others.

Clearly, a better understanding of the pathophysiology of these disorders and the development of novel, improved therapeutic treatments would fill a considerable unmet medical need. However, the cost of Phase II and Phase III clinical trials in pharmaceutical drug development is enormous and is growing annually, with the cost of central nervous system drug development higher than that of any other major therapeutic area. Furthermore, psychiatry is burdened, as in many medical disease trials, by a high placebo response. As a result, before embarking on costly trials, pharmaceutical companies and research funding agencies increasingly seek assurance that any specific biological target is relevant to the disease. So, there is a growing emphasis on first obtaining proof that a new chemical entity designed to alter the function of a specific target will do so in a predictable and safe manner. Of central importance to this approach is the availability of valid preclinical animal models for evaluating the potential efficacy of novel pharmacotherapeutics.

**Defining depression and anxiety**

Theories regarding the pathophysiology of depression have been put forward since Hippocrates’ model of melancholia as an excess of black bile. The modern medical concept of depression as a distinct disease state emerged in the second half of the nineteenth century with the ideas of the German psychiatrist Emil Kraepelin. Whereas theories such as Freud’s notion of depression as a manifestation of internalized anger or loss remain influential, contemporary approaches to diagnosis and treatment recognize depression as a disease of the central nervous system. However, a serious quandary for research into the neurobiological basis of depression and anxiety disorders, as well as attempts to model these conditions in non-humans, is that the precise neural mechanisms that are involved remain unknown. In all likelihood, depression is both biologically and genetically a heterogeneous disorder, with symptoms manifested at the psychological, behavioural and physiological level. Nonetheless, there are several symptoms that are seen in a substantial portion of depressed patients (Table 1), and although it is difficult to ascertain whether such features are the root cause of the disease or consequences of suffering from depression, they provide useful markers to study the pathophysiology of the disease. There are also various diagnostic tools that are used to identify and evaluate depression. These include the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association and the International Classification of Diseases (ICD-10) of the World Health Organization, as well as rating instruments such as the Hamilton Depression Scale.

The hallmark of anxiety disorders is a “marked, persistent, and excessive or unreasonable fear” that is experienced to a degree that significantly interferes with everyday life. These criteria are important to bear in mind because, unlike a depressive episode, a transient anxiety response to real danger is an appropriate, adaptive response in patients and non-patients alike. Another difference with depression is that DSM-IV classification of clinical anxiety distinguishes between numerous subdisorders of anxiety, the most common being generalized anxiety disorder, panic disorder (diagnosed with or without agoraphobia), specific phobia, social phobia, obsessive–compulsive disorder and post-traumatic stress disorder. These disorders are largely distinguished from one another by the nature of the stimulus provoking the anxiety (Table 2). Moreover, although there is epidemiological comorbidity between anxiety subdisorders, they...
Table 2 | How symptoms of anxiety disorders* might be modelled in mice

<table>
<thead>
<tr>
<th>Symptom</th>
<th>How might symptom be modelled in mice?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of places from which escape could be difficult (agoraphobia)</td>
<td>Increased avoidance of exposed, well-lit areas</td>
</tr>
<tr>
<td>Sudden onset of intense fearfulness, often with respiratory distress and fear of ‘going crazy’ (panic attack)</td>
<td>Increased flight from a predator</td>
</tr>
<tr>
<td>Anxiety provoked by social situations, leading to avoidance behaviour (social phobia)</td>
<td>Low social interaction with unfamiliar conspecific</td>
</tr>
<tr>
<td>Anxiety provoked by a specific feared object, leading to avoidance behaviour (specific phobia)</td>
<td>Conditioned taste avoidance</td>
</tr>
<tr>
<td>Re-experiencing a traumatic event, leading to increased arousal and avoidance of stimuli associated with the event (post-traumatic stress disorder)</td>
<td>Increased freezing response to fear-conditioned cue or context</td>
</tr>
<tr>
<td>Anxiety-provoking obsessions and anxiety-reducing compulsions (obsessive–compulsive disorder)</td>
<td>Increased marble burying and excessive grooming</td>
</tr>
<tr>
<td>Difficulty concentrating or mind going blank (generalized anxiety disorder)</td>
<td>Impaired sustained attention</td>
</tr>
<tr>
<td>Sleep disturbance/insomnia</td>
<td>Abnormal sleep architecture (measured using electroencephalography)</td>
</tr>
<tr>
<td>Autonomic hyperarousal (tachycardia, blushing, sweating and frequent urination)</td>
<td>Radiotelemetric measurement of heart rate dynamics during anxiety-provocation, such as increased stress-induced hyperthermia</td>
</tr>
<tr>
<td>Flashbacks of traumatic events</td>
<td>Impairment in extinction of fear memory</td>
</tr>
<tr>
<td>Cognitive bias towards ambiguous or weak threat cues</td>
<td>Increased fear conditioning to partial threat cue</td>
</tr>
<tr>
<td>Heightened startle response, particularly in threatening contexts</td>
<td>Increased acoustic startle response and fear-potentiated startle response</td>
</tr>
<tr>
<td>Separation anxiety</td>
<td>Increased ultrasonic vocalizations in pups separated from their mother</td>
</tr>
<tr>
<td>Feelings of losing control or going crazy during a panic attack</td>
<td>Cannot be modelled</td>
</tr>
</tbody>
</table>

*Symptoms used in the Diagnostic and Statistical Manual-IV diagnosis of anxiety disorders.

are, to some degree, differentially responsive to different classes of anxiolytic drug treatments, suggesting discrete neurobiological and genetic aetiologies. As in depression, psychiatrists have several rating scales to quantify anxiety severity and monitor treatment outcome, primarily the Hamilton Rating Scale for Anxiety and the Clinical Global Impression Scale18.

Given the complexity and heterogeneity of anxiety and depression, there have been growing calls for the diagnosis and treatment of depression and anxiety to focus on individual behavioural, physiological or neurochemical endpoints, rather than the entire syndrome19–21. Such diagnostic atomization is conceptualized in genetic terms by the notion of the endophenotype — that is, a heritable trait that provides a reliable marker for the disease in patients, or disease-risk in their relatives. Endophenotypes can be neuropsychological, cognitive, neurophysiological, neuroanatomical or biochemical in nature20 (see TABLES 1,2). These more discrete clinical features potentially provide a more effective approach to identifying the genetic and neurobiological underpinnings of human disease and represent more tractable entities to model in animals20,21.

Historically, depression and anxiety disorders have been regarded as separate clinical entities, predominantly because different drug treatments have been used to treat the disorders, usually tricyclic antidepressants and benzodiazepines, respectively. However, clinically, there is considerable comorbidity between the two disorders22. Indeed, as far back as Aubrey Lewis in the 1930s, authors have posited a continuum model from anxiety syndromes to mild, moderate and severe/psychotic depression2. The issue of comorbidity has important implications for the treatment of these conditions, in that drugs that are effective in both anxiety and depression would be particularly beneficial and cost effective, and there has been more focus on the development of such drugs in recent years23. This trend is largely a result of the success of the selective serotonin-reuptake inhibitor (SSRI) class of antidepressants in treating both depression and certain anxiety disorders. In addition, novel therapeutic targets, such as those acting at neuropeptide systems, are also predicted to have efficacy for both types of these disorders10. However, for the purpose of clarity and comparability with the current recommendations from the US Food and Drug Administration and current classifications by the main psychiatric bodies9,17, we discuss mouse models of depression and anxiety disorders separately.

**Why the mouse?**
Historically, research in non-humans, primarily rodents, has been central to efforts to understand the neural systems mediating emotion, how these
systems dysfunction under pathological conditions and how they can be therapeutically modulated. For decades, the rat was the species of choice in preclinical research — in part, because rats perform well in many of the cognitive and operant tasks that are the pillars of modern behavioural pharmacology. Moreover, the size and robustness of the rat, compared with smaller rodents such as the mouse, aids the application of invasive techniques, such as catheterization and cannula implantation, and facilitates toxicity testing of new compounds. However, in the past decade, as in other biomedical disciplines, there has been an explosion in the use of mice in neuropsychiatric research. The key driving force behind this trend has been the development and application of novel molecular technologies, such as gene targeting, which enable researchers to engineer precise genetic alterations to study the neural basis of behaviour24–26 (see TIMELINE). Although genetic modifications can be engineered in the rat and even in higher mammals, the mouse is uniquely amenable to these techniques27. Mice also have the practical and economic advantage of being relatively easy to breed and house in large numbers. As a result, whereas mice were certainly commonly used in behavioural pharmacological research before the application of these techniques, the proliferation of ‘gene knockout’, ‘gene knockin’ and ‘transgenic’ mice has forced researchers to quickly, and in some instances reluctantly, embrace the mouse in their research programmes. Given this burgeoning use of mutant mice in neuroscience research, it is an appropriate time to reinforce the ethical responsibilities of researchers using animal models. The principle of the ‘three Rs’ of reduce (the number of animals used), refine (experiments to minimize suffering) and replace (with non-animal techniques whenever possible) should guide all research using the mouse as a model to understand behaviour (for more details see RDS website given in Further information).

**Manipulating mice**

So far, about 80 different mutant lines have been reported to have phenotypes interpreted as abnormal ‘depression-related’ or ‘anxiety-related’ behaviour28–30. In some cases, these phenotypes were predictable from existing knowledge regarding the role of the gene/gene product in emotional behaviour and served to reinforce and refine existing hypotheses regarding the importance of certain systems in mediating these behaviours. For example, the ‘antidepressant-related’ phenotype found in noradrenaline transporter (NET) knockout mouse fits the profile of antidepressant efficacy of drugs that antagonize NET31. However, there...
are also numerous examples of phenotypic abnormalities in knockout and transgenic mice that potentially reveal novel mechanisms that subserve emotion. Such findings in mutant mice are particularly valuable when more traditional approaches (for example, selective pharmacological agonists and antagonists) to study the specific function of a gene product are impractical. For example, the engineering of mice with various mutations in the GABA_\(_{\text{A}}\) (\(\gamma\)-aminobutyric acid type A) receptor has driven development of novel anxiolytics that target specific subunits of the receptor with a better side-effect profile. Other recent cases in point are the group III metabotropic glutamate receptor mGluR7 knockout and galanin GAL-R1 receptor knockout mice, both of which show alterations in anxiety- or depression-related behaviours and highlight these receptors as potential novel therapeutic targets.

Although in this review, because of space constraints, we refer mainly to the use of mice in the context of gene targeting (reverse genetic approaches — that is, from gene to phenotype), another boon for mouse biomedical research has been the application of forward genetics approaches (phenotype to gene). For example, methods originally developed in model organisms such as Caenorhabditis elegans or Drosophila melanogaster that allow for the generation of random mutations, such as gene trapping and chemical mutagenesis, are being applied to the mouse to study behaviour. QUANTITATIVE TRAIT LOCUS ANALYSIS is another approach that holds promise for mapping the genes underlying anxiety and depression-related behaviours in mice, particularly where a behavioural phenotype can be practically and reliably assessed. Along similar lines, the observation that high levels of a depression or anxiety-related behaviour arise naturally in subpopulations of mice has been used by several researchers to selectively breed-in these phenotypes, thereby producing novel genetic models.

**Validity of mouse models**

An issue common to all the various techniques using the mouse to study anxiety and depression is evaluation of the usefulness and validity of mouse models. From the outset, Jacqueline Crawley’s admonition not to anthropomorphize putative emotion-related behaviours in mice has been well taken. It goes without saying that mice are not simply miniature versions of human beings. We can never fully recapitulate human depression or anxiety in the mouse and, indeed, cannot truly know whether a mouse is depressed or feeling anxious. Given the considerable differences in brain anatomy between humans and mice, particularly the greatly elaborated human cerebral cortex (FIG. 1) and the resultant capacity for processing complex psychological concepts, certain aspects of disease symptomatology, such as low self-esteem, suicidal ideation or ‘fear of going crazy’, are impossible to model in mice. Nonetheless, the cerebral cortex does not function in isolation — it is intimately interconnected with subcortical structures that are well conserved across mammalian species. The brains of vertebrates have a common structural organization, consisting of the cerebral hemispheres, diencephalon, midbrain, cerebellum, pons and medulla. Among mammals, and frequently across other vertebrate classes, the neural structures within these divisions and the circuits that interconnect them have marked similarities. In addition, there are many fundamental physiological and behavioural responses that have been evolutionarily conserved between species. Therefore, largely through inference, we can study these responses to elucidate behaviours and the neural circuits and genetic factors subserving them as a means to use lower species to understand human behaviour and disease.

Working from this premise, researchers have proposed specific criteria for evaluating whether an experimental procedure in an animal has validity as a model of a psychiatric disease. McKinney and Bunney suggest that the minimum requirements for a valid animal model of depression (although the criteria easily generalize to anxiety disorders and other psychiatric diseases) are that it: is ‘reasonably analogous’ to the human disorder in its manifestations or symptomatology; causes a behavioural change that can be monitored objectively; produces behavioural changes that are reversed by the same treatment modalities that are effective in humans; and is reproducible between...
such as the hippocampus and amygdala, are evolutionarily conserved from mouse to man. The potential functional significance of these species differences to emotional regulation and the implications for modelling emotional states in mice is yet to be fully understood. However, it is clear that many brain structures involved in limbic regulation of emotion, such as the hippocampus and amygdala, are evolutionarily conserved from mouse to man.

investigators. These principles provide a valuable guide to modelling anxiety and depression or endophenotypes of these disorders in the mouse.

Mouse models of depression

**Stress, coping and learned helplessness.** Exposure to trauma and stress has been shown to be one of the main predisposing factors to major depression and the disease is often viewed as a manifestation of an inability to cope with stress. Therefore, many models and tests for assessing depression-related behaviour in rodents involve exposure to stressful situations. Of these experimental procedures, the forced swim test (FST) (also known as Porsolt’s test; a behavioural despair test) is probably the most widely and most frequently used. The FST is based on the observation that rodents placed in an enclosed (inescapable) cylinder filled with tepid water will initially engage in vigorous escape-orientated movements, but then within minutes will exhibit increasing bouts of immobility. A related but not synonymous task is the tail suspension test (TST), in which mice hung upside-down by their tail also exhibit passive immobility after minutes of futile struggling, which emerged in the mid-1980s.

Interestingly, although the model was adapted for use in the mouse by Anisman and colleagues in the late 1970s, there has been a paucity of studies applying it to genetically modified mice. Another much-discussed issue is the precise meaning of immobility taken as evidence of increased depression-related behaviour in the mutant.

Despite their appeal, reasonable concerns have emerged about the validity of the FST and TST as models of depression. For example, the FST and TST are sensitive to acute antidepressant administration, whereas chronic treatment is required for full clinical efficacy, suggesting that they might not be tapping into the same long-term adaptive changes in neuronal circuitry that underlie antidepressant effects in humans. That said, several recent studies have shown effects of antidepressants in these tests after chronic treatment at much lower doses than those needed to induce effects after short-term treatment. Another much-discussed issue is the precise meaning of immobility behaviour and its relevance to depression. In this context, it is important to note that immobility in these tests seems to be the result of an inability or reluctance to maintain effort rather than a generalized hypoactivity. This in itself provides an interesting correlate with clinical observations that depressed patients show pronounced psychomotor impairments, particularly in those tests requiring sustained expenditure of effort.

The idea of stressor uncontrollability and passive versus active coping responses to stress provides the conceptual basis of several other rodent tests for depression. The learned helplessness model originates from the observation that dogs repeatedly exposed to electric shocks that were both inescapable and uncontrollable subsequently failed to flee the shocks even when offered a means of escape. In the rat, which until now has been used for most of the helplessness tests carried out in rodents, escape deficits have been found to be reversible by antidepressants. On the down side, only a certain percentage of animals develop helplessness behaviour and, in those that do, behavioural deficits only persist for 2–3 days. Interestingly, although the model was adapted for use in the mouse by Anisman and colleagues in the late 1970s, there has been a paucity of studies applying it to genetically modified mice.

Another model based on exposure to repeated but unpredictable stressors is the chronic mild stress (CMS) model, the use of which in rats was championed by Willner and colleagues. This model involves repeated exposure to relatively moderate stressors, such as wet bedding, constant lighting and food deprivation. The CMS procedure induces various long-term behavioural, neurochemical, neuroimmune and neuroendocrine alterations that resemble those observed in depressed patients, which are reversed only by chronic, but not...
Antidepressants from diverse classes reduce the time spent immobile in the forced swim test, indicating antidepressant-like effects. *P < 0.01. ‡P < 0.001 versus relevant control.

**Figure 2** Using the forced swim test to assess the role of the GABA_B receptors in depression-related behaviour. 

a When mice are placed in an inescapable cylinder of water, they become immobile. Antidepressants from diverse classes reduce the time spent immobile.

b–d Pharmacological antagonism (a) or genetic inactivation (b, c, d) of either of the two receptor subunits of the GABA_B (γ-aminobutyric acid) receptor (GABA_B1 or GABA_B2) induces antidepressant-like effects.

**Proportional Ratio Schedule**

Requires an increase in operant responding for reward until a 'break-point' is reached. The break-point determines the maximal amount of effort made to procure the reward and therefore the subject's level of motivation.

**Intracranial Self-Stimulation (ICSS)**

A direct measure of brain reward function that works by mice pressing lever or turning a wheel to receive electrical intracranial self-stimulation of brain regions that are activated by natural reinforcers.

Acute, treatment with a broad spectrum of antidepressants is effective, although the CMS model has been hampered by poor inter-laboratory reliability in rat studies. There are some promising recent reports of its use in mice. The mouse version of the model incorporates assessment of the animal's coat condition, which deteriorates in line with stress-induced deficits in grooming in an antidepressant-reversible manner.

This phenomenon has been considered analogous to the observation that depressed patients execute even the smallest tasks with great effort, often leading to poor personal hygiene. An important goal for future studies, and indeed an area in which several research groups are investing much effort, is a thorough assessment of the validity of the mouse CMS model across various laboratories.

**Alternative approaches to assessing depression-related behaviour** Anhedonia, the loss of interest in normally pleasurable, rewarding activities, is a core symptom of depression and a potentially useful endophenotype for modelling depression-related anhedonia in mice. 'Pleasure-seeking' in rodents can be assessed by simple preference for a highly palatable solution, such as sucrose, over water by measuring the willingness to work for a food or drink reward under a progressive ratio schedule, or through intracranial self-stimulation.

Recent work has shown that withdrawal from drugs of abuse, such as amphetamine, produces deficits in these reward-related behaviours. Amphetamine withdrawal also increases immobility in both the rat and mouse FST and mouse TST, induces escape deficits in the mouse learned-helplessness model and leads to decrements in sexual motivation. Given these converging findings, it will be important to assess next whether the effects of drug-withdrawal-induced anhedonia are reversed by antidepressants. In the longer term, this paradigm could provide a novel model for emotional disturbances seen in drug abuse, with potential for evaluating treatments for both depression and relapse to drug abuse. This is especially important given the high comorbidity between substance abuse and depression, with the prevalence of mood disorders being approximately fivefold higher in drug-dependence sufferers than the general population.

The bilateral removal of the olfactory bulbs of rodents results in a complex constellation of behavioural, neurochemical, neuroendocrine and neuro-immune alterations, many of which are comparable with changes seen in depression. The most consistent behavioural change of bulbectomy is a hyperactive response in a novel brightly lit open field apparatus, which seems to be related to increases in defensive behaviour. This hyperactivity is reversed by chronic, but not acute, antidepressant treatment at doses that do not compromise performance in sham-lesioned control animals. Bulbectomized animals also show heightened acoustic startle response to stress, marked deficits in circadian rhythms, cognitive deficits, elevated levels of circulating glucocorticoids and anhedonia-like behaviours, such as decreased sucrose preference and sexual behaviour. Several lines of evidence suggest that the behavioural sequelae induced by bulbectomy are not simply a consequence of loss of smell but rather a consequence of neuronal reorganization, including changes in synaptic strength and/or loss of spine density in subcortical limbic regions such as the amygdala and hippocampus.

A growing number of studies have begun to use this model in mice. Altered sleep patterns are one of the hallmark symptoms of depression. Interestingly, sleep deprivation in humans is one of the few symptoms for which fast-acting antidepressant treatments are available and many antidepressant medications affect paradoxical (rapid eye movement; REM) sleep. But there is still little research in rodents on the role of sleep in depression. In a recent study, which supports the potential usefulness of investigating sleep patterns in mice, mice that were selectively bred for high levels of immobility in the TST showed lighter and more fragmented sleep and decreased REM sleep latency, abnormalities that resemble those observed in depressed patients.

Further research on sleep and depression-related behaviours in mice is an interesting direction for future investigation.

**Mouse models of anxiety**

Exploratory-based approach–avoidance conflict tests. As noted earlier, the state of anxiety is a normal, adaptive response to danger, and as such is distinct from depression, which is by definition pathological. Working from the assumption that the same neurobiological systems...
medicate both normal and abnormal anxiety, many animal models of anxiety disorders have therefore tapped knowledge of the natural behavioural patterns of rats and mice to develop ethologically based behavioural tasks. Most popular among these are the exploratory ‘approach–avoidance’ tasks (TABLE 2). Many of these tasks were originally developed and validated on the basis of their ability to predict the effects of anxiolytics in rats, and have since been adapted for use in mice. However, mice are not little rats and it should be noted that rat tests have translated into mouse versions with varying success.

Presumably because of selective pressure on defence against predation, small rodents have an innate aversion to exposed, well-lit spaces. Moreover, mice are also a naturally foraging, exploratory species, and exploration-based tasks exploit the conflicting tendencies to approach versus avoid a potentially dangerous area. The aversive area takes different forms in different tests: open, elevated arms (elevated plus-maze), open, elevated quadrants (elevated zero-maze), a light compartment/arena (light/dark exploration test, dark/light emergence test), a mirrored arena (mirrored chamber test), a staircase (staircase test) or the central area of a brightly lit open field (open field test) (see FIG. 4); for a fuller description of these tests see REFS 28,80. Over a typical test session, non-drug-treated, non-mutant mice are expected to avoid these aversive areas and prefer to remain in the protected zones of the apparatus for most of the testing period (FIG. 5). As a measure of ‘anxiety-like behaviour’, this pattern of behaviour has intuitive appeal (‘face validity’), given that many anxiety disorders are typified by a pervasive avoidance of a feared object or situation (TABLE 2). The concept of conflict between opposing drives is also reminiscent of psychodynamic theories of human anxiety.

However, again the temptation to over- anthropomorphize should be avoided. As with the mouse depression models, the most important facet of these tasks as tests for assessing anxiety-like behaviour is their predictive validity; that is, avoidance behaviours are reduced by treatment with clinically efficacious anxiolytics, although principally by the benzodiazepine agonist class, which includes diazepam. The same logic is extended to the interpretation of phenotypic abnormalities in mutant mice on these tests: decreased avoidance of the more threatening areas of the apparatus (for example, elevated plus-maze open arms) in a mutant mouse, relative to a non-mutant, ‘wild-type’ control is interpreted as a reduced anxiety-like behaviour or an anxiolytic-like phenotype. In addition, because avoidance behaviour can be augmented by drugs with pro-anxiety effects in humans, these tests are also used to assess heightened anxiety-like phenotypes in mutant mice.

Although the approach–avoidance conflict tests continue to be a mainstay in assayong mouse anxiety-related behaviour36,38, there are major caveats associated with their use. For one, because these tests are based on the interplay between approach and avoidance, they do not satisfactorily dissociate decreased anxiety-related avoidance from increased novelty-seeking or impulsivity-related approach behaviour, as both will manifest as increased time spent in the novel, aversive area. Such ambiguity could be confounding in cases where a manipulation has potential effects on both emotion and novelty-seeking, as in, for example, phenotypic assessment of dopamine D₁-receptor-knockout mice, and will necessitate the use of specific tests of novelty-seeking and impulsivity. Behavioural performance on exploration-based tests is also heavily reliant on intact sensory and motor function in the mouse. Quantification of general measures of locomotor activity in a test (for example,
distance travelled in the light/dark test and entries into the closed arm in the elevated plus-maze) or in a non-anxiety-provoking environment (for example, home cage) can provide support for interpretation of a mutant phenotype or drug effects as being specific to anxiety-related behaviour. However, gene mutations with pleiotropic effects on brain function that impair tactile or visual acuity can also confound performance on these tests. Concerns about the specificity of an anxiety-related phenotype can be partially mitigated by assessment of sensory, neurological and motor functions. An additional approach is to measure certain forms of approach–avoidance conflict tests (for example, novelty-suppressed feeding) that could be more sensitive to treatment with SSRIs than others and further work clarifying which tests reliably predict the actions of a broad range of clinically effective anxiolytics will be valuable. The same issue also applies to the tests of depression-related behaviour, of which the validity of many is predicated on their ability to detect known antidepressants acting on monoaminergic neurotransmission. Therefore, if a gene mutation or novel drug treatment fails to alter behaviour in either the elevated plus-maze test or the FST, does this mean that it does not have potential anxiolytic or antidepressant actions, or that the tests do not measure the ‘right’ form of emotional behaviour? Unfortunately, there is no simple answer to this question. Validation of a mouse behavioural model on the basis of its ability to predict the actions of an existing anxiolytic or antidepressant alone will always carry with it the danger that the test will be insensitive to novel therapeutics with different mechanisms of action.

**Alternative approaches to assessing anxiety- and fear-related behaviour.** The limitations of the exploration-based tests for anxiety-like behaviour reinforce the need for new alternatives and prompt reconsideration of the use and further modification of currently less popular models. For example, punishment-based conflict procedures in rats have been used for more than 40 years in the identification and characterization of anxiolytic agents. In the Geller–Seifter task, rats are first trained to lever press for a food reward and are then subsequently punished for making these responses by administration of mild electric shocks. Clinically effective anxiolytic agents produce a selective increase in punished responses. However, the need for lengthy training periods (that is, months) has restricted the usefulness of the model for the high-throughput screening of pharmacological agents and mutant animals, and the test has not been widely translated into the mouse. A more practical version of the punished-conflict test was developed by Vogel and colleagues: here, water-deprived rats are provided with a drinking spout that delivers a mild shock after every 20 licks. Reference anxiolytics, such as diazepam, attenuate the shock-induced suppression of drinking. Although, the Vogel test has also recently been used successfully in mice, the task and punishment-based assays have generally fallen out of favour with the growing popularity of the more naturalistic approaches, such as the aforementioned exploration-based tests.

The shock-probe defensive burying test for anxiety-like behaviour is an attempt to combine ethological- and punishment-based approaches. This task, again originally developed and validated in rats, is based on the observation that rodents exposed to an electrified probe will bury the probe with cage sawdust, presumably as an innate response to prevent further contact. The amount of burying behaviour can be quantified and is reduced by anxiolytic treatment. Along similar lines, the finding that mice will spontaneously bury novel marbles placed in their home cage in an anxiolytic-sensitive manner has led to the development
of the marble burying test. Although this last test is less readily confounded by abnormalities in mouse pain perception that are potentially caused by a gene mutation or drug treatment rather than shock-based tasks, it has been less widely used.

Two other naturalistic tests for mouse anxiety-like behaviour warrant consideration. Adult rodents hear and emit ultrasound vocalizations (USVs) above the audible frequency range and, interestingly, fear and anxiety-like responses have been related to certain characteristic USV frequencies (typically 20–30 kHz). In rats, stressful/anxiety-provoking manipulations, such as inescapable footshock, airpuffs, withdrawal from stimulant drugs and exposure to an aggressive conspecific or predator, induce such USVs in an anxiolytic-reversible manner. As shown by Miczek and colleagues and others, separation of young mouse pups (between 1 and 21 days old) from their mother also evokes USVs (albeit at a higher range of >35 kHz range), and this behaviour has been used to measure anxiety-like responses in mutant mice notwithstanding due caution about its possible relevance to human affective processing. Another innate response of mice that has potential applicability as a quantifiable assay for anxiety-related phenotypes is the increase in core body temperature and autonomic arousal after exposure to stress. Methods have been successfully developed for assessing autonomic responses to fear- and anxiety-provoking stimuli using radiotelemetry as a novel means to phenotype mutant mice. Stress-induced hyperthermia (SIH) is a less technically demanding model that quantifies the degree of hyperthermia elicited by an acute mild stress (for example, rectal insertion of temperature probe). The degree of SIH is attenuated by anxiolytics and provides a simple readout of autonomic reactivity to stress in mutant mice. The SIH test circumvents confounding sedative or stimulant effects, although it is unsuitable for assessing drugs or mutations that affect basal cardiovascular or thermoregulatory processes.

Each test for anxiety-like behaviour comes with idiosyncrasies and limitations and no one test provides the ideal model of anxiety. Therefore, demonstrating that a gene mutation or drug treatment produces behavioural alterations on a battery of tests comprising various tasks would provide strong support for a true positive anxiety-related phenotype. A mutant line that had an anxiety-like phenotype that manifested in tests indexing anxiety from an increase in the output measure (for example, more shocks and higher autonomic arousal), as well as tests in which anxiety is inferred from the suppression of behaviour (for example, less exploration of a threatening environment), would represent a particularly strong case. The effectiveness of a test battery approach is further advocated by evidence that even among the ostensibly similar exploration-based mouse tasks, there are qualitative differences between tests, with each test measuring overlapping, but partially distinct, forms of anxiety-related behaviour.

The possibility that such differences between mouse tests for anxiety-like behaviour might, to some extent, parallel clinical differences between human anxiety subdisorders is intriguing, but still largely speculative. In this context, there have been attempts to develop rodent tasks that model a specific anxiety disorder. Panic disorder is particularly amenable to such efforts because it is diagnostically distinct from other disorders — the anxiety that is characteristic of a Panic Attack can be differentiated from generalized anxiety by its discrete, almost paroxysmal nature and its typically greater severity. This distinction has strong echoes in the seminal work of Blanchard and Blanchard on the natural defensive behaviour of rodents that describes differences between ‘anxiety’ and ‘fear’ behaviours. In their conceptualization, fear behaviours occur in response to explicit, imminent threats and are usually short-lived, evoking intense escape and avoidance of the threat whereas, by contrast, anxiety responses occur in response to less explicit, more generalized threats and sustain preparedness by increasing arousal and risk assessment. On this basis, Blanchard, Griebel and Blanchard developed the mouse defence test battery, in which fear-related (flight, freezing, defensive threat and attack) and anxiety-related (risk assessment) behaviours are measured after exposure to a natural predator (rat). Interestingly, the flight reaction is attenuated or exaggerated by pharmacological agents that reduce or promote panic attacks, respectively, in humans. Other approaches for studying panic-like responses in rats have not yet been widely applied to the mouse. These include electrical stimulation of periaqueductal grey brain region, administration of panicogenic agents such as sodium lactate or cholecystokinin, and exposure to predators (fox, cat and rat) or predator odour.

Cognitive studies of anxiety and depression

There remains considerable potential for developing novel approaches to modelling anxiety and depression in mice. One promising avenue for future research involves modelling the cognitive symptoms of these...
Many species. Investigators have recently begun exploring the relationship between CTA and anxiety124,125.

Pavlovian fear-conditioning tasks have been more extensively used in neuroscience to study the neural basis of learning and memory, rather than emotion per se. Nonetheless, this research has generated a large corpus of data indicating that conditioned fear behaviour recruits the same neural circuits implicated in human anxiety and depression, including the amygdala, hippocampus and prefrontal cortex126. Further modification of these models could provide additional insights into the role of these systems in the pathophysiology of affective disease. For example, measuring conditioned emotional responses to stimuli that are partial, incomplete representations of the learned stimulus (for example, an auditory tone of different frequency to the conditioned tone) could provide a means to assess responses to partial or ambiguous threat cues. This modified approach could have important clinical relevance given the abnormally high reactivity of individuals with anxiety disorders, such as post-traumatic stress disorder, to over-generalized threat cues that inappropriately evoke memories of stimuli previously associated with traumatic events127-129. Exposure to predator (for example, mouse defence test battery). Exposure to explicit cue associated with fear.

### Table 3 | Modelling fear and anxiety

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Nature of threat</th>
<th>Response evoked</th>
<th>Clinical manifestations</th>
<th>How it might be modeled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Potential, ambiguous, distant</td>
<td>Long-lasting/sustained, Hyperarousal and increased cognitive risk assessment</td>
<td>Generalized anxiety disorder (agoraphobia)</td>
<td>Tests based on approach-avoid conflict (for example, elevated plus-maze). Exposure to ambiguous/partial cue associated with fear</td>
</tr>
<tr>
<td>Fear</td>
<td>Explicit, proximal-imminent, unambiguous</td>
<td>Short-lived/phasis. Intense motivation to avoid and escape</td>
<td>Panic attack (specific phobia)</td>
<td>Exposure to predator (for example, mouse defence test battery). Exposure to explicit cue associated with fear</td>
</tr>
</tbody>
</table>

Conditions. As stated earlier, the rodent cortex is much more primitive than the human equivalent and clearly one cannot expect all aspects of cognitive processing to be present in mice. Nonetheless, rodents can perform sophisticated cognitive functions that are in part mediated by cortical structure and can be powerfully applied to the study of psychiatric disorders112.

Although depressed patients show pronounced cognitive deficits, such as impaired planning and executive function and a switch in attention towards negative stimuli113, there has been relatively little research effort directed at modelling cognitive behaviours that are pertinent to depression in mice. Cognitive disturbances, such as misappraisal and over-attention to threatening stimuli, are also seen in panic disorder, generalized anxiety disorder and phobias, whereas traumatic memories are a key feature of post-traumatic stress disorder9,114. So far, models for studying emotional cognition in rodents have been based on certain well-established concepts, such as Pavlovian fear conditioning115-117 based on the classic work of Pavlov118. This model measures fear-related behaviours that are induced by exposure to a previously innocuous stimulus (for example, auditory tone) that has been associated, through repeated pairings, with an innately aversive stimulus (for example, foot-shock). Evolution has favoured this form of learning as a means of rapidly ascertaining which environmental stimuli signal danger, and it is an essential component of many mammalian defensive behaviour systems119.

In the laboratory, the degree of conditioned fear can be readily quantified through various behaviours, such as freezing, startle, tachycardia, defensive burying and USV115-117,119. Disturbances in sleep have also recently been shown to be a sensitive readout of fear conditioning in rats120,121 and mice122, which is interesting given that sleep dysfunction is a diagnostic criterion for certain anxiety disorders6.

Conditioned taste aversion (CTA) is another conditioned learning phenomenon in which the subject learns to associate a novel flavour with delayed visceral malaise, such as that induced by lithium chloride123. Animals reduce their consumption of flavoured foods associated with this aversive response, and/or show a preference for other tastes. CTA develops rapidly, often after a single conditioning trial and like other fear-conditioning models is amygdala-dependent, with a neural circuitry that is evolutionarily preserved across many species. Investigators have recently begun exploring the relationship between CTA and anxiety124,125.
Experience of stressful events during childhood has long been thought to contribute to the pathophysiology of emotional disorders, and recent research suggests how early life trauma and neglect exert a profound and pervasive influence on risk for depression and anxiety disorders\(^{168}\). Indeed, it seems that early life trauma might not only increase risk for these disorders in adulthood, but could also precipitate illness onset, increase comorbidity among disorders and alter the efficacy of treatments for these conditions\(^{169}\). However, although there is evidence that genetic factors also exert a profound influence on risk for these disorders, the interplay between genes and early life stress is presently poorly understood. In rats, postnatal maternal separation can produce lasting increases in emotional behaviour and stressor reactivity, together with alterations in neurotransmitter systems that are implicated in emotionality, including corticosterone–releasing factor, serotonin, noradrenaline and glutamate\(^{169}\). Of note, Meaney and colleagues, among others, have shown that pups reared under conditions of relatively poor maternal care, or subject to maternal separation, develop various behavioural and neurochemical abnormalities that are relevant to anxiety and depression\(^{169}\). This raises the possibility of generating mouse models of postnatal stress, which is an especially attractive avenue of research given the capacity for studying the interactions between a specific gene and early life environment in mice\(^{170–172}\). For example, genetic differences between inbred mouse strains have been exploited to study how maternal behaviour affects emotional development using techniques such as cross-fostering and generation of inter-strain hybrids\(^{170,171}\). However, there remains a paucity of research in this area and a pressing need to identify reliable mouse models of early life stress.

Studies in the mouse have begun to provide important insights into how the brain systems mediating emotional behaviour develop during early life. Recently, Hen, Gross and colleagues found that mutant mice engineered to be deficient in a key serotonin receptor subtype (5-hydroxytryptamine (5-HT)\(_{1A}\)) during postnatal development, but not adulthood, produced permanent abnormalities in anxiety-like behaviour\(^{171}\). This finding concurs with a wider literature using mouse transgenics and knockouts that supports a key role for the serotonin system in orchestrating the formation of neural circuits mediating emotion\(^{173–175}\). The wider implication of such work is that mouse models can provide insight into how perturbation of the developing brain by stress, drugs or naturally occurring genetic variation can affect later risk for depression and anxiety disorders.

---

**Box 1 | Modelling early life origins of anxiety and depression**

As discussed, many of the tests used to measure these behaviours are easy to construct, conceptually attractive and require relatively minimal training (of mouse or experimenter). However, precisely because many tests of this type measure spontaneous behaviours, they might be relatively sensitive to variations in test procedure and environment. Indeed, it is known that the activity of mice in tests for emotional-related behaviours can be influenced by a host of procedural- and organism-specific variables, such as age, gender and housing conditions\(^{166,169,170}\). Unfortunately, it is difficult to ascertain which variables are crucial and the degree to which they will reliably affect anxiety- and depression-like behaviours. Studies by Crabbe, Wahlsten, Dudek and colleagues have convincingly shown that even ostensibly subtle variations in laboratory environment and test procedure can alter mouse anxiety-related behaviours\(^{166,169,170}\). There is also evidence that repeated testing in various tests for anxiety-like behaviour markedly alters baseline behaviours and anxiolytic-sensitivity in normal mice\(^{138}\). Similarly, in some studies it has been observed that repeated exposure to the mouse FST markedly alters depression-related behaviour on subsequent exposures to the test\(^{139}\). A related issue is the potential effects of testing mutant mice on a battery of behavioural assays. Given the cost and effort required to generate sufficient numbers of mutant mice and properly matched controls for behavioural studies, added to the need for replication of findings across different tests, it is often prudent to test the same cohort of mice on multiple tests for assessing emotion-related behaviours. Paylor and colleagues have recently provided useful information on how specific tests are differentially influenced by previous test history\(^{140}\). For these reasons, it is essential to consider test order carefully and the potential for previous experience to influence, possibly in a genotype-dependent manner, behavioural phenotypes on tests for anxiety- and depression-like behaviours. Furthermore, given the potential for inter-laboratory variations to affect the outcome of mutant studies, a more general recommendation is to realize that ‘standardized’ methods cannot simply be decoded from the methods section of a published paper to the effective use in one’s own laboratory without proper in-house validation\(^{141}\).

There are considerable differences in anxiety-like and depression-related behaviours across the commonly used mouse strains\(^{142–145}\). Some of the more widely reported findings to emerge from these studies are that certain strains, such as BALB/c substrains, have heightened sensitivity to stress and demonstrate exaggerated anxiety- and depression-related behaviours\(^{142–145}\). On this basis, some have postulated that the BALB/c strain could be a relevant strain in which to model pathological anxiety\(^{140}\). A practical consequence of these differences is that the strain, and therefore the genetic background, onto which a mutation is backcrossed can affect the detection of an anxiety-like or depression-related phenotype in a mutant mouse. Genetic background can exert effects on a mutant phenotype in several ways: by providing an inappropriate baseline level of behaviour in wild-type control animals; through the unwanted contribution of flanking genes derived from the embryonic stem cell donor strain; or from complex functional interactions between the mutation and background genes\(^{146}\). Therefore, careful consideration should be given to the choice of background strain for studies of anxiety and depression and, ideally, the mutation should be backcrossed onto one or more congenic backgrounds\(^{146}\).

On the positive side, mouse strain differences provide a principal resource for the study of genetic factors that underlie anxiety- and depression-related behaviours. For example, the BALB/cj and DBA/2j strains carry a mutant allele for the brain-specific serotonin-synthesizing enzyme tryptophan hydroxylase 2 (Tph2), which results in a considerably lower brain serotonin concentration in these strains compared with the C57BL/6j and 129X1/SvJ strains that do not carry the mutation\(^{147}\). This genetic difference could contribute to differences in anxiety- and depression-related behaviours between these strains\(^{148}\), which is an intriguing finding given a preliminary report that the human orthologue of this allele is associated with increased risk for depression\(^{148}\).

---

**FLANKING GENES**

DNA sequences on either side of a targeted gene mutation that derive from the embryonic donor mouse strain and could contain genes foreign to the host mouse that spuriously influence the behavioural phenotype of the host.

**CONGENIC**

A mutant line generated from repeated backcrossing to an inbred strain for ten generations or more.

**GALVANIC SKIN CONDUCTANCE RESPONSES**

A measure of electrical resistance used as a marker for changes in emotional arousal.
One of the hopes of modern translational research is that early proof-of-concept clinical trials for drug efficacy can be carried out in defined clinical subpopulations or in healthy volunteers after experimental manipulations. Acute anxiety-like symptomatology can be provoked in humans in a measurable fashion by chemical (lactate, cholecystokinin, caffeine, pentyleneetrazol, yohimbine, and CO₂ inhalation) or psychological (aversive pictures or situations and forced public speaking) means. Anxiety-like behaviour in rodents can be induced by using some of these manipulations. For example, Shekhar and colleagues have developed a panic model in which rats are first treated with GABA (γ-aminobutyric acid) synthesis inhibitors in the dorsal medial hypothalamus and then infused with lactate. This produces behavioural changes, such as escape, and physiological changes, including cardiovascular and respiratory alterations, that resemble features of panic in humans.

Pavlovian fear conditioning is a highly conserved behaviour that provides another valuable approach to translational research. Conditioning models such as fear-potentiated startle have been successfully used to delineate fear circuitry in rodents and are increasingly being utilized in human studies using readouts of conditioning such as the galvanic skin conductance response. Interestingly, given that most rodent models are exploratory-based approach–avoidance conflict tests, no human model with constructs based on such conflicts have been developed. Logistical difficulties in placing subjects in novel aversive situations might be one reason for the lack of development in this field. However, the recent emergence of virtual reality-based experimental situations could make this an interesting avenue for future research.

Assessment of anhedonia is one area that offers the possibility of identifying reliable readouts of ‘depression’ common to rodents and humans. Anhedonia can be easily monitored in mice (for example, using intracranial self-stimulation) as an altered response for appetitive stimuli. Recently, Pizzagalli and colleagues used a signal detection task to assess differentially reinforced stimuli and found that depressed patients did not exhibit a normal bias for stimuli associated with higher reinforcement (rewarding stimuli). It should be possible to devise analogous experiments in mice. Similarly, discrete symptomatological phenomena found in depression (endophenotypes), such as sleep disturbance, are also readily measurable in rodents (see references for reviews). In addition to behavioural changes, there are various specific physiological and neurochemical changes in depression that should be amenable for further translational investigation.

Perspective — from Castalia to the clinic
Hericatables contribute substantively to the risk of developing depression and anxiety disorders. As with other psychiatric diseases, these disorders are genetically complex; that is, they are influenced by multiple gene variants, each of which can be simplistically thought of as conferring relative susceptibility or resilience. Moreover, it is becoming increasingly clear that these disorders arise from a combination of environmental and genetic factors, which interact in a highly complex manner to affect risk. Not surprisingly, fear and anxiety-like behaviours in mice also seem to be polygenic and epistatic in nature. Therefore, studies in mutant mice are not going to discover the ‘gene for anxiety’ or the ‘gene for depression’. More realistically, mouse behavioural research can provide valid model systems to explore the role of a given gene in molecular pathways that influence depression- and anxiety-related behaviours. However, although mutant mice are often discussed as ‘genetic models’, they are in actuality rarely used to model directly the role of a human candidate gene variant in depression or anxiety. Rather, genetically modified animals have largely been used as a means to study the consequences of altering a specific gene product much in the same way as a highly selective pharmacological agent would activate or antagonize the function of a protein such as a receptor.

This is not to say that this approach is invalid. Indeed, as noted earlier, mutant mice are extremely valuable when dissection of the functional role of a molecule cannot be approached using more traditional strategies — for example, when pharmacological compounds are unavailable or have poor selectivity for a particular receptor subtype. However, as frequently pointed out, constitutive mutation of a gene raises concerns over the potential for the induction of developmental alterations that mask the normal function of a molecule or otherwise modify neural systems subserving emotion. In hindsight, the extent of these adaptations is not surprising given the considerable plasticity of the brain, especially during development. Nevertheless, such ‘knock-on’ effects of knockout can obfuscate the causal link between molecule and behaviour, and it is now widely accepted that emotion-related abnormalities in mutant mice must be carefully interpreted with this caveat in mind.

Fortunately, there are several emerging techniques that can help mitigate the problem of compensation in mutant mice. One powerful approach is to restrict mutation of a gene to specific brain regions or cell types. Induction of such ‘conditional’ mutations can also be withheld until after development to further limit the potential for adaptive changes. Highly promising alternatives to the gene-mutation strategy are also being realized, including RNA interference. Even with these important advances, behavioural research using the mouse does not offer a panacea for drug development. Mouse models are most effective when used in conjunction with other techniques to generate converging lines of evidence regarding the role of a molecule in the neural pathways mediating emotion.

In this context, whereas translational medicine in basic research and drug discovery efforts necessitates valid animal models of human disease, this approach is a two-way bridge. Preclinical research must inform clinical trials, but the converse is also essential. The development of clinical research tools that are informed by, and can parallel rather than specifically recapitulate, mouse models of anxiety and depression might well be the most fruitful path to understanding these diseases. A similar approach has been used by Robbins, Sahakian and colleagues to assess cognitive dysfunction in neuropsychiatric disorders, such as schizophrenia and Huntington’s disease, with considerable success.

One area of research in which clinical research currently outpaces laboratory research is in the field of non-invasive brain imaging. There has been a recent explosion of data on the neural circuits underlying anxiety or mood disorders from the field of psychiatric neuroimaging. These
findings should serve to inform laboratory studies using mouse models and so facilitate the testing of experimental hypotheses that are not feasible in human studies, including the influence of genetic manipulations on the function of these circuits and the emotional behaviours they mediate.

In his telling indictment of modern pharmaceutical research, the late David Horrobin argued that the field resembled the ‘Glass Bead Game’ described by the Nobel laureate Herman Hesse in his final novel. The academic inhabitants of the fictitious town of Castalia dedicate their lives to devising and solving Glass Bead Games that, although intellectually demanding, have little relevance to the practical needs of the outside world. The challenge for cross-species translational research in psychiatry is to successfully marry the academic and the prosaic to better understand the biological bases of mental illness and, ultimately, to treat it effectively. Given its unique strengths as an experimental system for studying genetics, neurobiology and behaviour, mouse models are central to meeting this challenge.
Reviews


References 143–145 describe the marked differences in anxiety- and depression-related behaviours found between different strains of mice.


170. Holmes, A. et al. Early life genetic, epigenetic and environmental factors shaping emotionality in rodents. Neurosci. Biobehav. Rev. (in press). There is growing application of novel approaches to experimentally manipulating the function of gene products to study mouse emotion-related behaviours, such as the nonviral RNA interference technique described in references 156 and 157.


Acknowledgements JFC is supported by a grant from the National Institutes of Mental Health/National Institute on Drug Abuse. AH is supported by the National Institute on Alcohol Abuse and Alcoholism intramural research programme and by the National Alliance for Research on Schizophrenia and Depression.

Competing interests statement The authors declare competing financial interests; see Web version for details.

Online links

FURTHER INFORMATION


Ensembl Mouse: http://www.ensembl.org/Mus_musculus/index.html

German Mouse Clinic: http://www.mouseclinic.de


National Institute of Mental Health: http://www.nimh.nih.gov/publication/anxiety.cfm

RDS: http://www.rds-online.org.uk

Tennessee Mouse Genome Consortium: http://rmouse.org

Trans-National Institutes of Health Initiative, Neuroim: http://www.neuroimice.org

Access to this interactive links box is free online.