The clinical implications of mouse models of enhanced anxiety

Simone B Sartori[†,1], **Rainer Landgraf**[2], and **Nicolas Singewald**[1]

[1]Department of Pharmacology & Toxicology, Institute of Pharmacy & Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Peter-Mayr-Street 1, A-6020, Innsbruck, Austria

[2]Max Planck Institute of Psychiatry, Department of Behavioral Neuroendocrinology, Munich, Germany

Abstract

Mice are increasingly overtaking the rat model organism in important aspects of anxiety research, including drug development. However, translating the results obtained in mouse studies into information that can be applied in clinics remains challenging. One reason may be that most of the studies so far have used animals displaying 'normal' anxiety rather than 'psychopathological' animal models with abnormal (elevated) anxiety, which more closely reflect core features and sensitivities to therapeutic interventions of human anxiety disorders, and which would, thus, narrow the translational gap. Here, we discuss manipulations aimed at persistently enhancing anxiety-related behavior in the laboratory mouse using phenotypic selection, genetic techniques and/or environmental manipulations. It is hoped that such models with enhanced construct validity will provide improved ways of studying the neurobiology and treatment of pathological anxiety. Examples of findings from mouse models of enhanced anxiety-related behavior will be discussed, as well as their relation to findings in anxiety disorder patients regarding neuroanatomy, neurobiology, genetic involvement and epigenetic modifications. Finally, we highlight novel targets for potential anxiolytic pharmacotherapeutics that have been established with the help of research involving mice. Since the use of psychopathological mouse models is only just beginning to increase, it is still unclear as to the extent to which such approaches will enhance the success rate of drug development in translating identified therapeutic targets into clinical trials and, thus, helping to introduce the next anxiolytic class of drugs.

Keywords

anxiety disorders; anxiolytic; benzodiazepine; drug development; inborn anxiety; mutant mice; neurokinin 1 receptor; neuropeptide S; psychopathology; stress

From physiological to pathological anxiety

Anxiety and fear, along with happiness, sadness, anger and shame, are basic emotions accompanying human beings throughout their whole life [1]. A clear delineation between anxiety and fear has, in general, turned out to be difficult and often depends on the discipline [2]. In the neurosciences, anxiety is defined as the response to an undetermined, potentially dangerous situation, while fear is defined as the response to an explicit hazard [2]. Therefore, although anxiety and fear appear to be closely related, there is increasing evidence that, qualitatively, trait fear and anxiety are two largely distinct emotions in terms

†Author for correspondence: Fax: +43 512 507 2931 ■ simone.sartori@uibk.ac.at.

of behavioral responses [2-3]. From an evolutionary perspective, anxiety is a reasonable and useful effect, warning us about danger and initiating adequate somatic, cognitive, emotional and behavioral responses in order to avoid harm and, thus, elevate the chances of survival. Nowadays, most of the anxiety states we experience are acceptable providing that they quicken our responses so that we can get through the situation, adequately cope with stressful challenges and that they cease soon after. However, in some individuals, these anxiety reactions may become persistent, uncontrollable, excessive and inappropriate, even after the withdrawal of the stimulus, lacking any adaptive value, and negatively influencing the quality of their everyday life [601]. Such reactions, which persist for at least 6 months, characterize pathological anxiety [601]. Pathological anxiety can be described as either a quantitative or qualitative variation of a normal state; which it is, however, still a matter of debate [3-5]. What it is that causes the crossing from physiological to pathological anxiety is a subject sparking intense research interest.

There is evidence that the simultaneous occurrence of various intrinsic and extrinsic factors is important for the etiology of an anxiety disorder. Specifically, a 30–40% estimated heritability across anxiety disorders suggests a moderate risk factor in the manifestation of an anxiety dis order [6]. Moreover, environmental factors such as diverse (negative) experiences, including early life stress, have been demonstrated to exert a critical impact on the development of an anxiety disorder [7,8]. Interestingly, the individual's susceptibility to environmental factors is modulated by a diverse range of genes [9-10].

Today, anxiety disorders are the most common neuropsychiatric disorders in the USA and Europe [11,12]. They represent some of the major health problems in the Western world in terms of costs of healthcare, sick-leave from work, disabilities and premature mortality [13]. Anxiety disorders encompass a spectrum of disorders exhibiting a wide range of symptoms and different degrees of severity, as well as variations in terms of age of onset, prevalence in males and females, and treatment responses. In addition, many patients with an anxiety disorder also suffer from other psychiatric disorders (e.g., 60% comorbidity with depression) and/or physical or organic diseases, further complicating the syndrome pattern [7,14,15]. The categorical classification systems of mental illnesses [16], both the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [17] and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [18], distinguish between several human anxiety syndromes, including generalized anxiety disorder, social phobia, specific phobias, panic disorder, post-traumatic stress disorder and obsessive-compulsive disorder. Interestingly, these classification systems do not distinguish categorically between anxiety and fear. These subdisorders have, in part, different sensitivities to anxiolytic treatments [19,20] and it is thought that they differ in their underlying neurobiology (e.g. [21,22]). However, there is also substantial comorbidity within these subcategories and what they do all have in common is an irrationally intense, uncontrollable feeling of anxiety, which suggests that these disorders have partly overlapping neurocircuitries (e.g., [21-23]).

Various classes of anxiolytic drugs are available for the treatment of anxiety disorders. The benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) are the current first-line treatments in most anxiety disorders [19,20,24]. However, these drugs are far from being ideal as SSRIs are characterized by partial nonresponse, a delayed onset of therapeutic action, a considerable high rate of relapse and adverse side effects, while benzodiazepines induce sedation and have a risk of drug dependence and tolerance, limiting their use mainly to short-term treatment [19,20,24]. Therefore, within the last 20 years, both the pharmaceutical industry and academia have put great efforts into anxiety research and have invested heavily in it. To date, no novel anxiolytic class with an improved pharmacological profile has progressed from its discovery, via preclinical and clinical trials, onto the market. This fact suggests that the strategies followed so far are not optimal and, thus, need to be

refined. In the course of drug development, the anxiolytic properties of substances are initially detected using mostly rodents in screening tests assessing anxiety-related behavior (see 'The assessment of anxiety-related behavior in mice'). At the moment, it is still a matter of debate as to whether these anxiety tests merely elicit physiological responses to an anxiety-provoking situation rather than reflecting abnormal, pathological anxiety as observed in clinically manifested anxiety disorders [25]. Therefore, another idea is to create animal models that closely mimic clinically manifested forms of anxiety and that are quantitatively and/or qualitatively superior to anxiety tests according to a proposed theory of pathological anxiety [4]. In this respect, validated animal models of enhanced anxiety-related behavior with face, construct and predictive validity (see 'Validity of mouse models of enhanced anxiety') may be pivotal to an improved understanding of the neurobiological and genetic mechanisms underlying anxiety disorders, allowing causal hypotheses to be tested and, thus, leading to the discovery of new treatment targets. In this respect, the laboratory mouse has become an invaluable preclinical tool.

From the human anxiety disorder to the mouse model organism

The mouse in anxiety research

Rodents have always played a central role in neuropsychiatric research. In particular, the rat has been the species of choice for many years since the sampling of tissue and diverse fluids, such as blood, can be relatively easily accomplished using appropriate invasive techniques compared with the mouse. Furthermore, in behavioral pharmacology, rats usually perform well in many cognitive and operant tasks. Nevertheless, over the last two decades laboratory mice have become competitors of the rat in anxiety research and this appears to parallel the increasing use of sophisticated molecular techniques such as gene targeting [26]. These molecular techniques, which can be applied particularly to the mouse genome [27], allow scientists to introduce genetic modifications at will in order to study the neurobiological basis of an anxious phenotype [26,28] or to confirm identified genetic associations underlying enhanced anxiety-related behavior at a functional level [29]. Therefore, the laboratory mouse is recognized as the pre-eminent model for modern genetic research into psychiatric diseases. Apart from this genetic aspect, mice offer some practical and economic advantages over rats in terms of their small size (e.g., dosing) and their minimal requirement of space and food.

The evolutionary relationship between humans & mice in anxiety regulation

Although the mouse and the human genome diverged approximately 75 million years ago, they have similar gene functions and share a number of neuroanatomical, neurochemical and behavioral commonalities. The mouse genome is smaller than the human genome, but there are only a few cases, in which no mouse counterpart can be found for a particular human gene [30]. Furthermore, in both humans and mice, the brain is structured into cerebral hemispheres, with a forebrain, a diencephalon, a midbrain, a hindbrain and a cerebellum [31]. While subcortical structures processing anxiety, such as the amygdala, the hippocampus, the thalamus and the hypothalamus are well conserved between the two species, the murine cerebral cortex is clearly reduced in comparison to that of man. Nevertheless, it retains many features representing the fundamental principles of cortical organization, function and development [32]. In this respect, the brain regions of humans and mice implicated in the processing of anxiety, involving the prefrontal cortex, the amygdala and the hippocampus, among others, are phylogenetically related [33-35]. Within these structures the neurotransmitter/modulator systems involved in signaling anxiety-related information are highly preserved, with considerable functional homology. Finally, anxiety reactions are evolutionarily adaptive and, thus, generally highly conserved in mammals [36]. Indeed, when species-specific inborn characteristics are taken into

consideration, analogous physiological and behavioral changes can be observed in mice and humans in response to an anxiety-provoking stimuli [33]. Typical anxiety features including the fight/flight responses, avoidance, freezing, urination/defecation, attention/vigilance, autonomic hyperarousal or muscular tension are present in both species.

The assessment of anxiety-related behavior in mice

In the laboratory mouse, an easily accessible behavioral readout, which is thought to reflect the emotional component of anxiety such as avoidance, escape or freezing behavior may be used as marker of a state of enhanced anxiety. Therefore, such behavior is often referred to as 'anxiety-related' or 'anxiety-like' behavior rather than as anxiety *per se*. Accordingly, numerous behavioral tests have been developed, originally in the rat, to assess the level of anxiety-related behavior. However, with the increasing use of the mouse it has become necessary to adapt these tests for the smaller species, and this has been done with varying degrees of success (e.g. [26,37]). In the field, these tests are often referred to as 'model', which can be misleading. As they elicit an acute emotional response, they are often considered as tests revealing 'state' anxiety [38] as opposed to 'model', which is thought to evoke pathology [39].

Tests of anxiety-related behavior can be roughly classified into unconditioned (ethologically-based procedures) and conditioned (learned procedures) (BOXES 1 & 2) [37,40]. While unconditioned paradigms utilize the natural or spontaneous reactions of a mouse to an innate, aversive stimulus (e.g., avoidance of exposed, brightly lit spaces), conditioned responses involve training sessions in which usually a neutral or rewarding stimulus is paired with an aversive, mildly painful stimulus. Conditioning processes occur in the etiology of many anxiety disorders, including phobias and post-traumatic stress disorder [41,42]. The inhibition of the learned fear response is often disturbed in these disorders and this can be investigated – for example, in extinction paradigms in both humans [43] and animals demonstrating impaired extinction [44-46]. The key feature of all of these anxiety tests is their predictive validity (see following section) since in these paradigms the anxiety-related behavior can be reduced by the administration of clinically effective anxiolytics, especially benzodiazepines (e.g., [24,47-49]). Only a few studies have applied benzodiazepine-validated anxiety tests to investigate the anxiolytic effects of chronic antidepressant treatment (more than 2 weeks of treatment) [50]. The hyponeophagia test, the mouse defense test battery, stress induced hyperthermia and marble burying appear to be the most reliable paradigms in detecting anxiolytic properties of SSRIs in a manner consistent with the time-course of their effects in humans [48-52].

Anxiety tests are frequently used in both industry and academia to screen for potential anxiolytic properties of compounds. Moreover, they fulfill face validity (see 'Validity of mouse models of enhanced anxiety'), as the avoidance of the feared stimulus is a hallmark of many anxiety disorders. Indeed, these tasks are based on assumed analogies between human and mouse symptoms of anxiety; however, it is thought that anxiety-related measures, assessed in various tasks using mice as subjects, may reflect different features of murine anxiety [4,53]. The procedures, peculiarities, pitfalls and validity of these tests are discussed in detail in various excellent reviews and book chapters (e.g., [4,24,26,28,39,47-49,54]).

Anxiety tests can assess specific features of behavior, endocrinology or physiology that are symptomatic in anxiety disorders [25]. Therefore, in the present article both conditioned and unconditioned anxiety tests will be presented in terms of their behavioral characterization of the described mouse models of enhanced anxiety. Specifically, we focused on studies where the enhanced anxiety-related behavior of the mouse model was evaluated in tests of unconditioned anxiety that include the open-field test, the light/dark test, social interaction,

the elevated plus or zero maze, ultrasonic vocalization and holeboard test, and in tests of conditioned anxiety that include the Vogel-conflict, fear-potentiated startle and conditioned-fear tasks. It should be emphasized that altered fear expression in the latter paradigm does not necessarily indicate altered fear but may be the result of changes in fear memory, and this must be controlled in any mouse model of enhanced anxiety-related behavior prior to further interpretation.

Mouse models of enhanced anxiety

A mouse model of enhanced anxiety-related behavior is aimed at reproducing the pathophysiology of the human anxiety disorder by experimentally manipulating the environment, the neurophysiology, the neurochemistry or the genetics (BOXES 1 & 2) [25]. Such mouse models are thought to reflect 'trait' anxiety – that is, a persistent and enduring tendency of a genetically predisposed individual to demonstrate an increased anxiety response irrespective of whether it reflects quantitatively and/or qualitatively abnormal physiological anxiety [4]. Ideally, these murine models should be phenotyped using multiple tests for unconditioned and conditioned anxiety-related behaviors in order to account for the multifaceted nature of anxiety and, thus, for different forms of clinical anxiety. However, since unambiguous measures of anxiety disorder subcategory-specific endophenotypes correlated with neurobiological changes and/or biomarkers are not available, creating mouse models reflecting anxiety disorder subcategories is currently difficult.

Interestingly, many of the listed studies only chose a limited number of anxiety tests, with the majority focusing on anxiety-related behaviors related to exploration–avoidance conflict – most likely because they seem to be the easiest to perform. Other forms of anxiety, such as social conflict and learned fear (BOXES 1 & 2), have been rarely considered. It should be noted that in all mouse models described in this section, potential discrepancies in observed anxiety-related traits may be explained by differences in the procedures prior to and/or during testing, including use of animals from different breeders, use of different sex and differences in the experimental setup as well as in the order in which the tests were carried out (e.g., [55-57]). These confounding factors may, thus, reduce the comparability of the results among different labs. In addition, the mouse models of enhanced anxiety-related behavior may also display signs of enhanced depression-related behavior, mirroring the high comorbidity between anxiety disorders and depression in humans [7,14]. Detailed discussion of aspects of this comorbidity, however, is beyond the scope of the present article.

Mice with naturally occurring high trait anxiety

Specific groups of mice display (genetically/epigenetically induced) enhanced levels of anxiety-related behavior. It may be that the anxious phenotype of a whole strain is elevated in comparison with that of another one, or that only individuals within one population are affected. This interindividual variability as a vulnerability factor for abnormal anxiety may provide the basis for a simple selection strategy, as well as for a breeding strategy. Since multiple genes (each with only little influence) are thought to contribute to the increased emotionality that represents the genetic risk factor of human anxiety disorders, pairs of mice exhibiting enhanced and normal anxiety-related behavior indeed form excellent models for investigating the genetic complexity of enhanced (pathological) anxiety.

Inbred mouse strains

With more than 450 strains accessible, inbred strains of mice provide a large natural source of a variety of genotypes as well as phenotypes for comparison [58]. A mouse strain is considered inbred when brother × sister mating has occurred for 20 or more generations and at least 98.6% homozygosity of the loci in each mouse is demonstrated [59]. The

characteristic behavioral and physical phenotypes of inbred mice are very stable as they are inherited by multiple genes. Inbred strains with a distinct behavioral trait are widely used in neuroscience owing to various advantages, including allowing the possibility of overcoming the problem of high genetic heterogeneity that is found in human studies [60,61].

Numerous studies have evaluated the inborn level of anxiety-related behavior of different inbred mouse strains, mainly using unconditioned tests of anxiety including the elevated plus or zero maze, and open-field and light/dark tests. Table 1 summarizes strains of mice displaying enhanced anxiety-related behavior in comparison with C57Bl/6 mice. The C57Bl/6 strain was chosen as the comparator strain because it is the most popular common mouse strain used in anxiety research [62]. Furthermore, C57Bl/6 mice are categorized as a strain with moderate naturally occurring levels of anxiety despite some minor differences between the J and N subtypes [63]. Therefore, wherever it is possible, we use the correct name of C57Bl/6 mice. Any other mouse strain displaying modest anxiety-related behaviors, apart from the C57Bl/6 strain, may be used as the control group.

Signs of enhanced anxiety-related behavior have been reported in mice of the 129, A/J, AKR/J, BALB/c, C3H/He and DBA/2J strains, when compared with the C57Bl/6 strain, in some – though not all – tasks assessing unconditioned and conditioned anxiety (see Table 1). Of these, the BALB/c, the A/J and DBA/2J strains display the strongest evidence of increased emotionality in the elevated plus maze, open-field and light/dark tests compared with C57Bl/6 mice, while no differences and even lower levels of inborn anxiety have also been described in BALB/c mice or in the other two strains compared with C57Bl/6 mice that have undergone the same tests (Table 1). For further phenotypic characterizations of different mouse strains, the mouse phenome database may also be consulted, providing a useful tool with which to judge and compare anxiety-related traits of mouse strains [602]. Moreover, inbred strains of mice also display altered responsiveness to anxiolytics, although all strains seem to respond to the anxiolytic effects of benzodiazepines [4,64-67]. Despite some discrepancies between studies, BALB/c, A/J and DBA/2J strains are suggested to represent the best inbred mouse strain models for pathological anxiety [4,68].

In contrast to the mouse strains discussed so far, inbred 129P3/J mice initially show little anxiety-related behavior towards an aversive environment compared with the anxious BALB/c mice. However, repeated exposure to the environment does not cause a waning of the behavioral responses in mice, rather, anxiety-related behavior increases in 129P3/J mice compared with BALB/c mice [69]. Therefore, it is suggested that 129P3/J mice may be an example of a mouse model of nonadaptive anxiety. However, this proposed model has yet to be tested carefully before further conclusions can be drawn. Furthermore, C57Bl/6N mice have been suggested to represent a mouse model specific for post-traumatic stress disorder [70]. Subjects of this strain display persistent and increasingly sensitized fear after exposure to a single, brief electric footshock, which coincides with blunted emotionality in the modified holeboard test and the social interaction [70]. This mouse model enables vulnerable and resistant individuals to be distinguished for developing signs of post-traumatic stress disorder in response to an aversive encounter, mimicking important aspects of epidemiological observations in humans exposed to trauma [71].

Finally, crosses of phenotypically contrasting strains (e.g., of an anxious and a nonanxious inbred strain, such as A/J and C57Bl/6J) are the origin of recombinant inbred strains such as the AXB/BXA or BXD strains [72-73] and recombinant congenic mouse strains such as the AcB/BcA [72]. Intercrosses and backcrosses, together with inbred mouse and recombinant mouse lines, are widely used for the genetic dissection of anxiety traits in the mouse – as, for example, carried out within the scope of quantitative trait loci (QTL) mapping studies [74] (see 'Genetic underpinnings of the anxiety trait'). In all of these approaches, one has to keep

in mind that inbred strains, while differing in trait anxiety, additionally differ in an unknown number of other traits, which makes unambiguous interpretations of phenotype–genotype associations difficult, if not impossible.

Selective breeding lines in mice

As an alternative approach to the uncontrolled inbreeding of mouse strains, selective breeding strategies for a specific endophenotype within one strain have proved to represent a powerful tool for investigating the genetic variability of complex, polygenetic traits such as anxiety [75]. The principle idea is to cluster a specific trait around the extremes of the whole spectrum typically observed in an outbred strain. The breeding protocol usually starts with a heterogeneous population of an outbred mouse strain that is tested for the particular trait of interest. Of those tested, individuals displaying the trait at the outermost ends of the response curve are mated. Their offspring, also displaying the extreme trait phenotypes, are further selectively bred. With every generation, the trait clusters more and more around the 'high and low poles' of the trait as demonstrated by the selective inbreeding of the high anxiety-related (HAB) and low anxiety-related (LAB) mouse lines. A specific advantage of selective breeding models is that they start from the same genetic background and any difference in the genome is then very likely to underlie their extreme behavioral trait, offering the possibility of investigating the heritability of this phenotype. While the confounding phenomenon of genetic drift can not entirely be eliminated, it is reduced – *inter alia* – by the parallel breeding of multiple families within a given line.

In the mouse, only a limited number of selective breeding models displaying signs of enhanced anxiety-related behavior are available (Table 2). At the Max-Planck-Institute of Psychiatry in Munich, the HAB, LAB and NAB mouse lines were initiated by deliberate selection and subsequent selective breeding of CD-1 mice for an extremely high, an extremely low and a normal level of anxiety-related behavior, displayed on the elevated plus maze (Figure 1 & Table 2). NAB mice thereby represent the population mean of unselected CD-1 mice. The high-anxiety trait of HAB animals has been confirmed in several other tests of anxiety including the light/dark, open-field and open-arm tests (Figure 1), as well as in different laboratories indicating a very robust phenotype [76-78] that appears to be largely independent of uterine environment, maternal care, sex and age [78]. Furthermore, HAB animals also display enhanced fear learning in classical cued and contextual fear conditioning paradigms suggesting that trait anxiety results in stronger fear memory and/or a weaker ability to inhibit fear responses in the HAB line (Figure 1) [79,80]. The positive association between learned (cued) fear acquisition and vulnerability to trait anxiety has very recently also been observed in healthy humans [81] and in patients with anxiety disorders [82]. The enhanced anxiety- and fear-related behavior of HAB mice is associated with reduced heart-rate variability in comparison with NAB mice (Figure 1), demonstrating that heart rate variability may be a sensitive, though not exclusive, biomarker for distinguishing between a normal and a high anxiety trait [80]. Enhanced anxiety- and fear-related behavior in HAB mice can both be reversed by anxiolytic drug treatment using either a benzodiazepine [76,79] or the selective neurokinin-1 receptor antagonist (NK1R-A) L-822,429 [79-80].

As with the HAB mouse line, the divergent short-term selective breeding of mice for extremely high or low levels of fear conditioning results in two mouse lines that also differ in terms of both the fear-potentiated startle paradigm and unconditioned tests of anxiety (Table 2) [83], further supporting a relationship between high fear conditioning and greater anxiety-like behavior. Very recently, another anxious mouse line was established based on differences in the level of anticipatory anxiety displayed during a handling procedure [84]. Mice approaching the experimenter's hand are the nonanxious NAX line while mice that do

not volunteer themselves to be handled represent the anxious AX line. Relative to NAX mice, AX animals show enhanced anxiety-related behaviors in the elevated plus maze, light/dark and open-field tests (Table 2) [84].

As another example, the North Carolina (NC) lines are based upon differences in social behavior [85,86]. Specifically, animals of the NC900 line carry out unprovoked attacks on their social partners whereas NC100 mice rarely attack and become immobile in social situations. Relative to NC100 mice, the highly aggressive line NC900 displays increased anxiety-like behavior in the elevated zero maze and open-field test but not in the light/dark test (Table 2) [87]. Although defensive aggression is not considered to be a general symptom of anxiety disorders [17], it occurs in post-traumatic stress disorder [88-90] and borderline personality disorder [91,92]. NC900 mice are less sensitive to the anxiolytic effects of diazepam, which may be due to the reduced diazepam-sensitive binding in brain areas known to be part of the anxiety circuitry [87]. In addition, some forms of anxiety-related behavior seem to be increased in 'mouse line 8', selectively bred for high voluntary wheel running in comparison with 'control line 2' (Table 2). Finally, the selection of mice for high resistance to convulsive effects of the benzodiazepine receptor inverse agonist β-carboline-3-carboxylate (β-CCM) [93] coincides with increased anxiety-related behaviors in the light/dark and holeboard tests in comparison with the β-CCM sensitive line. Since benzodiazepine receptor binding sites are reduced in the β-CCM resistant line [93], this finding further supports a role played by benzodiazepine binding sites in the modulation of anxiety-related behavior. The NC900 line, the high voluntary wheel running line and the β-CCM-resistant line nicely demonstrate that the deliberate selection for one selected trait often results in changes in other behaviors, not necessarily directly associated with the feature of interest that was chosen.

On-site selection of mice with enhanced anxiety-related behavior

Selective breeding approaches are, of course, tedious and time-consuming. Therefore, some research groups opt for an acute selection (stratification) in terms of an enhanced emotional reactivity in response to an anxiety-provoking situation. Like the successful selection principle of the HAB and NAB mouse lines, the elevated plus maze was used to acutely preselect animals with high, intermediate and/or low anxiety as a means for studying variations in the anxiolytic effects of the benzodiazepine nitrazepam [94] and the relation between trait anxiety and ethanol [95]. Similarly, C57BL/6 male mice can be classified into high- or low-anxiety traits according to their latency to freely enter an unfamiliar arena from their home cage [96]. On the other hand, C57Bl/6J mice pre-selected for voluntary wheel-running also exhibit an anxiogenic phenotype in the open-field, light/dark and elevated O-maze tests compared with sedentary animals [97].

Mutants with enhanced anxiety-like behavior

In 1994 Stenzel-Poore described the first transgenic mouse with an anxiogenic phenotype caused by targeted overexpression of corticotropin-releasing hormone [98]. Since then, numerous genetically engineered mice in which a specific gene was either knocked-out, knocked-in, overexpressed or replaced have been generated, resulting in increased anxiety-related behaviors. Mutant mice with a relatively robust enhanced anxiety-related behavior are summarized in Table 3 – we have excluded those models with approximately equal numbers of reports describing an enhanced, unaltered or reduced anxious phenotype, such as with the GAT1 transgenic mice [99,100] and the Fmr1 knockout mice [101-104], as well as those where the evidence of an anxious phenotype was rather limited (e.g., [105,106]) – though we cannot exclude the possibility that some may have been missed. Genetic manipulation of many different systems, including monoamines, GABA, neuropepeptides or molecules of the immune system was shown to result in increased anxiety-related behaviors

suggesting that these systems contribute to the anxious phenotype observed. Interestingly, the genetic background of the mutant seems to critically interfere with the genetic target and this, in many cases, determines whether or not enhanced emotionality could be monitored. This has been discussed in recent reviews [63,107].

Enhanced anxiety-related behavior observed in a mutant does not allow the final conclusion to be drawn that the altered expression of that gene underlies anxiety-related behavior. Anxiety disorders are complex mental diseases with a polygenetic etiology, while in mutants in most cases only one gene is intentionally affected. However, genetic manipulation performed in the laboratory usually induces large changes in gene function (e.g., the complete loss of function in knock-out animals) and congenic footprint phenomena [108], which may have potent effects on the anxiety phenotype. Therefore, the manipulation of genes and, subsequently, of their products in mutant mice can only provide incomplete information about their relation and contribution to anxiety and, potentially, to anxiety disorders. On the other hand, this polygenetic characteristic of anxiety disorders is indeed reflected by the large number of mutants displaying enhanced anxiety-related behaviors. Although the use of mouse mutants has proved to be a powerful tool in the identification and characterization of mechanisms controlling enhanced anxiety states, it must be considered that a targeted mutation affects the transcription of the gene of interest throughout the whole life of a mouse and, in particular, during its development. The mutation may thus trigger compensatory adaptations in other neuronal systems in an effort to maintain homeostasis, even if this proves to be unsuccessful. In both cases, it is not possible to ascertain whether the increased anxiety-related behavior is the resultant compensation or whether it is related to the function of the gene in terms of anxiety-related behavior.

As an alternative approach that overcomes many of these problems, conditional mutant mice have more recently been introduced using either gene mutation strategies or RNA interference (RNAi) techniques allowing temporal and regionally specific control of expression of the gene of interest. For example, using RNAi, the knockdown of phospholipase $C\beta4$ in the medial septum [109] and of calcineurin A in the amygdala [110] increased anxiety-like behavior in mice, while local knockdown of clock [111], corticotropin-releasing hormone receptor 1 [112], protein kinase $C\varepsilon$ [113] or glyoxalase 1 [29] caused a reduction in anxiety-related measures. Therefore, these data point towards specific sites of action of target genes regulating emotionality, which may help to further advance novel treatment strategies in anxiety disorders.

Environmental manipulations

Negative environmental influences have been demonstrated to be intimately linked to vulnerability to neuropsychiatric disorders, including anxiety disorders [7,8].

Early life environment

Rearing conditions, including poor maternal care and adverse early-life events, are proposed to be critically involved in the development of mental disorders, including anxiety disorders (for review see [114,115]). While it is very difficult to control for differences in the human environment, rearing conditions can be carefully controlled and manipulated in the laboratory. Given that mother-pup interactions shape the emotional behavior of the pups when they mature into adult rodents [116,117], maternal separation for longer periods of time is used to model adverse early life events, negatively influencing emotional behavior in the adult rodent [118,119]. By contrast, maternal separation for short periods of time (~15 min) is used to elicit opposite effects on anxiety-related behavior. The maternal separation protocol has been successfully applied to the rat [116,118,119], while in the mouse the same attempts to do so have turned out to be challenging.

Following maternal separation, adult male mice have been shown to display increased [117,120-122], unaltered [121,123-127] and even reduced [127,128] anxiety-related behaviors using different established tests. Therefore, it seems that maternal separation does not produce robust and reliable effects on murine emotionality in the strains tested, including BALB/c, C57Bl/6J, CD-1, 129Sv and DBA/2J mice [124,127] and, thus, it may be necessary to modify current murine separation protocols. Indeed, in a first attempt to accomplish this, George and coworkers [129] recently demonstrated increased anxiety-related behavior as assessed in the open-field and elevated plus maze tasks in adult mice following maternal separation in combination with early weaning. Early weaning *per se* may be an example of a novel procedure that causes a persistent increase in anxiety-like and aggressive behavior [130,131].

Chronic exposure to stress

It is not only early-life stress that has been associated with the manifestation of pathological anxiety in humans: repeated stressful experiences during later life have also been linked to this [7]. Therefore, mouse models of enhanced anxiety-related behavior may be generated by the repeated exposure of animals to stressful situations. Although most studies so far have been performed using rats, chronic stress usually results in some behavioral, neuroanatomical and neurochemical changes resembling those found in patients with anxiety disorders [132]. Various chronic stress procedures with different construct validity (see 'Validity of mouse models of enhanced anxiety') are applicable to mice. As social stressors are suggested to be very potent in enhancing the individual risk for developing pathological anxiety in both humans and animals [7], various paradigms have been developed taking into account this risk factor. Accordingly, increases in anxiety-related measures have been reported in mice in response to repeated exposure to an aggressive, dominant conspecific until attack and defeat occur [133-135], as a result of chronically subordinate housing [136-138], or by housing mice in a highly unstable social and hierarchical situation during their adolescence and young adult periods [139]. Indeed, the continuous disruption of social networks results, reproducibly, in enhanced anxiety-related behavior in adult male and female CD-1 mice, as assessed by the elevated plus maze and the novelty suppressed feeding paradigms [140-142]. Given that mice are social animals, long-term social isolation of mice is another chronic social stress model involving individual housing of mice in the post-weaning period. However, this procedure has revealed varying results in terms of anxiety-related behavior exhibited in the open-field, light/dark, social interaction and holeboard tests, and on the elevated plus maze where increases [122,134,143-145], no change [143-147] and even decreases [144,145,148] were observed. On the other hand, crowded social housing has also been shown to cause long-term effects in terms of increased anxiety-related behavior, depending on the strain involved [149].

In the unpredictable chronic mild stress paradigm animals are exposed to a choice of environmental stressors such as an empty cage or a tilted cage, cold or a reversed light–dark cycle and social stressors once per day for at least 2 weeks in a randomized, unpredictable order. Unpredictable chronic mild stress has been demonstrated to increase anxiety-related behavior in C57Bl/6N mice [150-152], BALB/c mice [153-154] and DBA/2 mice [152,153] as well as in some mutants [155], but not in C57Bl/6J mice [152,153]. However, anxiolytic-like effects of chronic mild stress have also been described in mice [152,156,157] and these findings are generally interpreted as anomalous [158].

To summarize, mouse models that involve chronic adverse environments, irrespective of whether they occur during early life or in adulthood, are of translational value in anxiety research. However, the anxiogenic effects of all the stress paradigms presented are variable. The inconsistencies may be due to methodological differences, such as duration and choice of stressors, the mouse strains used and the tests applied for revealing anxiety-related

behavior. An alternative explanation may involve the complex interactions between genetic and non-genetic factors [159]. In contrast to these harmful surroundings, inanimate and social stimulation by environmental enrichment has been demonstrated to reduce anxiety in both mice with normal and enhanced levels of anxiety-related behavior (e.g., [112,160,161]). However, it has to be noted that, similar to adverse environments, the positive effects of environmental enrichment are not always reproducible [162].

Nutrient-induced enhanced anxiety-related behavior in mice

There is increasing evidence of a link between alterations in nutrition and psychiatric diseases [163,164]. Specifically, changes in values of diverse micronutrients, including electrolytes and vitamins, have been linked to symptoms in psychiatric patients [165-167]. Influenced by these studies, mouse models of enhanced anxiety-related behavior have been created utilizing this possibility.

Magnesium deficiency

Magnesium (Mg) is an interesting candidate as it, among other actions, modulates NMDA receptor activity and NMDA-mediated mechanisms are suggested to contribute to (pathological) anxiety states [40]. An increasing number of clinical and preclinical studies proposes that changes in Mg homeostasis are involved in affective disorders [168], while relatively little is known about the influence of Mg on anxiety-related behavior. We have recently shown that feeding C57Bl/6J mice a low Mg-containing diet, providing approximately 10% of the daily requirement [169], changes the expression of proteins involved in NMDA signaling (amongst other processes) [170] and elicits enhanced anxiety-related behavior in several animal tests of anxiety, including the open-field and the light/dark tests (Figure 2) [171]. Confirming and corroborating these first findings, Mg-deficiency has also been found to enhance anxiety-related behavior in C57Bl/6N mice and the already highly emotional BALB/c mice (Figure 2) [172, MANUSCRIPT IN PREP.]. The enhanced anxiety-related behavior induced by Mg-deficiency can be reversed by treatment with either the benzodiazepine diazepam, desipramine or hypericum perforatum (Figure 2) [171,172, MANUSCRIPT IN PREP.].

Others

PubMed searches aimed at finding additional nutrient-induced mouse models of enhanced anxiety-related behaviors proved fruitless. One potential candidate was zinc, which in a similar way to Mg, mildly antagonizes NMDA receptor signaling (amongst other processes) [173]. Mice fed a zinc-deficient diet were shown to display enhanced anxiety-related behavior in the novelty suppressed feeding paradigm but not in other anxiety tests, such as the elevated plus maze or light/dark tests [174]. Vitamin B is another suspect, since its deficiency is suggested to contribute to functional decline. Although folate deficiency does not seem to affect anxiety-related behavior in young adult BALB/c mice [175], the adult offspring of mothers under prenatal folate deficiency, which is repleted at birth, can manifest later with increased anxiety 9–12 weeks after birth [176]

Chemical & pharmacological manipulations

Acute challenge tests

In contrast to the mouse models of enhanced anxiety-related behavior discussed so far, challenge tests using anxiogenic substances elicit states of acutely enhanced anxiety-related behavior. These procedures are based, in part, on observations in human volunteers and/or patients in whom diverse chemical agents, including sodium lactate, cholecystokinin, caffeine, pentylenetetrazol, yohimbine and CO_2 inhalation, provoke anxiety- or panic-like

reactions [177-179]. Many of these agents have been shown to engage and activate relevant anxiety-related brain areas and circuitries centered on the amygdala [180-183]. Interestingly, in regard to CO_2 stress, the amygdala has been identified as an important chemosensory site that detects hypercarbia and acidosis and initiates CO_2-induced fear responses [184]. The same substances may be used to boost anxiety in the laboratory mouse. For example, pentylentetrazole increases the anxiety-related behavior of various mouse strains, including the CD-1, Swiss, DBA/2, and C57Bl/6 mice, as displayed on the elevated plus maze or in the light/dark test in a dose-dependent manner [185-191]. Similar effects have been described in the mouse after application of the 5-HT2C receptor agonist meta-chlorophphenylpiperazine (mCPP) [189,192-195], but see [196,197]). Other compounds, such as cholecystokinin, sodium lactate, caffeine, yohimbine, CO_2 or the benzodiazepine inverse agonist FG-7142, have not been widely applied to mice for the induction of enhanced anxiety-related behavior.

The chronic corticosterone mouse model

On the basis of evidence of an association of some anxiety disorders with elevated glucocorticoid levels (Table 4) [8], long-term exposure to exogenous glucocorticoids in rodents is used to model chronic stress-induced changes in anxiety-related behaviors [198]. For that purpose, a low dose of corticosterone is administered via the drinking water to the mouse for several weeks. Then, increases in murine anxiety-related behaviors postregimen have been observed on the elevated plus maze [150,199] and in the open-field [150,200-202] and light/dark tests ([203], but see [198]).

High anxiety-related behavior induced by drug withdrawal

The initial mood-enhancing effects of recreational drugs are often followed by withdrawal symptoms with opposite effects on mood, including agitation, depression and anxiety and, as such, they have been utilized in order to induce an enhanced anxiety state in mice. Indeed, withdrawal of diverse psychostimulants after chronic administration has been shown to increase anxiety-related behavior in mice in a number of anxiety tests, inlcuding the elevated plus maze [204-206] and the light/dark test [205,207]. Specifically, (meth)amphetamine (e.g., [204]), ethanol (e.g., [205,208,209]) and nicotine (e.g., [206,207]) are the preferred substances used to induce a mouse model of prolonged enhanced anxiety after their removal.

N-ethyl-*N*-nitrosurea-induced random mutagenesis

The mutagen *N*-ethyl-*N*-nitrosurea (ENU) induces point mutations in murine genes at a high rate [210]. Following the injection of ENU into male mice, premeiotic stem cells are mutagenized, resulting in a large number of F1 animals carrying different mutations. ENU mutagenesis is a powerful phenotype-driven approach that involves identifying mutants with distinct behavioral patterns. In large-scale testing, pedigrees of ENU mutants have been identified displaying altered anxiety-related behaviors on the elevated plus maze [211], in the light/dark test [212], in fear conditioning [212-214], in the passive avoidance test [215] or in the open-field test [212,214-216]. So far, no studies of offspring of mice treated with ENU and displaying clear enhanced anxiety-related behavior have been published, but increased avoidance behavior towards an unprotected area has been reported in ENU pedigrees [217].

Validity of mouse models of enhanced anxiety

In 1984 Willner proposed three criteria, which valid animal models of any human psychiatric disease, including anxiety disorders, have to meet [218]. First, the behavioral and physiological responses observed in the model should reflect the hallmarks of the human condition, representing face validity. Second, construct including genetic validity requires

similarity between humans and animals in terms of the neurobiological mechanisms, as well as in the analogy to the etiological causes underlying the behavioral changes. Third, the behavioral changes displayed by the model should be reversed, or at least reduced, by clinically effective pharmacotherapies, revealing predictive validity.

Of these criteria, true construct validity is probably the most difficult to fulfill for an animal model of enhanced anxiety-related behavior. Nevertheless, most of the presented mouse models meet construct validity quite well, reflecting that both genes and environment are suggested risk factors in the development of an anxiety disorder [6,219] and that neurobiological similarities between mouse models of enhanced anxiety and anxiety patients can also be found (Table 4), although it must be emphasized that our knowledge about the pathogenesis and pathophysiology of anxiety disorders is still incomplete in terms of neuroanatomy, neurochemistry and neuroendocrinology (see 'Conclusion' and 'Future perspective'). Such models with enhanced construct validity could be well suited to be used as translational models and it is hoped that they will provide improved ways to study the neurobiology and treatment of pathological anxiety further.

Neurobiology of pathological anxiety: translational anxiety research

Genetic underpinnings of the anxiety trait

Both human and animal studies support the contribution of genes to the etiology of anxiety disorders. While it is clear that anxiety disorders are polygenic mental diseases, the success rate in identifying susceptibility genes of pathological anxiety is limited. Difficulties involved with gene mapping in human pathological anxiety include sample size, genetic heterogeneity, phenocopies as well as unknown genetic or haplotypic background. Many of these problems can be reduced using mouse models of enhanced anxiety-related behavior.

In mice, chromosomal loci, genes and polymorphisms for a variety of behavioral phenotypes relevant to humans have been identified, including anxiety and fear [220-224]. For example, in QTL studies, a significant association between an anxiety-related score and a genetic marker of known genomic location is drawn. Using recombinant inbred or congenic mice [72], F2 intercrosses from mice selected for either high or low anxiety-related behavior [225] and mice selected for high or low conditioned fear [83], small genetic effects underlying anxiety, fear and emotionality have been located. Specifically, on mouse chromosomes 1, 4, 5, 7, 8, 9, 10, 11, 13, 14, 18 and 19, loci contributing to multiple anxiety-related traits have been identified using a wide variety of anxiety tests ([83,225-230]; for review, see [231]). Considering the high homologies between mouse and human genotypes and phenotypes (see 'The evolutionary relationship between humans & mice in anxiety regulation'), QTL analyses in mice with enhanced anxiety-related behavior may guide linkage analysis studies in patients with anxiety disorders. For example, Smoller and coworkers followed the results of murine QTL analysis studies in a large multiplex degree, segregating panic disorder and agoraphobia [232]. Indeed, they report a linkage of panic disorder and/or agoraphobia to a locus on chromosomes 12q13, while other loci on chromosome 10q25–26 and on chromosome 1 were associated with severe anxiety proneness [232]. Although these findings, unfortunately, did not reach genome-wide levels of statistical significance, they nicely demonstrate the potential power of such targeted genome screens. Nevertheless, translating mouse QTL data to humans turned out to be difficult. The difficulties of QTL studies in general are discussed elsewhere [61,233].

Despite all the progress achieved, the genetic loci identified so far account for only a small fraction of the total variation, and they rarely map to individual genes. The low contribution of chromosomal loci and individual genes, respectively, to trait anxiety, together with the fact that demonstrable genetic influences explain only a small fraction of estimated

heritability in psychiatric conditions, indicates additional environmental/epigenetic effects (see 'Environmental stimuli and epigenetic mechanisms contributing to anxiety-related behavior'). Obstacles in identifying genes that causally contribute to a given trait variation include:

■ Identification of potentially functional DNA polymorphisms between alternative alleles of the candidate gene;

■ Differences in mRNA expression profiles between genotypes;

■ Expression in brain areas thought to be relevant to the trait;

■ Association between polymorphisms and trait variation in a freely segregating panel;

■ Replication in independent studies.

Candidates that 'survive' multiple testing are worth pursuing as potential biomarkers and targets for psychotherapy.

The situation is further complicated by epistatic effects, occurring between closely linked QTLs and even polymorphisms at a single locus, which often mask locus effects, and pleiotropic effects with alleles simultaneously affecting multiple and often functionally unrelated traits. Pleiotropy is probably the rule rather than the exception for many traits [234,235]. QTLs typically contain multiple genes and disentangling coincidence of location from pleiotropic action is difficult [236].

While genetic differences in trait anxiety help to identify candidates that contribute to phenotypic variation, they approach causality at best. Therefore, similar to clinical studies, we run association studies to test for causality between genetic and phenotypic variation, which goes far beyond conventional two-group comparisons. For selectively- and bidirectionally-inbred mice, the original population (i.e., outbred CD-1) or a freely segregating F2 panel may be used to create and harness variations to the fullest possible extent. Although such approaches are often hampered by confounding factors that *a priori* limit success (e.g., reduced statistical power, owing to lower sample population compared to that commonly used in clinical samples, where often thousands of subjects are included), minor, though significant contributions of polymorphisms in the vasopressin and *TMEM132D* genes could recently be demonstrated to corroborate human studies [224,237]. Then, based on reliable association studies, causality can further be tested by appropriate approaches, including agonist/antagonist, RNAi, knockout and viral vector strategies. Nevertheless, it remains a challenge to handle large numbers of potential loci, candidate genes and polymorphisms and it is problematic to distinguish the genuine ones. It is of note in this context that the anxiety phenotype is at least as variable as the genotype with all its imponderabilities, including state versus trait, repeated testing, maternal influences and cage hierarchy among others, further complicating or even masking potentially significant associations.

Examples of bridging mouse & human neurogenetics

It is becoming widely accepted that the pathobiology of anxiety disorder – as that of comorbid depression – relies beyond dysfunction of monoamine systems [238] and that advances in the understanding of neurobiological underpinnings of anxiety can only be made by focusing on those candidates that do not necessarily belong to the 'usual suspects'. For example, we have just begun to understand metabolic networks, for instance in mitochondria, as contributing to anxiety phenotypes.

One example, where the translational aspect from mouse to humans with pathological anxiety was quite successful, is the discovery of the regulator of G-protein signaling 2 (*Rgs2*) gene in anxiety-related behavior. Evidence for its possible involvement arose in QTL studies initially in mice and and then humans [226], suggesting *Rgs2* as an anxiety-associated quantitative trait gene. Indeed, two polymorphisms in this gene, rs4606 and rs3767488, have been associated with patients suffering from panic disorder ([239], but see negative findings in a Japanese cohort [240]), post-traumatic stress disorders [241] and general anxiety disorder [242], as well as with trait anxiety in general [243]. In further support, *Rgs2*-knockout mice display enhanced anxiety-related behaviors [226,244]. These findings arising from the mouse model organism, thus, suggest that *Rgs2* may play a role in the development of a nxiety in humans.

Despite the lack of evidence from QTL studies, altered expression of the zinc metallo-enzyme glyoxalase-1, which catalyzes the conversion of the highly reactive physiological metabolite, methylglyoxal, seems to impact anxiety-related behavior in inbred mouse strains [29] and in HAB mice selectively bred for high-trait anxiety [76,245], though in opposite ways. While Hovatta *et al.* [29] demonstrated elevated glyoxalase-1 gene expression to be linked to high anxiety levels, we described an inverse association, with HAB expressing less than LAB mice [76,245]. Support for the former finding came from Williams *et al.* [246], and for the latter from two recent papers. In the first, Fujimoto *et al.* described a reduced expression of glyoxalase-1 mRNA in mood disorder patients as compared with healthy subjects, a difference that disappeared in a remissive state [247]. In the second study, decreased levels of glyoxalase-1 were found in an inbred mouse strain selected for high anxiety-related behavior [84], further supporting its potential as molecular biomarker. Interestingly, an association between the Ala111Glu polymorphism of the glyoxalase-1 gene and panic disorder without agoraphobia has been previously found in an Italian population [248].

Evidence for another interesting candidate gene for anxiety phenotypes comes from a very recent paper summarizing mouse and human studies. Using genome-wide case-control association analysis in patients with panic disorder involving multiple psychiatric centers, two SNPs in the intron regions of *TMEM132D* gene were identified [237]. Furthermore, *TMEM132D* mRNA expression levels were found to be upregulated in the frontal cortex of post-mortem brains with risk genotypes for panic disorder. In an interspecies approach, the hypothesis that *TMEM132D* may be critically involved in the regulation of pathological anxiety and fear was tested by expression and association analyses in HAB mice selectively bred for high trait anxiety [76], confirming the human data. Indeed, *TMEM132D* mRNA expression was upregulated in the cingulate cortex of HAB mice and, remarkably, the SNP rs13478518, located in exon 9 of the *TMEM132D* gene, was significantly associated with the level of anxiety in a freely segregating F2 panel generated from cross-breeding HAB and LAB mice [237].

Another example for bridging mouse and human neurogenetics is the *BDNF* Met allele, likely to play an important role in the development of anxiety disorders [84]. Relative to the *BDNF* Val allele in humans and the wild-type gene in mice, the *BDNF* Met allele caused enhanced anxiety and impaired extinction of the conditioned fear response in both mice and humans (for review, see [249,250]). Using gene expression and MRI, respectively, the *BDNF* Met allele was further associated with decreased activity in the ventromedial prefrontal cortex, which is known to be critical in fear extinction, and increased activity in the amygdala, which is crucial for the acquisition and expression of fear conditioning. Although, according to Hariri [251] and Groves [252], the findings in human studies are, at best, inconclusive, this Met variant might determine how individuals respond to environmental stress exposure. Interestingly, deficits in extinction have recently been linked

to reduced dendritic complexity of neurons in the prefrontal cortex [253,254], to abnormal processing in the prefrontal cortex [44-46] and to high trait anxiety [45,255, MANUSCRIPT IN PREP.]. Moreover, in HAB mice, signs of hypoactivated prefrontal cortex and hyperactivated amygdala in response to mild anxiogenic stimulation were observed by Muigg *et al.* [77].

Together, data obtained independently in mice and humans suggest evolutionarily conserved neuroanatomical, genetic and neurochemical mechanisms underlying the regulation of anxiety-related behavior as well as their translational potential.

Alterations in functional neural circuits in pathological anxiety

Neuroimaging studies, in combination with symptom provocation, have revealed aberrant neuronal activation patterns in a number of anxiety disorders in brain areas implicated in the pathophysiology of anxiety disorders, including, for example, the amygdala, the prefrontal cortex, the hippocampus and the hypothalamus [22]. Interestingly, exaggerated amygdala reactivity is noted in social phobia, specific phobia and post-traumatic stress disorder [22]. Furthermore, an increased function of the dorsal anterior cingulate cortex is observed in specific phobias, in post-traumatic stress disorder and in generalized anxiety disorder, while diminished reactivity of the rostral anterior cingulate cortex may be specific to post-traumatic stress disorder [22]. Nevertheless, the information gained in such imaging studies is limited, owing to the presence of susceptibility artifacts and because of restricted spatial resolution even with the best (fMRI) techniques. Therefore, even up-to-date technologies of human imaging do not allow precise discrimination of small adjacent structures such as the hypothalamic and amygdaloid subnuclei or brain-stem regions.

Given that important basic neurocircuitries mediating anxiety are highly conserved among mammals [23,33-35], mouse models of enhanced anxiety-related behavior may be exploited in order to identify neuronal correlates of pathological anxiety at a subnuclear level. In the awake, freely-moving mouse neuronal activities can be measured, for example, by electrophysiological recordings or optical recordings of photons [256] and calcium [257]. However, these methods are very sophisticated and, to our knowledge, have not, or have only rarely, been exploited in mouse models of enhanced anxiety during emotional challenges. Alternatively, neuronal activation may be indirectly visualized by functional staining techniques of diverse neuronal activity markers whose expression has been proposed to correlate with the functional activation of neurons providing great spatial, even single-cell, resolution [23]. Such markers are, for example, immediate early genes, or cytochrome oxidase [258]. Of these, the immediate early gene *c-Fos* appears to be a widely used marker for neuronal activation in anxiety research [23].

Only a limited number of studies have addressed the question of where in the brain activation patterns differ between mice with enhanced anxiety-related behavior and those with normal anxiety-related behavior (Table 5). While in most of these studies, immediate early gene mappings were focused on one or just a few brain areas known to be part of the anxiety neurocircuitry, Muigg *et al.* provide a more complete picture through the rostro-caudal extent of the mouse brain [77]. In part, similar patterns of both hyper- and hypo-activation in specific brain areas have been revealed in different mouse models of enhanced anxiety-related behavior in response to diverse emotional challenges (Table 5) which have been previously shown to increase c-Fos expression in the normal rodent brain, though to different levels (for review see [23]).

In mice with high trait anxiety compared with their 'normal' anxiety controls, c-Fos induction in response to an anxiety-provoking stimulus is attenuated in the cingulate cortex [77,259-261], which seems to correlate to the rostral anterior cingulate cortex of humans [262], although determining exact homologies of cortical areas in humans and mice remains

a difficult task [263]. Furthermore, in the dentate gyrus of the hippocampus, activation is attenuated in high anxiety animals. By contrast, neuronal activation is facilitated in the paraventricular hypothalamus, in the amygdala (in its central and medial parts in particular) and in the dorsomedial periaqueductal grey [77,97,138,259,260]. While these observations fit well with observations in humans with pathological anxiety (for review see [22]), there is some inconsistency within the different mouse models (Table 5). As with variations in the human data (for review, see [22]), discrepancies in neuronal activation patterns in mouse models with enhanced anxiety levels may be explained by the different models and challenge paradigms used, which, as it has been suggested, may all elicit specific facets of anxiety that engage distinct parts of the anxiety circuitry [23]. For example, it was shown in HAB rats that the open-arm challenge activates the central amygdala only slightly, obscuring activation-processing differences between high- and low-anxiety animals in this subarea [264]. If social defeat was used as a challenge, this difference became increasingly evident [265]. Furthermore, in mutant mice, direct local effects of the altered gene product must be considered.

Taken together, these findings support and corroborate the human data indicating that dysregulations in specific brain areas that are known to play critical roles in anxiety [266] and conditioned fear neurocircuitries [35,267], contribute to enhanced (pathological) anxiety. In addition, to enable a better understanding of the pathophysiology of anxiety, this approach can also be used for the screening of novel drugs by determining the ability of therapeutics to reverse (normalize) aberrant activation patterns and neurochemical changes associated with enhanced anxiety [268-271]. Attenuation of amygdala reactivity seems to be important in humans [272-275] and animals [268]. So far, unfortunately, this strategy has not been used in mouse models of enhanced anxiety.

Environmental stimuli & epigenetic mechanisms contributing to anxiety-related behavior

Gene–environment interactions in shaping the anxiety phenotype assume that multiple genes influence susceptibility to environmental risk factors, including stress, and that the latter finally cause psychopathology [276]. This complex interaction includes the fact that exposure to stressful events does not always generate the disorder, this response heterogeneity being under genetic control (for review, see [277]). While exposure to defined environmental stimuli can easily be manipulated under experimental control, short-comings of experimental gene–environment interactions must be acknowledged, as they do not necessarily reflect naturally occurring conditions [278].

Animal models of genetic susceptibility versus resilience to environmental factors offer a valuable window for studying the contribution of postnatal maternal factors [279] and the effects of risk exposure on psychopathological processes. Male HAB mice, for instance, seem to be largely resistant to classical antidepressant drug treatment and thus may mimic endophenotypes typical of drug nonresponding, genetically predisposed patients. These properties make them ideal for gene–environment interaction studies, as their genotype is relatively well characterized beyond single genetic polymorphisms (FILIOU ET AL., UNPUBLISHED DATA). The resultant changes in brain neurobiology that underlie and confer risks for anxious behavior have been studied at multiple levels to confirm face and construct validity (i.e., they are related to human anxiety and do reveal mechanisms derived from theory). Only with the focus on such complex interactions, the question can be approached as to why different individuals exposed to the same environmental challenge or, *vice versa*, genetically identical individuals, exposed to different environments, experience different levels of anxiety.

One candidate gene that has been associated with trait anxiety encodes the serotonin receptor 1A (*5-HT1A*) with a promoter polymorphism being related to anxiety-linked

personality traits [280]. This receptor subtype provides an intriguing example of how genetic–maternal environmental risk may contribute to anxiety. In more detail, maternal deficiency in the 5-HT1A receptor resulted in an offspring phenotype reminiscent of psychopathology. More than the offspring's own receptor deficiency, the genotype of the mother seemed to be the prevailing mechanism in producing an anxious phenotype as measured on the elevated plus-maze. However, in the absence of a maternal genotype effect, the offspring's own receptor deficit was sufficient to elicit the phenotype, pointing to two different underlying mechanisms: one by inheritance of receptor deficiency and the other by nongenetic transmission associated with receptor deficiency in the mother, raising the possibility that maternal influences may increase the risk for anxiety via a nongenetic mechanism. This model of dual transmission of risk factors indicates that the overall effects of risk alleles can be higher than estimated by traditional genetic studies [280].

While epigenetic changes induced in the offspring remain to be elucidated, it becomes clear that complex behaviors such as anxiety are driven by multiple mechanisms. For studying the interaction between genetic and nongenetic factors in more detail, it might therefore be useful to generate models in which the genetic underpinnings of trait anxiety or, at least, the contribution of single polymorphisms or genes are well-described. Then, using a combination of expression, genotypic and epigenetic approaches, one could try to examine whether those genes are also prone to epigenetic modifications that either activate or silence them.

Epigenetics refers to stable changes in chromatin and DNA via acetylation and methylation that underlie long-lasting alterations in gene expression and that are not associated with changes in the primary DNA sequence itself [281]. While it is generally accepted that such phenomena may predispose an individual to anxiety disorders, in many cases methylation and acetylation profiles are not determined. Nevertheless, the implication of environmentally-induced behavioral alterations essentially suggests underlying mechanisms that are epigenetic in nature [282].

Childhood maltreatment, including early abuse and neglect, are predisposing factors for the development of psychopathology, leaving lasting imprints on mechanisms underlying cognition and emotionality. Key mediators of such neural plasticity are detectable particularly in the prefrontal cortex and hippocampus and include, among others, BDNF protein levels and indices of synaptic long-term potentiation. In an elegant series of experiments, Roth *et al.* succeeded in demonstrating that infant rat maltreatment results in reduced BDNF expression in the prefrontal cortex, owing to methylation of *BDNF* DNA through the lifespan to adulthood [283]. The epigenetic modification could be reduced with chronic treatment of a DNA methylation inhibitor. Interestingly, rats that have experienced adversity, mistreat their own offspring, with the latter also having significant DNA methylation, further highlighting the dynamic role of methylation in both gene regulation and transgenerational inheritance of phenotype. Along the same lines, Franklin *et al.* demonstrated that trait transmission in mice occurs through males, altering DNA methylation in the germline, and affects the offspring in a sex-dependent manner [284]. It is tempting to speculate that enriched environment might prove useful for reversing persisting effects of traumatic experiences in early life.

The experimental data suggest that, beginning early in development, an individual's genes, including epigenetic events, induce distinct changes in expression profile that occur in susceptible individuals only, shaping neural circuitry and neurometabolism characteristic of trait anxiety. Epigenetic modification thus opens enormous combinatorial options upon control of a wide range.

Novel targets for potential clinical pharmacotherapeutics

Mice with targeted mutations in the GABA-A receptors provide the basis for the search for novel anxiolytics targeting specific GABA-A receptor subunits only, as this was suspected to result in a better side-effect profile [285]. However, although the further clincal development of some α2-subunit specific GABA-A receptor agonists such as MRK 409 or TPA023 was determined due to unexpected side effects, GABA-A receptor subtype selective modulators are still considered as interesting non-sedative anxiolytics [286]. The development of positive allosteric modulators of the mGluR8 receptor and of mGluR5, 5-HT1A and 5-HT2C receptor antagonists as potential novel anxiolytics was promoted by results in mouse models with enhanced anxiety-related behavior. Anxiolytic properties of these antagonists/modulators have been demonstrated in various rodent anxiety tests (e.g., [287-294], for review see [295,296]) but, so far, they have not been processed into clinical trials for the treatment of anxiety disorders. Here, we want to focus in more detail on two novel targets as examples of how mouse models of enhanced anxiety related behavior contributed to their identification and/or characterization.

Neuropeptide S: a potential novel anxiolytic

The neuropeptide S (*NPS*) gene and the gene encoding its receptor (*NPSR*) are two of the promising candidates that are just at the start of extensive testing – and first results are very promising (for review, see [297]). NPS consists of 20 amino acids [298] and it is known to activate a G protein-coupled receptor elevating intracellular Ca^{2+} and cAMP [297]. Whereas the distribution of *NPS* precursor mRNA is very restricted in the CNS [298,299], the NPSR is expressed in many of its parts, particularly in the cortex, the thalamus, the hypothalamus and the amygdala [299,300] – brain areas known to regulate stress responses and to be part of the anxiety circuitry (see previous section).

In normal mice, NPS has anxiolytic effects in various unconditioned tests of anxiety including the elevated plus maze test and the stress-induced hyperthermia test [298,301-303] while also increasing wakefulness and arousal [298]. Recently, we could demonstrate that in classical Pavlovian fear conditioning, NPS also reduced the exaggerated conditioned fear responses in HAB mice to levels displayed by NAB mice [304]. This effect may be mediated via the G-protein coupled NPSR, as knockout of this receptor enhances anxiety-related behaviors ([305], but see [306]). Hence, the pharmacological spectrum of NPS is quite unique in comparison with other transmitters or drugs that influence emotional behavior in terms of anxiolysis and wakefulness. In humans, a single A-to-T SNP in the *NPSR* gene resulting in a ten-fold higher receptor functionality *in vitro* has been associated with overinterpretation of fear reactions in humans [307], increased amygdala responsiveness to fear-related stimuli [308] and panic disorder [309-311], providing further evidence of the potential of the NPS system to impact anxiety. Although a gain in receptor functioning in anxiety disorders, together with anxiolytic effects of NPS in mice, seems paradoxical, it is speculated that NPS may have different qualities during developmental stages with beneficial effects in adulthood [308].

In addition to its strong influence on stress-induced anxiety-related behavior, the NPS and its NPSR have been shown to be involved in many other physiological and pathological processes including depression-like behavior [306], drug seeking [312], food intake [313], respiratory function [314], asthma/atopy [315-318] and inflammatory bowel disease [319]. Therefore, the role of the NPS/NPSR system in health and disease needs to be better characterized in order to appraise its usefulness as a potential anxiolytic drug target.

Neurokinin-1 receptor antagonists in clinical trials for anxiety disorders

Many different interesting therapeutic actions including anxiolytic, antidepressant, antiemetic, antimigraine, antiaddiction, analgesic, anti-inflammatory, anti-cancer effects have been attributed to NK1R-A [320]. Indeed, they have been investigated in clinical trials for many years and, until now, the only US FDA approved NK1R-A is aprepitant (Emend™, Merck Sharp & Dohme, USA) for the indication of postoperative and chemotherapy-induced nausea. In neuroscience, following disappointing results in depression trials, the focus moved to anxiety disorders, despite sparse evidence concerning involvement of the substance P (SP) and NK1Rs in pathological anxiety (for review see [321]). Indeed, in 2005 Furmark *et al.* [322] reported positive effects of NK1R-A in patients with social phobia during a stimulus-provocation task; this, however, was not confirmed in another study [323], while in patients with post-traumatic stress disorders, it was not found to be superior to a placebo after short-term treatment [324].

These clinical anxiety trials are based on evidence from preclinical research demonstrating that NK1R-A including the novel, potent compound vestipitant [325] exert anxiolytic (and anti-depressant) effects in various species including rats, gerbils and mice (for review see [326]). Since most of this evidence was obtained in 'normal' animals, we decided to use the HAB mouse model for antagonist testing. Indeed, treatment of HABs with the selective NK1R-A L-822,429 was found to attenuate exaggerated conditioned fear expression [79,80], as well as their unconditioned anxiety response of HABs in the light/dark test (Figure 1) [327]. In addition, the treatment also normalizes the reduced heart rate variability observed in HABs to levels displayed by normal anxiety NABs (Figure 1) [80]. To gain insight into the role of the SP system in pathological anxiety, we used molecular biological and microdialysis approaches. It was found that HABs display enhanced *Tac1* gene expression, as well as exaggerated stress-induced SP release in the amygdala, a key brain area in fear and anxiety processing, suggesting dysregulated SP transmission as a result of genetic selection for an extremely anxious phenotype [328]. Thus, using a psychopathological mouse model that mimics important aspects of human anxiety disorders, we support and corroborate the so far limited human evidence of neurobiological and genetic mechanisms of SP (for review see [321]) underlying abnormal anxiety. This evidence derived from the use of HAB mice further strengthens the hope that NK1R antagonism may be a promising therapeutic approach for anxiety disorders, especially in individuals with a dysfunctional SP system, despite mixed clinical results so far [322-324].

Conclusion

Over the last two decades, building on data from human and rodent studies, our knowledge of the neurobiology of anxiety disorders has continuously increased, paralleling the increasing use of the laboratory mouse in anxiety research. In the present article, we have provided a summary of available mouse models of enhanced anxiety-related behavior and discussed examples of how and where such models are employed to advance the development of novel anxiolytic therapeutics (Figure 3). The discussed models mainly show improved validity, and in particular, face validity – that is, they closely reflect important symptomatology and they model aspects of human anxiety disorder endophenotypes. Of the models described so far, mice with inborn enhanced anxiety such as the HAB mouse line seem to meet translational value to a high degree, although it has to be noted that their validity is still incomplete. On the other hand, although astonishing homologies exist between mice and humans in terms of genes, brain mechanisms and anxiety-related responses, it will never be possible to model all aspects of clinically manifested anxiety disorders and even the most sophisticated mouse model of enhanced anxiety-related behavior will remain a reductionistic replication of the human disorder. This is also due to

the fact that the integrity of the murine model depends very much on our status of knowledge about the disease itself.

Bypassing this dilemma to a certain extent, the mouse provides a specific model organism to which partly unique (molecular) technologies can be applied in order to elucidate genetic mechanisms underlying anxiety disorders. Indeed, the involvement of TMEM132D and of the zinc metallo-enzyme, glyoxalase-1, in pathological anxiety represents two successful examples of bridging mouse and human neurogenetics [29,76,237,245]. Furthermore, mouse models of enhanced anxiety-related behavior are important for gaining insights into neurobiological mechanisms underlying pathological anxiety. Here, novel technologies may further help to limit brain regions to specific neuronal subpopulations modulating emotionality as demonstrated by Tye and coworkers, who identified amygdala projection neurons for reversible and bidirectional control of anxiety in mice by means of optogenetics [329]. The novel information can then be further tested in patients, using the technology that is available, such as imaging and post-mortem studies. For instance, an elevated expression of TMEM132D in the frontal cortex was observed in both HAB mice, selectively bred for high trait anxiety, and individuals with risk genotypes for panic disorder [237]. In addition, mouse models of enhanced anxiety-related behavior will be important for studying environmental stimuli and epigenetic modulations in the manifestation of an anxiety disorder. The information gained already and in the future will help to further improve subsequent mouse models of enhanced anxiety-related behavior (Figure 3). Using genetic tools, the mouse organism has proved ideal for elucidating the neurobiological function of identified susceptibility genes at specific loci in the brain. This has been, and will continue to be, particularly important, when classical pharmacological studies reach their limits, for example, when no selective ligands are available as demonstrated in the case of the GABA-A receptor subunits. Once the function of interesting systems has been elucidated, novel drug classes can be established (Figure 3).

Future perspective

It is clear that mouse models of enhanced anxiety-related behavior need to be refined continuously to fully reveal the therapeutic potential of a broad range of (novel) compounds. First, validation processes should be extended by means of objective, physiological readouts (e.g., [80]) and, wherever possible, pharmacological validation of the anxious phenotype, which may, however, interfere with the discovery of potentially novel targets. Thereby, intense collaborations between researchers from both the clinical and preclinical sides will be pivotal in order to improve the bidirectional characterization of patients and mouse models of enhanced anxiety. In the (near) future this may result in a better classification of anxiety disorders and may guide the development of mouse models of anxiety disorder subcategories (see initial attempts for post-traumatic stress disorder [70] or panic disorder [330,331]). Second, the mouse models described so far mostly reflect either genetic or environmental manipulations rather than mimicking the interaction of these two risk factors, though such interaction seems to be critical in the clinical manifestation of anxiety disorders [7,159]. Therefore, it is expected that the real clinical situation can be better modeled in mice by superimposing stressful environmental manipulations onto models with a well-defined genetic predisposition towards enhanced trait anxiety. Unfortunately, to date there have been only a limited number of such approaches whose findings have been published (e.g., [124,277,280,332,333]). What determines vulnerability to develop an anxiety disorder, together with treatment responses, may be causally addressed by genetic approaches in mouse models of enhanced anxiety-related behavior, providing fundamental insights into the construct of anxiety disorders. In the long run, clinical biological diagnostic tools will eventually be developed. Markers based on neurobiological and neurophysiological endophenotypes, as suggested for glyoxalase-1, could lead to a more precise classification

and, thus, diagnosis of anxiety disorders, both of which at the moment are based on symptoms specified in DSM-IV and ICD-10 [17,18]. Such adjustments will enhance the models' application for both the detection of novel targets with anxiolytic action and improve our understanding of the underlying pathophysiology of anxiety disorders, which is the basis for the development of novel anxiolytic drug classes with an improved pharmacologic profile (Figure 3).

The integration of mouse models of enhanced anxiety-related behavior into the drug discovery process will improve the screening for the drugs' clear anxiolytic potential before it advances into clinical trials. In parallel, these models may be used for distinguishing responders to anxiolytic drugs from nonresponders in order to improve pharmacotherapy, as this is still an unresolved area. In the future, the pharmacotherapy will be combined with techniques recording changes in the brain, such as functional imaging or microdialysis. An important aspect of using mouse models of enhanced anxiety-related behavior is to prove whether normalization of specific brain activity alterations is necessary/sufficient for successful treatment to take place, as this information can be obtained in humans in a very crude manner only. In this respect, non-invasive imaging techniques with high temporal and spatial resolution, which can be applied without inducing stress to awake, freely moving animals, will need to be developed. Then, pinning down causality by targeting dysfunctions in brain-activity processing in animal models of enhanced anxiety will guide the development of novel anxiolytic pharmacotherapies.

Acknowledgments

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Box 1

Anxiety tests: acute anxious states (state anxiety)

Unconditioned tests

- ■ Approach–avoidance conflict-based tests:
    - – Open-field test
    - – Light/dark test
    - – Elevated plus maze test
    - – Holeboard test
- ■ Interaction-based conflict tests:
    - – Social interaction
    - – Resident intruder
- ■ Others:
    - – Marble burying
    - – Hyponeophagia
    - – Stress-induced ultrasonic vocalizations
    - – Stress-induced hyperthermia

Conditioned (cognitive) tests

- ■ Conflict-based:
    - – Geller–Seifter test
    - – Vogel conflict test
    - – Four-plate test
    - – Conditioned place aversion
    - – Conditioned taste aversion
- ■ Others:
    - – Conditioned fear
    - – Conditioned emotional response

Box 2

Anxiety models: long-term enhanced anxious states (trait anxiety)

Inborn anxiety (e.g., strain, interindividual difference)

- Strain differences
- Interindividual differences
- Genetic models

Environmental manipulations

- Adverse rearing:
  - Maternal separation
  - Early weaning
  - Isolation housing
- Chronic stress exposure:
  - Chronic mild stress
  - Chronic social stress

Nutrient models

- Magnesium deficiency

Pharmacological models

- Chronic corticosterone treatment
- Drug withdrawal

Short-term enhanced anxious states

- Pharmacological models

Executive summary

Pathological anxiety

- ■ Anxiety disorders represent a quantitative and/or qualitative variation of 'normal' anxiety, which is still a matter of debate.

Pharmacotherapies used in anxiety disorders

- ■ Despite intense research, no true novel anxiolytic class with an improved pharmacotherapeutic profile has been introduced into therapy in the last four decades.

- ■ To date, after demonstration of its anxiolytic effects in preclinical trials, no novel, improved anxiolytic has so far made it via clinical trials onto the market. One explanation may be that their efficacy in animal testing was observed in physiological rather than pathophysiological anxiety states.

- ■ Animal models of enhanced anxiety-related behavior that mirror the pathophysiology of the human anxiety disorder may prove more effective in the development of novel anxiolytics.

Mouse models of enhanced anxiety-related behavior

- ■ Enhanced anxiety-related behavior is a persistent and enduring characteristic of animal models, reflecting trait anxiety.

- ■ Experimental manipulations reflecting the risk factors of anxiety disorders, including environmental and genetic manipulations, are used to induce enhanced anxiety-related behaviors in mice.

- ■ Mouse models of enhanced anxiety-related behavior demonstrate good face, and increasing construct validity and are hoped to improve the discovery of true novel anxiolytic drugs.

Translational anxiety research

- ■ The identification of candidate genes underlying the enhanced anxiety-related behavior of mouse models was successfully translated into information that can be applied to humans. By this means, an involvement of regulator of G-protein signaling 2, TMEM132D, glyoxalase-1 and BDNF in anxiety patients was demonstrated.

- ■ The demonstration in patients with anxiety of similar aberrant neuronal activation to that found in mouse models of enhanced anxiety-related behavior may be used for the screening of novel drugs by determining the ability of therapeutics to reverse (normalize) these changes associated with enhanced anxiety. So far, however, this strategy has not been used in mouse models of enhanced anxiety.

- ■ Mouse models of enhanced inborn anxiety-related behavior are ideal for studying genetic/epigenetic mechanisms contributing to pathological anxiety.

Novel targets for potential clinical pharmacotherapeutics

- ■ Mouse models of enhanced anxiety-related behavior have revealed interesting targets for novel anxiolytics, including specific GABA-A receptor subunits, the mGluR8, mGluR5, 5-HT1A, 5-HT2C and NK1 receptors as well as neuropeptide S. Their anxiolytic efficacy has been demonstrated in

anxiety tests and has been partly confirmed in humans. However, none of these drugs has so far received approval for treating anxiety disorders.
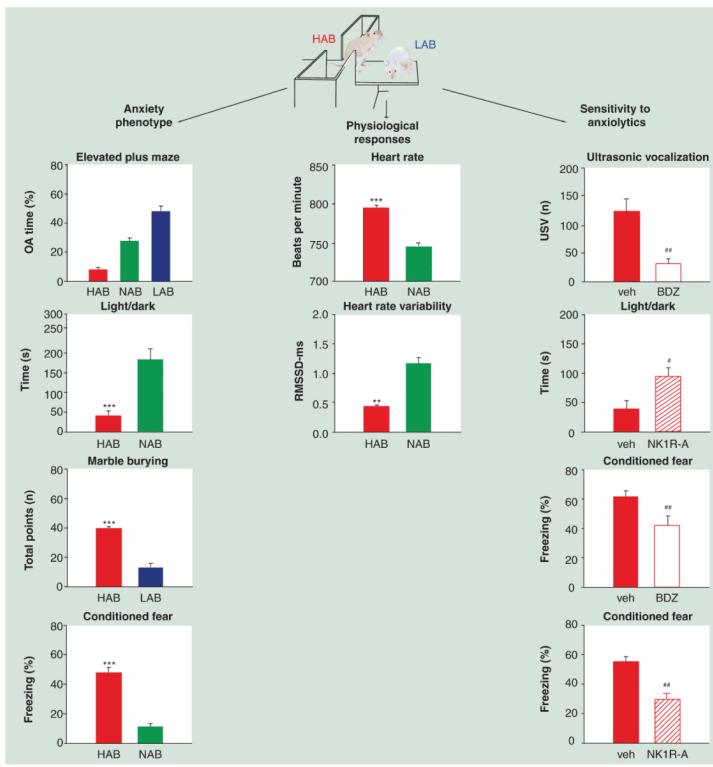
Figure 1. Validity of the high anxiety-related mouse model of high trait anxiety
Outbred CD-1 mice were selectively bred according to their high, normal or low anxiety-related behavior displayed on the elevated plus maze test (percentage of OA time), resulting in the HAB, NAB and LAB lines [76]. The anxious phenotype of HAB mice is confirmed by reduced time spent in the aversive, lit chamber of the light/dark test [327], by increased marble burying as indicated by the number of points reflecting the number and extent of the buried marbles (FRANK & LANDGRAF, UNPUBLISHED DATA) and by increased freezing levels in response to a conditioned stimulus [79,80]. Physiological signs of abnormal anxiety-related behavior reflecting construct validity are evident in terms of altered autonomic hyperarousal (as indicated by an increased heart rate [in beats per min]) and reduced heart rate variability (in RMSSD, with R being the peak of the QRS complex of the ECG wave) in response to emotional trauma [80]. Predictive validity of the HAB mouse model is demonstrated by attenuation of the enhanced anxiety- and conditioned-fear states after treatment with either a BDZ or a selective NK1R-A in the ultrasonic vocalization test [76], the light/dark test [327] and the conditioned fear test [79,80].
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ HAB versus NAB or LAB mice; #: $p < 0.05$; ##: $p < 0.01$ drug versus vehicle-treated HAB mice. BDZ: Benzodiazepine; HAB: High anxiety-related; LAB: Low anxiety-related; NK1R-A: Neurokinin-1 receptor antagonist; OA: Open arm; RMSSD: Root mean square of successive R-R interval differences of the ECG signal.
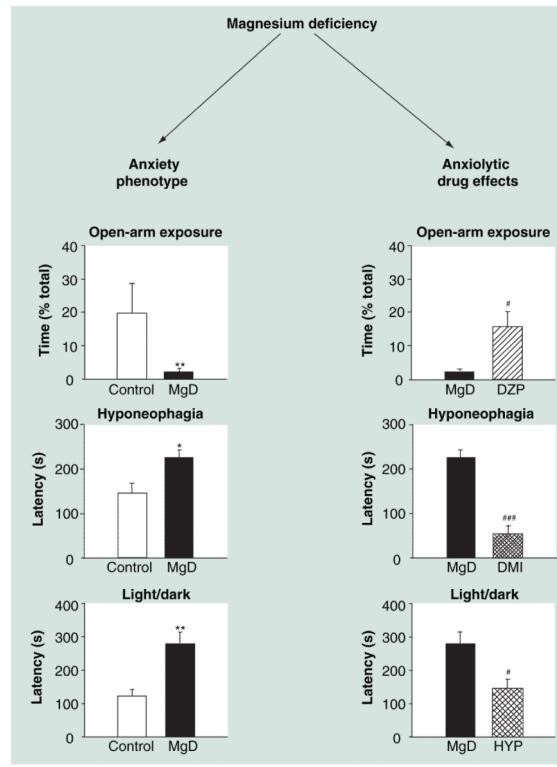
Figure 2. Validity of the magnesium-deficiency model as a mouse model of enhanced anxiety-related behavior

Compared with control mice, mice fed a low magnesium-containing diet (10% of the daily requirement) spend less time in the distal, aversive compartment of the open-arm exposure test and display enhanced latency to eat a pleasurable food in the hyponeophagia test [172, MANUSCRIPT IN PREP.], as well as enhanced latency to enter the brightly lit compartment of the light/dark test [171], indicating enhanced anxiety-related behavior. The anxious phenotype of MgD mice is reduced by acute treatment with the classical benzodiazepine DZP [172, MANUSCRIPT IN PREP.], as well as by chronic treatment with either the tricyclic antidepressant, DMI or HYP (St John's wort) [171].

*: $p < 0.05$; **: $p < 0.01$ MgD versus control mice; #: $p < 0.05$; ###: $p < 0.001$ drug versus vehicle-treated MgD mice.

DMI: Desipramine; DZP: Diazepam; HYP: Hypericum perforatum;
MgD: Magnesium-deficiency model.
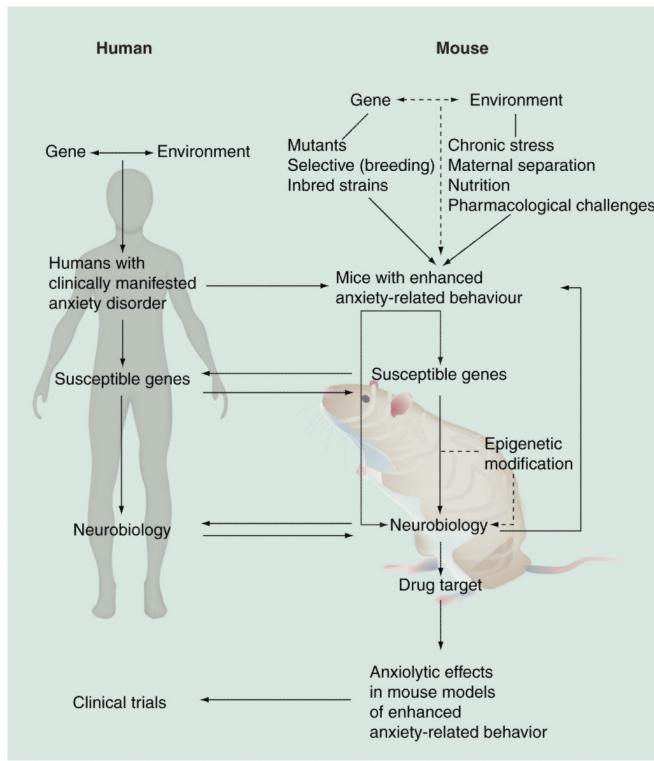
Figure 3. Strategy for translating research from mice to humans with the ultimate goal of developing novel anxiolytic drugs

Mouse models of enhanced anxiety-related behavior, induced by genetic or environmental manipulations and that closely resemble human symptomatology, increase the chances of identifying candidate genes for human anxiety disorders by reducing the problems of genetic heterogeneity and a variable environment. It is also important to study the involvement of these candidate genes in patients. Subsequently, elucidating the function of the identified gene using mouse models as well as the human population increases our knowledge of the neurobiology of anxiety disorders, which, at the same time, is necessary to improve the models. It is also necessary to test in mouse models the anxiolytic potential of possible novel anxiolytic drugs prior to clinical test phases. Dashed lines in the diagram indicate those aspects of anxiety research using mouse models of enhanced anxiety-related behavior that are just beginning to attract scientific interest, including gene-environment interactions and epigenetic modulations.

Table 1

Mouse models of enhanced anxiety-related behavior by strain adifferences

Anxious strain	Comparator strain	Anxiety-related behavior				
		Unconditioned anxiety			*Conditioned anxiety*	
129/Sv	C57Bl/6	↑	EPM	[334-335]	– –	–
		~	EPM, LD, OF	[334,336-337]	– –	–
		→	EPM, SI	[338]	– –	–
129S1/SvImJ	C57Bl/6	↑	OF, LD	[107,124,339]	↑ CF	[345]
		~	EPM, EZM, LD, OF, SI	[124,339,341-342]	– (imp-EXT)	[44,46,343]
129/SvEv	C57Bl/6	↑	EPM	[337]	– –	–
129S6/SvEv	C57Bl/6	↑	EPM, LD, OF	[107,344-346]	~ CF	[346]
					↑ CF	[345]
A/J†	C57Bl/6†	↑	EPM, EZM, LD, HB, mHB, OF, SI, USV	[60,68,107,339,341,342,344,345,347-351,369]	↑ CF, VC (imp-EXT)	[347,349,352] [349]
		~	EPM, HB, LD, SI	[340,348,349]	~ CF, FPS, VCT	[345,347,349]
				–	→ CF	[354]
AKR/J	C57Bl/6	↑	EPM, EZM, LD, OF	[342,344,347,348,355]	↑ CF, FPS	[347]
		~	OF, EZM	[342,344,348]	– –	–
BALB/c†	C57Bl/6†	↑	EPM, EZM, LD, OF, SI	[60,65,107,124,339,342,344,347,348,351, 356-365]	↑ CF, FPS (imp-EXT)	[345,347,366] [354]
		~	EPM, OF, SI	[65,124,336,337,341,344,345,367-370]	~ CF, FPS	[345,368]
		→	EPM, OF	[340,367,371,372]	→ CF	[354]
C3H/He	C57Bl/6	↑	EPM, LD, USV	[339,344,347,350,358,367,368]	↑ FPS	[368]
		~	EPM, EZM, OF, SI	[65,335,336,339,342,344,345,350,367,369,372, 373]	~ CF	[347]
		→	LD, OF, EPM	[107,340,342,348]	→ CF	[345]
DBA/2J†	C57BL/6†	↑	EPM, LD, OF, USV	[107,339,342,344,346-348,349,350,361,362,365,368,370,373]	↑ CF, FPS	[345,347]
		~	EPM, EZM, OF, SI	[336,340,342,345,347,350,370]	~ CF, FPS	[347,368,374]
		→	EPM, SI	[341,348]	→ CF	[345,346,375]

↑: Increased anxiety-related behavior; ↓: Decreased anxiety-related behavior; ~: Unaltered anxiety-related behavior; CF: Conditioned fear; EPM: Elevated plus maze; EZM: Elevated zero maze; FPS: Fear-potentiated startle; HB: Holeboard test; imp-EXT: Impaired extinction of conditioned fear; LD: Light/dark test; mHB: Modified holeboard test; OF: Open-field test; SI: Social interaction; USV: Stress-induced ultrasonic vocalization; VC: Vogel conflict test.

† Inbred mouse lines with strongest evidence for increased anxiety-related behavior.

Table 2

Mouse models of enhanced anxiety-related behavior by selective breeding approaches

Mouse model	Comparator	Selection criterion	Background	Anxiety-related behavior					
				Unconditioned anxiety			Conditioned anxiety		
Selection based on anxiety-related parameters									
HAB	NAB, LAB	Anxiety-related behavior on the EPM	CD-1	↑	LD, EPM, OA, USV	[76–77]	↑	CF (imp-EXT)	[255, MANUSCRIPT IN PREP, 375] [255, MANUSCRIPT IN PREP.]
High contextual fear conditioning	Low ocontextual fear conditioning	Contextual fear conditioning	C57Bl/6J × DBA/2J	↑	EZM, OF	[83]	↑	CF, FPS	[83]
				~	LD	[7]	–	–	–
AX	NAX	Anticipatory anxiety	MG15 × NMRI	↑	EPM, LD, OF	[84]	–	–	–
Selection based on other parameters									
NC900	NC100	Aggressive behavior towards a social partner	ICR	↑	OF, LD, EZM	[87]	–	–	–
Increased wheel-running – line 8	Control line 2	Voluntary wheel running	Hsd:ICR	↑	EPM	[376]	–	–	–
				~	OF	[376]	–	–	–
β-CCM-resistant line	β-CCM-sensitive line	Sensitivity to the to the convulsive effects of the inverse benzodiazepine receptor agonist β-CCM	Outbreed stock of inbred mice	↑	EPM, HB, LD	[377]	–	–	–
HAP	LAP	Alcohol preference	HS/Ibg mice	–	–		↑	FPS	[378,379]
Light line	Control, heavy lines	Bodyweight	Outbreed stock of inbred mice	↑	OF	[380]	–	–	–

↑: Increased anxiety-related behavior; ↓: Decreased anxiety-related behavior; ~: Unaltered anxiety-related behavior; AX: Anxious line; β-CCM: β-carboline-3-carboxylate; CF: Conditioned fear; EPM: Elevated plus maze; EZM: Elevated zero maze; FPS: Fear-potentiated startle; HAB: High anxiety behavior line; HAP: High alcohol preference line; HB: Holeboard test; imp-EXT: Impaired extinction of conditioned fear; LAB: Low anxiety behavior line; LAP: Low alcohol preference line; LD: Light/dark test; NAB: Normal anxiety behavior line; NAX: Nonanxious line; NC: North Carolina line; OA: Open-arm exposure test; OF: Open-feld test; USV: Maternal separation-induced ultrasonic vocalization.

Table 3

Mouse models of enhanced anxiety-related behavior by gene targeting

Mutant		Unconditioned anxiety-related behavior			Conditioned anxiety-related behavior	
Monoaminergic targets						
5-HT1A	KO	↑ EPM, OF, EZM	[381-383]	–	–	–
5-HT2C	OE	↑ EPM, OF	[384]	–	–	–
α2A	KO	↑ EPM, LD	[385-386]	↑ CF	[387]
nAChRα4	KO	↑ EPM,	[388]	–	–	–
COMT	KO	↑ LD, OF	[389], but see [390-391]	–	–	–
D1CT	TG	↑ LD, OF	[392-393]	–	–	–
D4	KO	↑ EPM, LD, OF	[394-395], but see [396]	~ CF	[395]
SERT	KO	↑ EPM, EZM, LD, OF, SI	[397-399], but see [400]	–	–	–
Glutamatergic targets						
NR2C-2B	RP	↑ EPM	[401]	–	–	–
GluR1	KO	↑ EPM, LD, SI	[402-404]	→ CF	[405-406]
mGluR5	KO	↑ EPM, LD	[407]	~ CF / → CF (imp-EXT)	[408] [409] [409]
mGluR8	KO	↑ EPM, OF	[410-414], but see [415]	→ CF	[415-416]
VGlutT1	HET	↑ LD	[417]	–	–	–
GABAergic targets						
GABA-Aγ2	HET,KO	↑ EPM, LD	[418,419]	↑ TFC	[418]
GABA-Aγ2L	KO	↑ EPM	[420]	–	–	–
GABA-B1	KO	↑ LD	[421]	–	–	–
GABA-B2	KO	↑ LD	[421]	–	–	–
GAD65	KO	↑ EZM, LD, OF	[422,423]	~ CF / → CF (imp-EXT)	[424] [425] [424]
Neuropeptidergic targets						
BDNF^{Met}	KI	↑ OF, EPM	[426-427]	→ CF	[427]

Mutant			Unconditioned anxiety-related behavior			Conditioned anxiety-related behavior	
CB1	KO	↑	EPM, LD, OF, SI	[428-433], but see [434]	~ →	CF CF (imp-EXT)	[435-438] [439] [435,437,438]
CCK	KO	↑	EPM	[440]	–	–	–
CCK1R	KO	↑	EPM	[441,442]	–	–	–
CRH	OE	↑	EPM, LD, OF, SI	[98,353,443-446]	~	CF, VC	[347]
CRH-BP	KO	↑	EPM, LD, OF	[447-448]	–	–	–
CRH-R2	KO	↑	EPM, LD, OF	[261,449-450]	–	–	–
αER	KO	↑	OF, LD	[451,452]	–	–	–
GR	OE	↑	EPM	[453,454], but see [455]	–	–	–
Mas	KO	↑	EPM	[456]	–	–	–
NPSR	KO	↑	OF, LD, EPM	[305], but see [306]	–	–	–
NPY	KO	↑	EPM, LD, OF	[457-459]	–	–	–
OFQ/N	KO	↑	EPM, LD, OF	[460-461]	↑	CF	[462]
PENK	KO	↑	EPM, EZM, LD, OF, SI, USV	[463-466]	↑	CF, FPS	[464,465]
Ucn	KO	↑	EPM, OF	[467], but see [468]	–	–	–
Immune system							
IFN-γ	KO	↑	EPM, OF	[469-471]	–	–	–
TNF-α	OE	↑	HB, LD	[472]	–	–	–
Other targets							
3xTg-AD	TG	↑	LD, OF	[473]	↑	CF	[473]
APP,Sw,Ind	TG	↑	LD, OF	[473]	↑	CF	[473]
α-CamKII	OE	↑	EZM, LD, OF, SI	[474]	–	–	–
Dhh	KO	~	LD, OF	[475]	↑	VC	[475]
eNOS	KO	↑	EPM, OF	[476,477]	–	–	–
Fut9	KO	↑	EPM, LD	[478]	–	–	–
Fyn	KO	↑	EPM, LD	[479,480]	↑	CF	[481], but see [482]
PAM	HET	↑	EZM	[483]	→	FPS	[483]
PSA	KO	↑	EPM, OF	[484]	–	–	–
Rgs2	KO	↑	LD	[244]	–	–	–

Mutant			Unconditioned anxiety-related behavior		Conditioned anxiety-related behavior	
Schnurri-2	KO	↑	OF	[485]	–	–
SF-1	KO	↑	EPM, LD, OF	[486]	–	–
Sim2	OE	↑	EZM, OF, SI	[487]	–	–
TAK1/TR4	KO	↑	SI, LD, OF	[488]	–	–
TgNTRK3	OE	↑	EPM	[490]	–	–
trkB^CaMKII-CRE	KO	↑	OF	[491]	–	–

↑: Increased anxiety-related behavior; ↓: Decreased anxiety-related behavior; ~: Unaltered anxiety-related behavior; 3xTg-AD: Alzheimer's disease transgenic mice expressing taurine; 5-HT1A: Serotonin 1A receptor; 5-HT2C: Serotonin 2C receptor; α2A: α2A-adrenergic receptor; αER: α-estrogen receptor; APPsw,Ind: Alzheimer's disease transgenic mice expressing human mutant β-amyloid precursor protein; BDNF: Brain-derived neurotrophic factor; CB: Cannabinoid receptor; CCK: Cholecystokinin; CCK1R: Cholecystokinin 1 receptor; CF: Conditioned fear; COMT: Catechol-O-methyltransferase; CRH: Corticotropin-releasing hormone; CRH-BP: Corticotropin-releasing hormone binding protein; CRH-R2: Corticotropin-releasing hormone 2 receptor; D1CT: Expression of a neuro-potentiating cholera toxin transgene in dopamine D1 receptor-expressing neurons; D4: Dopamine D4 receptor; Dhh: Desert hedgehog; eNOS: Endothelial nitric oxide synthase; EPM: Elevated plus maze; EZM: Elevated zero maze; FPS: Fear-potentiated startle; Fut9: Fucosyltransferase IX; Fyn: Fyn tyrosine kinase; GABA: γ-amino butyric acid; GAD: Glutamic acid decarboxylase; GluR1: AMP-A GluR1 subunit; GR: Glucocorticoid receptor; HB: Holeboard test; imp-EXT: Impaired extinction of conditioned fear; KI: Knock-in; KO: Knockout; LD: Light/dark test; Mas: Mas proto-oncogene; mGluR: Metabotropic glutamate receptor; nAchRα4: α4-nicotinic acetylcholine receptor; NPSR: Neuropeptide S receptor; NPY: Neuropeptide Y; NR2C-2B: NMDA receptor 2C-2B; OE: Overexpression; OF: Open-field test; OFQ/N: Orphanin FQ, nociceptin; PAM: Peptidylglycine α-amidating monooxygenase; PENK: Prepro-enkephaline; PSA: Puromycin-sensitive aminopeptidase; Rgs2: Regulator of G-protein signaling; RP: Replacement; SERT: Serotonin transporter; SF: Steroidogenic factor; SI: Social interaction; Sim2: Single-minded 2 gene; TAK1/TR4: Nuclear orphan receptor; TFC: Trace fear conditioning; TG: Transgenic; TgNTRK3: Transgenic mice overexpressing the full-length neurotrophin-3 receptor TrkC; trkB^CaMKII-CRE: Forebrain-specific knockout of the trkB receptor; Ucn: Urocortin; USV: Stress-induced ultrasonic vocalization; VC: Vogel conflict test; VGlutT1: Vesicular glutamate transporter 1.

Table 4

Comparison of neurobiological parameters between patients with anxiety disorder and mouse models of enhanced anxiety-related behavior

	Patients[†]		Mouse models	
Neuroanatomical (volume) alterations				
Anterior cingulate cortex	↓	[492–498]	–	–
Orbitofrontal cortex	↓	[497,499,500]	–	–
Hippocampus	↓	[497,501–503]	↓	[198,504]
Amygdala	↓	[494,498,505]	↓	[506]
Activity processing				
Amygdala	↑(↓)[‡]	[22]	↑(↓)[§]	[54,119,224,305,309,362,363,364]
Prefrontal cortex	↑ dACC	[22]	–	–
	↑↓[‡] rACC	[22]	↑↓ Cg	[77,183,259,261,507]
Neurochemistry				
GABA system	↓	[21]	↓	[87,508,509]
NA system	↑	[21]	↑	[136,510]
5-HT system	Not clear		–	–
DA system	Not clear		–	–
Neuropeptides	↑ CRH	[21]	↑ CRH	[511–514]
	↑↓ NPY	[21]	↓ NPY	[209]
	↑ SP	[515,516]	↑ SP	[328]
Physiological parameters including autonomic arousal				
Autonomic arousal	↑	[517–518]	↑	[80,385,519]
Sleep disturbance/insomnia	Yes	[17,520,599]	Yes	[362,521,522]
Neuroendocrinology				
CORT	↑↓	[21]	↑↓	[136,140,511,512,514,523]

↑: Increased; ↓: Decreased; 5-HT: Serotonin; Cg: Cingulate cortex; CORT: Cortisol/corticosterone; CRH: Corticotropin-releasing hormone; DA: Dopamine; dACC: Dorsal anterior cingulate cortex; NA: Noradrenaline; NPY: Neuropeptide Y; rACC: Rostral anterior cingulate cortex; SP: Substance P.

[†] Mainly post-traumatic stress disorder or panic disorder.

[‡] Based on a very small number of studies.

[§] Increased activation mainly in the central amygdala (see. Table 5).

Table 5

Functional mapping in mouse models of enhanced anxiety-related behavior

Mouse	model	Challenge	Marker	Cortex	Septum	BNST	Hippocampus	Hypothalamus	Thalamus	Amygdala	PAG	Hind-brain	Ref.
Mutants													
OXT KO	f	EPM	c-Fos	–	–	–	–	–	–	↑MeA	–	–	[524]
mGluR8 KO	m	Restraint	c-Fos	–	–	→	–	–	–	↓MeA	–	–	[525]
	f	Shaker	c-Fos	–	–	–	–	–	–	↓MeA	–	–	[526]
	m	EPM	c-Fos	–	–	–	–	–	↑CMT	–	–	–	[413]
ATP1α2 HET	m	CF	c-Fos	↑Pir	–	–	–	–	–	↑	–	–	[527]
CRHR2 KO	m	EPM	pCREB	↓Cg	–	→	–	↓VMH	–	↓BLA	–	–	[259]
Fyn KO	m	CF	c-Fos	–	–	–	–	↑PVN, LH	–	↑CeA, MeA, BMA, ACo ↓LA, BLA	↑	–	[481]
TgNTRK3	m	Restraint	c-Fos	↑PrL	↑LS	–	–	–	–	–	–	–	[528]
		Yohimbine	c-Fos	↑Cg	–	–	–	↓PVN	–	↑CeA	–	–	[183]
		Caffeine	c-Fos	↑Cg	–	–	–	–	–	↑BLA	–	–	[183]
BAFF OE	m	EPM	c-Fos	↑Cg	–	–	↑DG	↑PVN	–	↑BLA	–	–	[507]
Environmental manipulation													
CSC	m	OAE	c-Fos	–	↓LS	–	↓CA3	↓PVN	–	–	↑DMPAG	–	[138]
Mice with naturally occurring high trait anxiety													
HVWR	m	PO/OF	c-Fos	–	–	–	↓CA1, CA3, DG	–	–	–	–	–	[97]
HAB	m	OAE	c-Fos	↓Cg	↑LS	–	↓DG	↑LH, DMH, VMH, MPA	–	↑MeA, LA, ACo	↑DMPAG	↑LC	[77]
129P3/J	f	mHB	c-Fos	↓PrL	↓LS	↑	↓DG	–	–	↑CeA ~CeA, BLA	–	–	[69,260]
BALB/c	m	Restraint	c-Fos	↓Cg	–	–	↓DG	–	↑PV	–	–	–	[257]

↑: Hyperactivation; ↓: Hypoactivation; ~: Unaltered anxiety-related behavior; ACo: Cortical amygdala; ATP1a: Sodium pump α2 subunit; BAFF: B-cell activating factor; BLA: Basolateral amygdala; BMA: Basomedial amygdala; BNST: Bed nucleus of the stria terminalis; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; CeA: Central amygdala; CF: Conditioned fear expression; Cg: Cingulate cortex; CMT: Centromedial thalamus; CRHR2: Corticotropin-releasing hormone 2 receptor; CSC: Chronic subordinate colony; DG: Dentate gyrus; DMH: Dorsomedial hypothalamus; DMPAG: Dorsomedial PAG; EPM: Elevated plus maze; f: Female; Fyn: Fyn tyrosine kinase; HAB: High anxiety-related behavior; HET: Heterozygous; HVWR: High voluntary wheel running; KO: Knockout; LA: Lateral amygdala; LC: Locus coeruleus; LH: Lateral hypothalamus; LS: Lateral septum; m: Male; MeA: Medial amygdala; mGluR8: Metabotropic glutamate 8 receptor; mHB: Modified holeboard test; MPA: Medial preoptic area; OAE: Open-arm exposure; OE: Overexpressing; OXT: Oxytocin; PAG: Periaqueductal gray; Pir: Piriform cortex; PO/OF: Predator odor/open-field; PrL: Prelimbic cortex; PV: Paraventricular thalamus; PVN: Paraventricular hypothalamus; TgNTRK3: Transgenic mice overexpressing the full-length neurotrophin-3 receptor TrkC; VMH: Ventromedial hypothalamus.