

9

Mood and Anxiety Disorders

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9.1

Introduction

Mood and anxiety disorders are chronic, disabling conditions that impose enormous costs on both individuals and society at large [1–5]. These disorders are the most frequent diagnosed neuropsychiatric diseases in Western countries. According to a recent 3-year multimethod study covering 30 European countries and a population of 514 million people, anxiety and mood disorders had the highest 12-month prevalence estimates (total 14 and 6.9%, respectively) compared with all other psychiatric conditions [2]. Although there are many treatment options available for these disorders, drug discovery research in this area is still very active, with the objective of finding alternative, better tolerated, and more effective pharmacological treatments for anxiety and mood disorders.

The reliance on animal models of these conditions is crucial to find new treatments. Preclinical research has devised numerous ways to test for anxiety and mood, with well over 100 tests and models by recent counts [6]. The specifics of these tests have been described in many comprehensive reviews on this topic [6–9] and we will only briefly introduce the most frequently used ones here to illustrate the strengths and weaknesses of current approaches in general. One general consideration from the outset is validity. The validity of a test for anxiety/mood in an animal rests on three criteria: face validity (Does it measure something analogous to one or more human anxiety/mood symptoms?), predictive validity (Is it reliably sensitive to clinically efficacious anxiolytics/antidepressants?), and construct validity (Does it involve some of the same pathophysiological mechanisms found in human anxiety/mood disorders?) [10]. None of the available tests or models of anxiety or mood can be said to unequivocally meet these criteria.

9.2

Animal Models of Anxiety Disorders

9.2.1

Preclinical Measures of Anxiety

A group of tests that have been a mainstay of preclinical anxiety research for many years [11] assay anxiety-like behavior by generating a conflict between a drive to approach novel areas and simultaneously avoid potential threat therein (Figure 9.1). These simple tests that include the open-field, elevated plus maze, and light–dark exploration tests were developed in the 1980s to exploit the natural tendency of mainly rats [12] and mice [13,14], but also guinea pigs [15] and gerbils [16] to prefer enclosed areas over exposed/elevated places. They have been used in nearly 10 000 drug discovery-related experiments and continue to be very popular. More than half of the rodent-based experiments on anxiety-related drugs have employed one or more of these tests, and among them, by far the most commonly used has been the elevated plus maze.

While the approach–avoidance tests generate a conflict, the term “conflict-based test” has often been used to describe measures of the suppression of a behavior by mild electric shock. This group includes the Vogel conflict [17] and Geller–Seifter

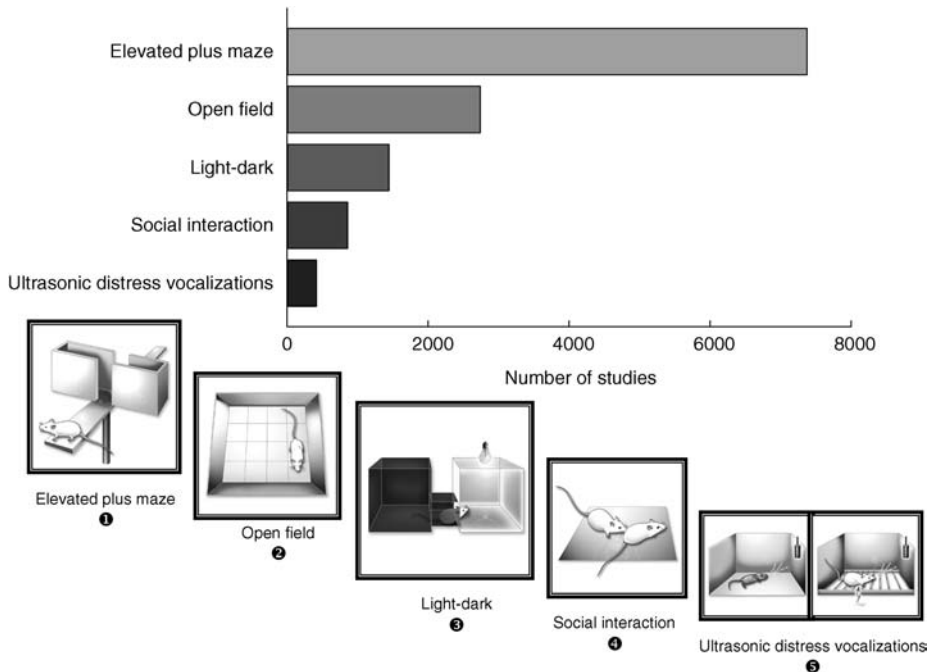


Figure 9.1 The five most commonly used tests in anxiolytic drug discovery. Values represent the number of experiments performed with each test as of 2012 (Sources: HCAPLUS, Medline, Embase, and Biosis.)

[18] tests, which measure anxiolytic-like activity as the maintenance of a behavioral response (licking and bar pressing) despite receipt of shock. These tests were part of many drug discovery programs in the 1980s and 1990s, but have fallen out of favor perhaps because they require animals to be trained over multiple days and are more labor intensive and time consuming than the approach–avoidance tasks.

Some anxiety tests have been designed to tap into fundamental defensive responses shown by animals in the face of immediate danger. Such defensive or “fear” behaviors can be conceptually distinguished from the anxiety states produced by less imminent, more ambiguous threats [11], and may be most relevant to anxiety disorders, such as panic disorder (PD) and posttraumatic stress disorder (PTSD). The mouse defense test battery (MDTB) was designed to provide multiple measures related to fear and anxiety, based on observations of how wild rodents respond to danger [19]. In this task, mice are placed in an oval runway and tested for responses (fight, flight, freeze, vocalize, scan, etc.) to an approaching anesthetized rat (a natural predator). Interestingly, specific behavioral measures in this test are sensitive to specific classes of anxiolytic medication, with, for example, benzodiazepines (BZ) that are effective in generalized anxiety disorder (GAD) reducing risk assessment and serotonergic agents that are efficacious in PD and PTSD, attenuating fight and flight behaviors [20]. In spite of these promising results, however, the task has not been widely adopted, again likely due to the training and technical demands involved. As a compromise, some researchers incorporated measures derived from the analysis of defensive behavior into the simpler anxiety-related assays such as the elevated plus maze, in some cases improving the sensitivity to certain anxiolytic classes [21].

Another set of fear-based tests involve variations on classical Pavlovian conditioning. Here, the animal learns to associate a context or specific environmental stimulus (e.g., a light or a sound) with electric shock to produce a conditioned fear response that can be quantified in various ways (freezing, escape, avoidance, startle, etc.). Studies of Pavlovian fear have contributed greatly to the understanding of the basic neural and molecular mechanisms of memory, but have not been traditionally considered tests for use in anxiolytic drug discovery. This may be changing, however, with the recent focus on devising ways to pharmacologically attenuate fearful memories through the process of reconsolidation or extinction [22] and, more generally, by a growing appreciation of abnormal learning and cognition in anxiety.

9.2.2

Preclinical Anxiety Models and Endophenotypes

Tests for anxiety, in which the animal is placed in an experimental situation to evoke an acute anxiety-like response, can be distinguished from models of anxiety, where the animal has been manipulated in some way to produce a more lasting increase in anxiety. The goal of anxiety models is to produce a form of abnormally elevated anxiety that more closely approximates to the pathology of an anxiety disorder (Table 9.1). This can be achieved, for example, by acutely or chronically subjecting animals to stressors prior to testing [23,24]. Another approach involves

Table 9.1 Modeling symptoms of anxiety disorders in rodents.

Symptom	Assay	Situation
Avoidance of places from which escape could be difficult	Exploration of exposed and well-lit spaces in the elevated plus maze and light–dark box	Acute avoidable
Anxiety provoked by situations for which opposing impulses lead to decisional uncertainty	Increase in punished responding in the punished drinking and four-plate tests	Acute avoidable
Anxiety provoking obsessions/impulsive behavior	Marble burying	Acute nonavoidable
Difficulty in concentrating	Cognitive impairment due to predator stress	Acute nonavoidable
Worry/difficult to control the worry	Risk assessment in the defense battery	Acute nonavoidable
Irritability/aggressivity	Defensive aggression in the defense battery, human threat	Acute nonavoidable
Sudden onset of intense fearfulness	Flight in the defense battery	Acute nonavoidable
Autonomic hyperarousal	Stress-induced hyperthermia	Acute nonavoidable
Difficulty in concentrating, hyperarousal (PTSD)	Trauma-induced long-term cognitive or adaptative deficits	Chronic nonavoidable

identifying genetic populations or engineering animals that are inherently anxiety prone. Examples of the former are inbred mouse strains, such as BALB/cJ, and selectively bred “high-anxiety behavior” rat and mouse lines [25,26]. Illustrative of the latter are the plethora of transgenic and gene knockout mice that have been generated and tested for anxiety-like phenotypes. These mutant mice have been valuable as models to screen for novel anxiolytics [27–29].

The term endophenotype describes a symptomatic feature or premorbid risk factor of an anxiety disorder that can be more readily quantifiable than the disease as a whole. Certain rodent behavioral measures can also be considered endophenotypes of specific anxiety symptoms: risk assessment and flight in the MDTB, for example, can be related to threat hypervigilance and threat avoidance in GAD and PD, respectively [19]. Moreover, assessing the extinction of fearful memories has become a popular measure in anxiety research because the procedures, as well as the underlying neurobiology, closely overlap in animals and humans, and extinction has a close therapeutic analog in the form of exposure therapy. The objective of many preclinical extinction studies is to screen for drugs that can be administered as adjuncts during exposure to strengthen the formation of extinction memories and thereby reduce the future recurrence of anxiety symptoms [30,31]. There have been some successes in developing clinically efficacious anxiolytics (e.g., D-cycloserine) based upon predictions from studies of fear extinction in rodents [32], and this is currently an active approach for further drug discovery.

9.3

Animal Models of Mood Disorders

9.3.1

Major Depressive Disorder

Given the subjective and heterogeneous nature of most of the core symptoms of major depressive disorder (MDD) and the lack of valid state markers, modeling this condition poses a number of substantial challenges. Further complication derives from the observation that current antidepressants, which all target monoaminergic neurotransmission, have inconsistent effects in the clinic (about 50% of patients will not respond to a first-line treatment). This has important implications for modeling as it limits the use of reference drugs as a validation criterion for novel drug effect. Despite these issues, there are several animal procedures that are claimed to model certain aspects of depressive symptoms and that are used extensively in antidepressant drug discovery (Figure 9.2).

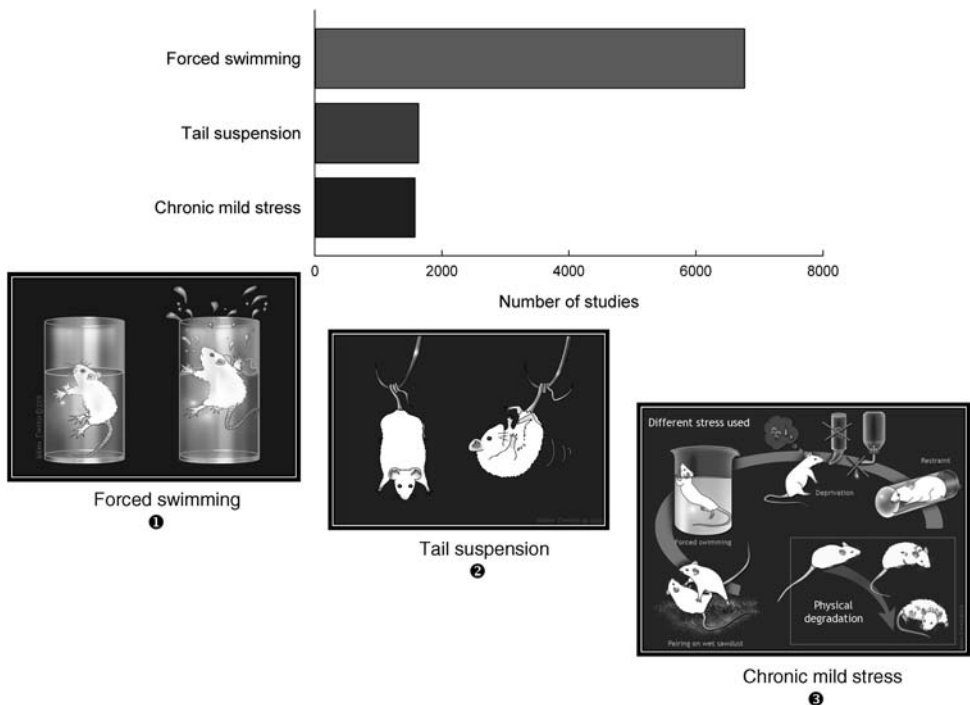


Figure 9.2 The three most commonly used tests in antidepressant drug discovery. Values represent the number of experiments performed with each test as of 2012 (Sources: HCAPLUS, Medline, Embase, and Biosis.)

9.3.1.1 Preclinical Measures of Depression

These models are based on epidemiological evidence that stress and adverse psychosocial experiences often precede the onset, or predict the recurrence, of depressive episodes. They can be subdivided into several categories based on the behavioral endpoint related to the depressive symptoms [33].

Negative Affect This refers to a form of behavioral passivity and quiescence, often referred to as “despair,” occurring in many species upon exposure to uncontrollable stress. This increase in inactivity can be delayed or normalized by antidepressants. Tests that measure this activity or escape deficit include either simple behavioral procedures (e.g., forced swimming [34] and tail suspension [35]) or more elaborate paradigms (e.g., learned helplessness [36]). By far the most widely utilized is the forced swimming test, which can be used with rats and mice. The common application of this test is linked directly to the robust and reproducible effects of monoamine reuptake inhibitors.

Positive Affect or Hedonia This refers to the ability to experience pleasure. Reduction in this behavior, often referred to as anhedonia, is commonly observed in MDD and represents a hallmark endophenotype of this condition [37]. Common behavioral tests used to quantify anhedonia in rodents are the sucrose preference test, intracranial self-stimulation (ICSS), and sexual behavior [38–40]. The sucrose preference test is based on the idea that repeated mild unpredictable stressors will lead to a reduction of sucrose consumption. The test is normally run under conditions of free access to sucrose and water, and anhedonia is quantified based on the ratio of sucrose to water consumption over that time. ICSS behavior allows a direct evaluation of the sensitivity to reward in animals. Several approaches, including electrical stimulation of basal forebrain [41] and ventral tegmental area [40], have been used. In this procedure, rats are allowed to electrically self-stimulate the targeted brain area. Following repeated exposure to a variety of stressors, stimulation threshold is generally increased in stressed rats, suggesting a decrease in the rewarding properties of brain stimulation (i.e., a correlate of anhedonia). Sexual behaviors have also been used to quantify anhedonia [42,43]. Pharmacological studies using antidepressants have shown that these deficits in hedonic behaviors can be normalized following chronic treatment of these agents.

Socioaffective Function Socioaffective alterations are another important feature of MDD symptoms [37]. Studies in primates and rats have demonstrated the occurrence of deficits in social behaviors upon repeated exposure to stressors, such as maternal separation or social defeat. The most salient aspects of socioaffective alterations are expression of a stereotypical prostrated and socially unresponsive posture (in primates), the exacerbation of socially submissive behaviors, and social avoidance (in primates and rats). Despite the strong face validity, primate models of socioaffective deficits have been rarely used in antidepressant drug discovery because of obvious technical and ethical limitations [44]. Rodent social stress models such as the social defeat paradigm [45] and tests of dominant–submissive

behavior such as the visible burrow system procedure [46,47] provide a number of valid alternatives to examine antidepressant drug effects.

Cognition According to the cognitive model of depression described by Aaron Beck ~40 years ago, biased acquisition and processing of information have a primary role in the development and maintenance of depression [48]. This model derives from the observation that MDD patients overemphasize negatively valenced information, resulting in difficulties in redirecting their attention or thoughts away from negative beliefs. Although pessimistic decision biases *per se* cannot be modeled in animals, there are several behavioral tasks of attention and executive function (e.g., CANTAB battery [49]) in rodents and primates that could serve to measure cognitive deficits in MDD models. Unfortunately, these tests are technically challenging and not necessarily suitable for drug testing.

9.3.1.2 Endophenotype Models of Depression

The last two decades have seen the emergence of endophenotype models of depression, with the engineering of animals that are inherently depression prone. For example, animals carrying mutations replicating naturally occurring single-nucleotide polymorphisms that alter the function or candidate genes for MDD, such as *BDNF* [50], *TPH2* [51], *5-HTT* [52], *DISC1* [53], or *CRHR1* [54], have been reported to display depression-like phenotypes. However, the lack of a highly penetrant mutation associated with MDD, along with the unclear epidemiological evidence that these genetic variants significantly increase the MDD risk, seriously questions the idea that these mutants represent valid models of depression. Another approach involves the identification of animal populations that display inherently depression-like behaviors. Examples are inbred rat strains, such as Flinders sensitive line (FSL) [55] and Wistar Kyoto (WKY) [56], and selectively bred, “high reaction to stress test” (HR) [57], “swim low-active” (SwLo) [58], or “inbred learned helpless” (cLH) [59] rat and mouse lines. These animals have been valuable as models to screen for novel anxiolytics.

9.3.2

Bipolar Disorder

Bipolar disorder (BPD) is phenotypically a very complex disease, characterized by vulnerability to episodic depression and mania and spontaneous cycling. Because of its heterogeneous clinical phenotype, along with the relative lack of knowledge about its underlying pathophysiology, the development of animal models for BPD has been difficult [60,61]. One approach for the development of appropriate tests has been to model separately a number of its critical behavioral aspects. For example, the most widely used test that has been validated in the context of mania includes psychostimulant-induced hyperactivity [62]. This test was developed on the basis of the observation that psychostimulants, such as amphetamine, induce mania in susceptible individuals and that mood stabilizers can prevent these effects. There have been attempts to model other components of the manic pole of

BPD in mice, such as reward seeking (using the sweet solution preference test), intrusive or aggressive behavior (using the resident–intruder paradigm), and increased vigor and resilience to despair (using a variation of the forced swim test). It has been suggested that these tests could be integrated into a coherent and continuous test battery [60].

Large-scale candidate and genome-wide association studies have generated a rapidly growing list of risk genes for BPD. Despite the uncertainty as to whether, and to what extent, risk variance causes gene dysfunction and whether risk genes are causally linked to behavioral abnormalities in BPD, there is a plethora of mutant rodent strains that have been generated using genetic (e.g., gene transgenic, knockout, or mutation knock-in manipulation) or other biological means (e.g., viral vector-based gene overexpression or knockdown), which show behavioral clusters or activity patterns reminiscent of mood syndromes [63]. These include *mCLOCK* [64], glutamate receptor 6 (*GluR6*)^{-/-} [65], extracellular signal-regulated kinase-1 (*ERK1*)^{-/-} [66], opioid receptor, and glycogen synthase kinase-3 (*GSK-3*)^{-/-} [67]. This so-called reverse translation model animal approach has so far been used to analyze the causal relationship between biological abnormalities resulting from genetic BPD risk variants, early-life environmental factors, and behavioral manifestations of BPD, but it will certainly be essential for the development of true novel drug therapies.

9.4

Translation to Clinics: Limitations and Difficulties

Most of the tests described were developed 30 years ago and have been used since then with little modifications. Because of the failure of virtually all anxiolytic and antidepressant drug development programs during the past decades, the capability of current models to detect new molecules with mechanisms of action different from the prototypical BZs and monoamine-interacting drugs has been repeatedly questioned. Several comprehensive reviews have been published in recent years discussing the pros and cons of each model and proposing guidelines for their improvement, with a strong consensus on the need to better incorporate etiological factors in the design of novel paradigms [33,68,69]. We summarize herein some of the potential solutions for how preclinical research in this area can be improved.

Classical conflict or despair tests, such as the elevated plus maze or forced swimming, have proven to be of limited utility for detecting non-BZ anxiolytic or nonmonoaminergic antidepressant activity, respectively, and should only be employed with this caveat in mind. On the other hand, their throughput is high and they can be used as first-line screening assays when performing selection from large libraries of compounds. As many anxiety and depression tests are highly sensitive to procedural variables and environment factors, the tests should be validated in-house and methods fully reported. Integrating results from multiple preclinical tests and developing tests that assess multiple symptom-related

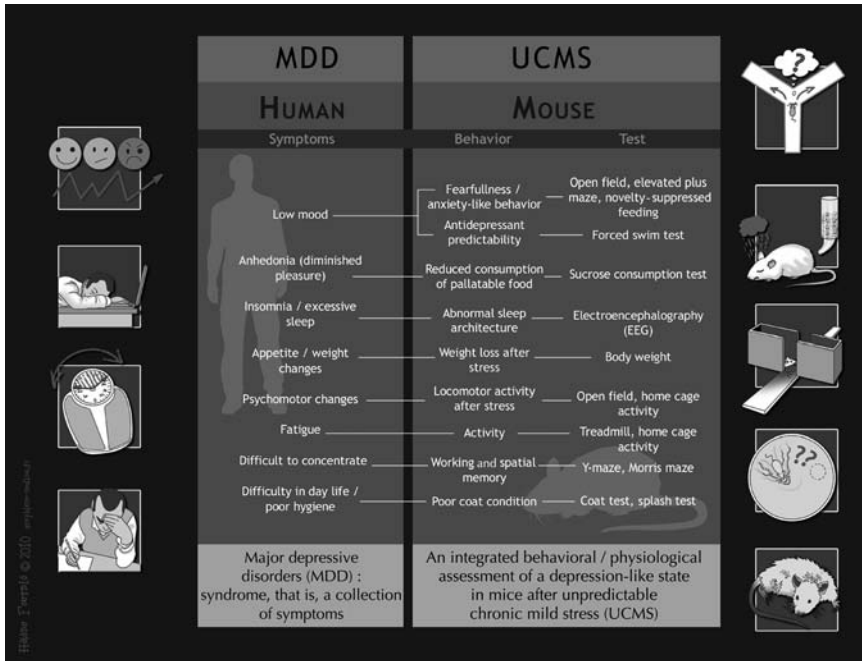


Figure 9.3 State markers of major depressive disorder and their mouse analogs in the chronic mild stress model.

behaviors (e.g., MDTB, chronic mild stress) (Figure 9.3) will increase confidence in the potential of a novel target. Anxiety tests and models that are based on abnormal learning and cognitive processes in anxiety disorders (e.g., fear generalization and impaired fear extinction) may offer a tractable and translatable approach. Anxiety or depression models that generate excessive levels of anxiety- or despair-like behavior (e.g., by chronic stress exposure, gene mutation, or selected breeding) may be closer to the clinical situation and thereby have better predictive power than simple assays. Because rodent strains vary greatly in anxiety- or depression-like behavior and response to known drugs, genetic background must be a principal consideration in choosing subjects and interpreting results.

Clearly, the growing burden of anxiety and mood disorders requires better treatment options. Future research advances in both biological information and behavioral methodology will be essential for the rapid development of true novel drug treatments for relieving anxiety and mood symptoms.

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