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Review

What's wrong with my mouse model? Advances and strategies in animal modeling of anxiety and depression

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Abstract

Stress plays a key role in pathogenesis of anxiety and depression. Animal models of these disorders are widely used in behavioral neuroscience to explore stress-evoked brain abnormalities, screen anxiolytic/antidepressant drugs and establish behavioral phenotypes of gene-targeted or transgenic animals. Here we discuss the current situation with these experimental models, and critically evaluate the state of the art in this field. Noting a deficit of fresh ideas and especially new paradigms for animal anxiety and depression models, we review existing challenges and outline important directions for further research in this field.

Keywords: Stress; Anxiety; Depression; Experimental (animal) models and tests; Exploration; Obsessive–compulsive behaviors; Stereotypies; Paradigm shifts

Contents

1. Introduction

Stress underlies anxiety and affective disorders [8,12,102,130,151,152,366]. Human anxiety is associated with excessive worries, and its formalized disorders include generalized anxiety, panic, social and separation anxiety, agoraphobia, post-traumatic stress and obsessive–compulsive (OCD) disorders [202,261,331,354]. Unipolar and bipolar depression constitute another common group of stress disorders with a wide spectrum of syndromes (depressed mood, anhedonia, sleep disturbances, negative thinking and suicidality) and unclear pathogenesis [79,165,368].

In her recent book "What's wrong with my mouse?" Crawley [73] comprehensively evaluated current animal models of anxiety and depression, which have also been discussed in detail in several recent reviews [20,78,79,195,257,337]. While researchers' confidence in these models varies [e.g., 69,338], they are indispensable for screening psychotropic drugs [109,288,346,368], phenotyping gene-targeted and transgenic

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Table 1
A brief history of animal models/tests and paradigm shifts in anxiety (A) and depression (D) research

Years	Field	Models	Paradigm shift
1930s	A	Hall introduced the open field test [136,137]	Objective measure of animal exploration
1950s	A	Berlyne studied of arousal and curiosity in the rat [32,33]	Curiosity theory of exploration
	A	Montgomery published his pioneering works on animal fear and exploration [243,244]	Motivation conflict theory
1960–1970s	A, D	Numerous pharmacological studies in animals (see [239] for details)	Drug-induced anxiety and depression
	D	Harlow developed separation depression theory [140,141] based on studies in non-human primates	Separation depression
	A	Geller and Vogel introduced conflict-based anxiety tests (review: [160,269,356,357]	Conflict models
	D	Seligman introduced the learned helpless model (review: [363]	Learned depression
	A, D	Accumulating reports focused on behavioral strain differences in exploration and activity (anxiety) and depression-like behaviors	Genetic models
	A	Gray developed behavioral inhibition theory [130,131]	Behavioral inhibition
1980s	D	Willner introduced a new model of animal depression based on reduced hedonic behaviors [363–365]	Anhedonic depression
	D	Porsolt used the forced swim test to show that "despair" can be used to assess antidepressant drugs in animals [282–284]	Despair depression
	A	Crawley introduced the light–dark anxiety test (review: [73])	
	A	File introduced the social interaction model of anxiety (review: [104])	Social anxiety
	A	Handley and Mittani [142] used the elevated plus maze (based on Montgomery's findings) to assess anxiety	
	D	Steru et al. [333] introduced the tail suspension test	
1990–2000s	A, D	Kudryavtseva et al. introduced the social defeat (confrontation) model [209–211]	Transitions from anxiety to depression
	D	Olfactobulbectomy model of depression (review: [198])	Lesioned limbic system as a model of depression
	A, D	Numerous mutant mice reported to have anxiety and depression phenotypes [240]	Gene-specific models
	A	Belzung and colleagues introduced free-exploratory paradigm [30,31]	Free (vs. forced) exploration
	A, D	Creation of gene-targeted mice with altered anxiety and depression phenotypes	
	A	Golani and his colleagues developed multiple "kinematics" behavioral indices sensitive to anxiety	Animal anxiety translated into kinematics
	A	Chapouthier and colleagues developed models of animal stress-evoked motorisensory disintegration [217,218]	Motorisensory models

animals [73,108,345], testing neurobiological hypotheses and finding candidate genes for human disorders [65,119,195,280].

Traditional anxiety models include exploration-based paradigms (e.g., open field, holeboard, elevated plus maze, light–dark box, mirrored chamber, social interaction tests) and conditioned or unconditioned threat responses [1,105,108,134, 160,205,264,298]; Table 1. Popular experimental models of depression include "despair" paradigms (such as Porsolt's forced swim, tail suspension tests and learned helplessness), as well as olfactory bulbectomy, maternal/social deprivation and "anhedonic" chronic mild stress [15,64,80–82,90,226,232, 233,363–365]. With the growing popularity of these tests in neuroscience, drug development and genetics research [76,103,115,207,240,251,314,316,345,348], it is timely to re-examine the current situation with animal models of anxiety and depression. The present review aims to discuss further challenges and outline strategic perspectives of research in this field.

2. State of the art: moving from Hall and Montgomery

In general, there are as many methodological and conceptual problems with animal experimental models of stress, as exist detailed protocols and useful recommendations on how to overcome these problems [20,75–77,116,297,330]. Certain features of human behavior and cognition cannot be fully reproduced in animals, which complicates potential translation of human symptoms into animal tests [78,207,368]. Animal paradigms often fail to reproduce complex multi-syndromal human disorders, show unwanted selectivity to particular neuromediatory systems [29,80,108,190], may constrain species-specific behaviors [362] or have questionable ability to detect novel compounds with unknown mechanism(s) of action [81,180,269,368].

Other problems with these models include conflicting time-course results [112], questionable reliability [5], over-sensitivity to external (environmental, epigenetic) or internal (genetic) factors, as well as their variable reproducibility even within the same laboratory [19,70,80,81,280,359,360]. Animal modeling may face "bottleneck" problems, as some aspects of brain pathogenesis may be limited to specific stages of development, or to a narrow range of cells in the brain [166]. There is an unclear link between behaviors and brain events [36], and some disorders have a considerable latent period between the onset and first clinical manifestations. There are also objective difficulties with mimicking (at a behavioral phenocopy level) versus modeling a "true" psychiatric state, and targeting behavioral versus physiological and cognitive components of pathogene-

sis [27,36,76,107,307,345]. Thus, understanding the potential benefits and weaknesses of the existing animal models is crucial for obtaining valid animal data to parallel and/or complement the available clinical findings [188,190].

Although we have witnessed marked progress in the field, thoughtful reviews (e.g., [79–81,90,107,112,127,157,195, 206,271,349]) seem to outnumber reports on new models or major modifications of the existing paradigms. This situation is clearly of concern, and raises questions as to how far we have progressed from the early works of Hall [136,137], Montgomery [243,244], Berlyne [32,33] and Gray [130,131] in advancing theoretical bases of animal behavior and its models. Examining the history of animal models (Table 1), one can see relatively few paradigm shifts in this field over the last few decades, as the growing globalization of scientific research makes it "safer" to publish data from well-accepted tests rather than to modify them or invent new methods. Clearly slowing further progress, this situation emphasizes the need to develop paradigms based on new principles, theories and approaches (see further).

3. Current discussions

Several important discussions in the field will be commented on here. First, while some authors stress stringent standardization of experimental conditions [350,358,359], others question its utility [369,370]. Although substantial inter-laboratory variability has been reported in the literature [70,358,360], other studies have shown that some behaviors and their patterning either remain stable in varying environmental conditions [184,359,367], or vary despite standardization [222]. Important factors that cannot be standardized are the individuality of animals and the experimenters [70,215]. Subsequent discussion in Science revealed other factors (such as diet, social status, handling/animal care procedures) that may confound data of Crabbe et al. [70] on marked behavioral variations in mice tested in different laboratories. Finally, although small within- and between-subject variability is usually desirable, there are cases when the study of the variability of the model system could lead to a better understanding of the phenomenon in question [119,206]. Thus, standardization alone may not solve the problem. Indeed, how do we know that the procedures selected as "reference" are the best, and cannot be improved further? For example, if one had implemented 100% standardization in 1930s, we would still use Hall's 3-min open field test and focus on defecation and urination.

Moreover, we mostly still test animals in standard (relatively small) boxes, a long-considered confound of their species-specific behavioral responses [362]. While not every laboratory is prepared to use playing fields or parking lots as their models (as in the latter study), it may indeed be necessary to assess what animals might do when their behavior is not constrained by a test apparatus [362]. Therefore, while controlling pre-testing and testing procedures [169], there would seem to be possible improvements to the existing protocols [86,115,143,159,255,256,266,285]—which may eventually also lead to new paradigms. As intra-laboratory reproducibility is core for experimental modeling [237,238], one may see constant development of specially-selected animal models and their modifications as an important part of behavioral neuroscience, and the diversity of models as a driving force of further progress of animal experimentation.

The selection of endpoints for behavioral research is another important topic for discussion [54,57,299–301]. Do we need more or less measures? While some authors favor ethologization [62,298,303], others prefer to measure a few "good" indices. An unfortunate trend currently observed in papers published in some top biomedical journals is that their behavioral data are limited to only few measures, in striking contrast with other types of data, such as microarray charts and molecular biology data (see, however, [220,276] as examples how such data may complement and parallel behavioral findings). With the growing number of published papers with limited behavioral data, it is critical to understand that behavioral endpoints can well be as important as genetic or neurochemical markers of anxiety and depression.

A related question is whether to model complex behavioral syndromes, or target simple behavioral (also neurophysiological, biochemical, anatomical or endocrine) "symptoms". Described in the literature as the endophenotyping approach [127], reducing complex behaviors into components may enhance clarity in animal experimentation. However, once a specific response is at least partially understood, it can be embedded into a complex phenotype to analyze overlap with other domains and responses, some of which may or may not be directly related to anxiety or depression (see further). Therefore, a behavioral dissection should include the following steps: identify endophenotypes → analyse their neurobiological rationale → assess interplay with other responses (domains) → re-construct their collective contribution to a complex pathogenesis → identify new endophenotypes. It is only by studying interactions between different domains that we can better understand complex brain disorders such as anxiety and depression. Again, not the number of phenotypes, but their interplay merits special attention. From this point of view, the current standards of 6+ rodent phenotypes to make a high-impact paper can be justly questioned [127].

Terminology is also key, since (as R. Feinman once noted) agreeing on terms solves 50% of a scientific problem. The discussion about "models" versus "tests" is not new [157,345,349], and scientists should recognize the difference between evoking pathology and the measuring of responses. For example, some authors indicate that open field is not a test, and tail suspension is not a model, whereas others use both terms as synonyms, sometimes also calling them "paradigms". In our opinion, models or tests are not "hereditary titles", and only the researcher can assign their roles to specific procedures. Indeed, the forced swim test does not induce depression (and therefore is not a model of depression-like behavior), but can detect antidepressant effects (as a test), while after repeated testing it may induce depression, and therefore become a model. The open field induces anxiety (as a model), is sensitive to anxiolytic drugs (as a test/screen) and detects antidepressant effects in depressed animals by reversing hypoactivity (again used as a test). The sensory contact paradigm leads to both anxiety and depression, and therefore may be the model of both disorders, and also a test (to screen for anxiolytic

or antidepressant drugs); see [37,209–211] for details. Thus, we may use procedures as models or tests, but should explain clearly in which capacity the procedure is used, to avoid misinterpreting the data or confusing the literature. In addition, there should also be a clear distinction between models or tests relevant to the risk factors, and the models relevant to pathogenesis per se; also see [5] for discussion on trait versus state models, and [97,98] on animal models of human behaviors versus psychopathologies.

Do models always work? Clearly not, and while the lack of positive results may be due to poor models of restricted validity [349], in some cases it is a lack of necessary skills (see [97,98] for discussion) that can lead to model's poor reproducibility, accompanied by misinterpretation of its rationale and endpoints. For example, the simplest behavior – animal immobility – has 19 other interpretations in addition to anxiogenic freezing, including those of a clear opposite nature [180]. Likewise, the lack of social contacts is not always a sign of animal depression [37], but may also be relevant to other traits, such as anxiety [182] or autism [248–250]. Therefore, caution is needed before concluding that a model does not work or has limited validity. As this requires more efforts to interpret (in Lorentz's terms) animal behaviors, we should neither anthropomorpize [73,157] nor simplify them [190], fitting into the "expected" schemes.

4. Deeper into anxiety and depression

Importantly, anxiety and depression, as both dramatic and debilitating multi-facetic psychiatric illnesses, demonstrate marked overlap and co-occurrence [113,260–263,331]. Many of their symptoms are similar, and mild anxiety can be difficult to distinguish from mild depression. Depression is common in anxiety patients and anxiety is often reported in depressed patients, both being predictors of poor outcome [260,263]. Over the past several decades, there has been intensive study of a variety of neurobiological mechanisms that underlie depression and anxiety, which has suggested they share common genetic determinants but partly different environmental triggers [155,199,200,305]. The fact that the symptoms of anxiety and depression may respond to the same treatments support the possibility of a common neurobiological dysfunction, though the neurobiological mechanisms of anxiety and depression have yet to be fully elucidated [188,263].

As experimental models of brain disorders imply some degree of specificity, an important question is whether we always need models to be specific. While some models lack specificity (e.g., failing to discriminate between anxiolytics and antidepressants [46,307]), others do not reflect some clinically important aspects (such as comorbidity [76]) because of their specificity. Kalueff and Nutt [188] have discussed genetic and pharmacological animal data, noting overlap between anxiety and depression—the pathogenic feature that needs to be addressed in animal models. Thus, in addition to "pure" anxiety and depression paradigms, there should be models that assess common pathogenic mechanisms, risk factors and comorbidity associated with these disorders (Table 2). Along this line, Hinojosa et al. [155] have recently re-evaluated an interesting genetic rat model that appears to be relevant to both anxiety and depression. Likewise, inbred Fawn-Hooded rats display increased depression-like behaviors [292], reduced social interaction (suggesting a possible model for social anxiety) [193], higher anxiety in novelty tests, and enhanced plasma corticosterone responses after exposure to stressors, such as open field or forced swim tests [138,139]. Many of these changes, which also are found together with other features of anxiety and depression such as changes in sleep, food intake and other neuroendocrine responses to anxiogenic drugs that involve the amygdala, corticotropin releasing hormone, and catecholamines are responsive in this rat strain to antidepressant and anti-bipolar drug such as lithium, with additional evidence implicating serotonergic system involvement [18,361]. Collectively, these findings suggest that the Fawn-Hooded rat strain represents a particularly interesting genetic model of several overlapping disorders, including depression, generalized anxiety disorder, social anxiety disorder and possibly bipolar disorder.

Transitions between anxiety and depression are well-known in clinical literature, and a better understanding of this pathogenetic aspect and its neural underpinning is also necessary. Kudryavtseva has made an important step in this direction by developing a mouse model that targets the dynamics of both disorders [209–211]. In this model, 10-day social defeats produces anxiety, whereas chronic social stress for 20 days leads to depression [16,17]. Today this paradigm is widely used in various laboratories worldwide, yielding interesting findings about different aspects of brain pathogenesis [37,342]. Using a similar strategy to model the dynamics of stress pathogenesis, another group [234] treated rats with intranasal $ZnSO_4$, demonstrating increased anxiety after 1-week anosmia, and pronounced depression following 4-week anosmia, again showing that new models may be created based on anxiety–depression transitions. Anxiogenic-like effects of 1-week anosmia were similar to that of 10 mg/kg pentylenetetrazole (a reference anxiogenic drug), and included reduced horizontal and vertical activity, accompanied by higher frequency of grooming bouts. The depression seen in rats after 3–4-week anosmia was similar to that generally seen in olfactobulbectomized animals [179,234].

In addition to modeling anxiety-depressive pathogenesis, paradigms may enable dissection of different anxiety or depression spectrum disorders (Fig. 1). For example, unipolar depression is more common [71] than is bipolar illness, which is characterized by alternating periods of manic (positive) and depressive (negative) episodes. While the existing animal depression models focus predominantly on depressive-like symptoms, the emerging clinical significance of bipolar disorders (affecting approximately 1% of the global population) implies the need to develop reliable models of manic states, and of the cyclic nature of bipolar illness [94,145,253]. For instance, ouabain injected into the rat brain induces hyper- and hypoactivity [88] resembling manic and depressive phases of bipolar depression (also see [94,287] for discussion of putative genetic and pharmacogenetic models of bipolar depression). Thus, conceptualizing parallels between human and animal data on different types of anxiety or depression may be a useful source of new or new-subgroup models, as specific as agitated depression with

Table 2
Strategies for experimental modeling of anxiety and depression

I. Modeling different subtypes of anxiety and depression
- Modeling better defined disorders (e.g., social anxiety, unipolar depression) vs. generalized anxiety or depression
- Modeling state vs. trait disorders (e.g., chronic vs. acute anxiety)
- Modeling different subtypes of specific disorders within a spectrum (e.g., bipolar vs. unipolar depression; post-traumatic stress vs. generalized anxiety)
- Exploring non-linear relationships between stress and anxiety or depression (e.g., "paradoxical" anxiolytic-like effects of mild arousal: [302])

II. Modeling anxiety–depression pathogenesis
- Modeling transitions between anxiety and depression
- Modeling comorbidity vs. anxious depression or anxiety with depressive components
- Modeling-specific behaviors whose psychiatric interpretations and classifications are still unclear (e.g., OCD-associated hoarding, stereotypies [228]; separation anxiety/depression [202]; "sickness behavior" [83])
- Targeting cognitive processes in animal models of anxiety and depression
- Analysis of genetic, epigenetic and gene × environment interactions
- Models exploring behavioral and cognitive therapy [68] approaches to anxiety, depression and related disorders (e.g., [274])
- Modeling psychosomatic aspects of anxiety and depression pathogenesis

III. Using a wider spectrum of methods and measures
- Extensive use of in vivo brain imaging in animals (including non-invasive neuroimaging, such as small-animal single-photon emission tomography)
- Use of non-exploratory behaviors (grooming, vocalization, defense) to assess animal anxiety and depression [40,41,93,372]
- Use of sophisticated methods of automated registration of animal behaviors [146]
- Detailed dissection of animal activity parameters (kinematics, velocity, turning characteristics) [52,111,174–178] that may be sensitive to anxiety or depression
- Use of non-behavioral "physiological" indices (hyperthermia, bradycardia) of anxiety (especially panic-like states) or depression, especially using minimally invasive techniques (e.g., telemetry) [48,268,275,310]
- Assessment of other biological (biochemical, immunological or endocrinological) markers of anxiety and depression to parallel behavioral observations
- Analysis of gene activity correlates of anxiety or depression (e.g., c-fos expression: [327], brain microarray data [61,220])
- Testing a wide spectrum of pharmacological agents from different classes vs. predominantly benzodiazepines psychopharmacology for anxiety [298] or serotonin reuptake inhibitors for depression [81]
- Use of virtual reality tests in anxiety and depression research (based on recently established rodent sensitivity to virtual environments [156])

IV. Modeling other disorders that are related to anxiety and depression
- Models beyond anxiety and depression (i.e., comorbidity with other psychiatric disorders, such as eating, sleep disorders, cognitive impairments, autism-like social behavior impairments)
- Modeling schizoaffective pathogenesis (targeting pathogenetic link between mood and psychotic disorders) and personality disorders (Fig. 1)
- Analysis of stress-evoked behavioral stereotypies related to anxiety, depression and OCSD
- Modeling-specific symptoms that were not targeted previously (e.g., anxiety-evoked motor/vestibular deficits, self-destructive behavior, manic component of bipolar disorder)

V. Use of "hybrid" models or tests
- Use of model-model, model-test and test-test "hybrid" paradigms for simultaneous profiling of anxiety and depression, and their subtypes
- Use of "hybrid" models to simultaneously assess anxiety/depression and other domains or disorders (e.g., cognitive functions, balancing problems)

VI. Studying other model objects and systems
- Use of cell cultures in animal behavioral models (e.g., neurotransplantation, including cross-species: [230])
- Use of in vitro models of anxiety/depression neurophysiology and neurochemistry (in a way similar to in vitro models of epilepsy; e.g., [279])
- Extensive use of primate models in translational research [24,25]
- Use of invertebrate (*Drosophila*, *C. elegans*), lower vertebrate (zebrafish) and other models (birds) to mimic brain mechanisms that may be relevant to anxiety and depression, or have rodent/human phenotype analogs of clinical/model interest
- Computerized emulation (in silico models) of animal behavior in different experimental paradigms (e.g., [311])
- Computerized modeling of genetic and pharmacogenetic (drug-behavior, gene-behavior, gene-drug-behavior) interactions in animal models
- Building "bioneuronetwork" models underlying animal anxiety and depression-like phenotypes (e.g., [66,254]), powered by bioinformatics analyses [201] and extensive publicly available on-line searchable databases [240,251]; see [355] for review

hypo-serotonin function, anxiety disorder subtypes with mood dysfunctions, and single-gene syndromes of wider interest.

Quantitative trait loci (QTL) [28,110,114] are becoming a useful tool to dissect animal anxiety and depression behaviors, and may sometimes yield interesting data on their neurobiology and genetics. For example, Yoshikawa et al. [373] linked animal depressive-like behavior in the despair tests to QTL on chromosomes 8 and 11, encoding α1, α6 and γ2 subunits of GABA-A receptors, known to be involved in both anxiety and depression in animals and humans [188]. Another elegant study started from QTLs implicated in mouse behavioral inhibition responses as targets for family-based association methods in humans, thereby linking anxiety-related personality trait to specific genes [328]. Other approaches include the use of selectively bred [95,125,264] mutant or transgenic animals with altered anxiety and depression phenotypes [37,240,339,340]. While genetic models based on synergetic alterations in these domains focus on common genetic mechanisms of these disorders, models that show reciprocal alterations (e.g., elevated anxiety and reduced depression in 5-HT1a receptor knockout mice [149]) enable a better dissection of disorder-specific neurobiological mechanisms.

In addition, numerous studies have analysed home-cage measures relevant to anxiety or depression [92], the effects of test batteries [236,278,300], inter-group variability [215], neo- and post-natal environmental influences [55,169,171,308]; as well as age [147], inter-species genetics [195] and sex differences [73,242,291,344] of these responses. Analysis of some visceral behaviors (such as grooming) may also be used to assess anxiety and depression [28,179,189,192,289,308]. Grooming, common in laboratory rodents, represents the longest (after sleep) activity in their repertoire, and is frequently seen during behavioral testing, sometimes being the most robust behavioral response [179,186,289]. Anxiety generally increases frequency of grooming bouts and impairs their sequential organization, whereas depression may lead to prolonged stereotypic bouts [189,192,179]. Numerous endo- and exogenous factors involved in anxiety and depression, such as neuromediators, hormones, drugs and genetic manipulations are known to influence grooming, making its analysis a useful tool in behavioral neuroscience of anxiety and depression [186,192].

Finally, as cognitive processes play a key role in clinical anxiety and depression [187,188], experimental models that simultaneously assess these domains [38,101,181,252,265,323] become important (see further).

5. Expanding beyond anxiety and depression: focus on obsessions, compulsions and impulsivity

The emerging link between clinical anxiety, depression and some other brain disorders prompts the need in animal models that specifically address this aspect of pathogenesis, and extend beyond anxiety and depression domains [112]. For example, given high comorbidity of anxiety and autism, the possibility to study this phenomenon in animal models of autism based on social interaction is particularly interesting [74,167,249,250,293,312], and is also relevant to social anxiety component of this illness [164]. Thus, it should not be surprising that across many inbred mouse strains, the strain suggested to be a genetic model of autism is BALB/c [51] known for its high baseline anxiety and emotional responsivity [251]. Moreover, genetic models like this may be highly relevant to modeling the interplay of autism spectrum disorders with anxiety, whose frequent comorbidity and common genetic determinants have long been recognized [153,212,241]. Again, not only social investigation-related behaviors, but also some other parameters (such as self- and hetero-grooming and barbering, sensitive to social and anxiety-related domains [185,186]) should be examined in detail (see, for example, [51] for discussion of poor barbering in BALB/c mice and its potential relation to autism-related traits).

OCD is an anxiety disorder that afflicts 2–3% of the population with recurrent intrusive thoughts and ritualized actions, causing significant stress and impairment [10]. Several disorders have been conceptualized as obsessive–compulsive spectrum disorders (OCSD) because they share obsessive–compulsive features, and similar patient characteristics, course, comorbidity, neurobiology, genetics and treatment responsivity [26,89,150]. Three distinct clusters have been found in OCSD, including "reward deficiency" (trichotillomania, Tourette's syndrome, pathological gambling, and hypersexual disorder), "impulsivity" (compulsive shopping, kleptomania, eating disorders, self-injury, and intermittent explosive disorder), and "somatic" (body dysmorphic disorder and hypochondriasis) [227]. Collectively, this implies further complexity and multi-dimensionality of these disorders, and reveals how closely related disorders can result in differential symptom presentation, stressing the need for more nuanced animal models of human behaviors.

OCSD are characterized by numerous anxiety-related phenotypes, cognitive and behavioral inhibition deficits, and frequent comorbidity with depression, implying that anxiety and depression may be an integral factor of obsessive–compulsive pathogenesis [6,59,106,148]. Thus, a new class of animal models related to anxiety/depression and obsessive–compulsive domains, could be developed based on phenomenological, ethological, physiological and pharmacogenetic paradigms of animal OCD-like behaviors [4,63,117,132,173,223,231]. Models of specific neuropsychologic aspects of OCD (reward, adjunctive and displacement behavior, perseveration, indecisiveness, spontaneous stereotypy) are important to unify the diverse behavioral manifestations of this disorder [206]. For example, primates reared in captivity often display stereotypic behaviors (reminiscent of human obsessive–compulsive or post-traumatic symptoms), which respond to selective serotonin reuptake inhibitors (SSRIs), paralleling research on human anxiety symptoms [161]. Many other behavioral and genetic models with both anxiety- and OCSD-related rationale have been recently reported in the literature [135,225,336]. Some OCD-related behaviors, such as repetitive grooming and barbering, have already been robustly modeled in animals [35,154]. Both domains not only share construct validity (as behavioral stereotypies) but also show striking analogy to several human OCD-like behaviors, such as compulsive washing and trichotillomania, which is conceptualized as an OCSD [154]. The sensitivity of these animal behaviors to anxiety and anxiotropic drugs [189,192] implies that targeting such behaviors would be of particular interest for modeling OCSD/anxiety pathogenesis.

Recent data suggest that it may be possible to model impulsivity, a key feature of many OCSDs [224]. A recent study reported that dopamine transporter heterozygous (+/−) mutant mice show normal activity and less anxiety, but are strikingly different in their novelty seeking from both wild type and hyperactive anxious knockout mice [281]. While novelty-seeking may be an anxiolytic-like response, mounting data indicates that it is a core personality aspect in many conditions, including impulsivity [203]. Therefore, models assessing behaviors related to anxiety and impulsivity may advance our understanding of animal performance in novelty tests, and enable parallels with similar human behavioral disorders.

As already mentioned, there is a strong similarity between OCD and Tourette's syndrome in terms of clinical symptoms, comorbidity and genetic determinants [58,128,148,277,294]. Tourette's syndrome is a neuropsychiatric movement disorder with unclear pathogenesis, frequently comorbid with obsessions, compulsions, hyperactivity, distractibility, impulsivity, anxiety and depression [58,227,320,326]. Given well-known

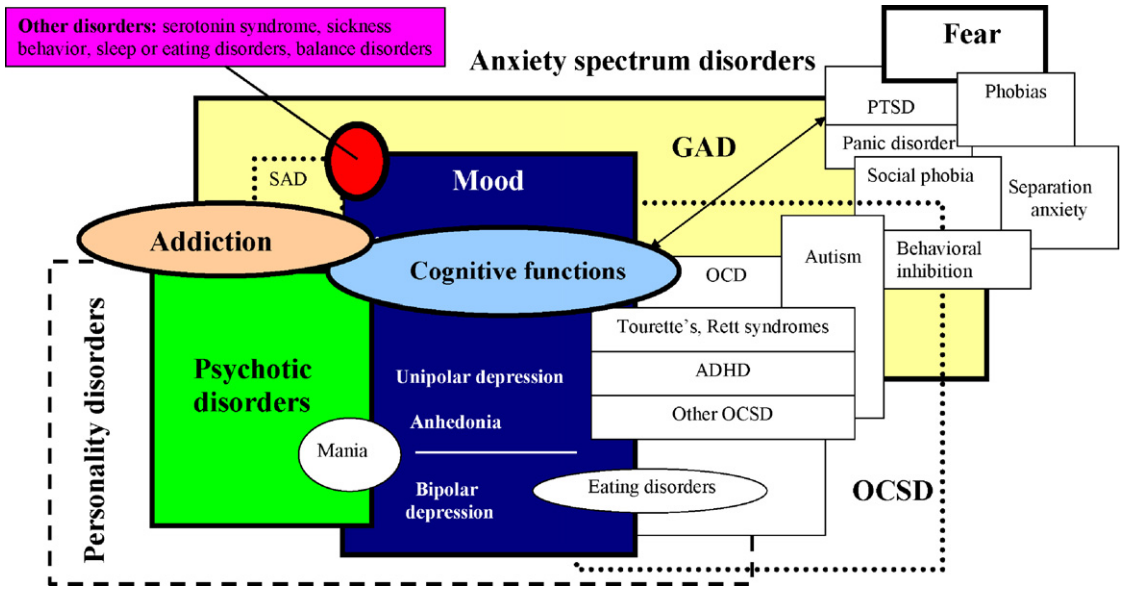

Fig. 1. Pathogenic clusters related to stress, anxiety and depression (according to [180,190,195,331], representing targets for animal modeling (see Table 2 for summary of strategies). GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; SAD, subsyndrome GAD; ADHD, attention deficit/hyperactivity disorder; OCD, obsessive–compulsive disorder; OCSD, obsessive–compulsive spectrum disorders.

Tourette's syndrome exacerbation after psychosocial stressors, and higher risks of anxiety and mood disorders in patients with Tourette's syndrome and Tourette + OCD [214,295,335], the development of animal models of Tourette's syndrome (Fig. 1) and especially those with Tourette/OCD profiles [3], including recent transgenic mice [56,259], offers new insights into the role of Tourette's syndrome/OCD-like disorders in the pathogenesis of anxiety and depression. Again, grooming-related behaviors may be especially useful for modeling Tourette's syndrome and the anxiety-Tourette interplay, given grooming stress-sensitivity (discussed above) and its regulation by basal ganglia [35]—the brain structures directly involved in Tourette's pathogenesis [2,335]. Well-known cephalocaudal progression of grooming resembles that of Tourette's symptoms, further strengthening parallels between human Tourette's syndrome and animal grooming [3].

Another related disorder is Rett syndrome, whose symptoms include motor and learning deficits, autism and tremor [246,247,319]. Recently, a genetic mouse model of this disorder has been developed, resembling many clinical symptoms of this disorder and displaying abnormal social interaction and higher anxiety [245,319]. The association between anxiety, autism- and a Rett-like phenotype in this mouse model is particularly interesting, since it parallels clinical data on common anxiety, depression and autism in patients with Rett syndrome [246,296,313].

The role of aggression in modulating stress-related responses should also be considered when developing new experimental models of stress. Arakawa [11] has recently demonstrated changes in exploratory behaviors associated with rat social dominance, while Shibata et al. [321] reported the effects of antidepressants on aggressive (muricidal) behavior in olfactobulbectomized rats. These and other like approaches (e.g., [37,162,211,336]) may lead to interesting models relevant to the interplay between human anxiety, depression and aggressiveness that has long been recognized in clinical literature [150,304,332,351].

Attention deficit hyperactivity disorder (ADHD) is another heterogeneous disorder with unknown etiology and frequent comorbidity with anxiety and depression [39,315]. Relevant to OCSD, aggression and impulsivity, this disorder is the most commonly diagnosed childhood psychiatric disorder [324], also co-occurring with autism, Tourette's syndrome and other OCSDs [50,334]. Thus, animal models of ADHD (Fig. 1) may help better our understanding of the etiology of this disorder and its pathogenetic link to anxiety, depression and cognitive dysfunctions. For example, the coloboma mice (recently suggested as a genetic model of ADHD, based on their profound hyperactivity, disturbed latent inhibition and higher impulsivity in the delayed reinforcement task) also display higher responsivity to stressors, such as saline injections [53], implying possible alterations in their anxiety domain. Forebrain-specific trkB-receptor knockout mice showed unaltered forced swim, elevated zero maze, or novel object test responses, but produced a stereotyped hyperlocomotion, reduced exploration, and impulsive reactions to novel stimuli, similar to ADHD [374]. Another example is a transgenic mouse bearing a human mutant thyroid receptor TRbeta1 [324], which displays inattention, hyperactivity, and impulsivity. Since thyroid hormones and their receptors are involved in the occurrence of anxiety and affective disorders [67], this and other like models may foster animal modeling of ADHD- and anxiety/depression-related pathogenesis (Fig. 1).

Further insights may also come from modeling the link between anxiety and depression with eating disorders, sleep disorders, personality disorders and psychoses, whose growing significance and co-morbidity is recognized in clinical literature [85,121,133,163,196]. For example, recent clinical and genetic data question traditional "Kraepelinian dichotomy", sug-

gesting that there may not be a clear biological distinction between schizophrenia and bipolar disorders [71]. Therefore, animal models relevant to bipolar disorders (such as those discussed above) may, in fact, be used for a more far-reaching purpose—modeling both mood and psychotic features of schizoaffective pathogenesis. Interestingly, some animal behaviors may also be relevant to psychotic-like states and anxiety. For example, injections of the anxiogenic drug picrotoxin into basolateral amygdala (implicated in both anxiety and schizophrenia) produced neural circuitry abnormalities similar to those seen in psychotic patients [34]. Paterlini et al. [276] have recently reported a genetic model of schizophrenia-related phenotypes in mice, also displaying reduced open field exploration (suggesting altered anxiety responses). Audet et al. [13,14] showed that repeated subchronic phencyclidine elicits psychotic-like behaviors in rats (manifest in hyperlocomotion and excessive grooming) and anxiogenic-like reduction of exploration. Moreover, disturbed grooming sequencing, also seen in this model, is consistent with its sensitivity to anxiety [189,192], further supporting its validity for modeling or mimicking mechanisms relevant to psychotic and emotional disorders.

Interestingly, Garner et al. [118] noted that stereotypic behaviors of caged parrots resemble stereotypies commonly seen in patients with autism, Tourette's syndrome, mental retardation and unmedicated chronic schizophrenia. Given likely involvement of basal ganglia in these recurrent perseverative behaviors [118], animal models based on basal ganglia motor system dysfunctions (such as aberrant grooming and stereotypies) may be relevant to modeling a cluster of brain disorders (Tourette's syndrome, psychoses, OCSD) already mentioned here in relation to anxiety and depression. Some evidence suggests that behavioral stereotypies in animals and humans are provoked by early stressors, and may represent "scars" of previous conflicts and frustrations [371]. Indeed, stereotypies are common in cages animals (that can serve as a simple model for such studies) and effectively reduced by improved environment [370], collectively supporting their utility as additional indirect indices of animal stress resposivity, potentially relevant to anxiety and depression domains.

6. Modeling other relevant brain disorders

In addition to modeling emotional and behavioral disorders, there are several other related psychiatric conditions that merit further scrutiny. For example, anxiety is often seen in serotonin syndrome [122,168], and may be an interesting target for experimental modeling. Serotonin syndrome is a serious disorder, commonly observed in humans with increased serotonergic tone due to antidepressant therapy [96,120,122]. A similar phenomenon has been reported in animals with pharmacologically elevated serotonin levels [45,170,172]. Notably, stress and anxiety may mimic some serotonin syndrome-like behaviors in animals, including Straub tail [197], hyperthermia [270], freezing (resembling ataxia and low/flat body posture), and backward gait (especially in anxious strains; see [73,180,190] for details). Stress-related hormones (such as thyrotropin releasing hormone [286]) also produce behaviors similar to those evoked by serotonergic drugs. Recent data on the attenuation of animal serotonin-like behaviors by anxiolytic drugs [258] support the link between anxiety and serotonin syndrome, implying the need for new models targeting these disorders. From this point of view, animals that display both anxiety and hypersensitivity to serotonergic drugs (such as serotonin transporter or 5-HT1a receptor knockout mice [183,240]) deserve special attention. Given the growing practice to treat anxiety by serotonergic antidepressants [235], and the risks of serotonin syndrome-related anxiety provoked by such therapy (leading to further clinical complications), animal models relevant to anxiety, depression and serotonin syndrome, may be of high clinical significance.

Several lines of evidence suggest that addiction represents an important domain implicated in pathogenesis of anxiety and depression. The use and abuse of substances (alcohol, nicotine, marijuana, inhalants, and other drugs) are commonly comorbid with human depression and anxiety [7,22,87]. They also share some common genetic determinants [99,123,124], generally paralleling the available animal data [25,219]. Self-medication of anxiety with ethanol or drugs provokes mood and substance use disorders, distress and suicidal behavior [44]. Finally, addictive behaviors predict individual vulnerability to anxiety and depression, and vise versa [144,375]. Therefore, animal models that target addictive behaviors may also enable a better focus on the integration of addictive, emotional and affective mechanisms of brain pathogenesis. For example, concurrent assessment of novelty responses and conditioned place preference for cocaine in mice may be useful for examining drug addiction with respect to anxiety-like behavior [49,322]. Genetic models based on animals with simultaneously altered addictive, anxious or depressive phenotypes [124,272,273,292,309,310], enable further understanding of the genetic mechanisms underlying the interplay between addiction, anxiety and depression.

Among recent developments in stress neurobiology, the concept of cytokine-mediated "sickness behavior" [9,23,83,84] is particularly attractive in regard to experimental modeling of anxiety and depression, both known to be associated with cytokine disregulation [60,84,91,216,290,343]. Animal data generally parallel these clinical findings, and show anxiogenic-like hypolocomotion, social deficits, and anhedonic depression provoked by pro-inflammatory cytokines [9,208,325]. In both animals and humans, sickness behavior was reversed by antidepressant treatment [9,290,343]; antidepressants are also reported to elevate anti-inflammatory cytokines in mice [208]. Likewise, mouse sickness behavior was predictably influenced by genetic manipulations altering the expression of cytokines or their receptors (review: [9,325]). Taken together, these data suggest that experimental models affecting the cytokine levels in animals and assessing their sickness behavior may be relevant to targeting specific "immunogenic" forms of anxiety and depression such as the 'PANDAS' (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) form of OCD [329].

Finally, the emerging pathogenetic link between anxiety, depression and vestibular/balancing disorders [21,43,100,267] prompts the need for new models targeting stress-evoked

motorisensory deficits. Several models exploring the sensitivity of animal balancing to anxiolytic and antidepressant drugs, and simultaneously assessing anxiety and anxiety-evoked motorisensory deficits [191,217,218,306,352] have been reported in the literature. Taken together, these findings confirm that a detailed analysis of motorisensory integration may be used to study anxiety and depression and their link to deficits in animal or human motor-sensory functions.

7. "Hybridizing" animal models

In addition to targeting specific domains, some models can simultaneously be relevant to several disorders, or their subtypes. Conceptualized as "hybrid models" [180], these models are particularly interesting from the animal modeling point of view. For example, the forced swim paradigm is a test of depression, but can also induce post-swim anxiety (serving as its model). Despite early claims of specificity to depression, this paradigm may also be used as a test of anxiety, due to sensitivity to some anxiolytic drugs [188], and possible anxiety-related (exploratory/escape-searching?) rationale [264]. In line with this, the Suok ropewalking test is a hybrid model of anxiety and balancing disorders [191]. Marble-burying is an anxiety-sensitive test, but responds to antidepressants [90] and has recently been used to assess compulsive-like stereotypic behaviors based on initial exploratory responses, turned into inappropriate repetition [229].

Likewise, holeboard test head dipping (nose poking) is traditionally used as a measure of anxiety (exploration [204]), but may also have compulsive rationale, resembling compulsive checking in OCD patients. Chou-Green et al. [63] used a modified (single-hole) holeboard to demonstrate perseverative head dipping in 5-HT2c receptor knockout mice. Similar compulsive head dipping (accompanied by other like responses, such as stereotypic locomotion and excessive self-aggressive grooming) has been also shown in rats following chronic lesions of median raphe nucleus [158].

The novelty-suppressed feeding test may be another example of "hybrid" tests. Anxiety in this test is assessed by measuring the latency to eat familiar food in a novel environment, and is predictably reduced by anxiolytic drugs [126]. In addition to being a test of anxiety, this model is highly sensitive to chronic (but not acute) antidepressants, suggesting its utility in dissecting between chronic versus acute effects of antidepressant treatments [126].

Finally, since cognitive mechanisms play a key role in stress pathogenesis [101,187,188,264,347], an in-depth analysis of memory in animal models of anxiety and depression may also be necessary. In addition to habituation in different paradigms [42,221], other studies have successfully used the elevated T-maze [129,353] and 3-D maze [98] for simultaneous profiling of anxiety, learning and memory. Likewise, the Morris water maze (known as a hippocampal memory paradigm) has been recently used as the forced swim test to assess depression-like behavioral despair [317,318]. Spontaneous alternation represents an important feature of rodent behavior, relevant to both cognitive functions (memory) and exploration [341,344]. Therefore, animal models based on alternation in Y- or T-mazes can be used to assess anxiety and spatial memory in rodents [73], representing yet another "hybrid" model simultaneously targeting different behavioral domains. Interestingly, rodent alternation has been recently used to assess OCD-like phenotypes [341,344], implying even greater potential of alternation-based tests in behavioral research. These and other examples strongly support the advantages (time-saving, focus on novel pathogenic phenomena, and minimization of test batteries effects) of a wider use of the "hybridization" strategy (Table 2) in behavioral neuroscience.

8. Concluding remarks: reinforcing the "mouse psychiatry"

The 1973 Nobel Prize to von Frisch, Lorentz, and Tinbergen marked a major success of behavioral analysis, and we should continue work in this direction, promoting the ideas of in-depth behavioral dissection of complex phenotypes and translating animal data into clinical research. While some authors recommend concentrating on a few models with high face and construct validity, care should be taken to heed famous warning [194] that the dangers are not in working with models, but in working with too few, and those too much alike, and in belittling the efforts to work with anything else. Today, 30 years later, we face the same challenge, with paradigms based on new principles necessary to prevent stagnation in the field.

Clearly, today's biological psychiatry needs new models of symptom formation, and a new language of description [36,195]. Current formal psychiatric approaches are compromised by a perhaps "artificial" heterogeneity, with insufficient appreciation of the commonalities of emotional, personality, behavioral, and addictive disorders [85,206,213]. Therefore, further innovation in animal models based on the current spectrum-oriented psychiatric theories is crucial in behavioral research of anxiety and depression. These may also relate to genetic linkage and association studies that are beginning to challenge even long-established Kraepelinian boundaries between psychiatric concepts as different as schizophrenia and depression/bipolar disorders [72].

Potential strategies for the development of new animal paradigms are summarized in Table 2. They include modeling different subtypes of anxiety and depression, their common pathogenesis, and the use of a wider spectrum of parameters, techniques and model objects. With psychiatric nomenclature and diagnostic criteria subject to constant modifications and reconsiderations [213,331], we may also benefit from targeting a wider cluster of related behavioral phenomena (e.g., OCSDs, addiction), expanding models beyond traditional "anxiety" and "depression" domains, and using "hybrid" models and tests. Together, these approaches will allow a better focus on the neurobiology of stress, enabling further integrative modeling of mood, behavioral and personality disorders consistent with recent trends and paradigmal shifts in modern psychiatry [195,213].

Importantly, we need new models not for the sake of modeling itself. While clever combinations of the existing models and their sophistication [46,47,307] may serve present needs, one of

the main reasons to invest time and efforts into new models of anxiety and depression is the possibility to discover new agents and, more importantly, new classes of psychotropic drugs, the need for which has long been recognized [316,368]. Another reason is that it will increase our understanding of pathogenesis of anxiety, depression and even psychotic and brain immune and other neurologic disorders, and the long-sought potential links between this broad sprecturm of neuropsychiatric disorders and other brain illnesses.

As a practical solution, the neuroscientific community should encourage researchers to introduce principally new models and bestow a higher priority for publishing their innovative research. We should encourage balanced and coherent research based on multi-disciplinary approaches using both single- and complex multi-domain models to explore the gap and overlap between distinct psychiatric illnesses. Finally, in addition to training in psychiatry and basic neuroscience [166], extensive professional training in neuroethology is crucial to ensure that scientists correctly build new models, diligently and critically evaluate animal responses, and avoid searching (despite all twists of scientific fashion [36]) for simple answers at the expense of complex behavioral phenotypes. Only in so doing, may we expect further advances in the neurobiology of anxiety, depression and other neuropsychiatric disorders.

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