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GENETIC DISORDERS (JF CUBELLS AND EB BINDER, SECTION EDITORS)

Animal Models of Stress Vulnerability and Resilience in Translational Research

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Abstract Stress has been identified as a key risk factor for a multitude of human pathologies. However, stress by itself is often not sufficient to induce a disease, as a large contribution comes from an individual's genetic background. Therefore, many stress models have been created to investigate this so-called gene–environment interaction for different diseases. Recently, evidence has been accumulating to indicate that not only the exposure to stress, but also the vulnerability to such an exposure can have a significant impact on the development of disease. Herein we review recent animal models of stress vulnerability and resilience, with special attention devoted to the readout parameters and the potential for translatability of the results.

Keywords Animals · Animal models · Stress · Stress vulnerability · Stress resilience · Translational research · Risk · Risk factors · Gene–environment interaction · Environment · Readouts · Validity · Social stress · Breeding lines · Subpopulations · KO · Knockout · Mismatch · Plasticity · Programming · Depression · Transgenic

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Introduction

Stress can be defined as the subjective state an individual experiences when being exposed to an actual or potential adverse situation. Stress therefore always involves a stimulus—the stressor—that is recognized by the brain as a threat to homeostasis and thereby elicits specific response mechanisms. These response mechanisms involve several physiologic systems, most prominently the sympathetic-adrenal-medullary system and the hypothalamic-pituitary-adrenal axis, which collectively mediate the stress response. An adequate response of these systems enables the individual to adapt to the changes in the external or internal environment that were perceived as stressors, and provides the resources to deal with the situation appropriately [1•].

The experience of stress is different for everyone. Every individual will rate stressful situations differently, and the perceived level of stress will vary greatly. This is why stressors are often categorized by their nature and not by their severity. Many authors distinguish between physical stressors (also called reactive, interoceptive, or systemic stressors) (eg, an immune challenge or cold conditions) and neurogenic stressors (also called predictive, exteroceptive, anticipatory, psychogenic, or processive stressors) [2, 3]. Although physical and neurogenic stressors activate different brain circuits, they share one essential feature—the adaptive value of the stress response is especially high for moderate and temporally confined stress exposures but becomes uncertain if stressors are very severe or chronic. In addition, unpredictable stressors seem to be more disease relevant than predictable stressors [4]. Especially in the case of a chronic stress exposure, continuous activation of stress response systems can lead to a maladaptive state of the bodily equilibrium called *allostasis* [5, 6].

The long-term physiologic consequences of chronic stress are predominantly viewed as maladaptive, as chronic stress has been repeatedly shown to be a major risk factor for the development of pathologies. Chronic stress exposure can, for example, increase the risk of cardiovascular diseases [7], metabolic disturbances [8], as well as affective disorders [9, 10]. Interestingly, not all stressed individuals develop a disease. The reports of inheritance of disease risks for stress-associated disorders [11] as well as the identification of specific genetic risk factors [12] point to the importance of gene–environment interactions. For example, studies investigating single nucleotide polymorphisms in the context of affective disorders could identify various single genetic risk loci [13–16] or even susceptible haplotypes [17, 18•].

Another recent field of interest focuses on the impact of multiple stress exposures throughout life. Indeed, the laboratory situation of only a single (chronic) stress episode is in real life the exception rather than the rule. Most individuals are exposed to several stress periods at different developmental time windows as well as in adulthood or senescence. Two major hypotheses have been proposed to explain the impact of these stress exposures: the cumulative stress hypothesis (CSH) and the match/mismatch hypothesis (MMH) [19]. The CSH states that stress exposures early in life predispose an individual to be more vulnerable to additional stress exposures later in life. This hypothesis is based on the notion of allostatic load—the wear and tear of the stress response systems over time [6]. Multiple stress exposures therefore would increase the allostatic load and the individual's vulnerability to stress-related disorders. In contrast, the MMH proposes that exposure to adverse situations during developmental periods of high programming sensitivity results in a phenotypic adaptation that is beneficial if the environment remains adverse. This implies that individuals exposed to early-life stress would benefit from a matched environment as adults (a stressful environment) but would be maladapted in a mismatched environment [20]. Intriguingly, there is clear experimental evidence for both hypotheses (eg, [21, 22] for CSH and [23, 24] for MMH), and it was therefore suggested that both hypotheses could apply under specific conditions, mainly dependent on the level of individual programming sensitivity [19]. Regardless of which of these theories turns out to be more valid, they agree on the fact that the interaction of early-life environment, adult environment, and genetic predisposition determines the vulnerability or resilience of an individual to stress-related disorders.

One burgeoning field in stress research is the investigation of stress vulnerability. This combines many of the previously addressed aspects but mainly the fact that individuals show different degrees of adaption. Data from stress vulnerability and resilience studies showed that often, only individuals who are vulnerable to the stressful experience show the characteristic "stressed" phenotype, while resilient individuals remain on par with controls, providing indirect evidence that mostly the vulnerable phenotypes show the molecular alterations important for disease-relevant investigations [25, 26]. This is of special importance for the investigation of stress-related disorders such as depression, in which effect sizes tend to be small and the experimental groups need to be strictly defined to detect effects with a low effect-to-noise ratio. In addition, the focus on the affected subpopulation increases the etiological relevance of such paradigms for translational research. The difficulties involved in modeling phenotypes of stress-related disorders such as depression in rodents are discussed in detail in the next section, but the use of animal models can be of great help. Nevertheless, due to ethical as well as technical reasons, extensive studies on genetic effects, especially regarding the central nervous system, can only be conducted in animals. However, in many studies in the field of stress research, animal models are very simplistic and largely neglect the interplay of genes and environments necessary to explain stress-related disorders. Therefore, the present review focuses on recent animal models specifically designed to distinguish between vulnerable and resilient phenotypes, and the correct use and interpretation of these models.

Tests and Readouts

Before considering the different concepts and models used to investigate individual vulnerability and resilience, it is necessary to reflect briefly on how the phenotypes in these models are measured and quantified. Any model system can only be as good as the readouts and measurements allow, and the perfect disease model will not be very useful if the readouts do not reflect the symptoms of the disease. Therefore, what is needed is a high degree of face validity of the applied tests to make them translatable to the clinical situation [27].

In contrast to other diseases, such as cancer, in which the readouts are rather clear, good behavioral phenotypes in animal models for stress-related psychiatric diseases are sparse. First of all, some aspects of psychiatric diseases are virtually impossible to model in most animals, such as the case of depression, feelings of guilt, or suicidal inclinations. Thus, tests for depression-like behavior are focusing on other parameters, such as loss of enjoyment (anhedonia), loss of motivation, sleep disturbances, anxiety, or cognitive deficits. However, the translatability of some of the applied tests is highly questionable.

A prime example of this is the forced swim test (FST), first developed by Porsolt and colleagues [28], which

measures active (struggling or swimming) and passive (floating) behavior of rats or mice in a beaker filled with water. This test was and still is very popular in depression research because it is relatively easy to perform and has the possibility for high-throughput testing [29]. As an acute dose of most of the currently available antidepressants decreases the time animals spend floating, this passive behavior was interpreted as depression-like behavior. From an anthropomorphic point of view, this is easily conceivable, as a floating rat or mouse gives the impression of "giving up," but how valid and translatable is this test really? While the effects of antidepressants in the FST are observable within minutes after treatment, antidepressant effects in humans with the same drugs take a few weeks of treatment to manifest. It is also well-known that warm water conditions or repeated testing increase the floating time in the FST [30], but few people would argue that, for example, warm water exposure increases depression-like behavior. Floating behavior in an inescapable situation is actually a valid and potentially successful strategy for the animals, as it saves energy resources and can increase the chance of survival. The increased floating time of animals after repeated or prolonged exposure to the FST therefore was interpreted as effects of learning and memory a long time ago [31], and it is astonishing and alarming that even today, some researchers claim that a few minutes of FST exposure could elicit depression in animals [32]. Thus, although the FST is undoubtedly a valid behavioral test whose results can be quite informative, its relation to depression is not as straightforward as interpreted by many authors.

Other often-used tests include the saccharin preference test for anhedonic behavior, sociability tests for antisocial behavior, the elevated plus maze test for anxiety-related behavior, and the Morris water maze for cognition. High-throughput tests are usually less informative and translatable, while tests with a high validity require a lot of time and can only be performed with a limited number of animals. In the often-used saccharin preference test, for example, it must be considered that the choice of two drinking bottles in the home cage does not involve any effort for the animals (but the readout can easily be confounded by differences in anxiety toward novel stimuli or differences in cognitive abilities). A combination of the preference for rewarding stimuli with a specific effort to obtain the reward (eg, a nose poke or lever press in an operant conditioning chamber) would be more informative with regard to depression-like behavior but also a lot more time consuming.

When analyzing the phenotype of animal models, it is therefore crucial to obtain as many different phenotypic readouts as possible, including behavioral, physiologic, neuroendocrine, or molecular parameters. Only in cases in which the observed phenotype of a model is broad and can be detected using different readouts can the model be regarded to have a high validity for a specific disorder and allow for a high degree of translatability (Fig. 1).

Concepts

When modelling gene–environment interaction, different approaches are feasible. One possibility is to modify the genome of animals, resulting in knockout (KO) or transgenic (knock-in) animals specific for selected candidate genes. For this approach, murine models are favored in comparison to other species due to technical advantages. Another possibility is the selection of subpopulations within the whole cohort of animals based on molecular or behavioral parameters, which would also reflect genetically or epigenetically defined populations. Finally, subpopulation selection can be used as a differentiating factor for selective breeding to putatively enhance the differences in the subgroups and isolate the genetic component transferred over the germ line. The following sections provide an overview of the different approaches, including examples of recent studies focusing on stress vulnerability. Therefore, it does not provide and should not be seen as a complete overview of all available models, but rather as an illustration of the concepts, also

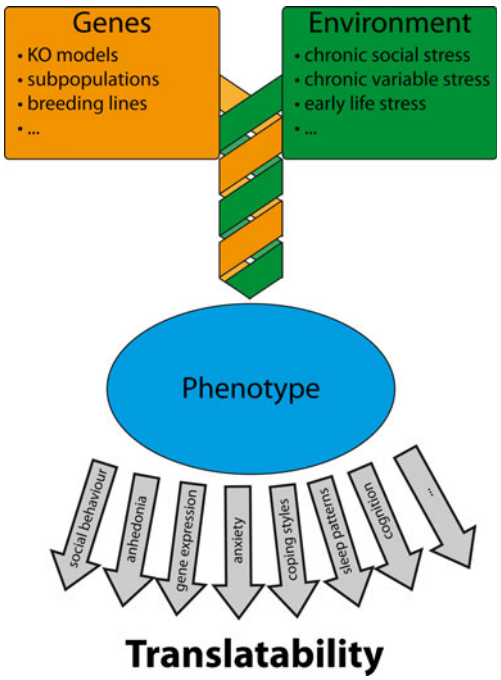

Fig. 1 Strategy for research models with high translational value. Genetic and environmental components are strongly intertwined and the choice and interaction of both components define the resulting phenotype. Good translatability of the results can then be reached by careful investigation of the phenotype. Assessing the phenotype not by a single or few, but by multiple meaningful readout parameters allows the identification of models that strongly fit the human pathologies and in turn greatly increases the chance that the results are translatable back to the human situation. KO, knockout

considering that many widespread models have been reviewed in detail elsewhere (eg, differences in the serotonergic system [33]).

Transgenic Models

With the refinement of techniques for directed genetic mutations or gene targeting, transgenic animal models have become more and more useful for the broad scientific community. In addition, as many transgenic lines are commercially available, research is no longer limited to institutions with specific transgenic facilities. In recent years, various genetic animal lines have been published, highlighting the influence of single genes on stress vulnerability or resilience. Recent studies range from genes known to be involved in the stress response to novel candidate genes. For example, studies from our group with a pituitary-specific KO of the glucocorticoid receptor showed that KO animals were protected from stress-induced elevated basal levels of corticosterone (CORT), but not from a stronger response to acute stress. In addition, stress exposure increased anxiety-like behavior in wild-type (WT), but not in KO animals [34]. Interesting findings were also revealed by studying Fkbp5, a co-chaperone of the glucocorticoid receptor. Here, animals that underwent chronic social defeat showed elevated basal levels of CORT and a stronger response to acute stress, all of which was blocked by a conventional Fkbp5 KO. In addition, KO animals also showed a blunted response to the combined dexamethasone/corticotropin-releasing hormone response test. No gene–environment interaction was found for anxiety-like behavior, but stressed KO animals showed stronger active coping strategies in the FST [35, 36]. Other interesting examples are models with a modulated glutamate transmission, which also has been implicated in depression [37]. VGLUT1 (vesicular glutamate transporter 1) KO mice, for example, show under stress a stronger anhedonic phenotype in the sucrose preference test, more immobility in the FST, and higher ambulation than their WT littermates. Interestingly, anxiety-like behavior as well as object recognition memory were modulated via stress in a genotype-independent manner. It should be noted that the heterozygous KO of VGLUT1 caused a (potentially compensatory) increase in VGLUT2 levels in the frontal cortex and the hippocampus [38]. Deficiency in neural cell adhesion molecule has also been proposed as a genetic model of stress vulnerability. Mice with a forebrain-specific KO of the neural cell adhesion molecule showed more passive coping strategies in the tail suspension test and cognitive impairment in the Morris water maze following a mild stress paradigm that did not produce a phenotype in WT animals. However, the model is very new, and characterization is still ongoing [39].

Using transgenic animal models has different advantages and limitations. These characteristics are mainly dependent on the type of KO. Conventional KO animals can provide information about the general function of the investigated gene, but in most cases, this approach ignores the fact that genes often have different and potentially even opposite functions in different tissues or cell types [40•], which can make interpretation of the results challenging. With the possibility of conditional KO, transgenic animals can reach specificity ranging from selective KO of a gene in the central nervous system or single brain regions to specific cell types. The same holds true for the time frame during which gene expression is modulated. The maturation of the stress system in different stages of development is a vital influence on stress vulnerability in adult life [41], and a KO of a specific gene can have completely different results in different developmental stages. Therefore, the most sophisticated are inducible KO systems that can be activated in a previously determined period [42]. The optimal approach obviously is the combination of conditional and inducible KO; however, the more complex the KO system, the more time consuming the breeding becomes. Thus, when using transgenic models, the planning of experiments should in the best case include consideration of how much specificity, be it spatial or temporal, is needed for each research question. Here it should be noted that improvements in molecular techniques such as viral vectors and optogenetics open up the possibility also to modify genes in a precise and time-specific manner.

Selection of Subpopulations

Another approach is to use the intrinsic heterogeneity of whole populations. Hereby, one or preferably more characteristics are investigated and the animals are grouped into subpopulations based on, for example, performance in a behavioral assay. For example, Bergström and colleagues [43] used chronic mild stress (CMS, also called chronic variable stress) to elicit an anhedonic phenotype in rats. However, not all rats developed this phenotype, so the cohort was split into CMS-resilient and CMS-susceptible animals, allowing the identification of molecular changes in these subphenotypes. One of the main findings was that brain-derived neurotrophic factor (BDNF) levels were higher in the hippocampus of resilient rats [43]. This model was also supplemented with a thorough investigation of genetic differences [44, 45] as well as noninvasive imaging techniques [46]. Despite the extensive investigations, only single potential candidate genes for stress resilience remain, and the authors themselves state that the resilient phenotype is most likely caused by a combination of many different factors. It also has been shown that when animals are selected based upon their CORT levels after recovery from

chronic stress, vulnerable animals show decreased levels of the glutamate receptor 1 (GluR1) and increased levels of GluR2 in the hippocampus [47•]. Interestingly, the opposite situation was found for the nucleus accumbens (NAc) in animals divided by their antisocial behavior following social defeat stress. Here susceptible animals show higher levels of GluR1 and decreased levels of GluR2. In addition, it was shown that GluR2 overexpression was able to reverse the susceptible phenotype; fluoxetine treatment increased GluR2 levels in the NAc; intra-NAc infusions of an AMPA receptor antagonist increased vulnerability; and the NAc of postmortem human depressed brain tissue had lower levels of GluR2, but not GluR1. At least for the NAc, this is probably mediated via ΔFosb and upstream via serum response factor [48, 49•]. Extensive studies in the same model focused mostly on the ventral tegmental area, the NAc, and the periaqueductal gray and showed increased levels of BDNF in the NAc following stress [50]. In addition, it has been shown that only susceptible animals develop an anhedonic phenotype (shown in the sucrose preference test) as well as differences in thermoregulation, while other parameters, such as anxiety-like behavior (elevated plus maze) or elevated CORT levels, were a general effect of the stress exposure. No effects were found in both the FST and the tail suspension test. This study also showed that the increased levels of BDNF in the NAc were only present in the susceptible subgroup, concomitant with increased levels of Akt [51], glycogen synthase kinase-3β, and extracellular signal–regulated kinase (ERK)1/ERK2 (downstream molecules of BDNF signaling). Infusion of recombinant BDNF increased susceptibility, while overexpression of ERK decreased susceptibility [52]. In addition, it has been shown that firing rates of ventral tegmental area dopamine neurons are higher specifically in susceptible animals ex vivo [52], as well as in in vivo studies (can be prevented by chronic antidepressant treatment) [53].

Working with subpopulations offers several benefits but is not without caveats. This approach can lay excellent groundwork for unbiased approaches such as whole-genome, transcriptome, proteome, epigenome, or metabolome studies. Due to the selection of a phenotype in contrast to a single gene, selecting subpopulations can help in identifying novel targets as well as networks. In addition, this approach is an excellent choice when the expected effect sizes are low, as in the field of affective disorders. Therefore, selection of extremes (and thereby omission of "unaffected" individuals) can help detect effects that would otherwise not be detectable due to a low signal-to-noise ratio. Some authors also argue that so-called population validity should be provided. This states that when a human pathology only affects a certain percentage of the population, this should be reflected in the animal model [20]. On the other hand, finding a meaningful parameter of selection can be a challenging task, as described previously. Furthermore, the subpopulations are often characterized after the stress exposure, which prevents clear assertions about the causality of the phenotypic variations on stress vulnerability. In any case, selecting a subpopulation provides a solid basis for gene–environment studies, as responders and nonresponders show distinct enrichment of specific genetic traits [47•], which in turn can then be investigated under different environmental conditions.

Selective Breeding

Another viable approach is the selection of a specific phenotype followed by selective breeding, aiming at enhancing and stabilizing the phenotype. After some generations, the phenotype of the breeding lines diverges and allows further characterization and investigation of the underlying molecular principles or the use as a disease model. For example, rats were bred for high or low levels of exploratory behavior (termed *high responders* and *low responders*). Following 4 weeks of CMS, it was shown that low-responder rats developed anhedonic symptoms (sucrose preference test) much faster and more strongly. The same was true for the novelty-induced suppression of feeding test (anxiety-like behavior), in which stressed low-responder rats took significantly longer times to approach as well as consume the palatable snack [26]. Another example would be animals that were bred for low and high short-term memory. Here it was shown that low short-term memory animals, with increased levels of GluR2, are significantly more affected by stress exposure, which was blocked by treatment with an AMPA receptor potentiator [47•]. Another quite thoroughly characterized model is the stress reactivity mouse line [54]. In this model, animals were bred based on high or low CORT response to an acute stressor. High-response animals show, among other parameters, disturbances in sleep patterns, cognitive deficits, and decreased levels of hippocampal BDNF [55–57].

The same advantages as seen with subpopulation selection apply here as well, with one major addition. As the phenotypic differences here are present before the stress exposure, careful study design allows the identification of causal factors. Nevertheless, selective breeding is a costly and time-consuming approach. In addition, the possibility of a genetic drift—potentially causing a shift in the phenotype—can be minimized but can never be completely prevented. Using selective breeding can be an excellent option to study gene–environment interaction and investigate the underlying genetic predisposition of vulnerability. For example, it has been used successfully to associate a specific sequence deletion in the promoter region of the vasopressin gene with extremes in anxiety behavior [58].

Conclusions

Selecting the right model for a specific research question is not easy. As everyone must deal with limited resources,

these resources should be spent in the most fruitful way. Models of stress vulnerability provide various unique benefits for the study of complex, stress-associated disorders, including 1) high etiologic relevance due to the combination of genes and environmental factors and 2) detection of small effect sizes due to "enrichment" of phenotypic differences.

Different models are best suited for different tasks. The selection of subpopulations or selective breeding studies are especially useful in hypothesis-neutral approaches. As differences in behavior are often based on a plethora of genetic differences, these approaches offer a great opportunity to investigate multiple potentially interacting pathways. Selective breeding has the additional advantage that causality can be more easily investigated. On the other hand, the selected genotypes may represent extremes as well that are not representative of the general population and also might not be easily modulated by environmental or pharmacologic challenges. In contrast, studies modulating single genes seem better suited to explore the effects of a specific gene or pathway.

Independent from the selected model, the phenotype and the readouts need to be clearly defined and relevant for the specific research question. When this basis is provided, it strongly enhances the reproducibility, generalization, and translational power of the experiment. For example, results from murine models will be more relevant for human depression if the phenotype shows different aspects also seen in the human pathology instead of only one characteristic. Interesting readouts here are also parameters that are found to be regulated not only in one specific, but in multiple models. In any case, a combination of genetic and environmental factors will be essential.

All in all, we conclude that stress vulnerability models provide a powerful tool for translational research. However, only with comprehensive characterization of the models and careful selection of meaningful readout parameters is it possible to benefit from these models and support the investigation of stress-related disorders and the understanding of the intricate interplay of the genome and the environment.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. • Joels M, Baram TZ. The neuro-symphony of stress. Nat Rev Neurosci. 2009;10:459–66. *This excellent review illustrates the complexity of the stress response*.
2. Dayas CV, Buller KM, Crane JW, et al. Stressor categorization: acute physical and psychological stressors elicit distinctive recruitment patterns in the amygdala and in medullary noradrenergic cell groups. Eur J Neurosci. 2001;14:1143–52.
3. Pacak K, Palkovits Ms. Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. Endocr Rev. 2001;22:502–48.
4. Koolhaas JM, Bartolomucci A, Buwalda B, et al. Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev. 2011;35:1291–301.
5. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873–904.
6. McEwen BS. Stress, Adaptation, and disease: allostasis and allostatic load. Ann N Y Acad Sci. 1998;840:33–44.
7. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. The Lancet. 2004;364:953–62.
8. Abraham NG, Brunner EJ, Eriksson JW, Robertson RP. Metabolic syndrome: psychosocial, neuroendocrine, and classical risk factors in type 2 diabetes. Ann N Y Acad Sci. 2007;1113:256–75.
9. Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci STKE. 2004;2004:re5.
10. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaption to disease. Nat Rev Neurosci. 2005;6:463–75.
11. Kendler KS. Genetic epidemiology in psychiatry: taking both genes and environment seriously. Arch Gen Psychiatry. 1995;52:895–9.
12. Cichon S, Craddock N, Daly M, et al. Genomewide association studies: history, rationale, and prospects for psychiatric disorders. Am J Psychiatry. 2009;166:540–56.
13. Binder EB, Bradley RG, Liu W, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299:1291–305.
14. Kohli MA, Salyakina D, Pfennig A, et al. Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. Arch Gen Psychiatry. 2010;67:348–59.
15. Green EK, Grozeva D, Jones I, et al. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry. 2010;15:1016–22.
16. McMahon FJ, Akula N, Schulze TG, et al. Meta-analysis of genome-wide association data identifies a risk locus for major mood disorders on 3p21.1. Nat Genet. 2010;42:128–31.
17. Demirkan A, Penninx BWJH, Hek K, et al. Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Mol Psychiatry. 2011;16:773–83.
18. • Ising M, Lucae S, Binder EB, et al. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. Arch Gen Psychiatry. 2009;66:966–75. *This study nicely showed that multiple, not single genes are involved in depression-related characteristics*.
19. Nederhoff E, Schmidt MV. Mismatch or cumulative stress: towards an integrated hypothesis of programming effects. Physiol Behav. 2012; doi:10.1016/j.physbeh.2011.12.008.
20. Schmidt MV. Animal models for depression and the mismatch hypothesis of disease. Psychoneuroendocrinology. 2011;36:330–8.
21. Veenema AH, Reber SO, Selch S, et al. Early life stress enhances the vulnerability to chronic psychosocial stress and experimental colitis in adult mice. Endocrinology. 2008;149:2727–36.
22. Uchida S, Hara K, Kobayashi A, et al. Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. The Journal of Neuroscience. 2010;30:15007–18.

23. Bilbo SD, Yirmiya R, Amat J, et al. Bacterial infection early in life protects against stressor-induced depressive-like symptoms in adult rats. Psychoneuroendocrinology. 2008;33:261–9.
24. Champagne DL, Bagot RC, van Hasselt F, et al. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. Int J Neurosci. 2008;28:6037–45.
25. Schmidt MV, Scharf SH, Sterlemann V, et al. High susceptibility to chronic social stress is associated with a depression-like phenotype. Psychoneuroendocrinology. 2010;35:635–43.
26. Stedenfeld KA, Clinton SM, Kerman IA, et al. Novelty-seeking behavior predicts vulnerability in a rodent model of depression. Physiol Behav. 2011;103:210–6.
27. Pryce CR, Seifritz E. A translational research framework for enhanced validity of mouse models of psychopathological states in depression. Psychoneuroendocrinology. 2011;36:308–29.
28. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977;266:730–2.
29. Pollak DD, Rey CE, Monje FJ. Rodent models in depression research: classical strategies and new directions. Ann Med. 2010;42:252–64.
30. Bächli H, Steiner MA, Habersetzer U, Wotjak CT. Increased water temperature renders single-housed C57BL/6 J mice susceptible to antidepressant treatment in the forced swim test. Behav Brain Res. 2008;187:67–71.
31. West AP. Neurobehavioral studies of forced swimming: the role of learning and memory in the forced swim test. Prog Neuropsychopharmacol Biol Psychiatry. 1990;14:863–77.
32. Sun P, Wang F, Wang L, et al. Increase in cortical pyramidal cell excitability accompanies depression-like behavior in mice: a transcranial magnetic stimulation study. J Neurosci. 2011;31:16464–72.
33. Lesch KP. When the serotonin transporter gene meets adversity: the contribution of animal models to understanding epigenetic mechanisms in affective disorders and resilience. In: Hagan JJ, editor. Molecular and functional models in neuropsychiatry. Berlin Heidelberg: Springer; 2011. p. 251–80.
34. Wagner KV, Wang XD, Liebl C, et al. Pituitary glucocorticoid receptor deletion reduces vulnerability to chronic stress. Psychoneuroendocrinology. 2011;36:579–87.
35. Hartmann J, Wagner KV, Liebl C, et al. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. Neuropharmacology. 2012;62:332–9.
36. O'Leary III JC, Dharia S, Blair LJ, et al. A new anti-depressive strategy for the elderly: ablation of FKBP5/FKBP51. PLoS One. 2011;6:e24840.
37. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropharmacology. 2012;62:63–77.
38. Garcia-Garcia AL, Elizalde N, Matrov D, et al. Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. Biol Psychiatry. 2009;66:275–82.
39. Bisaz R, Sandi C. Vulnerability of conditional NCAM-deficient mice to develop stress-induced behavioral alterations. Stress. 2012; doi:10.3109/10253890.2011.608226.
40. • Refojo D, Schweizer M, Kuehne C, et al. Glutamatergic and dopaminergic neurons mediate anxiogenic and anxiolytic effects of CRHR1. Science. 2011;333:1903–7. *Using state-of-the-art genetic approaches, this paper demonstrated that single genes can have very different functions in different brain regions or cell types*.
41. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10:434–45.
42. Andersson K, Winer L, Mork H, et al. Tamoxifen administration routes and dosage for inducible Cre-mediated gene disruption in mouse hearts. Transgenic Res. 2010;19:715–25.
43. Bergström A, Jayatissa MN, Mork A, Wiborg O. Stress sensitivity and resilience in the chronic mild stress rat model of depression; an in situ hybridization study. Brain Res. 2008;1196:41–52.
44. Bergström A, Jayatissa M, Thykjaer T, Wiborg O. Molecular pathways associated with stress resilience and drug resistance in the chronic mild stress rat model of depression—a gene expression study. J Mol Neurosci. 2007;33:201–15.
45. Christensen T, Bisgaard CF, Wiborg O. Biomarkers of anhedonic-like behavior, antidepressant drug refraction, and stress resilience in a rat model of depression. Neuroscience. 2011;196:66–79.
46. Palacios R, Campo A, Henningsen K, et al. Magnetic resonance imaging and spectroscopy reveal differential hippocampal changes in anhedonic and resilient subtypes of the chronic mild stress rat model. Biol Psychiatry. 2011;70:449–57.
47. • Schmidt MV, Trümbach D, Weber P, et al. Individual stress vulnerability is predicted by short-term memory and AMPA receptor subunit ratio in the hippocampus. J Neurosci. 2010;30:16949–58. *This paper identified a genetic polymorphism in the AMPA subunit GluR1 gene that is causally linked to differences in stress vulnerability.*
48. Vialou V, Maze I, Renthal W, et al. Serum response factor promotes resilience to chronic social stress through the induction of [delta]öFosB. J Neurosci. 2010;30:14585–92.
49. • Vialou V, Robison AJ, LaPlant QC, et al. [Delta]FosB in brain reward circuits mediates resilience to stress and antidepressant responses. Nat Neurosci. 2010;13:745–52. *This study nicely demonstrated the use of multiple techniques and approaches to achieve robust results*.
50. Berton O, McClung CA, DiLeone RJ, et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science. 2006;311:864–8.
51. Krishnan V, Han MH, Mazei-Robison M, et al. AKT Signaling within the ventral tegmental area regulates cellular and behavioral responses to stressful stimuli. Biol Psychiatr. 2008;64:691–700.
52. Krishnan V, Han MH, Graham DL, et al. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell. 2007;131:391–404.
53. Cao JL, Covington HE, Friedman AK, et al. Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. J Neurosci. 2010;30:16453–8.
54. Touma C, Bunck M, Glasl L, et al. Mice selected for high versus low stress reactivity: a new animal model for affective disorders. Psychoneuroendocrinology. 2008;33:839–62.
55. Fenzl T, Touma C, Romanowski C, et al. Sleep disturbances in highly stress reactive mice: modeling endophenotypes of major depression. BMC Neuroscience. 2011;12:29.
56. Knapman A, Heinzmann JM, Holsboer F, et al. Modeling psychotic and cognitive symptoms of affective disorders: disrupted latent inhibition and reversal learning deficits in highly stress reactive mice. Neurobiol Learn Mem. 2010;94:145–52.
57. Knapman A, Heinzmann JM, Hellweg R, et al. Increased stress reactivity is associated with cognitive deficits and decreased hippocampal brain-derived neurotrophic factor in a mouse model of affective disorders. J Psychiatr Res. 2010;44:566–75.
58. Bunck M, Czibere L, Horvath C, et al. A hypomorphic vasopressin allele prevents anxiety-related behavior. PLoS One. 2009;4:e5129.