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Criteria for Validating Mouse Models of Psychiatric Diseases

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Abstract

Animal models of human diseases are in widespread use for biomedical research. Mouse models with a mutation in a single gene or multiple genes are excellent research tools for understanding the role of a specific gene in the etiology of a human genetic disease. Ideally, the mouse phenotypes will recapitulate the human phenotypes exactly. However, exact matches are rare, particularly in mouse models of neuropsychiatric disorders. This article summarizes the current strategies for optimizing the validity of a mouse model of a human brain dysfunction. We address the common question raised by molecular geneticists and clinical researchers in psychiatry, “what is a ‘good enough’ mouse model”?

Keywords

mouse; model; behavior; phenotyping

FUNDAMENTAL CONSIDERATIONS

As molecular geneticists generate mutant models of human genetic diseases, a host of methodological questions arise. What are the criteria necessary to define the model organism? Which assays are most appropriate for phenotyping the disease model? How many tests are necessary, how many replications must be conducted, and which controls are essential? In the case of neuropsychiatric disorders, which behavioral assays are sufficiently analogous to the behavioral symptoms of the human syndrome? This overview discusses the basic concepts inherent in phenotyping animal models of human neuropsychiatric disorders.

Three criteria are commonly used to validate an animal model. (1) *Construct validity* incorporates a conceptual analogy to the cause of the human disease. Mutant mice with a targeted mutation in a gene implicated in a neuropsychiatric disorder have reasonable construct validity for that inactivation or polymorphism of the human gene. Neuroanatomical lesions, prenatal drug exposures, and environmental toxins offer other examples of putative causes of human diseases that can be replicated in animal models. For example, a mouse model of schizophrenia could test the hypothesis that the gene *COMT* confers susceptibility to schizophrenia by knocking out the *COMT* gene in the mouse genome [Babovic et al., 2007; O’Tuathaigh et al., 2007], or could evaluate a knockin of the humanized *DISC1* polymorphism found in some schizophrenic patients [Pletnikov et al., 2008]. (2) *Face validity* incorporates a conceptual analogy to the symptoms of the human disease. Behavioral symptoms, neuroanatomical pathology, neurophysiological responses, and neurochemical abnormalities are examples of disease components or *endophenotypes* that can be modeled in animals. Endophenotypes are single behavioral, anatomical,

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biochemical, and neurophysiological markers for a given disease. The temporal progression of a neurodevelopmental or neurodegenerative disease is approximated in the animal model by repeating assays to generate a longitudinal profile at appropriate ages. For example, autism is diagnosed by three behavioral criteria, in which aberrant reciprocal social interaction is the primary diagnostic symptom. Our automated three chambered social approach task assays aspects of sociability in mice that are most relevant to the first diagnostic symptom of autism, and can be used repeatedly in the same animals for longitudinal analyses of neurodevelopmental models [Moy et al., 2004; Nadler et al., 2004; Crawley, 2007a; Moy et al., 2007; Yang et al., 2007; McFarlane et al., 2008]. (3) *Predictive validity* incorporates specificity of responses to treatments that are effective in the human disease. A specific class of drugs that ameliorates the human symptoms should reverse the traits in the animal model. Classes of drugs that are ineffective in the human syndrome must similarly be ineffective in the animal model. For example, rodent models of depression rely on antidepressant drug reversal of immobility in the tail suspension and Porsolt forced swim tasks, which involve inescapable stressors [Porsolt et al., 1977, 1978a, 1978b; Steru et al., 1985; Detke et al., 1995; Cryan and Mombereau, 2004; Crowley et al., 2005].

Two major goals of animal models are (1) testing hypotheses about the mechanisms underlying the disease, and (2) translational evaluation of pharmacological, behavioral, and other treatments for the disease. The more similarities in construct, face, and predictive validity between the animal model and the human disease, the stronger the model, and the more useful it will be for meeting these two goals. Further criteria include quantitative measures that are amenable to standard statistical analyses, methodologies that can be readily applied by many laboratories, and robust traits that are easily detectable above background variability. More importantly, results will have to be reproducible in replications across cohorts of animals in the same laboratory, and in different laboratories across geographic locations. A highly valid behavioral phenotype of a targeted gene mutation must replicate in three independent cohorts of mice from several generations of the mutant mouse line, and in the same line tested in other laboratories.

FIRST STEPS IN THE BEHAVIORAL PHENOTYPING OF MUTANT MOUSE MODELS

Targeted gene mutation technology has provided an enormous contribution to understanding the role of genes in behavior. Transgenic mice, which may have a new gene added or an existing gene overexpressed, and knockout mice, in which there is a loss of function of a gene through deletion or mutation such that the protein is not correctly synthesized, have been developed for many neurotransmitters, receptors, second messengers, transporters, and transcription factors. Conditional and inducible promoters, knock-ins of humanized gene polymorphisms, and microinjections of viral vectors containing genes and RNA interference sequences into neuroanatomical locations provide further elegant research tools. Results from these various categories of mutant mouse models are leading to a better understanding of the neurological underpinnings of behavior, and the proximal causes of human genetic disorders.

Behavioral, electrophysiological, neuroanatomical, and pathological phenotyping assays, conducted in a rigorous and comprehensive manner, are central to determining the functional outcomes of genetic manipulations in the nervous system. While the present discussions focus on behavioral phenotyping, convergence of findings from multiple disciplines will strengthen the interpretation of analogies to the human disease. There are also other issues that are important to consider about the utility and limitations of mouse models of human genetic disorders. For example, the actions of one gene may be modified

by one or several other genes (epistasis) and the interactions of genes and environment [Rutter et al., 2006].

Evaluation of a new transgenic or knockout mouse starts with simple measures of general health, to rule out any gross abnormalities that might interfere with further behavioral testing [Crawley and Paylor, 1997; Bailey et al., 2006; Crawley et al., 2007]. Poor health is evidenced by labored breathing, blood crusted around the nose, very low body weight, abnormal rectal temperature, hypo-activity in a novel environment, hypersensitivity to handling, low activity in the home cage, absence of nest-building, poor coat appearance such as bald patches or sores, tremors, seizures, circling and/or other easily observed morphological abnormalities. Gross neurological functions are scored in an empty cage environment, including behaviors such as wild-running (general hyperactivity), excessive grooming, excessive freezing, and hunching while walking. Simple tests of neurological reflexes include eye blink, ear twitch, whisker twitch, and the righting reflex. This yes-or-no battery of quick tests can be conducted sequentially in the same mice. Usually the entire set of observational measures can be obtained from a set of 60 or 90 mice in 1 day.

Early detection of a general health issue will allow the investigator to then choose appropriate tasks within the behavioral domain of interest, to avoid confounds created by the physical problem. For example, if the mutant mice show impaired hearing, then choosing a cognitive task such as fear conditioning that contains a tone cue will not be useful. Instead, learning tasks that do not require intact hearing such as the Morris water maze, T-maze, or object recognition will be more appropriate. Rapid observational tests are available to examine each of the sensory modalities of a mutant mouse. Some afford measures of acuity, but most offer only present-or-absent criteria. Vision is assessed with an approaching object, such as a cotton swab, to determine whether the mouse blinks, and whether the mouse investigates or ignores the approaching object. A mouse with normal vision will usually approach the object. Alternatively, movement of the mouse from a brightly lit to a dark area of a cage assesses ability to see levels of illumination. Hearing is assessed simply with the Preyer acoustic startle, the reflexive flinch and eyeblink response to a sudden loud noise such as a hand clap near the ears [Henry and Willott, 1972; Huang et al., 1995]. Alternatively, automated acoustic startle equipment that delivers tones of varying decibel levels is used to score amplitude of whole body flinch and detect threshold levels of hearing [Logue et al., 1997; Paylor and Crawley, 1997; McCaughran et al., 1999; Willott et al., 2003]. Sensitivity to touch is measured by a flinch response to a toe pinch. Pain sensitivity is evaluated using standardized hot plate and tail flick equipment [D'Amour and Smith, 1941; O'Callaghan and Holtzman, 1985; Hole and Tjolsen, 1993; Bannon et al., 1995; King et al., 1997; Malmberg and Bannon, 1999]. Olfaction is measured by latency for the mouse to retrieve food buried 1 cm from the surface of the litter [Nelson et al., 1995; Takeda et al., 2001; Bakker et al., 2002; Luo et al., 2002; Wersinger et al., 2002], or to sniff a novel odor presented in a neutral environment. Alternatively, olfactory habituation/dishabituation task (Fig. 1) provides a more sensitive measure of detection of same and different odors, including social odors [Luo et al., 2002; Wrenn et al., 2003]. Highly sensitive analyses of sensory abilities require neurophysiological recording from the sensory nerve or sensory cortex during presentation of the relevant sensory cues [Erway et al., 1996; Steele and Morris, 1999; Pinto and Enroth-Cugell, 2000; Peachey and Ball, 2003]. Operant chamber tasks in which the trained mouse makes a nose poke response to a specific sensory cue, to obtain a food reinforcer, offer similarly sensitive assays of sensory abilities [Staubli et al., 1985; Eichenbaum et al., 1988; Zhang et al., 1998; Doty et al., 1999].

Automated and observer-scored tests are available to quickly evaluate motor functions of the mutant mice. A 5-min open field test allows a measure of general exploratory locomotion in a novel environment [Schmidt et al., 1982; Van Daal et al., 1987; Hess et al., 1992]. Total

distance and horizontal activity capture major motor deficits. Automated software includes a tentative measure of anxiety-like behavior, amount of time spent in the corners and near the walls, versus ventures out to the center of the open field (Fig. 2). Motor coordination and balance is evaluated by the latency to fall from an accelerating rotorod [Jones and Roberts, 1968; Sango et al., 1995; Sango et al., 1996; Chapillon et al., 1998; Carter et al., 1999; Rustay et al., 2003] (Fig. 3). The hindpaw footprint test detects ataxias, from measures of the stride length and variability [Barlow et al., 1996; Crawley and Paylor, 1997; Carter et al., 1999]. Muscle strength is evaluated using a hanging wire test [Sango et al., 1996].

BEHAVIORAL PHENOTYPING OF COMPLEX TRAITS RELEVANT TO PSYCHIATRIC DISEASES

Assuming that general health, neurological reflexes, sensory abilities, and motor functions are sufficiently normal to avoid confounds, the mutant mice now proceed on to testing for complex behaviors relevant to the human behavioral syndrome. Many behavioral tests are available within each behavioral domain, as described in the extensive behavioral neuroscience literature. Choosing multiple behavioral tests that have different sensory and motor requirements, mediated by different brain regions, may increase the generalization of the results. In addition, choices can be made that avoid sensory or motor abnormalities. For example, in the cognitive domain, some tasks may require a motor ability (e.g. swimming in the Morris water maze) or sensory ability (pain perception in fear conditioning) that is not specific to the domain (learning and memory) targeted by the test. Alternative tests such as T-maze, novel object recognition, and operant chamber tasks will reduce the likelihood of underinterpreting the learning abilities of a mutant strain. Multiple tests for each domain of complex behaviors are illustrated in Table I.

ENDOPHENOTYPES RELEVANT TO PSYCHIATRIC SYNDROMES

How do we model human emotional disorders in mice? On a practical level, it is impossible for researchers to know the true emotional state of a mouse. It is similarly impossible to relate that state directly to the human experience. Aberrant behaviors symptomatic of human mental illnesses may be uniquely human, particularly those that are mediated by brain pathways without homology in rodents, e.g. the expanded prefrontal cortex of the human brain. However, many similarities between human and mouse neuroanatomy, physiology and neurochemistry allow comparisons of some of the behavioral and physiological responses to specific stimuli and events between the two species. If we break down a disease into individual components of the symptoms, causes, and treatment responses, then it may be possible to model components of the human disease in mice, without undue anthropomorphism.

Anxiety-Related Behavioral Tests for Mice

Assays for anxiety-like behaviors in mice are mainly approach–avoidance conflict tests. Mice generally display high levels of exploration of a novel environment, but avoid brightly lit, open spaces. The elevated plus-maze (Fig. 4) and elevated zero maze present the subject mouse with the choice of spending time exploring the open areas of a plus-shaped or circular runway, elevated approximately 1 m from the floor, versus spending time exploring the enclosed arms and arcs of the elevated plus or circle [Handley and Mithani, 1984; Pellow et al., 1985; Lister, 1987; Shepherd et al., 1994; File, 1997; Heisler et al., 1998; Cook et al., 2001; Zorner et al., 2003; Mombereau et al., 2004]. Our light ↔ dark transitions test presents the subject mouse with the choice of exploring both a brightly lit open area and a dark enclosed area of a two-chambered cage [Crawley and Goodwin, 1980; Bailey et al., 2007]. Other anxiety-related tests include marble burying [Broekkamp et al., 1986; Deacon,

2006;Jacobson et al., 2007;Rorick-Kehn et al., 2007;Uday et al., 2007] and shock-probe burying [Sluyter et al., 1996;Sikiric et al., 2001;Degroot and Treit, 2002;Degroot and Nomikos, 2006;Gasparotto et al., 2007], and the Vogel thirsty lick conflict test [Vogel et al., 1971;Johnston and File, 1991]. All display predictive validity, as anxiolytic benzodiazepines shift the conflict towards more exploration of the aversive regions. Drugs working through specific subunit compositions of the GABA_A receptor produce specific anxiolytic effects on these tasks. Sedation appears to be mediated by neurons expressing GABA_A receptors containing the α 1 subunit, whereas anxiolysis is mediated by receptors containing α 2 and/or α 3 [Morris et al., 2006]. New drugs with selective efficacy for receptors containing α 2/ α 3 subunits have been developed and shown to produce anxiolytic effects in the elevated plus maze, fear-potentiated startle tests, punished responding in rats and primates [McKernan et al., 2000;Chilman-Blair et al., 2003;Rowlett et al., 2005]. Mouse models with mutations in various GABA_A subunits have been useful in screening for anxio-selective drugs with minimal sedative properties [Rudolph et al., 1999;Low et al., 2000;Crestani et al., 2001;Morris et al., 2006]. Usually two or three anxiety-related tests are conducted to validate the robustness of the drug response.

Depression-Related Behavioral Tests for Mice

Two assays commonly used to evaluate mouse models of depression are the tail-suspension test and the forced swim test [Porsolt et al., 1978a; Steru et al., 1985; Crowley et al., 2005; Cryan et al., 2005; Petit-Demouliere et al., 2005]. Both the tail suspension and forced swim tests measure the response to an inescapable stressor. For the first few minutes of swimming in a deep cylinder of water, or dangling from a bar on which the tail has been taped, mice will generally struggle to find an escape route. Subsequently, the mouse will stop struggling and float in the water or hang immobile. Time spent immobile is decreased by treatment with an antidepressant drug. These two tests focus on predictive validity only. Attempts to model the prominent anhedonia symptom of depression have employed a sucrose preference test [Cryan and Mombereau, 2004] that incorporates some face validity. Approaches to more comprehensive modeling of chronic social stressors relevant to the causes of depression include the Visible Burrow System [Blanchard et al., 1995]. This labor-intensive and time-consuming model is based on the natural tendency of mature male rodents to establish social hierarchies in the context of resource competition. Four males living in the large complex visible burrow environment will quickly establish a dominance hierarchy, wherein one becomes dominant and initiates frequent attacks towards the three subordinates. Subordinate rats and mice display myriad physiological and behavioral responses which are remarkably similar to stress-related symptoms in humans, such as avoidance, reduced activity, severe weight loss, increases in voluntary ethanol consumption [Blanchard et al., 1995]. This model has been fairly fruitful in advancing current understanding of a wide range of stress-related processes, including the alterations in the vasopressin and corticotrophin releasing factor (CRF) system, the serotonin and dopamine systems [Blanchard et al., 1991; Lucas et al., 2004], the galanin system [Holmes et al., 2003], hippocampal dendritic arborization [McKittrick et al., 2000], reproductive functions [Monder et al., 1994a, 1994b; Hardy et al., 2002], appetitive behaviors and alcohol consumption [Tamashiro et al., 2004; Choi et al., 2006; Tamashiro et al., 2006]. While the visible burrow system (VBS) model has superb face validity and construct validity as a model for stress-induced depression, its predictive validity remains to be determined. Other models for evaluating depressive-like effects in mutant mice include olfactory bulbectomy, learned helplessness, chronic mild stress and drug-withdrawal-induced anhedonia reviewed by Cryan and Mombereau [2004].

Schizophrenia-Related Behavioral Tests for Mice

Some of the symptoms of schizophrenia, such as auditory hallucinations and delusions, have not yet been modeled due to the difficulty of finding a correlate in animals. Deficits in sensory processing have proven more amenable to modeling in mice, including sensorimotor gating, working memory and social recognition. Sensorimotor gating is tested using prepulse inhibition of the startle response. A weak stimulus inhibits the subsequent response to a strong stimulus, if it is presented within 100 msec [Braff and Geyer, 1990; Geyer et al., 1990; Swerdlow et al., 1994; Geyer and Ellenbroek, 2003]. Prepulse inhibition is performed with a set of prepulse tones of increasing decibels preceding a loud acoustic stimulus, or preceding a tactile air puff directed at the eye. One major advantage of prepulse inhibition is that it can be run in various species including mouse, rat, and human with almost identical methods. Social cognition is tested in mice with assays of social interaction that are analogous to human measures of social interaction. A standard approach is to score interactions between a subject mouse and an unfamiliar stranger mouse of the same or different sex and strain, in an open field arena. The stranger mouse can be freely moving [Miyakawa et al., 2003], or contained in an enclosure that allows sniffing but not aggressive behaviors [Shi et al., 2003; Spencer et al., 2005; Sankoorikal et al., 2006]. This can also be done in an apparatus with multiple chambers (Fig. 5), to examine the mouse's preference for a chamber with a novel social partner versus a novel object [Nadler et al., 2004; Crawley et al., 2007; Yang et al., 2007; McFarlane et al., 2008]. Working memory deficits in schizophrenia are modeled with mouse working memory tasks such as the eight arm radial maze [Olton and Papas, 1979; Braida et al., 2004; Horwood et al., 2004], delayed or spontaneous alternation in the T-maze or Y-Maze and delayed matching to place in the Morris water maze [Steele and Morris, 1999; Fernandes et al., 2006; Duffy et al., 2008]. Schizophrenia is a complex disorder with a heterogeneous group of symptoms that present variably across patients. Validity of a mouse model for schizophrenia is greatest when phenotypes relevant to two or more of the symptoms appear.

TEST BATTERIES: HOW MUCH IS ENOUGH?

High-throughput screening is needed at early stages of preclinical drug development, forward genetics mutagenesis approaches, and analyses of large numbers of targeted gene mutation lines in core facilities. If only a small number of rapid behavioral tests can be conducted, which are the optimal choices? We suggest the quick measures of general health and neurological reflexes, to detect gross abnormalities, followed by one or two tests in the behavioral domain of interest. In the anxiety-related domain, the elevated plus maze is a good choice, as it includes within-task controls such as total arm entries to detect potential confounds of sedation and hyperactivity. In the depression-related domain, the tail suspension test works well in mice and is sensitive to chronic treatment with standard antidepressant drugs. In the schizophrenia-related domain, prepulse inhibition is most analogous to a discrete symptom commonly seen in the human disease. Recommendations for specific measures to include in rapid test batteries are available from several expert laboratories [Nolan et al., 2000; McIlwain et al., 2001; Rogers et al., 2001; Voikar et al., 2004; Godinho and Nolan, 2006; Paylor et al., 2006]. All of these tests can usually be conducted in the same mice. A cohort of mutant and control littermates are tested in a sequence that begins with the least stressful quick observational tests, followed by the more stressful complex tasks, e.g. elevated plus maze, prepulse inhibition, tail suspension, fear conditioning, and Morris water maze. Where positive findings are obtained, more in-depth follow-up behavioral tasks can then be pursued.

In some cases, one well-validated behavioral task provides the critical assay to address the investigator's hypothesis. Discovery of circadian rhythm genes illustrates this point. In the

early 1990s, Takahashi and coworkers at Northwestern University initiated a chemical mutagenesis project to discover genes that affect the circadian clock. Circadian wheel-running activity was employed as a single, well-validated, automated assay to screen about 300 mutagen-treated mice. The early detection of one mouse that exhibited a circadian period that was more than an hour longer than normal led to the discovery of the *Clock* gene [Vitaterna et al., 1994]. Follow-up investigations that similarly used the single circadian wheel-running assay subsequently discovered *mPer1* [Sun et al., 1997], *mPer2* [Albrecht et al., 1997], *mPer3* [Takumi et al., 1998], and BMAL1 [Gekakis et al., 1998].

CAVEATS

This brief overview of mouse behavioral phenotyping has alluded to the importance of control experiments for physical and procedural abilities to rule out artifactual explanations of deficits on complex behavioral tasks. Several other methodological issues are essential to consider. Numbers of mice are usually higher for behavioral assays than electrophysiological and neuroanatomical assays, because environmental factors in the home cage, such as dominance hierarchy status and maternal care, will influence behavior differentially across individuals within a treatment group [van Praag et al., 2000; Palanza et al., 2001; Benaroya-Milshtein et al., 2004; Wolfer et al., 2004; Lambert et al., 2005; Lazarov et al., 2005; Tucci et al., 2006; Champagne and Meaney, 2007; D'Andrea et al., 2007]. For most behavioral experiments, Ns of 10–20 per genotype and per sex are commonly used, for example, N =20 +/+ male, N =20 +/- male, N =20 -/- male, N =20 +/+ female, N =20 +/- female and N =20 -/- female. Genotypes need to be represented within each experimental test day, including +/+ and -/- littermates, to ensure that environmental variables in the home cage and during the experiment have equal effects across genotype groups. Background genes inherent in the inbred strain(s) used for the embryonic stem cells, blastulas, and breeding may interact directly or indirectly with the targeted gene of interest. Compendiums of behavioral traits for various inbred strains of mice are available [Lyon et al., 1996; Wehner and Silva, 1996; Banbury-Conference, 1997; Crawley et al., 1997; Jones and Mormede, 1999; Bolivar et al., 2000; Jackson and Abbott, 2000; Joyner, 2000; Cook et al., 2002; Holmes and Hariri, 2003; Bogue and Grubb, 2004], from which to choose the optimal breeding strain. Mixed genetic backgrounds often contribute extra variability to behavioral results. Backcrossing for 10 generations into a pure genetic background will lower the variability and increase the likelihood of detecting a subtle behavioral phenotype. These and other methodological issues are extensively discussed in the mouse behavioral neuroscience literature [Joyner, 2000; Nagy et al., 2002]. Development of collaborations with behavioral neuroscience laboratories may be a useful approach for molecular genetics laboratories to pursue behavioral phenotyping of mouse models of psychiatric disorders.

CONCLUSIONS

While it is premature to recommend a fixed set of “gold standard” behavioral tasks for mouse behavioral phenotyping, recommendations offered in this overview and in its references will serve to start the novice investigator on the right path. A “good enough” mouse model produces corroborative results in at least two tests within the behavioral domain (see Table I), without confounding artifacts as measured in relevant control tasks. Replication of findings in a second cohort of mice, using appropriate statistical analyses, will support the robustness of the mouse model to test hypotheses and development treatments. A more comprehensive review of behavioral assays and how to apply them to mutant mice may be found in source books including “What’s Wrong With My Mouse? Behavioral Phenotyping of Transgenic and Knockout Mice” [Crawley, 2007b], *Current Protocols in Neuroscience*, and in the many excellent review articles cited above.

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References

- Albrecht U, Sun ZS, Eichele G, Lee CC. A differential response of two putative mammalian circadian regulators, *mper1* and *mper2*, to light. *Cell* 1997;91(7):1055–1064. [PubMed: 9428527]
- Babovic D, O’Tuathaigh CM, O’Sullivan GJ, Clifford JJ, Tighe O, Croke DT, Karayiorgou M, Gogos JA, Cotter D, Waddington JL. Exploratory and habituation phenotype of heterozygous and homozygous COMT knockout mice. *Behav Brain Res* 2007;183(2):236–239. [PubMed: 17707921]
- Bailey KR, Rustay NR, Crawley JN. Behavioral phenotyping of transgenic and knockout mice: Practical concerns and potential pitfalls. *ILAR J/Natl Res Coun Instit Lab Anim Resour* 2006;47(2):124–131.
- Bailey KR, Pavlova MN, Rohde AD, Hohmann JG, Crawley JN. Galanin receptor subtype 2 (*GalR2*) null mutant mice display an anxiogenic-like phenotype specific to the elevated plus-maze. *Pharmacol Biochem Behav* 2007;86(1):8–20. [PubMed: 17257664]
- Bakker J, Honda S, Harada N, Balthazart J. The aromatase knock-out mouse provides new evidence that estradiol is required during development in the female for the expression of sociosexual behaviors in adulthood. *J Neurosci* 2002;22(20):9104–9112. [PubMed: 12388618]
- Banbury-Conference. Mutant mice and neuroscience: Recommendations concerning genetic background. Banbury Conference on genetic background in mice. *Neuron* 1997;19(4):755–759. [PubMed: 9354323]
- Bannon AW, Gunther KL, Decker MW. Is epibatidine really analgesic? Dissociation of the activity, temperature, and analgesic effects of (+/-)-epibatidine. *Pharmacol Biochem Behav* 1995;51(4):693–698. [PubMed: 7675845]
- Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, Wynshaw-Boris A. ATM-deficient mice: A paradigm of ataxia telangiectasia. *Cell* 1996;86(1):159–171. [PubMed: 8689683]
- Benaroya-Milshtein N, Hollander N, Apter A, Kukulansky T, Raz N, Wilf A, Yaniv I, Pick CG. Environmental enrichment in mice decreases anxiety, attenuates stress responses and enhances natural killer cell activity. *Eur J Neurosci* 2004;20(5):1341–1347. [PubMed: 15341605]
- Blanchard DC, Cholvanich P, Blanchard RJ, Clow DW, Hammer RP Jr, Rowlett JK, Bardo MT. Serotonin, but not dopamine, metabolites are increased in selected brain regions of subordinate male rats in a colony environment. *Brain Res* 1991;568(1–2):61–66. [PubMed: 1726073]
- Blanchard DC, Spencer RL, Weiss SM, Blanchard RJ, McEwen B, Sakai RR. Visible burrow system as a model of chronic social stress: Behavioral and neuroendocrine correlates. *Psychoneuroendocrinology* 1995;20(2):117–134. [PubMed: 7899533]
- Bogue MA, Grubb SC. The mouse phenome project. *Genetica* 2004;122(1):71–74. [PubMed: 15619963]
- Bolivar V, Cook M, Flaherty L. List of transgenic and knockout mice: Behavioral profiles. *Mamm Genome* 2000;11(4):260–274. [PubMed: 10754101]
- Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. *Arch Gen Psychiatry* 1990;47(2):181–188. [PubMed: 2405807]
- Braida D, Sacerdote P, Panerai AE, Bianchi M, Aloisi AM, Iosue S, Sala M. Cognitive function in young and adult IL (interleukin)-6 deficient mice. *Behav Brain Res* 2004;153(2):423–429. [PubMed: 15265638]
- Broekkamp CL, Rijk HW, Joly-Gelouin D, Lloyd KL. Major tranquilizers can be distinguished from minor tranquilizers on the basis of effects on marble burying and swim-induced grooming in mice. *Eur J Pharmacol* 1986;126(3):223–229. [PubMed: 2875886]
- Carter RJ, Lione LA, Humby T, Mangiarini L, Mahal A, Bates GP, Dunnett SB, Morton AJ. Characterization of progressive motor deficits in mice transgenic for the human Huntington’s disease mutation. *J Neurosci* 1999;19(8):3248–3257. [PubMed: 10191337]

- Champagne FA, Meaney MJ. Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. *Behav Neurosci* 2007;121(6):1353–1363. [PubMed: 18085888]
- Chapillon P, Lalonde R, Jones N, Caston J. Early development of synchronized walking on the rotarod in rats. Effects of training and handling. *Behav Brain Res* 1998;93(1–2):77–81. [PubMed: 9659989]
- Chilman-Blair K, Castaner J, Silvestre J. Ocinaplone. *Drugs Future* 2003;28:115–120.
- Choi DC, Nguyen MM, Tamashiro KL, Ma LY, Sakai RR, Herman JP. Chronic social stress in the visible burrow system modulates stress-related gene expression in the bed nucleus of the stria terminalis. *Physiol Behav* 2006;89(3):301–310. [PubMed: 16949112]
- Cook MN, Williams RW, Flaherty L. Anxiety-related behaviors in the elevated zero-maze are affected by genetic factors and retinal degeneration. *Behav Neurosci* 2001;115(2):468–476. [PubMed: 11345971]
- Cook MN, Bolivar VJ, McFadyen MP, Flaherty L. Behavioral differences among 129 substrains: Implications for knockout and transgenic mice. *Behav Neurosci* 2002;116(4):600–611. [PubMed: 12148927]
- Crawley JN. Mouse behavioral assays relevant to the symptoms of autism. *Brain Pathol (Zurich, Switzerland)* 2007a;17(4):448–459.
- Crawley, JN. What's wrong with my mouse? Behavioral phenotyping of transgenic and knockout mice. Hoboken: John Wiley & Sons, Inc; 2007b.
- Crawley J, Goodwin FK. Preliminary report of a simple animal behavior model for the anxiolytic effects of benzodiazepines. *Pharmacol Biochem Behav* 1980;13(2):167–170. [PubMed: 6106204]
- Crawley JN, Paylor R. A proposed test battery and constellations of specific behavioral paradigms to investigate the behavioral phenotypes of transgenic and knockout mice. *Hormon Behav* 1997;31(3):197–211.
- Crawley JN, Belknap JK, Collins A, Crabbe JC, Frankel W, Henderson N, Hitzemann RJ, Maxson SC, Miner LL, Silva AJ, Wehner JM, Wynshaw-Boris A, Paylor R. Behavioral phenotypes of inbred mouse strains: Implications and recommendations for molecular studies. *Psychopharmacology* 1997;132(2):107–124. [PubMed: 9266608]
- Crawley JN, Chen T, Puri A, Washburn R, Sullivan TL, Hill JM, Young NB, Nadler JJ, Moy SS, Young LJ, Caldwell HK, Young WS. Social approach behaviors in oxytocin knockout mice: Comparison of two independent lines tested in different laboratory environments. *Neuropeptides* 2007;41(3):145–163. [PubMed: 17420046]
- Crestani F, Low K, Keist R, Mandelli M, Mohler H, Rudolph U. Molecular targets for the myorelaxant action of diazepam. *Mol Pharmacol* 2001;59(3):442–445. [PubMed: 11179437]
- Crowley JJ, Blendy JA, Lucki I. Strain-dependent antidepressant-like effects of citalopram in the mouse tail suspension test. *Psychopharmacology* 2005;183(2):257–264. [PubMed: 16220334]
- Cryan JF, Mombereau C. In search of a depressed mouse: Utility of models for studying depression-related behavior in genetically modified mice. *Mol Psychiatry* 2004;9(4):326–357. [PubMed: 14743184]
- Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: Review of pharmacological and genetic studies in mice. *Neurosci Biobehav Rev* 2005;29(4–5):571–625. [PubMed: 15890404]
- D'Amour FE, Smith DL. A method for determining loss of pain sensation. *J Pharmacol Exp Therap* 1941;41:419–424.
- D'Andrea I, Alleva E, Branchi I. Communal nesting, an early social enrichment, affects social competences but not learning and memory abilities at adulthood. *Behav Brain Res* 2007;183(1):60–66. [PubMed: 17624451]
- Deacon RM. Digging and marble burying in mice: Simple methods for in vivo identification of biological impacts. *Nat Protocols* 2006;1(1):122–124.
- Degroot A, Nomikos GG. Genetic deletion of muscarinic M4 receptors is anxiolytic in the shock-probe burying model. *Eur J Pharmacol* 2006;531(1–3):183–186. [PubMed: 16455072]
- Degroot A, Treit D. Dorsal and ventral hippocampal cholinergic systems modulate anxiety in the plus-maze and shock-probe tests. *Brain Res* 2002;949(1–2):60–70. [PubMed: 12213300]

- Detke MJ, Wieland S, Lucki I. Blockade of the antidepressant-like effects of 8-OH-DPAT, buspirone and desipramine in the rat forced swim test by 5HT1A receptor antagonists. *Psychopharmacology* 1995;119(1):47–54. [PubMed: 7675949]
- Doty RL, Bagla R, Kim N. Physostigmine enhances performance on an odor mixture discrimination test. *Physiol Behav* 1999;65(4–5):801–804. [PubMed: 10073483]
- Duffy S, Labrie V, Roder JC. D-serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. *Neuropsychopharmacology* 2008;33(5):1004–1018. [PubMed: 17625504]
- Eichenbaum H, Fagan A, Mathews P, Cohen NJ. Hippocampal system dysfunction and odor discrimination learning in rats: Impairment or facilitation depending on representational demands. *Behav Neurosci* 1988;102(3):331–339. [PubMed: 3395444]
- Erway LC, Shiao YW, Davis RR, Krieg EF. Genetics of age-related hearing loss in mice. III. Susceptibility of inbred and F1 hybrid strains to noise-induced hearing loss. *Hear Res* 1996;93(1–2):181–187. [PubMed: 8735078]
- Fernandes C, Hoyle E, Dempster E, Schalkwyk LC, Collier DA. Performance deficit of alpha7 nicotinic receptor knockout mice in a delayed matching-to-place task suggests a mild impairment of working/episodic-like memory. *Genes Brain Behav* 2006;5(6):433–440. [PubMed: 16923147]
- File SE. Anxiolytic action of a neurokinin1 receptor antagonist in the social interaction test. *Pharmacol Biochem Behav* 1997;58(3):747–752. [PubMed: 9329068]
- Gasparotto OC, Carobrez SG, Bohus BG. Effects of LPS on the behavioural stress response of genetically selected aggressive and nonaggressive wild house mice. *Behav Brain Res* 2007;183(1):52–59. [PubMed: 17618697]
- Gekakis N, Staknis D, Nguyen HB, Davis FC, Wilsbacher LD, King DP, Takahashi JS, Weitz CJ. Role of the CLOCK protein in the mammalian circadian mechanism. *Science (New York, NY)* 1998;280(5369):1564–1569.
- Geyer MA, Ellenbroek B. Animal behavior models of the mechanisms underlying antipsychotic atypicality. *Prog Neuro-psychopharmacol Biol Psychiatry* 2003;27(7):1071–1079.
- Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. *Brain Res Bull* 1990;25(3):485–498. [PubMed: 2292046]
- Godinho SI, Nolan PM. The role of mutagenesis in defining genes in behaviour. *Eur J Hum Genet* 2006;14(6):651–659. [PubMed: 16721401]
- Handley SL, Mithani S. Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behaviour. *Naunyn-Schmiedeberg's Arch Pharmacol* 1984;327(1):1–5.
- Hardy MP, Sottas CM, Ge R, McKittrick CR, Tamashiro KL, McEwen BS, Haider SG, Markham CM, Blanchard RJ, Blanchard DC, Sakai RR. Trends of reproductive hormones in male rats during psychosocial stress: Role of glucocorticoid metabolism in behavioral dominance. *Biol Reprod* 2002;67(6):1750–1755. [PubMed: 12444049]
- Heisler LK, Chu HM, Brennan TJ, Danao JA, Bajwa P, Parsons LH, Tecott LH. Elevated anxiety and antidepressant-like responses in serotonin 5-HT1A receptor mutant mice. *Proc Natl Acad Sci USA* 1998;95(25):15049–15054. [PubMed: 9844013]
- Henry KR, Willott JF. Unilateral inhibition of audiogenic seizures and Preyer reflexes. *Nature* 1972;240(5382):481–482. [PubMed: 4565947]
- Hess EJ, Jinnah HA, Kozak CA, Wilson MC. Spontaneous locomotor hyperactivity in a mouse mutant with a deletion including the Snap gene on chromosome 2. *J Neurosci* 1992;12(7):2865–2874. [PubMed: 1613559]
- Hole K, Tjolsen A. The tail-flick and formalin tests in rodents: Changes in skin temperature as a confounding factor. *Pain* 1993;53(3):247–254. [PubMed: 8351154]
- Holmes A, Hariri AR. The serotonin transporter gene-linked polymorphism and negative emotionality: Placing single gene effects in the context of genetic background and environment. *Genes Brain Behav* 2003;2(6):332–335. [PubMed: 14653304]
- Holmes A, Kinney JW, Wrenn CC, Li Q, Yang RJ, Ma L, Vishwanath J, Saavedra MC, Innerfield CE, Jacoby AS, Shine J, Iismaa TP, Crawley JN. Galanin GAL-R1 receptor null mutant mice display

- increased anxiety-like behavior specific to the elevated plus-maze. *Neuropsychopharmacology* 2003;28(6):1031–1044. [PubMed: 12700679]
- Horwood JM, Ripley TL, Stephens DN. Evidence for disrupted NMDA receptor function in tissue plasminogen activator knockout mice. *Behav Brain Res* 2004;150(1–2):127–138. [PubMed: 15033286]
- Huang JM, Money MK, Berlin CI, Keats BJ. Auditory phenotyping of heterozygous sound-responsive (+/dn) and deafness (dn/dn) mice. *Hear Res* 1995;88(1–2):61–64. [PubMed: 8576004]
- Jackson, I.; Abbott, C. *Mouse genetics and transgenics: A practical approach*. Oxford: Oxford University Press; 2000.
- Jacobson LH, Bettler B, Kaupmann K, Cryan JF. Behavioral evaluation of mice deficient in GABA(B(1)) receptor isoforms in tests of unconditioned anxiety. *Psychopharmacology* 2007;190(4):541–553. [PubMed: 17171558]
- Johnston AL, File SE. Sex differences in animal tests of anxiety. *Physiol Behav* 1991;49(2):245–250. [PubMed: 2062894]
- Jones, B.; Mormede, P. *Neurobehavioral genetics: Methods and applications*. Boca Raton, FL: CRC Press; 1999.
- Jones BJ, Roberts DJ. A rotarod suitable for quantitative measurements of motor incoordination in naive mice. *Naunyn-Schmiedeberg's Archiv Exp Pathol Pharmacol* 1968;259(2):211.
- Joyner, A. *Gene targeting: A practical approach*. Oxford: Oxford University Press; 2000.
- King TE, Joyner RL, Grau JW. Tail-flick test. II. The role of supra-spinal systems and avoidance learning. *Behav Neurosci* 1997;111(4):754–767. [PubMed: 9267652]
- Lambert TJ, Fernandez SM, Frick KM. Different types of environmental enrichment have discrepant effects on spatial memory and synaptophysin levels in female mice. *Neurobiol Learn Memory* 2005;83(3):206–216.
- Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnic Z, Lee VM, Hersh LB, Sapolsky RM, Mirnic K, Sisodia SS. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* 2005;120(5):701–713. [PubMed: 15766532]
- Lister RG. The use of a plus-maze to measure anxiety in the mouse. *Psychopharmacology* 1987;92(2):180–185. [PubMed: 3110839]
- Logue SF, Owen EH, Rasmussen DL, Wehner JM. Assessment of locomotor activity, acoustic and tactile startle, and prepulse inhibition of startle in inbred mouse strains and F1 hybrids: Implications of genetic background for single gene and quantitative trait loci analyses. *Neuroscience* 1997;80(4):1075–1086. [PubMed: 9284061]
- Low K, Crestani F, Keist R, Benke D, Brunig I, Benson JA, Fritschy JM, Rulicke T, Bluethmann H, Mohler H, Rudolph U. Molecular and neuronal substrate for the selective attenuation of anxiety. *Science (New York, NY)* 2000;290(5489):131–134.
- Lucas LR, Celen Z, Tamashiro KL, Blanchard RJ, Blanchard DC, Markham C, Sakai RR, McEwen BS. Repeated exposure to social stress has long-term effects on indirect markers of dopaminergic activity in brain regions associated with motivated behavior. *Neuroscience* 2004;124(2):449–457. [PubMed: 14980394]
- Luo AH, Cannon EH, Wekesa KS, Lyman RF, Vandenberg JG, Anholt RR. Impaired olfactory behavior in mice deficient in the alpha subunit of G(o). *Brain Res* 2002;941(1–2):62–71. [PubMed: 12031548]
- Lyon, M.; Rastan, S.; Brown, SD. *Genetic variants and strains of the laboratory mouse*. New York: Oxford University Press; 1996.
- Malmberg, AB.; Bannan, AW. *Current protocols in neuroscience*. New York: Wiley; 1999. Models of nociception: Hot-plate, tail flick, and formalin tests in rodents; p. 8.9.1-8.9.16.
- McCaughran J Jr, Bell J, Hitzemann R. On the relationships of high-frequency hearing loss and cochlear pathology to the acoustic startle response (ASR) and prepulse inhibition of the ASR in the BXD recombinant inbred series. *Behav Genet* 1999;29(1):21–30. [PubMed: 10371755]
- McFarlane HG, Kusek GK, Yang M, Phoenix JL, Bolivar VJ, Crawley JN. Autism-like behavioral phenotypes in BTBR T +tf/J mice. *Genes Brain Behav* 2008;7(2):152–163. [PubMed: 17559418]
- McIlwain KL, Merriweather MY, Yuva-Paylor LA, Paylor R. The use of behavioral test batteries: Effects of training history. *Physiol Behav* 2001;73(5):705–717. [PubMed: 11566205]

- McKernan RM, Rosahl TW, Reynolds DS, Sur C, Wafford KA, Atack JR, Farrar S, Myers J, Cook G, Ferris P, Garrett L, Bristow L, Marshall G, Macaulay A, Brown N, Howell O, Moore KW, Carling RW, Street LJ, Castro JL, Ragan CI, Dawson GR, Whiting PJ. Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. *Nat Neurosci* 2000;3(6):587–592. [PubMed: 10816315]
- McKittrick CR, Magarinos AM, Blanchard DC, Blanchard RJ, McEwen BS, Sakai RR. Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites. *Synapse (New York, NY)* 2000;36(2):85–94.
- Miyakawa T, Leiter LM, Gerber DJ, Gainetdinov RR, Sotnikova TD, Zeng H, Caron MG, Tonegawa S. Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc Natl Acad Sci USA* 2003;100(15):8987–8992. [PubMed: 12851457]
- Mombereau C, Kaupmann K, Froestl W, Sansig G, van der Putten H, Cryan JF. Genetic and pharmacological evidence of a role for GABA(B) receptors in the modulation of anxiety- and antidepressant-like behavior. *Neuropsychopharmacology* 2004;29(6):1050–1062. [PubMed: 15039762]
- Monder C, Hardy MP, Blanchard RJ, Blanchard DC. Comparative aspects of 11 beta-hydroxysteroid dehydrogenase. Testicular 11 beta-hydroxysteroid dehydrogenase: Development of a model for the mediation of Leydig cell function by corticosteroids. *Steroids* 1994a;59(2):69–73. [PubMed: 8191550]
- Monder C, Sakai RR, Miroff Y, Blanchard DC, Blanchard RJ. Reciprocal changes in plasma corticosterone and testosterone in stressed male rats maintained in a visible burrow system: Evidence for a mediating role of testicular 11 beta-hydroxysteroid dehydrogenase. *Endocrinology* 1994b;134(3):1193–1198. [PubMed: 8119159]
- Morris HV, Dawson GR, Reynolds DS, Atack JR, Stephens DN. Both alpha2 and alpha3 GABAA receptor subtypes mediate the anxiolytic properties of benzodiazepine site ligands in the conditioned emotional response paradigm. *Eur J Neurosci* 2006;23(9):2495–2504. [PubMed: 16706856]
- Moy SS, Nadler JJ, Perez A, Barbaro RP, Johns JM, Magnuson TR, Piven J, Crawley JN. Sociability and preference for social novelty in five inbred strains: An approach to assess autistic-like behavior in mice. *Genes Brain Behav* 2004;3(5):287–302. [PubMed: 15344922]
- Moy SS, Nadler JJ, Young NB, Perez A, Holloway LP, Barbaro RP, Barbaro JR, Wilson LM, Threadgill DW, Lauder JM, Magnuson TR, Crawley JN. Mouse behavioral tasks relevant to autism: Phenotypes of 10 inbred strains. *Behav Brain Res* 2007;176(1):4–20. [PubMed: 16971002]
- Nadler JJ, Moy SS, Dold G, Trang D, Simmons N, Perez A, Young NB, Barbaro RP, Piven J, Magnuson TR, Crawley JN. Automated apparatus for quantitation of social approach behaviors in mice. *Genes Brain Behav* 2004;3(5):303–314. [PubMed: 15344923]
- Nagy, A.; Gertsenstein, M.; Vintersen, K.; Behringer, R. *Manipulating the Mouse Embryo: A Laboratory Manual*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2002.
- Nelson RJ, Demas GE, Huang PL, Fishman MC, Dawson VL, Dawson TM, Snyder SH. Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. *Nature* 1995;378(6555):383–386. [PubMed: 7477374]
- Nolan PM, Peters J, Vizzor L, Strivens M, Washbourne R, Hough T, Wells C, Glenister P, Thornton C, Martin J, Fisher E, Rogers D, Hagan J, Reavill C, Gray I, Wood J, Spurr N, Browne M, Rastan S, Hunter J, Brown SD. Implementation of a large-scale ENU mutagenesis program: Towards increasing the mouse mutant resource. *Mamm Genome* 2000;11(7):500–506. [PubMed: 10886012]
- O'Callaghan JP, Holtzman SG. Quantification of the analgesic activity of narcotic antagonists by a modified hot-plate procedure. *J Pharmacol Exp Therap* 1985;192:497–505.
- Olton DS, Papas BC. Spatial memory and hippocampal function. *Neuropsychologia* 1979;17(6):669–682. [PubMed: 522981]
- O'Tuathaigh CM, Babovic D, O'Meara G, Clifford JJ, Croke DT, Waddington JL. Susceptibility genes for schizophrenia: Characterisation of mutant mouse models at the level of phenotypic behaviour. *Neurosci Biobehav Rev* 2007;31(1):60–78. [PubMed: 16782199]

- Palanza P, Gioiosa L, Parmigiani S. Social stress in mice: Gender differences and effects of estrous cycle and social dominance. *Physiol Behav* 2001;73(3):411–420. [PubMed: 11438369]
- Paylor R, Crawley JN. Inbred strain differences in prepulse inhibition of the mouse startle response. *Psychopharmacology* 1997;132(2):169–180. [PubMed: 9266614]
- Paylor R, Spencer CM, Yuva-Paylor LA, Pieke-Dahl S. The use of behavioral test batteries. II. Effect of test interval. *Physiol Behav* 2006;87(1):95–102. [PubMed: 16197969]
- Peachey NS, Ball SL. Electrophysiological analysis of visual function in mutant mice. *Docum Ophthalmol* 2003;107(1):13–36.
- Pellow S, Chopin P, File SE, Briley M. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J Neurosci Methods* 1985;14(3):149–167. [PubMed: 2864480]
- Petit-Demouliere B, Chenu F, Bourin M. Forced swimming test in mice: A review of antidepressant activity. *Psychopharmacology* 2005;177(3):245–255. [PubMed: 15609067]
- Pinto LH, Enroth-Cugell C. Tests of the mouse visual system. *Mamm Genome* 2000;11(7):531–536. [PubMed: 10886018]
- Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H, Mori S, Moran TH, Ross CA. Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. *Mol Psychiatry* 2008;13(2):173–186. [PubMed: 17848917]
- Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: A primary screening test for antidepressants. *Arch Int Pharmacodyn Ther* 1977;229(2):327–336. [PubMed: 596982]
- Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: A new model sensitive to antidepressant treatments. *Eur J Pharmacol* 1978a;47(4):379–391. [PubMed: 204499]
- Porsolt RD, Bertin A, Jalfre M. “Behavioural despair” in rats and mice: Strain differences and the effects of imipramine. *Eur J Pharmacol* 1978b;51(3):291–294. [PubMed: 568552]
- Rogers DC, Peters J, Martin JE, Ball S, Nicholson SJ, Witherden AS, Hafezparast M, Latcham J, Robinson TL, Quilter CA, Fisher EM. SHIRPA, a protocol for behavioral assessment: Validation for longitudinal study of neurological dysfunction in mice. *Neurosci Lett* 2001;306(1–2):89–92. [PubMed: 11403965]
- Rorick-Kehn LM, Johnson BG, Knitowski KM, Salhoff CR, Witkin JM, Perry KW, Griffey KI, Tizzano JP, Monn JA, McKinzie DL, Schoepp DD. In vivo pharmacological characterization of the structurally novel, potent, selective mGlu2/3 receptor agonist LY404039 in animal models of psychiatric disorders. *Psychopharmacology* 2007;193(1):121–136. [PubMed: 17384937]
- Rowlett JK, Platt DM, Lelas S, Atack JR, Dawson GR. Different GABAA receptor subtypes mediate the anxiolytic, abuse-related, and motor effects of benzodiazepine-like drugs in primates. *Proc Natl Acad Sci USA* 2005;102(3):915–920. [PubMed: 15644443]
- Rudolph U, Crestani F, Benke D, Brunig I, Benson JA, Fritschy JM, Martin JR, Bluethmann H, Mohler H. Benzodiazepine actions mediated by specific gamma-aminobutyric acid(A) receptor subtypes. *Nature* 1999;401(6755):796–800. [PubMed: 10548105]
- Rustay NR, Wahlsten D, Crabbe JC. Influence of task parameters on rotarod performance and sensitivity to ethanol in mice. *Behav Brain Res* 2003;141(2):237–249. [PubMed: 12742261]
- Rutter M, Moffitt TE, Caspi A. Gene-environment interplay and psychopathology: Multiple varieties but real effects. *J Child Psychol Psychiatry Allied Discipl* 2006;47(3–4):226–261.
- Sango K, Yamanaka S, Hoffmann A, Okuda Y, Grinberg A, Westphal H, McDonald MP, Crawley JN, Sandhoff K, Suzuki K, Proia RL. Mouse models of Tay-Sachs and Sandhoff diseases differ in neurologic phenotype and ganglioside metabolism. *Nat Genet* 1995;11(2):170–176. [PubMed: 7550345]
- Sango K, McDonald MP, Crawley JN, Mack ML, Tiffit CJ, Skop E, Starr CM, Hoffmann A, Sandhoff K, Suzuki K, Proia RL. Mice lacking both subunits of lysosomal beta-hexosaminidase display gangliosidosis and mucopolysaccharidosis. *Nat Genet* 1996;14(3):348–352. [PubMed: 8896570]
- Sankoorikal GM, Kaercher KA, Boon CJ, Lee JK, Brodtkin ES. A mouse model system for genetic analysis of sociability: C57BL/6J versus BALB/cJ inbred mouse strains. *Biol Psychiatry* 2006;59(5):415–423. [PubMed: 16199013]
- Schmidt MJ, Sawyer BD, Perry KW, Fuller RW, Foreman MM, Ghetti B. Dopamine deficiency in the weaver mutant mouse. *J Neurosci* 1982;2(3):376–380. [PubMed: 7062116]

- Shepherd JK, Grewal SS, Fletcher A, Bill DJ, Dourish CT. Behavioural and pharmacological characterisation of the elevated “zero-maze” as an animal model of anxiety. *Psychopharmacology* 1994;116(1):56–64. [PubMed: 7862931]
- Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* 2003;23(1):297–302. [PubMed: 12514227]
- Sikiric P, Jelovac N, Jelovac-Gjeldum A, Dodig G, Staresinic M, Anic T, Zoricic I, Ferovic D, Aralica G, Buljat G, Prkacin I, Lovric-Bencic M, Separovic J, Seiwerth S, Rucman R, Petek M, Turkovic B, Ziger T. Anxiolytic effect of BPC-157, a gastric pentadecapeptide: Shock probe/burying test and light/dark test. *Acta Pharmacol Sin* 2001;22(3):225–230. [PubMed: 11742568]
- Sluyter F, Korte SM, Bohus B, Van Oortmerssen GA. Behavioral stress response of genetically selected aggressive and nonaggressive wild house mice in the shock-probe/defensive burying test. *Pharmacol Biochem Behav* 1996;54(1):113–116. [PubMed: 8728547]
- Spencer CM, Alekseyenko O, Serysheva E, Yuva-Paylor LA, Paylor R. Altered anxiety-related and social behaviors in the *Fmr1* knockout mouse model of fragile X syndrome. *Genes Brain Behav* 2005;4(7):420–430. [PubMed: 16176388]
- Staubli U, Ivy G, Lynch G. Hippocampal denervation causes rapid forgetting of olfactory information in rats. *Proc Natl Acad Sci* 1985;81(18):5885–5887. [PubMed: 6592592]
- Steele RJ, Morris RG. Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. *Hippocampus* 1999;9(2):118–136. [PubMed: 10226773]
- Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: A new method for screening antidepressants in mice. *Psychopharmacology* 1985;85(3):367–370. [PubMed: 3923523]
- Sun ZS, Albrecht U, Zhuchenko O, Bailey J, Eichele G, Lee CC. RIGUI, a putative mammalian ortholog of the *Drosophila* period gene. *Cell* 1997;90(6):1003–1011. [PubMed: 9323128]
- Swardlow NR, Zisook D, Taaid N. Seroquel (ICI 204,636) restores prepulse inhibition of acoustic startle in apomorphine-treated rats: Similarities to clozapine. *Psychopharmacology* 1994;114(4):675–678. [PubMed: 7855231]
- Takeda M, Sawano S, Imaizumi M, Fushiki T. Preference for corn oil in olfactory-blocked mice in the conditioned place preference test and the two-bottle choice test. *Life Sci* 2001;69(7):847–854. [PubMed: 11487096]
- Takumi T, Taguchi K, Miyake S, Sakakida Y, Takashima N, Matsubara C, Maebayashi Y, Okumura K, Takekida S, Yamamoto S, Yagita K, Yan L, Young MW, Okamura H. A light-independent oscillatory gene *mPer3* in mouse SCN and OVLT. *EMBO J* 1998;17(16):4753–4759. [PubMed: 9707434]
- Tamashiro KL, Nguyen MM, Fujikawa T, Xu T, Yun Ma L, Woods SC, Sakai RR. Metabolic and endocrine consequences of social stress in a visible burrow system. *Physiol Behav* 2004;80(5):683–693. [PubMed: 14984803]
- Tamashiro KL, Hegeman MA, Sakai RR. Chronic social stress in a changing dietary environment. *Physiol Behav* 2006;89(4):536–542. [PubMed: 16843504]
- Tucci V, Hardy A, Nolan PM. A comparison of physiological and behavioural parameters in C57BL/6J mice undergoing food or water restriction regimes. *Behav Brain Res* 2006;173(1):22–29. [PubMed: 16870275]
- Uday G, Pravinkumar B, Manish W, Sudhir U. LHRH antagonist attenuates the effect of fluoxetine on marble-burying behavior in mice. *Eur J Pharmacol* 2007;563(1–3):155–159. [PubMed: 17368614]
- Van Daal JH, De Kok YJ, Jenks BG, Wendelaar Bonga SE, Van Abeelen JH. A genotype-dependent hippocampal dynorphinergic mechanism controls mouse exploration. *Pharmacol Biochem Behav* 1987;28(4):465–468. [PubMed: 2893387]
- van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. *Nat Rev* 2000;1(3):191–198.
- Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, Dove WF, Pinto LH, Turek FW, Takahashi JS. Mutagenesis and mapping of a mouse gene, *Clock*, essential for circadian behavior. *Science (New York, NY)* 1994;264(5159):719–725.

- Vogel JR, Beer B, Clody DE. A simple and reliable conflict procedure for testing anti-anxiety agents. *Psychopharmacologia* 1971;21(1):1–7. [PubMed: 5105868]
- Voikar V, Vasar E, Rauvala H. Behavioral alterations induced by repeated testing in C57BL/6J and 129S2/Sv mice: Implications for phenotyping screens. *Genes Brain Behav* 2004;3(1):27–38. [PubMed: 14960013]
- Wehner JM, Silva A. Importance of strain differences in evaluations of learning and memory processes in null mutants. *Ment Retard Dev Disabil Res Rev* 1996;2:243–248.
- Wersinger SR, Ginns EI, O’Carroll AM, Lolait SJ, Young WS 3rd. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. *Mol Psychiatry* 2002;7(9):975–984. [PubMed: 12399951]
- Willott JF, Tanner L, O’Steen J, Johnson KR, Bogue MA, Gagnon L. Acoustic startle and prepulse inhibition in 40 inbred strains of mice. *Behav Neurosci* 2003;117(4):716–727. [PubMed: 12931957]
- Wolfer DP, Litvin O, Morf S, Nitsch RM, Lipp HP, Wurbel H. Laboratory animal welfare: Cage enrichment and mouse behaviour. *Nature* 2004;432(7019):821–822. [PubMed: 15602544]
- Wrenn CC, Harris AP, Saavedra MC, Crawley JN. Social transmission of food preference in mice: Methodology and application to galanin-overexpressing transgenic mice. *Behav Neurosci* 2003;117(1):21–31. [PubMed: 12619904]
- Yang M, Zhodzishsky V, Crawley JN. Social deficits in BTBR T +tf/J mice are unchanged by cross-fostering with C57BL/6J mothers. *Int J Dev Neurosci* 2007;25(8):515–521. [PubMed: 17980995]
- Zhang Y, Burk JA, Glode BM, Mair RG. Effects of thalamic and olfactory cortical lesions on continuous olfactory delayed nonmatching-to-sample and olfactory discrimination in rats (*Rattus norvegicus*). *Behav Neurosci* 1998;112(1):39–53. [PubMed: 9517814]
- Zorner B, Wolfer DP, Brandis D, Kretz O, Zacher C, Madani R, Grunwald I, Lipp HP, Klein R, Henn FA, Gass P. Forebrain-specific trkB-receptor knockout mice: Behaviorally more hyperactive than “depressive”. *Biol Psychiatry* 2003;54(10):972–982. [PubMed: 14625139]

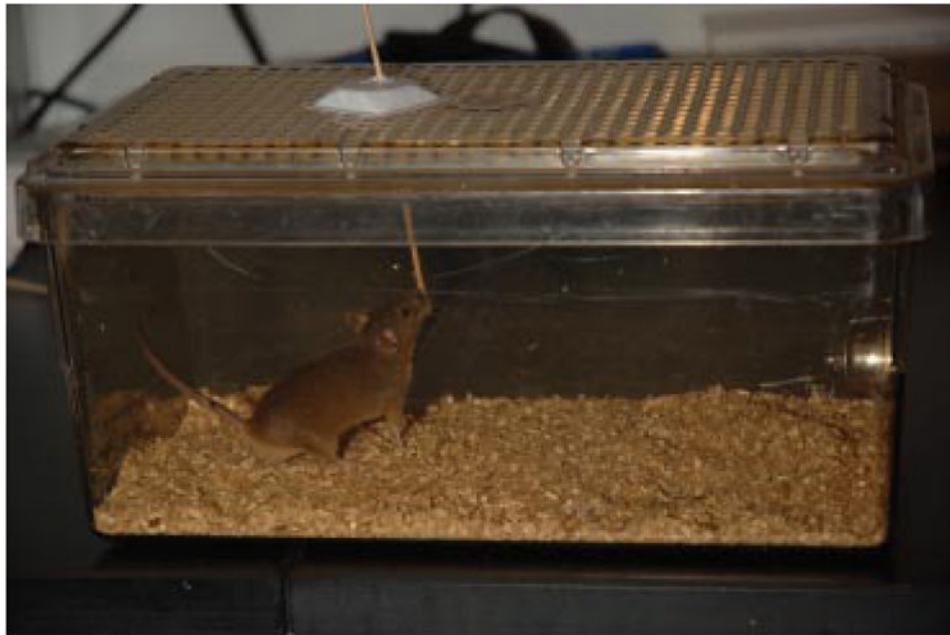


FIG. 1. Olfactory habituation/dishabituation. The mouse sniffs a cotton swab inserted into the cage lid. Time spent sniffing is scored with a stopwatch by a trained observer. A sequential series of cotton swabs are inserted and mice with normal olfaction will habituate to repeated exposures of the same odor and will dishabituate when presented with a new odor. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

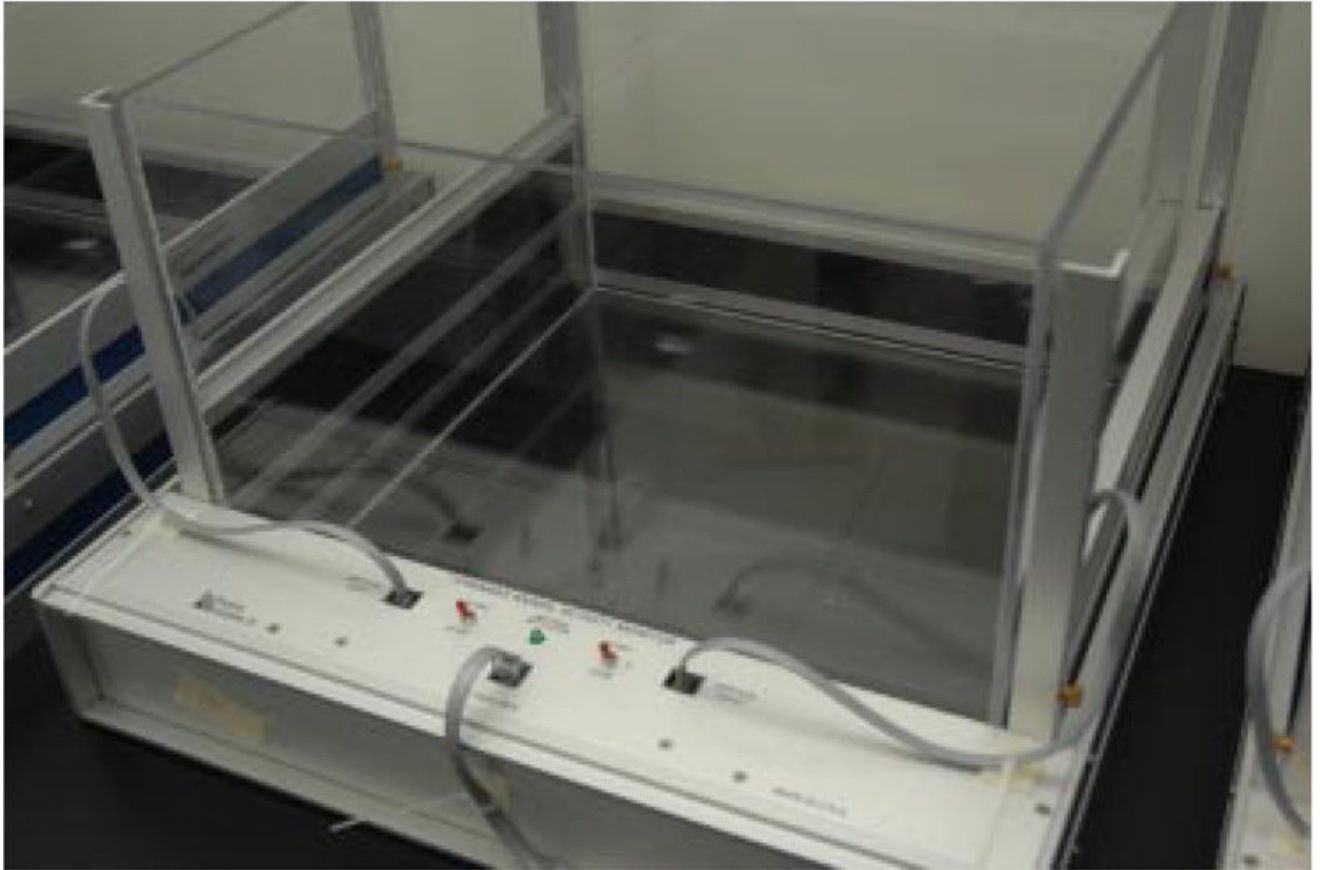


FIG. 2. Automated open field apparatus. Digiscan photocell-equipped automated open field. Locomotor activity is measured over time by a computer assisted analyzer. Beam breaks allow measurement of horizontal activity, total distance traveled, vertical activity, and time spent in the center of the open field. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



FIG. 3. Rotarod. The Ugo Basile/Stoelting rotarod is a rotating cylinder covered with grooved plastic divided into sections to allow testing multiple mice at one time. Mice walk forward on the cylinder as it rotates at a constant speed or at speeds increasing from 4 to 40 rpm over a 5-min test session. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

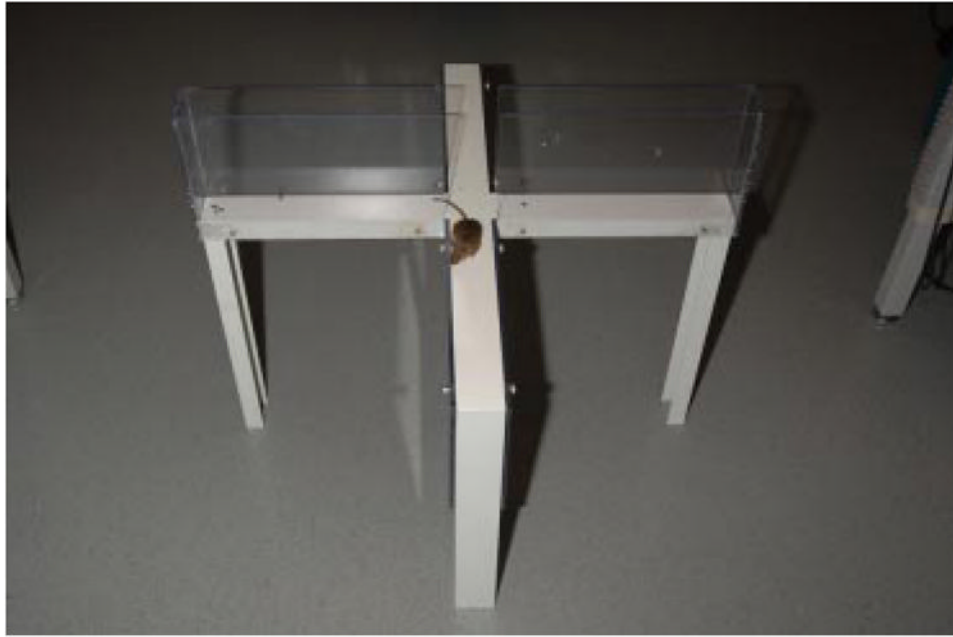
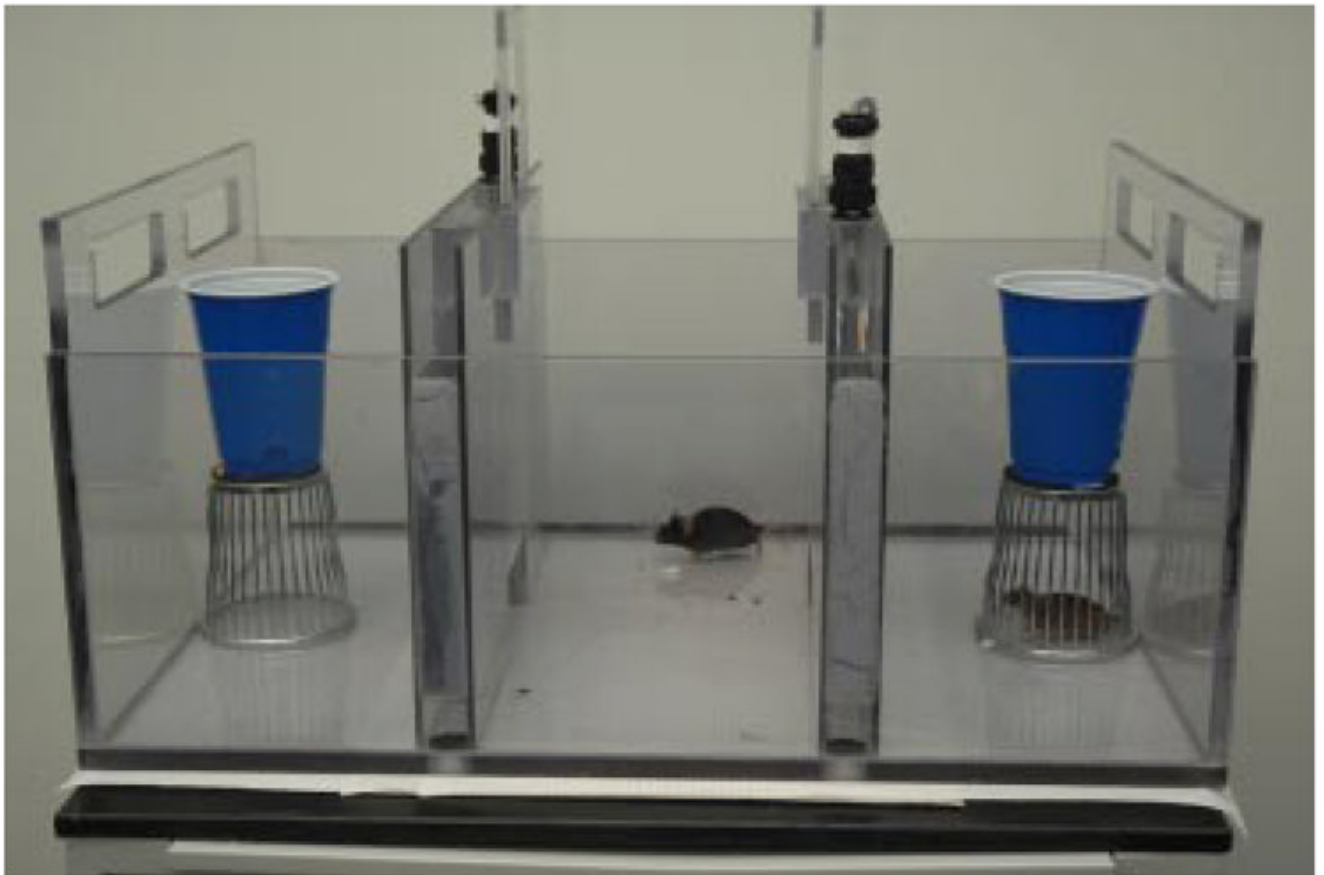


FIG. 4. Elevated plus maze. This is used to measure the conflict in the subject mouse between the natural tendency to avoid the open, narrow surface versus the tendency to explore a novel environment. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIG. 5.**

Sociability apparatus. The subject mouse is given a choice between exploring a habituated central start chamber or two side chambers, one containing a novel object, an empty wire cup or one containing an enclosed stranger mouse. Time spent in each chamber and entries into each chamber are automatically recorded by photocells located in the openings between the chambers. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

List of Behavioral Domains and Some Behavioral Tests Used to Screen for Each

Behavioral domain	Representative tests
Learning and memory	Spatial maze learning
	Morris water maze
	T-maze
	Y-maze
	Radial arm maze
	Barnes maze
	Conditioning tasks
	Eyeblink conditioning
	Cued and contextual fear conditioning
	Conditioned taste aversion
	Avoidance learning
	Passive avoidance
	Active avoidance
	Novel object recognition
	Set-shift discriminations
	Operant tasks
	Schedule controlled operant tasks
Social interactions	Social approach
	Reciprocal social interaction
	Social recognition
	Resident–intruder test for aggression
	Sexual
	Parental
Schizophrenia-related	Prepulse inhibition
	Sensitization to psychostimulants
	Social cognition
	Working memory
Anxiety	Elevated plus-maze
	Elevated zero-maze
	Light ↔ dark exploration
	Vogel thirsty lick conflict
	Marble burying
	Shock probe burying
Depression	Porsolt forced swim test
	Tail suspension
	Learned helplessness
	Anhedonia for sucrose consumption
	Olfactory bulbectomy
	Chronic mild stress

Behavioral domain	Representative tests
Drug abuse	Drug-withdrawal-induced anhedonia
	Self-administration
	Two bottle choice task
	Intravenous self-administration
	Intracranial self-administration
	Conditioned place preference
	Intracranial self-stimulation