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Review Article

Animal Model of Depression and Anxiety- PROS and CONS

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Abstract:
The benefits as well as the drawbacks of using animal models to investigate depression and anxiety are discussed in this abstract. One of the main causes of the global illness burden is major depression. The primary causes of this condition are the disorder's chronicity, recurrence, and inadequate response to antidepressant treatment. Reliable animal models are necessary for this field to advance. The current models either rely on controlling the environment that rodents are exposed to.These changes have the potential to affect particular biological and behavioral outcomes that are linked to various pathophysiological and symptomatic aspects of major depression.
Severe mental illness such as depression has an impact on world health. Its molecular mechanisms are investigated using a variety of animal models. Still, no plausible model is able to mimic the pathogenic mechanism. This review contrasts the benefits and drawbacks of prominent.
Keywords: Depression; animal model; behaviour test, anxiety

INTRODUCTION

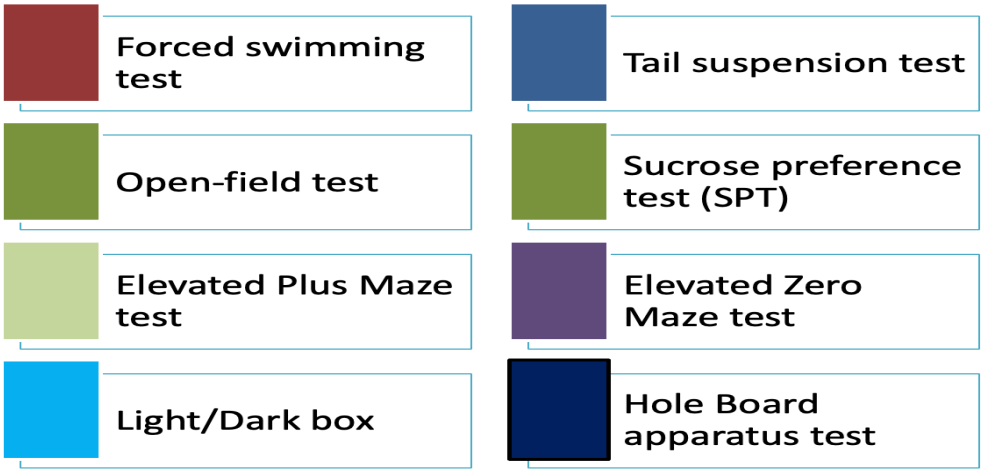
Major Depressive Disorder (MDD) is characterized by a number of core symptoms, which can be easily assessed in animals, as well as supplementary symptoms, which include sleep disturbance, changes in weight/appetite, and psychomotor alteration, as well as anxiety and social withdrawal. As a result, numerous assessments have been created to gauge these diverse elements. (1).

The diagnosis of anxiety disorders and depressive illnesses is based on behavior, relationships with others, and patient emotions. It is difficult to create a true animal model of these disorders since mental illness is distinct from other diseases and has unclear etiology. Maternal separation trials, learned helplessness, persistent moderate stress, and social dominance models are some of the early animal models of depression. A person's genetic background, stressful early experiences, and later stress responsiveness must all be taken into account in order to accurately model depression. More sophisticated gene-environment models may provide more insightful data. (3)

Depression is a severe mental illness that has an impact on people all over the world and raises the risk of suicide. In the US, its occurrence ranges from 13.3% to 17.1%. Understanding the fundamental processes of depression has been greatly aided by animal modeling, since research

indicates that 40–50% of cases are regulated by genes. Drugs or therapies that target specific symptoms can be produced by examining core symptoms in animal models. Face validity, concept validity, predictive validity, and density validity are requirements for a suitable animal model. This paper discusses and contrasts the benefits and drawbacks of the most widely used animal models of depression. Even though depression is common, research on its etiology is still in its early stages, and there are few reliable animal models available.(2)

Different types of animal model test are mentioned below:



❖ FORCED SWIMMING TEST

Among the most popular methods for antidepressant screening. For this test to have acceptable reliability, many aspects must be taken into account. (7)

Tests involve placing rodents in uncomfortable situations, causing them to exhibit active behaviors, eventually displaying bouts of immobility, gradually increasing in intensity. (1)

The forced swimming test (FST), a rat model, is used to assess a drug's potential antidepressant properties. It concerns animals that are compelled to assume an immovable posture and withstand inevitable stress. One way to conceptualize immobility is as a switch that activates cognitive functions necessary for survival and adaptation. Nonetheless, some have questioned if desperation is a hallmark of melancholy. The design of the fst is controversial because different species of rodents interact with antidepressants at different reactive baselines. The FST's lack of statistical power for clinical applications may hinder meta-analyses, despite the fact that it has been used to evaluate modeling and drug-therapeutic efficiency.(2)

When rodents are made to swim in a cylinder from which they cannot escape, their behaviour- is scored as either active (swimming and climbing) or passive (immobility). (4)

Advantages:

1. It is a quick and accurate technique for evaluating possible advertising efforts. (8)

3. It can be easily mechanized, which enables quick screening of a lot of substances.(8)
4. The relative ease of use and the absence of the need for drug interactions.(5)
5. It uses a lot of compounds in a quick and inexpensive manner.
6. It is highly automated, making it a useful tool for testing a model group.
7. It is a broad-spectrum technique with high predictive validity for evaluating antidepressant efficacy. (2)

Disadvantages:

1. Its face and construct validity are weak.

2. Ads work well as an acute treatment for FST; this does not, however, align with the clinical time course of their action.
3. The acute stressor that causes immobility behavior is not ecologically meaningful, which contributes to the low construct validity.
4. One of the most popular testing techniques for ad screening is still the FST. (8)
5. The mortality rate is high.
6. It is not applicable to assessing the etiologic mechanism of depression in humans or animals.
7. The forced swimming test's immobility time (IMFST) cannot be precisely measured due to the abundance of environmental interruption causes. (2)

❖ ELEVATED PLUS MAZE TEST

The Open field test and the Elevated Plus Maze (epm) test share certain similarities in that they both examine the anxiolytic impact on animals(12) The EPM test, when combined with the OFT test, can evaluate anxiety-related behavior changes in depression, while cognitive tests like spontaneous alternation can also be used.. (2,13)

The study involves placing rats in a plus-maze with two open and two enclosed arms, elevated to 50 cm, 30 minutes after i.p. administration of a test drug or standard. Rats are housed in pairs for ten days, with six rats per dose. Metrics measured include arm entries, time spent in open and enclosed arms, and are conducted in a room with sound attenuation.(5)

The elevated plus-maze is a popular behavioral test for assessing genetically engineered mice or anxiety-modulating medications, offering practical convenience without complicated scheduling or animal training. (3).

Advantages:

1. The test has several advantages over other paradigms for measuring anxiety that entail administering shocks or depriving subjects of food or water.(6)
2. The test has the benefit of simultaneously and in the same animals measuring anxiety and learning/memory (by calculating the percentage of time spent in an uncomfortable enclosed arm).(9)

Disadvantages:

1. This test is time consuming.(5)

❖ ELEVATED ZERO MAZE

Animals are placed in one of the closed quadrants designated as the starting quadrant and anxiety relatedbehaviors are recorded by both the observer and through a video system.(3)

❖ TAIL SUSPENSION TEST

The point of the test is to put a mice in an uncomfortable condition—such as hanging by its tail—from which it cannot escape. Animals have active behaviors (struggling) in the beginning. But eventually, because there is no way out of it, the animals begin to exhibit periods of immobility, which subsequently increase. (1)In addition, it is possible to view immobility as an adaptive behavior because it allows the animal to deal with its circumstances without expending energy in pointless ways. Indeed, certain depression models have been linked to increased difficulties in unavoidable circumstances, indicating that more care should be exercised in interpreting test results and that researchers should be encouraged to employ more suitable controls to bolster the validity of their findings.(1)

Rats are subjected to painful conditions during tests, which initially cause them to behave actively before they finally demonstrate periods of immobility that get progressively more intense.(2)

Advantages:

1. Its conduction is cheap, its methodological simplicity makes it simply automatable, and it can identify a wide range of ads regardless of their underlying processes.
2. Another benefit of TST over FST is that mice exhibit poorer behavior in activities involving water, but they outperform rats in extensive tests conducted on dry land. (8)

3. It has the ability to evaluate antidepressant effectiveness in a variety of model animals at the same time.
4. It requires less money and labor than other options.
5. It can serve as an additional test to the FST (in some situations, such hypothermia, the TST can be used in place of the FST to measure animal behavior).
6. It is applicable to rats and mice alike. When weighed against the limited accuracy of the FST, the TST can be viewed as a gentle stimulation technique that poses minimal harm to animals.(2)

Disadvantages:

1. Has a rapid onset of action, in contrast to individuals receiving the same medications over an extended period of time.(8)
2. Certain inbred mouse strains that are frequently employed, like the c57bl/6, may not be appropriate for TST because of their propensity to grab with their front paws and climb to the horizontal. (8)
3. Since it is an auxiliary method that depends on other tests, it is an incomplete protocol.
4. The antidepressant pharmacodynamic impact in the TST develops too quickly to forecast the right course of treatment for depressive patients. (2)

❖ OPEN-FIELD TEST (OFT)

When an animal is stranded in a completely foreign and isolated area, their initial response can reveal their emotional state. The open-field test frequently simulates hazardous environments, assesses the animals' independent behavior, and shows the animals' level of tension. Animals typically avoid unfamiliar environments and roam constantly about a black box, rarely entering its center. Nonetheless, because rats are naturally curious, this will lead them to investigate the center, where researchers can see how depressed the rats are. Researchers may easily spot instances of decreased activity in depressed animals, such as those that run for shorter periods of time, by tracking the movements of the animals with a three-dimensional (3d) image sensor.Every rat that has the oft should be cleaned down in a prior way for the fst in order to get rid of any smells that might draw in other rats. Rats are frequently treated with antidepressants that are widely used.(2,11)

Advantages:

1. It causes less damage to animals
2. It significantly improves treatment similarity prediction.
3. It works well for gauging hopelessness and despair.
4. It may be used to examine animal models of anxiety, therefore it serves two purposes.
5. It is more practical and efficient than other tests due to its semi-automatic functioning, which is akin to the fst.(2)

Disadvantages:

1.It takes a lot of time.
2.It is susceptible to changes in its surroundings..
3.Its concept validity for etiology research is minimal. (2)

❖ SUCROSE PREFERENCE TEST (SPT)

In Sucrose preference test animals have the choice between tap water or water containing sucrose/saccharose, and the cookie test in which animals are offered a chocolate cookie instead of regular pellets.(1)

Advantages:

1. It is the easiest test for anhedonia in animals that are depressed.
2. It causes less damage to animals
3. It can be applied to research on the co-occurrence of pain and depression. (2)

Disadvantages:

1. It takes three days to prepare for this demanding test.
2. It is too crude to depict animals' depressed states with any degree of accuracy.(2)

❖ NOVELTY-SUPPRESSED FEEDING

In order to determine the degree of anxiety, the novelty suppressed feeding test measures the latency to eat in a novel setting. (1)

The mice are returned to their home cage with the pellets after they begin eating, and their feed intake is monitored for an additional five minutes. Similarly, the cookie test, which was originally intended to measure anhedonia, may also be used to measure cookie consumption, which measures appetite. An increase in appetite results in a shift in food intake regardless of how tasty the food is, whereas anhedonia results in a decrease in the consumption of palatable food.(1).

Based on hyponeophagia, the novelty-suppressed feeding (NSF) test offers a sensitive paradigm for evaluating the effectiveness of antidepressants. The amount of food consumed and the amount of time spent looking for food are the two main criteria used by the NSF.(2)

Advantages:

1. The test's benefit is that it makes screening processes simpler.(5)
2. There are certain benefits to using this test as an animal model to investigate the neurological underpinnings of antidepressant effects.(2)
3. When examining an anxious mood during an antidepressant treatment course, these two competing conditions show excellent construct validity.
4. Because the function of hippocampal neurogenesis is directly linked to the latency of the NSF test, researchers can now examine the relationship between a neural circuit and an antidepressant effect.(2)

Disadvantages:

1. The biggest drawback of the NSF exam is that it cannot be used in conjunction w-ith other behavioral tests..(2)

❖ LIGHT / DARK MODEL

When given anxiolytics, animals in a two-chambered system that allows them to freely travel between a well-lit open field and a dark nook exhibit increased crossings between the two chambers and increased locomotor activity. There is a record of the quantity of crossings between the light and dark places.(5)

The base of the light/dark test is mice' natural aversion to brightly lit environments as well as their innate exploring behavior in response to light and new environments, which are minor stresses. When an animal is exposed to new objects or an unfamiliar habitat, a natural conflict scenario arises. They want to explore and the innate fear of the unknown (neophobia) are at odds with one another. The combined outcome of these inclinations in unfamiliar circumstances is reflected in the exploratory activity. Anxiolytic activity is thus suggested to be measured in the light/dark test by a drug-induced increase in behavior in the white section of a two-compartment box. An increase in transitions is thought to indicate anxiolytic activity in the absence of an increase in spontaneous movement. Interestingly, this effect only appears in specific mouse strains or when specific medicines are used. (4).

Advantages

The test has the benefit of being rather easy and exposing the animals to no painful stimuli.(5)

1. Its benefits include being quick and simple to employ, without requiring the animals to be trained beforehand, using natural triggers instead of depriving them of food or water. (4)

❖ LEARNED HELPLESSNESS

Learned helplessness is a well-validated animal paradigm in which animals are subjected to unexpected and uncontrollable electrical foot-shock stress, resulting in a depressive-like state.varied laboratories have varied techniques for inducing learned helplessness, which might take place in a single day or over several days of recurrent exposure. The most well-known approach to applying inescapable stress is by the use of foot shock in shuttle boxes, tail shock, or a triadic design consisting of escapeable shock, yoked-inescapable shock, and restricted control. (8)

Rats are first given many electric shocks to their feet in a contained chamber during this operation. After that, the participants are put in a different room with a grid floor and given a small shock with a chance to get away. When rats are exposed to the unescapable shock for the

first time, they usually manage to get away from it quite fast. However, when rats are subjected to the learned helplessness paradigm before, they often do not learn how to avoid shocks. The development of hopelessness is influenced by two key features: the unpredictability and the uncontrollability of the stressors (in this case, shocks). These two ideas are often confused, but they can be distinguished because there are circumstances where a subject has some control over an entirely predictable situation (such as a stressor that is applied frequently and from which the subject cannot escape) and circumstances where a subject has control over events that are beyond his or her control (such as when a skinner box lever is used to stop the stressor from occurring when it does). It has been demonstrated that predictability or controllability is sufficient to prevent the emergence of helplessness. (3)

Advantages:

1. Learned helplessness has the advantage of being a model with symptoms similar to serious depression, most of which can be reversed with many acute (subchronic) treatments with ad (usually for 3-5 d). (8)
2. Moreover, there appears to be a correlation between the behavioral (such as learning) and cognitive (such as neurovegetative abnormalities) outcomes, which aids in the understanding of the symptomatology of depression in humans. Learned helplessness is an intriguing paradigm to investigate the etiology of depression because of its superior face and prediction validities.(8)
3. This paradigm can also be broadly used to assess the capacity of mice with various mutations to escape, where target genes related to depression may influence the susceptibility to develop a depressive-like state. (8)
4. Studying how genetic changes in several species affect symptoms similar to depression is a simple task. (2)

Drawbacks:

1. The majority of depressive-like symptoms don't last long enough after the uncontrollable shock stops..(8)
2. Furthermore, different laboratories may use different methodologies to implement the paradigm.The susceptibility of distinct strains to acquired helplessness following unmanageable shock varies. For instance, lewis, brown norway, fischer f-344, sasco holtzman, and kyoto and Charles River Holtzmann lines are almost immune to the effects of inescapable shock, but harlan sprague-dawley is the intermediate. Uncontrollably high foot shock causes significant performance disadvantages in mice only in certain strains; in other strains, the interference is negligible or nonexistent.(8)
3. The behavioral outcomes are significantly influenced by the subjective criteria.
4. The stimulated responses of different model animal species vary. (2)

❖ CHRONIC MILD STRESS (CMS)

This long-term inescapable stimulation technique consists of a daily series of randomly administered trials, including electric shock, ice walking, fixation, day and night reversal, tail clipping, and food or water deprivation. Behavioral tests, such as open-field and sucrose preference tests, are conducted following a 3-week period. A number of favorable outcomes, including a lower cycle number in the open-field test and a decreased desire for sugar water, can be obtained with the preliminary model.(10)

Advantages (8&2) **:**

1. High predictive validity (long-term exposure to a broad range of advertisements reverses behavioral changes). Additionally, antidepressants that were once used to treat patients have a significant therapeutic impact on animals with CMS.
2. Face validity (almost all demonstrable symptoms of depression have been reproduced) as cms not only simulates the clinical symptoms of most depression

cases in humans, but also emphasizes anhedonia as a crucial and measurable feature.
3. Construct validity (cms demonstrates a close causal relationship between depression risk factors and treatment modalities and generates a widespread decrease in responsiveness to rewards similar to anhedonia, the primary symptom of depression).
4. The most popular and reliable animal model of depression that is now available is most likely the CMS model.
5. The best antidepressant for additional study on the pathogenic cause of depression can be chosen using this model.

Drawbacks:

1. The practical challenge of conducting labor-intensive, space-demanding, and time-consuming cms experiments.
2. Establishing the method in a new laboratory setting might be challenging.
3. It is difficult to replicate data between laboratories. (8)
4. The CMS model's numerous high-frequency procedures lead to comparatively low efficiency and a greater number of operators as well as a significant amount of experimental space.
5. Compared to other approaches, the mortality of model animals is higher due to the high-density stimulation.
6. Varying experimental setups and assessment standards could result in inaccurate findings. (2)

❖ SOCIAL DEFEAT STRESS

Advantages:

1. It is commonly believed that the social defeat stress serves as a model for depression in people.
2. This model provides additional evidence that the only way to cure social aversion is by chronic ad administration—as opposed to acute.(8)
3. Outstanding concept and face validity, given that the majority of clinical depression instances can be replicated.
4. The model shows that social engagement can mitigate depression to a minor extent.
5. In this paradigm, chronic antidepressants partially alleviate the symptoms of depression.
6. A simpler modeling procedure and a modeling duration that is less than the typical depression modeling time of 20 days.(2)

Disadvantages:

1. A brief period paradigm increases the likelihood of the anxiety phenotype because, according to a prior study, depression takes 20 days to emerge.For this model, only male rodents are acceptable, as female mice or rats do not engage in combat when confronted by an intruder. (8)
2. This model's symptoms can be mistaken for anxiety symptoms, which could lead to mistakes being made by researchers.
3. This model disregards gender variations in favor of simulating the fundamental mechanisms of depression in male patients in a social setting. (2)

❖ CHRONIC SOCIAL INSTABILITY

With a few exceptions, the social defeat model does not cause females to exhibit depressive-like responses when they observe aggressiveness. Psychosocial stress and the development of depressive-like behaviors are more common among women. But there aren't many animal models of depression that are based on females. A few research have looked into the idea of creating a model of social sadness that is appropriate for women. Rats and mice with chronic social instability in females might exhibit depressive-like symptoms, including altered circadian rhythms, reduced hunger, raised cortisol and adrenal levels, and decreased liking for sucrose, which indicates anhedonia. A recent study showed that chronic instability during adolescence can induce anxiety-like behaviors in male rats. However, chronic social instability has some contradictory results among

studies, possibly due to discrepancies between protocols. Future research should design reproducible protocols for comparison between studies.(1)

CONCLUSION

Different modeling methods produce different selectivities on antidepressants, making it difficult to predict therapeutic effects using a single animal model. The pharmacologic model has low reliability but high efficiency, making it suitable for labs with limited time. The learned helplessness, chronic mild stress, and social defeat stress models have high specificity, similar to depression symptoms in humans. Behavioral tests like forced swimming, open-field, tail suspension, and sucrose preference can indirectly model depressed animals, but have low specificity. A successful modeling process should include multiple methods to increase depression incidence in animals.

Depression modeling approaches	**Advantages**	**Disadvantages**
Learned helplessness model	1. Face validity and high concept 2. Addresses nearly all symptoms of depression 3. Simulates depressive brain circuit changes 4. Encourages genetic research	1. Brief period of depression 2. Sensitivity to subjective effects 3. Effects of various species
Chronic mild stress model	1. Excellent face, construct, and validity of prediction 2. Promotes choosing the best antidepressants 3. Assesses anhedonia 4. Aids in identifying depression risk factors	1. Can waste effort and resources 2. A high death rate 3. Sensitivity to environmental effects
Social defeat stress model	1. Excellent face, construct, and validity of prediction 2. Shows signs of social contact 3. Shorter time spent modeling	1. Can be mistaken for anxiety 2. Cannot model female animals
Behavioural tests		
Forced swimming test (FST)	1. Low cost and quick 2. Mostly mechanized 3. Wide range of antidepressant usage 4. Good validity for prediction	1. A high mortality rate 2. Incapable of determining the etiologic mechanism 3. The forced swimming test (IMFST) measure's immobility time is not accurate enough.
Tail suspension test (TST)	1. A useful examination 2. Minimal cost and labor needs 3. An addition to the first 4. Fits both rats and mice	1. An inadequate protocol for persuading 2. Antidepressant pharmacodynamic effect that is too great
Open-field test (OFT)	1. Convenient and efficient 2. Less injury to wildlife 3. A strong indicator of therapeutic similarity 4. Able to discern dejection and despair	1. Takes more time 2. Not precisely enough 3. Sensitive to changes in surroundings
Sucrose preference test (SPT)	1. Is able to exhibit anhedonia 2. Less injury to wildlife 3. Excellent for examining further comorbidities	1. A test that requires preparation time 2. Low accuracy
Elevated Plus Maze Test(EPM)	1. benefit of simultaneously and in the same animals measuring anxiety and learning/memory	**1.** Time consuming process

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