Measuring mood in rodents: from mazes to touchscreens

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ABSTRACT

Mood disorders - depression in particular - affect a large percentage of the population and account for a large part of worldwide burden both on a health and economic basis. Animal models are essential for expanding scientific knowledge of these disorders as they allow for specific and precise manipulations of the brain that are not possible in humans. However, because of the complexity and individual variability of depression, developing and assessing appropriate animal models is a major challenge. To further understand the causes of this variability, there has been an increased interest in the neurological underpinnings of the illness. This review will discuss the techniques used to assess and measure depression-like phenotypes in animals as well as models of the illness and tasks used to measure behavioural phenotypes. There has been increasing precision and sophistication in the development of animal models, from lesion to transgenic models, and advances in tasks from basic aversive tasks to more advanced touchscreen tasks. This review explores the use of animal models for depression and argues that touchscreen tasks may be better suited for assessing and measuring depression-like behaviour in rodent models as these tasks are less aversive, more translatable, and potentially more powerful in detecting subtle differences across treatment groups.

INTRODUCTION

Depressive disorders contribute substantially to global burden as they are a major cause of disability and premature death by suicide.[1] Depressive disorders have many subtypes, generally characterized by lowered affect and motivation, reduced feelings of pleasure (ie anhedonia), and cognitive deficits (eg those related to attention).[2,3] Variable symptomatology and treatment response suggest that depression may more likely be an umbrella term for closely related mood disturbances that arise from different physiological and neurological dysfunctions.[4] Consequently, there has been an increased interest in the molecular, cellular, and circuit mechanisms of many aspects of mood.

The hippocampus, most often associated with learning and memory, has become a region of interest concerning emotional regulation as well as depression.[5,6] The hippocampus supports the growth of new neurons in adulthood in a process known as adult hippocampal neurogenesis (AHN). Animal models are required in order to directly manipulate and study AHN. However, animal models cannot be used to study all factors, especially those more unique to the human condition (eg emotional experience, rumination) and human biology (eg large-scale gene interactions), as rodent biology is much less complex than in humans.[4] This relative simplicity enables investigation into specific mechanisms implicated in mood as the genetic code can be manipulated (eg transgenic strains) and external variables can be controlled (eg standardized animal housing conditions).

Given that the effects of life experience and genetic influence cannot be removed or controlled for properly in humans, studies using rodent models have provided some of the most compelling evidence supporting a functional role for neurogenesis in depression. This review will focus on this evidence and examine the variety of behavioural tasks used to assess mood in animal models, with an emphasis on the use of touchscreen testing systems in animal testing of mood-related behaviour.

NEUROGENESIS AND DEPRESSION

Reduced hippocampal volume has been linked to susceptibility to stress-induced psychopathology and depression diagnosis in animal subjects and human participants, respectively.[5,7,8] Many factors contribute to this loss of hippocampal volume. One hypothesis is reduced AHN. Some rodent models of mood disorders exhibit lower AHN levels than controls, and impaired AHN can alter behavioural responses to stressors.[9,10] Postmortem studies in humans suggest reduced AHN in those with depression when compared to healthy controls.[8]

Further evidence implicating AHN as a contributing factor to depression is related to the neurological effects of antidepressant treatment. Treatment with antidepressant drugs such as fluoxetine have been found to enhance AHN in rodents, non-human primates, and humans.[8,11,12] However, the evidence for a casual role for AHN in depression is inconclusive due to contradictory findings.[13] Whereas one study found that enhancing AHN produced antidepressant behavioural effects in a rodent model, another found behavioural effects without impacting AHN.[9,14] This discrepancy may be due to differences in methodologies used, including animal models (eg transgenic strains to knockdown neurogenesis vs selective breeding for a high anxiety-like behavioural phenotype) and testing conditions (eg stress paradigms prior to behavioural testing on inherently stressful tasks, such as the forced swim test [FST]).[9,14]

ANIMAL MODELS OF DEPRESSION

A well-known model for depression in humans is the diathesis-stress model. In this model, the disorder manifests after an underlying genetic vulnerability (ie diathesis) is combined with an environmental trigger (ie stress). The use of chronic stress paradigms to elicit a depression-like phenotype in animals capitalizes on this proposed model. The stressors used can be physical (eg restraint), biological (eg stress hormone injection), or social (eg subordination by an aggressor).[10,15-18] Animals subjected to these various forms of chronic stress exhibit depression-like and anxiety-like behaviours when tested on conventional tasks, such as the elevated plus maze and FST.[15] These models are designed to simulate environmental aspects that may be relevant to mood disorders in humans.

Animal models via biological manipulation are typically used

to determine the necessity of specific networks or biochemical systems for depression-like phenotypes. These models are commonly accomplished with transgenic strains, in which specific cells or biochemical systems are targeted via genomic manipulation. Transgenic strains used to model depression include knockout mice, wherein a gene is silenced to cease production of associated proteins (eg via the Cre-lox system).[19] Conditional knockout strains which require a trigger to activate the knockout enable direct manipulation of neurogenesis. For example, nestin-thymidine kinase (TK) mice have TK expression driven by the nestin gene promoter, resulting in co-expression of nestin and TK. Nestin, an intermediate filament protein, is present in neural stem cells.[20] The antiviral drug valganciclovir binds to the TK active site, replacing the endogenous nucleoside ligand, and results in the incorporation of a guanosine analog into the DNA backbone.[21] This analog cannot be read by DNA polymerase, ceasing cell replication. As this process occurs in cells with nestin, neural stem cells no longer undergo replication, effectively knocking down neurogenesis. Transgenic strains only account for one aspect of depression in humans and lack the environmental aspect. Despite this translational limitation, precise targeting enables certain processes to be ruled out as causal factors.

MOOD IN RODENTS: CONVENTIONAL BEHAVIOURAL TASKS

The tasks traditionally used to assess depression-like mood include the sucrose preference test (SPT) and FST. SPT assesses anhedonic behaviour and is based on the animal's preference for sweet over bland substances (ie sucrose water over tap water). Anhedonia is indicated by decreased sucrose consumption relative to controls.[10,22] FST is the hallmark task of learned helplessness, wherein an animal is left in a water-filled cylinder. A depression-like phenotype is indicated by decreased latency to immobility (ie struggle cessation) and increased time spent immobile.[10,23]

There are two main disadvantages of these conventional tasks. First, tasks used to assess behavioural aspects of depression in humans differ from those described. They are typically cognitive-based or involve affective appraisal of images and may be coupled with neuroimaging. Tasks used with rodents are designed to target rodent-specific behaviours and are used to infer mood states (eg preference for sweetness as an index of anhedonia). Using substantially different tasks across species compromises the ability to extrapolate rodent findings to the human population and increases the likelihood that different neural processes are being assessed. Second, the use of highly stressful and aversive tasks like FST introduces the stress response as a potential confounding variable as stress is known to impact behaviour and physiology.

BENEFITS OF OPERANT TOUCHSCREEN SYSTEMS

The touchscreen operant behavioural chambers were created with the goal of increased translatability of rodent findings. Touchscreen tasks are designed to mimic those used in humans, many of which are modified versions of the Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks.[24,25] The touchscreen chambers in which the tasks are performed are less aversive than conventional tasks. Rodents are rewarded for optimal responses with strawberry milkshake, whereas incorrect responses are punished with bright light instead of traditional aversive physical stimuli (eg foot shock).

Rodent touchscreen tasks assessing mood-related cognition impaired in humans with depression include progressive ratio (PR), which assesses motivation, and probabilistic reversal learning (PRL), which assesses sensitivity to positive and negative feedback information.[2,3,26-29] PR involves giving a certain number of responses to a stimulus to obtain a reward, which increases incrementally with each trial.[26] The point at which the rodent stops responding is taken to be a measure of motivation, where stopping earlier corresponds to less motivation. In human studies, PR is often administered via touchscreen and those with depression consistently stop responding sooner than those who are not depressed.[28] In rodents, the task is very similar: a white square (stimulus) is presented on-screen and the rodent must poke the square with their nose to receive reward.

PRL relies on the notion that a cognitive impairment exists in depression. In the rodent task, there is a binary choice between stimuli where one is coded as correct and the other as incorrect. A response to the correct stimulus results in reward delivery 80% of the time, but no reward for the other 20%, and vice versa for the incorrect stimulus. The use of probabilistic feedback enables win-stay/lose-shift scores to be calculated, where win-stay is the likelihood of responding to the same stimulus if rewarded on the preceding trial and lose-shift is the likelihood of responding to the opposite stimulus if the one chosen was not rewarded in the preceding trial. These scores are taken to be indices of sensitivity to feedback information.[27] Humans with depression have been shown to exhibit decreased sensitivity to response feedback, indicated by a lack of reaction time adjustment following negative and positive feedback and blunted fMRI activation patterns associated with the reaction time adjustments.[29] Similarly, a depression-like behavioural phenotype in a rodent would present as decreased lose-shift and/or win-stay behaviour, indicating the rodent is not sensitive to negative and/or positive feedback information, respectively.

Touchscreen tasks are particularly useful because the same tasks can be used in both rodents and humans, maximizing the likelihood that the same neural mechanisms are being used.[24] Another advantage of touchscreen use, particularly when dealing with complex phenomena, is the increased ability to standardize task protocols due to the use of software for task program execution. In contrast, many conventional tasks have procedural variations — which may be one reason behind mixed findings across laboratories. For instance, the number of trials used varies across studies, with some using multiple exposures to FST and others only using a single trial.[9,10,14] There are also slight variations in the apparatus dimensions and material used for FST across studies.[9,14] SPT is subject to a greater degree of variation, with some studies subjecting their animals to food and water deprivation whereas others do not.[9,10] Additionally, the concentration of sucrose used and exposure time (eg hours vs days), as well as whether a baseline intake measure is taken, vary.[9,10,30] As a result, comparing findings across studies becomes difficult. Due to the increased potential for

task standardization using computer-run execution, touchscreen systems may reduce procedural variability and, in turn, increase the potential for replicability.

CONCLUSION

Neurogenesis is implicated in playing a functional role in mood regulation and, when dysregulated, may be one of the precipitating factors of human depression and rodent depression-like phenotypes. However, the mechanism by which neurogenesis influences mood regulation is unclear, highlighting the need for better and more translatable methods to study the necessity of neurogenesis in mood. Touchscreen tasks may fill this need as they provide many benefits that complement conventional behavioural tasks, allowing for a more complete understanding of the neurological underpinnings of mood disorders. With the use of touchscreen tasks, the data acquired from animal subjects may be more easily extrapolated to humans, especially since they can be used across species. A multitude of mood-related cognitive tasks exist for touchscreen systems, which may enable researchers to determine subtle differences that may underlie the high degree of variability seen in symptomatology and response to antidepressant treatment. In particular, the capacity for standardizing touchscreen-based tasks may enable greater potential for data replicability.

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