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From rodents to humans: Rodent behavioral paradigms for social behavioral disorders

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Abstract:

Social cognition guides social behavior. Subjects with proper social cognition should be able to: (1) have reasonable social motivation, (2) recognize other people and infer their intentions, and (3) weigh social hierarchies and other values. The choice of appropriate behavioral paradigms enables the use of rodents to study social behavior disorders in humans, thus enabling research to go deeper into neural mechanisms. This paper reviews commonly used rodent behavioral paradigms in studies of social behavior disorders. We focused specifically on sorting out ways to transfer the study of human social behavior to rodents through behavioral paradigms.

Keywords:

Behavioral paradigm, dominance hierarchy, social behavioral disorders, social motivation, social recognition

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Introduction

Everyone lives in society and inevitably has to relate to other people. Human beings are fundamentally social creatures that take pleasure in getting along with others.[1] Even the simplest social interactions involve very complex information-processing and decision-making processes.[2] Almost all psychiatric disorders co-occur with or are defined by deviant social behavior, such as depression, anxiety, Parkinson's,[3] Alzheimer's,[4] autism spectrum disorders (ASD), attention deficit, and hyperactivity disorder. Take ASD as an example: Kanner first described and named ASD, and summarized its core symptoms as problems with social interaction, repetitive behaviors, and a lack of interest in people and things.[5] Previous studies in human genetics and pathology have revealed changes at multiple levels in people with mental illness; however, because of the uncertain origins and unexplained clinical heterogeneity of brain disorders,[6] studies at the nervous system level are still needed to understand the specific mechanisms of psychiatric disorders and abnormal social behaviors.

About 35 years ago, shared interests between psychologists and biologists in how to explain social behavior on the neural level led to the birth of social neuroscience.[7] Although non-human primates (NHPs) share a close phylogenetic relationship with humans, with similar developmental pathways in neuroanatomy, physiology, and genetics, as well as cognitive, emotional, and social behaviors, and have played an important role in the study of almost all diseases of the nervous system, such as stroke,[8] ASD,[9] Alzheimer's,[10] depression,[11] there are still a number of inconveniences associated with NHP models in terms of ethics, building, preservation, and financial aspects. Since rodents have been the primary model organisms used in biomedical research for more than a century,[12] and they exhibited a certain amount of sociality as herd animals, it was natural to consider using rodents

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in neuroscientific studies of social behavior [Figure 1]. Several studies have shown that rodents exhibit behavioral deficits similar to the symptoms of psychiatric disorders in humans, including problems with social interaction, repetitive behaviors, lack of interest, etc.[13] However, social interactions in humans are extremely complex, highly dynamic, emotional, and experience based.[14] Therefore, using rodent models to study social behaviors requires a suitable way to consider and control the research methods of social behaviors. We need rigorous experimental designs to minimize the high risk of false positives and false negatives in the behavioral phenotype of rodents.[15]

Here, we briefly review previous works on social behaviors using rodents, summarize rodent behavioral paradigms commonly used in works of three areas (social motivation, social recognition, dominance hierarchy), and highlight their strengths and areas for improvement.

Social motivation

At the human level, social motivation can be defined as a psychological tendency and biological mechanism that inclines individuals to seek and enjoy social interactions and strive to cultivate and maintain social bonds.[16] Lack of social motivation causes individuals to avoid socializing with other individuals, often referred to as social avoidance, which is one of the core symptoms needed to confirm a diagnosis of depression[17] and also an important early marker of ASD.[18] Many brain regions are associated with social motivation, including the prefrontal cortex (PFC), the nucleus accumbens, and the limbic system.[19] Recently, it has also been shown that the cingulate cortex may also be involved in social behavior disorders.[18]

For rodent models, the simplest, easiest to perform, and most easily documented social behavioral test is the Open Field Test (OFT), [Figure 2a].[20] Archer first mentioned using the OFT to test social behavior in mice.[21] For nearly a century, the OFT has been widely used in behavioral studies in mice because of its simplicity and easily distinguishable test results.[22-24] Classic OFT requires a well-lit area several times larger than the home cage, and the floor can be marked as subdivided areas to better quantify mice behavior. Each behavior of the mice during the subject period, including sniffing, grooming, head lifting, and digging is interpreted as reflecting a different emotional response.[25-27]

The tools used to characterize and analyze test results vary, while image analysis of video recordings is the most common method.[28-30] Methods to analyze the recorded videos may involve manual frame-by-frame analysis by researchers, which is not only time-consuming but also prone to false negative and false positive results.[20] Several automated analysis software for behavior videos have been developed, and although they still have areas for improvement, such as the need to rely on a homogeneous solid color background or the high accuracy requirements for recorded video, they have been able to save a great deal of researcher time and ensure uniformity of data processing.[20,31-33]

Another behavioral test commonly used to evaluate the sociality of mice is the three-chamber social test, which was designed by Moy *et al*. in 2004 based on the principles of group living and sociality in mice and the formation of certain social memories [Figure 2b].[34] A mentally healthy mouse usually tends to spend more time with another mouse, particularly a novel

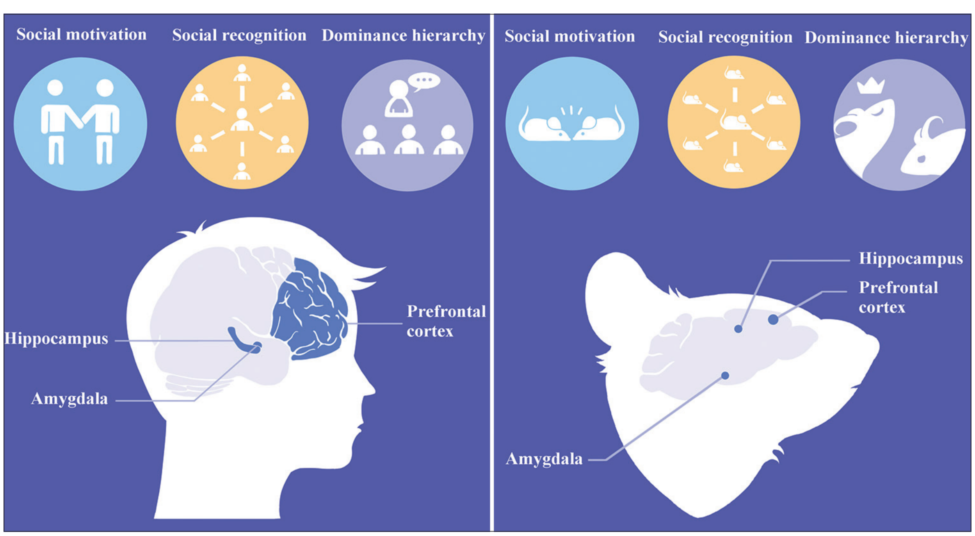

Figure 1: Social decision-making, the human and the rodent brain. Choosing who to socialize with, recognizing with others, and judging one's social rank in relation to others are social decisions that are also in other species that also live in groups

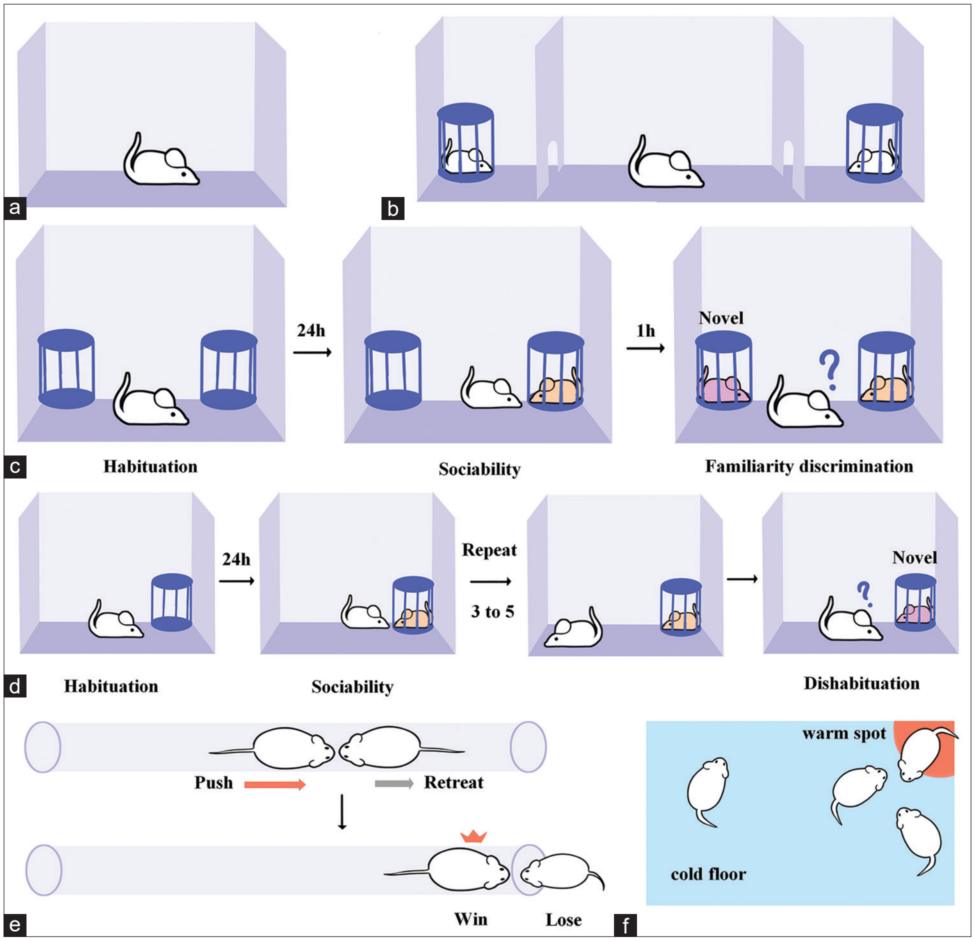

Figure 2: Commonly used rodent behavioral paradigms. (a) The open field test. (b) The three-chamber test. (c) Familiarity discrimination test. (d) Habituation–dishabituation paradigm. (e) The tube test. (f) The warm spot test

mouse, than with objects.[34-38] As the name implies, the three-chamber social test contains three connected chambers. In the middle is the larger central chamber, which is used to house the experimental mice. The mouse providing social stimulus will be placed in the small cage in one corner of the side chamber, thus limiting its movement so that preventing it from making physical contact with the subject mouse and aggressive and sexual behaviors, which are not the primary behavior of researchers' interest.[38,39] Compared to social interaction tests involving two free-moving animals, the three-compartment test is more intuitive, easier to record and analyze, and has the advantages of high experimental control and simple objective scoring.[34,37,38]

One of the most obvious limitations of the three-chamber test is that it can only accommodate a maximum of two variables. When performing social behavior tests, time spent in the lateral chamber is usually used to represent social preferences; further improvements should be to record more detailed social behaviors, such as specific sniffing time, and grooming time.[40]

Social recognition

Social recognition can be broadly defined as the mental process of identifying and interpreting social signals and the flexible ability to use these signals to guide appropriate social behavior in a changing environment.[34,41] It is considered necessary for animals to form other complex social memories, such as long-term attachments, and is, therefore, evolutionarily conservative.[41,42] At the human level, social identification is the process of forming an awareness of self and others, including empathy and moral decision-making. People with ASD often have facial recognition impairment, which can manifest early in life.[43,44] Social recognition in rodents is crucial for reproduction, the establishment of dominance hierarchies, and the formation of pairwise relationships in monogamous species.[45] For rodents, social recognition relies on the integration of olfactory, auditory, and somatosensory cues.[46] Although the sources of access to social identity information cues are more different in humans and rodents, social recognition involves the same brain regions and neural circuits such as the medial PFC,[47] hippocampus,[48] and amygdala.[49] This makes it possible to use mice to study social recognition disorders to aid in the treatment of humans. The social recognition tests commonly used in laboratories are dependent on the natural tendency of rodents to socialize with a novel conspecific, which does not need the use of artificial stimuli.[42,50]

One behavioral paradigm commonly used to examine social recognition functions in mice is the familiarity discrimination test [Figure 2c].[45-47,51-53] Engelmann proposed this behavioral paradigm in 1995, which was modified from Thor and Holloway's social recognition procedure.[50] The familiarity discrimination test for mice usually needs two steps and an arena with two chambers. In step one, the subject mice and one or more conspecific mice provided with the stimulus undergo one or more familiarizations, with intervals usually added in between allow for encoding and consolidation of social memory; in step two, mice will choose between familiar and novel mice, usually spending more time socializing with novel conspecifics. The advantage of the familiarity discrimination test is its ability to reflect specific differences between experimental groups through the specific time of social behaviors and the specific social behaviors that occur, thus providing a direct assessment of the social recognition status of the mice. An area for improvement for this intuitive and patterned test is that this paradigm does not usually yield conclusive evidence, as the familiarity of the mice in the familiarity discrimination test with the mice providing the stimuli and their identity when interacting socially with them (e.g., providing juvenile mice to interact with the subject mice, or providing mice of the opposite sex to interact with the subject mice[54,55]) is controlled by researchers.

Another behavioral paradigm commonly used to examine social recognition functions in mice is the habituation–dishabituation paradigm [Figure 2d].[56-58] Habituation–dishabituation paradigm was first used by Swoboda in the study of vowel discrimination in 2-week-old infants.[59] Beauchamp and Wellington applied it to works with guinea pigs,[60] and Thor and Holloway applied it to works with rats.[61] The core concept of habituation–dishabituation paradigm is its two steps, as the name implies. In step one, the subject mice will be exposed to the same stimuli either singly or repeatedly, and when the same stimuli are repeatedly presented, the subject mice typically exhibit reduced social exploration (habituation). In step two, by providing a new, unfamiliar social stimulus, the subject mice will exhibit increased social investigation (dishabituation). In contrast to the familiarity discrimination test, the habituation–dishabituation paradigm is characterized by the possibility to exclude that the habituation response is simply due to a loss of interest in all social stimuli; however, it is less suitable for examining differences between stimuli across experimental groups. In behavioral studies in mice, habituation–dishabituation paradigm is commonly used in experimental designs related to olfactory and odor stimuli rather than those related to allowing mice to explore freely.[62-66]

The improved version of the three-chamber test is also commonly used to examine social recognition function in mice.[67,68] The OFT was also commonly used in earlier works for direct social recognition testing.[69,70] The information that mice gain from the social recognition process tends to guide social preference and social motivation, which makes researchers usually not focus on just one aspect.

Dominance hierarchy

Dominance hierarchies maintain social stability and distribute social resources through competitive activities, while friendly social activities build social relationships by establishing social preferences and social motivation. Dominance hierarchies are manifested in species, including insects, fish, rodents, primates, and humans.[71-75] With competition comes failure, and social failure often tends to affect brain areas associated with fear and memory, such as the amygdala and the hippocampus, which in turn affects brain areas such as the PFC leads to depression, anxiety, and other mental disorders.[76] Moreover, past social trauma can result in severe social behavior disorders. Social trauma has been found to influence social behaviors by affecting the lateral septum.[77] Price's social competition hypothesis explains the depressive state as an unconscious, involuntary losing strategy that biases individuals toward accepting failure.[78] Previous studies have found that in mice, the establishment of dominance hierarchies is not only related to the size and strength gap between the parties but also to intrinsic physiological and psychological factors,[79] making it interesting to study the relationship between neural circuits and dominance hierarchies.

The most classic test to study dominance hierarchy is the tube test [Figure 2e], which was first designed by Lindzey in 1961.[80] The tube test uses a long, clear tube with a diameter that can only accommodate the passage of one adult mouse. Mice will be placed from both sides at the beginning of the test, and finally, the rank is judged by the space occupied by each mouse when their positions are stable, or one mouse is pushed completely out of the tube. Tube test is simple and easy to perform, yields highly linear and stable conclusions, and introduces little stress that is not harmful to the animals.[81] In addition, since the behavior of mice in the tube test can be simplified to push, resistance, or retreat, and mice will only move at a one-dimensional level due to the limitation of the tube, the tube test is easy to combine with the algorithm analysis, making the data analysis process more time saving and stable.[26,81] Manual judgment is still essential, for example, in cases where a mouse does not show resistance or pushing behavior but simply remains stationary in place until the opponent mouse retreats.[79] In such cases, it is necessary to carefully distinguish the specific reasons why a mouse achieves a dominant position.

The establishment of dominance hierarchies involves social competition, and the stresses associated with social competition are often associated with mental illness.[82] Depressed individuals are often psychologically and physically oriented toward social competition, focusing on social status and social hierarchy.[83] Price's social competition hypothesis explains the depressive state as an unconscious, involuntary losing strategy that biases individuals toward accepting failure.[78] Fan *et al*. demonstrate an interesting situation called the "Forced loss" paradigm: forcibly making a dominant mouse lose its social rank by forcing a dominant mouse to lose to an inferior opponent mouse by blocking the end of the tube of the inferior mouse so that the mouse cannot retreat. This can trigger depression-like behavior.[82] In this paradigm, the ability of the dominant rank mice is not diminished, but the mice will continue to fail in the following competition after being forced to fail.

In addition to the tube test, other tests can also tell the dominance level of mice. One example is the warm spot test [Figure 2f], which is designed by taking advantage of animals' natural tendency to stay warm and avoid the cold.[81] It creates a warm spot that can accommodate only one mouse in a cage with a cold floor using a heating pad, thus forcing mice to compete and judging social rank from the length of time they occupy the warm spot. Researchers often use multiple tests in a single work to demonstrate that the ranks of mice are credible and stable.[79]

Conclusions

With the development of psychology and neurology, there is an increasing attention to mental health and mental illness. However, how our brains respond to social interactions is difficult to dissect, even in a controlled laboratory setting.[84] We need tools that can advance research to the cellular and molecular level. Rodents have long been a popular animal organism for researchers. In this review, we attempted to sort out ways to transfer the study of human social behavior to rodents through behavioral paradigms. The existence of so much homology in social behavior guided by social cognition allows us to study social behavior disorders and their neural mechanisms using rodents.

In addition to improvements to the behavioral paradigm and the process of results analyzing, the type of animal model used could also be further investigated. For example, social behavior has distinct sexual dimorphism characteristics. Most current behavioral paradigms have been designed for adult male mice, but males and females respond differently when faced with social and societal stress. It has been shown that the same brain regions may control different behaviors in male and female mice; for example, the medial amygdala promotes infanticidal behavior in males but nurturing behavior in females.[85] Many researchers have begun to notice this difference and have focused on the behavioral differences between male and female mice in the same behavioral paradigm.[86] Another example is adolescent psychiatric disorders are an area of increasing interest and are often associated with abnormal neurological development. For example, Rett syndrome (RTT), which has gained increasing attention in recent years and is now thought to be associated with loss of functions mutations in the X-linked methyl-CpG-binding protein 2 gene, is prevalent in girls and severely affects the neurodevelopment of socially relevant brain regions in children.[87] The consensus is that normal social interactions in childhood are crucial for the formation of proper social cognition in adulthood. There are many interesting studies on juvenile play behavior in rodents, which could potentially be used in the future to intervene in adolescents with ASD, RTT, and other disorders.[88,89] Further research and behavioral paradigms related to the development of social behavior in adolescent rodents are yet to be investigated.

Furthermore, in terms of technology, in addition to new techniques such as optogenetics, fiber-optic recording, and endoscope, whole-brain functional magnetic resonance imaging, and calcium imaging are applied to related studies.[90-92] Since almost all neural implant devices (optical fiber, grin lens, etc.) require an external connection line, which has the potential to impede animal movement or even trigger stress and anxiety in the animal, the work of Yoon *et al*. reports on a miniaturized, wireless neural probe system targeting behavioral neuropharmacology aspects that allow for long-term drug delivery and simultaneous monitoring of neural signals and behavioral changes.[93] They have demonstrated its feasibility using food competition trials. Rodents provide a valuable tool for studying social behavior at the cellular and molecular level by delving into specific brain regions and neural circuits. They may thus reveal therapeutic targets for a variety of neuropsychiatric disorders.

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Conflicts of interest

There are no conflicts of interest.

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