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Review article

Ethological and multi-behavioral analysis of learning and memory performance in laboratory rodent models

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ABSTRACT

Behavioral studies using animal models have widely contributed to advancing our understanding of the neuroregulatory mechanisms of human cognitive states and disorders. A variety of behavioral tests and theoretical models have been developed that provide a standardized toolbox of behavioral test paradigms available to researchers, and thus allow rapid progress in studies of the molecular-genetic bases of behavior relevant to neurocognitive diseases. However, a growing effort to utilize standardized paradigms has overlooked the diverse behavioral characteristics of test rodents expressed in standardized test situations. This review describes two popular test paradigms for cognitive assessment in rodents: social recognition and fear conditioning tasks. An extensive assessment of observed behavior during testing indicates a need to further elucidate the sequential strategic processes employed by test animals in conjunction with the use of standardized test settings and dependent variables. The present study calls specific attention to the considerable but improvable problem of the appropriateness and applicability of these standardized test paradigms; it thereby unravels the essential contribution of multi-behavioral assessment to further advancing neuroscience research using rodent behavioral models.

Contents

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1. Rodent behavioral models

1.1. Advantages of behavioral studies using animal models

Laboratory rodents have been utilized in a wide range of biomedical and translational studies as animal models of biological and pathological processes underlying human diseases (Denayer et al., 2014). Animal models are essential to bridging the translational gap between preclinical and clinical research, as they provide rich means of testing hypotheses in a highly controlled environment. It should be noted that an animal model, a simple representation of a complex existing system, does not attempt to recreate a human disease exactly in all its clinical aspects in an animal. Rather, it mimics a particular symptom/aspect of a target disease or state. To this extent, the behavior of laboratory rodents as measured in a variety of experimental settings provides an important model system for investigating brain function as well as the biological nature and pathophysiology of human diseases (Nestler and Hyman, 2010).

The vast majority of laboratory animals used in research are mice or rats with drastically increasing in importance due to the growing use of transgenic techniques and increasing understanding of the value and tractability of studying their behaviors (Crusio et al., 2013). Rodent behavioral models provide insight into the functional basis of the target behavior but do not need to resemble the appearance of human behaviors (Nestler and Hyman, 2010; Blanchard et al., 2013). This feature is an essential prerequisite of animal models that has received much less attention and thus is poorly understood in behavioral studies using animal models. Laboratory animals possess unique genetic and species backgrounds, and thus they express particular behavior that is closely relevant to species-typical biological needs and vital functions associated with a certain, natal environment (Dixon, 2004; Blanchard et al., 2013). However, the current trend toward standardization of behavioral test protocols requires the behavior of animals to resemble a simplified form of human behavior. The use of standardized procedures and measurements employed thus tends to omit species-typical characteristics of observed behaviors, which compromises the validity of behavioral interpretations (Gerlai and Clayton, 1999).

In this review, we will step back to consider what test animals actually do during testing and describe the diverse behavioral strategies expressed by laboratory rodents. This approach based on multi-behavioral assessment will shed light on the strengths of behavioral studies using laboratory rodents and thus may contribute to further advancing neuroscience research.

1.2. Associations between ethological background and behavior of laboratory rodents

Ancestors of laboratory rodents lived near humans; thus, they evolutionarily acquired behavioral features adaptive to living environment near human living (Crowcroft, 1973). Certain behaviors of rodents expressed in experimental settings involve functions with adaptive value in original natural circumstances. An ethological approach, linking to a key for elucidating these functions, is crucial for assessing the original meaning of the expressed behavior (Olsson et al., 2003; Peters et al., 2015).

Laboratory mice and rats are descended from originally captive animals, which indicates selection from a large and varied original gene pool that sustained a species' high adaptivity to multiple environmental challenges (Dixon, 1998). Subsequent domestication over generations may have resulted in further elimination of certain rodent phenotypes undesirable to human experimenters and caretakers, such as hyper-aggression to human handling and hyper-defensiveness to caging or testing environments (Blanchard, 2010). Indeed, the intensity and variety of some behaviors expressed by laboratory rodents have declined compared to original wild species (Blanchard et al., 1986, 1998a). Furthermore, most strains of laboratory rodents have been artificially inbred and therefore possess identical or even modified gene information within their strains or siblings, which results in diminished genetic diversity underlying behavioral expressions (Blanchard, 2010). Such selective breeding and genetic manipulation in fact interferes with animals' ability to adapt to the laboratory environment (Olsson et al., 2003). Nonetheless, laboratory rodents retain much of their species-typical behaviors when they are confronted with a situation where they need to express these behaviors, e.g., in an inducible experimental setting (Dewsbury, 1983; Sluyter and van Oortmerssen, 2000). This retention of wild behaviors has become increasingly important in translational studies using animal models (Peters et al., 2015).

It is essential to study laboratory animals as evolved biological systems in which a particular behavior expressed in an experimental setting has been selected from a constellation of interactions between social and physiological systems and gene function, based on species-typical survival and reproductive strategies. Laboratory animals largely retain their behavioral repertoire based on the adaptive values of those behaviors; such animals also share mutual characteristics with those involved in human health and disease (Dixon, 1998; Denayer et al., 2014). The ethological view recognizes that individual differences in observed behavior are not just 'noise' but represent different ontogenetic backgrounds that ultimately contribute to individual survival and reproductive success in a wide array of environmental niches. Understanding such species-typical demands and ontogenetic behavioral features is vital for assessing the functional meaning of behavior in laboratory rodents.

1.3. Standardization of behavioral test paradigms

Modern protocols for behavioral studies using animal models propose developing a standardized set of behavioral tasks. Designing rodent behavioral tasks that are relevant to human cognitive functions or states requires referring to different standards for test validity. Effective animal models should incorporate (1) face validity, i.e., strong analogies to the behavioral endophenotypes of human symptoms; (2) construct validity, i.e., targeting a similar biological mechanism to that which causes the human disease; and (3) predictive validity, i.e., analogous response to treatments that affect symptoms in the human disease (Hogg, 1996). Rodent behavioral assays have been developed primarily based on face validity, i.e, the ability of a task to appear to measure what it is supposed to measure.

For instance, the elevated plus-maze has been developed by File and colleagues (File, 1993) as a simple but powerful method for assessing anxiety responses in rodents. The equipment consists of two discrete arm areas connected in a plus shape that exploits an innate preference in rodents for a dimly lit, narrow place over a bright open space. Rodents' anxiety behavior is assessed by the ratio of time spent on the open (aversive) arms to time spent on the closed (less aversive) arms, which is supposed to mimic and thus represent a certain psychological state, i.e., anxiety; a trend to remain in the closed arms indicates heightened anxiety (Hogg, 1996). To this extent, anxiety behavior can also be determined with a level of spontaneous motor activity or a deficit in sensory cognitive abilities such as visual or attention impairment (Walf and Frye, 2007). These tests' reliability and validity may be improved by focusing upon what the animals actually do in the maze. Accordingly, other ethological measures have been developed to sustain the reliability of the measurement, including head dips, rearing, and stretched-attend postures (Rodgers and Johnson, 1995).

In the same fashion, a variety of memory tests for rodent models have been developed to measure psychological states and neuro-

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