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Research report

Genetic and dopaminergic modulation of reversal learning in a touchscreen-based operant procedure for mice

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Abstract

Mice are uniquely suited as experimental subjects for various approaches to the study of the molecular and genetic basis of behavior, and there has been a corresponding explosion in the use of mice in behavioral neuroscience. Rats and monkeys, however, remain the preferred species for high-order cognitive models largely due to the unavailability of valid, reliable and translatable endpoint measures of behavior in the mouse. Here we present further development and validation of a touchscreen-based operant method for measuring cognition that is comparable to methods used in other species and human patients. C57BL/6J mice were found to show good performance on visual discrimination and reversal learning using this method. Demonstrating the sensitivity of the paradigm to genetic factors, C57BL/6J and DBA/2J mice exhibited marked differences in discrimination and reversal learning. Systemic treatment with the selective D1-like agonist, SKF81297, produced an impairment in the early phase of reversal learning, but did not alter visual discrimination, in C57BL/6J mice. The same treatment impaired spatial working memory on the T-maze delayed alternation task, but did not alter control measures of behavior including motivation and locomotor activity. These data demonstrate the sensitivity of visual discrimination and reversal learning measured by this method to genetic factors and pharmacological challenge, and thereby provide an extension and further validation of the method for measuring cognition in mice. When combined with emerging molecular techniques uniquely suited to this species such as genetic engineering and RNA modification this paradigm could provide a powerful new tool for behavioral neuroscience.

Keywords: Mouse; Discrimination; Reversal; Cognition; Strain; Gene; Dopamine; SKF81297; D1 receptor

1. Introduction

Mice are uniquely suited as experimental subjects for various approaches to the study of the molecular and genetic basis of behavior, such as genetic engineering and quantitative trait loci analysis. As a result there has been a recent explosion in the use of mice in behavioral neuroscience, which in turn has spurred the need for valid and reliable endpoint measures of brain functions including behavior in the mouse [16]. This issue is particularly pertinent to paradigms measuring cognition, which have a longer tradition of use in the rat than the mouse. A small but growing literature has demonstrated that mice are capable of performing complex behaviors that model human cognitive functions ranging from attention, impulse-control, and working memory [3,26,31,33].

Bussey, Saksida, Rothblat and colleagues have recently described an automated instrumental learning procedure in which mice readily acquired stimulus-reward contingencies by nosepoking at visual stimuli presented on a touch-sensitive monitor [5,8]. This paradigm is similar to that previously used in rats [6,7,9] and monkeys [18] and has features comparable to automated systems used in evaluating cognitive function in human patient groups [42]. Thus it has considerable potential for mouse-to-human translational studies of brain function and neuropathology.

A form of cognition commonly assessed in animals is reversal learning. The ability to respond adaptively to a reversal in reward contingency of a learned discrimination pair measures

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the behavioral flexibility to inhibit previously rewarded behavior [11,27] As such, reversal learning may assay features of certain neuropsychiatric conditions characterized by cognitive inflexibility, impulsivity, and risk-taking, such as schizophrenia and drug addiction [11]. In this context, previous research has demonstrated that reversal learning in rats and monkeys [7,18,27,32] recruits brain regions implicated in the pathophysiology of these neuropsychiatric conditions [34]. Common variants of reversal learning in rodents include odor discrimination reversals [29,43], left/right lever reversals [19], spatial reversal on a T-maze [2], and discrimination reversals using visual stimuli [5,6,8,9]. Of these, the latter is most similar to that used with nonhuman primates and humans and is therefore highly conducive to cross-species comparisons.

The main aim of the present study was to further evaluate the utility of a touchscreen-based operant system for measuring cognitive function in mice, via assessment of visual discrimination and reversal learning. We first developed an in-house procedure for measuring visual discrimination and reversal learning in C57BL/6J inbred mice, the most commonly used mouse strain in behavioral neuroscience. Next, to test for possible strain differences in visual discrimination and reversal learning, we compared the performance of C57BL/6J with another popular mouse strain, DBA/2J. Differences between these two strains would provide a lead into studies aimed at identifying genetic factors underlying these behaviors because of the availability of C57BL/6J × DBA/2J recombinant inbred strains [13].

We next assessed the sensitivity of the paradigm to pharmacological insult. A growing corpus of data supports an important role for the dopamine system in modulating cognition; more specifically, dopaminergic neurotransmission mediated through the D1-like (i.e. D1, D5) receptor subfamily [23,24,44]. For example, loss of D1-like receptor function has been associated with working memory deficits in humans, non-human primates, and rodents [30,35], for review see [41]. However, although there is evidence that dopamine function supports some aspects of reversal learning (for review see [11]), a specific role of D1-like receptors in reversal learning has not been elucidated. In the present study we tested the effects of systemic treatment with the selective D1-like receptor agonist, SKF81297, on visual discrimination and reversal learning in C57BL/6J using the touchscreen-based system. Because of the novelty of the paradigm, we also conducted an experiment as a positive control for the effects of D1-like receptor agonist on a more well-established task for cognitive flexibility [2] that has been previously shown to be impaired by the drug [30], T-maze delayed alternation working memory.

2. Materials and methods

2.1. Subjects

Subjects were male C57BL/6J and DBA/2J mice obtained from The Jackson Laboratory (Bar Harbor, ME) aged 8–12-weeks old at the start of behavioral testing. Mice were housed in groups of 4–5/cage in a temperature- and humidity-controlled vivarium under a 12 h light/dark cycle (lights on 06:00 h). Mice were maintained on a restricted diet and kept at 85% of free-feeding body weight during behavioral testing in order to ensure sufficient motivation to work for food rewards. Mice were fed upon return to the home cage after testing. Testing was conducted during the light phase of the light/dark cycle after mice were acclimated to the testing room for 1 h. All experimental procedures were approved by the National Institute on Alcohol Abuse and Alcoholism Animal Care and Use Committee and strictly followed the NIH guidelines 'Using Animals in Intramural Research'.

2.2. Touchscreen-based operant system

The apparatus was a modified version of that previously described [5,6,8,9]. The operant chamber measuring 21.6 cm × 17.8 cm × 12.7 cm (model # ENV-307W, Med Associates, St. Albans, VT) was housed within a sound and light-attenuating box (Med Associates, St. Albans, VT). The grid floor of the chamber was covered with solid Plexiglas to facilitate ambulation. A pellet dispenser delivering 14 mg dustless pellets (#F05684, BioServ, Frenchtown, NJ) into a pellet tray located at one end of the chamber. At the opposite end of the chamber there was a touch-sensitive screen ('touchscreen') (Light Industrial Metal Cased TFT LCD Monitor, Craft Data Limited, Chesham, U.K.), a houselight, and a tone generator. The touchscreen was covered by a black Plexiglas panel that had 2 cm × 5 cm windows separated by 0.5 cm and located at a height of 6.5 cm from the floor of the chamber. Stimuli on the touchscreen were visible through the windows (1 stimulus/window) (Fig. 1A). Stimulus presentation was controlled

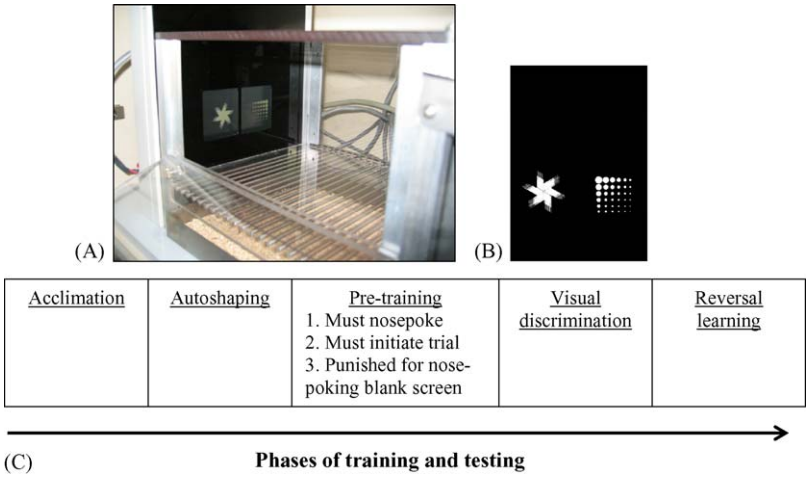

Fig. 1. Apparatus and testing protocol for the touchscreen-based operant procedure. (A) A mouse's eye view of the touchscreen. (B) Stimuli used for visual discrimination and reversal learning. (C) Schematic description of the phases of training and testing.