



Research report

Intact and impaired executive abilities in the BTBR mouse model of autism

Hanna L.H. Rutz, Lawrence A. Rothblat*

Department of Psychology, The George Washington University, 2125G Street, NW, Washington, DC 20052, United States

HIGHLIGHTS

- ▶ BTBR mice show both intact and impaired executive abilities.
- ▶ BTBR mice are not impaired on discrimination acquisition or reversal learning.
- ▶ BTBR mice are impaired on a task requiring context-dependent responses.

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ABSTRACT

BTBR T+tf/J (BTBR) inbred mice are frequently used as a model of autism spectrum disorders (ASD) as they display social deficits and repetitive behaviors that resemble the symptoms of the human syndrome. Since deficits on tasks that measure cognitive (executive) control are also reliable phenotypes in ASD, we wanted to determine whether executive abilities were compromised in the mouse model. BTBR mice were trained on two visual discrimination paradigms requiring differing degrees of cognitive control. BTBR mice performed normally on a visual discrimination reversal where rule switching was relatively automatic, but were severely impaired on a task-switch paradigm that required the active use of contextual information to switch between rules in a flexible manner. The present findings further characterize the behavior of BTBR mice as a model of ASD. Moreover, the demonstration of both intact and impaired executive functions in BTBR mice illustrates the importance of developing new cognitive assays for comprehensive behavioral assessment of mouse models of human brain disorders.

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1. Introduction

The BTBR T+tf/J (BTBR) inbred mouse is becoming one of the most thoroughly characterized animal models for autism spectrum disorders (ASD). BTBR mice display cortical underconnectivity (lacking a corpus callosum and having a reduced hippocampal commissure [1]), carry a deletion of the DISC1 gene [2], and exhibit alterations in serotonin transmission [3]. More recently it has been shown that Ras/Raf/ERK1/2 signaling is significantly up-regulated in the frontal cortex of BTBR mice [4] as it is in the brains of individuals with ASD [5]. The behavioral phenotype of BTBR mice also reflects the autistic syndrome. BTBR mice exhibit minimal social interaction and impaired play [6–8], unusual patterns of vocalizations [9,10], and enhanced repetitive and stereotyped behaviors [7,8,11,12].

In addition to the primary diagnostic criteria (social, communication, repetitive) [13], ASD is characterized by a constellation of cognitive impairments that are particularly evident on tasks that require some degree of cognitive (executive) control [14].

Cognitive control refers to the ability to switch between tasks that use different rules and requires some degree of working memory and response inhibition for behavioral flexibility. In mice, such cognitive functions have been modeled by using discrimination learning paradigms, such as discrimination reversal learning tasks where subjects must first learn to respond to one of two cues, then switch to the previously unrewarded cue. As in human studies, performance is generally believed to measure behavioral flexibility, reflecting an ability (or inability) to inhibit prepotent responses. Despite the fact BTBR mice display a number of autism-like behaviors, previous reports suggest their cognitive abilities may be intact. BTBR mice perform well on visual discrimination tasks [15] and, reportedly, are not impaired on reversal learning [8,16].

Although cognitive control deficits are typical in ASD, they are not apparent on all tests [17]. Tasks requiring simple inhibition (e.g., Stroop, Go/No-Go, Stop-Signal, and negative priming) are learned normally [18,19]. The most consistent evidence for cognitive control dysfunction in ASD comes from task-switching studies requiring the ability to flexibly shift from one set of rules to another in a context specific manner. Switching is particularly difficult when one of the rules involves inhibiting a prepotent response. Two tasks that have been used successfully in children are the “Preparing to Overcome Prepotency (POP)” task [20,21] and the “Dots” task

* Corresponding author. Tel.: +1 202 994 6809; fax: +1 202 994 1602.

E-mail address: lar@gwu.edu (L.A. Rothblat).

[22,23]. For successful performance on these tasks, subjects must learn two sets of stimulus–response (S–R) mappings and switch between the two in the appropriate situation. On S–R compatible trials, the subject must respond to the side where the target is presented. On S–R incompatible trials, the subject must suppress the prepotent tendency to respond to the target and instead learn to respond to the opposite side. Compared with simple discrimination reversal where cognitive control is more automatic, these task-switching paradigms require the active use of contextual information to flexibly adjust responses.

We have previously shown that when tested in a computer-automated touchscreen apparatus [24,25], mice can be trained on a variety of visual discrimination tasks including discrimination reversal [26] and perceptual set-shifting [24] that are analogous to those used with humans. Since contextual processing tasks used with autistic children employ visual discrimination paradigms, we were able to develop a rule switching paradigm for mice that incorporates similar cognitive demands. The purpose of the present experiment was to see if BTBR mice would be impaired when rule switching involves the active use of contextual information, but perform normally on a discrimination reversal task where rule switching is relatively static.

2. Materials and methods

2.1. Animals

Male C57BL/6J ($n=10$) and BTBR ($n=10$) mice aged 12 weeks at the beginning of the experiment were obtained from Jackson Laboratories (Bar Harbor, ME). Animals were separated, weighed and housed individually in plastic cages on a 12 h light–dark cycle with unlimited access to water for the duration of the experiment. The mice were allowed seven days of free feeding during which they were weighed once per day and accustomed to handling. The animals were then put on a restricted diet until they were reduced to 85% of their free feeding weight. Between 12 and 16 weeks of age, food allotment was gradually increased approximately 10% to adjust for growth. All experimental procedures were conducted within the guidelines of the Institutional Care and Use Committee of The George Washington University.

2.2. Apparatus

The apparatus and training methods were similar to those previously described by Brigman and Rothblat [26]. All pretraining and testing was conducted in a dimly lit room (approximately 3 lx). Mice were initially trained to bar press in a modified Skinner box. They were then transferred to the touchscreen apparatus, a Plexiglas chamber measuring 22 cm \times 24 cm \times 19 cm. An external pellet dispenser (Model ENV 203–20, MED Associates, St. Albans, VT) was connected to a food well on the rear wall of the chamber. An initiate lever was located above the food well. A computer monitor (15 in.) on which the stimuli were presented was placed on the other end of the chamber. An infra-red touchscreen (Model 3457, CarrollTouch International, Tokyo, Japan) was attached to the front of the touchscreen.

2.3. Discrimination acquisition and reversal

Animals were pretrained to initiate a trial by bar press and touch a visual stimulus for food reward (Noyes, 20 mg). Initiation of the next trial could then occur 5 s after the response. This pre-training allowed the mice to acclimate to the testing chamber and continued until the mouse completed 20 trials in 20 min or less, two days in a row. Following pretraining, the mice learned a two-choice pattern discrimination. Animals were again required to initiate each trial by depressing the bar. However, now each press resulted in the presentation of two stimuli, each appearing pseudorandomly on the left or right side. Stimuli were composed of black lines on a gray background with a horizontal line rewarded (S+) and an X unrewarded (S–). A nose touch of S+ resulted in a tone, reward of one food pellet, and an advance to the next trial. A nose touch of S– resulted in no reward and a 20 s delay before the animal could reinitiate. Subjects were tested for 20 trials per session (referred to as first-presentation trials); each mouse completed one testing session per day. A correction procedure was used so that following an incorrect response on a trial, that screen was repeated until the animal responded correctly (repeated trials). Criterion for the discrimination and reversal problems was set at 80% correct first-presentation trials on two consecutive sessions. After completing the pattern discrimination problem, animals were moved to the reversal problem on the next testing session. All procedures were similar to the previous problem, except now the reinforcement contingencies were reversed such that the previous S– (horizontal line) was now rewarded and the previous S+ (X) was unrewarded.

2.4. Contextual rule switching (CRS) task

Following criterion performance on the discrimination reversal, the mice were trained on a new contextual rule switching (CRS) task for 15 consecutive days. Testing began with a block of 10 S–R compatible trials (cued by a black circle) where the mouse was rewarded for responding to the side where the target was presented (Fig. 1). After this block of 10 trials, the mouse was returned to the home cage for 5 min. Testing then resumed with a block of 10 S–R incompatible trials (cued by a white circle). For these trials, the mouse must inhibit a prepotent response and utilize a different rule, i.e., press the side opposite the white circle (Fig. 1b). A correction procedure was also used for the CRS task whereby incorrect trials were repeated until the mouse made a correct response.

2.5. Behavioral measures and statistical analysis

For discrimination acquisition and reversal learning, analysis of variance (ANOVA) was used to analyze differences between strains on sessions to criterion, total errors on first-presentation trials, total errors on repeated trials, and total incorrect responses (first presentation and repeated). Additionally, reversal performance was analyzed by categorizing the repetitive error scores of individual mice as “stimulus perseverative errors” if they occurred on sessions where performance was <39% correct or “learning errors” if they occurred on sessions where performance was >39% [26–28]. “Stimulus perseveration errors” tend to occur at the beginning of the reversal problem while “learning errors” tend to occur during the later stages of learning. For the CRS task, a repeated measures ANOVA was used to analyze first presentation and repeated errors for both S–R compatible and incompatible trials over the 15 days of testing. Further comparisons were made after adjusting for multiple measures with the Bonferroni correction.

3. Results

3.1. Discrimination acquisition

BTBR mice required a mean of 6.8 ± 1.2 sessions to reach criterion on the visual discrimination task; C57BL/6J mice required a mean of 5.3 ± 0.7 sessions. No significant differences were found as measured by sessions ($F(1,18)=1.25$, $p=0.278$). Comparison of first presentation errors made by the BTBR (39.6 ± 7.5) and C57BL/6J (26.1 ± 4.0) also revealed no significant differences ($F(1,18)=2.49$, $p=0.132$). Similarly, BTBR (68.2 ± 13.8) and C57BL/6J (39.3 ± 5.6) did not significantly differ on total incorrect responses ($F(1,18)=3.77$, $p=0.068$).

3.2. Discrimination reversal

The BTBR ($10.9 \pm .9$) mice did not require significantly more ($F(1,18)=0.95$, $p=0.342$) sessions than C57BL/6J animals (9.6 ± 0.9) to reach criterion on the discrimination reversal task. ANOVA revealed the groups did not significantly differ on first presentation errors (BTBR = 88.2 ± 9.5 ; C57BL/6J = 77.3 ± 8.3 ; $F(1,18)=0.74$, $p=0.400$), repeated errors (BTBR = 145.3 ± 10.9 ; C57BL/6J = 160.4 ± 25.5 ; $F(1,18)=0.30$, $p=0.592$), or total incorrect responses (BTBR = 233.5 ± 18.2 ; C57BL/6J = 237.7 ± 26.3 ; $F(1,18)=0.2$, $p=0.897$) (Fig. 2). The groups did not differ significantly in number of stimulus perseveration (BTBR = 91.3 ± 15.5 ; C57BL/6J = 132.7 ± 31.7 ; $F(1,18)=1.38$, $p=0.256$) or learning (BTBR = 142.2 ± 13.0 ; C57BL/6J = 105.0 ± 13.3 ; $F(1,18)=4.01$, $p=0.001$) errors.

3.3. CRS task

On the S–R incompatible component of the CRS task, BTBR (86.5 ± 2.1) made significantly more first presentation errors than C57BL/6J mice (68.4 ± 2.2 ; $F(1,18)=35.66$, $p<0.0001$). To determine how performance changed throughout the course of testing, the proportion of errors on first presentation trials was analyzed in 3 five session blocks (Fig. 3). A repeated measures ANOVA revealed a significant Block effect, i.e., performance of both strains improved with training ($F(2,36)=81.51$, $p<0.0001$) and a significant Block \times Strain interaction ($F(2,36)=7.80$, $p=0.0015$).

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