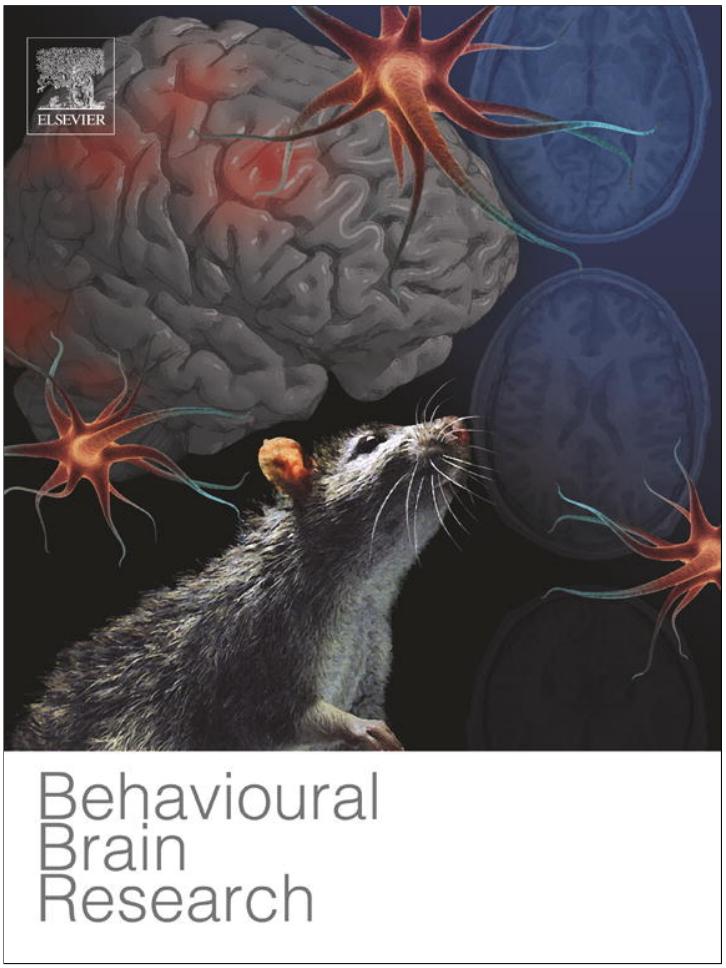

(This is a sample cover image for this issue. The actual cover is not yet available at this time.)

Behavioural Brain Research 234 (2012) 33–37

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

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.

ARTICLE INFO

Article history:
Received 25 April 2012
Received in revised form 28 May 2012
Accepted 29 May 2012
Available online xxx

Keywords:
Autism
Mice
Executive functions
Cognitive control
Response inhibition
Discrimination learning

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.

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).

0166-4328/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2012.05.048

[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 × 24 cm × 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; $F(1,18) = 02$, $p = 0.897$) (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; $F(1,18) = 4.01$, $p = 0.601$) 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 × Strain interaction ($F(2,36) = 7.80$, $p = 0.0015$).

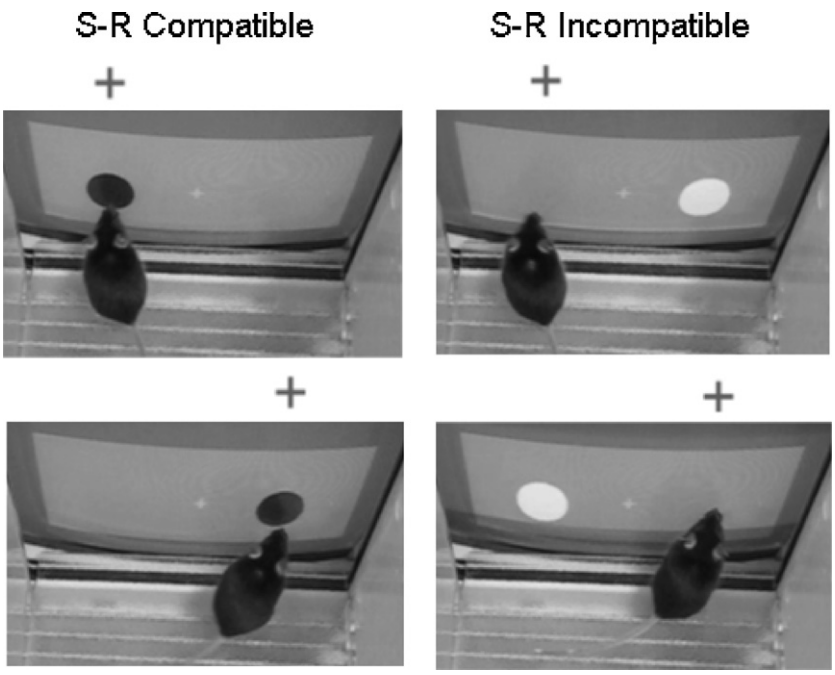

Fig. 1. Contextual rule switching (CRS) task. For 15 consecutive days mice were presented with both S–R compatible and S–R incompatible trials. On S–R compatible trials (e.g., cued by a black circle), the mouse was rewarded for responding to the side where the target was presented. On S–R incompatible trials, the mouse was rewarded for pressing the side opposite to the white circle. The correct response (+) in each condition is indicated.

Whereas the performance of the two strains did not differ significantly during the initial block of testing on first presentation errors (BTBR = 34.0 ± 1.0; C57BL/6J = 33.0 ± 1.4; $F(1,18) = 0.33$, $p = 0.571$), BTBR mice made significantly more first presentation errors on sessions 6 through 10 (BTBR = 28.9 ± 0.5; C57BL/6J = 19.9 ± 1.1; $F(1,18) = 56.16$, $p < 0.0001$) and on the final block, sessions 11 through 15 (BTBR = 23.6 ± 1.4; C57BL/6J = 15.5 ± 1.2; $F(1,18) = 18.53$, $p = 0.0004$). Analysis of repetitive errors on S–R incompatible trials showed a similar pattern. BTBR made more repetitive errors over the 15 test sessions (BTBR = 186.4 ± 15.6, C57BL/6J = 120.6 ± 16.5; $F(1,18) = 8.39$, $p = 0.0096$). The strain difference in repetitive errors was not seen in the first five sessions of testing (BTBR = 115.0 ± 10.5; C57BL/6J = 101.9 ± 17.0; $F(1,18) = 0.43$, $p = 0.52$), but BTBR made more repetitive errors on the middle (BTBR = 47.4 ± 5.0; C57BL/6J = 10.9 ± 2.1; $F(1,18) = 45.26$, $p < 0.0001$) and final (BTBR = 23.9 ± 3.9; C57BL/6J = 7.8 ± 1.8; $F(1,18) = 14$, $p = 0.0014$) blocks of testing.

First presentation and repetitive errors were also analyzed for the S–R compatible condition. On the first 10 S–R compatible trials (session 1), which occurred prior to testing on the S–R incompatible condition, there were only occasional errors made by mice in either group (BTBR 1.0 ± 0.3; C57BL/6J = 1.0 ± 0.3). As training continued, however, the superior learning of the S–R incompatible rule impacted C57BL/6J performance on S–R compatible trials. Over the final 14 S–R compatible sessions, C57BL/6J made significantly more errors on first presentation trials (BTBR = 17.5 ± 2.3, C57BL/6J = 29.4 ± 1.5; $F(1,18) = 18.5$, $p = 0.0004$), however, there was no differences in the number of repetitive errors (BTBR = 6.9 ± 2.2, C57BL/6J = 7.8 ± 1.6; $F(1,18) = 0.11$, $p = 0.7436$).

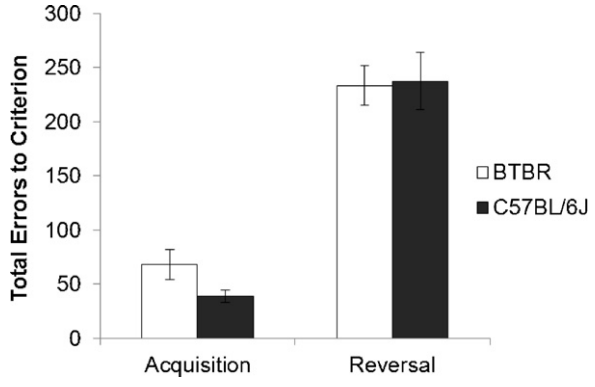

Fig. 2. Performance of BTBR ($n = 10$) and C57BL/6J ($n = 10$) mice did not differ significantly on acquisition and reversal of a visual discrimination. A graph of mean (±SEM) total errors to criterion for BTBR (white) and C57BL/6J (shaded) mice.

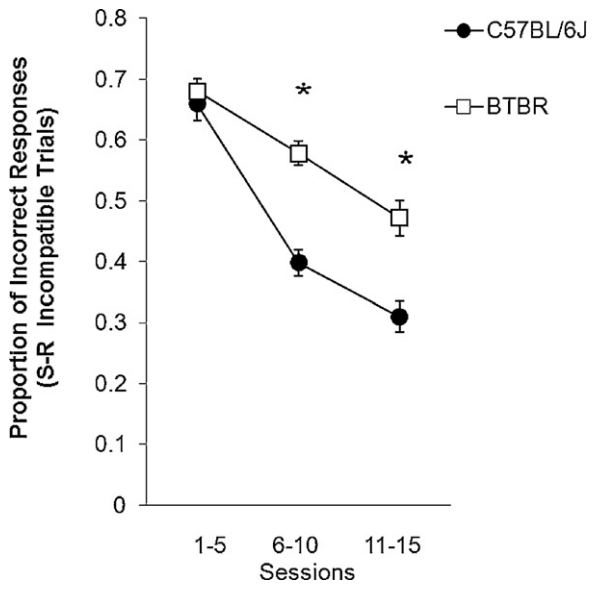

Fig. 3. Impaired performance of BTBR ($n = 10$) compared to C57BL/6J ($n = 10$) mice on S–R incompatible trials of the CRS task. Mean proportion (±SEM) of incorrect responses on S–R incompatible trials (first presentation) over 15 testing sessions. Whereas, the performance of the two strains did not differ during the initial block of testing, BTBR mice made significantly more errors thereafter. *$p < 001$.

4. Discussion

It is now well documented that BTBR mice exhibit behavioral traits that are similar to the diagnostic symptoms of ASD, including minimal social interactions, abnormal patterns of vocalizations, and repetitive behaviors [13]. Children and adults with ASD also display a specific cognitive phenotype. While executive function deficits are among the most frequently reported symptoms of ASD, not all executive abilities are compromised. The present results demonstrate that BTBR display a similar pattern of cognitive impairments. BTBR mice learned to discriminate line stimuli as readily as C57BL/6J controls. Moreover, no differences between BTBR and control mice were evident on discrimination reversal either in early perseverative or later attention-type errors.

While their ability to inhibit prepotent responding on the discrimination reversal was not impaired, BTBR mice made significantly more errors on the S–R incompatible component of CRS, a task that required inhibiting contextually inappropriate responses. On S–R incompatible trials, BTBR made more first-choice, as well as repeated, errors over the 15 days of testing. Thus, similar to individuals with ASD, BTBR mice exhibit deficits in cognitive control on rule switching tasks that require active use of contextual information but perform normally on tasks where rule switching is more automatic. Perhaps not surprisingly, BTBR made fewer errors on S–R compatible trials than C57BL/6J mice. Whereas the S–R compatible performance of C57BL/6J mice was slightly compromised as they learned a second, opposing S–R mapping, BTBR mice continued to respond automatically on compatible trials throughout CRS testing. Hikosaka and Isoda have recently distinguished between two modes of behavioral switching, retrospective and prospective [29]. Switching that occurs such as on discrimination reversal is based solely on error feedback, whereas prospective switching, needed for successful performance on the CRS task, requires the use of contextual cues. The present results indicate that BTBR mice are able to switch a behavioral routine retrospectively, but are severely impaired when prospective switching is essential. Amodeo et al. also found that task demands are critical in determining whether BTBR mice exhibit intact or impaired executive functions [30]. Here, mice of the BTBR strain learned a spatial discrimination and spatial reversal as readily as C57BL/6J when tested with 100% reinforcement, but were impaired when task demands were increased by shifting reward to an 80%/20% schedule.

While it is now evident that BTBR mice display both cognitive and social phenotypes that resemble ASD, the neural mechanisms responsible for the abnormalities remain unknown. BTBR mice display a number of neuroanatomical and neurochemical alterations that could contribute to these behavioral differences. Previous findings indicate that the ability to inhibit perseverative responding and attend to critical aspects of stimuli during reversal learning require different cognitive processes and depend on different subregions of the prefrontal cortex [26,28]. The fact that BTBR mice were not impaired on any stage of the reversal task suggests the neural disruption in these animals is not specific to prefrontal circuits. Other studies have focused on abnormalities in neural connectivity that characterized the strain, e.g., lack of a corpus callosum, to explain the behavioral characteristics of BTBR mice (low sociability, high levels of repetitive behavior) that resemble ASD. However, LP/J mice, an inbred strain genetically close to BTBR, but with an intact callosum, display similar ASD-like traits [31]. Moreover, these investigators found that early postnatal lesions of the corpus callosum in C57BL/6J mice had no effect on these behaviors. Although BTBR mice were not impaired on the reversal problem, they displayed a striking deficit on CRS, a task designed as a mouse analogue of cognitive control paradigms (e.g., Dots, Preparing to Overcome Prepotency Task) used to show executive deficits in ASD [20,23]. Imaging studies have shown that the impairments evident in individuals with ASD may be related to functional underconnectivity between frontal and parietal regions [21]. Thus, while the callosal abnormality may in itself be an insufficient explanation for the behavioral phenotype of BTBR mice, it may reflect a more general disruption of white matter pathways. Interestingly, the BTBR and LP/J strains carry a deletion of the DISC1 (Disrupted In Schizophrenia 1) gene [2]. DISC1 is a major risk factor for a variety of neurodevelopmental disorders including ASD [32,33]. Animal studies of the DISC1 protein have established several roles for DISC1 in neuronal development including proliferation, migration, and differentiation [34]. Osbun et al. have recently found that DISC1 is highly expressed in the embryonic corpus callosum and is likely critical for neurite outgrowth throughout the cerebral cortex [35].

The present findings add to the expanding literature showing resemblances in behavioral symptoms between BTBR mice and individuals with ASD. As the mechanisms underlying ASD remain poorly understood, a relevant animal model will be invaluable in helping unravel underlying circuit dysfunctions and aid in the investigation of potential therapeutic avenues. The demonstration of both intact and impaired executive functions in BTBR mice illustrates the importance of developing new cognitive assays, such as the CRS task, for accurate assessment of cognitive abilities in animal models of ASD and other human brain disorders.

References

[1] Wahlsten D. Survey of 21 inbred mouse strains in two laboratories reveals that BTBR T/+tf/tf has severely reduced hippocampal commissure and absent corpus callosum. Brain Research 2003;971:47–54.
[2] Clapcote SJ, Roder JC. Deletion polymorphism of Disc1 is common to all 129 mouse substrains: implications for gene-targeting studies of brain function. Genetics 2006;173:2407–10.
[3] Gould GG, Hensler JG, Burke TF, Benno RH, Onaivi ES, Daws LC. Density and function of central serotonin (5-HT) transporters, 5-HT1A and 5-HT2A receptors, and effects of their targeting on BTBR T+tf/J mouse social behavior. Journal of Neurochemistry 2011;116:291–303.
[4] Yang K, Sheikh AM, Malik M, Wen G, Zou H, Brown WT, et al. Up-regulation of Ras/Raf/ERK1/2 signaling and ERK5 in the brain of autistic subjects. Genes, Brain and Behavior 2011;10:834–43.
[5] Zou H, Yu Y, Sheikh AM, Malik M, Yang K, Wen G, et al. Association of upregulated Ras/Raf/ERK1/2 signaling with autism. Genes, Brain and Behavior 2011;10:615–24.
[6] Bolivar VJ, Walters SR, Phoenix JL. Assessing autism-like behavior in mice: variations in social interactions among inbred strains. Behavioural Brain Research 2007;176:21–6.
[7] McFarlane HG, Kusek GK, Yang M, Phoenix JL, Bolivar VJ, Crawley JN. Autism-like behavioral phenotypes in BTBR T+tf/J mice. Genes, Brain and Behavior 2008;7:152–63.
[8] Moy SS, Nadler J, Young N, Perez A, Holloway L, Barbaro R, et al. Mouse behavioral tasks relevant to autism: phenotypes of 10 inbred strains. Behavioural Brain Research 2007;176:4–20.
[9] Scattoni ML, Gandhy SU, Ricceri L, Crawley JN. Unusual repertoire of vocalizations in the BTBR T+tf/J mouse model of autism. PLoS ONE 2008;3:e3067.
[10] Wohr M, Roullet FI, Crawley JN. Reduced scent marking and ultrasonic vocalizations in the BTBR T+tf/J mouse model of autism. Genes, Brain and Behavior 2011;10:35–43.
[11] Moy SS, Nadler JJ, Young NB, Nonneman RJ, Segall SK, Andrade GM, et al. Social approach and repetitive behavior in eleven inbred mouse strains. Behavioural Brain Research 2008;191:118–29.
[12] Pearson BL, Pobbe RL, Defensor EB, Oasay L, Bolivar VJ, Blanchard DC, et al. Motor and cognitive stereotypies in the BTBR T+tf/J mouse model of autism. Genes, Brain and Behavior 2011;10:228–35.
[13] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition Washington, DC: American Psychiatric Association; 2000 [text revision ed.].
[14] Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. Journal of Child Psychology and Psychiatry 1996;37:51–87.
[15] Brown RE. Behavioural phenotyping of transgenic mice. Canadian Journal of Experimental Psychology 2007;61:328–44.
[16] Zagreda L, Goodman J, Druin DP, McDonald D, Diamond A. Cognitive deficits in a genetic mouse model of the most common biochemical cause of human mental retardation. The Journal of Neuroscience 1999;19:6175–82.
[17] Hill EL. Evaluating the theory of executive dysfunction in autism. Developmental Review 2004;24:189–233.
[18] Ozonoff S, Strayer DL. Inhibitory function in nonretarded children with autism. Journal of Autism and Developmental Disorders 1997;27:59–77.

[19] Ozonoff S, Jensen J. Brief report: specific executive function profiles in three neurodevelopmental disorders. Journal of Autism and Developmental Disorders 1999;29:171–7.
[20] Solomon M, Ozonoff SJ, Cummings N, Carter CS. Cognitive control in autism spectrum disorders. International Journal of Developmental Neuroscience 2008;26:239–47.
[21] Solomon M, Ozonoff SJ, Ursu S, Ravizza S, Cummings N, Ly S, et al. The neural substrates of cognitive control deficits in autism spectrum disorders. Neuropsychologia 2009;47:2515–26.
[22] Davidson MC, Amso D, Anderson LC, Diamond A. Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. Neuropsychologia 2006;44:2037–78.
[23] Diamond A, Briand L, Fossella J, Gehlbach L. Genetic and neurochemical modulation of prefrontal cognitive functions in children. The American Journal of Psychiatry 2004;161:125–32.
[24] Brigman JL, Bussey TJ, Saksida LM, Rothblat LA. Discrimination of multidimensional visual stimuli by mice: intra- and extradimensional shifts. Behavioral Neuroscience 2005;119:839–42.
[25] Bussey TJ, Saksida LM, Rothblat LA. Discrimination of computer-graphic stimuli by mice: a method for the behavioral characterization of transgenic and gene-knockout models. Behavioral Neuroscience 2001;115:957–60.
[26] Brigman JL, Rothblat LA. Stimulus specific deficit on visual reversal learning after lesions of medial prefrontal cortex in the mouse. Behavioural Brain Research 2008;187:405–10.
[27] Brigman JL, Padukiewicz KE, Sutherland ML, Rothblat LA. Executive functions in the heterozygous reeler mouse model of schizophrenia. Behavioral Neuroscience 2006;120:984–8.
[28] Chudasama Y, Robbins TW. Dissociable contributions of the orbitofrontal and infralimbic cortex to pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. The Journal of Neuroscience 2003;23:8771–80.
[29] Hikosaka O, Isoda M. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. Trends in Cognitive Sciences 2010;14:154–61.
[30] Amodeo DA, Jones JH, Sweeney JA, Ragozzino ME. Differences in BTBR T+tf/J and C57BL/6J mice on probabilistic reversal learning and stereotyped behaviors. Behavioural Brain Research 2012;227:64–72.
[31] Yang M, Clarke AM, Crawley JN. Postnatal lesion evidence against a primary role for the corpus callosum in mouse sociability. European Journal of Neuroscience 2009;29:1663–77.
[32] Kilpinen H, Ylisaukko-Oja T, Hennah W, Palo OM, Varilo T, Vanhala R, et al. Association of DISC1 with autism and Asperger syndrome. Molecular Psychiatry 2008;13:187–96.
[33] Sawamura N, Sawa A. Disrupted-in-schizophrenia-1 (DISC1): a key susceptibility factor for major mental illnesses. Annals of the New York Academy of Sciences 2006;1086:126–33.
[34] Lee FH, Fadel MP, Preston-Maher K, Cordes SP, Clapcote SJ, Price DJ, et al. Disc1 point mutations in mice affect development of the cerebral cortex. The Journal of Neuroscience 2011;31:3197–206.
[35] Osbun N, Li J, O'Driscoll MC, Strominger Z, Wakahiro M, Rider E, et al. Genetic and functional analyses identify DISC1 as a novel callosal agenesis candidate gene. American Journal of Medical Genetics Part A 2011;155A:1865–76.