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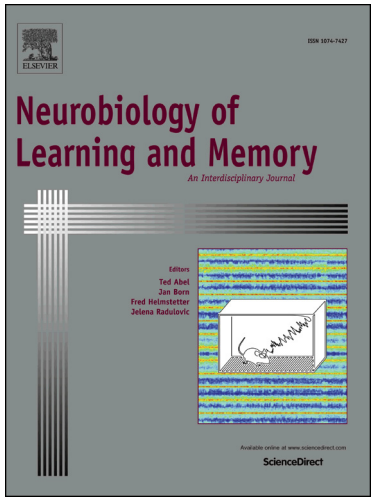

Mice heterozygous for an inactivated allele of the schizophrenia associated *Brd1* gene display selective cognitive deficits with translational relevance to schizophrenia

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Title: Mice heterozygous for an inactivated allele of the schizophrenia associated *Brd1* gene display selective cognitive deficits with translational relevance to schizophrenia

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ABSTRACT

Schizophrenia is a debilitating brain disorder characterized by disturbances of emotion, perception and cognition. Cognitive impairments predict functional outcome in schizophrenia and are detectable even in the prodromal stage of the disorder. However, our understanding of the underlying neurobiology is limited and procognitive treatments remain elusive. We recently demonstrated that mice heterozygous for an inactivated allele of the schizophrenia-associated *Brd1* gene (*Brd1*$^{+/-}$ mice) display behaviors reminiscent of schizophrenia, including impaired social cognition and long-term memory. Here, we further characterize performance of these mice by following the preclinical guidelines recommended by the 'Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)' and 'Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS)' initiatives to maximize translational value. *Brd1*$^{+/-}$ mice exhibit relational encoding deficits, compromised working and long term memory, as well as impaired executive cognitive functioning with cognitive behaviors relying on medial prefrontal cortex being particularly affected. Akin to patients with schizophrenia, the cognitive deficits displayed by *Brd1*$^{+/-}$ mice are not global, but selective. Our results underline the value of *Brd1*$^{+/-}$ mice as a promising tool for studying the neurobiology of cognitive deficits in schizophrenia.

INTRODUCTION

The distal end of chromosome 22q is known to harbor genes implicated in brain functions as evident from patients with 22q13 deletion syndrome (22q13 DS) in whom intellectual disability, impaired learning as well as autism and bipolar disorder have been reported (Nesslinger et al., 1994; Phelan & McDermid, 2011). The region seems to harbor a shared schizophrenia and bipolar disorder susceptibility locus (Jorgensen et al., 2002) and case-control studies have repeatedly found associations of the bromodomain containing 1 gene (*BRD1)* within this region, to both disorders (Nyegaard et al., 2010; Purcell et al., 2009; Severinsen et al., 2006). Notably, *BRD1* features among the highest ranking schizophrenia associations in a combined GWAS meta-analysis and family-based replication study (Aberg et al., 2013), is located in a genome-wide significant schizophrenia risk locus identified using an Empirical Bayes statistical approach (Andreassen, Thompson, & Dale, 2014), and shows gene-wise significant association in the currently largest schizophrenia GWAS mega-analysis (Pardiñas et al., 2016). Furthermore, a schizophrenia case with a disruptive nonsense mutation in *BRD1,* which is highly intolerant to loss of function mutations (Lek et al., 2016), was recently reported (Purcell et al., 2014). *BRD1* encodes the bromodomain containing 1 protein (BRD1), which has been identified in complexes possessing acetyltransferase activity towards histone H3 (Doyon et al., 2006; Fryland et al., 2016; Mishima et al., 2011), and has been shown to control the expression of large gene sets (Fryland et al., 2016; Mishima et al., 2011; Qvist et al., 2016; Rajkumar et al., 2015). Intriguingly, the BRD1 interaction network is significantly enriched with genes implicated with early brain development and psychiatric illness (Fryland et al., 2016), thus emphasizing its role in managing mental health through transcriptional control.

We have recently reported changes in behaviors, neurochemistry and neuronal signaling in a genetically modified mouse strain heterozygous for a inactivated allele of the *Brd1* gene (*Brd1*$^{+/-}$ mice) (Qvist et al., 2016). In line with its role in chromatin remodeling, decreased *Brd1* expression affected cerebral expression of large gene sets enriched with genes implicated in the etiopathology of mental disorders (Qvist et al., 2016). In concordance, *Brd1*$^{+/-}$ mice were characterized by altered social behaviors, deficits in social cognition, impaired associative learning and long term memory combined with increased sensitivity to psychostimulants - including, impaired Prepulse inhibition (PPI) and working memory performance upon challenge with Phencyclidine (PCP) (Qvist et al., 2016). While acknowledging that several of the observed phenotypes, including cognitive deficits, are central in 22q13 DS, bipolar disorder, and other neuropsychiatric disorders, the constellation of phenotype characteristics of *Brd1*$^{+/-}$ mice appears to have special translational relevance to schizophrenia.

Schizophrenia is a clinically heterogeneous disorder (Jablensky, 2010; Kendell & Jablensky, 2003) and the degree of cognitive deficits vary among patients. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Marder & Fenton, 2004) and the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Carter & Barch, 2007) initiatives have collectively identified nine cognitive domains that are affected in schizophrenia (**Table 1**) and have suggested corresponding pre-clinical rodent tasks to assess several of these cognitive domains (Arguello & Gogos, 2010; Dudchenko, Talpos, Young, & Baxter, 2013; Gilmour et al., 2013; Lustig, Kozak, Sarter, Young, & Robbins, 2013; Markou et al., 2013; Siegel, Talpos, & Geyer, 2013; J. Young & Geyer, 2015; J. W. Young, Powell, Risbrough, Marston, & Geyer, 2009). In the present study, we have performed an extensive cognitive characterization of *Brd1*$^{+/-}$ mice

using a battery of behavioral tasks focused on assessing important cognitive domains affected in schizophrenia.

METHODS

Animals: A mouse line heterozygous for a targeted deletion in the *Brd1* gene was generated by TaconicArtemis GmbH (Cologne, Germany) on a congenic C57BL/6NTac genetic background as previously described (Qvist et al., 2016). Mice were bred and housed until the age of 6 weeks at Taconic MB A/S (Lille Skensved, Denmark) and tail biopsies were collected for Polymerase Chain Reaction based genotyping after weaning (P21). Only male mice were used in the study. For tests, conducted at the facilities of H. Lundbeck A/S (HLu), 4-8 $Brd1^{+/-}$ and wild type (WT) mice were group housed under controlled laboratory conditions (temperature:21±2°C; humidity:55±5%) for a minimum of one week before behavioral testing. For tests, conducted at the facilities of Aarhus University (AU), mice were group housed 2–6 mice per cage and maintained on 23±2°C temperature. Mice were kept on a 12:12h light–dark cycle. Mice were housed in Macrolon (type II) cages with standard sawdust bedding and standard rodent food and tap water available *ad libitum* (unless stated differently). The cages were enriched with igloos, wooden chew blocks and paper for nesting.

Delayed alternation (DA - HLu): Mice were housed in pairs of two ($Brd1^{+/-}$/WT) one week prior to training and throughout the test period with water access limited to 20 hours/day following test session. Test was conducted in a Y-maze of grey Plexiglas, placed on down-flow table. All arms of the maze were of similar dimensions (20.7 × 8 × 12 cm) with two-cup drinking units at the end of each choice arm. Center-most cup contained 15µl Chocolate milk (Matilde (mild), Arla Foods Amba, Denmark) at all times to mask odor cues from the reward cups. Only reward cups were accessible during trials.

During habituation phase (day 1 and 2), mice were placed in the maze and allowed to explore both goal arms with free access to rewards. During training (day 3-9), mice were placed at the base of the start arm and allowed one information run, in which, one choice arm was blocked (randomly alternating between trials). Once reward was consumed, mice were gently guided back to the start arm. Mice were then allowed to choose between the previously entered arm and the un-explored arm (choice run). 6 such paired information/choice runs were conducted on the first day of training and then 10 trials per day until mice reached a criterion of 9 correct choices out of 10. On the day of the test (day 10), only mice reaching the 90% criterion with 7 days of training were included. Mice were given 20 balanced trials with or without 90 seconds retention between information and choice runs. Average performance was scored for each delay.

Eight arm radial maze (8ARM - AU): Food access was limited to 8 hours per day on the days before the test (9 a.m. to 5 p.m.), while they had free access to water, until their body weights were reduced to approximately 85% of their free feeding weight. The apparatus had 8 arms (30 × 5 cm) with 15 cm high non-transparent walls, radiating from an octagonal central platform. Distal end of each arm had a well to keep the food pellets and the proximal end was guarded by a door. Test room was illuminated at 50 lux. Maze was provided with multiple fixed internal cues in the form of stickers (flags on baited arms, hearts on non-baited arms). During the first training session, food pellets were scattered on the whole maze and mice were allowed to explore freely for 15 minutes. In two additional 15 minutes training sessions (one session/day), food pellets were available in all 8 arms – but only in wells. The protocol included 10 trials (one trial/day), during which only three (always the 1st, 2nd and the 4th.) arms were baited. Mice were placed in the central platform of the maze and, after a 10 seconds confinement period, doors of all arms were opened simultaneously. Trial were terminated once mice

completed eating all three food pellets or after a period of 10 minutes. Behaviors were recorded and were scored by the Ethovision XT 8.0 software (Noldus, Spink, & Tegelenbosch, 2001). We defined working memory errors as the number of re-entries to baited arms. We defined long-term reference memory errors as the number of entries to never-baited arms (Zlomuzica, Ruocco, Sadile, Huston, & Dere, 2009).

Morris water maze (MWM - HLu): Our test settings and procedures were essentially as described in Podhorna & Didriksen (Podhorna & Didriksen, 2005). Briefly, each mouse received 4 trials per day for 4 consecutive days. Starting position for each trial was randomized and trials were terminated, when platform (always located in the North quadrant) was found or when 60 seconds had elapsed. If the mouse did not find the platform, it was gently guided there. All mice were allowed to orientate on the platform for 15 seconds after each trial. Probe test was performed with the platform removed, followed by a flag test with position of platform clearly marked. Latency to locate the platform was measured in three consecutive trials. Distance travelled in each quadrant was analyzed using EthoVision 3.0 software (Noldus, The Netherlands).

Context and cue dependent fear conditioning (AU): We tested mice in an automated TSC fear conditioning system v8.06 (TSE systems GmbH, Germany). On the first day, mice were placed in an illuminated chamber with transparent walls and metal grid floor (context A). After 120 seconds of acclimation period, 5 pairings of conditioned stimulus (CS) were provided (30 seconds, 80db, white noise), followed by unconditioned stimulus (UCS) (0.7mA foot shock for 2 seconds). Inter-pairing intervals varied with an average of 60 seconds (30-120 seconds). 120 seconds of consolidation period was allowed. On the next day, mice were returned to context A and freezing behavior was assessed for three minutes, without CS or UCS. During day three, mice were placed in a novel dark opaque

chamber with wooden floor (context B). One CS, not followed by the UCS, was provided after 120 seconds acclimation period and mice were observed for three minutes. This was followed by a series of 14 CS without UCS, with 15 seconds interval between the stimuli. After this cue extinction procedure, 120 seconds of consolidation was allowed. On the fourth day, mice were returned to context B. After 120 seconds of acclimation period, one CS was provided, not followed by the UCS, and mice were observed for extinction retrieval behaviors for 5 minutes. The principal index of learning was freezing behavior defined by the absence of any visible movements except those required for respiration (Whittle, Hauschild, Lubec, Holmes, & Singewald, 2010) and was scored by TSC FCS v8.06 software.

Attentional Set Shifting Task (ASST - HLu): The apparatus was the same as used by Laurent & Podhorna (Laurent & Podhorna, 2004). During trials, cylindrical plastic food cups (40 mm diameter, 35 mm high) cups were filled with a layer of scented digging medium (20 mm) and one cup was baited with a small piece of cereal (30 mg; Honey Nut Loop, Kellogg). Small pieces of grained bait were mixed with digging media to mask for eventual odor cues.

Tactile stimuli (type of digging medium) or olfactory stimuli (scent of the digging medium) indicated the presence or absence of reward in cups. Three linked odor and digging medium pairs were used (See **Table S1**). The combinations of exemplars were the same for all mice and one of the components of the exemplar was pseudo-randomly associated with the reward.

The procedure was a modified from Colacicco *et al.* (Colacicco, Welzl, Lipp, & Würbel, 2002) and consisted of 2 parts; a 3-day habituation/training period and a 4-day testing period. From three days prior to the onset of training and onwards, mice were food restricted by allowing only 18 hours of access to food per day (3 p.m. to 9 a.m.) to reduce body weight to approximately 85% of their free feeding weight.

Habituation and training: Following feeding, a food bowl, filled with sawdust, pieces of reward as well as small mixture of experimental digging media (each day a different selection), was left in the home cage overnight. Mice were habituated to the testing cage by allowing them to freely explore the setting for 10 minutes. On the last day of habituation/training, mice were given consecutive trials with unlimited free access to two sawdust-filled baited bowls in the testing cage. This was sufficient to guarantee reliable digging on the subsequent discrimination trials.

Testing: In the first 4 trials on day 1 (exploratory trials), mice were allowed to dig in both bowls, and an error was recorded if the first dig occurred in the unbaited bowl. From trial 5 and onward, mice were allowed to dig in one bowl only. If mice started to dig in the unbaited bowl, an error was recorded and the trial was terminated immediately. The side of stimulus presentation varied pseudo-randomly. Testing continued until mice reached the criterion of 6 consecutive correct trials.

Experimental design: Male *Brd1*$^{+/-}$ mice and their WT littermates were tested in young adulthood (8-11 weeks of age) in their light cycle. Each group consisted of 9-15 mice (see figure legends for exact numbers). Observer was always blinded to the genotypes of the mice. Mazes and choice chamber were cleaned with ethanol between tests to avoid olfactory cues. All studies were carried out in accordance with Danish legislation, and permission for the experiments was granted by the animal welfare committee, appointed by the Danish Ministry of Food, Agriculture and Fisheries – Danish Veterinary and Food Administration.

Data analyses: All variables were initially analyzed using descriptive statistics. We checked whether all continuous variables followed Gaussian distribution by one-sample Kolmogorov-Smirnov tests. t-test or Mann-Whitney U tests were used to assess the statistical significance of the differences on a continuous variable between two groups. Two-way repeated measures analysis of variance

(RMANOVA) was used to assess the differences evolving over time. All analyses were completed using Graphpad Prism 5.04 (GraphPad software, San Diego, CA, USA).

RESULTS

Delayed alternation: In rodents, working memory has classically been synonymous with short-term spatial or visual-spatial memory (Dudchenko et al., 2013) and delay-dependent tasks has been suggested as a way of assessing this domain in mice (J. Young & Geyer, 2015)**.** In this study, we employed the delayed alternation variant of the Y maze task (Rossi et al., 2012). All mice learned to complete the spatial discrimination task with a 90% criterion level of alternation within the 7 day training session with no overall difference in performance between genotypes (**Figure 1a,** genotype effect, $F_{1, 22}$=1.03, p=0.322). Further, *Brd1*$^{+/-}$ and WT mice displayed similar levels of alternation when choice runs followed immediately after information runs, but when a 90 seconds delay was introduced, *Brd1*$^{+/-}$ mice displayed significantly less alternation than WT mice (**Figure 1b and Figure S1**, genotype effect, $F_{1.36}$=6.438 , p=0.016).

8 arm radial maze: 8ARM is widely used with many variations to assess spatial and non-spatial working as well as reference memory of mice (Sharma, Rakoczy, & Brown-Borg, 2010) and has been recommended as a preclinical CNTRICS task for assessing memory in rodents (Dudchenko et al., 2013). Consistent with the outcome of the delayed alternation task, we found that *Brd1*$^{+/-}$ mice made significantly more working memory errors than the WT controls (**Figure 1c**, genotype effect, $F_{1, 27}$=8.10, p=0.008) in the 8ARM. Additionally, *Brd1*$^{+/-}$ mice made significantly more entries into unbaited arms than WT mice (**Figure 1d**, genotype effect, $F_{1, 27}$=11.04, p=0.003).

Morris water maze: MWM assesses spatial reference memory that relies on extra-maze visual cues and the task has been suggested as a preclinical MATRICS rodent task for visual learning and memory (J. W. Young et al., 2009). *Brd1*$^{+/-}$ mice did not differ significantly from the WT controls on escape distance (**Figure 1e**, genotype effect, $F_{1, 25}$=0.48, p=0.490) during the acquisition phase. In the probe

test, both *Brd1*$^{+/-}$ and WT mice spent significantly more time in the target quadrant than in other quadrants, and *Brd1*$^{+/-}$ mice did not differ significantly from WT mice on their performance (**Figure 1f and Figure S2a**, t-test with Welch's correction, p=0.934). Flag test confirmed that both groups were motivated to escape the water and that vision was not impaired in *Brd1*$^{+/-}$ mice (**Figure S2b**, t-test with Welch's correction, p=0.229).

Cue and context dependent fear conditioning: Fear conditioning (FC) paradigm has been employed to test relational encoding and retrieval in several mutant mouse models for schizophrenia (Bhardwaj et al., 2009; Qiu et al., 2006; Tang et al., 1999) and has been suggested as a test for associative learning and declarative memory (Arguello & Gogos, 2010). *Brd1*$^{+/-}$ mice did not differ significantly on their baseline activity in context A before first presentation of UCS (**Figure S3a**, t-test, p=0.619). During the acquisition phase, *Brd1*$^{+/-}$ mice displayed significantly less freezing behaviors than WT mice (**Figure 2a**, genotype effect, $F_{1, 28}$=11.56, p=0.002). When returned to the context A on the second day, *Brd1*$^{+/-}$ mice displayed significantly less freezing behaviors than WT mice (**Figure 2b and Figure S3b**, t-test, p<0.001). On the third day, *Brd1*$^{+/-}$ and WT mice did not differ significantly on their freezing behaviors in novel context B, before first presentation of CS (**Figure S3c**, Mann Whitney U test, p=0.144). However, after first presentation of CS without UCS, *Brd1*$^{+/-}$ mice showed significantly less freezing behaviors than the WT mice (**Figure 2c and Figure S3d**, Mann-Whitney U test, p=0.017). Genotypes did not differ significantly on their extinction retrieval behaviors on fourth day of testing (**Figure S3e**, t-test, p=0.785).

Attentional set shifting task: ASST examines the ability to learn new rules, to alter behavior when facing reversal conditions and to acquire, maintain as well as shift attentional sets (Gilmour et al., 2013; J. Young & Geyer, 2015). *Brd1*$^{+/-}$ and WT mice both learned to readily dig for the bait in the

food bowls during the training sessions and appeared equally motivated to search for food in the initial simple discrimination (SD) phase of the task. However, *Brd1*$^{+/-}$ mice required significantly more trials to reach criteria in the SD test (**Figure 3 and Figure S4**, t-test, p=0.017) than WT mice. Compound discrimination (CD) task was considered a repetition of the SD task. Hence, after learning the SD task, the performance of WT and *Brd1*$^{+/-}$ mice did not differ significantly in CD task (**Figure 3 and Figure S4**, Mann-Whitney U test, p=0.384). Similarly, *Brd1*$^{+/-}$ mice performed *at par* with WT controls in the compound discrimination repeat (CDR) task (**Figure 3 and Figure S4**, t-test, p=0.197), demonstrating that reversal learning was unaffected by decreased *Brd1* expression. *Brd1*$^{+/-}$ mice did not differ significantly from WT mice on the number of trials required to complete and to repeat the intra-dimensional (ID) shift tasks (**Figure 3 and Figure S4**, t-test, p=0.153 and Mann-Whitney U test, p=0.471, respectively), and showed that they were capable of forming and maintaining attentional sets. *Brd1*$^{+/-}$ mice needed more trials to solve the extra-dimensional (ED) shift than the preceding ID shift (**Figure 3 and Figure S4**, t-test, p<0.001), suggesting the development of an attentional set in the mice during the task. The same was the case for WT mice although much less pronounced (**Figure 3 and Figure S4,** Mann-Whitney U test, p=0.048). When comparing *Brd1*$^{+/-}$ and WT mice on their performance in the ED shift, *Brd1*$^{+/-}$ mice required significantly more trials to criteria (**Figure 3 and Figure S4**, t-test, p=0.023).

DISCUSSION

Effective treatments for cognitive symptoms remain an unmet need in schizophrenia. While advances have been made towards understanding the underlying neurobiology, further insight is essential for translational success (Aleman, 2014; Lett, Voineskos, Kennedy, Levine, & Daskalakis, 2014; J. Young & Geyer, 2015). Following strong and replicated genetic association findings of *BRD1* with schizophrenia (Aberg et al., 2013; Andreassen et al., 2014; Nyegaard et al., 2010; Pardiñas et al., 2016; Purcell et al., 2009; Severinsen et al., 2006), behavioral alterations with translational relevance to schizophrenia, including impaired performance in a number of cognitive tasks, have been documented in *Brd1*$^{+/-}$ mice (Qvist et al., 2016). The present study elaborates the cognitive characterization of *Brd1*$^{+/-}$ mice by employing additional rodent tasks with translational value to the cognitive domains affected in schizophrenia. These results further highlight the *Brd1*$^{+/-}$ mouse model as a valuable tool for studying the neurobiology of schizophrenia. We summarize the cognitive deficits of *Brd1*$^{+/-}$ mice in **Table 2**.

Although none of the cognitive deficits are pathognomonic of schizophrenia, the MATRICS and CNTRICS initiatives have specifically highlighted working memory, speed of processing, attention and vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, perception, long term memory and social cognition as affected domains in schizophrenia (Carter & Barch, 2007; Marder & Fenton, 2004). Except verbal learning and memory, the other cognitive domains can be tested in rodent models with varying levels of difficulty (J. W. Young et al., 2009). We have already reported long-term social and declarative memory deficits in *Brd1*$^{+/-}$ mice. Additionally, *Brd1*$^{+/-}$ mice displayed reduced capacity in the glutamatergic transmission to support

perception and working memory as measured by PPI and spontaneous- and continuous alternation tasks in Y maze when challenged by PCP (Qvist et al., 2016).

In the present study, we employed the cognitively more challenging delayed variant of the Y maze alternation task and by this, *Brd1*$^{+/-}$ mice displayed working memory deficits without PCP challenge. Delayed memory is more impaired than immediate recall in schizophrenia (Calev, 2001; Dougherty et al., 1998). Although ceiling effects limits our ability to detect performance changes, *Brd1*$^{+/-}$ mice did not differ from WT mice when there was no delay between information and choice runs but where significantly impaired when a delay of 90 seconds was introduced. It has however been argued that animal tasks for assessing working memory with translational relevance to schizophrenia should assess span capacity rather than delay capacity (Dudchenko et al., 2013; Gold et al., 2010). Hence we tested *Brd1*$^{+/-}$ mice in 8ARM, which more selectively assesses span capacity (J. Young & Geyer, 2015). We applied a setup with clear intra-maze cues which thereby predominantly assessed non-spatial memory (Schwegler & Crusio, 1995). Performance of *Brd1*$^{+/-}$ mice in the maze confirmed reduced working memory and additionally showed that non-spatial reference memory is disrupted in *Brd1*$^{+/-}$ mice. Intriguingly, *Brd1*$^{+/-}$ mice did not display deficits during MWM, in which performance relies on navigation by means of extra-maze cues and thus spatial memory. However, unlike 8ARM and DA, which involves appetitive motivation, MWM facilitates higher degree of aversive escape motivation and rodents require significantly fewer trials to learn MWM task than 8ARM (Ormerod & Beninger, 2002). Thus, the tendency for rapid learning and emotional arousal (McGaugh, 2013) might have influenced the findings in MWM.

Conditioning curves during FC additionally showed that *Brd1*$^{+/-}$ mice were significantly impaired in learning the associations. Encoding deficits, which are common in schizophrenia (Barch &

Ceaser, 2012), may explain these findings in *Brd1*$^{+/-}$ mice. Further suggestive of learning deficits, *Brd1*$^{+/-}$ mice were significantly slower at learning the SD task in the ASST paradigm. We have previously demonstrated that post acquisition freezing is similar in *Brd1*$^{+/-}$ and WT mice in an alternative FC setup, and that *Brd1*$^{+/-}$ mice display context dependent memory deficits (Qvist et al., 2016). In this study, we additionally show cue dependent memory deficits in *Brd1*$^{+/-}$ mice, thus paralleling the declarative memory deficits in schizophrenia. Seen in the light of previously reported remote social recognition deficits (Qvist et al., 2016), long term memory appear robustly affected in *Brd1*$^{+/-}$ mice.

ASST paradigms are highly analogous to the Wisconsin Card Sorting Task (WCST) which has been extensively studied in patients with schizophrenia (J. W. Young et al., 2009) and can be a useful clinical marker in schizophrenia (Ceaser et al., 2008). *Brd1*$^{+/-}$ mice displayed impaired performance in the extradimensional shift tasks. These deficits indicate a state of cognitive inflexibility as reported in patients suffering from schizophrenia (Pantelis et al., 1999). The ability to form attentional sets was intact in *Brd1*$^{+/-}$ mice, thus demonstrating that their cognitive deficits are not global, but selective, as in schizophrenia (Kuperberg & Heckers, 2000). Reversal learning deficits which have been reported in patients with schizophrenia (McKirdy et al., 2009) were, however, not found in *Brd1*$^{+/-}$ mice, suggesting that their cortical dysfunction is more pronounced in certain frontal regions than others. Specifically, in mice, the medial prefrontal cortex (PFC) is implicated in short-, and long term memory (Euston, Gruber, & McNaughton, 2012) as well as fear memories (Corcoran & Quirk, 2007). In the ASST paradigm, ED shifting performance is impaired in humans with damage to the dorsolateral prefrontal cortex (PFC) (Manes et al., 2002), but the functionally homologue region in rodents is the medial PFC (Bissonette et al., 2008; Brown & Bowman, 2002; Placek, Dippel, Jones, & Brady, 2013).

Reversal learning performance, on the other hand, depends on orbitofrontal functioning across species (Bissonette et al., 2008; Hornak et al., 2004; Placek et al., 2013) and is independent of mPFC function (Placek et al., 2013). Besides medial prefrontal abnormalities, cue- and context dependent associative memory deficits in *Brd1*$^{+/-}$ mice further indicate impaired function of limbic structures like amygdala and hippocampus (Johnson, McGuire, Lazarus, & Palmer, 2012).

Dysfunctions in several cortical and limbic regions have been studied in patients with schizophrenia and alterations in neurotransmission, including frontal dopaminergic deficits, parvalbumin containing GABAergic interneuron abnormalities (Lewis, Curley, Glausier, & Volk, 2012) and NMDA receptor hypofunction (Gilmour et al., 2012) seem to contribute to the cognitive deficits in schizophrenia. Reflecting these features of schizophrenia, *Brd1*$^{+/-}$ mice have pronounced loss of parvalbumin immunoreactive neurons, altered expression of genes implicated in glutamatergic receptor signaling as well as dopamine and serotonin receptors in the anterior cingulate cortex (Qvist et al., 2016). The ability of the NMDA receptor antagonist PCP to uncover working memory deficits of *Brd1*$^{+/-}$ mice hints at reduced capacity in glutamatergic transmission and cortical GABAergic abnormalities and reduced levels of hippocampal dopamine (DA) in *Brd1*$^{+/-}$ mice have further been reported (Qvist et al., 2016).

Cognitive deficits predict functional outcome in schizophrenia (Green, 2006; Green, Kern, & Heaton, 2004) and other brain disorders (Trivedi, 2006). However, available therapeutic options to manage cognitive deficits in mental illness are limited. *Brd1*$^{+/-}$ mice display construct and face validity for schizophrenia (Qvist et al., 2016). In the present study we further highlight their face validity as their cognitive behaviors appear to parallel the cognitive impairments displayed by schizophrenia patients. Given that *BRD1* acts as a transcriptional regulator through epigenetic mechanisms, the

potential importance of the *Brd1*$^{+/-}$ mouse model is emphasized by the current clinical trials with histone deacetylase inhibitors aimed at the treatment of cognitive deficits in schizophrenia (Kline, 2016). Hence, further investigations evaluating the genetic liability of *BRD1* on neurodevelopment and brain functioning are warranted in order to understand the underlying neurobiology of cognitive deficits in schizophrenia.

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LEGENDS TO FIGURES

Figure 1

Brd1$^{+/-}$ mice display impaired cognitive performance in tests addressing learning- and memory. **a**) In the delayed alternation task, *Brd1*$^{+/-}$ mice (*n*=10) and WT mice (*n*=10) both learned to complete the spatial discrimination task with a 90% criterion level of alternation within the 7 day training session with no overall difference in performance between genotypes (**Figure 1a,** genotype effect, $F_{1, 22}$=1.03, *p*=0.322). **b**) When choice run followed immediately after information run, performance of *Brd1*$^{+/-}$ mice did not differ from WT mice, however, in delay testing, performance of *Brd1*$^{+/-}$ mice was significantly worse than WT mice (genotype effect, $F_{1,36}$=6.438 , *p*=0.016, followed by Tukey's *post hoc* test$_{90\ \text{seconds delay}}$, *p*=0.006) demonstrating that their spatial working memory was impaired, Dotted line marks 50% random alternation level. **c**) In the 8 arm radial maze, *Brd1*$^{+/-}$ mice (*n*=15) displayed significantly more entries into already visited arms ($F_{1, 27}$=8.10, *p*=0.008) **d**) and more entries into unbaited arms than WT mice (*n*=14, $F_{1, 27}$=11.04, *p*=0.003) suggestive of impaired working memory and non-spatial reference memory. **e**) *Brd1*$^{+/-}$ (*n*=12) and WT mice (*n*=12) performed equally well in locating the hidden platform in Morris water maze (genotype effect, $F_{1, 25}$=0.48, p=0.490. **f**) Similarly, no difference was seen between the groups in the probe trial (t-test with Welch's correction, *p*=0.934). Data shown are mean + or ±SEM for each group. **p*<0.05 ***p*<0.01 and *n* = number of animals tested.

Figure 2

Brd1$^{+/-}$ mice display impaired encoding and declarative memory in Fear Conditioning test. **a**) *Brd1*$^{+/-}$ mice (n=15) displayed less freezing than the WT mice (n=15) during the conditioning phase ($F_{1, 28}$=11.56, p=0.002). **b**) *Brd1*$^{+/-}$ mice displayed less freezing behaviors (t-test, p<0.001) within the first three minutes, after entering into the conditioned context on the second day, suggestive of context dependent memory deficits. **c**) *Brd1*$^{+/-}$ mice displayed less freezing behaviors (Mann-Whitney U test, p=0.017) during the first presentation of CS (30 seconds) in the novel context on the third day, suggestive of cue dependent memory deficits. Data shown are mean + or ±SEM for each group. *p<0.05; ** p<0.01; *** p<0.001 and n = number of animals tested.

Figure 3

Brd1$^{+/-}$ mice show altered Attentional set-shifting task (ASST) performance. The number of trials to reach the 6 consecutive correct responses (trials-to-criterion) differed significantly between *Brd1*$^{+/-}$ (*n*=9) and WT mice (*n*=9) in the SD task (t-test, *p*=0.017). However in the CD task, performance did not differ between groups (Mann-Whitney U test, *p*=0.384), thus indicating that *Brd1*$^{+/-}$ mice were slower at learning the discrimination than WT littermates. Reversal learning appeared intact in *Brd1*$^{+/-}$ mice (t-test, *p*=0.197) and genotypes performed *at par* in ID shift (t-test, *p*=0.153) and repeat task (Mann-Whitney U test, *p*=0.471). *Brd1*$^{+/-}$ performed significantly worse than WT mice in the ED task (t-test, *p*=0.023), thus revealing executive dysfunction. SD, simple discrimination; CD, complex discrimination; CDR, CD reverse; CDRre, CDR repeat; ID, intradimensional shift; IDre, ID repeat; ED, extradimensional shift. Data shown are mean +SEM for each group. *: *P*<0.05 and *n* = number of animals tested.

Table 1 | An overview of the 9 partly overlapping cognitive domains affected in schizophrenia identified by the MATRICS and CNTRICS initiatives	
MATRICS domains*	**CNTRICS domains****
Speed of processing	Perception
Attention/Vigilance	Attention
Problem solving/reasoning	Executive control
Working memory	Working memory
Verbal learning and memory	Long term memory
Visual learning and memory	
Social cognition	Social/Emotional processing

*(Marder & Fenton, 2004) **(Carter & Barch, 2007)

Table 2 | Summary of cognitive findings in male *Brd1*$^{+/-}$ mice				
Cognitive domain	**Task**	**Cognitive construct**	**Phenotype**	
			Qvist et al., 2016*	**This study**
Perception / precognition	Prepulse inhibition	- Gain control	↓(PCP)	
Working memory	Spontaneous alternation	- Working memory	↓(PCP)*	
	Continuous alternation		↓(PCP)*	
	Delayed alternation			↓
	8 arm radial maze			↓
Long term memory	8 arm radial maze	- Non-spatial reference memory		↓
	Morris water maze	- Spatial reference memory		-
	Fear conditioning			
	- Context dependent retrieval	- Associative memory	↓	↓
	- Cue dependent retrieval			↓
	Social recognition	- Social long term memory	↓	
Learning	Morris water maze	- Visual learning	-	
	Fear Conditioning			
	- Acquisition	- Associative learning	↓	↓
	Attentional set shifting			
	- Simple discrimination	- Rule learning		↓
Social cognition	Social recognition	- Social identification	↓	
Reasoning and problem solving	Attentional set shifting			
	- Reversal discrimination	- Cognitive flexibility / executive functioning		-
	- Extradimensional set shift			↓

PCP: Phencyclidine; ↓: Impaired; -: Intact; *: Reported in (Qvist et al., 2016)

Figure 1

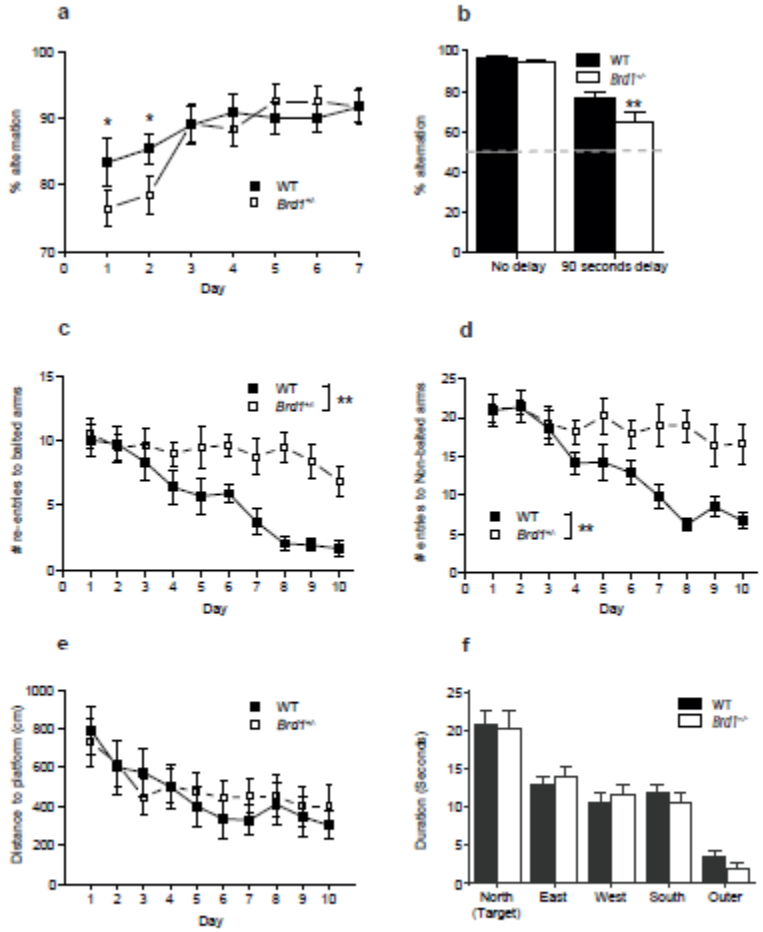

Figure 2

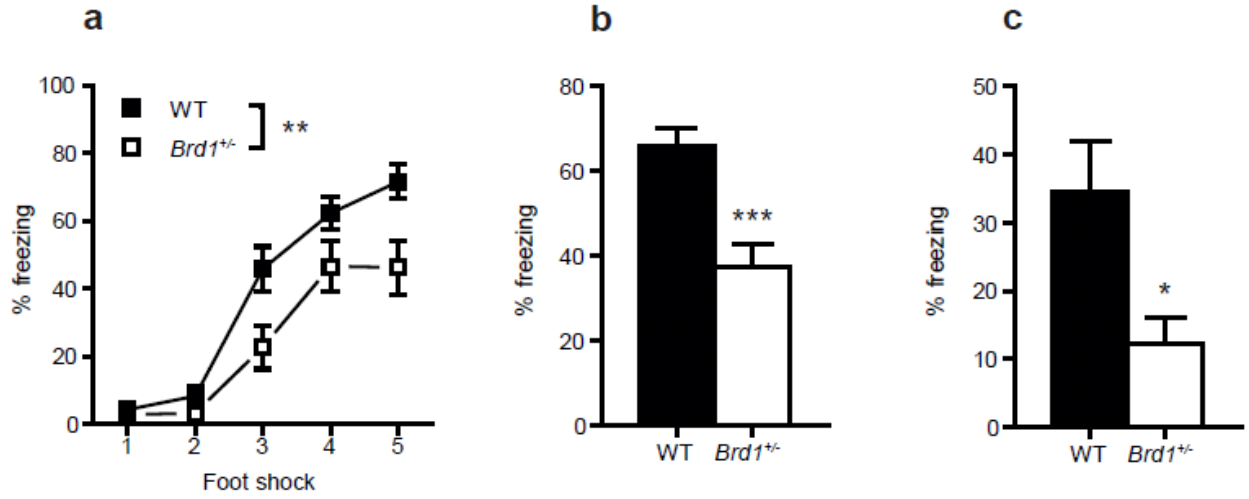

Figure 3