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## Neurobehavioral abnormalities in the dysbindin-1 mutant, *sandy*, on a C57BL/6J genetic background

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### Abstract

Sandy mice have a deletion mutation in the gene encoding dysbindin-1, *Dtnbp1*, with consequent reduction of the protein in heterozygotes and its loss in homozygotes. The sandy mouse thus serves as an animal model of dysbindin-1 function. Since this protein is concentrated in synaptic tissue and affects transmitter release, it may affect neuronal processes that mediate behavior. To investigate the neurobehavioral effects of the *Dtnbp1* mutation, we studied littermate sandy and wild-type controls on a C57BL/6J genetic background. The three animal groups were indistinguishable in their external physical characteristics, sensorimotor skills, and indices of anxiety-like behaviors. In the open field, however, homozygous animals were hyperactive and appeared to show less habituation to the initially novel environment. In the Morris water maze, homozygous animals displayed clear deficits in spatial learning and memory with marginal deficits in visual association learning. Apart from the last mentioned deficits, these abnormalities are consistent with hippocampal dysfunction and in some cases with elevated dopaminergic transmission via D2 dopamine receptors. Since similar deficits in spatial learning and memory have been found in schizophrenia, where decreased dysbindin-1 has been found in the hippocampus, the sandy mouse may also model certain aspects of cognition and behavior relevant to schizophrenia.

### Keywords

anxiety; DTNBP1; dysbindin; habituation; hippocampus; locomotor activity; motor coordination; learning; memory; schizophrenia; water maze

## INTRODUCTION

The sandy or *sd*y mouse is named for an autosomal recessive coat color mutation leading to sandy-colored fur in homozygous (i.e., *sd*y/*sd*y) animals (Swank et al., 1991). The mutation occurred spontaneously in the DBA/2J mouse strain at the Jackson Laboratory in 1983, but its specific locus remained unknown until Li et al. (2003) reported that *sd*y mice have a 38,129 nucleotide deletion in the dystrobrevin binding protein 1 (*Dtnbp1*) gene and that transgenic addition of the complete gene largely restores normal DBA/2J coat color and corrects other phenotypic abnormalities. *Dtnbp1* encodes the protein dysbindin-1, which is reduced in heterozygous (i.e., *sd*y/+) mice and is absent in *sd*y/*sd*y mice (Li et al., 2003). The *sd*y mouse thus serves as an animal model of dysbindin-1 functions.

Discovered by Benson et al. (2001), dysbindin-1 is the largest and most ubiquitously expressed member of the dysbindin protein family (Talbot et al., 2008). It is a highly

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conserved protein expressed by neuronal cell bodies throughout the central nervous system (Talbot et al., 2008). As shown by immunohistochemistry at the electron microscopic level and by western blotting of tissue fractions, dysbindin-1 is also highly concentrated in synaptic tissue, including synaptic vesicles and postsynaptic densities (Talbot et al., 2006). Since this applies to both the cerebral cortex and the hippocampal formation, where loss of dysbindin-1 impairs glutamatergic transmission (Chen et al., 2008; Numakawa et al., 2004), there is reason to believe dysbindin-1 plays a role in neuronal processes mediating animal behavior. Preliminary reports support that view (Askari et al., 2007; Jentsch et al., 2007). These reports, however, are based on studies of *sdv* mice on the original DBA/2J background. Unlike more robust C57BL/6J (BL6) mice, DBA/2J mice are homozygous for four mutations that can affect behavior: (1) cadherin 23<sup>ahl</sup> (Cdh23<sup>ahl</sup> = Cdh<sup>753A</sup>) associated with an age-related hearing loss (Johnson et al., 2000, 2006), (2–3) glycoprotein (transmembrane) nmbR<sup>150X</sup> (GpnmbR<sup>150X</sup>) and tyrosinase-related protein 1<sup>isa</sup> (Tyrp1<sup>isa</sup>) both associated with pigmentary glaucoma (Howell et al., 2007), and finally (4) hemolytic complement<sup>0</sup> (Hc<sup>0</sup>) associated with loss of immune complement component 5 (Wetsel et al., 1990) which impairs inflammatory responses to infection (Allegretti et al. (2005), as well as neuronal and astrocytic responses to excitotoxicity (Pasinetti et al., 2006).

In the present study, we provide the first characterization of the *sdv* behavioral phenotype in animals on a BL6 background for six generations using a battery of neurobehavioral tests. The results revealed that loss of dysbindin-1 is not associated with abnormalities in sensorimotor functions, but is associated with hyperactivity and with deficits in spatial learning and memory ability that are indicative of disrupted hippocampal function (Morris, 2007). Analogous deficits have been found in schizophrenia (Hanlon et al. (2006) with which genetic variation in DTNBP1 has often been associated (Allen et al., 2008; Duan et al., 2007; Williams et al., 2005) and in which reduced synaptic dysbindin-1 has been reported (Talbot et al., 2004). *Sdv* mice may thus model certain features of schizophrenia.

## METHODS & MATERIALS

### Animals

**Breeding**—As noted earlier, the *sdv* autosomal recessive mutation arose spontaneously in DBA/2J mice at the Jackson Laboratory and were maintained as a closed breeding colony using obligate *sdv*/+ mice. The Jackson Laboratory later backcrossed *sdv*/*sdv* mice on the original DBA background with pure C57BL/6J mice for 5 generations and were then intercrossed to obtain homozygous *sdv*/BL6 mice. We again mated males of these sixth generation homozygotes from the Jackson Laboratory with female BL6 mice from the same source. Female and male *sdv*/+ offspring of this mating were then intercrossed to produce all the wild-type, *sdv*/+, and *sdv*/*sdv* mice tested in this study.

**Genotyping & PCR**—While *sdv*/*sdv* mice are readily identified by their sand-colored fur, the coat color of *sdv*/+ mice is not sufficiently different from that of wild type animals to allow reliable identification. All animals were thus genotyped using a duplex polymerase chain reaction (PCR) procedure designed to yield PCR products across the segment of *Dtnbp1* deleted in *sdv* mice (Li et al., 2003). The primers for the wild-type gene, yielding a PCR product of 472 base pairs, were SE3R (5'-AGCTCCACCTGCTGAACATT-3') and SE3F (5'-TGAGCCATTAGGAGATAAGAGCA-3'). The primers for the *sdv* gene, yielding a product of 274 base pairs, were SF (5'-TCCTTGCTTCGTTCTCTGCT-3') and SR (5'-CTTGCCAGCCTTCGTATTGT-3'). The 472 base pair product is detected only in wild-type and *sdv*/+ mice, while the 274 base pair product is detected only in the *sdv*/+ and *sdv*/*sdv* mice. The 472 base pair product is not detected in *sdv*/*sdv* mice.

**Husbandry**—The present study was conducted on 3 genotypes×2 sexes = 6 groups of 10–11 mice each. Mice were housed in same sex cages, 5 per cage and maintained in a temperature/humidity controlled room under circadian light cycle of 12 hrs light/dark with the light cycle beginning at 7:00 am. Mice had access to food and water *ad libitum*. Mice were weaned at postnatal day 21, and all testing began when mice were 3–4 month of age. Animals were allowed to acclimate to testing rooms for one hour prior to testing. All behavioral tests were performed between 10:30 a.m. - 6:00 p.m. The animals had never experienced any form of behavioral testing prior to the studies described here, and the order of the testing was designed to proceed from the least stressful to the most stressful tests. While behavioral testing was conducted blind to genotype for the wild-type versus heterozygous *sdyl*/*+* mice, the pale coat color of homozygous *sdyl*/*sdyl* mice precluded completely blind testing. All procedures related to animals were performed in accordance with University of Pennsylvania Institutional Animal Care and Use Committee and University Laboratory Animal Resources policies and guidelines.

### Experimental Behavioral Procedures

**Neurological Tests**—The neurological screen was adapted from the Irwin screen (1968), which has been widely used for testing neurological toxicity of drug candidates by pharmaceutical companies. This neurological screen is similar to phase 1 of the SHIRPA screen (Rogers et al., 2001). The mouse was weighed, then placed into an empty cage and observed for 3 min. A number of physical characteristics, including poor grooming, bald patches, absence of whiskers, labored breathing and blood around the nostrils, were characterized and recorded. Several behavioral responses were assessed (i.e., jumping, sniffing, rearing, approaching an object, movement throughout the cage, and urination and defecation). Visual acuity was assessed by placing the animal on a visual cliff platform (28 cm from the ground) for 2 min. Behavioral responses were recorded (i.e. approach to edge and poking nose over the edge). Lastly, sensorimotor reflexes (stabilization, righting, eye blink, ear twitch and whisker touch) were evaluated and recorded. The animals' behaviors during the neurological test were scored qualitatively in real time by the same investigator.

**Open Field Exploration**—Spontaneous locomotor activity was evaluated using the open field exploration test 24 h after neurological tests. The square opaque white plexiglass apparatus (40×40×32 cm [Everything Plastic, Philadelphia, PA]) was cleaned prior to testing and between animals with 95% ethanol. A video camera was mounted directly above the apparatus. The field was divided virtually into two regions of interest: a center area (15×15 cm) and a peripheral area (Viewpoint VideoTrack version 2.0, Champagne Au Mont D'or, France; see Behavioral Analysis). A lamp with a 60W bulb approximately 1.92 m away and 1.40 m above the apparatus was the sole source of illumination, providing an illumination intensity of 7 lux in the center of the field. The animals were placed in the center of the open field and given two five-minute sessions, 35 min apart. Distance traveled and time spent in the brighter center (which tends to be aversive to mice) vs. peripheral areas during the two 5-min sessions were recorded automatically using the Viewpoint tracking system.

**Rotarod**—Motor coordination and balance were assessed using an accelerating rotarod (San Diego Instruments, Inc.) 24 h after the open field test. Mice were first habituated to the rotating rod at a constant speed of 4 rpm for 300 s (5 min), during which time latency to fall was not recorded. The habituation trial was only performed on the first day. If a mouse fell off, it was quickly placed back on top of the rod until the 5-min trial was completed. Mice were subsequently exposed to a rotating rod starting at 4 rpm and linearly accelerated to 40 rpm over a 5-min period. Three trials were administered per day with a maximum time of 300 s (5 min) and a 30 min inter-trial rest interval for 5 days consecutively. Performances in

the daily trials were averaged for data analysis. Animals were tested at approximately the same time each day.

**Elevated Zero Maze**—Anxiety-like behavior was assessed using the elevated zero maze 24 h after the rotarod. The maze is a circular platform (62 cm wide) consisting of two opposing open and closed quadrants. A lamp with a 60W bulb approximately 1.92 m away and 1.4 m above the maze was the sole source of illumination, providing an illumination intensity of 7 lux from the center of the maze. The maze was cleaned prior to testing and between animal tests with 95% ethanol. A video camera was mounted directly above the maze. Mice were placed in one of the closed quadrants and activity was recorded automatically for 5 min using the Viewpoint VideoTrack version 2.0 (see Behavioral Analysis).

**Morris Water Maze**—24 h after the elevated zero maze, spatial learning and memory were assessed with the water maze as described by Morris (1984) and adapted for mice. The mouse water maze consisted of a circular pool (1.2 m diameter and 36 cm high), filled to a depth of 17 cm. The pool circumference was divided into four virtual quadrants and arbitrarily marked with the start positions: north (N), south (S), east (E) and west (W). The water was opacified with white non-toxic Crayola paint. The water temperature was between 22°C and 24°C during testing. The platform was made of transparent Plexiglas (10 cm×10 cm), and its placement in the N quadrant of the pool remained fixed throughout training. The top of the platform was 1 cm below the surface of the water. The pool was surrounded by various distal spatial cues and illuminated by two lamps. All trials were recorded with a video camera (see Behavioral Analysis) situated above the pool. To prevent hypothermia, trials were separated from each other by a period of 20 min. Each animal rested on warming mats between trials.

**Pretraining**—Before the first trial, each animal was placed on the visible platform whose submerged location was made visible by an attached flag as a proximal cue for 10 s. The animals were then placed in the water and allowed to swim for 10 s before being guided back to the platform, where they were allowed to rest for 10 s.

**Visible Training**—Each trial began by placing the animal in the water at the edge of the pool facing the wall from different quadrants. During the trial, each mouse was allowed 60 s to locate the platform. If the mouse failed to reach the fixed platform in the allotted time, it was guided to the platform. The start locations sequence was S, W and E. Each mouse was given two blocks of three trials for two consecutive days.

**Hidden Training**—The flag was removed from the platform. Each mouse was placed in the water and allowed 60 s to locate the platforms. It was given two blocks of three trials daily until the wild-type animals were able to locate the fixed platform in 15 s or less. The start locations sequence was S, W and E. Hidden platform training was performed for 5 days with two blocks of three trials.

**Probe Trial**—On the final day of hidden training, the platform was removed from the pool, and the mouse was placed in the quadrant directly across from where the platform had been. Each animal was allowed 60 s to search the pool. At the end of the trial, the mice were removed by hand.

During the platform trials, latencies (the time to reach the platform from the start location) were measured. Data from trials/day were averaged. In the probe trials, the performance measures were the mean swim speed, percentage of time spent in the each quadrant and the

number of annulus crossings (number of times an animal crossed the exact place where the platform had been located during training).

### Behavioral Analysis

Open field exploration and elevated zero maze tests were video tracked using Viewpoint VideoTrack Version 2.0. The system recorded distance traveled by the animals and the time spent in defined areas. The Morris water maze test was videotaped using a Sony DCR-TRV 280 video camera mounted above the pool. The raw data were analyzed by the Smart software version 2.0 (San Diego Instruments, Inc.).

### Statistical Analysis

Data were analyzed with a statistical software package, GraphPad Prism 5.0 for Windows, (San Diego, CA) and JMP6 (SAS, Cary, NC). Normality of the data for each variable was determined using the D'Agostino & Pearson (1973) test. One way analysis of variance (ANOVA) was used for analysis of weight. For analysis of the open field data, the distance variable could not be considered normal and was not transformable to be sufficiently close to normally distributed to allow application of normal based statistical approaches. Therefore, to compare the open field distance across genotype and sex, a nonparametric version of a repeated measures ANOVA was used, as described in Brunner et al. (2002) The model used (denoted F2\_LD\_F1 in the book) allowed for three factors, two non-repeated (sex and genotype) and one repeated (time). For analysis of the data from rotarod, elevated zero maze, and Morris water maze, repeated measures ANOVAs and one-sample t-tests were used. All analyses compared group differences by genotype, sex, and genotype by sex interactions. All figures display the mean  $\pm$  SE. For all analyses, significance was defined as  $p \leq 0.05$ .

## RESULTS

### Physical and Neurological Tests

There were no qualitative differences in physical characteristics, visual acuity or sensorimotor reflexes among genotypes or sex. Body weight of same sex animals did not differ among genotypes, but all females as expected had significantly lower weight than males for all genotypes ( $F_{[1,57]} = 0.62$ ,  $p < 0.0001$ ; data not shown) and a marginally significant genotype by sex interaction with females weighing less than their male counterparts ( $F_{[2,57]} = 3.2$ ,  $p < 0.05$ ; data not shown).

### Open Field Exploration

Non-parametric repeated measures ANOVA found a significant effect of genotype on locomotor activity in the two open field sessions (Figure 1a; Box-Approximation with Chi-square "B"  $_{[1.8,47.4]} = 81.99$ ,  $p = 0.000$ ). Post hoc individual group comparisons showed that the *sdv/sdv* mice were significantly more active than the littermate wild-type ( $F_{[1,40]} = 217.96$ ;  $p < 0.000$ ) and *sdv/+* mice during both sessions;  $F_{[1,40]} = 92.24$ ;  $p < 0.000$ , respectively). *Sdv/+* mice did not differ from wild-type littermates in locomotor activity ( $F_{[1,40]} = 0.003$ ;  $p = 0.96$ ).

There was also a significant effect of session on locomotor activity ( $B_{(1)} = 20.1$ ;  $p = 0.00001$ ) and an interaction between genotype and session ( $B_{[1,8]} = 6.26$ ;  $p < 0.003$ ). Within mouse genotype comparisons of session 1 and session 2 showed less activity in the second session relative to the first for the wild-type mice (Wilcoxon sign-rank  $Z_{[20]} = 9.5$ ,  $p = 0.000$ ) and *sdv/+* mice ( $Z_{[20]} = 67.5$ ,  $p < 0.02$ ), suggesting habituation to the open field whereas the *sdv/sdv* mice showed no difference in distance traveled in the open field



between sessions ( $Z_{[20]} = 2.5$ ,  $p = 0.39$ ), suggesting a lack of habituation (Figure 1a). There were no significant effects of sex.

All genotypes exhibited a clear preference for the periphery of the open-field box as indicated by the amount of time spent there (Figure 1b). There was no significant difference in amount of time spent in the center of the open field between wild type and *sdyl/sdy* mice in either session. Group data from the first session showed that wild-type mice spent an average of  $13.75 \pm 2.05$  seconds and *sdyl/sdy* mice  $14.00 \pm 2.50$  s in the center of the field. In the second session, wild-type mice spent an average time of  $15.13 \pm 3.29$  and *sdyl/sdy*  $19.12 \pm 4.16$  seconds in the center of the field. Similarly, there were no differences for the *sdyl/+* mice compared to either of the other genotypes, nor between males and females for any group. Since preference for the periphery is generally considered an index of anxiety, these results provided no evidence for increased anxiety in the *sdyl/sdy* mice.

### Rotarod

The performance of all three groups of mice improved over the five days of training; however, there was a marginally significant main effect of genotype (Figure 2; repeated measures ANOVA  $F_{[2,57]} = 3.17$ ,  $p < 0.05$ ). Posthoc group comparisons showed that both *sdyl/sdy* and *sdyl/+* mice had better motor balance skills than wild-type mice ( $F_{[1,40]} = 5.1$ ,  $p < 0.03$ ;  $F_{[1,40]} = 4.7$ ,  $p = 0.03$  respectively). No performance difference were found between *sdyl/sdy* and *sdyl/+* mice ( $F_{[1,40]} = 0.4$ ,  $p = 0.53$ ). Sex had a significant effect ( $F_{[1,57]} = 14.1$ ,  $p = 0.0004$ ), with females performing better than males in the *sdyl/sdy* ( $F_{[1,19]} = 13.5$ ,  $p < 0.002$ ) and *sdyl/+* ( $F_{[1,19]} = 9.45$ ,  $p < 0.007$ ) groups, but not the wild-type group ( $F_{[1,19]} = 0.49$ ,  $p = 0.49$ ). There was a trend towards an interaction between genotype and sex observed (Figure 2;  $F_{[2,57]} = 2.63$ ,  $p = 0.08$ ).

### Elevated Zero Maze

Consistent with the open field test findings of hyperactivity, there were significant differences between groups for total distance traveled in the elevated zero maze (Figure 3a;  $F_{[2,57]} = 7.08$ ;  $p < 0.002$ ). Posthoc Student's t-tests found that both *sdyl/sdy* ( $p < 0.0005$ ) and *sdyl/+* ( $p < 0.04$ ) traveled greater distances in the open quadrants than wild-type mice. There was also a significant effect of sex ( $F_{[1,57]} = 5.43$ ;  $p < 0.03$ ) with female mice traveling a greater distance than males in the allotted time. There was also a significant genotype by sex interaction ( $F_{[2,57]} = 3.9$ ;  $p < 0.03$ ). *Sdyl/sdy* females traveled greater distances than other females of both genotypes while for the males, both *sdyl/sdy* and *sdyl/+* genotypes traveled greater distances than their male wild-type counterparts. There was a trend towards an effect of genotype on time spent in the open quadrants (Figure 3b;  $F_{[2,57]} = 2.88$ ;  $p = 0.06$ ) with post hoc analyses showing more time spent in the open arms for *sdyl/sdy* ( $p = 0.06$ ) and *sdyl/+* ( $p = 0.03$ ). There was no effect of sex nor interaction between sex and genotype on time spent in the open arms ( $F_{[1,57]} = 0.48$ ;  $p = 0.48$  and  $F_{[2,57]} = 0.62$ ;  $p = 0.54$ , respectively).

### Morris Water Maze

Repeated measures ANOVA revealed significant differences among genotype groups in the latencies of acquisition in the visible platform (Figure 4a;  $F_{[2,56]} = 8.97$ ,  $p = 0.0004$ ), with *sdyl/sdy* mice exhibiting a longer latency to reach the platform than both the WT ( $p = 0.04$ ) and *sdyl/+* ( $p = 0.004$ ) groups in post-hoc analyses. There were no effects of sex ( $F_{[1,56]} = 2.13$ ,  $p = 0.15$ ) and no genotype x sex interaction ( $F_{[2,56]} = 0.04$ ,  $p = 0.95$ ).

Highly significant differences in escape latencies were observed among groups in the hidden platform trials (Figure 4a;  $F_{[2,56]} = 9.09$ ,  $p = 0.0004$ ). This was driven by the *sdyl/sdy* group of mice, most of which never reached criterion performance. Post hoc individual group comparisons showed significant differences between the *sdyl/sdy* mice and wild-type ( $F_{[1,39]}$

= 16.04,  $p = 0.0003$ ) and *sdyl*+ mice ( $F_{[1,40]} = 6.68$ ,  $p < 0.02$ ) while there was no difference in escape latencies between wild-type and *sdyl*+ mice ( $F_{[1,39]} = 2.30$ ,  $p = 0.14$ ). On the first day of hidden platform training, wild-type mice found the hidden platform after an average of  $20.4 \pm 2.6$  seconds compared to  $22.3 \pm 2.0$  seconds for the *sdyl*/*sdyl* mice ( $p = 0.74$ ). After meeting test criterion on the final day of hidden platform training, wild-type mice had an average escape latency of  $6.8 \pm 1.9$  seconds while *sdyl*/*sdyl* mice had an average escape latency of  $17.6 \pm 11.6$  seconds ( $p < 0.00002$ ). As in the visible platform training, there were no significant effects of sex ( $F_{[1,56]} = 0.39$ ,  $p = 0.53$ ) nor were there any significant interactions between genotype and sex ( $F_{[2,56]} = 0.82$ ,  $p = 0.44$ ) on the hidden platform trials.

Probe trial measurements of time spent in the correct quadrant demonstrated significant effects of genotype on preference for the target quadrant (Figure 4b,  $F_{[2,56]} = 4.78$ ,  $p = 0.01$ ). Preference for the target quadrant was attenuated in the *sdyl*/*sdyl* mice compared to the other two groups with post hoc individual comparison showing *sdyl*/*sdyl* spent significantly less time in the target quadrant than wild-type ( $p = 0.004$ ) or *sdyl*+ ( $p = 0.03$ ). In kind, time spent in the opposite quadrant also differed ( $F_{[2,56]} = 3.73$ ,  $p < 0.03$ ), with post-hoc individual comparison showing *sdyl*/*sdyl* mice spending significantly more time in the opposite quadrant than wild-type ( $p = 0.01$ ) or *sdyl*+ ( $p < 0.05$ ). *Sdyl*/*sdyl* mice had fewer annulus crossings than wild-type or *sdyl*+ (Figure 4c), though differences among groups were not significant ( $F_{[2,56]} = 1.9$ ,  $p = 0.16$ ). While impaired relative to the other two groups, the *sdyl*/*sdyl* mice did still exhibit spatial learning as evidenced by significantly greater time spent in the target quadrant than would be predicted by chance (i.e., 25%;  $t_{20} = 3.5$ ,  $p < 0.003$ ). Finally, there were no significant differences among groups for swim speed ( $F_{[2,56]} = 0.8$ ,  $p = 0.43$ ; Figure 4d).

## DISCUSSION

While the *sdyl* mutation arose in DBA/2J mice (Swank et al., 1991), we have investigated its behavioral phenotype in *sdyl*/BL6 mice to avoid effects on behavioral performance due to other mutations in DBA/2J mice (see Introduction). We found that *sdyl*+ and *sdyl*/*sdyl* mice are normal in physical appearance and in sensorimotor abilities, but that the *sdyl*/*sdyl* are hyperactive in the open field and elevated zero maze, do not habituate in exploratory behavior, and display spatial learning and memory deficits in the Morris water maze. As expanded upon below, these abnormalities are consistent with dysfunction of the hippocampal formation, where synaptic dysbindin-1 is normally abundant (Talbot et al., 2004, 2006) and where evoked excitatory responses in hippocampal field CA1 are diminished in *sdyl*/*sdyl* mice (Chen et al., (2008).

The *sdyl*/*sdyl* mice traveled significantly greater distances than their wild-type littermates in the open field and elevated zero maze tests. They showed no differences compared to wild-type mice in their preference for the periphery of the open field or for the closed quadrants in the elevated zero maze. Consequently, their hyperactivity is not readily attributable to increased anxiety. Since they showed no impairments in motor coordination on the rotarod, their hyperactivity was also not attributable to loss of motor control. These results differ from conflicting reports on homozygous *sdyl*/DBA mice. Feng et al. (2008) found no locomotor abnormalities in such mice. Hattori et al. (2008) reported that such animals were hypoactive over the first fifteen minutes in the open field and showed evidence of anxiety in that field and in the elevated plus maze. Yet Askari et al. (2007) found that *sdyl*/DBA mice – like homozygous *sdyl*/BL6 mice – are hyperactive in the open field and show no evidence of anxiety on the elevated plus maze.

The observed hyperactivity of homozygous *sdyl*/BL6 mice may reflect an abnormality in dopaminergic activity. Such an abnormality is expected given that dysbindin-1 loss in *sdyl*/*sdyl* mice is associated with elevated rates of dopamine turnover in both the hippocampal formation and in corticolimbic regions suggestive of increased dopamine release in those brain areas (Murotani et al. (2007) and (that in vitro knockdown of dysbindin-1 in cultured cerebrocortical neurons (as occurs naturally in *sdyl* mice) leads to increased cell surface expression of the dopamine D2 receptor (D2R), but not of the D1 receptor Iizuka et al. (2007). The opposite condition in D2R knockout mice leads to decreased locomotion (hypoactivity or bradykinesia: see Glickstein & Schmauss, 2001).

Increased cell surface expression of D2R in the hippocampus combined with increased dopamine release in that structure could promote hyperactivity for three related reasons. First, dopamine activation of D2R in hippocampal field CA1 depolarizes the resting membrane potential in 50% of the pyramidal cells tested and reduces the after-hyperpolarization in 67% of those cells (Berretta et al., 1990). Second, CA1 pyramidal cells in the ventral hippocampus innervate nucleus accumbens (Friedman et al., 2002; van Groen & Wyss, 1990), an area modulating motor activity along with other striatal structures (David et al., 2005; Taepavarapruk et al., 2000). Third, activation of ventral hippocampal output to nucleus accumbens is known to induce hyperactivity (Bast et al., 2001), an effect dependent on ventral hippocampal dopamine receptors as shown by its blockage with the D1R antagonist SCH 23390 and its initial attenuation with the D2R antagonist raclopride (Zornoza et al., 2005). Hyperactivity may also result from altered dopaminergic activity in the nucleus accumbens itself. Loss of dysbindin-1 in *sdyl*/*sdyl* mice is expected to elevate cell-surface expression of D2R not only in the hippocampus, but also in nucleus accumbens. This could promote hyperlocomotion, because the ventral hippocampus exerts a tonic facilitation of locomotor activity via D2-like postsynaptic receptors within nucleus accumbens (Rouillon et al., 2007).

The performance of *sdyl*/*sdyl* mice in the Morris water maze is also suggestive of hippocampal dysfunction. Performance of *sdyl*/*sdyl* mice in the hidden platform trials compared to the other two groups indicated a spatial learning deficit, while in the probe trial, *sdyl*/*sdyl* displayed less preference for the location where the hidden platform had been. Probe trial performance is dependent on both the strength of the acquired information, as well as recollection of that information. Thus, the impairment in the *sdyl*/*sdyl* mice could reflect impaired spatial memory as well as poorer initial learning and acquisition. Such a pattern of deficits in water maze performance is characteristic of rodents suffering hippocampal lesions (D'Hooge & De Deyn, 2001; Morris, 2007).

In the visible platform stage of the Morris water maze, the *sdyl*/*sdyl* mice exhibited a marginally longer average escape latency compared to the wild-type and *sdyl*/+ animals. This is consistent with impairment in visual associative learning and suggests dysfunction of brain regions outside the hippocampus as well. Unlike the case for hyperactivity, the impaired water maze performance of *sdyl*/*sdyl* mice is not consistent with increased hippocampal dopaminergic activity, which should facilitate spatial learning and memory (Stuchlik et al., 2007; Wilkerson & Levin, 1999). The impaired performance in the water maze may instead be due to decreased responsiveness of hippocampal field CA1 to excitatory input from CA3 reported in *sdyl*/*sdyl* mice (Chen et al., 2008). Normal responsiveness to such input is important for spatial memory, but not for visual association memory as indicated by the finding that CA1-specific knockout of NMDA glutamate receptors impairs location of the hidden, but not the visible, platform in the Morris water maze (Tsien et al., 1996).



Since dysbindin-1 is reduced in the brains of *sdv* mice (see Li et al., 2003) and of schizophrenia cases (Straub et al., 2004; Talbot et al., 2004), it can be asked whether these mice display phenotypical features of schizophrenia. That appears to be true for most behavioral abnormalities of *sdv/sdv* mice that have been reported to date. Their hyperactivity in the open field is shared by diverse mouse models of schizophrenia (Powell and Miyakawa, 2006; see also Mohn et al., 1999, Hikidia et al., 2007, Powell et al., 2007), which may have the same causes as the psychomotor agitation estimated to frequently occur in schizophrenia patients admitted for emergency psychiatric care in the U.S. (Marco and Vaughan, 2005). Impaired habituation of *sdv/sdv* mice in the open field likewise resembles the decreased habituation to diverse stimuli reported in schizophrenia (e.g., Taiminen et al., 2000; Meincke et al., 2004; Holt et al., 2005). The learning and memory deficits shown by *sdv/sdv* mice in the Morris water maze also resemble those shown by schizophrenia cases in a virtual Morris water maze task (Hanlon et al., 2006). Finally, while not yet tested in *sdv/BL6* mice, the decreased social interactions of homozygous *sdv/DBA* mice (Feng et al., 2008; Hattori et al., 2008) is consistent with impaired social functions, especially impaired social cognition, in schizophrenia (see Couture et al., 2006 and Yager and Ehmann, 2006).

We cannot expect, however, that a mouse strain with just one of the biological anomalies found in schizophrenia will model all aspects of that disorder. That limitation is suggested by studies on *sdv/DBA* mice. These animals show no deficits in prepulse inhibition (Hattori et al., 2008; see also Li et al., 2003), which is a frequently cited abnormality in schizophrenia (Quednow et al., 2008; Turetsky et al., 2007) and in diverse mouse models of that disorder (Clapcote et al., 2007, Erbel-Sieler et al., 2004; Fradley et al., 2005; Miyakawa et al., 2003; Stefansson et al., 2002). Homozygous *sdv/DBA* mice also do not react in a consistent manner to psychotomimetic drugs. While they display increased locomotor activation after an acute dose of the NMDA receptor antagonist MK-801, they display decreased locomotor activation after an acute dose of D-amphetamine (Askari et al., 2007).

The present results on Morris water maze performance nevertheless suggest that the *sdv* mouse may model at least some important dysbindin-1 related cognitive deficits of schizophrenia. This is consistent with an increasing number of studies showing that single nucleotide polymorphisms in DTNBP1 associated with schizophrenia are also associated in that disorder with lower general cognitive ability (Burdick et al., 2006, 2007), lower scores on verbal, performance, and full-scale IQ tests (Zinstock et al., 2007), and deficits in several tasks of attentional response control and/or working memory (Donohoe et al., 2007). Since the dysbindin-1 reductions in *sdv* mice are not dependent on these SNPs, but rather upon a deletion mutation partially overlapping the SNP locations, such mice cannot be said to model cognitive endophenotypes of schizophrenia. But they may model cognitive deficits related to altered DTNBP1 gene expression in general.

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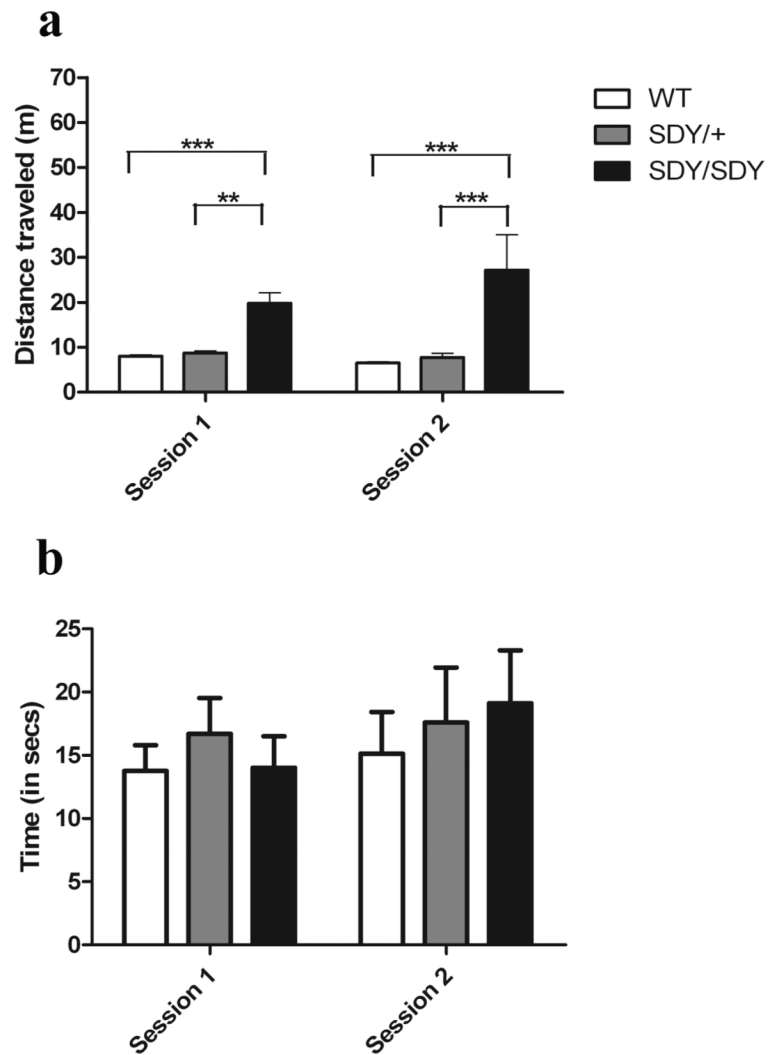
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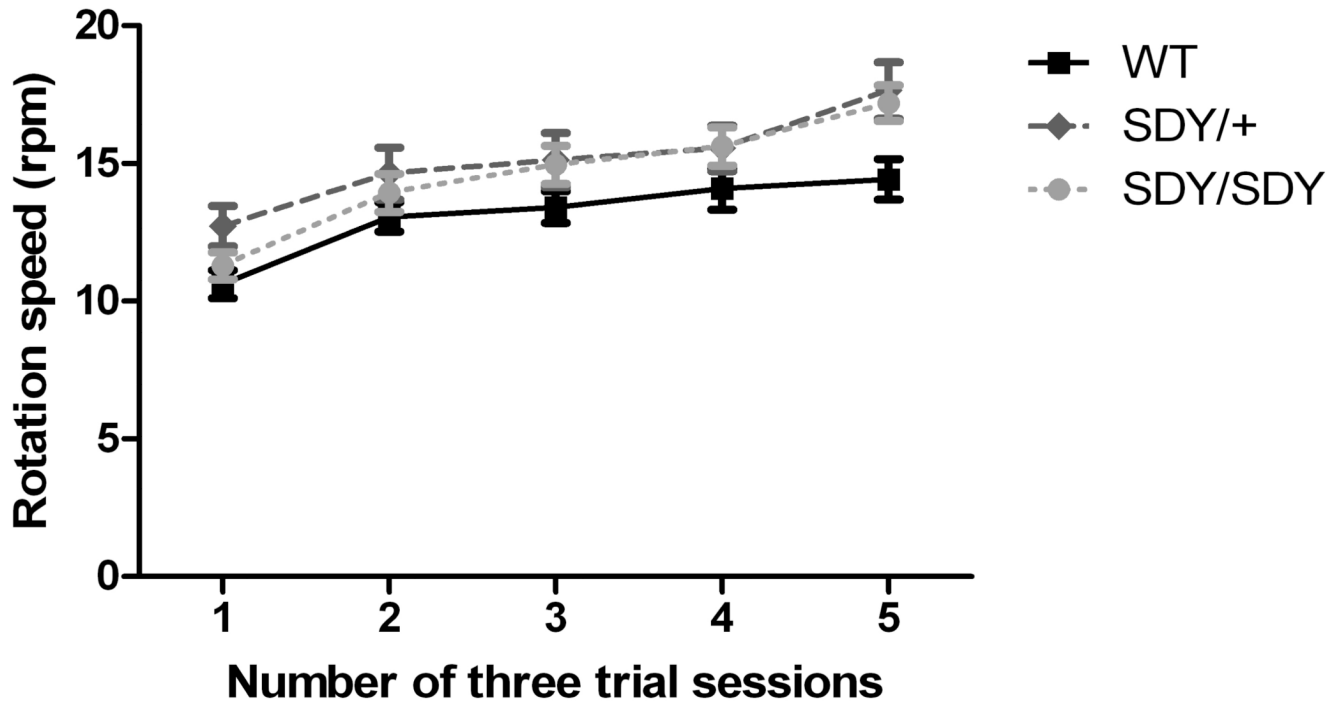
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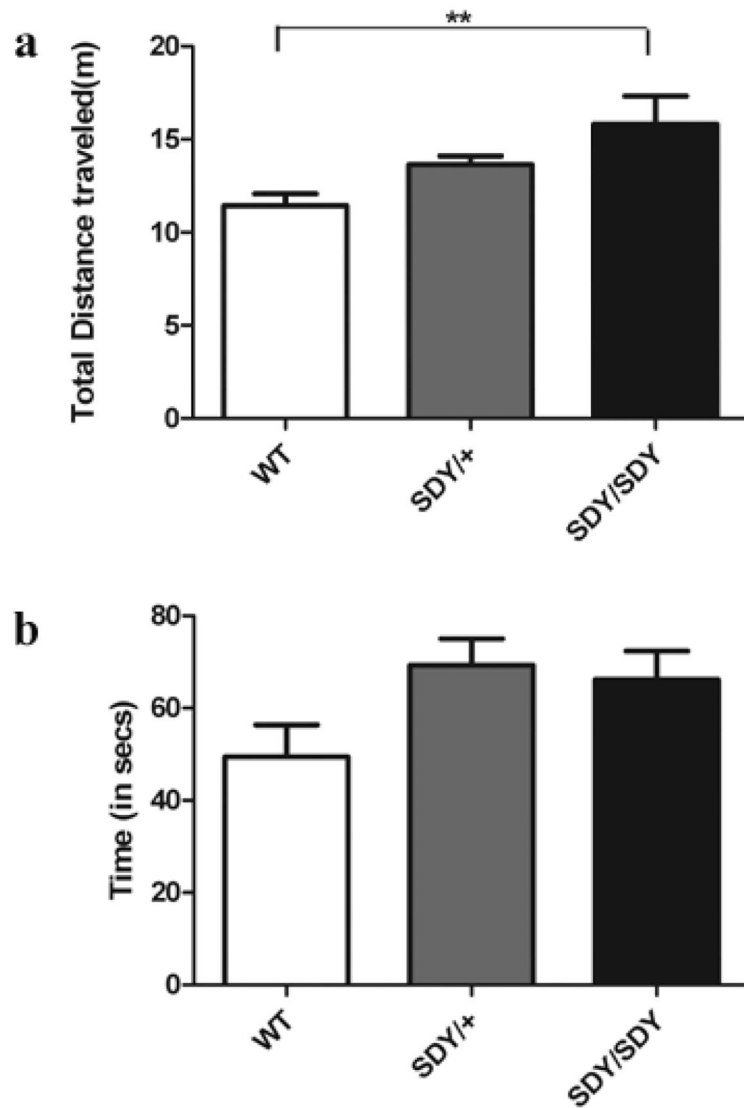
**Figure 1. Open Field**

(a) Total distance traveled during the two 5 minute sessions in meters (m) and (b) total time spent in the center of the open field during the two 5 minute sessions for wild-type (WT) (□), *sdY/+* (■), and *sdY/sdY* (■) mice. \*\*  $p < 0.001$ , \*\*\*  $p < 0.0001$ . The amount of time expected in the center field by chance (42s) is larger than the observed times.



**Figure 2. Rotarod Performance**

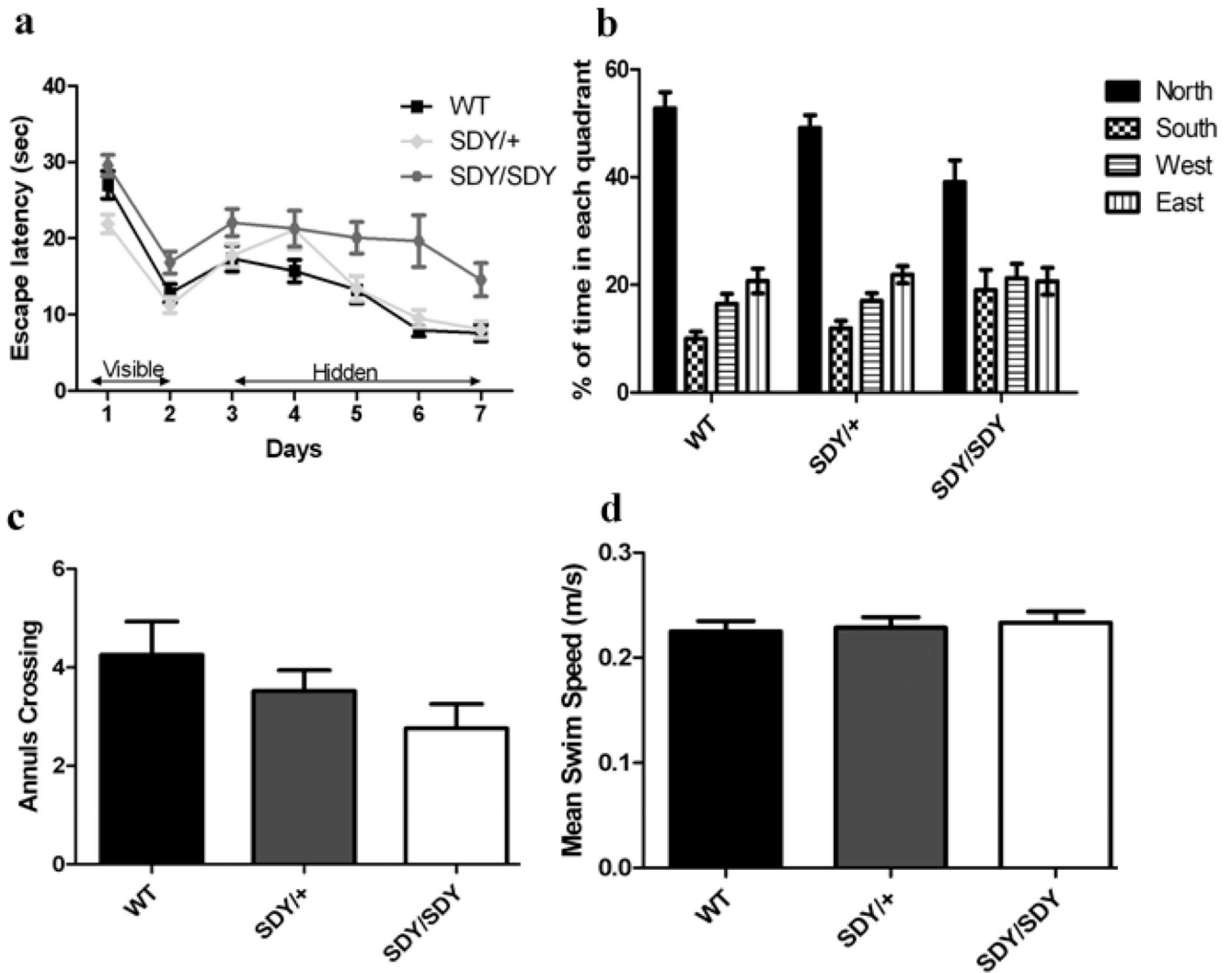
Improvement in the time animals managed to stay atop accelerating rotarod on the 5 sessions with 3 trials per session. Symbols indicate WT (■), *sdY/+* (◆), and *sdY/sdY* (●) mice. No significant differences among groups were found.



**Figure 3. Elevated Zero Maze**

(a) Total distance in meters traveled during the 5 minute session and (b) total time spent in the open arms during the 5 minute session for WT (□), *sdyl*+ (■) and *sdylsdyl* mice (■).

\*\*Difference at  $p = 0.002$



**Figure 4. Morris Water Maze**

(a) Escape latency (s) during visible and hidden platform for WT (■), *sdyl/yl* (◆), and *sdyl/sdyl* (●) mice, (b) percentage of time spent in all quadrants during probe trial, (c) annulus crossings during probe trial soon after final hidden platform trial for WT (■), *sdyl/yl* (◆), and *sdyl/sdyl* (□) mice, and (d) average swim speed during the probe trial for WT mice (■), *sdyl/yl* (◆), and *sdyl/sdyl* mice (□).