

Research report

Spatial memory deficits in segmental trisomic Ts65Dn mice

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Abstract

Spatial memory was assessed in the segmental trisomic 16 mouse (Ts65Dn), a potential model for Down syndrome (DS), using the 12-arm radial maze (RAM). Ts65Dn mice have a portion of mouse chromosome 16 syntenic to the distal end of human chromosome 21 triplicated. On each of 8 daily trials of the RAM, Ts65Dn mice made fewer correct choices than control mice and performed at or near chance levels, indicating a deficit in spatial working memory. On trials 9 and 10, Ts65Dn mice performed as well as control mice on the initial 12 choices, but required a greater number of choices to complete the RAM. The improved performance of Ts65Dn mice on trials 9 and 10 was lost when the animals were retested after a 50-day retention period, suggesting that long-term memory is also defective. These results are not likely explained by differences in either response bias or perceptual discrimination. Ts65Dn and control mice displayed comparable levels of performance in spontaneous alternation in a T-maze, demonstrating that simple spatial memory was not impaired. In the elevated plus maze, Ts65Dn mice did not display higher anxiety levels which could affect their performance in the RAM. In fact, Ts65Dn mice visited open arms on the elevated plus maze more frequently and spent more time on open arms than did control mice. Taken together, these results provide evidence for short- and long-term spatial memory deficits in Ts65Dn mice.

Keywords: Learning; Memory; Down syndrome; Trisomy; Animal model; Behavioral genetics

1. Introduction

Down syndrome (DS, trisomy 21) is the most common genetic form of profound learning and memory deficits in humans [8,14,20,21,34,37,42,51,52]. Cognitive deficits include impaired verbal memory, contingency detection tasks, and object concept development, as well as deficits in both short- and long-term memory [38,42]. Many of these deficits are similar to those observed in early Alzheimer's disease [8,20]. At the neuroanatomical level, gross brain weight is reduced in DS patients; relatively smaller hippocampal size and abnormalities in dendritic spine density in both the hippocampus and cerebral cortex have also been reported in DS patients [3,17,49,50]. Previous research has found that children with DS exhibit deficits in spatial learning [37,52]. Some of the deficits may be due to effects of instability

of performance; this instability is due to problems in consolidating new cognitive skills and in recalling these new skills [37,52].

Because DS has both genotypic and phenotypic variability [31], it is difficult to control for differences among individuals, even with learning and memory deficits which are two of the hallmarks of DS. Therefore, DS awaits an appropriate animal model for a thorough study of behavior. Mouse chromosome 16 is partially syntenic with human chromosome 21 [43], raising the interesting possibility that trisomy of mouse chromosome 16 (Ts16) may be a model for DS. Ts16 mice show both morphological and physiological similarities to DS, including abnormalities of the central nervous system, heart anomalies, growth retardation, and immunological deficits (reviewed in [32]). Ts16 mice, however, typically die in utero or shortly after birth so they do not provide an appropriate model for assessing adult DS behavior. Furthermore, mouse chromosome 16 conserves segments from 3 other human chromosomes in addition to human

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chromosome 21, viz. chromosomes 3, 16, 22. Recently, in order to refine the DS phenotype in an animal model, a partial Ts16 mouse, the segmental trisomic mouse (Ts65Dn), was developed in which only the segment of mouse chromosome 16 syntenic to human chromosome 21 has been triplicated [9]. Ts65Dn mice display phenotypic abnormalities which resemble those seen in DS [15]. For example, these mice demonstrate mild hydrocephalus, early onset obesity and tremors [11]. Ts65Dn male mice differ significantly from control mice in the display of increased offensive and decreased defensive aggressive behavior [30]. Nocturnal hyperactivity has also been observed in male Ts65Dn mice [44]. Additionally, Ts65Dn mice make more total arm entries and visit open arms of an elevated arm maze more frequently than control mice [9].

Learning and memory ability has yet to be fully examined in Ts65Dn mice. Recent studies of learning and memory ability in Ts65Dn mice have reported learning deficits in the Morris water maze [16,44], a task commonly used to assess spatial memory [36]. These results provide preliminary evidence that Ts65Dn mice can learn a task requiring spatial cues, albeit more slowly than controls. In both cued and place learning trials, the amount of time required for Ts65Dn mice to find the platform and the number of trials of training to achieve the shortest escape latencies was greater than controls [16,44]. In addition, in probe trials, Ts65Dn mice spent significantly less time searching in the correct quadrant (i.e., the quadrant that had contained the platform) than control mice in both studies. These findings suggest that Ts65Dn mice have a deficit in spatial learning similar to animals with hippocampal damage. The purpose of the present study was to provide additional characterization of both short- and long-term spatial memory in the Ts65Dn mouse, as determined by performance in a T-maze and a 12-arm radial maze.

2. Materials and methods

2.1. Animals

Ten male segmental trisomic mice (Ts[17(16)]65Dn) (hereafter referred to as Ts65Dn), the generation of which was described previously [10] and 10 control B6C3HF1 strain male house mice (*Mus musculus*) (between 4 and 6 months of age) were obtained from Jackson Laboratories (Bar Harbor, ME). The controls for Ts65Dn were from the same genetic background, a B6C3HF1 mouse. This mouse is a hybrid background of C57BL/6JEi × C3H/HeSnJ. The hybrid background was generated from two control strains, C57BL/6J and C3H, both of which have been found to perform well in the radial arm maze [45]. Animals were individually housed in our laboratory in the Psychology Department

of the Johns Hopkins University in a light–dark (LD) 16:8 h photoperiod (lights on 07.00 h EST) at $20 \pm 2^\circ\text{C}$ and relative humidity of $50 \pm 5\%$. Given the potential for increased aggression in Ts65Dn mice when group-housed [30], animals were housed individually. Food (Prolab 1000; Syracuse, NY) and tap water were available ad libitum until the onset of testing. The C3H strain, from which Ts65Dn mice were generated, carries the retinal degeneration (*rd*) allele. Prior to behavioral testing, direct examination of the retina by slit lamp found all animals to be free of retinal degeneration. All animals were coded with random experimental numbers to ensure that the experimenters remained blind to the experimental groups.

2.2. Radial arm maze (RAM) learning

2.2.1. Apparatus

The apparatus was a 12-arm radial maze constructed of 2-cm-thick plywood. The circular central arena of the maze was 25 cm in diameter. The arms were 6 cm wide and 42 cm in length. A small, detachable plastic food cup ($4 \times 4 \times 1$ cm deep) was located at the end of each arm. A clear plexiglass wall (8 cm high × 30 cm long) was attached to the arms to prevent the animals from jumping from arm to arm without returning to the central arena. A metal door, that slid in a vertical track, was located at the entrance to each arm and allowed selected arms to be closed. The maze was elevated 75 cm above the floor of the experimental room. The room was 3.3×2.4 m and contained a number of salient extra-maze stimuli. It was illuminated by fluorescent lighting providing approximately 180 lux of illumination at maze level.

2.2.2. Shaping

Initial body weights were determined for all animals before behavioral testing. Animals were food restricted to 4 g of lab chow daily to maintain animals at 85% of their initial body weight. During the first 3 days of exposure to the experimental apparatus, the mice were placed in the RAM individually for 5 min periods. Food pellets were located in the food cups, on the arms, and in the central arena. The animals were allowed to explore the maze and consume the food pellets.

2.2.3. Free choice

Beginning on day 4, animals were run in a free-choice procedure for one session a day. Prior to each session, a pellet of food was placed in each food cup. The doors to all 12 arms were open throughout the trial. The animal was placed in the central arena and allowed to visit arms until all 12 arms had been visited or 5 min had elapsed. All animals typically visited all arms of the RAM and consumed the food pellets. The animal's choices were recorded. The arms were wiped down with

warm water and soap between trials. All animals were tested in this manner for 10 consecutive free-choice trials. The number of correct choices each animal made in the initial 12-arm choices and the number of choices required to finish the maze (i.e., visit each arm at least once) were recorded. After each daily testing period, food was given and both groups of animals showed similar food intake.

After each animal had finished 10 trials, they were tested for two additional sensory discrimination probe trials. Prior to each trial, a randomly selected subset of 6 of the 12 arms was baited while the other six arms remained unbaited. Other aspects of the probe trials were identical to the earlier trials. These probe trials were used to assess whether the mice were choosing baited arms over unbaited arms on the basis of sensory cues, such as the sight or smell of the food. If unbaited arms can be discriminated from baited ones and are therefore less likely to be visited, then these arms would be visited later in the choice sequence than baited arms.

2.2.4. Long-term retention

Fifty days after the last free-choice trial (trial 10), the mice were again food-restricted as above and reintroduced to the RAM for two subsequent trials (trials 11 and 12). The animals' choices were recorded as above.

2.3. Spontaneous alternation behavior

2.3.1. Apparatus

The 12-arm RAM was manipulated so that 9 of 12 arms were closed off and the remaining 3 open arms were arranged in a T-formation. No food cups or food were present on the maze during testing.

2.3.2. Procedure

A discrete trial task was utilized in which the animal was placed at the end of one arm and allowed to explore either of the two remaining arms. After the animal chose one of the arms, the choice was recorded and the animal was removed and placed back at the original starting point. The mouse was again allowed to choose one of the remaining arms. Each animal was run for 5 trials and their choices were recorded.

2.4. Elevated plus maze

2.4.1. Apparatus

The elevated plus maze was constructed of 2-cm-thick plywood with two open arms and two closed arms. The arms of the maze were 67 cm long and 5.5 cm wide. The closed arms had 15-cm-high, bronze-tinted plexiglass walls and a 65-cm-long detachable roof. The maze was mounted on a camera tripod elevated 75 cm from the floor.

2.4.2. Procedure

The mouse was placed in the central arena and allowed access to all 4 arms. Choice behavior was observed for 5 min and the number of visits to each arm and the time spent in each arm, as well as the central arena were recorded. The maze arms were wiped down with warm water and soap between trials.

2.5. Statistical analyses

Two estimates of chance performance were generated for use with statistical comparisons of the RAM data. The strict estimate of chance (S) assumed that the animals randomly selected arms from among the 12 possible arms during each choice. A modified estimate of chance (M) [6] is designed to take into account any systematicity in the arm-to-arm movement patterns (e.g., visiting adjacent arms in a clockwise fashion) that may increase choice accuracy independent of spatial memory. To test this possibility, the data for individual subjects were used to construct transition probability matrices. Given that an animal was either in one of the 12 arms or had just started the trial and had not visited any arm, the probability of moving from that arm or from the start position to any of the 12 arms was calculated for each animal. The resulting transition probability matrices were used in Monte Carlo simulations in which arms were chosen using the same probabilities as the animals. Specifically, Monte Carlo simulations were based on 1000 computer-generated simulations using each animal's respective transition probability matrix. If choice systematicity (i.e., response bias) can account for the tendency to avoid revisits without memory for previously visited cells, then the simulations should perform as well as the animals. Previous studies have validated the use of this procedure to control for response bias in the RAM [6,7].

A two-way mixed model analysis of variance (ANOVA) was conducted on the radial arm maze data. Individual post hoc comparisons were conducted using Tukey HSD tests. In the analysis of the probe trial data, the initial visit to each cell was ranked according to its ordinal position among the 12 initial visits (e.g., the first arm entered during a given trial is given a ranking of 1). A Wilcoxon rank sum test was performed on these rankings. Spontaneous alternation data were analyzed using χ^2 tests. Elevated plus maze data were analyzed using independent Student's *t*-tests. All statistical analyses were conducted using Sigmasat and were considered statistically significant if $P < 0.05$.

3. Results

3.1. Radial arm maze performance

Daily performance on the RAM was analyzed in two ways. First, for each trial, the number of correct choices

out of the initial 12 choices was determined for each animal. A 'correct' choice was defined as entering (and obtaining food) in an arm that had not previously been visited during that trial. Second, the total number of entries during each trial required to complete the maze was recorded. Maze completion was defined as entering all 12 arms at least once and obtaining the food pellets.

Overall, Ts65Dn mice made fewer correct choices in the initial 12 choices (Fig. 1) and required a greater number of choices to finish the maze (i.e., visit all 12 arms at least once) compared to control mice between trials 1–8. Control mice were significantly above both the strict and modified estimates of chance across all 10 trials ($P < 0.05$ in both cases). Ts65Dn mice did not differ from the modified estimate of chance performance during trials 1–8 ($P > 0.05$). By trial 9, Ts65Dn animals were making a similar number of correct choices in the initial 12 choices as controls, significantly above the number expected by the modified estimate of chance ($P < 0.05$). There was also a significant trial by genotype interaction in performance in Ts65Dn mice, as assessed by the number of correct in the initial 12 choices ($P < 0.05$). The mean number of choices required to finish the maze was significantly greater for Ts65Dn mice (24.2) compared to controls (20.1) ($P < 0.05$). There was no significant difference between the rank sums for baited vs. unbaited arms in the sensory discrimination probe trials

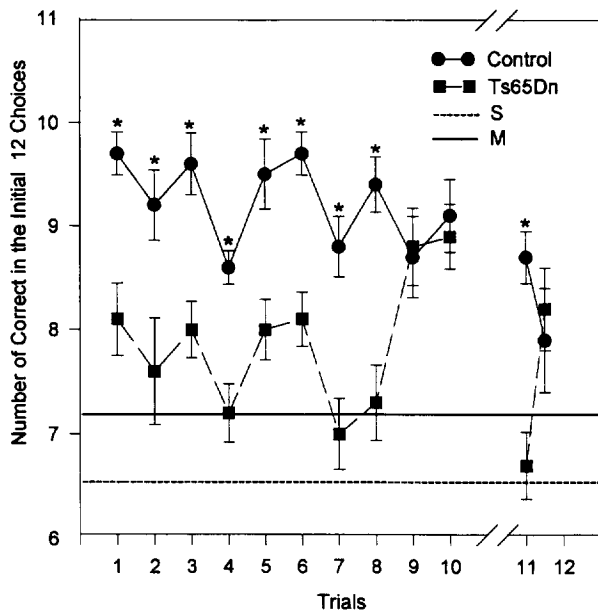


Fig. 1. Radial arm maze. Mean (\pm standard error of the mean (S.E.M.)) choice accuracy of control and Ts65Dn mice on the 12-arm radial maze. Two estimates of chance performance are indicated. The first estimate (S, broken line) assumes random selection from among the 12 arms during each arm choice. The second estimate (M, solid line) accounts for response bias as determined by a Monte Carlo simulation. The break between trial 10 and trial 11 represents the 50-day retention interval in which the animals were not run on the maze. *Statistically significant difference between groups ($P < 0.05$).

for either group ($P > 0.05$ in both cases). Body weights did not differ between control and Ts65Dn mice or across trials for either experimental group ($P > 0.05$ in both cases).

After a 50-day retention period, Ts65Dn mice again made fewer correct choices in the initial 12 choices than control mice during trial 11 ($P < 0.05$) (Fig. 1). Ts65Dn mice did not perform significantly above chance on trial 11 ($P > 0.05$). Also, the mean number of choices to finish the maze was greater for Ts65Dn (27.0) compared to control mice (21.0) during trial 11 ($P < 0.05$). There were no significant differences between genotypes in either the number correct in the initial 12 choices (Fig. 1) or the number of choices required to finish on trial 12 ($P > 0.05$ in both cases).

3.2. Spontaneous alternation

Both control and Ts65Dn mice displayed spontaneous alternation, choosing the opposite arm than to that initially chosen significantly more than expected by chance ($P < 0.05$ in both cases) (Fig. 2). Control and Ts65Dn mice did not differ in the degree of spontaneous alternation behavior ($P > 0.05$).

3.3. Elevated plus maze performance

Like control mice, Ts65Dn mice made a greater number of visits to the closed arms than to the open arms ($P < 0.05$). Ts65Dn mice made a greater number of visits and spent a greater amount of time on the open arms compared to control mice ($P < 0.05$ in both cases) (Fig. 3). Ts65Dn and control mice did not differ in the amount of time spent in the central arena ($P > 0.05$) or

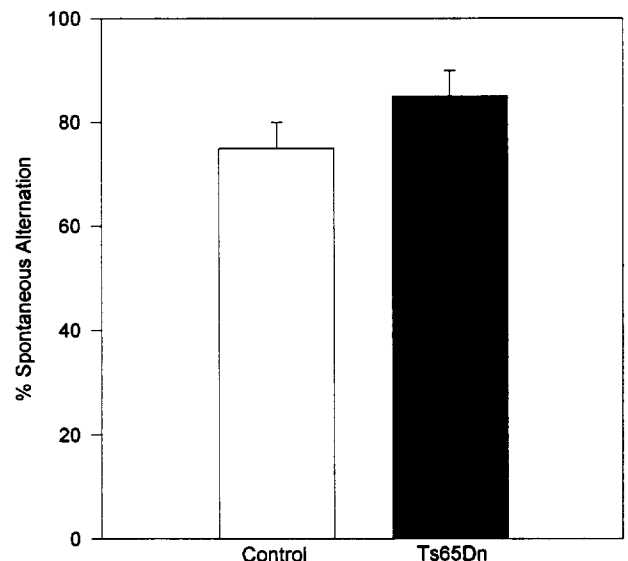


Fig. 2. Spontaneous alternation. Percentage of spontaneous alternation behavior between control and Ts65Dn mice.

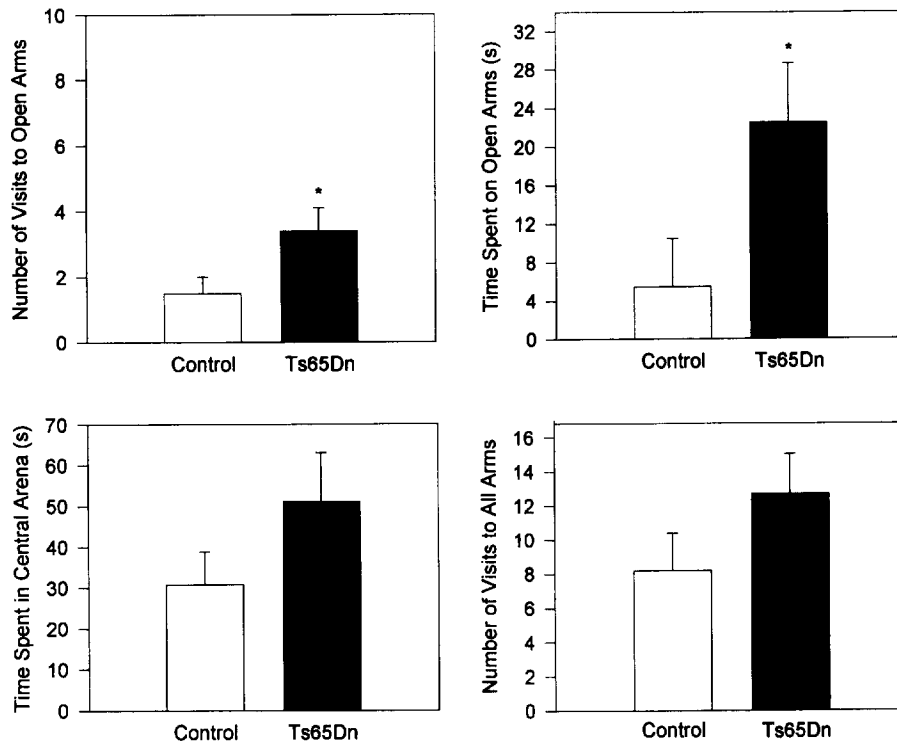


Fig. 3. Elevated plus maze. a: mean (\pm S.E.M.) number of visits to the open arms of the elevated plus maze in control and Ts65Dn mice. b: mean (\pm S.E.M.) time (s) spent on the open arms of the elevated plus maze in control and Ts65Dn mice. c: mean (\pm S.E.M.) time spent in the central arena of the elevated plus maze in control and Ts65Dn mice. d: mean (\pm S.E.M.) number of visits to all arms of the elevated plus maze in control and Ts65Dn mice. *Statistically significant difference ($P < 0.05$) for all figures.

the total number of visits to both open and closed arms ($P > 0.05$).

4. Discussion

Ts65Dn mice displayed significantly impaired performance on the RAM task relative to control mice on trials 1–8. In contrast to control mice, Ts65Dn mice performed at or near both the strict and modified estimates of chance (Fig. 1). By trials 9 and 10, Ts65Dn mice improved in initial choice accuracy from the near chance levels seen in trials 1–8, to levels of choice accuracy comparable to control mice. The number of choices required to finish the maze remained higher than controls. Initial choice accuracy and the number of choices required to finish the maze remained constant in control mice over trials 1–10, indicating that control mice were already significantly above chance levels at trial 1 (i.e., after the 3-day shaping period); therefore, they may have already been performing at peak levels at the start of the free-choice phase of the experiment. On the other hand, Ts65Dn mice performed initially at a level near chance and improved across trials (i.e., there was a learning curve). The most likely interpretation of the poor performance of Ts65Dn mice in trials 1–8 is that they have impaired spatial working memory. The

improved performance on trials 9 and 10 indicates that Ts65Dn mice can learn the RAM task, although more slowly than control mice. Ts65Dn mice do not perform exactly as animals with hippocampal lesions; lesioned animals do not show improvement across RAM trials [29].

After a 50-day retention interval, Ts65Dn mice exhibited impaired long-term retention of the RAM task (i.e., they returned to near-chance levels). This lack of long-term memory was not found in control mice. The impairment, however, was short lived, as Ts65Dn mice returned to choice accuracy levels comparable to control mice after a single trial. Whether retrieval or storage of spatial memory is defective in Ts65Dn mice cannot be determined from these results. The transient nature of the deficit in retention, however, suggests a deficit in memory retrieval rather than storage. Another possibility is that Ts65Dn mice are unable to consolidate new memories, as has been suggested for DS patients [52].

Both Ts65Dn and control mice displayed comparable levels of spontaneous alternation behavior (SAB).

SAB has been reported to range from 65 to 88% in laboratory strains of mice [26]. The levels of SAB in Ts65Dn mice reported here are comparable to previous findings for laboratory-bred mice of approximately the same age [35]. A critical component of SAB is that the mouse maintain a simple short-term memory of the

previously visited arm; it has been suggested SAB requires a rudimentary form of working memory [45,48]. The finding that Ts65Dn mice display normal levels of SAB, unlike the impairment typically seen in animals with hippocampal lesions [28], suggests that their working memory is not impaired for simple working memory tasks over relatively short time intervals. Recent research has also utilized SAB to assess simple working memory in β -APP 751 transgenic mice, and while no deficits were reported for this task in mice at 6 months of age, older mice (12 months) showed impaired SAB [35].

SAB has also been linked to exploratory behavior in rodents that can affect RAM exploration patterns [12,40]. Because Ts65Dn mice do not differ from control mice in SAB, differences in maze performance are not likely explained by differences in maze exploration patterns unrelated to learning and memory. It is possible, however, that control animals are using a choice algorithm or response bias (e.g., always choosing adjacent arms) independent of memory and that this bias has been temporarily disrupted in Ts65Dn mice. Control mice, however, perform significantly better than the modified estimate of chance. Because response bias is incorporated in this estimate, response bias cannot explain the above chance performance in these animals.

Another possible explanation of above-chance performance is that control mice are using some sort of perceptual cues (e.g., the smell or sight of food) to visit unvisited arms and therefore avoid previously visited ones. However, there is no difference in preference for baited vs. unbaited arms in the probe trial data. Thus there is no evidence that the physical presence of food on the arms can explain above-chance performance.

A further alternative explanation for the maze performance deficit seen in Ts65Dn mice is that the genetic manipulation affected their overall sensorimotor ability and these deficits affected choice accuracy *independently* of learning and memory. Our previous analysis of Ts65Dn mice, however, has ruled out this possibility [30]. No differences were found between Ts65Dn and control mice on a battery of sensorimotor tests, including forelimb strength, turning ability, balance, coordination, motor or visual reflexes, and olfactory ability [29].

Rodents generally prefer closed arms as compared to the open arms, making more visits and spending significantly more time on the closed arms. Ts65Dn visited open arms of the elevated plus maze more often and spent more time in those arms than control mice, as previously reported [9]. However, in contrast with previous findings [9], both Ts65Dn and control mice did not differ in the total number of arms visited or their preference for closed over open arms. The number of visits and the amount of time spent on the open arms has traditionally been used as an index of anxiety [18,33]. Levels of anxiety should correspond to the

amount of time spent on the closed compared to the open arms. Based on these results, Ts65Dn mice display similar locomotor activity and exploratory behavior, but appear less anxious than control mice. Therefore, the impaired maze performance demonstrated by trisomic mice is not likely explained by a higher level of anxiety or exploratory behavior relative to control mice. Alternatively, the behavior of Ts65Dn mice in the elevated plus maze may be viewed as a failure to process environmental cues appropriately. Ts65Dn mice demonstrate less aversion to the open arms, visiting open arms more often than control mice. Control mice, in contrast, demonstrate a clear preference for closed arms over open arms. This is not the only example of inappropriate behavior in Ts65Dn mice. For example, these mice are more aggressive in offensive aggression tests than control mice [30]. The extent to which this potential lack of appropriate behavior or motivation may influence the formulation of an effective search strategy in the radial arm maze requires further testing.

Relatively young animals (<6 months) were used in the present study. Many learning and memory deficits and related neuropathological changes including those present in DS and in related Alzheimer's disease, however, occur more conspicuously in older individuals [20,23–25,27,47]. It is possible that the spatial memory deficits present in Ts65Dn mice would be more profound in aged animals. Aging studies are in progress to assess whether Ts65Dn mice display increased cognitive deficits with age, as has been reported for the β -APP 751 transgenic mice [35].

These findings of impairments in spatial memory in Ts65Dn mice suggest a possible involvement of the hippocampus. A decrease in spatial memory is found in animals with hippocampal lesions [13,29,39,41] and in mice with hippocampal disruptions due to genetic manipulations [1,19,24]. Spatial memory has been significantly correlated with variations in the size of the hippocampal intra- and infrapyramidal mossy fiber pathway [46]. In addition, hippocampal slices prepared from strains with large mossy fiber projections revealed a larger population spike after tetanic stimulation than from strains with a smaller mossy fiber projection [22]. Also, hippocampal long-term potentiation (LTP) [4,5] appears to be correlated with spatial memory [2]. The improvement in RAM performance seen in Ts65Dn mice with repeated trials, however, does not fully mimic the pattern observed following hippocampal damage where performance remains below controls across all trials [28].

Ts65Dn mice demonstrate impairments in both short- and long-term spatial memory that cannot be explained by other behavioral or sensorimotor anomalies. Since learning and memory deficits are a substantial component of DS in humans, our findings may significantly expand the applicability of the Ts65Dn mouse in study-

ing the physiological mechanisms underlying cognitive deficits in DS.

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