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Strain-dependent differences in neuroplasticity markers related to memory

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MAIN POINTS

- Hippocampal-dependent spatial memory deficits are a core feature of several neurological and psychiatric disorders, and rodent strain differences may influence the translational relevance of preclinical findings.
- Although Wistar, Sprague Dawley, and Long Evans rats all acquired spatial memory under identical conditions, strain-specific differences in behavioral performance suggest that cognitive outcomes may be differentially interpreted depending on the animal model used.
- Strain-dependent variations in hippocampal BDNF and DCX expression indicate that baseline neuroplasticity profiles differ between commonly used rat strains, which may critically affect the interpretation of therapeutic and biomarker studies targeting learning and memory dysfunction.

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ABSTRACT

Aim: Spatial learning and memory both rely critically on hippocampal plasticity which are a core feature of several neurological and psychiatric disorders; but commonly used different rat strains might exhibit differences in these processes which may influence the translational relevance of preclinical findings Herein, we examined the long-term spatial memory of adult Wistar (n=5), Sprague Dawley (n=6), and Long Evans (n=5) rats, and their hippocampal expression of two plasticity markers: brain-derived neurotrophic factor (BDNF) and doublecortin (DCX).

Materials and Methods: The animals were trained in the Morris water maze for four days, followed by a probe trial with no platform. Hippocampal BDNF and DCX protein levels were quantified by Western blotting.

Results: All strains learned the task, as indicated by a decrease in escape latency and swim distance over time. Sprague Dawley rats swam faster than the other strains, suggesting that swim distance evaluates learning independently of speed. On the first training day, Wistar rats swam the shortest distances, whereas by the final day Long Evans rats did. In the probe trial, Sprague Dawley rats spent a greater proportion of time in the target quadrant than Wistar rats did. Long Evans rats displayed an intermediate pattern. At the molecular level, Sprague--Dawley rats had higher hippocampal BDNF levels than Wistar and Long-Evans rats. DCX levels were higher in Sprague Dawley and Long Evans rats than in Wistar rats.

Conclusion: These findings suggest that although all three strains can acquire and retain spatial memory under identical conditions, they differ in behavioral strategies and hippocampal plasticity. Therefore, strain background should be carefully considered when designing and interpreting rodent studies of learning and memory.

Keywords: BDNF, DCX, Morris water maze; Rat strains; Spatial learning and memory

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INTRODUCTION

The capacity for spatial learning and memory is critical for living beings to develop proper relationships with their environments and to move about them. In mammals, the hippocampus is the primary brain region associated with learning and memory. The hippocampus is involved in the experience-dependent synaptic plasticity that determines the formation and reorganization of synaptic connections [1,2]. The association of spatial memory and hippocampal plasticity is the reason that tasks that involve movement (like the Morris Water Maze) are commonly used to study the cognitive abilities and its cellular mechanisms in rodents [3,4].

At the cellular level, brain-derived neurotrophic factor (BDNF) is regarded as a key molecule for the survival and differentiation of neurons. Besides its basal functions, BDNF also plays a role in activity-dependent synaptic plasticity, especially in hippocampal circuits. BDNF contributes directly to several forms of hippocampus-dependent learning and memory functions by regulating synaptic strength and connectivity [5,6]. The induction and expression of long-term potentiation (LTP), the physiological basis of memory, also depend on BDNF. Furthermore, increased expression of BDNF in

the hippocampus is associated with training on spatial navigation tasks while BDNF signaling impairment disrupts spatial learning and memory [7-10].

Doublecortin (DCX), one of the microtubule-associated proteins expressed by immature neurons, is another well-established marker of hippocampal plasticity [11]. In the adult brain, expression of DCX is primarily seen in the subventricular and subgranular zone [12]. These areas are responsible for the lifelong neurogenic process, as they ensure a steady supply of newly formed neurons [13]. Numerous studies have established the strong association of newly formed hippocampal neurons with adult learning and memory [14-17]. This indicates that the adult-generated hippocampal neurons tracked by DCX expression are a vital part of the circuitry underlying learning and memory. Thus, the number of DCX-positive cells and the morphological changes of these cells could account for differences in cognitive function. Moreover, in studies of hippocampal functions, DCX has served as a significant integrative tool at the molecular, cellular, and behavior levels [18]. Overall, BDNF and DCX are complementary markers of molecular and cellular processes underlying spatial long-term memory.

Behavioral neuroscience and neuropsychopharmacology have extensively utilized laboratory rodents [19,20]. Previous studies have demonstrated that different strains of rats (Wistar, Sprague Dawley, and Long Evans) exhibit distinct profiles of learning and memory abilities. Gokcek-Sarac and her colleagues investigated the performance of three strains of rats in a partially baited radial arm maze and found differences in spatial learning among strains [21]. The Sprague Dawley rats showed the worst performance in working and reference memory tasks, while Wistar rats and the outcrossed Wistar/Sprague-Dawley rats, who learned the task most rapidly, demonstrated better working memory. Long Evans rats exhibited an intermediate performance level [2]. In a different study, Long Evans rats also successfully learned a lever-press response in a two-object discrimination test. They demonstrated the only strain that exhibited clear short-term object recognition. However, albino Wistar and Sprague-Dawley rats showed relatively better performance in the swim maze but poorer discrimination learning [22]. Another study examined the effects of drugs. The rats were administered intracerebroventricular galanin and then tested in the Morris water maze. It was found that galanin clearly impaired the spatial learning and probe trial performance of Wistar and Sprague Dawley rats, while Long Evans rats were largely unaffected [23].

The present study aims to investigate strain-dependent differences in spatial long-term memory and hippocampal neuroplasticity markers in Wistar, Sprague Dawley, and Long Evans rats. Specifically, we compared their performance on a hippocampus-dependent spatial memory task and explored the relationship between this behavioral variability and hippocampal BDNF levels and DCX-defined immature neuron populations.

MATERIALS AND METHODS

Animals

In the present study, 4-month-old Wistar (W, n=5), Sprague Dawley (SD, n=6), and Long Evans Hooded (LE, n=5) rat strains were used. All animals were housed under standard laboratory conditions (22 ± 2 °C, 12 h light/dark cycle) with free access to food and water. All experimental procedures were conducted in accordance with the ethical principles of the ARRIVE Guidelines and were approved by the Istanbul Medeniyet University Animal Experiments Local Ethics Committee (İMÜ-HADYEK) (Approval no: 2025/3-1, Date: 26.03.2025).

Behavioral experiments

At the beginning of the experiment, the spatial learning and memory performance of all rats was assessed using the Morris Water Maze (MWM). The MWM apparatus consisted of a circular tank (125 cm in diameter and 60 cm in height) filled with opaque water, containing a hidden platform. To assess learning performance, rats were trained for 4 consecutive days, with 4 trials per day, to locate the hidden platform that remained in a fixed location using spatial cues. The rats were considered to have learned the task when the escape latency fell below 10 seconds. The latency to reach the hidden platform, the distance swum, and the swimming speed of the rats were monitored for 60 seconds using an automated video tracking system (EthoVision XT, Noldus Information Technology, Netherlands).

On the 5th day, a probe trial was applied to all rats. Therefore, the hidden platform was removed from the pool, and the time each rat spent in the target quadrant where the platform had previously been located was recorded using an automated video tracking system to evaluate spatial memory retention.

Sample collection and homogenization

At the end of the behavioral experiments, the rats were euthanized with ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) anesthesia. Their brains were removed and frozen on dry ice, and hippocampal tissues were dissected for molecular analysis. The samples were transferred to sterile tubes and stored at -80 °C until analysis.

Frozen tissues were homogenized using a lysis buffer containing 1M Tris-HCl (pH 6.8), 0.5 M EDTA, β-mercaptoethanol, 100% glycerol, bromophenol blue, distilled water, and a freshly added protease inhibitor. Homogenates were kept on ice for 20 min, then centrifuged at 14000 rpm for 15 min at 4 °C. The resulting supernatants were aliquoted into sterile tubes and stored at -20 °C until analysis.

Western blotting

First, total protein concentrations were determined using the Pierce BCA Protein Assay kit (Thermo Scientific, USA).

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Equal amounts of protein were separated by SDS-PAGE and transferred onto PVDF membranes using the Trans Blot Turbo system (Bio-Rad Laboratories, California, USA). The membranes were blocked with 5% non-fat milk in 0.1% Tween 20/0.1 M Tris-buffered saline (TBST) for 1 h at room temperature. After rinsing with TBST, the membranes were incubated overnight at 4°C with the primary antibodies BDNF (1:1000; Santa Cruz, USA) and DCX (1:1000; Thermo Scientific, USA), both diluted in blocking solution. After washing with TBST, membranes were incubated for 1 h at room temperature with horseradish peroxidase-conjugated goat anti-rabbit (1:5000; Cell Signaling Technologies, USA) secondary antibodies, diluted in blocking solution. Protein loading was controlled by reprobing membranes with the β-tubulin antibody (1:1000; Cell Signaling Technologies, USA). Protein bands were visualized using enhanced chemiluminescence (Advansta, USA) and detected with a CCD camera on the Fusion FX7 imaging system (Vilber Lourmat, France). Densitometric analysis of protein levels was performed using ImageJ.

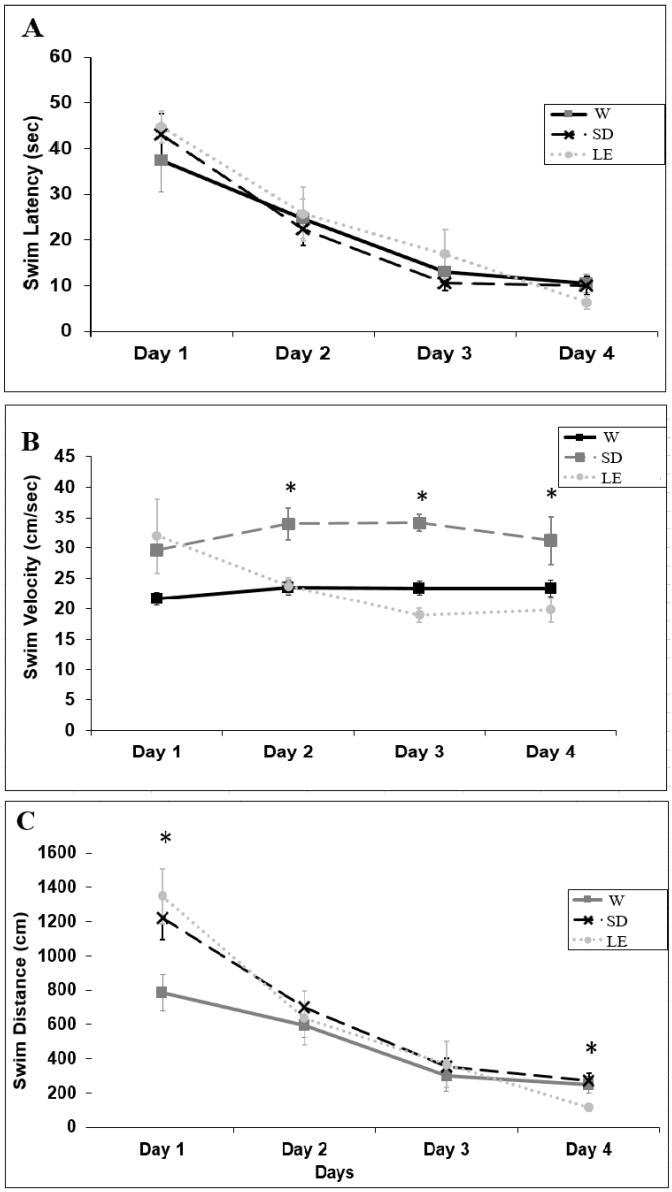

Figure 1. Acquisition of water-maze performance across four training days in three rat strains. (A) Swim latency (sec) to reach the hidden platform, (B) Swim velocity (cm/sec), and (C) Swim distance (cm) traveled to the platform are shown for Wistar (W), Sprague Dawley (SD), and Long Evans (LE) rats. Data are mean ± SD. Asterisks indicate significant differences at $p < 0.05$.

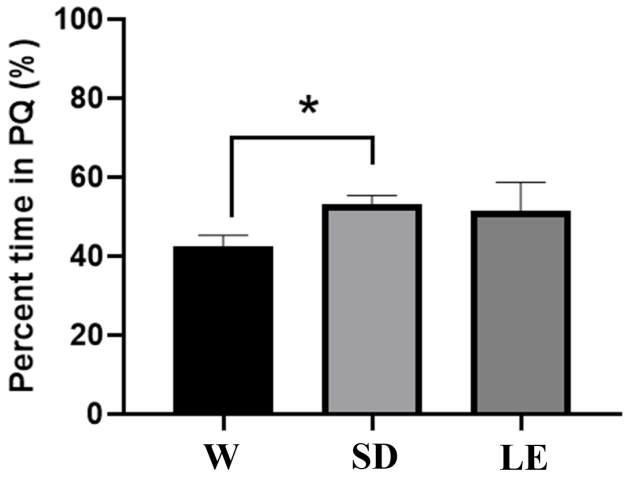

Figure 2. Probe trial performance in the water maze in three rat strains. Percent time spent in the platform quadrant (PQ) during the probe test is shown for Wistar (W), Sprague Dawley (SD), and Long Evans (LE) rats. Bars represent mean ± SD. Asterisks indicate significant differences at $p < 0.05$.

Statistical analysis

Statistical analyses were performed in GraphPad Prism 10 (GraphPad Software Inc., San Diego, CA). Data are reported as mean ± standard deviation (SD). A post hoc power analysis was performed using G*Power (version 3.1.9.7). Based on the observed effect size (0.332) and an alpha level of 0.05, the study's achieved statistical power was 0.74. Normality was assessed with the Shapiro-Wilk test. For statistical comparisons, the Kruskal-Wallis test with the Dunn-Bonferroni post hoc test, one-way ANOVA, and repeated-measures ANOVA with the LSD post hoc test were employed. In addition, Pearson's correlation test was used to assess linear correlations between probe data and molecular outcomes (BDNF and DCX values) within each group. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

Spatial learning and memory performances

Figure 1 shows the MWM acquisition performance across all rat strains. In the current study, according to two-way repeated measure ANOVA (strain X day), there were no between-group differences ($F(2,13) = 0.15$, $p = 0.86$) or day × group interactions ($F(6,39) = 0.83$, $p = 0.56$) for latency to

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Table 1. The data of swim latency, swim velocity, and swim distance traveled to the platform in the Morris water maze for Wistar (n=5), Sprague Dawley (n=6), and Long Evans (n=5) rats.

Strain	Wistar		Sprague Dawley		Long Evans	
Swim latency (sec)						
DAYS	Mean	SD	Mean	SD	Mean	SD
1	37.4	15.3	43.1	11.4	44.8	7.8
2	24.6	9.7	22.3	8.7	25.7	13.1
3	13.1	9.1	10.6	3.9	16.9	12.2
4	10.4	4.4	9.9	5.0	6.3	3.3
Swim velocity (cm/sec)						
DAYS	Mean	SD	Mean	SD	Mean	SD
1	784.7	238.9	1222.1	308.2	1348.1	357.6
2	592.2	151.0	697.6	233.6	636.1	349.5
3	300.9	208.0	354.6	111.3	365.9	302.2
4	246.7	107.3	270.4	103.4	114.1	44.7
Swim distance (cm)						
DAYS	Mean	SD	Mean	SD	Mean	SD
1	21.7	2.5	29.7	1.3	27.7	7.1
2	23.5	2.8	33.9	6.4	23.7	2.9
3	23.4	2.5	34.1	3.6	18.9	2.6
4	23.4	3.1	31.2	6.7	19.8	4.6
Probe (% time in the Platform Quadrant)						
Median		(Min-Max)	Median	(Min-Max)	Median	(Min-Max)
43.0		33.0-49.0	51.5	47.0-62.0	45.0	35.0-77.0

Data are mean ± SD and median (minimum-maximum).

Table 2. The results of Pearson's correlation of Probe trial percent time correlations with BDNF and DCX values.

Probe trial percent time correlations with	Wistar (n=5)	Sprague Dawley (n=6)	Long Evans (n=5)
BDNF	r = 0.28, p = 0.81	r = 0.85, p = 0.35	r = -0.54, p = 0.64
DCX	r = -0.66, p = 0.54	r = 0.98, p = 0.12	r =- 0.80, p = 0.41

the escape platform. In addition, a significant decrease day by day in the latency to reach the hidden platform ($F(3,39) = 58.52$, $p < 0.001$) was observed in MWM training (Figure 1A). However, there were significant between-group differences ($F(2,13) = 23.23$, $p \leq 0.001$) and day × group interactions ($F(6,39) = 3.23$, $p = 0.01$) in the swim velocities of rat strains without any change day by day ($F(3,39) = 1.02$, $p = 0.39$) (Figure 1B). According to the post hoc LSD test, Sprague Dawley rats were faster than other rat strains ($p < 0.05$). Due to these differences in the swim velocities, swim distances were calculated to determine the more accurate learning performances [24]. According to two-way repeated measure ANOVA, while there was insignificant between-group differences ($F(2,13) = 1.6$, $p = 0.24$) among rat strains, there was a significant day × group interactions ($F(6,39) = 2.93$, $P = 0.02$) and day-effect ($F(3,39) = 64.27$, $p < 0.001$) for swim distance (Figure 1C). According to the post hoc LSD test, Wistar rats swam shorter distances than other strains on the first day of training ($p = 0.03$ for Sprague Dawley and $p = 0.01$ for Long Evans), whereas Long Evans rats swam shorter distances to reach the hidden platform on the fourth day of training ($p = 0.01$ for Sprague Dawley and $p = 0.04$ for Wistar) (Figure 1C). The corresponding descriptive statistics are provided in Table 1 to complement the graphical representations

For the MWM probe trial, which measures the time spent in the platform quadrant in the absence of an escape platform, strains differed slightly in the percentage of time spent there ($p = 0.08$) (Figure 2). As shown in Figure 2, a significant increase in the percentage of time spent in the platform quadrant was observed in Sprague Dawley rats compared with Wistar rats ($p = 0.03$). On the other hand, there was no significant difference in the percentage of time spent in the platform quadrant between Sprague Dawley rats and Long Evans rats ($p = 0.8$). While there was an increase in the percentage of time spent in the platform quadrant in the Long Evans rats compared to the Wistar rats, it did not reach the accepted significance level ($p = 0.2$) (Figure 2).

Molecular outcomes

To determine molecular mechanisms underlying strain-dependent differences in learning and memory, the relative levels of BDNF and DCX in hippocampal tissues from dif-

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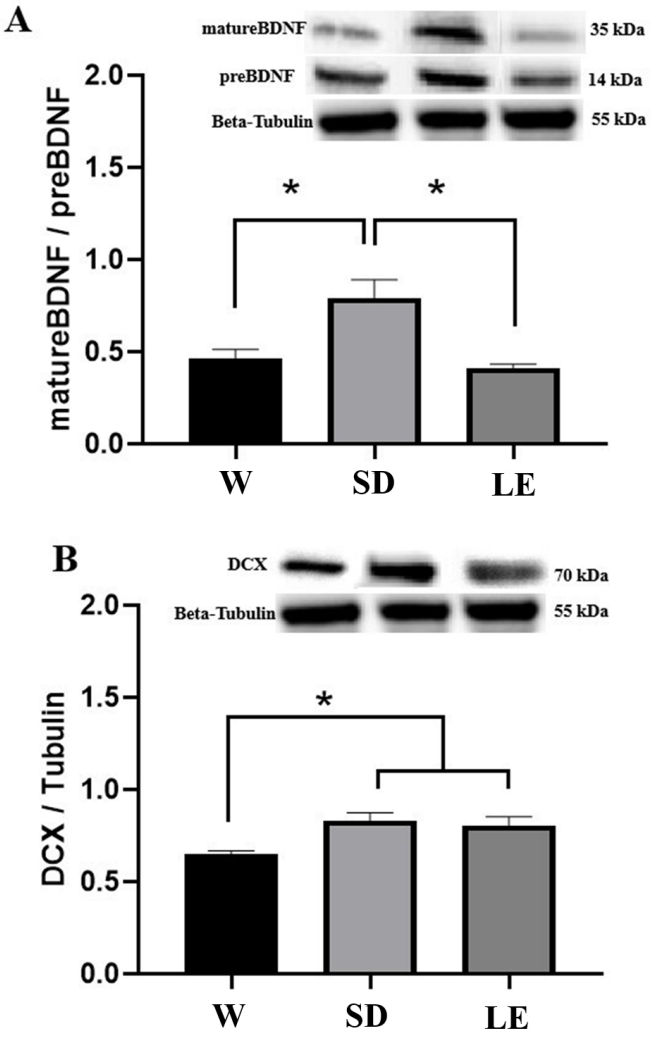

Figure 3. Hippocampal brain-derived neurotrophic factor (BDNF) and doublecortin (DCX) protein levels in three rat strains. (A) Representative Western blots and quantification of the ratio of matureBDNF to preBDNF in hippocampal tissue from Wistar (W), Sprague Dawley (SD), and Long Evans (LE) rats; β-tubulin served as a loading control. (B) Representative Western blots and quantification of DCX expression normalized to β-tubulin (DCX/tubulin) in the same samples. Bars represent mean ± SD for each strain. Asterisks indicate significant differences at $p < 0.05$. kDa: kilodalton.

ferent rat strains were evaluated (Figure 3). In the present study, there was a statistically significant increase in the mature BDNF levels of Sprague Dawley rats (0.79 ± 0.08) compared to the Wistar rats (0.46 ± 0.04) ($p = 0.01$) and Long Evans rats (0.41 ± 0.02) ($p = 0.006$) (Figure 3A). On the other hand, compared to that of the Wistar rats (0.65 ± 0.01), the DCX levels were significantly higher in the Sprague Dawley rats (0.83 ± 0.03) ($p = 0.01$) and Long Evans rats (0.81 ± 0.04) ($p = 0.03$) (Figure 3B).

Application of Pearson's correlation test to examine correlations between percent time spent in the target quadrant and BDNF and DCX values showed no correlation across strains (Table 2).

DISCUSSION

Variability in learning and memory performance among rat strains plays an important role in understanding and generalizing behavioral neuroscience findings. In a systematic comparison of seven male rat strains (Wistar, Wistar Kyoto, Sprague Dawley, Long Evans, LT, SHR, and BD-IX), Rybnikova and colleagues examined open-field behavior, anxiety- and depression-like behavior, circulating stress and thyroid hormones, and blood antioxidant capacity [25]. They found strain-specific differences rather than a single "standard" behavioral pattern. Locomotor and exploratory activity, anxiety scores, immobility in the forced swim test, the balance of glucocorticoids, thyroid-stimulating hormone and thyroxine levels, and total antioxidant activity significantly varied between strains [25]. Another comparative study examined Long-Evans and Sprague-Dawley rats housed in standard or enriched cages. Researchers used a broad behavioral battery, relevant to neuropsychiatric models, to conduct a detailed gene × environment study. The experiment demonstrated that both strain and environment influence behavior. Long Evans rats were more active, had lower prepulse inhibition, and learned operant tasks faster than Sprague-Dawley rats. Enriched housing reduced anxiety-like behavior and improved learning abilities, particularly in Long Evans rats. It slightly reduced prepulse inhibition in Sprague–Dawley rats. These findings overall highlight that strain and housing together affect cognitive and behavioral performance [26]. Therefore, this study compared long-term spatial memory and hippocampal plasticity markers (BDNF and DCX) among three commonly used rat strains: Wistar, Sprague Dawley, and Long Evans. Across all three strains, we observed a consistent learning pattern in the Morris water maze, indicated by decreases in escape latency and swim distance over the course of training. At the same time, we observed modest differences in swimming performance, probe trial results, and hippocampal BDNF and DCX protein expression levels that were clearly related to strain. These results support the hypothesis that both cognitive performance and learning- and memory-related molecular pathways are affected by genetic background and phenotypic characteristics of strains.

In the Morris water maze, escape latency is commonly used as a measure of learning. However, there are other factors besides spatial memory that may affect this measure, such as differences in swimming speed [24]. In this study, Sprague-Dawley rats swam faster than Wistar and Long-Evans rats. Although no significant difference in spatial learning ability was observed, their swim latencies were shorter. To address this, we also examined swim distance (path length) because it is less influenced by differences in swimming speed and represents how directly the rats swam toward the hidden platform. With this measure, we found that, on the first day of training, Wistar rats swam shorter distances, whereas, by the last day, Long Evans rats swam the shortest distances. These findings support the notion that Wistar rats demonstrated bet-

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ter task acquisition, while Long Evans rats navigated the maze more efficiently by the end of training. This is likely more indicative of differences in the strains' learning strategies than of one strain having better performance than the other. Data from the probe trial provide information about spatial memory retention. In the probe trial, Sprague Dawley rats spend a higher percentage of time in the target quadrant than Wistar rats. Long Evans rats exhibited an intermediate pattern that did not differ significantly from the other two strains. Together with the acquisition data, these results indicate that all three strains demonstrated a degree of spatial memory for the location of the platform, but Sprague Dawley rats displayed marginally greater retention than Wistar rats under our experimental conditions. The absence of significant behavioral differences is not surprising, since all the animals were healthy, age-matched adults tested with the same standardized protocol. However, prior reports of the differences between Wistar, Sprague Dawley, and Long Evans rats are dependent to the specific types of learning and memory performance across various tasks [21-23].

While evaluating the results from the Morris water maze, researchers should also consider the role of visual function. Given that this task relies on distal visual cues, strain-related differences in vision may have affected performance, particularly when comparing the Wistar and Sprague Dawley albino strains with the Long Evans pigmented strain. Kumar et al. [27] found strain-specific variations in performance on visual and spatial tasks suggesting that pigmented rats probably have better visual acuity when compared with albino rats, and reduced vision can affect place learning in the water maze. Meanwhile, it should be mentioned that albino rodents are widely used in studies of behavior, including spatial learning tasks such as the Morris water maze [28]. In the present study, the visual cues, positioned at different locations around the maze, were clear and simple and were placed at distances designed to fall within the detection range of albino animals. Nevertheless, no additional visual examination has not been carried out, which should be considered a limitation. Therefore, the differences observed between strains should be interpreted with caution, as they may reflect not only variation in hippocampus-dependent memory processes but also, to some extent, differences in visual acuity.

The molecular results also provide evidence for these behavioral differences. In particular, hippocampal BDNF levels in Sprague-Dawley rats were significantly higher than in Wistar and Long-Evans rats. BDNF is important as a master regulator of synaptic plasticity, long-term potentiation, and the consolidation of memory, and as such it plays a crucial role [5-7]. In our study, Sprague-Dawley rats, which exhibited the highest BDNF levels, showed superior probe performance compared with Wistar rats. Although no direct correlation analyses were performed between BDNF and behavior, this pattern is consistent with the idea that higher levels of BDNF in the hippocampus may support more enduring retention of spatial memory. Additionally, baseline or experience-induced differences in BDNF levels between strains may indicate distinct sensitivities to training, stress, or environmental cues during the task.

DCX expression levels also differed by strain. DCX expression in the hippocampus is higher in Sprague Dawley and Long Evans rats than in Wistar rats. DCX is expressed in immature neurons in the neurogenic niches and is used as a marker for neurogenesis in the adult hippocampus [11,12,14]. The presence of higher levels of DCX in the Sprague Dawley and Long Evans rat strains likely indicates a greater number of newborn granule cells. Since adult-born hippocampal neurons play a role in learning and memory, particularly in tasks requiring pattern discrimination and adaptable spatial information processing [15,17,18], the lower DCX levels observed in Wistar rats might partially explain their poorer performance in the probe test and their swimming patterns during later training sessions. This finding is consistent with studies showing that spatial navigation experience increases the pool of DCX-positive neurons [12].

CONCLUSION

The study showed that all three rat strains, Wistar, Sprague Dawley, and Long Evans, acquired and retained spatial memory as assessed using the MWM. In particular, Sprague Dawley rats exhibited the greatest memory retention and the highest hippocampal levels of BDNF and DCX. Long-Evans rats exhibited the best search strategies by the end of the training sessions. This was, however, coupled with the Wistar rats consistently displaying poorer probe performance and lower expression of the plasticity markers. Although these gaps are relatively small, their consistent presence indicates that the particular rat strain is not an arbitrary variable. It is a principal component that dictates the behavior and the accompanying plasticity that the hippocampus undergoes. Thus, differences among rat strains are a key factor to consider when evaluating behavioral subfields. This must be done, especially in the field of behavioral neuroscience, when designing the experiment, interpreting results, and finalizing your findings from various studies.

Ethics Committee Approval: This study was approved by the Istanbul Medeniyet University Local Ethics Committee for Animal Experiments (İMÜ-HADYEK) (Approval no: 2025/3-1, Date: 26.03.2025).

Peer-review: Externally peer-reviewed.

Conflict of Interest: There is no conflict of interest

Author Contributions: Concept: ID, EK, BE; Design: ID, EK, BE; Supervision: BE; Materials: ID and EK; Data Collection and/or Processing: ID and BE; Analysis and/or Interpretation: BE and EK; Literature Search: ID; Writing Manuscript: ID; Critical Review: ID, EK, BE.

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