Journal of Behavioral and Brain Science, **2012, 2, 156-161**
http://dx.doi.org/10.4236/jbbs.2012.22018 Published Online May 2012 (http://www.SciRP.org/journal/jbbs)

Dissociation between Performances in Water Maze and Spontaneous Alternation in BALB/c versus A/J Mice

Julien Celestine[1*], Arnaud Tanti[2], Arnaud Aubert[3]
[1]INSERM U930 E2 Neurogénétique et Neurométabolomique CHRU de Tours, Hôpital Bretonneau, 2 Boulevard Tonnellé, Bât B1A, 1er Etage, 37044 Tours Cedex 9, France
[2]Faculté des Sciences et Techniques, Université François Rabelais, Tours, France
[3]EA 2114, Psychologie des Ages de la Vie, Université de Tours, 3 Rue des Tanneurs, 37041 Tours Cedex 1, France
Email: [*]julien.celestine@etu.univ-tours.fr

Received March 7, 2011; revised April 15, 2011; accepted May 7, 2011

ABSTRACT

Learning processes are extensively studied in behavioral neuroscience. As experimental models, Morris Water Maze (MWM) and Spontaneous Alternation (SA) represent two of the most frequently used laboratory tests to respectively address spatial vs non-spatial tasks. Several factors have been shown to impact on those learning, including strain, gender, apparatus, conditioning, vision, lighting conditions and stress level. In order to focus on the later, we compared the acquisition of two learning tasks (MWM and SA) in BALB/c and A/J mice, which are known as fearful and stress-sensitive strains. Here, we report that BALB/c mice exhibited higher performances than A/J mice in the MWM (*i.e*. spatial reference memory task), whereas A/J mice performed better in the SA (*i.e*. spatial working memory task). These results indicate dissociated processes in the acquisition of spatial vs non-spatial tasks, and emphasize a varying influence of emotional reactivity on different forms of cognition.

Keywords: Morris Water Maze; Spontaneous Alternation; Behavior; BALB/c; A/J; Learning

1. Introduction

Emotions are commonly described as the processes whereby brain could evaluate stimuli, basically as pleasant or unpleasant [1-3], promoting either approach or avoidance behaviors, thus supporting individual adaptation and survival. Such a key role in behavioral guidance and decision making is growingly been emphasized [1,2], and it emotions are now commonly regarded as adaptive processes signaling relevant cues about environmental changes. However, assessment of emotions remains a difficult task [4], and especially in non-human animals where verbal information is unavailable. Nevertheless, human and non-human darwinian emotions share many biobehavioral features [5]. This evolutionary common ground allows the investigation of emotional state by using animal models [4].

It has been argued that emotions represent a warning system and a way to optimize action [6]. That is the reason why animals could exhibit very different behaviors under normal or stressful conditions. Throughout the evolution of species, some behavioral mechanisms were selected on the basis of their significant survival benefit. Such behaviors like fear-induced freezing or fleeing are considered are widespread evolutionary stable strategies [7,8]. The selection of the final response (*i.e*. freezing or fleeing) is largely dependent on actual emotional arousal triggered by environmental cues. Emotions act as potent factors for rapid adaptive decision making processes. Therefore, they represent modulatory tools for cognition rather than inhibitory factors.

Advances in psychology and neurosciences have also shown that core cognitive functions such as learning and memory share many complex interactions with emotional processes. For example, patients suffering from various mood disorders also express memory impairments, and corresponding animal models were developed [4,5] to better understand the mechanisms underlying these relations. Among the diverse experimental tests designed to assess learning and memory in animals, two main categories of tests consist in reference versus working memory tasks [9,10], especially in rodent studies [11-16]. Morris Water Maze (MWM) [17] and Spontaneous Alternation (SA) [18] for example became standard tasks to explore such functions. Indeed, they are versatile and allow many variations to assess specific processes and/or factors (e.g. pharmacological agents, genetic background and neurological preparation).

While those behavioral models were generally designed for rats, mice are nowadays the main animal model in

[*]Corresponding author.

behavioral neurosciences. Many mice strains are available, which constitute as many convenient models to assess the roles and functions of various bio-behavioral systems. A growing set of literature shows strain differences of performances in different experimental paradigms [14-16,19-26]. For instance, it is commonly considered that BALB/c and A/J mice albino strains have lower performances in mazes due to impaired visual capabilities, thus leading other strains such as C57BL6 [27] to be preferred. Nevertheless, the poor visual capabilities of BALB/c and A/J mice are not necessarily the only factor that could account for their learning performances. Many factors and individual characteristics are known to influence learning, such as strain, gender, apparatus features, conditioning set, perceptive capabilities, lighting and stress [14-16,21,22,28-30]. More specifically, BALB/c and A/J are known to for displaying high emotional reactivity compared to other mouse strains. Using two standard forms of reference and working memory tasks (*i.e.* MWM and SA respectively), the aim of the present study was to further understand the differences in learning performances of two mice strains, respectively BALB/c and A/J mice, regarded both as highly emotional and poor learners. We aimed to show in that the relativity of the "poor learner" label of these strains by demonstrating that in specifics conditions of testing, they can express efficient learning. Indeed, whereas these strains are commonly used in many stress studies [31], additional information about their respective learning performances would be needed to better differentiate the potentialities of these animal models, especially in the scope to better understand the relations between cognition, emotions and stress. Using two different forms of standardized spatial tasks (*i.e.* Morris water maze and spontaneous alternation) involving partly different cognitive processes (*i.e.* reference memory and working memory respectively), we showed that each strain performed better in a specific task.

2. Materials and Methods

2.1. Animals

A total of 10 male BALB/c mice (Janvier©, France) and 10 male A/J mice (Harlan©, France) were used in this study. Ice were 7-week old at their arrival to the laboratory and 10-week old at the time of testing. Prior to testing, they were housed in groups of 5, in standard cages containing food pellets and water *Ad libitum*. They were housed in a room kept at constant temperature (21˚C ± 1˚C) on a 12/12 controlled light/dark cycle with lights on at 6 a.m. Animals of the two strains were randomized and tested each day at 2 p.m. After each day of testing, mice returns into the rearing room in the conditions describe above. All experiments were carried out in accordance with the European Community Council directive 86/609/EEC.

2.2. Apparatuses

2.2.1. Morris Water Maze

The apparatus consisted of a circular pool (diameter: 90 cm; high: 30 cm) filled with opaque water (23˚C ± 1˚C) in which a platform (7 × 6 cm) is located 20 cm from the border in order to unable escape possibility. The water used in each tests was kept at constant temperature (23˚C ± 1˚C) and removed every day after the end of the session.

Pool was divided in 4 equal quadrants G, A1, A2, O, which respectively represent the goal quadrant (in which the platform is located), the two adjacent quadrants and the opposite one. The experimental room was lighted with a halogen lamp (85 lux), and various fixed visual cues were available 85 cm from the pool, on the walls.

2.2.2. Spontaneous Alternation

To run spontaneous alternation, an X-maze apparatus was used. An X-maze consisted of four wooden arms (10 cm wide; 60 cm long; 10 cm height), with a 90 angle between two adjacent arms. The maze surface was covered with sawdust to make the apparatus less aversive. The experimental room was lighted with a halogen lamp (85 lx), and provided various visual cues fixed on surrounding walls.

2.3. Behavioral Recordings

2.3.1. Morris Water Maze

In this task BALB/c (n = 10) and A/J mice (n = 10) had to learn the location of the hidden platform. The time to find the platform was recorded and used as the main learning parameter.

During familiarization session, platform was located 1 cm above the water (*i.e.* in a visible position) in the G quadrant. Mice were maintained 60 seconds on the platform and were successively placed in the water at the different starting points (A1, A2, O). During the learning phase, platform was concealed one centimeter under the water level. The learning phase consisted in one learning session per day during 4 consecutive days. One session consisted in three trials, respectively departing from O, A1 and A2 quadrants in a random order. If a mouse did not find the platform after 60 seconds, it was brought out the water to the platform. Mice were allowed to rest during 60 sec on the platform at the end of each trial, before the beginning of the next trial.

Probe test was undertaken 24 hr after the end of the conditioning process. During the probe test, there was no platform in the pool. The test begun with the introduction of mice in the center of the pool. The time spent in each quadrant was recorded within the 60-sec period of ob-

servation. Samples for probe test, samples sizes of each group of mice were decreased to n = 8 due to accidental mortality.

2.3.2. Spontaneous Alternation

This paradigm uses the spontaneous tendency of mice to move from one arm of the maze to another. At the beginning of the test, BALB/c (n = 8) and A/J (n = 8) mice were placed at the center of the maze and the sequence of entries into the three arms was recorded over a period of 10 min, an arm entry being determined as the four paws within that arm. The total number of arm entries was recorded and the spontaneous alternation score was calculated as the number of alternations (*i.e*. entries in three different arms consecutively) divided by the total number of possible alternations (*i.e*. total number of arm entries-two) and multiplied by 100.

2.4. Statistical Analyses

To allow a valid use of parametric statistical tests, normality and homoscedasticity of data was checked before each test, using Shapiro-Wilk's and Bartlett's tests respectively. When parametric assumptions were not satisfied, data were submitted to a Log10 transform to reach the criteria. Learning performances of mice in the MWM were analyzed with a two-way repeated ANOVA (strain × training session). When main analysis showed a significant effect of one of the main factors, post-hoc pairwise analyses were done using the Holm-Sidak procedure. The differences between strains in the probe test were analyzed with unpaired Student's t-test. Student's t-test was also used to analyze spontaneous alternation scores, number of arm entries and alternation percentage in the SA (within and between subjects' comparisons respectively). Comparisons between strains were done using unpaired t-tests while comparisons of performances of each strain with random scores were done using one-sample t-tests.

3. Results

3.1. Morris Water Maze

Figure 1 shows the mean latency to reach the hidden platform during acquisition sessions in BALB/c (n = 10) and A/J mice (n = 10). A two-way repeated ANOVA showed a significant difference in latency to find the hidden platform between the two strains ($F_{1,54}$ = 5.365; p = 0.033), revealing a globally shorter latency in BALB/c mice compared to A/J (mean latencies: 24.97 sec vs 35.15 sec respectively). It also showed a significant difference for latency to find the hidden platform between training day ($F_{3,54}$ = 5.093; p = 0.004). Post-hoc comparisons showed that latency to find the platform was significantly smaller from session 4 relative to session 1 in BALB/c (Holm-Sidak's p = 0.004) but not in A/J mice (Holm-Sidak's p = 0.178). Moreover, test showed that latency to find the platform was not significantly different between the two strains on session 1 (Holm-Sidak's p = 0.382), but was significantly shorter in BALB/c mice for session 4 compared to A/J mice (Holm-Sidak's p = 0.034).

Figure 2 illustrates performances of BALB/c (n = 8) and A/J mice (n = 8) in the probe test. Independent Student's t-test showed that BALB/c express significantly longer swimming time in the goal quadrant (G) compared to A/J (t = 2.274; df = 14; p = 0.0392).

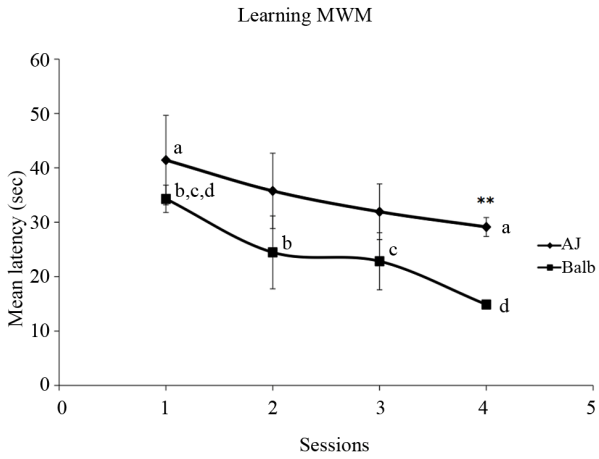

Figure 1. Mean (±SEM) escape latencies (in seconds) on successive sessions. Each point represents the average score over three trials. (a) Indicates significant difference inside A/J group (n = 10); (b), (c) Indicate significant difference inside BALB/c group (n = 10); **: p < 0.01: significant difference between the two strains in session 4.

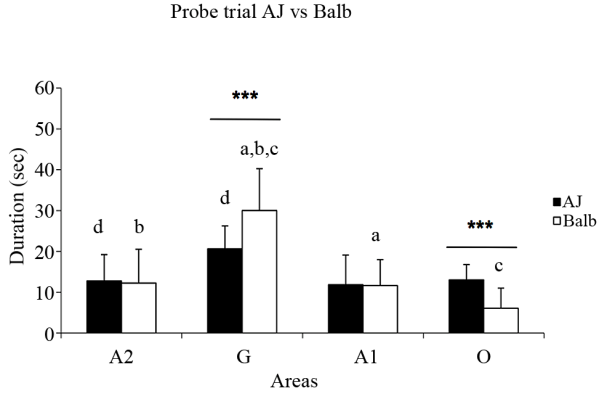

Figure 2. Mean (±SEM) time spent in each quadrant (seconds) during probe test. G is the goal quadrant, A1 and A2 are the adjacent quadrants, and O is the opposite quadrant. (a)-(c) Indicate significant difference between quadrant inside BALB/c group (n = 8); (d) Indicate significant difference between quadrants inside A/J group (n = 8); ***: p < 0.001: significant difference between the two strains in quadrant G and O.

3.2. Spontaneous Alternation

BALB/c mice (n = 8) showed an alternation rate (mean ± SEM: 54.4% ± 3%) not significantly different from a random arm entries sequence (one-sample t-test: t = 1.4667; df = 7; p = 0.1859). On the contrary, A/J mice (n = 8) expressed a significantly higher alternation rate (mean ± SEM: 70.8% ± 4.2%) than BALB/c mice (unpaired t-test: t = 3.177; df = 14; p = 0.0067), and significantly different from a random arm entries sequence (one-sample t-test: t = 4.9524; df = 7; p = 0.0017). Finally, the total number of arm-entries was however higher in BALB/c mice compared to A/J mice (unpaired t-test: t = 5.168; df = 14; p = 0.0001).

4. Discussion

In this study, we compared learning performances of two strains of mice (BALB/c and A/J) known for their high emotional reactivity and poor learning skills. Each strain was submitted to a spatial memory task (MWM) and a spatial working memory learning task (SA).

Results showed that contrary to A/J mice, BALB/c learned the location of the MWM hidden platform in 4 days (**Figure 1**). Probe test has shown that BALB/c express better abilities to restore the learning information than A/J strain. Moreover, results of spontaneous alternation test were the opposite, and A/Js' performances in this test were significantly better than BALB/c.

Stress studies involve a limited choice of mice strains (including BALB/c and A/J mice), which are selected on the basis of their sensitivity to stressors [31]. In addition, throughout the literature BALB/c and A/J strains are commonly considered as unable or very inefficient in spatial task resolution [21]. This work shows that in the contrary, these strains are able to efficiently learn a task, but with opposite potentialities, BALB/c performing better than A/J in spatial reference task while A/J mice were better than BALB/c in spatial working task. Since the strains tested in this study are commonly used for their high emotional reactivity, our results can be discussed in terms of relations between emotion and learning [32]. Indeed, our results point out a relation between strain (BALB/c vs A/J), and learning type (spatial vs non-spatial). BALB/c and A/J are known to exhibit low locomotor activity and high level of emotional reactivity compared to other mouse strains [21]. Such an emotional reactivity is generally expressed in mazes as wall hugging, floating [5,14,16,19-21,29,33-38] or anxiety-like behaviors [15,27]. However, supporting the differences showed in our results, few studies reveal that BALB/c have better learning performances than A/J throughout spatial learning [36]. Interestingly, it has been shown that A/J mice exhibit a higher emotional reactivity than BALB/c. It was indirectly reviewed by several authors which showed a differentiation between those two strains for example in the open field test or anxiety like behavior [19,21,37,39,40]. Hence, the less emotionally reactive strain tested in our study (*i.e*. BALB/c) expressed better performances in the spatial MWM task, thus further supporting the known inverse relation between sensitivity to stress and spatial cognition.

As suggested by the germinal works of Donald Hebb [41], performances in many tasks (hence cognitive processes), are a function of the degree of emotional arousal. Indeed, a general rule was described in which emotional arousal influences performances with an inverted U-shape relation, where lowest and highest emotional loads are associated with lowest performances (*i.e*. poor motivation to solve the task and inhibitory emotional over-load respectively). However, our results support previous suggestions that such emotion-cognition relation would not be uni-dimensional, but would be task-dependent.

In conclusion, our study shows that whereas considered as poor learners, BALB/c and A/J mice can perform efficiently in different learning tasks. More specifically, our results revealed that BALB/c mice performed better than A/J mice in a spatial learning task (MWM) while A/J mice acquired faster a non-spatial task (SA). Considering the fact that BALB/c and less emotionally reactive than A/J mice, this suggests that the influence of emotional arousal on cognition (inhibition or facilitation) depends on the nature of the task (reference vs working memory) and involved neural substrates (e.g. hippocampus).

Indeed MWM and SA as spatial and non-spatial tasks are respectively hippocampus-dependent and non-dependent. Conveniently, influence of emotion and stress on hippocampus has been extensively studied [13,32-35, 42,43]. Indeed many studies have investigated and demonstrated so far the impairment of hippocampus spatial learning in response to stress procedure such as learned helplessness or chronic mild stress [13,44]. Furthermore, limbic system is largely implicated in emotional response. Particularly the amygdala and also the hippocampus in fear context [45-48]. This link is very consistent with the behavioral differentiation observed between those two strains. In fact our results are in line with an inverse relationship between hippocampus processing efficiency and HPA axis activity.

If conflicting hippocampal activations between emotional and spatial processes could constitute a substantial hypothesis to understand why a lower emotional arousal would allow better performances in spatial tasks, further studies would be then needed to better understand why high emotional arousal would be beneficial to a discriminant task.

5. Acknowledgements

Authors thank Catherine Belzung for providing logistic support (*i.e*. animals and experimental facilities). J. Célestine and A. Tanti designed the experimental protocol and

collected data. J. Célestine and A. Aubert undertook statistical analysis. All authors revised draft of the manuscripts and have approved the final manuscript. Finally, authors thank Helen Morrison for language revision.

REFERENCES

[1] J. LeDoux, "The Emotional Brain: The Mysterious Underpinnings of Emotional Life," Simon & Schuster, New York, 1996.

[2] J. E. Ledoux, "Emotion Circuits in the Brain," *Annual Review of Neurosciences*, Vol. 23, 2000, pp. 155-184. doi:10.1146/annurev.neuro.23.1.155

[3] J. Panksepp, "Evolution Constructed the Potential for Subjective Experience within the Neurodynamics of the Mammalian Brain," In: P. Ekman and R. J. Davidson, Eds., *The Nature of Emotion*: *Fundamental Questions*, 1994, pp. 396-399.

[4] E. S. Paul, E. J. Harding and M. Mendi, "Measuring Emotional Processes in Animals: The Utility of a Cognitive Approach," *Neuroscience and Biobehavioral Reviews*, Vol. 29, No. 3, 2005, pp. 469-491. doi:10.1016/j.neubiorev.2005.01.002

[5] A. Cabanac and M. Cabanac, "Heart Rate Response to Gentle Handling of Frog and Lizard," *Behavioural Processes*, Vol. 52, No. 2-3, 2000, pp. 89-95. doi:10.1016/S0376-6357(00)00108-X

[6] M. Cabanac, "Emotion and Phylogeny," *Japanese Journal of Physiology*, Vol. 49, No. 1, 1999, pp. 1-10. doi:10.2170/jjphysiol.49.1

[7] A. Fischer, M. Radulovic, C. Schrick, F. Sananbenesi, J. Godovac-Zimmermann and J. Radulovic, "Hippocampal Mek/Erk Signaling Mediates Extinction of Contextual Freezing Behavior," *Neurobiology of Learning and Memory*, Vol. 87, No. 1, 2007, pp. 149-158. doi:10.1016/j.nlm.2006.08.003

[8] M. R. Holahan and N. M. White, "Amygdala c-Fos Inducting Corresponds to Unconditioned and Conditioned Aversive Stimuli but Not to Freezing," *Behavioural Brain Research*, Vol. 152, 2004, pp. 109-120.

[9] N. Graindorge, C. Alves, A. S. Darmaillacq, R. Chichery, L. Dickel and C. Bellanger, "Effects of Dorsal and Ventral Vertical Lobe Electrolytic Lesions on Spatial Learning and Locomotor Activity in Sepia Officinalis," *Behavioral Neuroscience*, Vol. 120, No. 5, 2006, pp. 1151-1158. doi:10.1037/0735-7044.120.5.1151

[10] C. Alves, J. G. Boal, R. Chichery and L. Dickel, "Orientation in the Cuttlefish Sepia Officinalis: Response versus Place Learning," *Animal Cognition*, Vol. 10, No. 1, 2007, pp. 29-36. doi:10.1007/s10071-006-0027-6

[11] E.-T. Ang, G. S. Dawe, P. T. H. Wong, S. Moochhala and Y.-K. Ng, "Alterations in Spatial Learning and Memory after Forced Exercise," *Brain Research*, Vol. 1113, No. 1, 2006, pp. 186-193. doi:10.1016/j.brainres.2006.07.023

[12] R. A. Countryman, N. L. Kaban and P. J. Colombo, "Hippocampal c-Fos Is Necessary for Long-Term Memory of a Socially Transmitted Food Preference," *Neurobiology of Learning and Memory*, Vol. 84, No. 3, 2005, p. 175. doi:10.1016/j.nlm.2005.07.005

[13] L. Song, W. Che, W. Min-Wei, Y. Murakami and K. Matsumoto, "Impairment of the Spatial Learning and Memory Induced by Learned Helplessness and Chronic Mild Stress," *Pharmacology, Biochemistry, and Behavior*, Vol. 83, No. 2, 2006, pp. 186-193. doi:10.1016/j.pbb.2006.01.004

[14] J. N. Crawley, J. K. Belknap, A. Collins, J. C. Crabbe, W. Frankel, N. Henderson, *et al.*, "Behavioral Phenotypes of Inbred Mouse Strains: Implications and Recommendations for Molecular Studies," *Psychopharmacology*, Vol. 132, No. 2, 1997, pp. 107-124. doi:10.1007/s002130050327

[15] K. Klapdor and F. J. van der Staay, "The Morris Water-Escape Task in Mice: Strain Differences and Effects of Intra-Maze Contrast and Brightness," *Physiology & Behavior*, Vol. 60, No. 5, 1996, pp. 1247-1254. doi:10.1016/S0031-9384(96)00224-7

[16] P. Carlier and M. Jamon, "Observational Learning in C57BL/6j Mice," *Behavioral Brain Research*, Vol. 174, No. 1, 2006, pp. 125-131. doi:10.1016/j.bbr.2006.07.014

[17] R. G. M. Morris, P. Garrud, J. N. P. Rawlins and J. O'Keefe, "Place Navigation Impaired in Rats with Hippocampal Lesions," *Nature*, Vol. 297, 1982, pp. 681-683. doi:10.1038/297681a0

[18] R. Lalonde, "The Neurobiological Basis of Spontaneous Alternation," *Neuroscience & Biobehavioral Reviews*, Vol. 26, No. 1, 2002, pp. 91-104. doi:10.1016/S0149-7634(01)00041-0

[19] D. Wahlsten, S. F. Cooper and J. C. Crabbe, "Different Rankings of Inbred Mouse Strains on the Morris Maze and a Refined 4-Arm Water Escape Task," *Behavioral Brain Research*, Vol. 165, No. 1, 2005, pp. 36-51. doi:10.1016/j.bbr.2005.06.047

[20] D. Wahlsten, N. R. Rustay, P. Metten and J. C. Crabbe, "In Search of a Better Mouse Test," *Trends in Neurosciences*, Vol. 26, No. 3, 2003, pp. 132-136. doi:10.1016/S0166-2236(03)00033-X

[21] V. Carola, F. D'Olimpio, E. Brunamonti, A. Bevilacqua, P. Renzi and F. Mangia, "Anxiety-Related Behaviour in C57BL/6-BALB/c Chimeric Mice," *Behavioral Brain Research*, Vol. 150, No. 1-2, 2004, pp. 25-32.

[22] V. Kazlauckas, J. Schuh, O. P. Dall'Igna, G. S. Pereira, C. D. Bonan and D. R. Lara, "Behavioral and Cognitive Profile of Mice with High and Low Exploratory Phenotypes," *Behavioural Brain Research*, Vol. 162, No. 2, 2005, p. 272. doi:10.1016/j.bbr.2005.03.021

[23] S. J. Clapcote and J. C. Roder, "Survey of Embryonic Stem Cell Line Source Strains in the Water Maze Reveals Superior Reversal Learning of 129S6/SvEvTac Mice," *Behavioural Brain Research*, Vol. 152, 2004, pp. 35-48.

[24] E. H. Owen, S. F. Logue, D. L. Rasmussen and J. M. Wehner, "Assessment of Learning by the Morris Water Task and Fear Conditioning in Inbred Mouse Strains and F1 Hybrids: Implications of Genetic Background for Single Genemutations and Quantitative Trai Loci Analyses," *Neuroscience*, Vol. 80, No. 4, 1997, pp. 1087-1099. doi:10.1016/S0306-4522(97)00165-6

[25] V. Voikar, S. Koks, E. Vasar and H. Rauvala, "Strain and Gender Differences in the Behavior of Mouse Lines Commonly Used in Transgenic Studies," *Physiology & Behavior*, Vol. 72, No. 1-2, 2001, pp. 271-281. doi:10.1016/S0031-9384(00)00405-4

[26] M. Yoshida, K. Goto and S. Watanabe, "Task-Dependent Strain Difference of Spatial Learning in C57BL/6N and BALB/c Mice," *Physiology and Behavior*, Vol. 73, No. 1-2, 2001, pp. 37-42. doi:10.1016/S0031-9384(01)00419-X

[27] K. Klapdor and F. J. Van Der Staay, "Repeated Acquisition of a Spatial Navigation Task in Mice: Effects of Spacing of Trials and of Unilateral Middle Cerebral Artery Occlusion," *Physiology & Behavior*, Vol. 63, No. 5, 1998, pp. 903-909. doi:10.1016/S0031-9384(98)00003-1

[28] D. Van Dam, G. Lenders and P. P. De Deyn, "Effect of Morris Water Maze Diameter on Visual-Spatial Learning in Different Mouse Strains," *Neurobiology of Learning and Memory*, Vol. 85, No. 2, 2006, pp. 164-172. doi:10.1016/j.nlm.2005.09.006

[29] R. D'Hooge and P. P. De Deyn, "Applications of the Morris Water Maze in the Study of Learning and Memory," *Brain Research Reviews*, Vol. 36, No. 1, 2001, pp. 60-90. doi:10.1016/S0165-0173(01)00067-4

[30] P. Chapillon and A. Debouzie, "BALB/c Mice Are Not So Bad in the Morris Water Maze," *Behavioral Brain Research*, Vol. 117, No. 1-2, 2000, pp. 115-118. doi:10.1016/S0166-4328(00)00292-8

[31] Y. Ibarguen-Vargas, A. Surget, C. Touma, R. Palme and C. Belzung, "Multifaceted Strain-Specific Effects in a Mouse Model of Depression and of Antidepressant Reversal," *Psychoneuroendocrinology*, Vol. 33, No. 10, 2008, pp. 1357-1368. doi:10.1016/j.psyneuen.2008.07.010

[32] K. Yamada, Y. Santo-Yamada and K. Wada, "Stress-Induced Impairment of Inhibitory Avoidance Learning in Female Neuromedin B Receptor-Deficient Mice," *Physiology & Behavior*, Vol. 78, No. 2, 2003, p. 303. doi:10.1016/S0031-9384(02)00979-4

[33] D. D. Francis, D. M. Zaharia, N. Shanks and H. Anisman, "Stress-Induced Disturbances in Morris Water-Maze Performance: Interstain Variability," *Physiology and Behavior*, Vol. 58, No. 1, 1995, pp. 57-65. doi:10.1016/0031-9384(95)00009-8

[34] C. Pittenger and R. S. Duman, "Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms," *Neuropsychopharmacology*, Vol. 33, No. 1, 2007, pp. 88-109. doi:10.1038/sj.npp.1301574

[35] L. Santarelli, M. Saxe, C. Gross, A. Surget, F. Battaglia, S. Dulawa, *et al.*, "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants," *Science*, Vol. 301, No. 5634, 2003, pp. 805-809. doi:10.1126/science.1083328

[36] R. E. Brown and A. A. Wong, "The Influence of Visual Ability on Learning and Memory Performance in 13 Strains of Mice," *Learning & Memory*, Vol. 14, 2007, pp. 134-144. doi:10.1101/lm.473907

[37] S. S. Moy, J. J. Nadler, N. B. Young, A. Perez, L. P. Holloway, R. P. Barbaro, *et al.*, "Mouse Behavioral Tasks Relevant to Autism: Phenotypes of 10 Inbred Strains," *Behavioural Brain Research*, Vol. 176, No. 1, 2007, pp. 4-20. doi:10.1016/j.bbr.2006.07.030

[38] M. Upchurch and J. M. Wehner, "Differences between Inbred Strains of Mice in Morris Water Maze Performance," *Behavior Genetics*, Vol. 18, No. 1, 1988, pp. 55-68. doi:10.1007/BF01067075

[39] J. C. Crabbe, D. Wahlsten and B. C. Dudek, "Genetics of Mouse Behavior: Interactions with Laboratory Environment," *Science*, Vol. 284, No. 5420, 1999, pp. 1670-1672. doi:10.1126/science.284.5420.1670

[40] V. Carola, F. D'Olimpio, E. Brunamonti, F. Mangia and P. Renzi, "Evaluation of the Elevated Plus-Maze and Open-Field Tests for the Assessment of Anxiety-Related Behaviour in Inbred Mice," *Behavioral Brain Research*, Vol. 134, No. 1-2, 2002, pp. 49-57. doi:10.1016/S0166-4328(01)00452-1

[41] D. O. Hebb, "Drives and the C.N.S. (Conceptual Nervous System)," *Psychological Review*, Vol. 62, 1955, pp. 243-254. doi:10.1037/h0041823

[42] A. Briones-Aranda, L. Rocha and O. Picazo, "Influence of Forced Swimming Stress on 5-HT1A Receptors and Serotonin Levels in Mouse Brain," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, Vol. 29, No. 2, 2005, pp. 275-281. doi:10.1016/j.pnpbp.2004.11.011

[43] Y. Xu, B. Ku, L. Tie, H. Yao, W. Jiang, X. Ma, *et al.*, "Curcumin Reverses the Effects of Chronic Stress on Behavior, the HPA Axis, BDNF Expression and Phosphorylation of CREB," *Brain Research*, Vol. 1122, No. 1, 2006, pp. 56-64. doi:10.1016/j.brainres.2006.09.009

[44] A. Olariu, M. H. Tran, K. Yamada, M. Mizuno, V. Hefco and T. Nabeshima, "Memory Deficits and Increased Emotionality Induced by Beta-Amyloid (25-35) Are Correlated with the Reduced Acetylcholine Release and Altered Phorbol Dibutyrate Binding in the Hippocampus," *Journal of Neural Transmission*, Vol. 108, No. 8-9, 2001, pp. 1065-1079. doi:10.1007/s007020170025

[45] N. M. Conejo, M. Lopez, R. Cantora, H. Gonzalez-Pardo, L. Lopez, A. Begega, *et al.*, "Effects of Pavlovian Fear Conditioning on Septohippocampal Metabolism in Rats," *Neuroscience Letters*, Vol. 373, No. 2, 2005, pp. 94-98. doi:10.1016/j.neulet.2004.09.066

[46] M. Fujisaki, K. Hashimoto, M. Iyo and T. Chiba, "Role of the Amygdalo-Hippocampal Transition Area in the Fear Expression: Evaluation by Behavior and Immediate Early Gene Expression," *Neuroscience*, Vol. 124, No. 1, 2004, pp. 247-260. doi:10.1016/j.neuroscience.2003.11.022

[47] C.-H. Lin, S.-H. Yeh, C.-H. Lin, K.-T. Lu, T.-H. Leu, W.-C. Chang, *et al.*, "A role of PI-3 Kinase Signaling Pathway in Fear Conditioning and Synaptic Plasticity in the Amygdala," *Neuron*, Vol. 31, No. 5, 2001, pp. 841-851. doi:10.1016/S0896-6273(01)00433-0

[48] P. Barnes and M. Good, "Impaired Pavlovian Cued Fear Conditioning in Tg2576 Mice Expressing a Human Mutant Amyloid Precursor Protein Gene," *Behavioral Brain Research*, Vol. 157, No. 1, 2005, pp. 107-117. doi:10.1016/j.bbr.2004.06.014

