Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU28763

Influences of Paternal Fear Conditioning Experience in the F1-Offspring Hippocampus: Engram Cell and Odor-Specific Neuron

Xi Cheng

School of International Department, The Affiliated High School of SCNU, Guangzhou, China
chengx.avianna2024@gdhfi.com

Abstract. Previous studies have shown that fear learning experiences in the parental generation can influence the sensitivity of their offspring to specific odors through intergenerational epigenetic mechanisms. However, whether this intergenerational influence increases the sensitivity of neurons that receive specific odors, increases sensitivity to electric shock stimuli, or enhances the storage capacity of fear memories has not been thoroughly investigated. To explore this question, this study designed a three stage experiments. The study used ArcCreERT2 mice crossed with Rosa26-loxP-tdTomato mice to generate double-transgenic mice. Fluorescent protein labeling was used to label neuronal activity, and the activity of hippocampal neurons in F1 offspring mice was independently assessed during exposure to a single conditioned stimulus (acetophenone odor), an unconditioned stimulus (foot electric shock), and fear memory storage (engram cell). We expected that offspring mice whose fathers had undergone specific odor fear learning would exhibit significantly more activation of engram cells—neurons in the hippocampus that store odor fear learning—when exposed to specific odor fear learning, compared to other control groups. Additionally, at the behavioral level, fear responses would be more persistent and intense. Revealing the impact of parental fear experiences on different aspects of offspring fear learning not only detail the specific aspects where the intergenerational inheritance of odors affects, but also provides insights for clinical treatment of intergenerational trauma such as post-traumatic stress disorder in the future.

Keywords: Transgenerational inheritance, epigenetic mechanism, odor-specific fear conditioning, hippocampus, fluorescent protein labeling, engram cell

1. Introduction

The effects of transgenerational epigenetics on offspring have long been a central issue in neuroscience [1]. Transgenerational epigenetics refers to the phenomenon in which parental epigenetic modifications regulate gene expression patterns without altering the basic sequence and structure of DNA, and transmit the modified information to offspring and even multiple generations via gametes [2]. Recent studies have shown that parental experiences may influence offspring behavior and the nervous system through epigenetic mechanisms [3-5]. In Dias and Ressler's 2014

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.AU28763

paper, it was noted that when parental mice formed fear-learning memories in response to a specific odor, their offspring who had not been exposed to that odor also exhibited heightened sensitivity to it, accompanied by an increase in the number of glomeruli in the olfactory bulb [4]. This finding lays the foundation for the transgenerational epigenetic transmission of fear experiences and further expands the key research findings in this field. However, there are still some areas in this study that require further refinement, such as whether the offspring's responses to different stimulus conditions are influenced by parental epigenetic effects. To address these questions, in this paper, we used fluorescent staining to label neurons responding to different stimuli and observed the extent to which parental experiences influence the offspring. The main tests compared the offspring of father with acetophenone fear conditioning (F1-ace) with untrained mice (F1-home) and offspring trained with different odors called propanol (f1-prop) in terms of specific odor sensitivity, generalized shock sensitivity, and overall fear memory storage capacity to determine if there was a significant enhancement. We hypothesis that F1-ace mice will show significant enhancement in specific odor (acetophenone) sensitivity and overall fear memory storage capacity, but no increase in generalized electric shock sensitivity. These findings can deepen the understanding of the mechanisms of how parental experiences are encoded and inherited. Also, it helps to differentiate between specific and general forms of hereditary fear responses, which could have significant implications for the clinical treatment of intergenerational trauma [6,7].

2. Material

Mouse strain: Double transgenic mice were obtained by crossing ArcCreERT2 mice with Rosa26-loxP-tdTomato (Ai14) mice (Figure 1). All experiments were performed using littermate mice to ensure genetic consistency [8].

Odor: Both acetophenone and propanol were used at a 10% concentration diluted with propylene glycol [4].

Fluorescent Protein Labeling: Following fear conditioning, a 10 mg/mL solution of tamoxifen (TAM) is injected into the mouse's abdominal cavity, activating enhanced yellow fluorescent protein (EYEP) to label neurons active during encoding. Similarly, after fear learning, TAM injection activates the Arc gene in mice, labeling neurons activated during retrieval [9]. The advantage of red fluorescent proteins like tdTomato is that they are brighter and more photostable than ordinary fluorescent proteins [10], making them suitable for imaging deep tissues like the hippocampus, facilitating long-term tracking and quantitative analysis.

Grouping: In terms of grouping, we divided the double-transgenic mice into three groups with following division: the parental generation paired with the odor acetophenone and fear learning electric shock (F0-ace), the parental generation paired with the odor propanol and fear learning electric shock (F0-prop), and the home cage group that had not undergone fear training (F0-home). Each group consisted of 10 male mice without mating experience (Figure 1).

Breeding: Select male mice aged 10–16 weeks with no mating experience and female mice that have not undergone fear conditioning to collect sperm and eggs for in vitro fertilization (IVF) (Figure 1). The entire sperm and egg collection process is completed within 5 minutes to ensure cell viability. Place the in vitro fertilized embryos in an incubator at 37°C under a mixed gas environment (5% CO_2, 5% O_2, and 90% N_2) [11]. Offspring mice obtained through IVF, F1 mice, were separated from their parents after birth to exclude the influence of behavioral learning and social transmission.

DOI: 10.54254/2753-8818/2025.AU28763

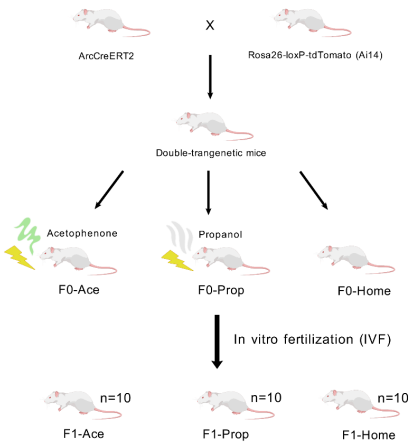

Figure 1. The process for F0 preparation and F1 grouping [12]

3. Methodology

3.1. Preparation

We divided the experiment into three parts. The premise of these three experiments was to first ensure that the parent mice formed odor-fear memories, and then measure three aspects in their offspring mice: Specific Odor sensitivity (CS), General Electric shock sensitivity (US), and overall Fear memory storage capacity. Each sub-stage corresponded to an independent experiment.

The parent mice in the experimental group and control group were subjected to fear learning. The parental mice in the experimental group were placed in a behavioral chamber equipped with a grid floor and an odor delivery system. Mice in the F0-ace group were exposed to 10% acetophenone for 10 seconds followed by a 25V foot electric shock; mice in the F0-prop group were exposed to 10% propanol for 10 seconds followed by a 25V foot electric shock. The odor fear conditioning for the experimental group was repeated five times, with each session spaced 120 seconds apart, over a total of three days learning process [4]. Finally, the formation of fear conditioning memory was assessed by measuring the increased fear potential startle (FPS) values of the experimental group's parental mice in response to a specific odor [13]. The control group (F0-home) mice did not undergo any fear learning.

3.2. Experiment design

3.2.1. Experiment 1: exploring the neuron increase for specific odor sensitivity in F1

Three offspring mice were selected from each of the F1-ace, F1-prop, and F1-home groups and exposed to an experimental chamber containing 10% acetophenone for 5 minutes. Thirty minutes later, 2mg of TAM at a concentration of 10 mg/ml was injected into the mice's abdominal cavities to label active neurons during odor exposure (Figure 2). Hippocampal slices were then observed using Fluoview confocal microscopy to examine fluorescent neurons, and the number of activated neurons in the experimental group was compared with that in the control group [9].

DOI: 10.54254/2753-8818/2025.AU28763

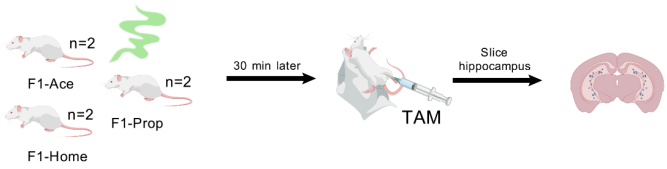

Figure 2. Experiment 1: odor sensitivity test on F1 [12]

3.2.2. Experiment 2: testing the generalization of electrical shock sensitivity in F1

Three mice were selected from each of the three groups of offspring (F1-ace, F1-prop, and F1-home) and placed in an experimental box with a grid floor. They were given an unconditioned stimulus of a 25V electrical shock to the foot, lasting 3 seconds, repeated three times. Thirty minutes later, TAM was injected into the mice's abdominal cavities to label active neurons during the shock. Hippocampal slices were prepared, and fluorescently labeled neurons were observed (Figure 3). The number of activated neurons was compared between the experimental and control groups [9].

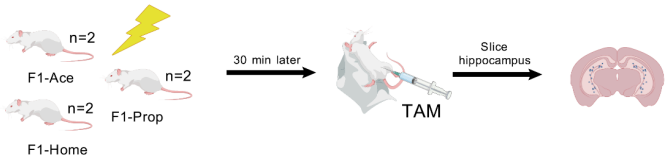

Figure 3. Experiment 2: electric shock test on F1 [12]

3.2.3. Experiment 3: comparing the engram cell quantity for examining overall fear memory storage capacity

Four offspring mice were selected from each of the F1-ace, F1-prop, and F1-home groups and placed in experimental boxes equipped with grid floors and odor transmission systems for odor fear conditioning. The offspring mice were exposed to 10% acetophenone for 10 seconds, followed by a 20V unconditioned stimulus (foot shock) lasting 2 seconds, repeated three times with 120-second intervals. Then, two mice from each group were selected, and 30 minutes later, TAM was injected into the mice. Hippocampal slices were prepared, and the number of labeled neurons during the encoding period was observed. The remaining two mice in each group were placed in the same experimental chamber on the fifth day after the learning phase ended. The mice were again exposed to 10% acetophenone, and their fear responses were observed. Freezing duration and intensity were recorded using a double-blind method. Thirty minutes later, TAM was injected into the mice's abdominal cavities, and the number of activated neurons during the retrieval period was counted. Finally, the fluorescent images of hippocampal neurons from both processes were overlaid (Figure 4). We propose that neurons activated in both processes are specific engram cells involved in the formation and storage of fear memory. The number of engram cells in different experimental groups was then compared and discussed [4].

DOI: 10.54254/2753-8818/2025.AU28763

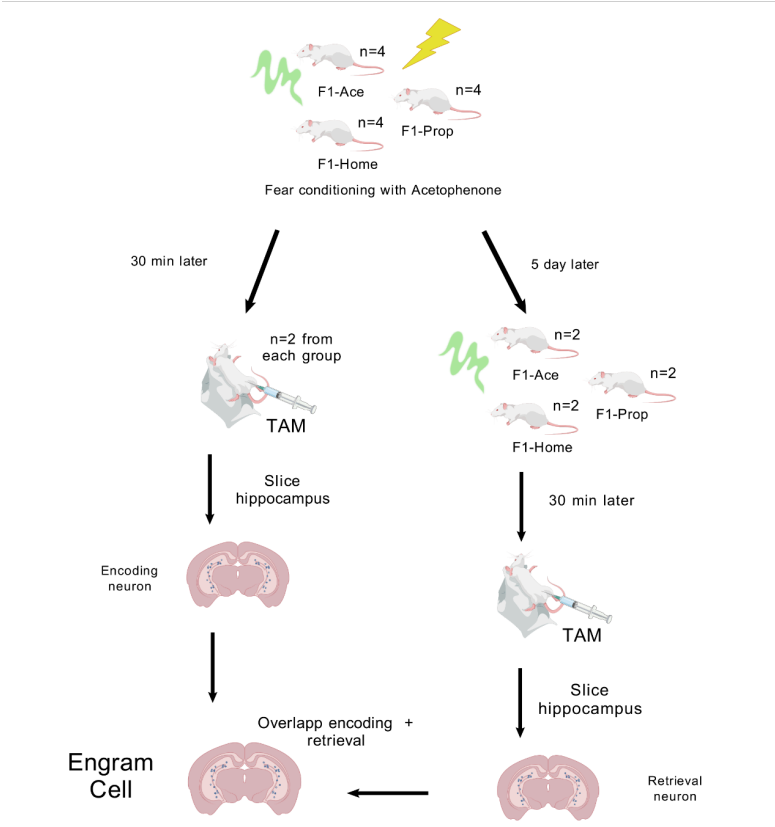

Figure 4. Experiment 3: comparing memory storage capacity: engram cell [12]

All experiments were conducted using a double-blind method and automated software to record data, thereby avoiding subjective factors that could cause bias in behavioral measurements [14].

4. Expected result

For Experiment 1, there are two possible outcomes. The first possible result is that the number of neurons activated by a specific odor in the F1-ace group is significantly higher than in the other groups (Figure 5). In the second possible result, there is little difference in the number of neurons activated by a single odor in the F1 mice (Figure 6).

DOI: 10.54254/2753-8818/2025.AU28763

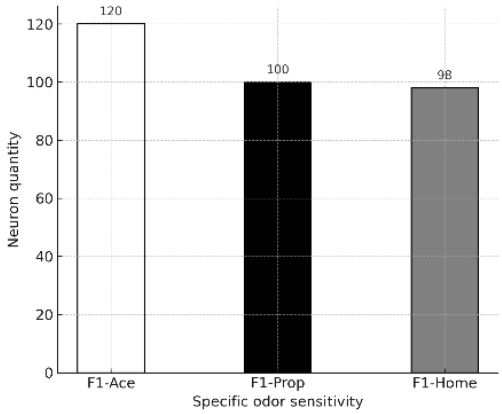

Figure 5. Experiment 1: F1-Ace with higher neural activation of acetophenone

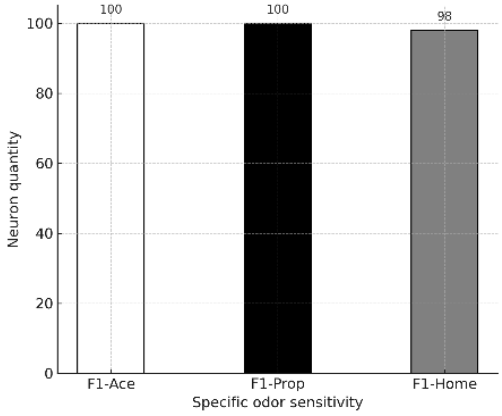

Figure 6. Experiment 1: F1 mice share same amount of neural activation of acetophenone

For Experiment 2, the most likely outcome is that in the foot electric shock (US) alone, F1 mice may show no significant increase in response and no increase in the number of neurons (Figure 7).

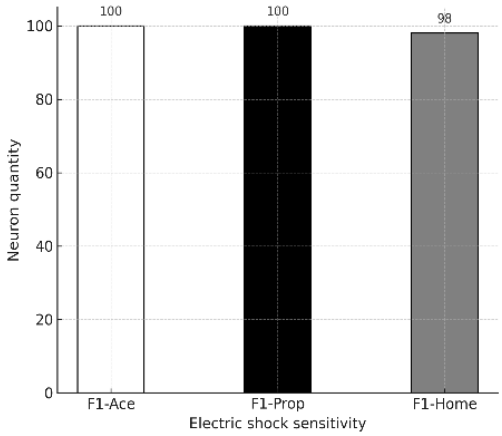

Figure 7. Experiment 2: neuron activated for electric shock in F1 mice

For Experiment 3, there are two possible outcomes for the hypothesis. The first possibility is that after odor fear conditioning, when F1-ace are re-exposed to a specific odor, the number of activated

DOI: 10.54254/2753-8818/2025.AU28763

engram cells is significantly higher than that of F1-prop and F1-home, and they exhibit a stronger fear response, such as longer freezing (Figure 8). The second possibility is that the number of activated engram cells is similar in all f1 mice, but f1-ace exhibit a stronger behavioral fear response (Figure 9).

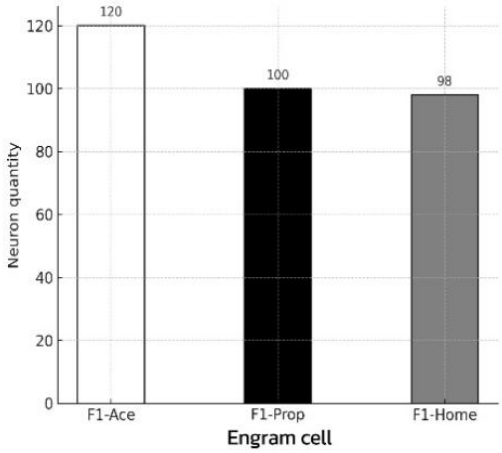

Figure 8. Experiment 3: engram cell higher than F1-prop and f1-home

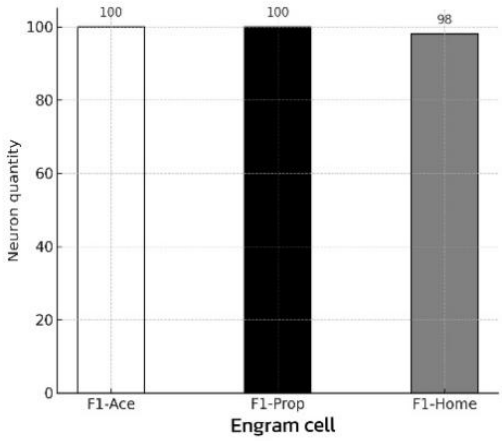

Figure 9. Experiment 3: No difference of engram cell quantity in F1

5. Discussion

In this paper, we designed three experiments to investigate whether paternal fear experience has an effect on memory encoding and retrieval in offspring. The main findings were that offspring with paternal odor-specific learning had a significant increase in engram cells in the hippocampus and increased sensitivity to specific odors. Paternal experience epigenetically influences neuronal activity, recruitment, and formation in offspring. These findings provide neural-level evidence for genetic influences and mechanisms of transgenerational memory.

5.1. Neuron for odor exposure greater in F1-Ace: higher quality of neuron signal transmission and activation of hippocampal neuron

For the first results of Experiment 1, the F1-ace activated more neuron in hippocampus than other control group. The primary reason is that F1-ace mice can transmit stronger neural signals to the

DOI: 10.54254/2753-8818/2025.AU28763

hippocampus. The mechanism may involve enhanced synaptic connections or increased density of neurons in F1-ace. For example, the number of glomerular neurons in the olfactory bulb is significantly higher in F1-ace compared to F1-prop and F1-home [4]. Therefore, when mice are exposed to acetophenone, more olfactory neurons are activated, resulting in stronger signal transmission to the hippocampus and activation of memory neurons. F1-ace exhibits stronger behavioral sensitivity to specific odors and greater neuronal activation. Another potential reason is a reduction in the excitability threshold of neurons. The parental fear experience of odors can be viewed as a form of stress or threaten. In a natural environment, offspring are highly likely to inherit this adaptive response to the environment to ensure survival [15]. Therefore, the parental fear experience downregulates the offspring's threshold for acetophenone through epigenetic mechanisms, inherently making the offspring more sensitive to such odors [4], meaning that even weak concentrations or brief exposures to odors can activate odor neurons in f1-ace mice.

5.2. Neuron for odor exposure maintain same level in F1: activation is contextual dependency

Regarding the second result, there isn’t any differences between groups in hippocampal neuron activation to acetophenone. This can be explained by the fact that neuronal activation is contextual dependency [16,17] and requires specific conditions to be induced, such as the presence of fear memory formation scenarios or other stimuli [18,19]. Odor alone cannot influence the number of activated neurons in the hippocampus.

5.3. Generalized electrical shock sensitivity unchanged in F1: contextual memory in hippocampus

In the Experiment 2, the F1 mice didn’t show any increase in sensitive to the electric shock. The likely reason is that the intergenerational genetic influence primarily targets an increase in aversion indices toward specific odors, rather than a general increase in sensitivity to aversive stimuli. The presence of a single unconditioned stimulus alone does not result in a bias in the offspring [17]. If the offspring mice also exhibit enhanced responses to single electric shocks, it is impossible to distinguish whether the enhanced responses following fear conditioning stem from the inheritance of memories associated with specific odors or from an exaggerated response to aversive stimuli. As a result, the intergenerational inheritance of effects on the offspring is highly specific to particular odors and does not reflect a general increase in sensitivity to aversive stimuli.

5.4. Engram cell increases in F1-Ace: higher neural input and recruitment

Experiment 3 serves as the central experiment of this protocol, and its underlying causes can be examined from multiple perspectives. For Experiment 3, the primary potential causes for the increase in engram cell in F1-ace can be attributed to two main factors.

Parental fear experiences may alter epigenetic mechanisms in offspring. This includes influencing neural development and neural circuits, neuronal excitability thresholds, and synaptic plasticity [5]. For example, F1-ace offspring exhibited higher sensitivity to acetophenone and physiologically more glomeruli [4]. More glomeruli may be able to output stronger neural signals and ultimately connect to the hippocampus, leading to the activation of more neurons in the hippocampus. From the perspective of changes in hippocampal neuronal activity, epigenetic mechanisms make the F1-ace offspring's hippocampus more sensitive to this specific factor. When receiving specific odor-related inputs, their neuronal assemblies are more easily activated and recruited, increasing the likelihood of

DOI: 10.54254/2753-8818/2025.AU28763

the F1-ace offspring physiologically forming and encoding this specific memory [20]. This physiological mechanism may result in a higher proportion or number of neurons being involved in memory formation during learning, even with the same training intensity as F1-home and F1-prop, leading to a higher total number of engram cell and other memory neuron compared to the control group, as well as better encoding and retrieval effects [4].

5.5. Same amount of engram cell in F1: insufficient strength of transgenerational inheritance and compensatory mechanism

F1 mice share the same amount of engram cell. This result can be explained by the two following reasons. There is insufficient strength of transgenerational experience. Although the parental generation underwent fear conditioning training, this experience did not have a direct and significant impact on the offspring's ability to encode specific odor fear memories at the hippocampal level [21]. For example, F1-ace mice exhibited only sensitivity to acetophenone without training, rather than fear responses such as freezing or startle [4]. Because the intensity of odor fear had significantly decreased after transgenerational inheritance, it was insufficient to activate more hippocampal neurons in the offspring following the same fear conditioning.

If the number of neurons is similar, but F1-ace mice exhibit stronger fear behavior, such as longer freezing, this may suggest the presence of other compensatory mechanisms. Although specific memories may be encoded by only a small subset of activated cells, differences in the strength of their connections, firing patterns, or integration with other brain regions may lead to distinct memory expressions. the number of neurons encoding specific memories in the hippocampus may be the same, but the neurons in F1-ace may have better signal transmission, leading to stronger memory expression [22]. Thus, although there is no difference in quantity, there is an improvement in the quality of signal transmission. Additionally, the brain regions active during the formation of fear learning memories are not limited to the hippocampus but also include the medial prefrontal cortex (mPFC) and the basolateral complex of the amygdala (BLA) [23]. The BLA, as the central hub for fear information processing, regulates the activity of the mPFC and other neural circuits [24]. Enhanced projections from other fear learning brain regions to their own internal areas and to the hippocampus also influence the formation of final memories. For example, the medial prefrontal cortex, as an inhibitory region for memory, exhibits reduced connectivity for fear memories in certain subregions, leading to delayed memory extinction and stronger fear responses in mice [25,26]. Therefore, the activation levels of these regions are highly correlated with the overall recall performance in later stages [27]. Parental experiences are likely to have influenced their structural connectivity. Additionally, if multiple brain regions jointly store fear learning memories, the fear conditioning experiences of F1 mice may be distributed across other brain regions, resulting in less noticeable changes in the hippocampus.

In summary, if the fear response of F1-ace is more pronounced but there is no difference in the neural quantity, it may be because its paternal memory lacked sufficient experience and strength across generations, resulting in changes in the regulatory circuits of other brain regions, or because the memory neurons formed during the offspring mouse's fear conditioning memory process were dispersed to other brain regions.

6. Limitation

Measurement for single Brain region: The brain regions observed in the experiment are limited. The neural encoding of fear memories is a complex process that is not carried out independently by a

DOI: 10.54254/2753-8818/2025.AU28763

single brain region. Not only does the hippocampus play a role in contextual memory, but the prefrontal cortex and amygdala also participate in the encoding and retrieval of fear learning memories [25,27]. Therefore, focusing solely on the hippocampus may not fully reflect the neural changes associated with fear memory [28].

Tamoxifen setting: The timing, concentration, and dose of tamoxifen injection can be further optimized. From the perspective of injection timing, neuronal expression is a dynamic process [29], and different injection timings can influence the final data presented [30]. On the other hand, regarding injection dose and concentration, TAM, as a selective estrogen receptor modulator, has not been confirmed to have no effect on mice's physiology, such as hormones level [31]. The dosage of TAM also varies depending on the animal's age and other factors, with some transgenic mice requiring higher TAM dosages and interval l [30]. Therefore, knowledge regarding the most effective injection dosage and timing remains insufficient.

Sex difference: The lack of consideration for the impact of gender differences, including both parental and offspring generations. Individuals of different genders inherently exhibit differences in developmental timing and outcomes [32]. Additionally, the intergenerational genetic pathways and mechanisms of parental and maternal lineages differ, although both influence the epigenetic expression of offspring, the extent and nature of these influences vary [5,33]. Similarly, the gender of offspring also influences the extent to which they are affected [34].

7. Conclusion

This paper primarily addresses the question of whether parental fear experiences can influence the encoding and retrieval of fear memories in offspring through transgenerational epigenetic mechanisms. The main finding is that offspring of parents with prior fear conditioning experience exhibit a significant increase in the number of engram cells associated with specific odors, along with enhanced responsiveness to those odors. When offspring mice are exposed alone to foot electric shock (US), the activation level of hippocampal neurons does not increase. These three findings indicate that the intergenerational inheritance effect is not an increase in general sensitivity to aversive or unconditioned stimuli, but rather an overall enhancement of memory for specific contextual stimuli and conditions.

References

[1] Fitz-James, M. H., & Cavalli, G. (2022). Molecular mechanisms of transgenerational epigenetic inheritance. Nature Reviews. Genetics, 23(6), 325–341. https: //doi.org/10.1038/s41576-021-00438-5

[2] Li, Y. (2021). Modern epigenetics methods in biological research. Methods (San Diego, Calif.), 187, 104–113. https: //doi.org/10.1016/j.ymeth.2020.06.022

[3] Cai, H., Chen, M., Gao, Y., Ruan, J., He, C., & Zuo, Z. (2023). Transgenerational Effects and Mechanisms of Tributyltin Exposure on Neurodevelopment in the Male Offspring of Rats. Environmental Science & Technology, 57(28), 10201–10210. https: //doi.org/10.1021/acs.est.3c01546

[4] Dias, B. G., & Ressler, K. J. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. Nature Neuroscience, 17(1), 89–96. https: //doi.org/10.1038/nn.3594

[5] Yehuda, R., & Lehrner, A. (2018). Intergenerational transmission of trauma effects: Putative role of epigenetic mechanisms. World Psychiatry, 17(3), 243–257. https: //doi.org/10.1002/wps.20568

[6] Conching, A. K. S., & Thayer, Z. (2019). Biological pathways for historical trauma to affect health: A conceptual model focusing on epigenetic modifications. Social Science & Medicine, 230, 74–82. https: //doi.org/10.1016/j.socscimed.2019.04.001

[7] Kwapis, J. L., & Wood, M. A. (2014). Epigenetic mechanisms in fear conditioning: Implications for treating post-traumatic stress disorder. Trends in Neurosciences, 37(12), 706–720. https: //doi.org/10.1016/j.tins.2014.08.005

DOI: 10.54254/2753-8818/2025.AU28763

[8] Xu, C., Li, S., Cai, Y., Lu, J., Teng, Y., Yang, X., & Wang, J. (2024). Generation of Slco1a4-CreERT2-tdTomato Knock-in Mice for Specific Cerebrovascular Endothelial Cell Targeting. International Journal of Molecular Sciences, 25(9), 4666. https: //doi.org/10.3390/ijms25094666
[9] Denny, C. A., Kheirbek, M. A., Alba, E. L., Tanaka, K. F., Brachman, R. A., Laughman, K. B., Tomm, N. K., Turi, G. F., Losonczy, A., & Hen, R. (2014). Hippocampal Memory Traces Are Differentially Modulated by Experience, Time, and Adult Neurogenesis. Neuron, 83(1), 189–201. https: //doi.org/10.1016/j.neuron.2014.05.018
[10] Shaner, N. C., Campbell, R. E., Steinbach, P. A., Giepmans, B. N. G., Palmer, A. E., & Tsien, R. Y. (2004). Improved monomeric red, orange and yellow fluorescent proteins derived from Discosoma sp. Red fluorescent protein. Nature Biotechnology, 22(12), 1567–1572. https: //doi.org/10.1038/nbt1037
[11] Taft, R. (2017). In Vitro Fertilization in Mice. Cold Spring Harbor Protocols, 2017(11), pdb.prot094508. https: //doi.org/10.1101/pdb.prot094508
[12] JJiang, S, Li, H, Zhang, L, Mu, W, Zhang, Y, Chen, T, Wu, J, Tang, H, Zheng, S, Liu, Y, Wu, Y, Luo, X, Xie, Y, & Ren, J. (2025). Generic Diagramming Platform (GDP): A comprehensive database of high-quality biomedical graphics. Nucleic acids research, 53(D1), D1670–D1676. https: //doi.org/10.1093/nar/gkae973
[13] Risbrough, V. B., & Geyer, M. A. (2005). Anxiogenic treatments do not increase fear-potentiated startle in mice. Biological Psychiatry, 57(1), 33–43. https: //doi.org/10.1016/j.biopsych.2004.10.006
[14] Aoued, H. S., Sannigrahi, S., Doshi, N., Morrison, F. G., Linsenbaum, H., Hunter, S. C., Walum, H., Baman, J., Yao, B., Jin, P., Ressler, K. J., & Dias, B. G. (2019). Reversing Behavioral, Neuroanatomical, and Germline Influences of Intergenerational Stress. Biological Psychiatry, 85(3), 248–256. https: //doi.org/10.1016/j.biopsych.2018.07.028
[15] Silberman, D. M., Acosta, G. B., & Zorrilla Zubilete, M. A. (2016). Long-term effects of early life stress exposure: Role of epigenetic mechanisms. Pharmacological Research, 109, 64–73. https: //doi.org/10.1016/j.phrs.2015.12.033
[16] Lisman, J., Buzsáki, G., Eichenbaum, H., Nadel, L., Ranganath, C., & Redish, A. D. (2017). Viewpoints: How the hippocampus contributes to memory, navigation and cognition. Nature Neuroscience, 20(11), 1434–1447. https: //doi.org/10.1038/nn.4661
[17] Williams, Z. M. (2016). Transgenerational influence of sensorimotor training on offspring behavior and its neural basis in Drosophila. Neurobiology of Learning and Memory, 131, 166–175. https: //doi.org/10.1016/j.nlm.2016.03.023
[18] Chaaya, N., Battle, A. R., & Johnson, L. R. (2018). An update on contextual fear memory mechanisms: Transition between Amygdala and Hippocampus. Neuroscience and Biobehavioral Reviews, 92, 43–54. https: //doi.org/10.1016/j.neubiorev.2018.05.013
[19] Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: Implications for fear conditioning, extinction and psychopathology. Nature Reviews Neuroscience, 14(6), 417–428. https: //doi.org/10.1038/nrn3492
[20] Gapp, K., Jawaid, A., Sarkies, P., Bohacek, J., Pelczar, P., Prados, J., Farinelli, L., Miska, E., & Mansuy, I. M. (2014). Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nature Neuroscience, 17(5), 667–669. https: //doi.org/10.1038/nn.3695
[21] Dietz, D. M., LaPlant, Q., Watts, E. L., Hodes, G. E., Russo, S. J., Feng, J., Oosting, R. S., Vialou, V., & Nestler, E. J. (2011). Paternal Transmission of Stress-Induced Pathologies. Biological Psychiatry, 70(5), 408–414. https: //doi.org/10.1016/j.biopsych.2011.05.005
[22] Rao-Ruiz, P., Visser, E., Mitrić, M., Smit, A. B., & van den Oever, M. C. (2021). A Synaptic Framework for the Persistence of Memory Engrams. Frontiers in Synaptic Neuroscience, 13. https: //doi.org/10.3389/fnsyn.2021.661476
[23] Zelikowsky, M., Hersman, S., Chawla, M. K., Barnes, C. A., & Fanselow, M. S. (2014). Neuronal Ensembles in Amygdala, Hippocampus, and Prefrontal Cortex Track Differential Components of Contextual Fear. Journal of Neuroscience, 34(25), 8462–8466. https: //doi.org/10.1523/JNEUROSCI.3624-13.2014
[24] Garcia, R., Vouimba, R. M., Baudry, M., & Thompson, R. F. (1999). The amygdala modulates prefrontal cortex activity relative to conditioned fear. Nature, 402(6759), 294–296. https: //doi.org/10.1038/46286
[25] Giustino, T. F., & Maren, S. (2015). The Role of the Medial Prefrontal Cortex in the Conditioning and Extinction of Fear. Frontiers in Behavioral Neuroscience, 9, 298. https: //doi.org/10.3389/fnbeh.2015.00298
[26] Marek, R., Xu, L., Sullivan, R. K. P., & Sah, P. (2018). Excitatory connections between the prelimbic and infralimbic medial prefrontal cortex show a role for the prelimbic cortex in fear extinction. Nature Neuroscience, 21(5), 654–658. https: //doi.org/10.1038/s41593-018-0137-x
[27] McGaugh, J. L. (2004). THE AMYGDALA MODULATES THE CONSOLIDATION OF MEMORIES OF EMOTIONALLY AROUSING EXPERIENCES. Annual Review of Neuroscience, 27(Volume 27, 2004), 1–28. https: //doi.org/10.1146/annurev.neuro.27.070203.144157

DOI: 10.54254/2753-8818/2025.AU28763

[28] Arias, N., Méndez, M., & Arias, J. L. (2015). The importance of the context in the hippocampus and brain related areas throughout the performance of a fear conditioning task. Hippocampus, 25(11), 1242–1249. https: //doi.org/10.1002/hipo.22430
[29] Hogg, P. W., Coleman, P., Dellazizzo Toth, T., & Haas, K. (2022). Quantifying neuronal structural changes over time using dynamic morphometrics. Trends in Neurosciences, 45(2), 106–119. https: //doi.org/10.1016/j.tins.2021.10.011
[30] Donocoff, R. S., Teteloshvili, N., Chung, H., Shoulson, R., & Creusot, R. J. (2020). Optimization of tamoxifen-induced Cre activity and its effect on immune cell populations. Scientific Reports, 10(1), 15244. https: //doi.org/10.1038/s41598-020-72179-0
[31] Zhong, Z. A., Sun, W., Chen, H., Zhang, H., Lay, Y. E., Lane, N. E., & Yao, W. (2015). Optimizing tamoxifen-inducible Cre/loxp system to reduce tamoxifen effect on bone turnover in long bones of young mice. Bone, 81, 614–619. https: //doi.org/10.1016/j.bone.2015.07.034
[32] Aiken, C. E., & Ozanne, S. E. (2013). Sex differences in developmental programming models. https: //doi.org/10.1530/REP-11-0489
[33] Sandovici, I., Fernandez-Twinn, D. S., Hufnagel, A., Constância, M., & Ozanne, S. E. (2022). Sex differences in the intergenerational inheritance of metabolic traits. Nature Metabolism, 4(5), 507–523. https: //doi.org/10.1038/s42255-022-00570-4
[34] Dunn, G. A., Morgan, C. P., & Bale, T. L. (2011). Sex-specificity in transgenerational epigenetic programming. Hormones and Behavior, 59(3), 290–295. https: //doi.org/10.1016/j.yhbeh.2010.05.004