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Pentylenetetrazole-induced seizures cause impairment of memory acquisition and consolidation in zebrafish (*Danio rerio*)

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ABSTRACT

Epilepsy is characterized by the occurrence of seizures, and the high prevalence of epilepsy-associated comorbidities affects the quality of patients' life. We investigated the effects of pentylenetetrazole (PTZ) exposure in zebrafish cognitive performance on inhibitory avoidance test. The animals were exposed to 7.5 mM PTZ for 10 min, in the acquisition (before training) and in the consolidation memory phases (after training). In the acquisition phase, the animals were submitted to PTZ-induced seizures and trained in periods of 1, 24, or 48 h after exposure, and 24 h after training were tested. In the consolidation phase, animals were trained and exposed to PTZ 10 min after training and were tested 24 h later. Control groups in periods of 1, 24, or 48 h before or 10 min after training showed a significantly increased latency to enter the dark compartment. The latencies between training and test sessions did not differ in PTZ groups of animals exposed and trained 1 and 24 h or exposed to PTZ 10 min after training. At 48 h, animals exposed to PTZ showed an increased latency to enter the dark compartment. Animals exposed to PTZ and trained 1 h later increased the traveled distance, when compared to the control group. Traveled distance did not differ in animals that were exposed to PTZ and trained 24 and 48 h, or 10 min after training. Our findings indicate that PTZ causes a cognitive deficit in the pre-and post-training phase, allowing us to explore the influence of seizures at different memory phases.

1. Introduction

Epilepsy is a chronic disease that affects around 70 million people worldwide [1,2]. This neurological condition is characterized by a predisposition to generate recurrent and spontaneous seizures caused by abnormal and excessive neuronal activity [1]. In addition to seizures, a high prevalence of epilepsy-associated comorbidities is noticed, leading to poor quality of life for patients [3].

Psychiatric and neurological comorbidities are common in 30–50 % of patients with epilepsy [4]. Memory problems are frequently reported, especially in temporal lobe epilepsy, where brain structures associated with memory processes are directly involved in seizures [5]. The persistence of cognitive deficits changes according to the type and severity of the seizures, which may persist for minutes to days [6].

Individuals with epilepsy may suffer from episodic amnesia, long-term forgetfulness where new-acquired memories fade over days to weeks, and remote memory impairment where remote facts about their life are forgotten [6–8]. Mechanisms underlying epilepsy-related cognitive dysfunction remain unclear, especially neurobehavioral responses observed in the post-ictal period.

The GABAergic system plays an important role in cognitive processes, such as memory acquisition and consolidation. Acquisition refers to the processes that mediate the initial learning of the association between a stimulus and a given situation (short-term memory formation). In contrast, consolidation refers to the time-dependent, stabilization of process that transforms short-term memories into permanent or persistent long-term memories [9,10]. Studies have shown changes in the memory process through the modulation of the GABAergic system by its agonists and antagonists [11–14].

Zebrafish is a suitable model organism for investigating the mechanisms behind epilepsy and the biological effects of brain function modulation [15–17]. In zebrafish larvae and adults, the Pentylenetetrazole (PTZ)-induced seizure model is characterized by progressive behavioral changes that occur in a few minutes and they are very similar to seizure patterns seen in rodents [18,19]. Neuroanatomic analyzes and electrophysiological responses show that the telencephalon of teleost

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fishes contain a similar function structure to the mammalian hippocampus, which may be associated with memory and learning conditions [20].

Therefore, considering: (i) epilepsy related-comorbidities are poorly explored in zebrafish, (ii) the relevance of investigating memory processes behind seizures, and (iii) a better understanding of epilepsy-related neurobehavioral phenotypes of zebrafish, this study aimed to evaluate the adult zebrafish cognitive performance on inhibitory avoidance task after seizures induced by PTZ.

2. Materials and methods

2.1. Animals

A total of 381 adult zebrafish (*Danio rerio*) of the wild-type AB strain (5–7 months old, ~ 50:50 male:female ratio) were used in the experiments. Animals were obtained from our breeding colony and kept in automated recirculating systems (Zebtec, Tecniplast, Italy) with reverse-osmosis-filtered water and conditions recommended for the species [21]. Temperature (28 °C ± 2 °C), pH (7.0–7.5), conductivity (300–700 μS), ammonia (<0.02 mg/L), hardness (80–300 mg/L), nitrite (<1 mg/L), nitrate (<50 mg/L), and chloride (0 mg/L) were monitored. Fish were maintained under 14 h light:10 h dark photoperiod cycle and fed with commercial flakes (TetraMin Tropical Flake Fish®) three times a day [22]. All protocols were approved by the Institutional Animal Care Committee from Pontifícia Universidade Católica do Rio Grande do Sul (CEUA- PUCRS, protocol number 9427). This study was registered in the Sistema Nacional de Gestão do Patrimônio Genético e Conhecimento Tradicional Associado-SISGEN (Protocol No. A3B073D).

2.2. Experimental design

This study investigated the effects of PTZ-induced seizures on zebrafish cognitive performance (Fig. 1). To verify the influence of seizures on the memory formation process, the animals were exposed to the seizure agent in the acquisition phase (before training) and in the memory consolidation phase (after training). In the memory acquisition phase, the animals were submitted to PTZ-induced seizures and then trained in periods of 1, 24, or 48 h after exposure, and 24 h after training were tested. They were submitted to the locomotor test 10 min before training. In the consolidation phase, the animals were trained in the inhibitory avoidance apparatus and then exposed to PTZ 10 min after training and were submitted to the test session 24 h after the training session, and they had locomotor activity evaluated next to the test session.

The experiments were performed between 9 a.m. and 11 a.m., and 24 h before the beginning of the experiment, the animals were separated in 2 L aquarium (8 fish per tank). No experimental procedure was carried out in the space intended for the maintenance of fish to avoid any type of behavioral stress. The animals were fed twice a day at 12 p.m. and 5 p.m. Animals were not fed before the experiment.

2.3. PTZ-induced seizures

In zebrafish, seizures induced by PTZ are characterized by progressive behavioral changes, which can be identified in three stages: (i) increased swimming activity (stage I); (ii) rapid and circle swimming (stage II); and (iii) loss of posture and immobility for 1–3 s (stage III).

The animals were individually exposed to 500 ml of 7.5 mM PTZ solution in a glass tank (15x 15 x6; L x H x W) for 10 min. Zebrafish had the behavior recorded on video, and the latency to the first episode of seizure activity in each stage was identified according described in the literature [15,18].

2.4. Behavioral analysis

2.4.1. Inhibitory avoidance

Memory was assessed through the inhibitory avoidance test as described in the literature [23]. The test apparatus consists of an aquarium (7 cm high x 9 cm wide x 18 cm long) with a mobile guillotine-type partition 9 × 7 cm), which divides the aquarium into two areas of the same size, one dark (8 lux) and the other light (130 lux). The dark and light compartments are covered by opaque plastic self-adhesive films in black and white colors, respectively, covering external walls, bottom, and corresponding sides of the movable partition. The aquarium water level was 3 cm high and the partition was raised 2 cm above the bottom of the aquarium to allow the animals to move freely from one compartment to the other of the apparatus. In the dark area, two electrodes were placed, which when activated produced an electric shock of 3 ± 0.2 V. The animals were trained and tested individually in the inhibitory avoidance apparatus.

During the training session, the fish were placed in the clear area of the aquarium with the partition closed and, after 1 min of acclimatization, the partition was raised, allowing the animals to transition to the dark side through the opening. After the animal crosses to the dark side, the partition was closed and the animal received a pulsed electric shock administered for 5 s. The animals were then removed and placed in their respective aquariums. After 24 h, the test session occurred, where the fish were submitted to the same protocol; however, they did not receive the shock. In this way, the animals had their cognitive performance evaluated through the latency to enter the dark area and this parameter is used as an index of memory retention.

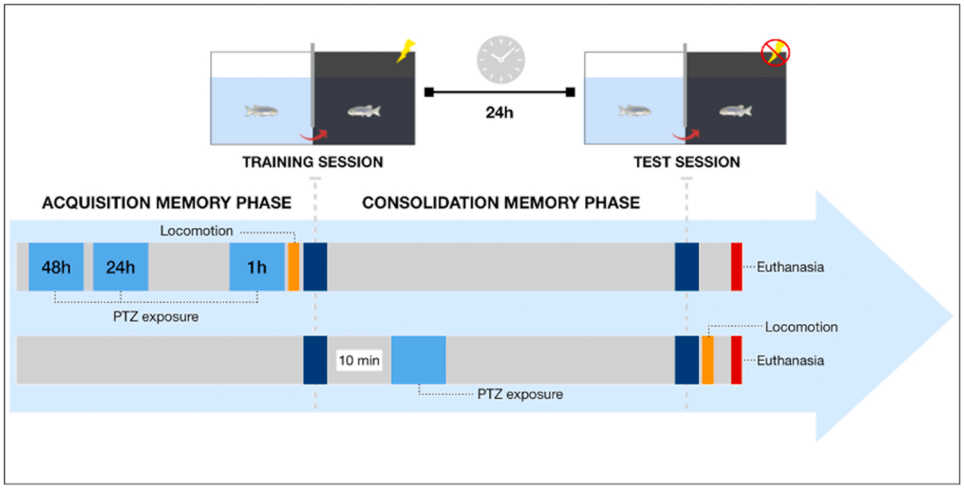

Fig. 1. : Schematic representation of the experimental procedures. In the acquisition memory phase, animals were submitted to PTZ-induced seizures and trained 1, 24, or 48 h after exposure, and 24 h after training fish were tested. They were submitted to the locomotor test 10 min before training session. In the consolidation phase, the animals were trained and then exposed to PTZ 10 min after training and were submitted to the test session 24 h after the training session. They had locomotor activity evaluated after to the test session.

2.4.2. Locomotor activity

Adult locomotor activity was performed as described in the literature [24,25]. Fish were placed individually in a glass tank (30 cm long x 15 cm high x 10 cm wide) filled with 2 L of non-chlorinated water and recorded on video for 7 min, being the first minute to habituate the fish. The videos were analyzed using EthoVision XT® tracking software (version 11.5, Noldus, Wageningen, Netherlands) at a rate of 30 positions per second. The distance travelled (m) parameter was chosen to verify possible locomotor alterations.

2.5. Statistical analysis

Behavioral data are expressed as mean ± standard error of the mean (SEM). For all comparisons, a significance level of $p < 0.05$ was considered. The distribution of the data was evaluated for normality by the Shapiro-Wilk test. Parametric data from the locomotor test were evaluated by Student's t-test. Nonparametric data of latencies to enter the dark area in training and test sessions were analyzed by Mann-Whitney U test. GraphPad Prism 8 (La Jolla, CA, USA) software was used for statistical analysis.

3. Results

3.1. Behavioral seizure parameters

To investigate seizure development, Fig. 2 shows the latency to the first behavioral manifestation of each seizure stage (I, II, III) in periods of 1 (Fig. 2A), 24 (Fig. 2B), or 48 (Fig. 2C) hours before the training session or 10 min after the training session (Fig. 2D). All animals showed progressive behavioral alterations and reached all seizures stages. We compared the latency to reach stage III for all treatments and no significant differences in the latency to reach stage III for all conditions tested were observed (data not shown).

3.2. Effects of PTZ-induced seizures on inhibitory avoidance

Fig. 3 shows the effects of animals submitted to PTZ-induced seizures and then trained 1 (Fig. 3A), 24 (Fig. 3B), or 48 (Fig. 3C) hours after exposure, or exposure to PTZ 10 min after the training session (Fig. 3D). Mann-Whitney U test revealed that control groups in periods of 1, 24 or 48 h before training session, or 10 min after training session showed a significant increase in the latency to enter the dark compartment in test session ($p = 0.0393$; $p = 0.0069$; $p < 0.0001$; $p = 0.0034$, respectively). Conversely, the latencies to enter in the dark compartment between training and test sessions did not differ in animals that were submitted to PTZ-induced seizures and then trained 1 and 24 h or exposed to PTZ 10 min after the training session ($p = 0.1205$; $p = 0.4142$; $p = 0,1383$, respectively). At 48 h, animals exposed to PTZ showed an increased latency to enter in the dark compartment in the test session ($p = 0.0364$).

3.3. Effects of PTZ-induced seizures on locomotor activity

Fig. 4 shows the influence of each treatment on traveled distance by animals. The Student's t-test revealed that animals submitted to PTZ-induced seizures and then trained 1 h after exposure increased the traveled distance when compared to the control group (Fig. 4A, $p = 0.0046$). Conversely, traveled distance did not differ in animals that were submitted to PTZ-induced seizures and then trained 24 and 48 h, and exposed to PTZ 10 min after the training session (Fig. 4B, $p = 0.5755$; Fig. 4C, $p = 0.4909$; Fig. 4D, $p = 0.4701$).

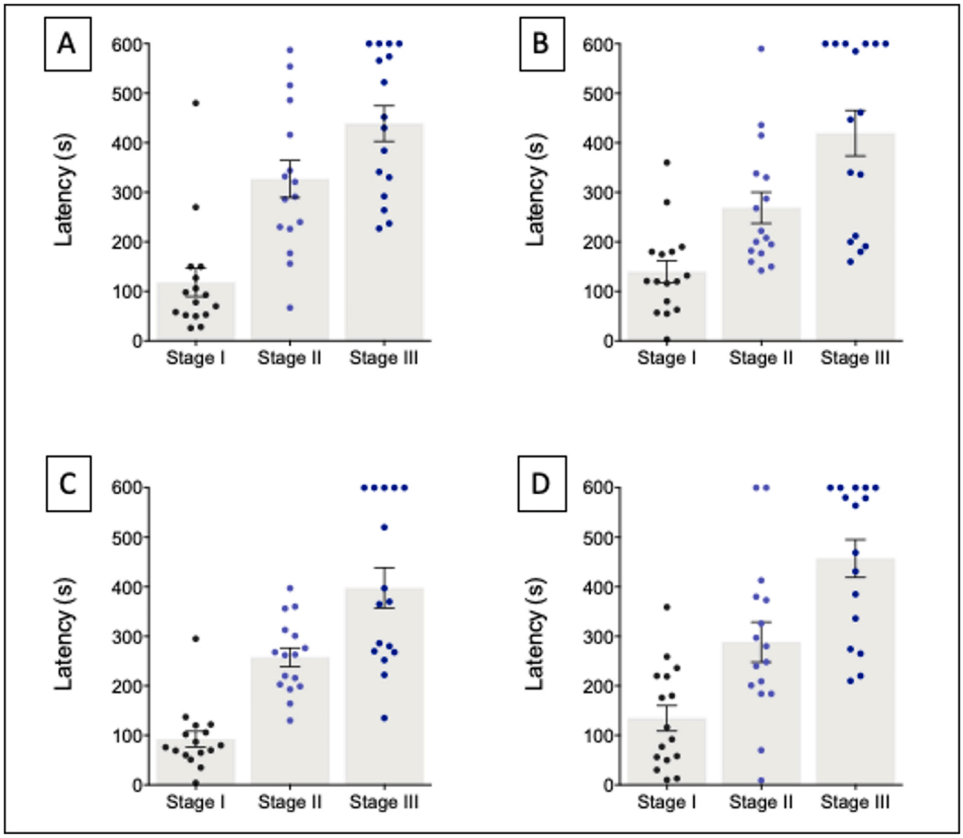

Fig. 2. : Latency to first manifestation of each stage of PTZ-induced seizures at different periods. Exposure to 7.5 mM PTZ (A) 1 h before training session, (B) 24 h before training session, (C) 48 h before training session and (D) exposure to 7.5 mM PTZ after training session. All animals reached the stages I, II, and III (n = 16 per group).

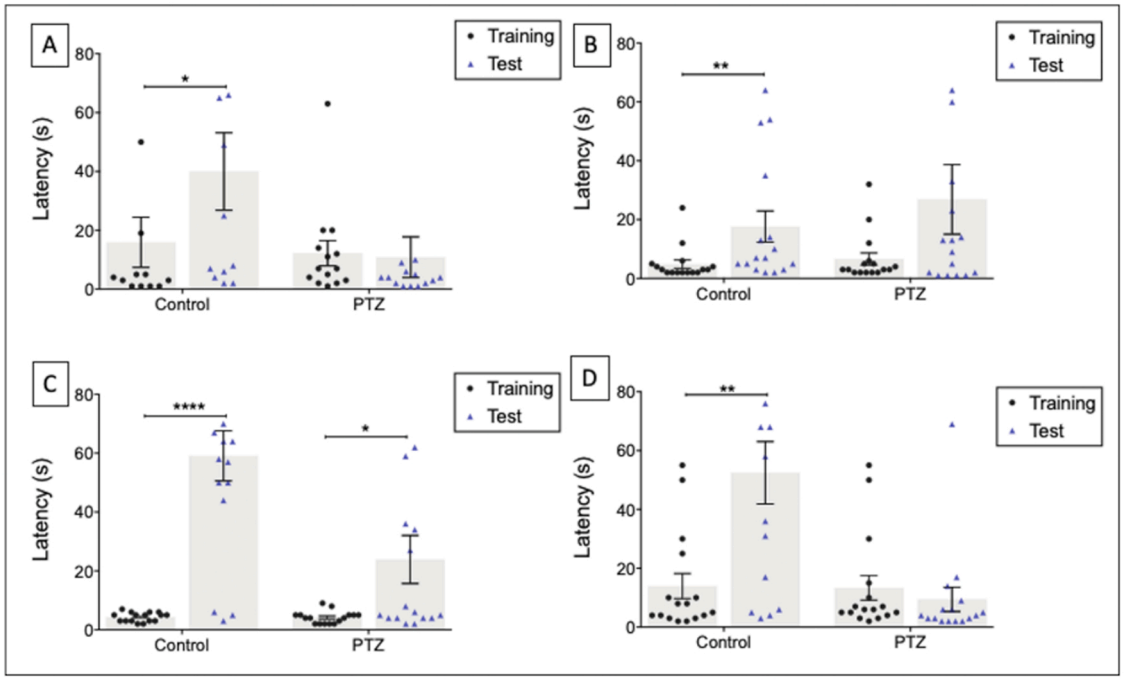

Fig. 3. : Latency to enter in the dark area during the training and test session on inhibitory avoidance test (A) 1 h, (B) 24 h, and (C) 48 h before training session, and (D) after training session. * $p < 0.05$, ** $p < 0.01$, ****$p < 0.0001$ indicate differences between training and test session of each group compared by the Mann-Whitney test. All data were expressed as mean ± S.E.M (n = 10–16 per group).

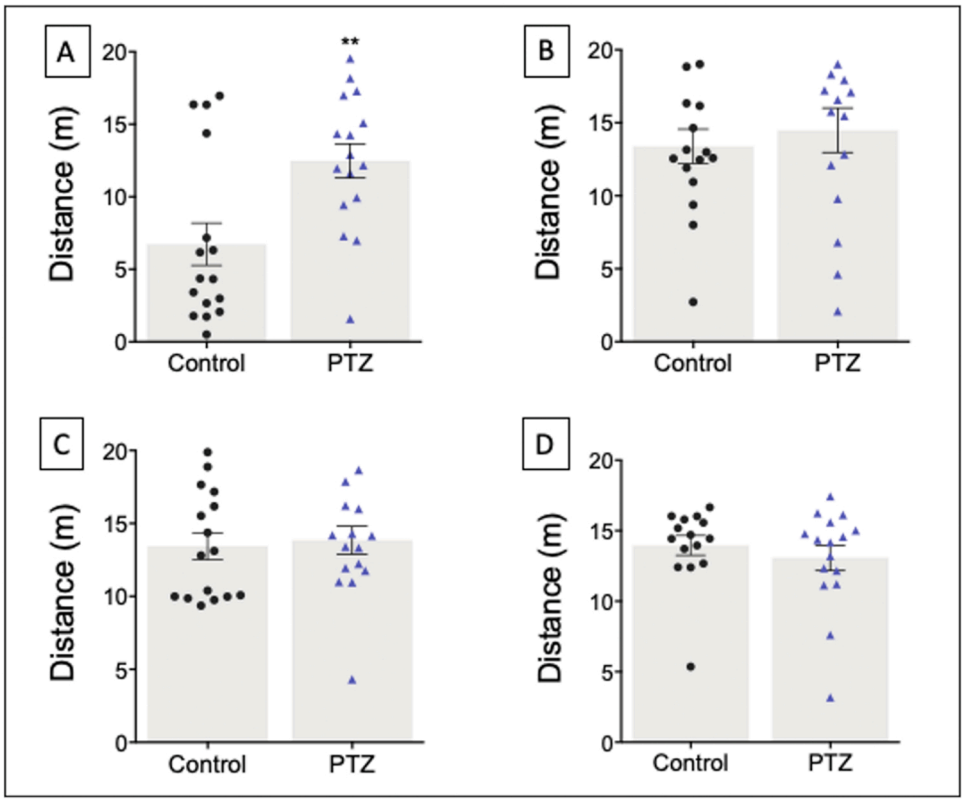

Fig. 4. : Effects of seizures induced by 7.5 mM PTZ on zebrafish distance traveled (A) 1 h, (B) 24 h and (C) 48 h before training session, and (D) after training session. ** $p < 0.01$ indicates differences between control and PTZ groups. Data were analyzed by the Student's t-test. All data were expressed as mean ± S.E.M (n = 16 per group).

4. Discussion

Here we evaluated the cognitive deficit induced by the convulsant PTZ to reproduce cognitive dysfunctions as epilepsy-related comorbidities, as well as verify the influence of seizures at different periods during the inhibitory avoidance test. Fish were exposed to PTZ (7.5 mM for 10 min) in the acquisition memory phase, at 1 h, 24 h, 48 h before the training session, and 10 min after the training session in the consolidation memory phase.

Problems in the process of short-and long-term memory formation are commonly associated with epilepsy [7]. Difficulties to process, storing, and retrieving information may be related to the extent and location of possible brain-impaired structures, as well as the frequency and severity of seizures [6]. In animal models, seizure induction has already been shown to cause cognitive impairment [13,26,27], but the effects of seizures on the memory formation process remain poorly understood.

In the memory acquisition phase, our results showed that PTZ seizures induced 1 h before the training session were able to impair the animals' cognitive performance in the test session, i.e., the animals did not show memory retention.

However, at the locomotor behavior task, the PTZ caused an increase in the distance traveled parameter. Changes in the swimming pattern of animals may cause an equivocated behavioral response during the inhibitory avoidance test. Therefore, the exposure to PTZ 1 h before the training session does not generate a robust response because of the altered zebrafish locomotor behavior. On the other hand, the PTZ exposure 24 h before the training session impaired the cognitive performance of the animals without altering the locomotor activity, reinforcing the deleterious effects of PTZ on learning. Animals exposed to PTZ 48 h before the training session did not show cognitive deficit or locomotor alteration. Our results demonstrated a PTZ time-dependent effect on zebrafish behavior and cognition at the acquisition memory phase.

In the memory consolidation phase, we observed that PTZ impaired the cognitive performance of zebrafish since the exposure to PTZ occurred 10 min after the training session. Changes in the distance traveled parameter were not observed. Importantly, the locomotor behavior was not altered 24 h after the exposure period, thus this response is not associated with locomotor changes but with a learning response. Similar findings were reported earlier and memory consolidation impaired by PTZ exposure immediately after the training session was observed in adult zebrafish at the inhibitory avoidance test [28]. PTZ also induced memory deficits when zebrafish were tested in a T-maze apparatus. Moreover, the PTZ-treated group showed lower levels of GABA and higher levels of glutamate when compared to the control group [26,29].

A study demonstrated that rats submitted to a single injection of a convulsive dose of PTZ before training impaired the acquisition of spatial memory in the Morris water maze test and conditioned fear test [13]. However, PTZ administration after training did not affect memory consolidation. These findings suggest that seizures would have different effects on the acquisition and consolidation of spatial memory and conditioned fear. In contrast, our results demonstrated a PTZ-induced cognitive deficit observed both in the acquisition phase and in the memory consolidation phase during the inhibitory avoidance test.

Cognitive dysfunction caused by seizures is directly associated with an alteration in neurotransmitters [6–8]. An imbalance in brain glutamate and GABA levels is observed during the seizures, indicating increased levels of glutamate and the depletion of GABA [30]. Consequently, this imbalance between excitatory and inhibitory neurotransmission is strongly related to the memory impairment associated with seizures. Thus, changes in the levels of neurotransmitters and molecules involved in the process of memory formation would better describe the findings in this work.

As a limitation of this work, we can highlight that the pharmacological model induced by PTZ only reproduces behavioral phenotypes and electroencephalographic changes observed in seizures [18]. However, it is known that genetic models would be able to mimic epilepsy [31]; however, it is relevant to highlight that animal models are not able to fully represent the complexity of epilepsy, as observed in humans[32].

The importance of verifying the influence of seizures at different periods during the inhibitory avoidance test is a way to better understand the comorbidities associated with epilepsy. Our study shows a cognitive deficit vulnerability window between seizures and memory formation. Thus, this work contributes to future studies that may eventually search treatments for memory impairment caused by epilepsy, as well as investigate the association between cognitive deficit and seizures.

In summary, our data describe alterations in the phases of memory acquisition and consolidation, caused by a seizure inducer, in the inhibitory avoidance test. Due to the robust responses, our results support the use of zebrafish as an effective model for studies of comorbidities associated with epilepsy, such as cognitive deficits.

CRediT authorship contribution statement

Kanandra Taisa Bertoncello: Conceptualization, Investigation, Methodology, Writing – original draft, Data curation. **Rodrigo Zanandrea:** Investigation, Data curation. **Carla Denise Bonan:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Conflict of Interest

The authors declare no conflict of interest.

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