

An acute seizure prior to memory reactivation transiently impairs associative memory performance in C57BL/6J mice

Matthew S. Binder,^{1,4} Andrew D. Kim,^{1,4} and Joaquin N. Lugo^{1,2,3}

¹Department of Psychology and Neuroscience, Baylor University, Waco, Texas 76798, USA; ²Institute of Biomedical Studies, Baylor University, Waco, Texas 76798, USA; ³Department of Biology, Baylor University, Waco, Texas 76798, USA

Memory deficits significantly decrease an individual's quality of life and are a pervasive comorbidity of epilepsy. Despite the various distinct processes of memory, the majority of epilepsy research has focused on seizures during the encoding phase of memory, therefore the effects of a seizure on other memory processes is relatively unknown. In the present study, we investigated how a single seizure affects memory reactivation in C57BL/6J adult mice using an associative conditioning paradigm. Initially, mice were trained to associate a tone (conditioned stimulus), with the presence of a shock (unconditioned stimulus). Flurothyl was then administered 1 h before, 1 h after, or 6 h before a memory reactivation trial. The learned association was then assessed by presenting a conditioned stimulus in a new context 24 h or 1 wk after memory reactivation. We found that mice receiving a seizure 1 h prior to reactivation exhibited a deficit in memory 24 h later but not 1 wk later. When mice were administered a seizure 6 h before or 1 h after reactivation, there were no differences in memory between seizure and control animals. Altogether, our study indicates that an acute seizure during memory reactivation leads to a temporary deficit in associative memory in adult mice. These findings suggest that the cognitive impact of a seizure may depend on the timing of the seizure relative to the memory process that is active.

[Supplemental material is available for this article.]

Epilepsy is a condition that is defined by the presence of two or more unprovoked seizures occurring more than 24 h apart or one unprovoked seizure that has a high (>60%) probability of future seizures (Fisher et al. 2005). Epilepsy is one of the most common neurological diseases, occurring in approximately 50 million individuals worldwide (WHO 2019). The onset of seizures in epilepsy produces numerous pathological alterations in the brain such as neurodegeneration, abnormal neurogenesis, oxidative stress, inflammation, and disruption of the blood-brain barrier (Fabene et al. 2010; Shin et al. 2011; Librizzi et al. 2012; Cho et al. 2015; Valle-Dorado et al. 2015). Due to the host of underlying changes that accompany seizures, epilepsy is associated with various comorbid conditions that can further affect an individual's quality of life. One of the most prominent and pervasive comorbid conditions associated with epilepsy are deficits in memory, as individuals with epilepsy rank memory problems as one of their foremost concerns (McAuley et al. 2010). However, despite the threat to quality of life that memory deficits pose, the time course of impairment and the precise effect of a seizure on memory is not well understood.

Murine seizure models have been used to elucidate the memory deficits associated with epilepsy. Studies have consistently found that persistent and pervasive seizures result in impairments in spatial, as well as episodic-like, memory (Inostroza et al. 2013; Pearson et al. 2014). While seizure paradigms that induce multiple seizures have been predominately utilized in previous studies, recent research has also demonstrated that a single seizure has deleterious effects on memory. Mao et al. (2009) found that inducing an acute pentylenetetrazol (PTZ) seizure 30 min prior to a learning

task resulted in long-term memory deficits in both spatial and contextual memory (Mao et al. 2009). Similarly, Holley and Lugo (2016) found that an acute flurothyl-induced seizure impaired associative learning when administered 1 h prior to the learning task (Holley and Lugo 2016). A follow-up study found that the administration of flurothyl 1 h prior to the training phase of the trace fear conditioning paradigm resulted in long-term hippocampal-dependent memory impairments (Holley et al. 2018). Altogether, past studies indicate that both chronic and acute seizures result in significant memory deficits.

Despite the many studies that have examined memory impairments in epilepsy, the majority of studies have focused on the encoding aspect of a memory and consequently, few studies have examined the effect of a seizure on memory reconsolidation or reactivation. Memory reconsolidation is the process of previous memories being reactivated and put into a labile state. This allows the memory to be modified or changed based on present information then actively reconsolidated in order to maintain its strength (McKenzie and Eichenbaum 2011; Sandrini et al. 2018). Previous studies have shown that pharmacological or behavioral disruptions in reconsolidation can lead to permanent alterations in memory (Monfils et al. 2009; Clem and Huganir 2010). However, despite the importance of reconsolidation to the healthy maintenance of memories, it has not been assessed following a seizure. This is significant, as any seizure-induced disruption in reconsolidation could contribute to the memory deficits observed in individuals with epilepsy.

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⁴These authors contributed equally to this work.
Corresponding author: joaquin_lugo@baylor.edu

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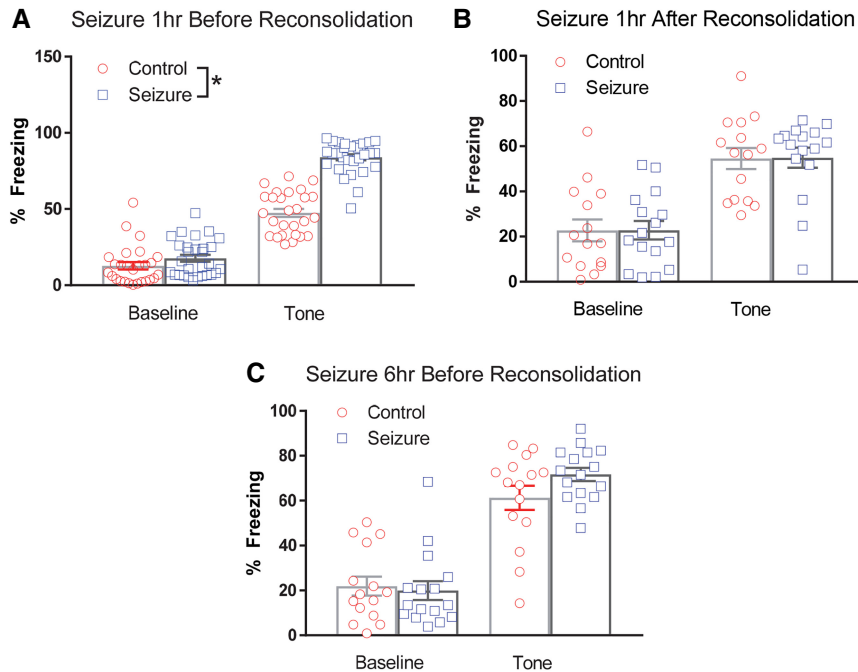


Figure 1. Freezing behavior for the reconsolidation trial. (A) Mice that received a seizure 1 h before memory reactivation displayed significantly increased freezing behavior in response to the CS than control mice ($n_{\text{control}} = 27$, $n_{\text{seizure}} = 29$). (B) Mice that received a seizure 1 h after memory reactivation did not display any significant differences in freezing behavior ($n_{\text{control}} = 15$, $n_{\text{seizure}} = 16$). (C) Mice that were administered a seizure 6 h before memory reactivation also did not display any differences in freezing behavior ($n_{\text{control}} = 15$, $n_{\text{seizure}} = 16$). The error bars denote the SEM. (*) $P < 0.05$.

In order to elucidate whether an acute seizure can impact the reactivation process of memory, the present study utilized associative fear conditioning and administered flurothyl 1 h before, 1 h after, or 6 h before a reactivation trial. The learned association was then assessed 24 h or 1 wk after reactivation in order to determine the short- and long-term impact of an acute seizure on memory. Based on the findings of Holley and Lugo (2016), we hypothesized that a single seizure 1 h prior to memory reactivation would impair reactivation when the mice were tested 24 h and 1 wk later. Additionally, we postulated that no differences would be observed between groups when flurothyl was administered 1 h after reactivation or 6 h before reactivation.

Results

Acquisition trial

In the delay fear conditioning test the mice learned to associate a white noise (conditioned stimulus (CS)) with a mild footshock (unconditioned stimulus (US)). A repeated measures ANOVA with seizure as the between subjects factor and time as the within subjects factors was run, detecting a main effect of time ($F_{(4,476)} = 443.99$, $P < 0.001$), with mice freezing significantly more in response to the CS and intertrial intervals than at baseline. There was no time by seizure interaction ($F_{(4,476)} = 0.25$, $P = 0.91$). When examining the between subjects factors, there was no main effect of seizure ($F_{(1,117)} = 0.53$, $P = 0.47$) (Supplemental Fig. 1).

Reactivation trial

The reactivation trial consisted of presenting a reminder cue for a 20 sec duration in the absence of any footshock. When a repeated

measures ANOVA was run for animals receiving a seizure 1 h before the reactivation trial there was a within subjects main effect of time ($F_{(1,54)} = 399.92$, $P < 0.001$), and a time by seizure interaction ($F_{(1,54)} = 38.84$, $P < 0.001$). The time by seizure interaction was further assessed by the Sidak multiple comparison test. A difference was found for the CS ($P < 0.001$), but not for the baseline ($P = 0.24$). Seizure mice froze more in response to the CS than controls. When assessing the between subjects factors, a main effect of seizure was observed ($F_{(1,54)} = 97.70$, $P < 0.001$). Seizure-treated animals exhibited a significant increase in freezing overall relative to the controls (Fig. 1A).

When assessing the percent freezing in mice receiving an acute seizure 1 h after the reactivation trial, there was a main effect of time ($F_{(1,29)} = 39.00$, $P < 0.001$), with mice freezing more in response to the CS than at baseline. There was no time by seizure interaction ($F_{(1,29)} = 0.001$, $P = 0.98$). For the between subjects variable, there was no main effect of seizure ($F_{(1,29)} = 0.003$, $P = 0.96$) (Fig. 1B).

For mice receiving a seizure 6 h before the reactivation trial, there was a main effect of time ($F_{(1,29)} = 130.02$, $P < 0.001$), in that mice froze more in response to the CS than at baseline. There was no time by seizure interaction ($F_{(1,29)} = 2.41$, $P = 0.13$). There was also no main effect of seizure for the between subjects variable ($F_{(1,29)} = 0.90$, $P = 0.35$) (Fig. 1C).

New context trial 24 h timepoint

The novel context trial took place 24 h after the reactivation trial in a cage that was modified to mitigate previous memory cues and presented a CS for a 3-min duration. When mice received a seizure 1 h prior to the reactivation trial then were assessed 24 h later in a new context, there was a main effect of time ($F_{(1,26)} = 569.98$, $P < 0.001$), with mice displaying more freezing in response to the CS than at baseline. There was no time by seizure interaction ($F_{(1,26)} = 1.25$, $P = 0.27$). For between subjects comparisons, there was a main effect of seizure ($F_{(1,26)} = 5.96$, $P = 0.02$), with seizure-treated animals exhibiting increased overall freezing relative to control animals (Fig. 2A).

Mice that were administered a seizure 1 h after the reactivation trial displayed a main effect of time ($F_{(1,29)} = 574.53$, $P < 0.001$), and an interaction between time and seizure ($F_{(1,29)} = 7.60$, $P = 0.01$) when tested 24 h later. The time by seizure interaction was further assessed by running the Sidak multiple comparison test. However, no significant difference was found for baseline ($P = 0.39$) nor the CS ($P = 0.08$) between seizure and control animals. No main effect of seizure for the between subjects comparison was observed ($F_{(1,29)} = 0.28$, $P = 0.60$) (Fig. 2B).

When mice that received a seizure 6 h before the reactivation trial were assessed in a new context 24 h later there was a main effect of time ($F_{(1,27)} = 262.07$, $P < 0.001$), with mice displaying increased freezing for the CS relative to the baseline. There was no time by seizure interaction ($F_{(1,27)} = 2.19$, $P = 0.15$). There was also no main effect of seizure for the between subjects variable ($F_{(1,27)} = 0.13$, $P = 0.72$) (Fig. 2C).

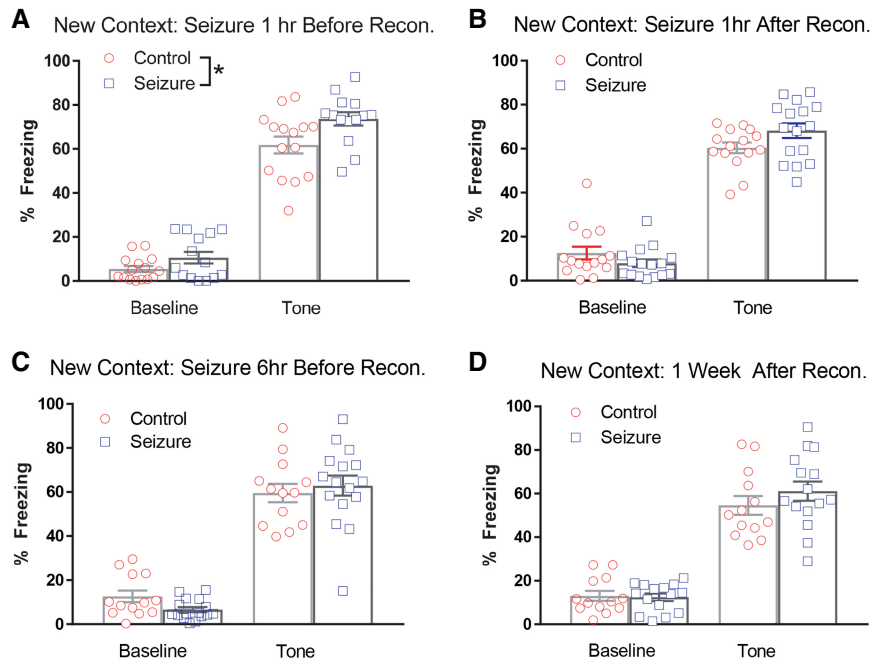


Figure 2. Freezing behavior for the new context trial. (A) Mice that received a seizure 1 h before the reactivation trial displayed significantly increased freezing behavior in response to the CS than control mice when assessed in a new context 24 h later ($n_{\text{control}} 14$, $n_{\text{seizure}} 14$). (B) Mice that received a seizure 1 h after the reactivation trial did not display any significant differences in freezing behavior ($n_{\text{control}} 15$, $n_{\text{seizure}} 16$). (C) No changes in freezing were found between seizure and control mice when flurothyl was administered 6 h prior to the reactivation trial ($n_{\text{control}} 15$, $n_{\text{seizure}} 16$). (D). No differences in freezing behavior were found when mice that received a seizure 1 h before the reactivation trial were assessed 1 wk later ($n_{\text{control}} 13$, $n_{\text{seizure}} 15$). The error bars denote the SEM. (*) $P < 0.05$.

New context trial 1 wk timepoint

To assess any long-term memory deficits following an acute seizure, mice were assessed in a new context 1 wk following the memory reactivation trial. Mice that received a seizure 1 wk prior to the novel context paradigm displayed a main effect of time ($F_{(1,26)} = 219.82$, $P < 0.001$), with mice again exhibiting increased freezing in response to the CS relative to the baseline. There was no time by seizure interaction ($F_{(1,26)} = 1.39$, $P = 0.25$). For the between-subjects variable, there was also no main effect of seizure ($F_{(1,26)} = 0.63$, $P = 0.43$) (Fig. 2D).

Discussion

McAuley et al. (2010) found that the second most important concern for individuals with epilepsy is deficits in memory. However, the majority of epilepsy research has focused only on the effect of a seizure on the encoding or storage processes of memory. Our study is the first to investigate the effects of an acute seizure on memory reactivation in mice. We found that when flurothyl is administered 1 h before reactivation there is a deficit in memory in a new context 24 h later. However, this deficit was not present 1 wk later. Similarly, no deficits in memory were observed in a new context when the seizure was administered 6 h before or 1 h after the memory reactivation trial.

Holley and Lugo (2016) investigated flurothyl's effect on associative memory when a seizure was induced 1 or 6 h prior to, or 1 h after, the acquisition phase of delay fear conditioning. They found that when a seizure was induced 1 h prior to learning a CS-US pairing, there were alterations in memory the following day in a new context, indicating a deficit in amygdala-dependent memory

(Holley and Lugo 2016). Similarly, our study found that a seizure 1 h before memory reactivation results in an increased freezing response 24 h later in a new context. Specifically, our study found an increase in freezing behavior at baseline and in response to the tone in seizure-treated animals. This may be attributed to a lack of contextual precision in flurothyl-treated mice that leads to contextual fear memory generalization. Therefore, even though the mice are placed in a changed testing environment, seizure-treated animals may not accurately recall all the contextual cues from previous test days, resulting in the mice exhibiting a generalized fear response to the new environment. Altogether, our findings complement the existing literature and indicate that a seizure 1 h prior to memory reactivation results in memory deficits similar to when a seizure is induced 1 h prior to acquisition.

Disruptions during reconsolidation have previously been shown to lead to long-lasting effects on memory. Monfils et al. (2009) conditioned rats to fear a tone then presented a retrieval trial to induce memory reconsolidation. Following the retrieval trial, reconsolidation was disrupted by an extinction trial. This leads to the fear memory being weakened both 24 h and 1 mo later (Monfils et al. 2009). Another study found that when reconsolidation is disrupted by the pres-

ence of a distractor, a brief air puff applied to the face of the rat, freezing behavior is irregular up to 20 d later when compared to control mice (Crestani et al. 2015). Our study found that a disruption in the reactivation of a memory leads to an impairment 24 h later but not 1 wk later. Due to the chronic effects of reconsolidation disruption, we expected a similar deficit to be present at both timepoints. One possible explanation why this was not observed, may be due to the physiological changes that occur after a seizure. Seizures cause a host of underlying molecular changes, ranging from morphological changes, to increases in neurotrophic factors, to cell death, and immune activation, causing both short- and long-term neuronal alterations (Glass and Dragunow 1995; Binder et al. 2001; Vezzani et al. 2011; Teocchi and D'Souza-Li 2016). Therefore, it is possible that at the 1-wk timepoint these underlying processes are active in such a way as to normalize memory performance. An alternative explanation could be the molecular and behavioral bimodal effects of seizures. Zeng et al. (2009) found that seizures can lead to an increase in a protein known to be up-regulated by seizures, phosphorylated-S6 (p-S6), immediately following seizure induction but that this increase is normalized 24 h later. However, when p-S6 was assessed 3 d postseizure, levels were again elevated and remained elevated for several weeks (Zeng et al. 2009). Holley et al. (2018) found that a seizure during the acquisition of the CS did not impair hippocampal-dependent memory 24 h following seizure induction, however, there were memory deficits present both 1 and 2 wk following induction. These studies indicate that seizures can exert different effects on proteins associated with seizures, as well as on memory performance, depending on the time of assessment. They also indicate that an acute seizure induced deficit may normalize only to reemerge at a later timepoint, in a bimodal manner. Future studies investigating the molecular

underpinnings of seizures and memory reactivation, as well as seizures' long-term effects on memory reactivation, would help to better elucidate this relationship.

Previous studies have demonstrated that seizures can lead to an acute decrease in locomotor behavior (Driver-Dunckley et al. 2011; Holley and Lugo 2016; van Buel et al. 2017). Specifically, Holley and Lugo (2016) showed that a single flurothyl-induced seizure impairs locomotion in the open field test 2 h after a seizure but did not affect locomotion 24 h later. Holley and Lugo (2016) also found that a seizure 1 h prior to the acquisition of a conditioned stimulus resulted in increased freezing 1 h later. However, a seizure 6 h prior to acquisition did not affect the baseline freezing behavior of seizure animals, indicating that flurothyl induction leads to only a temporary decrease in locomotion (Holley and Lugo 2016). Our results support this, as we also observed an acute increase in freezing behavior in the reactivation trial 1 h after flurothyl induction, but no changes in baseline freezing in mice receiving a seizure 6 h prior. Altogether, the literature indicates that the increased freezing observed in the reactivation trial 1 h after seizure induction is most likely due to the effects of a seizure on movement, not memory. However, the literature also indicates that this effect is temporary and demonstrates that any changes in freezing at least 24 h following reconsolidation, is specific to memory.

Studies examining acute seizures induced via the chemoconvulsant pentylenetetrazol (PTZ) have also been shown to impair memory. Mao et al. (2009) found that acute PTZ administration impaired the acquisition and retrieval of spatial and contextual memory. However, memory reconsolidation was not affected in either assessment (Mao et al. 2009). When coupled with our results and other flurothyl studies, it is apparent that a single acute seizure can affect different memory processes across both hippocampal and amygdala-based paradigms. Therefore, while the majority of epilepsy memory research has been conducted using chronic seizure models, our study is a part of a growing body of literature which indicates that a single acute seizure may lead to similar impairments. However, more studies need to be done in order to better understand this relationship and its implications.

Conclusion

Our study expands the acute seizure literature while providing support for previous findings investigating the impact of an acute seizure on memory. Our primary result, that flurothyl leads to a transient deficit in memory, suggests that a seizure affects memory differently depending on when the seizure occurs and when the memory is assessed. More broadly, our findings indicate that the impact of an acute seizure on memory is variable and thus should be taken into account when considering how seizures affect a patient's quality of life.

Materials and Methods

Subjects

We used adult male and female C57BL/6 mice that were purchased from Jackson Laboratories and were bred at Baylor University to produce male and female offspring. A total of 118 mice, 62 males and 56 females were used in this study, forming eight groups. Testing took place between postnatal days 60–70. The groups consisted of male and female mice that received a seizure 1 h before, 6 h before, or 1 h after the reactivation trial, as well as a group that was assessed in a novel context 1 wk after the initial seizure. Each group had at least six mice, as determined per an a priori power analysis. The mice were group-housed in standard acrylic mouse cages with ad libitum access to both food and water. The colony was maintained at 22°C on a 12 h light/12 h dark diurnal cycle.

All procedures performed complied with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health and were approved by the Baylor University Institutional Animal Care and Use Committee.

Flurothyl induction

Flurothyl is a GABA_A antagonist that induces acute seizures in rodents and has been used previously by our laboratory and others to investigate the effects of acute seizures on memory (Truitt et al. 1960; Prichard et al. 1969; Holley and Lugo 2016; Holley et al. 2018). All experimental seizures were induced under a standard fume hood inside a clear acrylic (29 × 16 × 15 cm) inhalation chamber. All mice were allowed to acclimate to the room for 30 min prior to induction. During the procedure, the seizure-designated mouse was placed into a clean transfer cage, and then placed into the acrylic inhalation chamber. Undiluted flurothyl (bis-2,2,2-trifluoroethylether), obtained from Sigma-Aldrich (product number: 287571), was pumped into the chamber using an extended glass syringe (14.57 mm) and the Harvard Apparatus model 11 Plus syringe pump at a rate of 30 μL per minute. Flurothyl was allowed to drip at a constant rate onto a platform containing a paper towel strip until the mice exhibited a tonic-clonic seizure as determined by the Racine scale (Racine 1972). A control mouse was placed in a second acrylic inhalation chamber in parallel with the seizure-designated mouse. After a seizure was induced, both mice were removed from the chambers and placed into individual transfer cages and were monitored for 1 h, allowing time to recover.

Fear conditioning

Fear conditioning was measured using two Coulbourn Habitest fear conditioning chambers (26 × 22 × 18 cm) placed inside of sound dampening, isolation cubicles. The chamber inside the cubicles consisted of two metal walls, two acrylic walls, and a barred metal floor which delivered mild electric footshocks. These electric footshocks were generated by the Coulbourn Precision Animal Shockers, which were manually calibrated using an ENV-420 Amp Meter (Med Associates Inc.) prior to testing of the initial habituation trial. A static noise tone was generated by PYLE PRO PCA2 stereo amplifiers that played through speakers mounted on the rear side of the isolation chamber. Prior to testing, the tone was calibrated at 80 dB for both cubicles. Freezing behavior was recorded and analyzed using the FreezeFrame 3 software (Coulbourn) for each testing day.

The delay fear conditioning paradigm consisted of three protocols: acquisition, a memory reactivation trial, and a novel context trial. For the acquisition trial, there was a 2-min baseline period, followed by the presentation of the conditioned stimulus (CS) for 20 sec (80 dB white noise tone) as previously described (Lugo et al. 2012). The white noise was immediately followed by a mild footshock (2 sec, 0.70 mA), which served as the unconditioned stimulus (US). This was followed by an intertrial interval of 1 min, which was preceded by an identical tone and shock pairing, for a total of two pairings. After each mouse was tested, the chamber was cleaned with 30% isopropyl alcohol.

The memory reactivation protocol consisted of a reminder cue that took place 72 h after the acquisition trial (Monfils et al. 2009). Specifically, the mice habituated in the chamber for 3-min then received a reminder cue that was comprised of an 80 dB white noise stimulus presented for 20 sec, followed by a 2-min postcue period. In this trial, no shock was administered.

The third trial tested delay fear conditioning within a novel context. A novel context was created by altering the texture, color, sound, and shape of the chambers using acrylic inserts/flooring and a fan, as well as by adding a novel odor (vanilla extract; Adam's extracts, USA). Freezing behavior was measured for a total of 6 min. In the first 3-min period the mouse habituated to the novel environment. Next, an 80 dB white noise tone (the conditioned stimulus) was presented for a 3-min duration, concluding the trial.

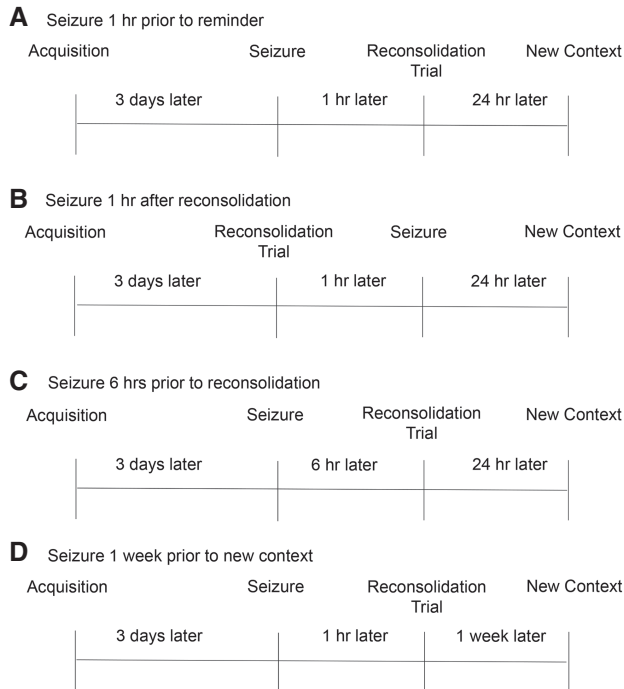


Figure 3. Time course for methodology. Mice received a seizure either 1 h before a reconsolidation trial (A), 1 h after the reconsolidation trial (B), or 6 h before the reconsolidation trial (C). Memory was assessed in a new context either 24 h later (A–C), or 1 wk later (D).

Seizure induction protocols

For this study, all of the seizures were induced prior to or proceeding the reactivation trial, with four different seizure timepoints being used. Each timepoint is detailed in Figure 3A–D. The first protocol induced an acute seizure 1 h before the reactivation trial (Fig. 3A). The second protocol induced a seizure 1 h after the reactivation trial (Fig. 3B). In order to best assess the relevancy of the timing of the seizure, the third protocol induced a seizure 6 h before the reactivation trial (Fig. 3C). The last protocol induced an acute seizure 1 h before the reactivation trial but assessed fear conditioning in a novel context 1 wk later instead of 24 h later (Fig. 3D). This was done to assess any long-term effects of an acute seizure on the reactivation of memory.

Statistical analysis

A power analysis was conducted using GPower 3.1. All data was analyzed using GraphPad Prism 7 software (GraphPad Software, Inc.) or SPSS 25.0 (IBM). Since there were no seizure by sex interactions, the male and female groups were compiled together. To assess percent freezing, a measure of learning in the fear conditioning paradigm, repeated measures ANOVAs were run. For the acquisition trial, Seizure [flurothyl, control] was the between subjects factors and Time [baseline, tone 1, intertrial interval 1, tone 2, and intertrial interval 2] was the within subjects factor. For the reactivation and novel context trials, the between subjects factor was Seizure [flurothyl, control], with the within subjects factor being Time [baseline, CS]. Any significant interactions were clarified by running the Sidak multiple comparison test. A value of $P < 0.05$ was considered significant for each statistical test, with figures depicting the mean \pm standard error of the mean (SEM).

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