EVALUATING THE ROLE OF MEMORY IN A RODENT MODEL OF EPILEPSY

RITWIK DAS
Bachelor of Medicine, Bachelor of Surgery, Government Medical College and Hospital, 2011

A thesis submitted
in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE

in

NEUROSCIENCE

Department of Neuroscience
University of Lethbridge
LETHBRIDGE, ALBERTA, CANADA

EVALUATING THE ROLE OF MEMORY IN A RODENT MODEL OF EPILEPSY

RITWIK DAS

Date of Defense: March 23, 2023

Dr. Artur Luczak Thesis Supervisor	Professor	Ph.D
Dr. Aaron Gruber Thesis Examination Committee	Professor	Ph.D
Dr. Ian Whishaw Thesis Examination Committee	Professor	Ph.D
Dr. David Euston Chair, Thesis Examination Committee	Associate Professor	Ph.D

DEDICATION

To my wife, Deeksha who stood by me and provided me the courage to be in Science.

ABSTRACT

Epileptogenesis is a complex and not well understood phenomenon. It has been largely described as pathology occurring because of an imbalance between excitatory and inhibitory brain networks. Through our experiments we attempted to show that epileptogenesis could be "hijacking" the brain mechanisms responsible for memory formation. We began by using an associative experimental design, pairing auditory and visual cues with electrically kindled evoked seizures to design a rodent model of reflex seizures. Reflex seizures are a clinical phenomenon characterized by convulsive episodes induced by specific sensory stimuli or cognitive actions. Our experiment failed to establish a reflex seizure model in rodents, but interestingly we observed behavior and electrophysiology similar to fear conditioning, with significant freezing in animals paired with cues.

Using the same animals, we investigated memory reconsolidation blocking therapies, which rely upon replaying neuronal activity but instead of strengthening, involved synapses are weakened. We used rapamycin to weaken neuronal circuitry replayed with the sensory cues and evoked seizures to weaken epileptic networks. Although this was aimed as an exploratory study, the drug therapy abolished seizures in two animals, demonstrating promising results.

Acknowledgements

I would like to express my heartfelt appreciation to Dr. Artur Luczak for his unwavering support and guidance throughout my graduate studies. His mentorship has been instrumental in shaping me into a better scientist, and I am deeply grateful for his contributions to my research.

I would also like to thank my supervisory committee members, Dr. Aaron Gruber and Dr. Ian Whishaw, for their invaluable input and guidance. Dr. Whishaw's lessons on how to be a scientist have been an enduring source of inspiration, while Dr. Gruber's kindness in sharing expensive equipment has been truly remarkable. Additionally, I am grateful to Dr. Bryan Kolb and Dr. Cam Teskey for generously sharing their time and expertise in assisting me with finding relevant literature and techniques for my research on Kindling. Dr. Teskey's graciousness in allowing me to visit his lab and sharing the Kindling protocol has been invaluable to my work.I'm grateful to my colleagues and friends for their essential role in making my graduate studies a success. Their unwavering moral support and assistance helped me navigate the challenges of this journey. Specifically, I owe a debt of gratitude to Adam Neuman for inspiring me with his work in Epilepsy, Dr. Rui Pais for broadening my perspective with engaging discussions on predictive coding, Aubrey Demchuk for teaching me the basics of histology and brain sectioning, Dr. Mike Eckert for imparting the basic principles of Electrophysiology, Dr Surjeet Singh for helping me with Raspberry Pi and Vicki Ivan for teaching me the basics of drug formulation and injections.

I'm especially grateful to three people who have been indispensable to my academic pursuits: Dr. Ingrid Esteves for spending countless hours helping me troubleshoot my

experiments and teaching me the basics of rodent surgery; HaoRan Chang for sharing his programming expertise and providing insights on data analysis and Neuroscience; and my wife Deeksha for her unwavering support, patience, and love.

I'd like to express my gratitude to my current and former lab members, Dr. Reza Torabi, Dr. Yoshimasa Kubo, Carlos Howey, and Rubal Singh, for their invaluable contributions and insightful discussions throughout my research. I also extend special thanks to the Animal care staff, including Karen Dow-Cazal, Moira Holley, James Cazal, and Dr. Isabelle Gauthier, for their exceptional animal care and helpful suggestions in addressing potential confounding factors.

I want to thank my parents, Buddha and Karobi, for their unwavering commitment to excellence, which has served as a constant source of inspiration for me. My aunt Mallika and uncle Pushpinder, who played a pivotal role in my early academic development. My mother-in-law Santosh has been a constant source of emotional support and love. Their unwavering belief in me has given me the courage to pursue my dreams even when the road was tough.

I'm grateful to Vidisha for sharing her expertise in biomedical devices and inspiring insightful discussions. Dr. Aman Biswas and Dr. Subroto Biswas, my pre-med professors, for teaching me the value of perseverance and determination in the face of challenges. Lastly, I want to thank Dr. Fabrizio Gabbiani for welcoming me into academia and allowing me to work with him on my first academic project.

It takes a village to raise a child, and in my case, a community of exceptional individuals to achieve my academic goals. Their unwavering support, guidance, and expertise have been invaluable, and I am deeply grateful for their contributions to my success.

Table of Contents

List of Figures

List of Abbreviations

1. IIS = during inter-ictal spiking
2. LAC = light and auditory cue conditioned group
3. UC = unconditioned group
4. PC = pilot conditioned group
5. LTP = long term potentiation
6. LFP = local field potentials
7. RGB = red, green blue image
8. BLA = basolateral amygdalar nucleus
9. dmPFC = dorsal medial prefrontal cortex
10. CWT = continuous wavelet transform
11. IIS = inter-ictal spiking
12. SWS = slow wave sleep
13. SWR = sharp wave-ripple
14. HFO = High frequency oscillations

Chapter 1: Introduction

Epilepsy is a common, albeit serious brain condition, affecting over 70 million people worldwide with the highest prevalence in infants and older age groups (Thijs et al., 2019). Epilepsy is a disorder exhibiting spontaneous seizures, which emerge unpredictably (Fisher et al., 2005, 2017). This is a chronic condition of the brain due to excessive and hypersynchronous, but usually self-limited activity of neurons (Blume et al., 2001). Seizures comes from the Latin word 'sacire', meaning to take possession of, is characterized by unprovoked muscle contractions and spasms, unconsciousness, abnormal behaviors, and emotions (Noachtar & Peters, 2009). This 'possession' has a medieval interpretation, which describes the epileptic affliction as demonic intrusion by which the individual behaves as a reluctant participant of the intruder's will (Temkin, 1994). Although this interpretation is incorrect, this sums up the clinical picture of epilepsy. Generalized tonic-clonic seizures exhibit sudden, spontaneous action of involuntary spasms, often leading to loss of consciousness followed by recovery with the individual having no memory of the episode (Beniczky et al., 2022).

On that note, to ensure a clearer grasp of our research, let's acquaint ourselves with some key terminology. Seizures are a sign of tissue irritation that is visible in a plethora of brain disorders, like trauma, infection, vascular abnormalities, developmental disorders, metabolic disturbances, and genetic defects (Feindel, 2020). They can be focal, restricted to one cerebral hemisphere or generalized, afflicting neuronal networks in both the hemispheres (Chang et al., 2017). They can present as sensory disturbances (e.g., flashing lights), autonomic dysfunctions (e.g., sweating), motor involvement (e.g., involuntary

repetitive movements). In some individuals, there is subjective presentation described as internal feelings of impending events, illusions, déjà vu amongst others called aura.

1.1 Rationale

Through our research, we aim to view epilepsy as a condition characterized by pathological networks that disrupt the normal physiological pathways involved in memory formation. By studying these networks and their effects on the brain, we hope to gain a better understanding of how epilepsy can affect cognitive function and develop more effective treatments for this condition. During sleep and quiet wakefulness, memory patterns are frequently replayed to consolidate memories (McGaugh, 2000). For example, patterns of neuronal activity evoked during a behavioral task are later spontaneously replayed when an animal is resting or sleeping (M. A. Wilson & McNaughton, 1994). It has been proposed that epileptic activity is "hijacking" those memory consolidation processes, where repetitive memory replay generates aberrant oscillatory network activity (Augusto et al., 2019; Beenhakker & Huguenard, 2009; Mendes et al., 2021). Recent work in our lab provided new evidence for this hypothesis (Neumann et al., 2017). Using chronic neuronal recordings in epileptic rats, we found that ictal activity patterns were similar to neuronal patterns occurring spontaneously between seizures. This observation suggests that ictal activity could be a "memory pattern" which gets trapped in attractor-like dynamics *(Dr. B.L. McNaughton personal communication to Dr. Artur Luczak)*.

The condition described as reflex epilepsy provides a promising avenue for identifying neural networks associated with 'seizing' neurons predictably. Reflex epilepsy is clinically described as a tendency to experience seizures due to the presentation of a specific stimulus or the performance of a cognitive activity (Fisher et al., 2014). Building

a model of reflex seizure would enable us to identify how the brain transforms from selective activity of neurons (as observed during a particular task or encoding sensory information) to hypersynchronous circuits during convulsive behavior. Our research aims at studying the association between memories specific to the stimuli eliciting reflex seizures. Weakening this association would lead to a decrease in the amount of hyperexcitable tissue recruited during a seizure leading to eventual end of pathology. The reliability of inducing seizures with presentation of specific stimuli would provide an opportunity to test drug therapies to prevent the onset of this disease entity.

1.2 Theory & Hypothesis

Wieser's theory of critical mass states that a sensory stimulus triggers a critical amount of cortical tissue which leads to an increased activation of epileptogenic neurons causing a seizure (Wieser, 1998). Our hypothesis is that forming a constant temporal association between sensory stimuli (cues) and evoked seizures (by electrical stimulation following the kindling model of epilepsy (Teskey, 2020)) would potentially lead to two possible outcomes. Firstly, by this continual temporal pairing, the sensory cues would themselves be able to drive a critical mass of neurons to fire synchronously and lead to the development of an experimental model of reflex seizure. Secondly, utilizing this model of reflex seizure, ablate the memories of the sensory cues using protein synthesis blockers (working on memory pathways inside the brain) leading to reduction and finally prevention of seizures.

Chapter 2: Epileptic seizures and link to memory processes[1] (Das & Luczak, 2022)

Most seizures are spontaneous, meaning that they do not have any clearly identifiable trigger, and can occur at any time, including sleep (Amengual-Gual et al., 2019; Karoly et al., 2021; Matos et al., 2011). However, in a subset of epileptic patients, spontaneous seizures are preceded by auras: a sensation of particular smell, lights, or certain thoughts (Boada et al., 2020; Gupta et al., 1983), which suggest that 'internal' triggers of seizures may be potentially identified. Moreover, about 5% of epileptic patients, have reflex seizures which are evoked by specific stimuli (Engel, 2001, 2006; Fisher et al., 2017; Koutroumanidis & Panayiotopoulos, 2004). For example, reflex seizures in some patients may be elicited by flickering lights, certain sounds, or specific activities (Xue & Ritaccio, 2006). A patient may experience both 'spontaneous' and 'reflex' seizures, suggesting the same underlying mechanisms (Koutroumanidis & Panayiotopoulos, 2004). It was also reported that performing a specific action (for example, toothbrushing) as well as just thinking about that action can induce seizures (Navarro et al., 2006). Thus, there is emerging evidence that spontaneous seizures could be a form of reflex seizures where instead of external stimuli, the memory circuits can initiate seizures by activating neuronal patterns representing particular stimuli (Irmen et al., 2015).

In this chapter we present experimental and clinical studies to illustrate the close relationship between epileptogenesis and memory consolidation mechanisms. We begin with describing the interictal events, and how it relates to memory consolidation processes. Next, we describe kindling model used for seizure induction, and its relation to

[1] This chapter is adapted from a review I published in 2022 in AIMS Neuroscience (Das & Luczak, 2022)

long-term potentiation (LTP), a model for memory formation (Nguyen et al., 1994). We also discuss how cognitive decline in Alzheimer's disease has been related to the development of convulsive pathways (Palop et al., 2007). Finally, we will review how reflex seizures could be triggered by specific memories, and we propose how memory extinction therapies could provide a novel approach to reduce seizures. The central idea of this chapter is that memory formation processes and epilepsy may be closely related, which could help in developing new therapies.

2.1 Seizure related consolidation and memory related changes during sleep

Seizure related consolidation refers to the changes that occur in the neuronal activity after the seizure epoch, consisting of reactivation of brain networks associated with the pathology during the subsequent post-ictal period. Seizures induce highly coherent activity in selected neuronal populations. During subsequent sleep, connections between neurons involved in the convulsive episode are strengthened as compared to pre-seizure connection strength (Bower et al., 2015). This modification of selected synapses participating in seizures shows similarity to the changes observed after learning during subsequent sleep, where connections between neurons involved in the learned task are also selectively strengthened (Bower et al., 2015; M. A. Wilson & McNaughton, 1994). Similarly, activity patterns during inter-ictal spiking (IIS) can be consolidated during the following sleep (de Curtis & Avanzini, 2001). For a detailed explanation of IIS please refer to the review by Curtis and Avanziani (de Curtis & Avanzini, 2001). Briefly, IIS is a brief electrographic event lasting 250 milliseconds consisting of a fast sharp wave and longer lasting slow wave (Prince & Connors, 1986; Staley & Dudek, 2006). The IISs recorded minutes before the seizure event display similarity in shape and synchrony with

‘reactivated’ IISs during the post-seizure periods including the slow wave sleep period (Bower et al., 2017). IIS propagation is seen to be promoted by sleep, with the non-rapid eye movement (NREM) period particularly inducing greater spike production and propagation (Del Felice et al., 2015; Lambert et al., 2018; Sparks et al., 2020). These studies provide evidence that seizure induced activity can be consolidated in neuronal circuits using similar mechanism as used for normal learning and memory formation (M. A. Wilson & McNaughton, 1994).

Moreover, in childhood epilepsy the presence of IISs disturbs the spatiotemporal coupling mechanisms associated with sleep related memory consolidation (Georgopoulou et al., 2021). The interplay of IIS with slow wave sleep (SWS) was suggested to affect the spindle-ripple interaction responsible for normal information transfer associated with memory (Buzsáki, 1996; Hahn et al., 2020; Halász et al., 2019; McClelland et al., 1995; Squire, 2004; Stickgold, 2005). The interaction of hippocampal IIS with cortical spindles during the NREM sleep has been associated with impaired memory consolidation (Gelinas et al., 2016). Studies have shown that IISs disrupt memory and cognition in both animal models (Kleen et al., 2010) and epileptic patients (Kleen et al., 2013). Recent studies indicate that this is possibly due to intrahippocampal IISs disrupting memory consolidation during sleep involving the hippocampal and cortical circuits (Lambert et al., 2020, 2021). Those results suggest that IISs could be ‘hijacking’ and disturbing normal memory processes (Arbune et al., 2021; Maharathi et al., 2019).

2.2 High frequency oscillations (HFOs)

An important part of the memory consolidation process is sharp wave-ripple (SWR) activity. SWRs are recorded from the hippocampus as large amplitude negative

deflections with occasional co-occurrence of short duration fast oscillations called ripples (110–200 Hz) typically during sleep or rest (Buzsáki, 2015). SWRs reactivate the same sequential neuronal patterns, which were involved before in learning during wakefulness (M. A. Wilson & McNaughton, 1994). In epilepsy, brain networks generate pathological HFOs, which are similar to SWRs. Pathological HFOs are around 80 to 500 Hz in frequency and can be further divided into slower 50-250 Hz and fast 250-500 Hz oscillations (Jacobs et al., 2008, 2010). The fast oscillations usually originate in the epileptogenic area (Jacobs et al., 2008, 2010). The pathological HFOs are also associated with memory impairments (Jacobs et al., 2016) and were shown to disrupt the cognitive functionality of the hippocampus, especially when it's part of the epileptic circuit (S. Liu & Parvizi, 2019). Although, pathological HFOs may involve distinct subnetworks of neurons as compared to SWRs (Ewell et al., 2019), there is a strong overlap between the mechanisms underlying SWRs and pathological HFOs (Karlócai et al., 2014). This led to the suggestion that normal physiological processes which are involved in SWR can be "reused" to generate epileptic HFOs (Augusto et al., 2019; Beenhakker & Huguenard, 2009).

2.3 Neuronal plasticity mechanisms in epilepsy and in memory processes

2.3.1 Kindling and long-term potentiation (LTP)

Kindling is a mechanism by which specific brain regions are sensitized by an external stimulation to generate electrographic epileptiform discharges leading to behavioral seizures (Teskey, 2020). The stimulation, which could be electrical, chemical, optogenetic, or sensory (for example, tactile or auditory (Cela et al., 2019; Goddard, 1967; Marescaux et al., 1987; Shimada & Yamagata, 2018; Teskey, 2020)), recruit neurons to become part of the 'kindled' circuit. The behavioral seizures occur later when the kindled activity

spreads to the motor cortex (McIntyre et al., 2002). This progression of seizures in the animal, from initially just electrographic activity to bilateral tonic-clonic activity with loss of balance, was categorized into five behavioral stages by Ronald J. Racine (Racine, 1972). The neural changes induced by kindling are usually long lasting (Goddard et al., 1969; Goddard & Douglas, 1975). The resemblance of kindling to chronic focal epilepsy in human patients has resulted in using it as a common epilepsy model in animals (Kundap et al., 2019; McNamara, 1989; Metcalf et al., 2019; Wada, 1977).

At the molecular level, the N-methyl-D-aspartate (NMDA) receptors, which are involved in synaptic plasticity underlying normal memory processes, also play an important role in producing seizure activity due to kindling. In particular, kindling increases the expression of NMDA receptors in the dentate granule cells, favoring the formation of excitatory circuits that is associated with the increased susceptibility to seizures (Mody & Heinemann, 1987). As a result of those changes in NMDA receptors, granule cells produce long duration synaptic currents, leading to a burst spiking mode (Dalby & Mody, 2003; Lynch et al., 2000). This increased activity then propagates into the CA3 area of the hippocampus from the dentate gyrus contributing to the developing epileptic circuits (Lynch et al., 2000).

The lasting synaptic changes leading to convulsive behavior are akin to the physiological mechanisms forming memory engrams (Goddard & Douglas, 1975), which is mediated by LTP (Bliss et al., 2018). LTP increases the synaptic strength that can last for years (Citri & Malenka, 2008; Malenka & Nicoll, 1999) serving as a basis for memory at the cellular level (Abraham et al., 2019; Bliss & Collingridge, 1993). The LTP can be experimentally induced by repetitive, high frequency stimulation of afferent connections (Lømo, 2003), most widely

studied in the Schaffer collaterals and the perforant pathway (Nicoll, 2017). At the synaptic level, LTP is typically mediated by NMDA receptors (Kauer et al., 1988), similarly as described above in the kindling model.

2.3.2 Low frequency electrical stimulation (LFS) and long-term depression (LTD)

As opposed to high frequency electrical stimulation used in kindling, low frequency electrical brain stimulation has been shown to reduce epileptic seizures in animal models (Mihály et al., 2020; Paschen et al., 2020; Ruan et al., 2020). In an in vitro study, LFS of Schaffer collaterals has been shown to reduce the epileptiform activity in a gradual and persistent fashion (Albensi et al., 2004). Likewise, in a study in young rat pups, 1 Hz LFS was shown to reduce after-discharges as well as behavioral seizures (Velíšek et al., 2002). The main mechanism by which the LFS reduces the response of the stimulated pathways is LTD (Chapman et al., 2021; Wagner & Alger, 1996). LTD is the opposing process to LTP, and it is implicated in the clearing of old memory traces (Malleret et al., 2010; Nicholls et al., 2008). Similarly, as kindling and LTP, the LFS and LTD is NMDA depended, as it can be blocked by a NMDA receptor antagonist (Albensi et al., 2004). Thus, cellular plasticity mechanisms involved in memory formation/disintegration (LTP/LTD) are also playing a crucial part in processes inducing/reversing epileptic activity (kindling/LFS).

2.4 Memory impairments and their relation to seizures

Alzheimer's disease which causes severe memory impairments, was also shown to be accompanied by similar network abnormalities and interneuron dysfunction as in epileptic circuits (Palop & Mucke, 2016; Sasaguri et al., 2017). Alzheimer's disease leads to a hypersynchronous activity which was suggested to accelerate the progression of dementia

(Bezzina et al., 2015). Hypersynchronous activity, similar to ictal activity, was observed in both animal models of Alzheimer's disease and in clinical studies (Busche & Konnerth, 2016; Noebels, 2011; Ramírez-Toraño et al., 2021). For instance, imaging studies using fMRI showed hyperactivity in the hippocampus, which was also accompanied by cognitive impairments in the pattern separation (Yassa et al., 2010). Alzheimer's patients were also reported to have silent hippocampal seizures and epileptiform spikes during sleep (Lam et al., 2017). Memory impairments and increase in the incidence of epilepsy and seizures is also commonly observed in normally aging animals, including humans (≥ 60 years old) (Jacob et al., 2019; Leppik & Birnbaum, 2010; D. Liu et al., 2018; Olafsson et al., 2005; I. A. Wilson et al., 2006). Importantly, antiepileptic drugs were shown to offer new therapeutic potential for memory impairments in elderly animals and humans (Koh et al., 2010; Sanchez et al., 2012), which provides strong support for common underlying neuronal circuit changes in epilepsy and in memory impairments.

2.5 Reflex epilepsy – seizures triggered by memories

Reflex epilepsy refers to any syndromic disorder where the seizures are triggered by a specific stimulus, activity, or memory (Wolf, 2017). Wieser's theory of critical mass states that in reflex seizures, a sensory stimulus may trigger a critical amount of cortical tissue which leads to increased activation of epileptogenic neurons causing a seizure (Arslan et al., 2013; Wieser, 1998). Thus, the specific sensory stimulus may lead to over-activation in specific brain regions which can induce seizures in susceptible patients (Ferlazzo et al., 2005). Consistently with this theory, it was reported that in patients with generalized seizures, there are regions of hyper-excitability overlapping with regions responsible for encoding sensory stimuli and complex cognitive tasks (Szűcs et al.,

2019b). Interestingly, even spontaneous ‘thoughts’ could activate the critical mass of epileptogenic neurons, which could provide an explanation of how reflex seizures could be triggered by a memory recall. For example, it was reported that memory from childhood was triggering seizures in a 69-year-old woman (Falip et al., 2018). In another example, specific memories of music led to convulsive episodes (Gelisse et al., 2003; Jallon et al., 1989; Tezer et al., 2014). This shows that memories have an ability to activate the epileptic pathways, similarly to sensory stimuli.

In experimental rodent models reflex seizures have been reported during performance of specific tasks. In a study where rats underwent pre-training on a place learning task, where they had to find a platform hidden beneath opaque water, displayed convulsive behavior. The seizures occurred primarily while they were swimming following granule cell lesions in the dentate gyrus and the $CA_{3\text{-}4}$ region of the hippocampus (Whishaw, 1987).

Even in a normal brain, the same neuronal population can be activated by external stimuli as well as by internally generated spontaneous neuronal activity. For example, patterns of neuronal population activity which are triggered by sound or tactile stimuli, could be also observed during spontaneous activity in awake, resting animals (Luczak et al., 2009, 2015). Thus, although reflex seizures are only reported in a small percentage of epilepsy patients, they could involve the same mechanisms as spontaneous seizures. For instance, a typical feature during a reflex seizure is the presence of widely synchronized slow waves during the seizures (Bortel et al., 2019). Similarly, in epileptic patients with spontaneous (non-reflex) seizures, increased slow wave activity was observed as compared to healthy controls (Boly et al., 2017; Sitnikova et al., 2020; van Luijtelaar et

al., 2011). This suggests common mechanisms underlying spontaneous and reflex seizure. Therefore, we propose that spontaneous seizures could be seen as a special case of reflex seizures, where internally generated activity like memory patterns can initiate seizures similarly to stimulus driven processes.

2.6 Treatment of epileptic disorder by targeting memory reactivation processes?

In the sections above, we provided arguments that epileptic circuits could be formed in a similar way as memory traces, by strengthening selected pathways. Therefore, extinctions treatments used to reduce traumatic memories may also be applicable to weaken aberrant connections involved in seizures (Silva et al., 2021). Below we will discuss such methods, which may provide new directions in developing treatments for epileptic patients.

During memory reactivation, patterns of neuronal activity from a previous learning experience are replayed during subsequent sleep or rest period (Genzel et al., 2020). Reactivation of memories makes them susceptible to modification (Nader et al., 2000; Winters et al., 2009). Thus, by targeting specific memories during the reconsolidation processes it is possible to weaken those memory traces (Simon et al., 2018). For example, reactivated fear memories coupled with protein synthesis inhibitors injected into the amygdala led to amnesia related to a fear inducing stimulus (Nader et al., 2000). Similarly, beta-adrenergic receptor blocker propranolol has been shown to be effective in ameliorating post-traumatic stress disorder (PTSD) related memories (Brunet et al., 2018; Schwabe et al., 2012). Propranolol was shown to also interfere with memory reconsolidation processes when administered after exposure to stressful stimuli in animals (Cahill et al., 2000) and in humans (Soeter & Kindt, 2015). This is possibly due to

the blockade of noradrenergic activity in the amygdala during the reconsolidation process which is responsible for the encoding of emotionally enhanced memories associated with PTSD (LaBar & Cabeza, 2006; Liang et al., 1986). Thus, this type of exposure therapy has been proven to be a valuable option for fear memory extinction (Dunsmoor et al., 2015).

Targeting similar mechanisms may also be worth exploring in animal models of epilepsy. Exposure therapy coupled with protein synthesis inhibitors could be the most directly applied to reduce reflex seizures. For instance, Blundell et al (Blundell et al., 2008), showed that injecting rapamycin after exposure to conditional fear stimuli blocked traumatic memory reconsolidation and decreased the emotional strength of an established traumatic memory. This suggests that epileptic animals could be briefly exposed to a place or task in which they were conditioned to develop reflex seizures, and right after exposure, they could be intraperitoneally injected with rapamycin, which inhibits protein synthesis needed for the memory reconsolidation process. This treatment could be applied once daily over a period of few days. We propose that such treatment could result in reduction of seizures.

The same principles could be probably also applicable to spontaneous seizures. As described in previous sections, connections in epileptic circuits are selectively strengthened in the post-seizure period, by using likely the same mechanisms as memory consolidation processes (Bower et al., 2015). Thus, administrating protein synthesis inhibitors right after seizure could block those processes, resulting in weakening connections involved in the epileptic activity. However, the possibility of treating epilepsy with protein synthesis inhibitors should be taken with extreme caution as more animal experiments are needed to establish the safety and efficiency of such approaches.

2.7 Conclusion

In only about two-thirds of patients, seizures can be controlled with medication (Galanopoulou et al., 2012). This underlines the need for exploring novel options for epilepsy treatment. In this perspective, we present a close relation between memory formation and epileptogenesis. We propose that treatments used to reduce traumatic memories could also provide new options to explore for curtailing seizures.

We described that brain activity in epilepsy is similar to what is observed in the physiological processes associated with memory formation. Activity patterns such as fast ripples are associated with the recurrent neuronal excitation in epilepsy (González Otárula et al., 2019) and are involved in memory formation. Moreover, the seizure associated cell ensembles are reactivated during slow wave sleep in a similar fashion as memory patterns after learning of a new task (Bower et al., 2017). There is also evidence to suggest that seizure associated with neuronal reactivation and consolidation may lead to a relocation of the epileptogenic focus from the hippocampus to the neocortex in a manner reminiscent of the transfer of memory traces from the hippocampus to the cortex (Bower et al., 2015). This suggests that epilepsy may involve the recruitment of the normal physiological memory processes to form epileptic circuits.

Memory extinction therapies have shown promise for disorders like PTSD, in which traumatic memories are specifically reactivated and their subsequent reconsolidation is blocked (Roullet et al., 2021). Specifically, the neuronal activity is replayed but instead of strengthening, involved synapses are weakened. Thus, the use of targeted memory reactivation to weaken the neuronal circuitry associated with memories or stimuli triggering reflex seizures could lead to a decrease in the ictal episodes (Falip et al., 2018;

Trenite et al., 2019). Similarly, administrating memory reconsolidation blockers after a spontaneous seizure may weaken epileptic networks. We propose that memory extinction treatments should be explored in animal models of epilepsy as it could offer a promising avenue for helping epileptic patients, especially considering that non-invasive extinctions therapies have been proved to be safe in humans.

Chapter 3: Materials and methods

3.1 Subjects

This study included six male C57BL/6J mice, imported from Jackson Laboratories (Bar Harbor) at around 6 months of age, as well as two female C57BL/6J mice (from in-house breeding colony). The female mice were part of a pilot study and were approximately 6 months old at the time of surgery, where they were electrically kindled for 40 days. They were studied alongside the male mice a year later to test the safety of the rapamycin drug.

The animals (n= 8) were divided into 3 groups, the light auditory tone conditioned (LAC) or experimental group (n=4), the unconditioned (UC) or control group (n=2) and the pilot conditioned (PC) group (n=2).

3.2 Surgery

Bipolar electrodes were implanted bilaterally in the basolateral amygdalar nucleus, and a unipolar electrode inserted into the dorsal hippocampus. Ground electrodes were placed on the cerebellar surface. The amygdalar nuclei are located at coordinates 1.3 mm posterior to bregma, 3.2 mm lateral to the midline, and 4.6 mm ventral to the skull (Paxinos & Franklin, 2019). Meanwhile, the hippocampus can be found at coordinates 2.3 mm posterior to bregma, 1.5 mm lateral to the midline, and 1.3 mm ventral to the skull (Paxinos & Franklin, 2019).

3.3 Habituation

Mice in all three groups were habituated to the same recording cage for a time- period of 10 days after allowing a post-surgical recovery time of at least 7 days.

3.4 Kindling and Cue pairing

Post habituation, one of the amygdalar electrodes will be electrically 'kindled' and paired with an auditory tone and light flash (generated by 2 LED bulbs). This cue pairing will be maintained from day 1 of electrical kindling in the LAC group (n = 4). In the UC cohort (n = 2) the mice will only be exposed to the kindling stimulus, while in the PC group the animals like in LAC group, were exposed to the paired association of the kindling, light LED flash and auditory tone.

Kindling is an experimental technique of evoking seizures by presentation of sub-threshold convulsive stimuli at regular intervals (Goddard, 1967, 1983; Goddard et al., 1969; Teskey, 2020). This leads to a progressive and predictable increase in the intensity of seizures, as measured both behaviorally and electrophysiologically. The stimulation can be chemical (de Deyn et al., 1992), electrical (Goddard et al., 1969), physiological (Dutra Moraes et al., 2000; Parra et al., 2003) and recently optogenetic in nature (Cela et al., 2019).

For our experiments electrical stimulations were employed as we needed seizures to occur only with stimulus presentation in a predictable fashion. For the electrical kindling a 60 Hz stimulus train of biphasic pulses was programmed using a Master 8 Pulse Stimulator. The Master 8 produces a constant voltage stimulus, which is then converted to a constant current via a Stimulus isolator unit, A-385 (from World Precision Instruments).

3.5 Recording

The two parameters we are using in our experiments as measure of seizure are videographic and electrographic behavior. For electrophysiology, the stimulating electrode in the amygdala (which can be tuned into recording mode by a mechanical switch), the contralateral amygdalar electrode and a hippocampal electrode are used. All the electrodes are referenced to the cerebellar ground electrode. In addition, as the amygdalar electrodes are bipolar, one of the tips is used for referencing. The electrographic data received from the animal is fed into a unitary gain preamplifier which helps to reference the electrodes and feed the signal into an analog amplifier (Grass Technologies 7P122G Low Level D.C. Amplifier). The signal is then digitized through Axon Digidata 1550A Low-Noise Digitizer and displayed onto the recording computer using Axoscope software.

The video data is acquired through a Raspberry Pi 5 MP (mega-pixel) Camera connected to Raspberry Pi 3 Model B. The Raspberry Pi serves several purposes, the first of which has already been stated. It especially plays a key role in generating the three simulations: generates a pure auditory tone around 10 KHz, sends an electrical signal to light up the LEDs and provides an input to trigger the Master 8 stimulator. The final function that the Pi serves is to synchronize the video data with the electrophysiological signal. This is essential because both clocks, namely in the computer recording brain signals and Pi receiving the video file depicting the animal's behavior. So, to make the Raspberry Pi do all these functions, a Python code was written to fire signals to the digitizer connected to the electrophysiology computer whenever a frame is captured by the Pi camera. Similar

time stamps are sent to the digitizer when the auditory tone, LED flash and electrical kindling stimulus are set off.

3.6 Experimental design

The experiment is divided into three phases. In the first phase, a mouse model for reflex epilepsy is established. The second phase investigates the impact of cues on eliciting seizures through reduced current intensity. In the final phase, the study explores the effect of intraperitoneal injection of the drug rapamycin on elicited seizures and evaluates whether pairing cues enhances the drug's impact.

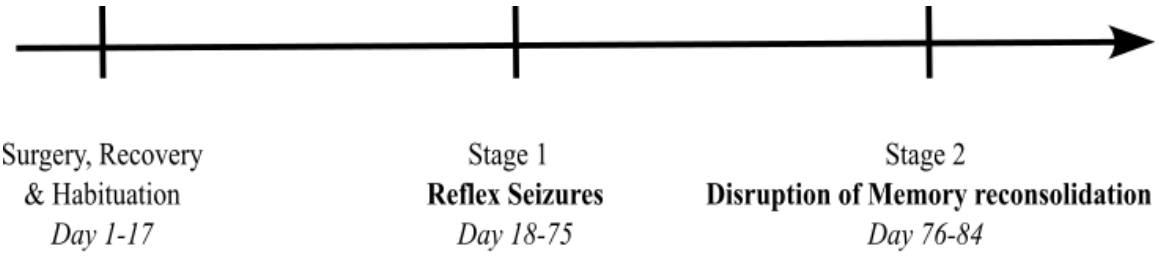


Figure 1: A summary of the timeline of the experiment. The details of the experimental design of each stage will be explained in the subsequent section. Please note that each of the three animal groups (LAC, UC, and PC) will experience all three stages in a sequential manner.

3.6.1 Experiment Stage 1

After about fourteen days of cue pairing (LED light flash and auditory tone) with kindling stimulus in the LAC cohort, the mice will be exposed to the cues alone to test their behavioral reaction. The UC mice will also be exposed to the cues (after exposure to kindling alone during the training sessions) to test their reaction and check for specificity of the response triggered in LAC group. The rationale behind this is to determine whether the cue association formed during the training sessions got incorporated into the brain networks associated with seizures. The evoking of seizures by the cues is not

enough evidence that associating cues with the kindling stimulus has led to a model of reflex seizures. To provide evidence, it is pertinent that the cue presentation do not trigger seizures in control animals (UC group), who have not previously had cue-association with seizures. This is the reasoning behind presentation of cues to the UC animals and comparing their response to the LAC group. It is also important to emphasize that kindling is an experimental technique in which the intensity of the evoked seizures gradually increases. The epileptic circuit inside the brain could be incomplete (the entire motor cortex might not be influenced) and not strengthened (due to lack of enough repetitions). To account for that multiple test sessions were conducted after adequate number of trainings were performed. We have no less than two test sessions in our study design with each of them preceded by sufficient number of training periods.

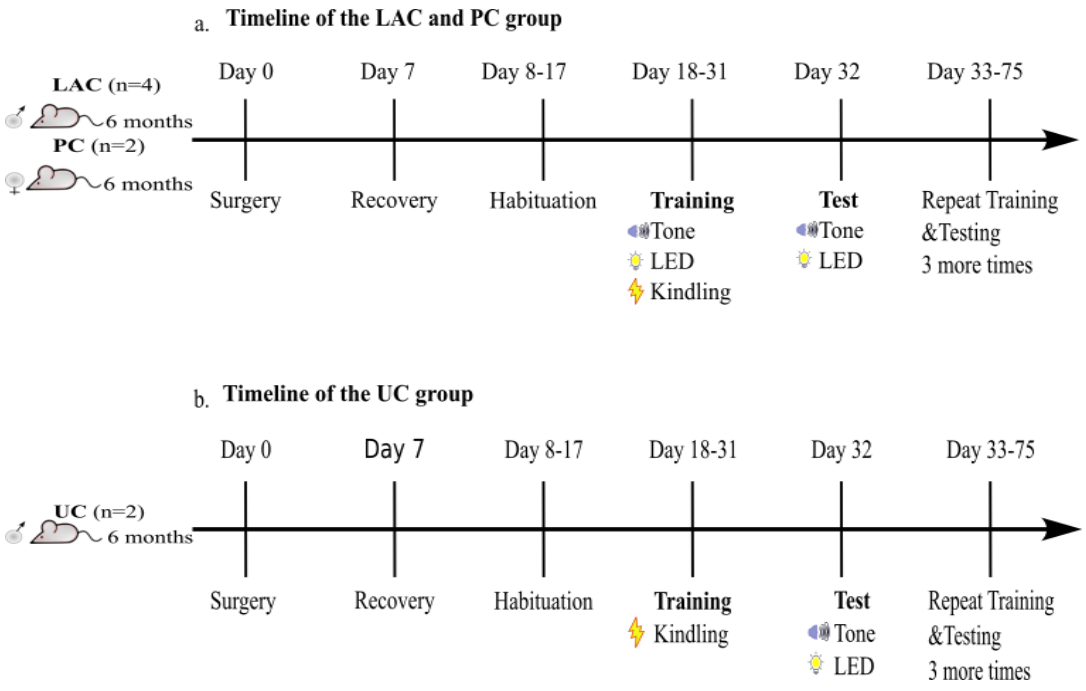


Figure 2: Timeline of the experiment stage 1. The figure panel shows the timeline for the first part of the experiment for the two groups of animals. This comprises of the training session to kindle seizures and associate them with tone and LED flash in the experimental (*LAC) group in figure 1a. After training, the strength of association and the probable

triggering of seizures by the cues alone was evaluated every tenth day (test). In the control group (*UC group), the training days comprised of kindling seizures alone, with presentation of cues to check for specificity of the association in the LAC (experimental) cohort.

3.6.2 Experiment Stage 2

After completing stage 1 of the experiment, we evaluate if the association of cues with the kindling stimulus results in lowering the threshold at which we can evoke seizures. In our LAC group, we continue pairing the kindling stimulus with light and tone but decreasing the amplitude of current (for kindling) by ten percent (of the original level) daily. For our UC group, we present the kindling stimulus alone (as earlier) but like in the LAC cohort the current amplitude is decreased by the same amount. Once the threshold is reached at which seizures are no longer evoked in both groups, the values (for LAC and UC cohort) are compared to observe if associating cues with seizures helps to 'strengthen' the epileptic circuit. If seizures are evoked at a lower threshold (e.g., @ ten percent of original current strength in the LAC animals versus twenty per cent in UC animals) in the LAC group, there would seem to be a role of pairing cues with kindling in augmenting seizures.

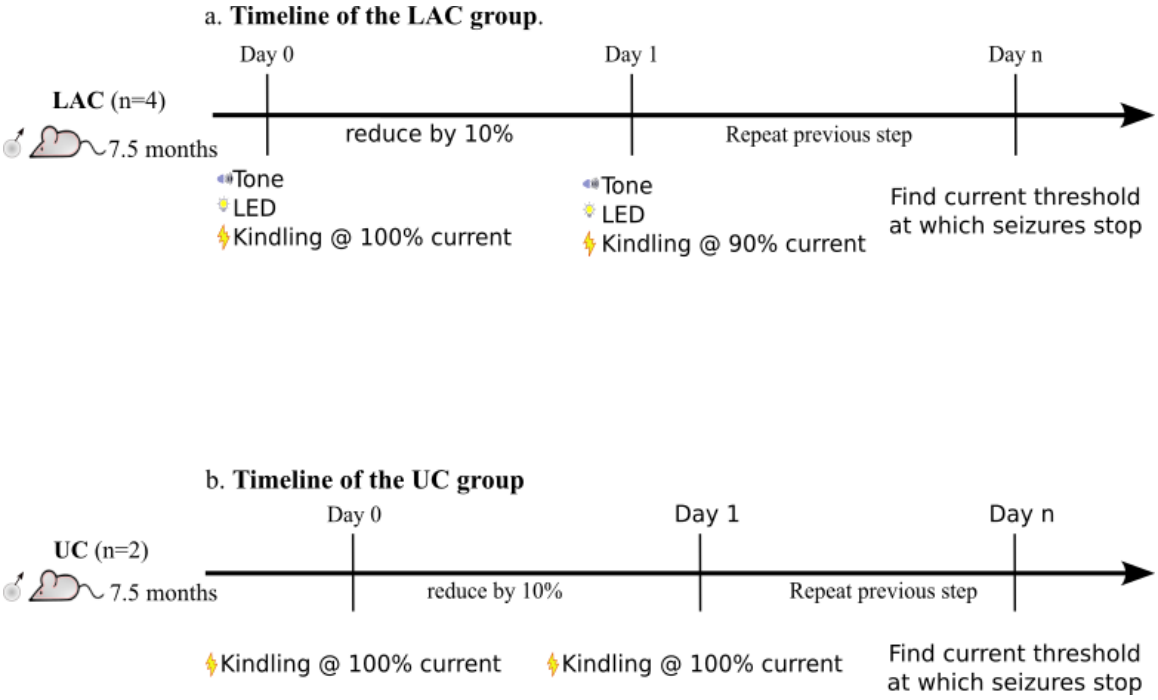


Figure 3: Timeline of the experiment stage 2. This figure panel depicts the experimental design and timeline for our two groups of animals, LAC group (2a) and UC group (2b). In the LAC group the animals are given the same exposure as before, cues (auditory tone and LED flash) paired with the electrical kindling. In addition, the kindling stimulus's current amplitude is reduced by ten percent (of the original level) daily till we reach a (current) threshold at which seizures can no longer be evoked. Similarly, in the UC group the animals are exposed only to the kindling stimulus (as before), but the current amplitude is decreased by ten percent (as in the LAC cohort) till no seizures are evoked.

3.6.3 Experiment Stage 3

Injecting rapamycin (protein synthesis blocking drug) after exposure to conditional fear stimuli blocked traumatic memory reconsolidation and decreased the emotional strength of an established traumatic memory (Blundell et al., 2008; MacCallum & Blundell, 2020). Based on this experimental data, the animals with epilepsy (n = 7; LAC = 3, UC = 2 and PC = 2) were briefly exposed to the place and/or stimuli to which they were previously conditioned. Kindly note that one of the LAC animals was excluded from this stage of the experiments due to failure of the recording and stimulating electrodes.

They were then given an intraperitoneal injection of rapamycin immediately following the exposure. All the animals were injected with the drug and there were no sham doses. The motivation behind not having any controls for the drug was the following. This part of the experiment was majorly explorative in nature, and we wanted to investigate if the auditory and LED cues affected the drug efficacy. Another reason for this undertaking was to establish the safety of the drugs. We followed the same protocol as described in the reference for the fear conditioning experiments, using the same drug calculator that was provided to us by the experimentalists. The drugs were administered systemically (intraperitoneally) at a dosage of 40 mg/kg and an injection volume of 10 ml/kg. This comes out to be around .25 ml to .4ml per injection day for our animals. As we were administering the drug for about four days unlike the fear conditioning studies (single dose or followed by repeat shot) and observing the long-lasting effect of the drug on seizures, only the pilot animals were initially tested upon to test for safety. Following the first dose, daily they were weighed, their fur assessed, amount of stool pellets and urine spots observed for possible signs of distress in the animals. After a few days of testing the pilot animals, two more animals from the LAC group were administered rapamycin. The long-term outcome of the drug was observed in the four animals (LAC = 2, PC = 2) for a month, including both the effect on evoked seizures and any adverse consequences. Following this, rest of the animals (LAC = 1, UC =2) were tested in a similar way. The UC animals were administered rapamycin after the seizures were evoked in the recording cage in the absence of auditory and light cues (as before). The remaining LAC animal was injected with the drug following seizure precipitation associated with the cues (as previously). The summary of this stage of the experiments are summarized in figure 3.

The one remaining animal was not given any drug therapy as the implant (which helps to connect the animal to the stimulator and amplifier) had become unviable. With no way to record the electrophysiology signal or evoke seizures anymore, this animal was excluded from this stage of the experiment.

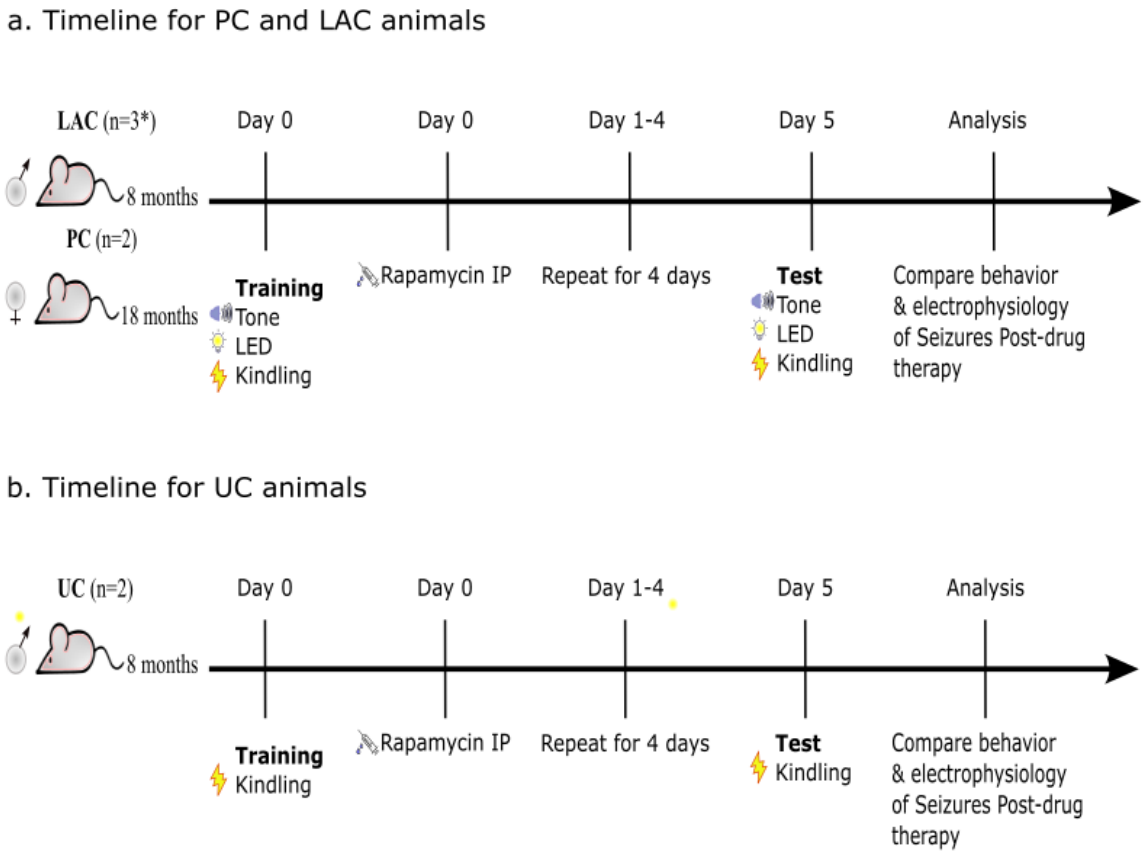


Figure 4: Timeline of the experiment stage 3. Timeline for the drug injections in our three groups of animals (i. pilot conditioned PC group; ii. Light auditory conditioned, LAC group; and iii. un-conditioned cue, UC group). Figure panel 3a illustrates the experimental design for drug injection for the PC and LAC group, while 3b shows the same for the control group. The analysis is to compare two affects using behavioral seizures (Racine stages) and duration of electrographic as the measurement parameters i.) between the groups (the PC, LAC, and UC group) and ii.) within groups over days.

* One of the LAC animals was excluded from this stage of the experiments due to failure of the recording and stimulating electrodes.

3.7 Analysis

3.7.1 Local Field potential Analysis - Visualization

For visualization we are going to employ continuous wavelet transform (CWT). Before going into the steps of how this technique was employed for our analysis, let me explain what wavelets and the advantages it has over Fourier analysis.

Mathematically, a wavelet is a small wave-like oscillation with a finite duration and in many cases, it has a mean value of zero. First, we create a single waveform, sometimes referred to as a mother wavelet, which can be dilated and contracted to formulate an assembly of wavelets, which can then be used to represent a time varying data. This representation is possible because these wavelets can portray the various frequencies in the time series data. The resulting combination of the wavelets can then replicate the data precisely. An analogy of how this process works is to consider a band where the bass player is the mother wavelet while the lead guitar, violin and the other instruments be considered as the set of wavelets. Their synchrony leads to the production of the musical piece being played out.

Fourier transform is one of the more popular techniques for analyzing the frequency content of temporal data structures. The time series data is converted into frequency domain by representing it as a sum of sinusoidals with different frequencies. This is possible by a mathematical function called convolution. Convolution is the process of taking the dot product of two vectors of unequal lengths, with the smaller vector sliding along the longer one and computing the dot product at each step.

Wavelet analysis is also based upon convolution but there are certain advantages of using this technique to visualize and quantify results when compared to Fourier analysis. Firstly, although it is possible with Fourier analysis (short time Fourier transform) to decompose the time series local field potentials brain signal into time series frequency plot, the results are contaminated with edge artifacts. Secondly, wavelets utilize constant relative bandwidth analysis which uses short windows for high frequency and longer windows for lower frequencies resulting in a smoother data representation with less noise contamination.

For our analysis we use complex valued wavelets, namely Morse wavelets, to perform continuous wavelet transform.

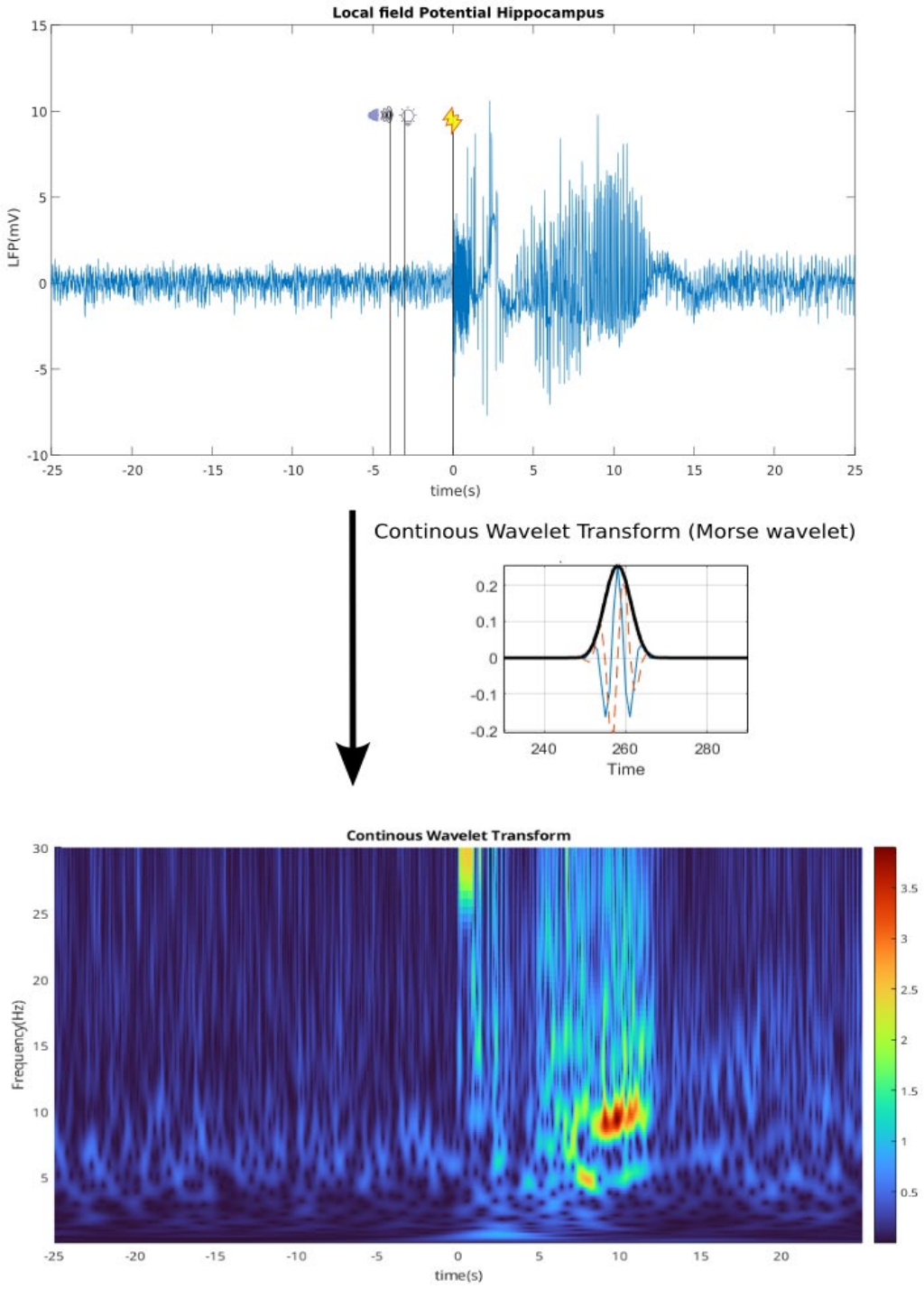


Figure 5. Continuous wavelet transform. Data points around the stimuli are extracted and then convolved with Morse wavelets to visualize the effect of stimuli and the qualitative representation of seizures. The CWT analysis shows transition of the power of the LFP (in the raw signal) to higher frequencies.

3.7.2 Local field potential - Quantifying the duration and amplitude of evoked seizures.

When attempting to measure the severity of seizures or detect their occurrence, two crucial factors to consider are the amplitude of the electrical activity associated with seizures, and the duration of this abnormal signal. Our analysis tries to figure out a suitable threshold of the local field potentials recorded from the vicinity of the regions where the seizure activity is evoked by kindling and the brain areas where it propagates. To begin, we carefully select relevant brain signals during the recording session to establish a baseline measure of the electrical activity. This baseline measurement is taken within a time frame ranging from 30 to 90 seconds after the start of the session. As seizures are characterized by a heightened amplitude of local field potentials, we use a threshold of 4.5 standard deviations above the electrical potential recorded during the baseline period to detect seizure activity. Once the kindling stimulus is presented, any electrical activity exceeding the established threshold is identified as an electrographic seizure. The duration of the seizure is determined by measuring the time elapsed from the delivery of the stimulus to the point at which the local field potentials return to below the threshold level. After determining the duration of the seizure, we calculate the average voltage of the electrical activity during this period and normalize it to the baseline activity to quantify the amplitude of the evoked seizures. This normalization step is crucial for making meaningful comparisons of the local field potentials between different animals.

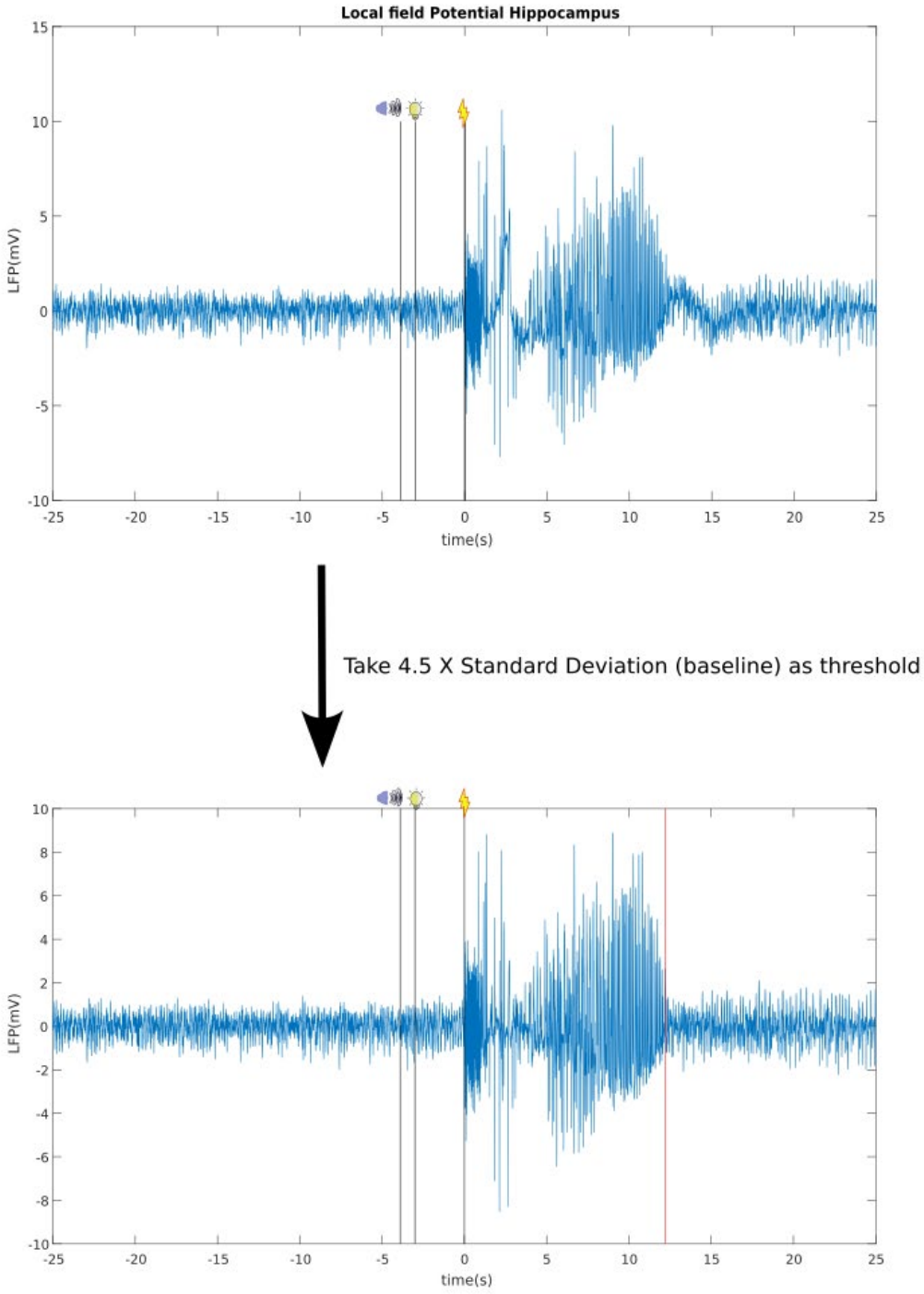


Figure 6: Duration of seizures. Using 4.5 standard deviations from the baseline, a threshold value was measured which was used to mark the end of seizures.

3.8 Video analysis

For the video analysis, we start with video data time synchronized with the electrophysiology data and the timings of the stimuli presentation. This synchronization was achieved by using a Raspberry Pi, which sent a pulse to the digitizer connected to the computer capturing electrophysiology signal each time a frame was captured by a Raspberry Pi camera. Similar pulses, corresponding to auditory, light flash and electrical stimulation (for kindling) were sent to the same digitizer. The accuracy of our code for time synchronization was (to be calculated). Frames, twenty seconds prior and after delivery of the sensory stimulation were extracted, followed by preprocessing to convert each frame from RGB to grayscale and finally applying a reliable threshold to highlight the mouse in each frame. To evaluate the movement, a frame-differencing technique was applied which built a mask to track the mouse across frames.

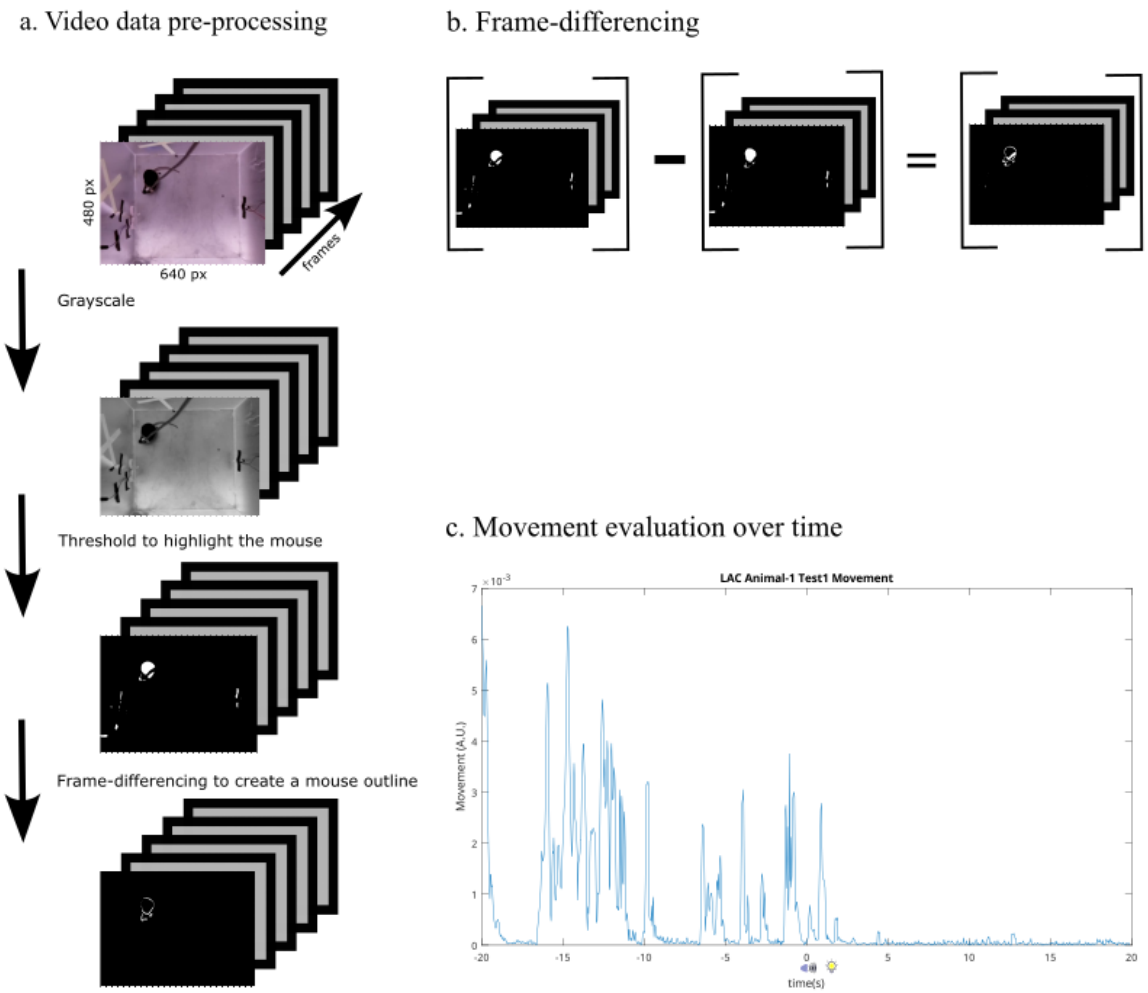


Figure 7: Video analysis. In 7a. the pre-processing steps for video analysis is illustrated. The frames 20 seconds before and after stimulation were extracted. Each of the extracted frames is in color (RGB) with a resolution of 640 pixels (width) and 480 pixels (height). The RGB frames were then grayscale, followed by taking an appropriate threshold to focus on the mice. Finally frame-differencing (explained in the next figure) was done to create a mask around the mouse which is used to trace the movement over frames. In 7b frame-differencing using the diff MATLAB function, matrix differencing between thresholded frames (every 5th frame) was performed which was able to approximate the movement of the mouse across time. This 'movement' was evaluated and compared before and after the presentation of stimuli. Figure 7c displays movement of the mouse during the test session over time. This represents the speed of the mouse as it moves around in the recording cage.

Chapter 4: Results

4.1 Kindling led to advanced seizures in all animals.

The animals were exposed to electrical stimulation to evoke seizures paired with sensory stimulation (LED flash and pure auditory tone in LAC animals and only kindling stimulation in UC group). As shown in the figure below (figure 8), the three vertical bars represent the timestamps of the stimulation in an experimental (LAC group) animal. In contrast, the UC cohort received only the kindling stimulation represented by a single vertical bar consisting of a 60 Hz train of bipolar pulses lasting one second, one millisecond in duration with an interpulse interval of one millisecond. In the LAC group, the stimulation protocol begins with the presentation of a pure auditory tone, followed one second later by a LED flash, finally terminating with the kindling stimulation (as in the UC group). The animals belonging to both LAC and UC group were kindled once daily starting with a current amplitude of 50 microamperes and then increased by the same amount everyday till seizures (at least electrographic seizures of 5 seconds duration termed afterdischarges) are evoked. Upon reaching this threshold, all animals received this amplitude of current stimuli once daily.

We use the traditional Racine scale (Racine, 1972) to recognize the behavioral seizures till stage 5 and the modified Racine scale (Lüttjohann et al., 2009; van Erum et al., 2019) to score stages 6 and beyond. The animal's progression of behavioral seizures, observed daily as it advanced through Racine stages, was also evident during a stimulation session when the animal had reached advanced seizure stages. This is shown in the sequential frames during a training session for both LAC (figure 8) and UC animals after they had progressed to advanced seizures. The next figure panels (figure 8b) display the timeline

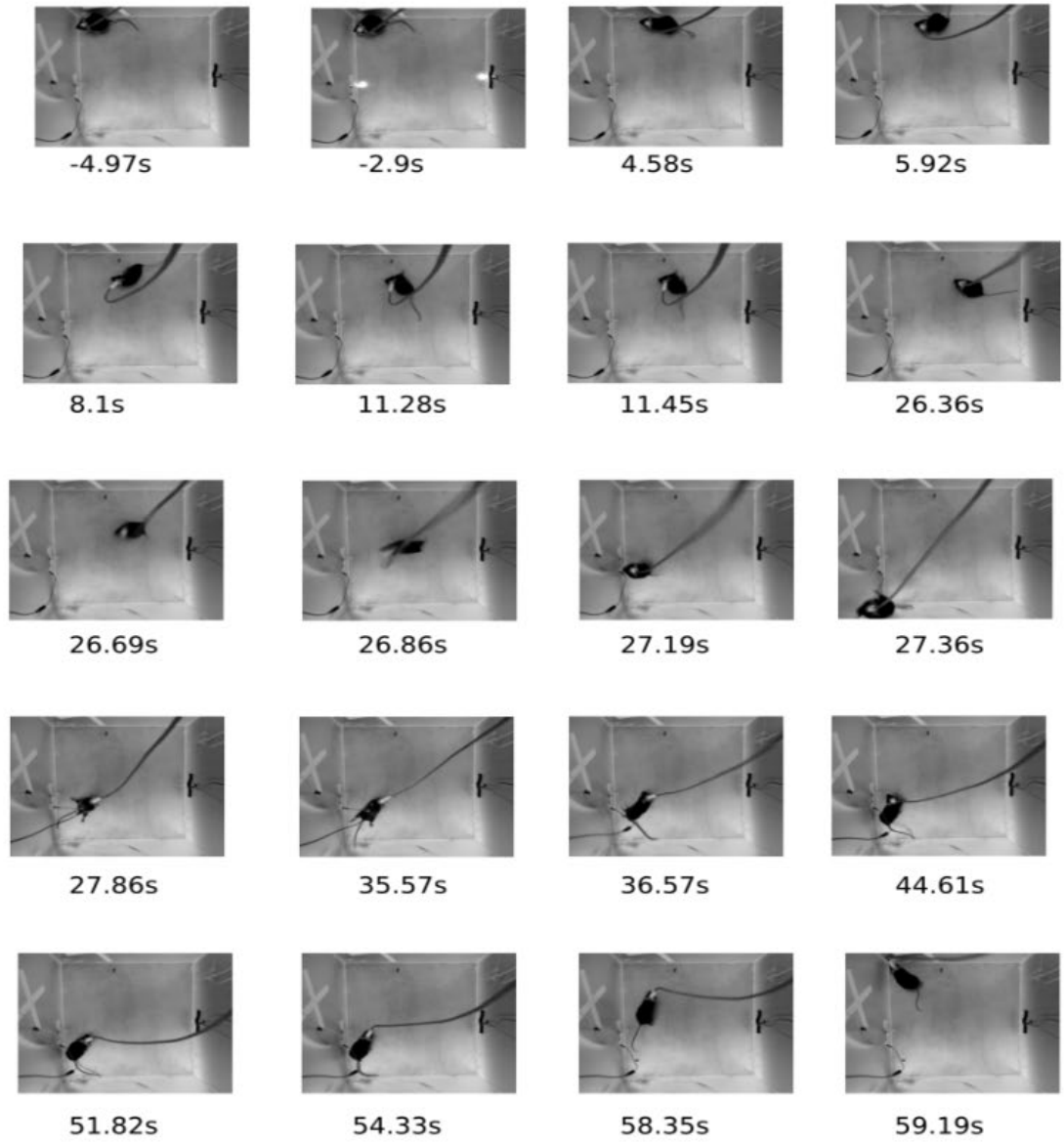
for the specific session in both the animals, five seconds prior to the stimulations till the time period when they recover from the convulsions and start moving in the recording cage. In figure 8 we observe frames corresponding to the training session of a LAC animal, during which it progresses through the various Racine stages of behavioral seizures. The first frame shows the baseline behavior of the mouse, sitting in a corner of the cage. The second frame observed around three seconds before the kindling stimulus is delivered, we observe a light flash generated by the LED lights. At around five seconds (labelled 4.58 seconds in figure 9) we can see the convulsions spread over the trunk region (stages 1 to 3), evidenced by the straightening of the dorsal body of the mouse, accompanied by the tail pointing up (due to uncontrolled clonus of the sacrococcygeal muscle). The LAC animal progresses to stage 5, loosing balance and falling to one side experiencing clonic to tonic contractions in the upper limb and notably clonic movements in the lower limbs in frames labelled 8.1 to 11.28 seconds. At 11.45 seconds, all the animal's four limbs go into a tonic phase, with animal attempting to sit up but then progressing into stage 6 characterized by wild jumping with clonic-tonic-clonic seizures (frames 26.69 to 27.19 seconds). The animal tries to regain balance by clutching the wires connecting the LED light (on the left side of the cage – frames 27.86 to 35.57 seconds). Finally, the seizures end, and the animal lies motionless (frame 36.57 seconds) on the side, regaining balance (51.82 seconds) and then lying still (54.33 seconds). In the last frame (frame – 58.35 seconds), the animal starts moving around in the cage. We observed a similar progression of seizures in one of our UC animals, characterized by initial convulsions that spread to the trunk, followed by sacrococcygeal clonic-tonic contractions and forelimb clonus (Racine stage 3), progressing to rearing (Racine stage

4). The seizures advanced to a loss of balance and falling to one side (Racine stage 5), culminating in wild jumping around within the recording cage (Modified Racine stage 6). Kindly note that the UC cohort of animals are only exposed to the electrical kindling stimulus.

Moving over to the electrographic seizures evoked by the electrical kindling, we have figure 9 representing the brain activity recorded in the dorsal hippocampus (from the hemisphere ipsilateral to the stimulating amygdalar electrodes) in the LAC and UC animal respectively. The electrographic activity corresponds to the session mentioned previously where we discussed the behavioral seizures in the same LAC and UC animals. The top figure panels in both figures 9a and 9b show the raw electrical activity recorded from the hippocampi from the LAC and UC animals respectively, 25 seconds before and after the presentation of the stimuli. We can observe the presentation of the auditory tone and LED flash (labelled with vertical bars and icons) just before the kindling stimulation (at time = 0 s) in the LAC animal in figure 8b. In the subsequent figures 9a and 9b, we depict the time frequency analysis of the electrophysiological signal from the respective animals. There are two features in the electrical brain activity that are associated with seizures, namely increase in amplitude of signal and transition to higher frequencies. These two features are observed in our data as well, visually both plots (figures 9a and 9b) display an increase in the amplitude of electrical potentials (the local field potentials in both animals) some seconds after the kindling stimulus is presented. The time frequency representation of the local field potentials (figures 9a and 9b) unveils a shift from the baseline brain oscillations (5-10 Hz) to higher frequencies with an increase in the amplitude.

The animals (both LAC and UC group) displayed an increase in the duration of afterdischarges (evoked electrographic seizures recorded at the stimulation electrodes as in seen figure 8A-B). We quantified this duration by using the technique described in the analysis section 3.7.2. This finding is supported by a two-way Anova (figure 10A-B) study of afterdischarge duration in both groups over days, resulting in a p-value of 5.59e-06 over the first seventeen days of stimulation. The Anova did not reveal any difference in the afterdischarge duration between the groups as evidenced by a p-value of 0.624 and neither a difference between groups across days (p-value = 0.502). These results imply that there is progressive increase in the duration of afterdischarges as the kindling stimulus is presented over days. But a lack of statistical difference in the duration of seizures between LAC and UC animals signal that auditory and visual cue may not play a role in facilitating epileptogenic activity in the brain using our experimental design. In the following section, we investigate whether the cues can induce seizures and the potential impact on the animal's behavior and local field potentials as a result of associating them with the kindling stimulus.

a. Video frames illustrating behavioral seizuresin LAC animal



b. Timeline for the training session for LAC animal

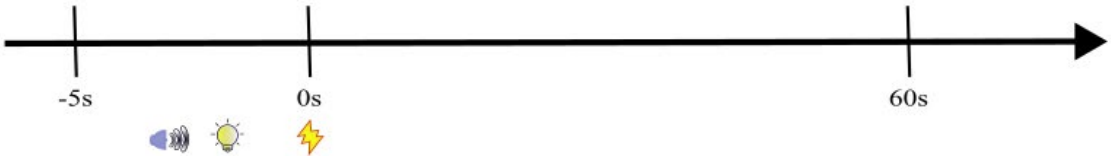
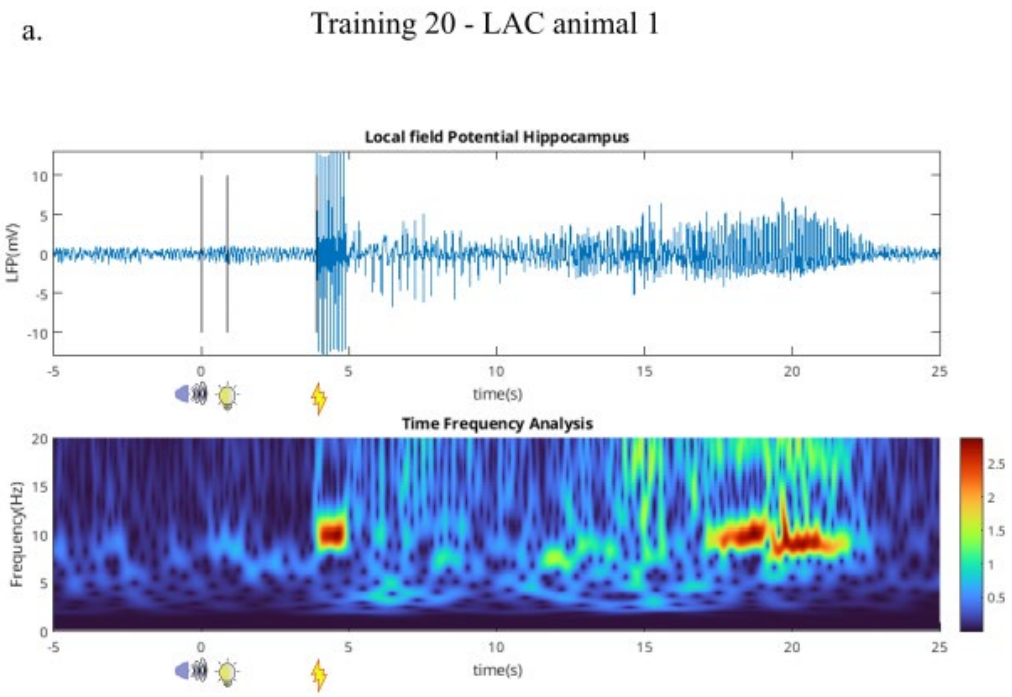


Figure 8: Behavioral seizures in LAC animals. This figure illustrates serial behavioral changes observed in a LAC animal during a training period. Figure panel 8b displays the timeline for a single experimental training session. The timeline shows frames taken 5

seconds before and 60 seconds after the presentation of stimuli. The frame at -4.97 seconds shows the animal resting, followed by the LED flash 3 seconds before the animal experiences an electrical stimulation-induced seizure. The frame at 4.58 seconds shows the animal's trunk muscles contracting, causing the body to flatten. At 5.92 seconds, the tail experiences dorsiflexion due to contraction of the sacro-coccygeal muscle. This is followed by clonic and then tonic contraction of the forelimbs. At 11.28 and 11.45 seconds, the hind limbs exhibit clonic contraction, causing the animal to lose balance (Racine Stage 5). The animal then wildly jumps (Stage 6) in the cage from 26.36 to 27.36 seconds, ending with the animal grasping the wires connected to the LED and falling to its side at 36.57 seconds. The animal begins to recover at 44.61 seconds but remains at rest until it starts moving again at 58.35 and 59.19 seconds.

a.



b.

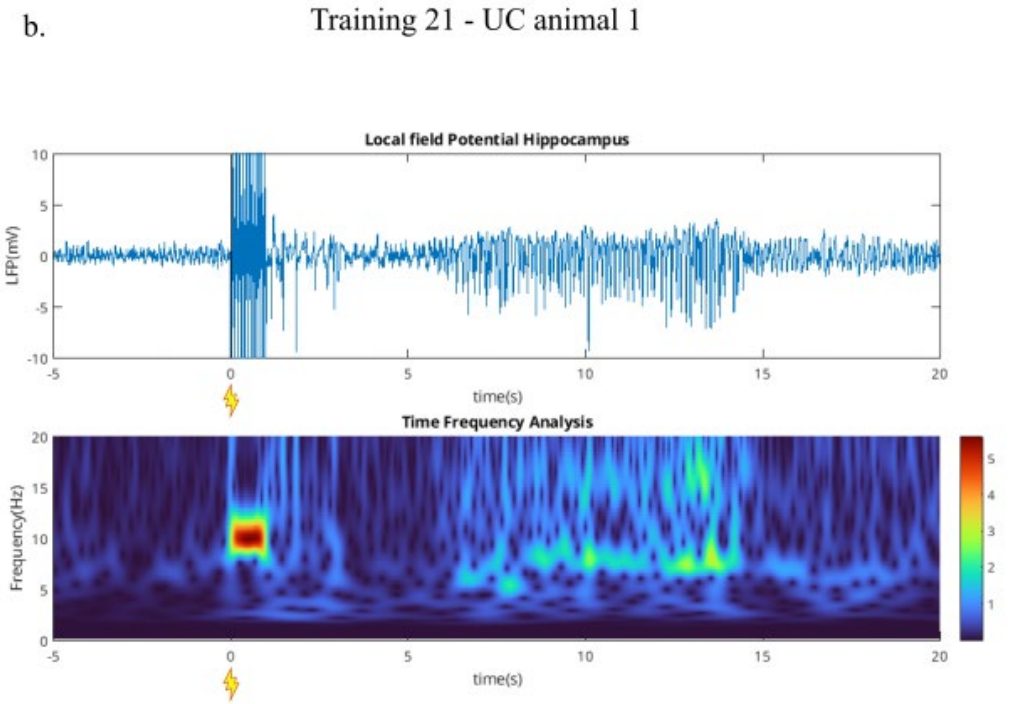


Figure 9: LFP analysis using continuous wavelet transform for LAC and UC animal. The top panel of 9a shows the local field potential recorded from the hippocampus in one of the LAC animals. The bottom panel of 10a shows a time frequency analysis using a continuous wavelet transform using a Morse wavelet. Similarly, the top panel of 9b

shows the local field potential recorded from the hippocampus in one of the UC animals from a training session and the bottom panel of 10b shows a time frequency analysis. In both 9a and 9b, we observe a transition to high frequency and high amplitude oscillations in the local field potentials. The shift to an increase in the power of higher frequency bands is displayed in the time frequency analysis graphs for both the LAC and UC animals.

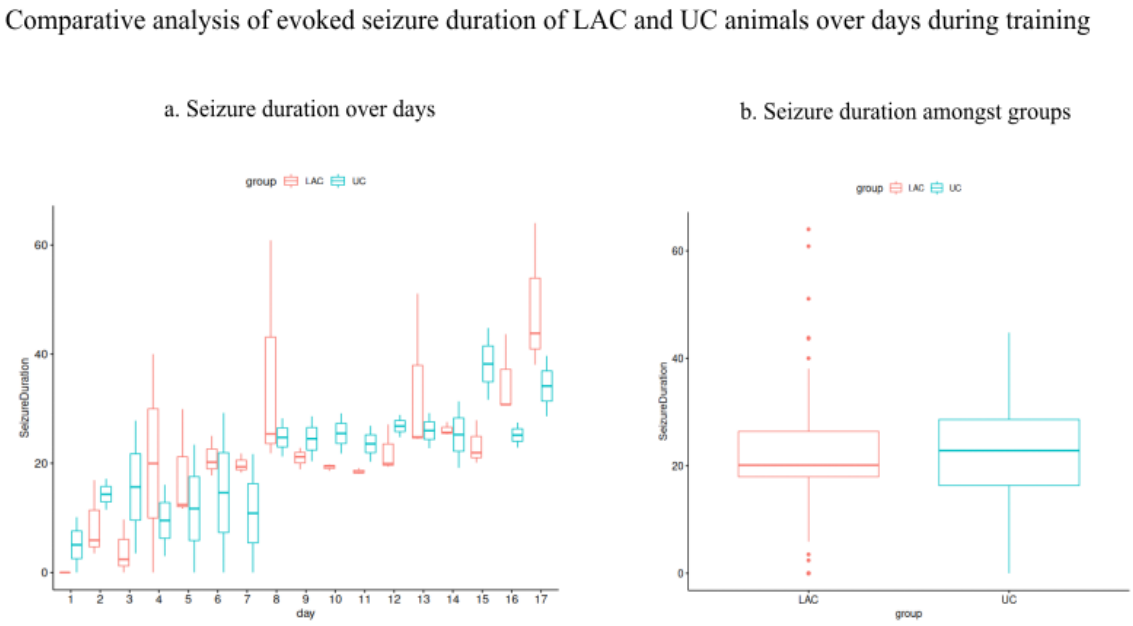


Figure 10: A. Plot shows effect within groups (group 1 = LAC and group 2 = UC) over days. The two-way Anova shows a significant difference in the evoked afterdischarge duration over days in both the group with a p-value of 5.59e-06 ***. Note there is no interaction amongst the independent variables' groups and day (p-value = 0.502).
B. Boxplot showing a comparison between the two groups (group 1 = LAC & group 2 = UC). A two-way Anova shows a p value of 0.624 implying no difference between groups.

4.2 No seizures with presentation of light & sound cues

A crucial aspect of our experiments was to figure out if the auditory and visual cues could trigger seizures on their own without the need for the kindling impulse. As illustrated in Figure 14, we have conducted test sessions on both LAC and UC animals. The top two panels depict the results from a LAC animal, while the bottom two panels display the results from an UC animal. The vertical bars with icons represent the presentation of auditory and visual cues in the absence of the kindling stimulus during these test sessions. In order to accurately assess the occurrence of seizures, we employed the same parameters utilized in our previous results section. These included analyzing the video frames for behavioral seizures, amplitude of local field potentials following the presentation of stimuli, as well as generating time-frequency graphs to identify electrographic epileptic activity.

Visually, we can observe two distinct features in figure 11 which is in clear distinction to the features observed during evoked seizures using kindling. The local field potentials show a similar pattern both before and after presentation of the auditory and visual cues. There is no increase in amplitude and a lack of high frequency oscillations akin during kindling in the LAC animal. Similarly, the time-frequency graphs constructed using continuous wavelet transform, display a lack thereof transition to higher frequency bands upon presentation with the cues alone.

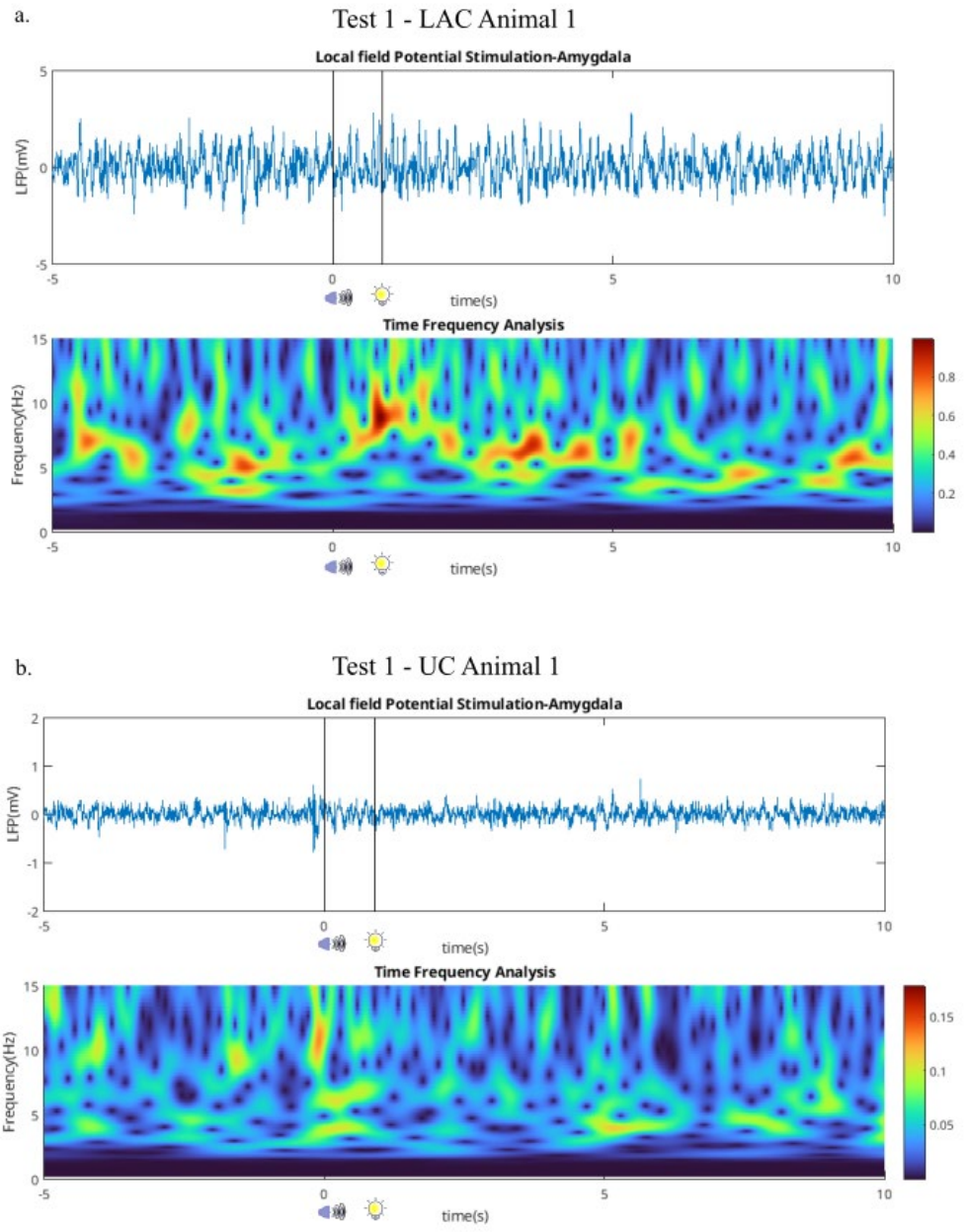


Figure 11. No seizures were triggered by the presentation of auditory and light cues in both the LAC and the UC group as depicted in the recordings from the stimulation electrodes in the amygdala. The two vertical bars show the auditory and the light cues, depicting the presentation of the physiological stimuli alone. There are no seizures elicited as demonstrated by the absence of high amplitude and high frequency transition in the local field potential and no change in the time-frequency graphs when compared to the training sessions depicted in figure 9.

4.3 Behavioral features akin to 'Fear Conditioning'

The experimental animals displayed reduced mobility and seemed to occupy the same spot in the recording cage for a longer duration following the presentation of compound cues. To quantify this, video data was extracted 20 seconds before and after the cues were administered. The video analysis as mentioned above in the methods section using frame differencing was employed.

I will briefly summarize the steps of the analysis and then discuss the statistics supporting this finding. Using electrophysiology data as a reference, the time stamps for stimulation (auditory tone and light flash) were recorded. Next, video frames corresponding to the recorded time stamps were extracted, covering a time window of twenty seconds before and after the stimulation. Every fifth frame (in RGB format) was selected from this time window and processed - grayscaled and thresholded to focus on the mouse. Consecutive frames were subtracted to form a mask, which represents the movement across time. The movement of the animal was analyzed by comparing the average motion in the twenty second period before and after the stimulus, using the created mask. We conducted a two-way ANOVA to analyze the differences in mean movement between the pre-stimulation and post-stimulation periods amongst LAC and UC groups and across days. The results revealed a significant difference between the UC and LAC groups in terms of movement during the experiment. Specifically, the UC group did not exhibit any significant change in movement, while the LAC group displayed freezing behavior upon presentation of auditory and visual cues. This was supported by an ANOVA test, which yielded a p-value of 0.00377, indicating a statistically significant difference between the groups. The ANOVA analysis also revealed that there was an insignificant difference across days,

with a p-value of 0.0536. Additionally, the interaction between groups and days was also found to be marginally significant, with a p-value of 0.0497. This suggests that the effect of the groups on the movement varied across the days of the experiment, however caution should be exercised when interpreting these findings as the groups were not evenly matched and the sample size was limited. Another noteworthy observation was the brief response exhibited by the UC animals upon being presented with the cues. This may have been attributed to the novelty of the stimulus, given that these animals had not encountered the cues prior to the test sessions. However, in contrast to the LAC animals, the UC animals only displayed a short-term reaction without any sustained freezing response, as seen in the LAC animals.

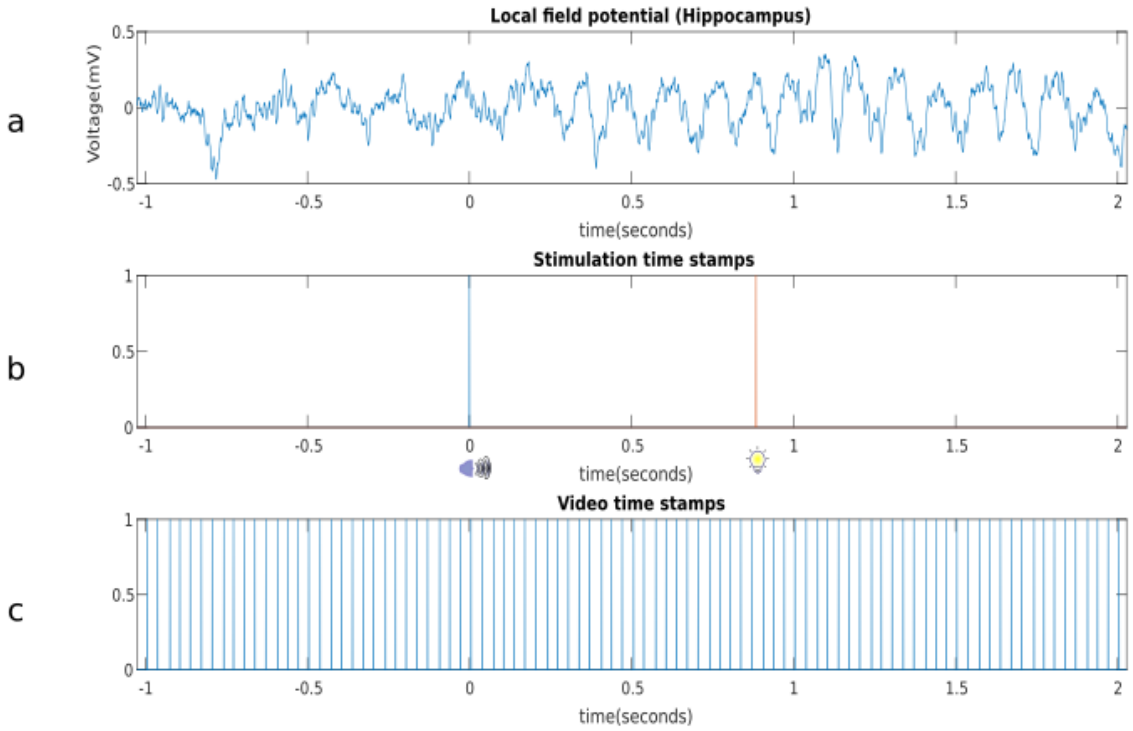


Figure 12. Time synchronization of data. The top panel (a) shows the raw signal recorded from the hippocampus. The middle panel (b) shows the time stamps of the stimulus complex, including an auditory tone and an LED flash, during the test session. The bottom panel (c) displays the video timestamps for each frame captured by the Raspberry Pi camera. All channels are synchronized on the same timeline.

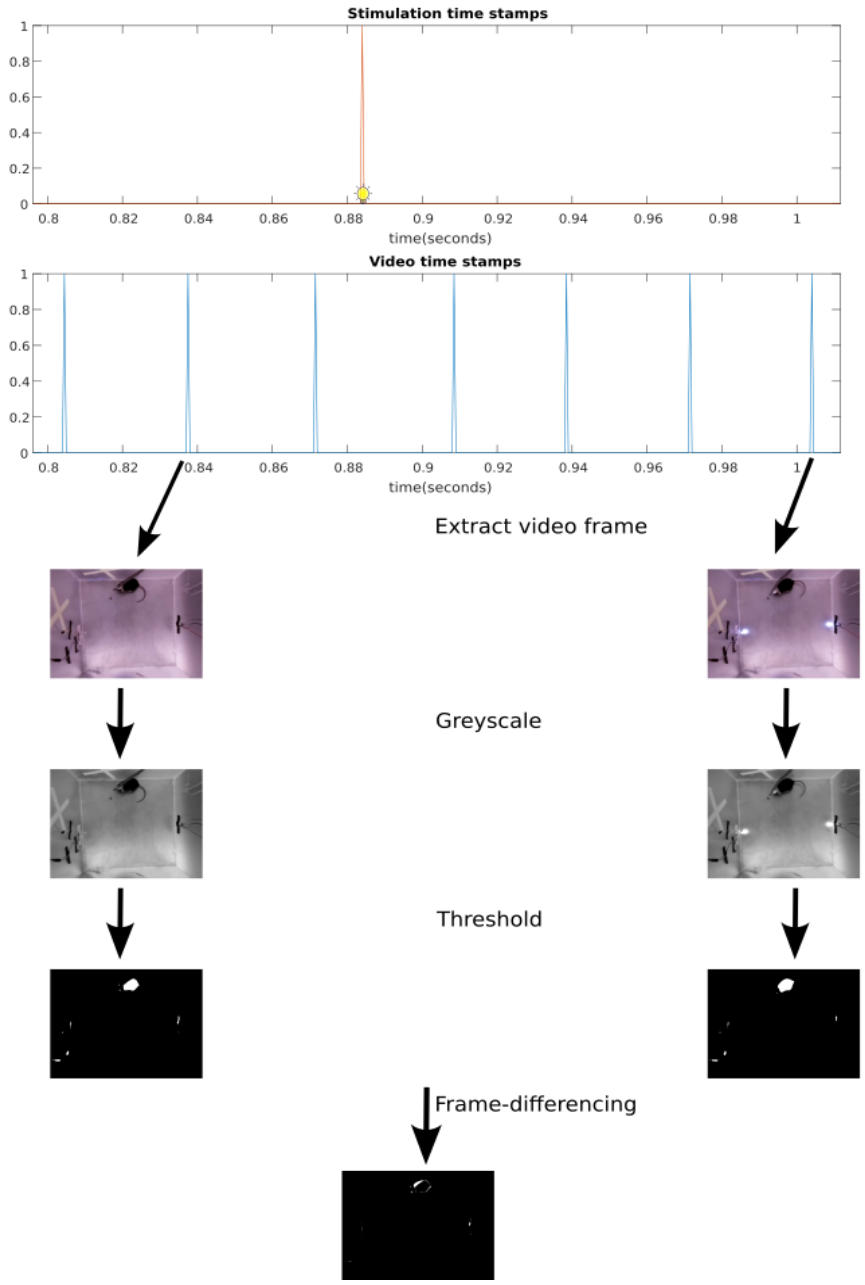


Figure 13. The following figure displays extraction of every fifth frame from the video data using the Axoscope time stamps, followed by image preprocessing. This comprises of first converting the RGB files to greyscale, followed by taking an appropriate threshold to capture the mouse and then perform frame-differencing to track the movement of the mouse.

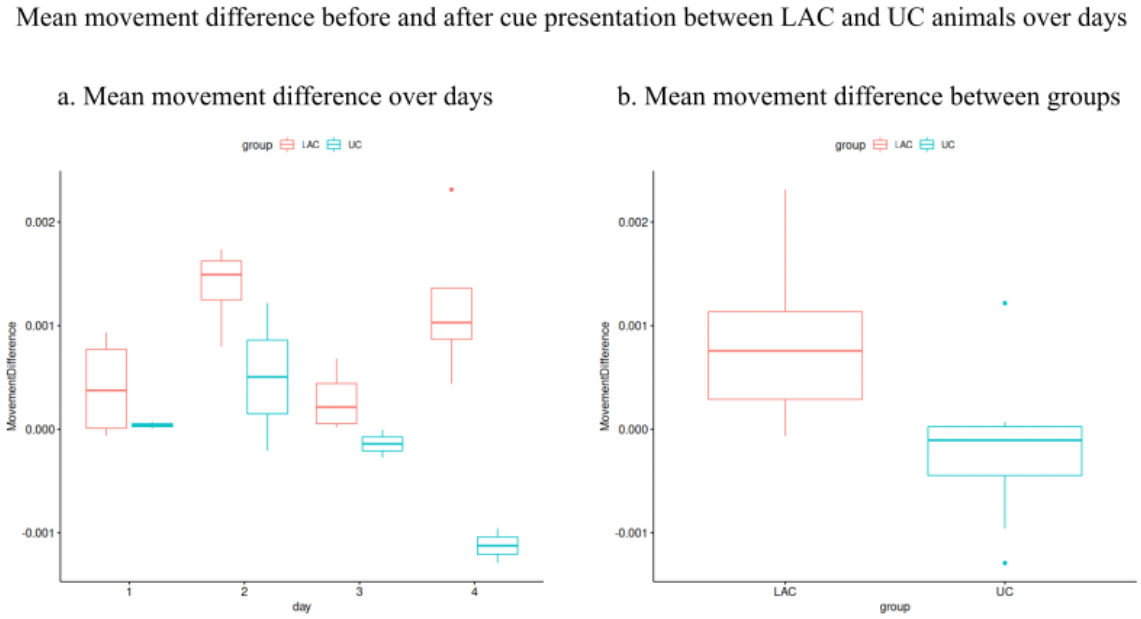


Figure 14: Boxplot showing comparison of mean difference of movement in LAC and UC group over days. On the x-axis we have test session days (test session days = 1 to 4) when the animals (both LAC and UC) were exposed to the light and auditory cues alone after adequate number of training sessions in the intervening period. In both panel 15a & 14b, on the y-axis, we measure the mean movement difference before and after the cue presentation during the test session days. Figure panel 14a demonstrates comparison of mean difference in movement between LAC and UC group across days. Across days (within factor Anova) has a p-value of 0.0536. The boxplots in figure 14b shows a significant difference between the groups as the p-value is 0.00377 **.

4.4 Effect on afterdischarges due to lowering of current amplitude of kindling

The previous stages of the experiment failed to establish a brain circuit by associating the cues with kindling, where the cues themselves could trigger seizures. So, in this section, we examine the impact of auditory and visual cues on reducing the amplitude of kindling stimulus needed to induce seizures. The details of the experimental design for this section are described under materials and methods (Experiment-Stage 2, Figure 3). In summary for both the groups, we decrease daily the kindling current by ten percent of the amplitude at which we were evoking seizures during the training days (as in Stage 1 of the experiment, Figure 2). As before, the LAC group is exposed to the auditory and visual cues before being kindled, while the UC animals are exposed only to the kindling stimulus.

We monitor seizure intensity evoked by daily reduced electrical impulses using the duration of afterdischarges as a metric, as shown in Figure 15. To investigate the impact of cues on seizure intensity, we conduct a two-way ANOVA study comparing the duration of cue-conditioned LAC group with the UC group. The results indicate no significant difference between the groups (p-value 0.73). Our evaluation of the effect of gradually reducing the current amplitude over days also reveals no significant impact, as indicated by a p-value of 0.71.

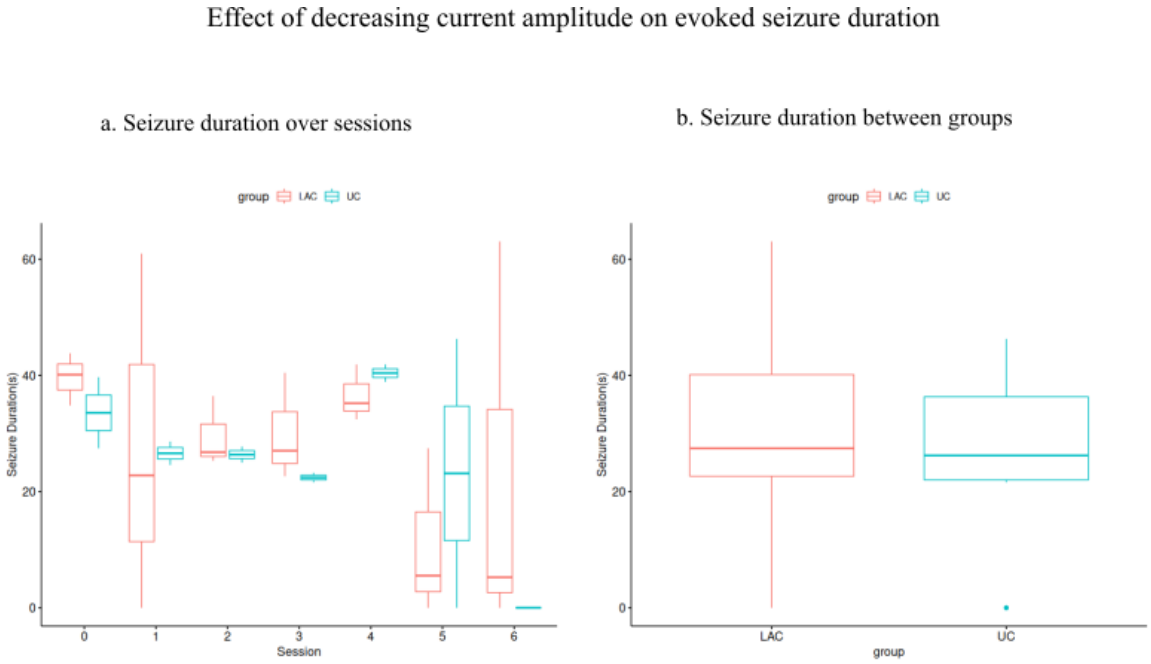


Figure 15: Boxplot showing comparison of seizures evoked in LAC and UC group. The following figure displays the effect of decreasing the amplitude of electric current delivered at the stimulation electrodes. There is no significant difference between the groups over days (15a) nor any significant difference between the groups (15b) as revealed by two-way Anova study.

4.5 Effect of Rapamycin on evoked seizures

Following the reduction of current amplitude to a level where seizures can no longer be triggered, the animals are then stimulated at the original current strength that elicited daily seizures, as in the first experimental stage. The PC group is also added in this experimental stage to test the safety of the drug (as mentioned before in the methods section). Once seizures can be evoked in all three groups, namely LAC (n=3), UC (n=2) and PC (n=2), the animals will be tested for the effect of drug on the seizures. There are a few key points we would like to mention before the results are discussed. Firstly, not all the animals were tested at once. Initially we started by injecting the drug in our two PC animals to check for the drug tolerance and any acute side effects. After verifying these issues in our PC group, the drug injections were started in two LAC animals. We then waited for a time period of at least two weeks to check for the chronic side effects of the drug in our four animals till we injected the remaining animals. During this time period the remaining animals were not stimulated to evoke seizures. But before we injected the drug, we made sure that the animals were experiencing the same behavioral stage and duration of electrographic seizures as before. Secondly, all the animals did not receive the same number of drug injections. The reason for this non-uniformity was one of the PC animals stopped experiencing seizures, twenty-four hours following the first rapamycin dose. As this was meant to be an exploratory stage of experimentation, we tried to observe if there was incremental effect of the drug over days. But for our analysis, we only evaluated the effect of the drug for four days, which was the minimum number of doses received by all the animals. Thirdly, we administered the drug after inducing seizures during each session. Therefore, we assessed the drug's impact the next day, using

the first day of testing prior to rapamycin injection as the baseline. Keeping these cautionary points in mind, lets proceed onto the results section for the drug administration stage of our experiments.

We begin by evaluating the duration of afterdischarges triggered by kindling associated with auditory and visual cues in LAC and PC animals, and only electrical kindling in the UC cohort. The PC animals as observed in figure 16a have a lower duration of seizures on the baseline day (labelled as day 0 on x-axis). One LAC animal showed a departure of 2.3 standard deviations from the mean of baseline measurements in both LAC and UC animals. Following the first drug injection, one PC animal exhibited a failure to trigger seizure with the stimulus. A similar effect was observed in one of the LAC animals, where seizures could not be evoked, thirty days following the last drug administration. Even after increasing the current amplitude all the way up to 150 percent of the previous threshold (current amplitude of the baseline day), the two animals did not show any behavioral or electrographic seizures. An ANOVA study showed a difference between groups with a p-value of 0.0385. This was probably because the animals from the PC group had a significant difference in the afterdischarge duration on the baseline day to begin with (figure 16b). The UC and LAC animals seemed to have a similar duration of afterdischarges on all days following the rapamycin administration (figure 16b).

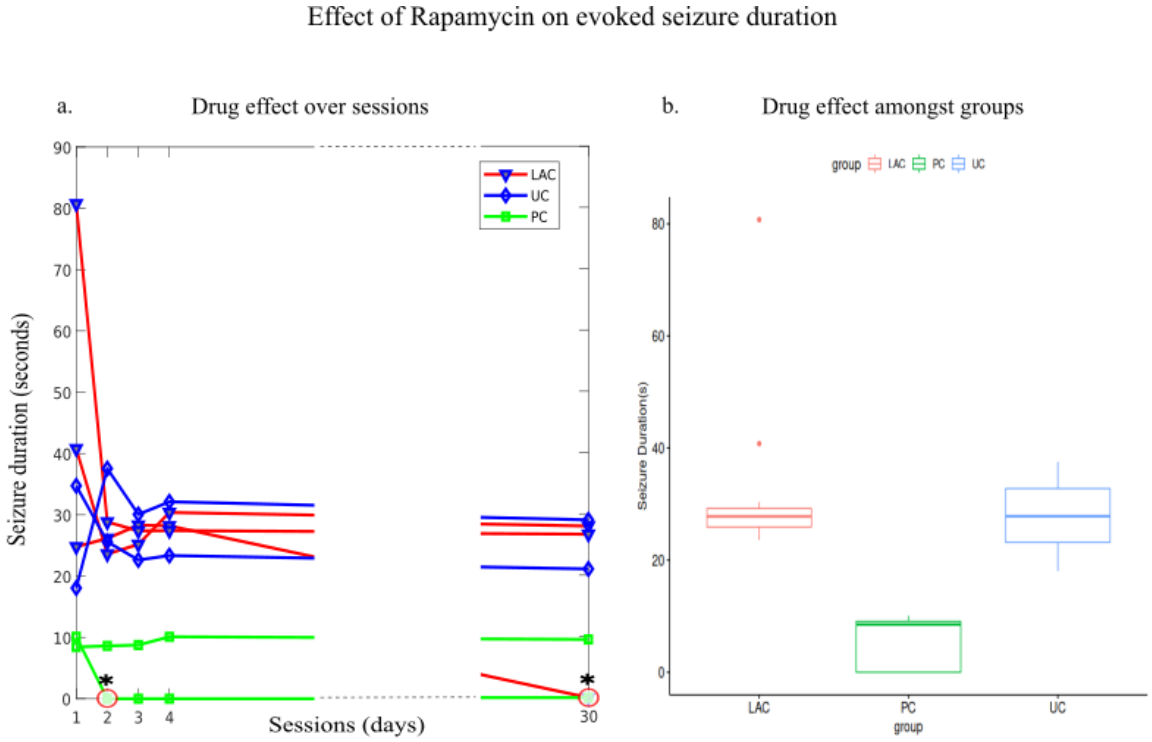


Figure 16. Effect od rapamycin drug on the duration of evoked seizures. The figure panel 16a identifies the duration of electrographic seizures over days in our animals. The pilot animals (PC) had low grade seizures when compared to the experimental and control animals. In one of the PC animals the seizures stopped abruptly following the first drug administration (marked with a red circle and an asterisk*), and the seizures did not reappear even when the amplitude of electric current was increased by 150%. A similar change was observed in one of the LAC animals thirty days following the last drug administration marked with another red circle with an asterisk*. Boxplot in figure 16b shows comparison of the mean duration of evoked seizures in LAC, UC, and PC group. There is a significant difference between the three groups with p-value is 0.0385. This effect might be because in the PC group the duration and amplitude of evoked seizures was considerably low as compared to the other two groups.

Chapter 5: Discussion

The purpose of this study is to broaden our understanding of seizures as more than an abnormal hypersynchronous event manifesting due to an imbalance between excitatory and inhibitory brain circuits (Badawy et al., 2009; Clark & Wilson, 1999; McCormick & Contreras, 2001).

5.1 Rodent model of reflex seizures: Future directions

We began by trying to replicate a mouse model of epilepsy, where specific sensory cues can evoke a convulsive episode, replicating the clinical picture of reflex seizures (Szűcs et al., 2019a). The results of the initial phase of our experiment (as outlined in Section 4.2) indicate that consistently pairing the sensory cues with 'kindled' seizures did not successfully establish a mouse reflex seizure model, where the cues alone can trigger seizures. We propose some ways how the experimental design can be modified to increase the probability of establishing this rodent model. One of the inspirations for our study is the work published by Dr. Ian Whishaw in 1987, which we briefly touched upon in the introductory section 2.5 (Whishaw, 1987). There are two features of this study that we can incorporate in our future experiments. First, we can try to expose our animals to a more complex task, involving encoding of spatial cues leading to successful completion. We will electrically kindle the animal in relation to the cues. Secondly, we can attempt to selectively lesion regions of the dentate gyrus and CA3-4 hippocampal regions after the animals are successfully pre-trained on the task. Afterwards we can expose the lesioned animals to the task and present the spatial cues to evoke reflex seizures. The dentate gyrus is believed to play a critical role in preventing the spread of seizure activity to the hippocampus due to its function as a "filter" mechanism (Alger & Teyler, 1976; Heinemann

et al., 1992; Lothman et al., 1992; McNaughton et al., 1981). But this seizure preventing action deteriorates over time with the development of chronic epilepsy caused by the process of kindling (Behr et al., 1996, 1998). The breakdown of this gating mechanism is believed to result from a combination of single neuron and local network alterations (Ribak et al., 2012). As a result, the spread of seizure activity becomes more and more difficult to control, leading to an increase in the severity and frequency of seizures. The damage induced by kainic acid in the dentate gyrus of rats causing loss of neurons with reorganization of axons associated with epilepsy resembles human temporal lobe epilepsy (Goldberg & Coulter, 2013). We can utilize these 'pro-epileptic' structural alterations in the dentate gyrus as a means of evoking seizures through cues which are possibly already part of the epileptogenic circuit.

5.2 Behavioral changes akin to fear conditioning

Our experimental model generated some interesting behavioral results. As illustrated in section 4.3, we observed that the cue pairing triggered a behavioral response akin to fear conditioning. The response was only seen in the LAC mice cohort, where auditory and visual cues were paired with the evoked seizures. In contrast, the UC mice, who did not experience cue-seizure pairing, did not display the behavioral alteration. These findings are interesting because retrograde amnesia is associated with seizures, specifically generalized seizures (Duncan, 1949; JUS & JUS, 1962; McGaugh, 2000; Naik et al., 2021).

Electroconvulsive therapy (ECT), a treatment inducing generalized tonic-clonic convulsions recommended for medically intractable affective disorders, usually causes retrograde amnesia affecting both episodic and semantic memory (Enev et al., 2007; Landry et al., 2021; Meechan et al., 2022; Meeter et al., 2011; Nikolin et al., 2022;

SQUIRE et al., 1976). Seizures can overwhelm mechanisms responsible for long-term potentiation (LTP) thereby hindering the formation of new memories (Naik et al., 2021). This is further supported by a study in which rats subjected to electroconvulsive seizures were unable to create memories for a spatial task that involved a water maze (Reid & Stewart, 1997). The study also found a correlation between the rats' impaired task performance and the effects of the seizures on LTP (Reid & Stewart, 1997). The ability of LAC animals to recall sensory cues presented prior to seizures raises an important question: how do they remember these cues?

A possible explanation is that the sensory cues may be processed by the brain in a way that enhances their salience making them more likely to be remembered. This statement is supported by recent work done in the field of fear conditioning. A 2-6 Hz oscillation (peak at 4 Hz) in the dorsal medial prefrontal (dmPFC) and basolateral amygdalar (BLA) nucleus cortices of mice was observed, which correlated with behavioral freezing (Karalis et al., 2016). This oscillation was different from the theta oscillations in the hippocampus and was likely driven by the dmPFC activity, suggesting that the dmPFC may be influencing the BLA activity (Karalis et al., 2016; Likhtik et al., 2014).

In our study, the LAC group demonstrated a response characterized by a shift in local field potential changes from the higher theta range (6-10 Hz) to the lower theta range (4-6 Hz), as shown in Figure 18 in Section 3.4. In contrast, the UC group did not exhibit such a response when exposed to the auditory and light cues during the test session. Our results reveal a striking similarity in the response elicited by cues conditioned with evoked seizures and fear conditioning. To further validate our findings, we plan to replicate our experiments with electrodes implanted in the dmPFC and assess if we

observe similar results. Nonetheless, the question remains: how do events become salient, given the retrograde amnesia commonly associated with seizures?

5.3 Novel drug therapies in epilepsy

The rapamycin drug therapy, as indicated in figure 16 in section 4.5, is associated with the disappearance of evoked seizures in two animals. The first animal to display this change belonged to the PC group and the effect was observed twenty-four hours after the first drug administration. The second animal belonged to the LAC cohort, and the effect was observed approximately thirty days after the final drug administration. Notably, in both animals, the seizures could not be induced even when the current amplitude of the kindling stimulus was increased to 150% of the original threshold over the following days. It is worth mentioning that both animals belonged to groups in which evoked seizures were paired with auditory and visual cues.

However, these results should be interpreted with caution due to several factors. Firstly, the PC animal that was seizure-free after drug therapy was older than the LAC and UC animals, was not kindled as regularly, and had shorter duration of evoked seizures and lower grade of behavioral seizures before drug therapy. This suggests that the drug's effectiveness may have been influenced by these pre-existing differences between the animals. Secondly, the effect observed in the LAC animal was not immediate, unlike in the PC mouse, indicating non-uniform results. Thirdly, the effect in the LAC animal may have been due to changes in brain tissue surrounding the stimulating electrodes, such as sclerosis or bleeding. Fourthly, the effects in the LAC mouse were not globally experienced in the brain, as stimulation of the contralateral amygdalar electrodes elicited both behavioral and electrographic seizures. Even if the drug was interrupting the

epileptic circuit, its effect may be localized around the stimulating electrodes, rather than the entire seizure circuit in the brain. Fifthly, the lack of controls raises questions about the validity of the results. Finally, our rationale for using this drug is based on its ability to block memory reconsolidation, as demonstrated in animal models of fear conditioning mimicking post-traumatic stress disorder clinically (Blundell et al., 2008; Kida, 2018; MacCallum & Blundell, 2020) However, the anti-convulsive effect of this drug due to interruption of memory reconsolidation requires further exploration before drawing any definitive conclusions. Furthermore, this drug acts on multiple pathways and has diverse effects inside the brain. Therefore, we need to investigate the role of these pathways in interrupting seizures, and we will briefly describe these effects in the upcoming paragraphs.

Rapamycin has shown promising benefits in treating epilepsy, both in rodent models and clinical trials. The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase, which plays an essential role in pathways responsible for cell growth and proliferation, synaptic plasticity, regulation of neuronal structure, expression of ionic channels and neurotransmitter receptors (Goldberg & Coulter, 2013). In rodent models, mTOR has been linked to the development of epilepsy, with studies showing that inhibiting this pathway using rapamycin can confer several benefits (Zeng et al., 2009). Specifically, rapamycin has been shown to prevent neuronal cell death, limit neurogenesis, reduce disorganization of neural tissue, suppress astrogliosis, and inhibit mossy fiber sprouting (Goldberg & Coulter, 2013; Hodges & Lugo, 2020; Lipton & Sahin, 2014).

Everolimus, a second-generation rapamycin derivative, has been demonstrated to be more efficacious in preventing neuroinflammation and seizures in mice (Yang et al., 2017).

The results of a phase 3 clinical trial in tuberous sclerosis patients show that the addition of everolimus as an adjunct to standard treatment significantly reduces seizure frequency compared to placebo (French et al., 2016). These findings support the further exploration of the efficacy of rapamycin and other related mTOR inhibitors in treating epilepsy. In addition, these drugs not only exhibit the memory reconsolidation blocking effect (Blundell et al., 2008; MacCallum & Blundell, 2020), but also impact synaptic plasticity and neural circuit reorganization (Goldberg & Coulter, 2013). This highlights the importance of investigating the potential link between their antiepileptic properties and their ability to prevent the 'hijacking' of memory formation mechanisms.

Our study is limited as we are studying the brain at a mesoscopic scale or population activity of neurons. To better explain the mechanisms, we plan to replicate the study at a single cell level using two-photon calcium imaging. This will enable us to identify cellular populations associated with the epileptic circuit. The memory consolidation blocking drugs, specifically mTOR blocking drugs, can then be administered after reactivating these seizure-associated neuronal groups to weaken the epileptic circuit.

Based on the findings presented in this thesis, we are currently in the process of preparing a manuscript that will include more comprehensive analyses and additional control data. Due to the time constraints associated with completing this MSc program, we were unable to include all of these results in this thesis. Therefore, we invite the reader to refer to our forthcoming manuscript for the final results, detailed analyses, and plots

Dr. Wilder Penfield, the founder of the Montreal Neurological Institute & Hospital, observed that while presenting subthreshold stimulation to identify epileptic foci often evoked old forgotten memories in his patients (Penfield, 1952). His work seeks to foster a

discussion around how the healthy brain, capable of storing experiences, can become trapped in a cycle of synchronous, uncontrolled seizure activity. By shedding light on the mechanisms underlying this phenomenon, we hope to deepen our understanding of neurological disorders and advance the development of more effective treatments.

References

Abraham, W. C., Jones, O. D., & Glanzman, D. L. (2019). Is plasticity of synapses the mechanism of long-term memory storage? *Npj Science of Learning*, *4*(1), 9. https://doi.org/10.1038/s41539-019-0048-y

Albensi, B. C., Ata, G., Schmidt, E., Waterman, J. D., & Janigro, D. (2004). Activation of long-term synaptic plasticity causes suppression of epileptiform activity in rat hippocampal slices. *Brain Research*, *998*(1), 56–64. https://doi.org/https://doi.org/10.1016/j.brainres.2003.11.010

Alger, B. E., & Teyler, T. J. (1976). Long-term and short-term plasticity in the CA1, CA3, and dentate regions of the rat hippocampal slice. *Brain Research*, *110*(3), 463–480. https://doi.org/10.1016/0006-8993(76)90858-1

Amengual-Gual, M., Sánchez Fernández, I., & Loddenkemper, T. (2019). Patterns of epileptic seizure occurrence. *Brain Research*, *1703*, 3–12. https://doi.org/10.1016/J.BRAINRES.2018.02.032

Arbune, A. A., Meritam Larsen, P., Wüstenhagen, S., Terney, D., Gardella, E., & Beniczky, S. (2021). Modulation in time of the interictal spiking pattern related to epileptic seizures. *Clinical Neurophysiology*, *132*(5), 1083–1088. https://doi.org/10.1016/J.CLINPH.2021.01.026

Arslan, Y., Yilmaz, Z., Mülayim, S., & Zorlu, Y. (2013). Eating Epilepsy After Resection of Frontal Meningioma : A Case Report. *Epilepsi: Journal of the Turkish Epilepsi Society*, *19*(2). https://doi.org/10.5505/epilepsi.2013.19483

Augusto, R., Mendes, V., Zacharias, L. R., Ruggiero, R. N., Pereira Leite, J., Flavio, M., Moraes, D., & Lopes-Aguiar, C. (2019). *Hijacking of hippocampal-cortical oscillatory coupling during sleep in temporal lobe epilepsy*. https://doi.org/10.1016/j.yebeh.2019.106608

Badawy, R. A. B., Harvey, A. S., & Macdonell, R. A. L. (2009). Cortical hyperexcitability and epileptogenesis: Understanding the mechanisms of epilepsy – Part 1. *Journal of Clinical Neuroscience*, *16*(3), 355–365. https://doi.org/https://doi.org/10.1016/j.jocn.2008.08.026

Beenhakker, M. P., & Huguenard, J. R. (2009). Neurons that Fire Together Also Conspire Together: Is Normal Sleep Circuitry Hijacked to Generate Epilepsy? *Neuron*, *62*(5), 612–632. https://doi.org/https://doi.org/10.1016/j.neuron.2009.05.015

Behr, J., Gloveli, T., Gutierrez, R., & Heinemann, U. (1996). Spread of low Mg2+ induced epileptiform activity from the rat entorhinal cortex to the hippocampus after kindling studied in vitro. *Neuroscience Letters*, *216*(1), 41–44. https://doi.org/10.1016/0304-3940(96)13019-6

Behr, J., Lyson, K. J., & Mody, I. (1998). Enhanced Propagation of Epileptiform Activity Through the Kindled Dentate Gyrus. *Journal of Neurophysiology*, *79*(4), 1726–1732. https://doi.org/10.1152/jn.1998.79.4.1726

Beniczky, S., Tatum, W. O., Blumenfeld, H., Stefan, H., Mani, J., Maillard, L., Fahoum, F., Vinayan, K. P., Mayor, L. C., Vlachou, M., Margitta, S., Ryvlin, P., & Philippe, K. (2022). Seizure semiology: ILAE glossary of terms and their significance. *Epileptic Disorders*, *24*(3), 447–495. https://doi.org/10.1684/EPD.2022.1430

Bezzina, C., Verret, L., Juan, C., Remaud, J., Halley, H., Rampon, C., & Dahan, L. (2015). Early onset of hypersynchronous network activity and expression of a marker of chronic seizures

in the Tg2576 mouse model of Alzheimer's disease. *PLoS ONE*, *10*(3). https://doi.org/10.1371/journal.pone.0119910

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31–39. https://doi.org/10.1038/361031a0

Bliss, T. V. P., Collingridge, G. L., Morris, R. G. M., & Reymann, K. G. (2018). Long-term potentiation in the hippocampus: discovery, mechanisms and function. *Neuroforum*, *24*(3), A103–A120. https://doi.org/10.1515/NF-2017-A059

Blume, W. T., Lüders, H. O., Mizrahi, E., Tassinari, C., Boas, W. V. E., & Engel, J. (2001). Glossary of Descriptive Terminology for Ictal Semiology: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia*, *42*(9), 1212–1218. https://doi.org/10.1046/J.1528-1157.2001.22001.X

Blundell, J., Kouser, M., & Powell, C. M. (2008). Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. *Neurobiology of Learning and Memory*, *90*(1), 28–35. https://doi.org/10.1016/J.NLM.2007.12.004

Boada, C., Grossman, S., Dugan, P., & French, J. (2020). Aura Semiology as a Predictor of Outcomes Following Epilepsy Surgery (634). *Neurology*, *94*(15 Supplement).

Boly, M., Jones, B., Findlay, G., Plumley, E., Mensen, A., Hermann, B., Tononi, G., & Maganti, R. (2017). Altered sleep homeostasis correlates with cognitive impairment in patients with focal epilepsy. *Brain*, *140*(4), 1026–1040. https://doi.org/10.1093/BRAIN/AWX017

Bortel, A., Yao, Z. S., & Shmuel, A. (2019). A rat model of somatosensory-evoked reflex seizures induced by peripheral stimulation. *Epilepsy Research*, *157*, 106209. https://doi.org/10.1016/J.EPLEPSYRES.2019.106209

Bower, M. R., Kucewicz, M. T., st. Louis, E. K., Meyer, F. B., Marsh, W. R., Stead, M., & Worrell, G. A. (2017). Reactivation of seizure-related changes to interictal spike shape and synchrony during postseizure sleep in patients. *Epilepsia*, *58*(1), 94–104. https://doi.org/https://doi.org/10.1111/epi.13614

Bower, M. R., Stead, M., Bower, R. S., Kucewicz, M. T., Sulc, V., Cimbalnik, J., Brinkmann, B. H., Vasoli, V. M., st. Louis, E. K., Meyer, F. B., Marsh, W. R., & Worrell, G. A. (2015). Evidence for Consolidation of Neuronal Assemblies after Seizures in Humans. *The Journal of Neuroscience*, *35*(3), 999 LP – 1010. https://doi.org/10.1523/JNEUROSCI.3019-14.2015

Brunet, A., Saumier, D., Liu, A., Streiner, D. L., Tremblay, J., & Pitman, R. K. (2018). Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial. *American Journal of Psychiatry*, *175*(5), 427–433. https://doi.org/10.1176/appi.ajp.2017.17050481

Busche, M. A., & Konnerth, A. (2016). Impairments of neural circuit function in Alzheimer's disease. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1700). https://doi.org/10.1098/RSTB.2015.0429

Buzsáki, G. (1996). The Hippocampo-Neocortical Dialogue. *Cerebral Cortex*, *6*(2), 81–92. https://doi.org/10.1093/cercor/6.2.81

Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, *25*(10), 1073–1188. https://doi.org/10.1002/HIPO.22488

Cahill, L., Pham, C. A., & Setlow, B. (2000). Impaired Memory Consolidation in Rats Produced with β-Adrenergic Blockade. *Neurobiology of Learning and Memory*, *74*(3), 259–266. https://doi.org/10.1006/NLME.1999.3950

Cela, E., McFarlan, A. R., Chung, A. J., Wang, T., Chierzi, S., Murai, K. K., & Sjöström, P. J. (2019). An Optogenetic Kindling Model of Neocortical Epilepsy. *Scientific Reports 2019 9:1*, *9*(1), 1–12. https://doi.org/10.1038/s41598-019-41533-2

Chang, R. S. kwan, Leung, C. Y. W., Ho, C. C. A., & Yung, A. (2017). Classifications of seizures and epilepsies, where are we? – A brief historical review and update. *Journal of the Formosan Medical Association*, *116*(10), 736–741. https://doi.org/10.1016/J.JFMA.2017.06.001

Chapman, K. B., Yousef, T. A., Foster, A., Stanton-Hicks, M. D., & Helmond, N. van. (2021). Mechanisms for the Clinical Utility of Low-Frequency Stimulation in Neuromodulation of the Dorsal Root Ganglion. *Neuromodulation: Technology at the Neural Interface*, *24*(4), 738–745. https://doi.org/10.1111/NER.13323

Citri, A., & Malenka, R. C. (2008). Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms. *Neuropsychopharmacology*, *33*(1), 18–41. https://doi.org/10.1038/sj.npp.1301559

Clark, S., & Wilson, W. A. (1999). Mechanisms of epileptogenesis. *Advances in Neurology*, *79*, 607–630.

Dalby, N. O., & Mody, I. (2003). Activation of NMDA Receptors in Rat Dentate Gyrus Granule Cells by Spontaneous and Evoked Transmitter Release. *Journal of Neurophysiology*, *90*(2), 786–797. https://doi.org/10.1152/jn.00118.2003

Das, R., & Luczak, A. (2022). Epileptic seizures and link to memory processes. *AIMS Neuroscience*, *9*(1), 114–127. https://doi.org/10.3934/Neuroscience.2022007

de Curtis, M., & Avanzini, G. (2001). Interictal spikes in focal epileptogenesis. *Progress in Neurobiology*, *63*(5), 541–567. https://doi.org/https://doi.org/10.1016/S0301-0082(00)00026-5

de Deyn, P. P., D'Hooge, R., Marescau, B., & Pei, Y.-Q. (1992). Chemical models of epilepsy with some reference to their applicability in the development of anticonvulsants. *Epilepsy Research*, *12*(2), 87–110. https://doi.org/https://doi.org/10.1016/0920-1211(92)90030-W

Del Felice, A., Storti, S. F., & Manganotti, P. (2015). Sleep affects cortical source modularity in temporal lobe epilepsy: A high-density EEG study. *Clinical Neurophysiology*, *126*(9), 1677–1683. https://doi.org/https://doi.org/10.1016/j.clinph.2014.12.003

Duncan, C. P. (1949). The retroactive effect of electroshock on learning. *Journal of Comparative and Physiological Psychology*, *42*(1), 32–44. https://doi.org/10.1037/h0058173

Dunsmoor, J. E., Niv, Y., Daw, N., & Phelps, E. A. (2015). Rethinking Extinction. *Neuron*, *88*(1), 47–63. https://doi.org/https://doi.org/10.1016/j.neuron.2015.09.028

Dutra Moraes, M. F., Galvis-Alonso, O. Y., & Garcia-Cairasco, N. (2000). Audiogenic kindling in the Wistar rat: a potential model for recruitment of limbic structures. *Epilepsy Research*, *39*(3), 251–259. https://doi.org/https://doi.org/10.1016/S0920-1211(00)00107-8

Enev, M., McNally, K. A., Varghese, G., Zubal, I. G., Ostroff, R. B., & Blumenfeld, H. (2007). Imaging Onset and Propagation of ECT-induced Seizures. *Epilepsia*, *48*(2), 238–244. https://doi.org/10.1111/j.1528-1167.2007.00919.x

Engel, J. (2001). A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia*, *42*(6), 796–803. https://doi.org/10.1046/J.1528-1157.2001.10401.X

Engel, J. (2006). ILAE classification of epilepsy syndromes. *Epilepsy Research*, *70*, 5–10. https://doi.org/https://doi.org/10.1016/j.eplepsyres.2005.11.014

Ewell, L. A., Fischer, K. B., Leibold, C., Leutgeb, S., & Leutgeb, J. K. (2019). The impact of pathological high-frequency oscillations on hippocampal network activity in rats with chronic epilepsy. *ELife*, *8*. https://doi.org/10.7554/ELIFE.42148

Falip, M., Rodriguez-Bel, L., Castañer, S., Miro, J., Jaraba, S., Mora, J., Bas, J., & Carreño, M. (2018). Musicogenic reflex seizures in epilepsy with glutamic acid decarbocylase antibodies. *Acta Neurologica Scandinavica*, *137*(2), 272–276. https://doi.org/10.1111/ANE.12799

Feindel, W. (2020). Role of Brain Science in the Evolution of Epilepsy Surgery. *McGill Journal of Medicine*, *1*(2). https://doi.org/10.26443/mjm.v1i2.724

Ferlazzo, E., Zifkin, B. G., Andermann, E., & Andermann, F. (2005). Cortical triggers in generalized reflex seizures and epilepsies. *Brain*, *128*(4), 700–710. https://doi.org/10.1093/brain/awh446

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*, *55*(4). https://doi.org/10.1111/epi.12550

Fisher, R. S., Cross, J. H., D'Souza, C., French, J. A., Haut, S. R., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshé, S. L., Peltola, J., Perez, E. R., Scheffer, I. E., Schulze-Bonhage, A., Somerville, E., Sperling, M., Yacubian, E. M., & Zuberi, S. M. (2017). Instruction manual for

the ILAE 2017 operational classification of seizure types. *Epilepsia*, *58*(4), 531–542. https://doi.org/10.1111/EPI.13671

Fisher, R. S., van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. (2005). Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, *46*(4), 470–472. https://doi.org/10.1111/J.0013-9580.2005.66104.X

French, J. A., Lawson, J. A., Yapici, Z., Ikeda, H., Polster, T., Nabbout, R., Curatolo, P., de Vries, P. J., Dlugos, D. J., Berkowitz, N., Voi, M., Peyrard, S., Pelov, D., & Franz, D. N. (2016). Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *The Lancet*, *388*(10056), 2153–2163. https://doi.org/https://doi.org/10.1016/S0140-6736(16)31419-2

Galanopoulou, A. S., Buckmaster, P. S., Staley, K. J., Moshe, S. L., Perucca, E., Jr, J. E., Lo, W., Noebels, J. L., Pitka, A., Stables, J., White, H. S., Brien, T. J. O., & Simonato, M. (2012). *Identification of new epilepsy treatments : Issues in preclinical methodology*. *53*(3), 571–582. https://doi.org/10.1111/j.1528-1167.2011.03391.x

Gelinas, J. N., Khodagholy, D., Thesen, T., Devinsky, O., & Buzsáki, G. (2016). Interictal epileptiform discharges induce hippocampal–cortical coupling in temporal lobe epilepsy. *Nature Medicine*, *22*(6), 641–648. https://doi.org/10.1038/nm.4084

Gelisse, P., Thomas, P., Padovani, R., Hassan-Sebbag, N., & Pasquier, J. (2003). Ictal SPECT in a case of pure musicogenic epilepsy . *Epileptic Disorders*, *5*(3), 133–137.

Genzel, L., Dragoi, G., Frank, L., Ganguly, K., de la Prida, L., Pfeiffer, B., & Robertson, E. (2020). A consensus statement: defining terms for reactivation analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *375*(1799), 20200001. https://doi.org/10.1098/rstb.2020.0001

Georgopoulou, V., Spruyt, K., Garganis, K., & Kosmidis, M. H. (2021). Altered Sleep-Related Consolidation and Neurocognitive Comorbidity in CECTS. In *Frontiers in Human Neuroscience* (Vol. 15, p. 244). Frontiers. https://doi.org/10.3389/fnhum.2021.563807

Goddard, G. v. (1967). Development of Epileptic Seizures through Brain Stimulation at Low Intensity. *Nature*, *214*(5092), 1020–1021. https://doi.org/10.1038/2141020a0

Goddard, G. v. (1983). The kindling model of epilepsy. *Trends in Neurosciences*, *6*, 275–279. https://doi.org/https://doi.org/10.1016/0166-2236(83)90118-2

Goddard, G. v, & Douglas, R. M. (1975). Does the engram of kindling model the engram of normal long term memory? *Canadian Journal of Neurological Sciences*, *2*(4), 385–394.

Goddard, G. v, McIntyre, D. C., & Leech, C. K. (1969). A permanent change in brain function resulting from daily electrical stimulation. *Experimental Neurology*, *25*(3), 295–330. https://doi.org/https://doi.org/10.1016/0014-4886(69)90128-9

Goldberg, E. M., & Coulter, D. A. (2013). Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. *Nature Reviews Neuroscience*, *14*(5), 337–349. https://doi.org/10.1038/nrn3482

González Otárula, K. A., von Ellenrieder, N., Cuello-Oderiz, C., Dubeau, F., & Gotman, J. (2019). High-Frequency Oscillation Networks and Surgical Outcome in Adult Focal Epilepsy. *Annals of Neurology*, *85*(4), 485–494. https://doi.org/https://doi.org/10.1002/ana.25442

Gupta, A. K., Jeavons, P. M., Hughes, R. C., & Covanis, A. (1983). Aura in temporal lobe epilepsy: clinical and electroencephalographic correlation. *Journal of Neurology, Neurosurgery & Psychiatry*, *46*(12), 1079–1083. https://doi.org/10.1136/JNNP.46.12.1079

Hahn, M. A., Heib, D., Schabus, M., Hoedlmoser, K., & Helfrich, R. F. (2020). Slow oscillation-spindle coupling predicts enhanced memory formation from childhood to adolescence. *ELife*, *9*, 1–21. https://doi.org/10.7554/ELIFE.53730

Halász, P., Bódizs, R., Ujma, P. P., Fabó, D., & Szűcs, A. (2019). Strong relationship between NREM sleep, epilepsy and plastic functions — A conceptual review on the neurophysiology background. *Epilepsy Research*, *150*, 95–105. https://doi.org/10.1016/J.EPLEPSYRES.2018.11.008

Heinemann, U., Beck, H., Dreier, J. P., Ficker, E., Stabel, J., & Zhang, C. L. (1992). The dentate gyrus as a regulated gate for the propagation of epileptiform activity. *Epilepsy Research. Supplement*, *7*, 273–280. http://europepmc.org/abstract/MED/1334666

Hodges, S. L., & Lugo, J. N. (2020). Therapeutic role of targeting mTOR signaling and neuroinflammation in epilepsy. *Epilepsy Research*, *161*, 106282. https://doi.org/https://doi.org/10.1016/j.eplepsyres.2020.106282

Irmen, F., Wehner, T., & Lemieux, L. (2015). Do reflex seizures and spontaneous seizures form a continuum? – Triggering factors and possible common mechanisms. *Seizure*, *25*, 72–79. https://doi.org/10.1016/J.SEIZURE.2014.12.006

Jacob, L., Bohlken, J., Schmitz, B., & Kostev, K. (2019). Incidence of epilepsy and associated factors in elderly patients in Germany. *Epilepsy & Behavior*, *90*, 107–111. https://doi.org/10.1016/J.YEBEH.2018.10.035

Jacobs, J., Banks, S., Zelmann, R., Zijlmans, M., Jones-Gotman, M., & Gotman, J. (2016). Spontaneous ripples in the hippocampus correlate with epileptogenicity and not memory function in patients with refractory epilepsy. *Epilepsy & Behavior*, *62*, 258–266. https://doi.org/10.1016/J.YEBEH.2016.05.025

Jacobs, J., LeVan, P., Chander, R., Hall, J., Dubeau, F., & Gotman, J. (2008). Interictal high-frequency oscillations (80–500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. *Epilepsia*, *49*(11), 1893–1907. https://doi.org/https://doi.org/10.1111/j.1528-1167.2008.01656.x

Jacobs, J., Zijlmans, M., Zelmann, R., Chatillon, C.-É., Hall, J., Olivier, A., Dubeau, F., & Gotman, J. (2010). High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Annals of Neurology*, *67*(2), 209–220. https://doi.org/https://doi.org/10.1002/ana.21847

Jallon, P., Heraut, L. A., & Vanelle, J. M. (1989). Musicogenic epilepsy. *Reflex Seizures and Reflex Epilepsies, Editions Médicine et Hygiène, Geneva*, 269–274.

JUS, A., & JUS, K. (1962). Retrograde Amnesia in Petit Mal. *Archives of General Psychiatry*, *6*(2), 163–167. https://doi.org/10.1001/archpsyc.1962.01710200055007

Karalis, N., Dejean, C., Chaudun, F., Khoder, S., Rozeske, R. R., Wurtz, H., Bagur, S., Benchenane, K., Sirota, A., Courtin, J., & Herry, C. (2016). 4-Hz oscillations synchronize prefrontal–amygdala circuits during fear behavior. *Nature Neuroscience*, *19*(4), 605–612. https://doi.org/10.1038/nn.4251

Karlócai, M. R., Kohus, Z., Káli, S., Ulbert, I., Szabó, G., Máté, Z., Freund, T. F., & Gulyás, A. I. (2014). Physiological sharp wave-ripples and interictal events in vitro: what's the difference? *Brain*, *137*(2), 463–485. https://doi.org/10.1093/BRAIN/AWT348

Karoly, P. J., Rao, V. R., Gregg, N. M., Worrell, G. A., Bernard, C., Cook, M. J., & Baud, M. O. (2021). Cycles in epilepsy. *Nature Reviews Neurology 2021 17:5*, *17*(5), 267–284. https://doi.org/10.1038/s41582-021-00464-1

Kauer, J. A., Malenka, R. C., & Nicoll, R. A. (1988). A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. *Neuron*, *1*(10), 911–917. https://doi.org/https://doi.org/10.1016/0896-6273(88)90148-1

Kida, S. (2018). Reconsolidation/destabilization, extinction and forgetting of fear memory as therapeutic targets for PTSD. *Psychopharmacology 2018 236:1*, *236*(1), 49–57. https://doi.org/10.1007/S00213-018-5086-2

Kleen, J. K., Scott, R. C., Holmes, G. L., & Lenck-Santini, P. P. (2010). Hippocampal interictal spikes disrupt cognition in rats. *Annals of Neurology*, *67*(2), 250–257. https://doi.org/https://doi.org/10.1002/ana.21896

Kleen, J. K., Scott, R. C., Holmes, G. L., Roberts, D. W., Rundle, M. M., Testorf, M., Lenck-Santini, P.-P., & Jobst, B. C. (2013). Hippocampal interictal epileptiform activity disrupts cognition in humans. *Neurology*, *81*(1), 18–24. https://doi.org/10.1212/WNL.0b013e318297ee50

Koh, M. T., Haberman, R. P., Foti, S., McCown, T. J., & Gallagher, M. (2010). Treatment Strategies Targeting Excess Hippocampal Activity Benefit Aged Rats with Cognitive Impairment. *Neuropsychopharmacology*, *35*(4), 1016–1025. https://doi.org/10.1038/npp.2009.207

Koutroumanidis, M., & Panayiotopoulos, C. (2004). Reflex seizures and reflex epilepsies. In *Epilepsy in Children, 2E* (pp. 243–249). CRC Press. https://doi.org/10.1201/b13560-36

Kundap, U. P., Paudel, Y. N., Kumari, Y., Othman, I., & Shaikh, Mohd. F. (2019). Embelin Prevents Seizure and Associated Cognitive Impairments in a Pentylenetetrazole-Induced Kindling Zebrafish Model. *Frontiers in Pharmacology*, *0*(MAR), 315. https://doi.org/10.3389/FPHAR.2019.00315

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience*, *7*(1), 54–64. https://doi.org/10.1038/nrn1825

Lam, A. D., Deck, G., Goldman, A., Eskandar, E. N., Noebels, J., & Cole, A. J. (2017). Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nature Medicine*, *23*(6), 678–680. https://doi.org/10.1038/nm.4330

Lambert, I., Roehri, N., Giusiano, B., Carron, R., Wendling, F., Benar, C., & Bartolomei, F. (2018). Brain regions and epileptogenicity influence epileptic interictal spike production and propagation during NREM sleep in comparison with wakefulness. *Epilepsia*, *59*(1), 235–243. https://doi.org/https://doi.org/10.1111/epi.13958

Lambert, I., Tramoni-Negre, E., Lagarde, S., Pizzo, F., Trebuchon-Da Fonseca, A., Bartolomei, F., & Felician, O. (2021). Accelerated long-term forgetting in focal epilepsy: Do interictal spikes during sleep matter? *Epilepsia*, *62*(3), 563–569. https://doi.org/https://doi.org/10.1111/epi.16823

Lambert, I., Tramoni-Negre, E., Lagarde, S., Roehri, N., Giusiano, B., Trebuchon-Da Fonseca, A., Carron, R., Benar, C.-G., Felician, O., & Bartolomei, F. (2020). Hippocampal Interictal Spikes

during Sleep Impact Long-Term Memory Consolidation. *Annals of Neurology*, *87*(6), 976–987. https://doi.org/https://doi.org/10.1002/ana.25744

Landry, M., Moreno, A., Patry, S., Potvin, S., & Lemasson, M. (2021). Current Practices of Electroconvulsive Therapy in Mental Disorders. *The Journal of ECT*, *37*(2), 119–127. https://doi.org/10.1097/YCT.0000000000000723

Leppik, I. E., & Birnbaum, A. K. (2010). Epilepsy in the Elderly. *Annals of the New York Academy of Sciences*, *1184*, 208. https://doi.org/10.1111/J.1749-6632.2009.05113.X

Liang, K. C., Juler, R. G., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Research*, *368*(1), 125–133. https://doi.org/https://doi.org/10.1016/0006-8993(86)91049-8

Likhtik, E., Stujenske, J. M., A Topiwala, M., Harris, A. Z., & Gordon, J. A. (2014). Prefrontal entrainment of amygdala activity signals safety in learned fear and innate anxiety. *Nature Neuroscience*, *17*(1), 106–113. https://doi.org/10.1038/nn.3582

Lipton, J. O., & Sahin, M. (2014). The Neurology of mTOR. *Neuron*, *84*(2), 275–291. https://doi.org/https://doi.org/10.1016/j.neuron.2014.09.034

Liu, D., Lu, H., Stein, E., Zhou, Z., Yang, Y., & Mattson, M. P. (2018). Brain regional synchronous activity predicts tauopathy in 3×TgAD mice. *Neurobiology of Aging*, *70*, 160–169. https://doi.org/10.1016/J.NEUROBIOLAGING.2018.06.016

Liu, S., & Parvizi, J. (2019). Cognitive refractory state caused by spontaneous epileptic high-frequency oscillations in the human brain. *Science Translational Medicine*, *11*(514). https://doi.org/10.1126/SCITRANSLMED.AAX7830/SUPPL_FILE/AAX7830_SM.PDF

Lømo, T. (2003). The discovery of long-term potentiation. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1432), 617–620. https://doi.org/10.1098/rstb.2002.1226

Lothman, E. W., Stringer, J. L., & Bertram, E. H. (1992). The dentate gyrus as a control point for seizures in the hippocampus and beyond. *Epilepsy Research. Supplement*, *7*, 301–313. http://europepmc.org/abstract/MED/1334669

Luczak, A., Barthó, P., & Harris, K. D. (2009). Spontaneous Events Outline the Realm of Possible Sensory Responses in Neocortical Populations. *Neuron*, *62*(3), 413–425. https://doi.org/10.1016/J.NEURON.2009.03.014

Luczak, A., McNaughton, B. L., & Harris, K. D. (2015). Packet-based communication in the cortex. *Nature Reviews Neuroscience 2015 16:12*, *16*(12), 745–755. https://doi.org/10.1038/nrn4026

Lüttjohann, A., Fabene, P. F., & van Luijtelaar, G. (2009). A revised Racine's scale for PTZ-induced seizures in rats. *Physiology & Behavior*, *98*(5), 579–586. https://doi.org/https://doi.org/10.1016/j.physbeh.2009.09.005

Lynch, M., Sayin, Ü., Golarai, G., & Sutula, T. (2000). NMDA Receptor-Dependent Plasticity of Granule Cell Spiking in the Dentate Gyrus of Normal and Epileptic Rats. *Journal of Neurophysiology*, *84*(6), 2868–2879. https://doi.org/10.1152/jn.2000.84.6.2868

MacCallum, P. E., & Blundell, J. (2020). The mTORC1 inhibitor rapamycin and the mTORC1/2 inhibitor AZD2014 impair the consolidation and persistence of contextual fear memory. *Psychopharmacology*, *237*(9), 2795–2808. https://doi.org/10.1007/S00213-020-05573-1/FIGURES/3

Maharathi, B., Wlodarski, R., Bagla, S., Asano, E., Hua, J., Patton, J., & Loeb, J. A. (2019). Interictal spike connectivity in human epileptic neocortex. *Clinical Neurophysiology*, *130*(2), 270–279. https://doi.org/10.1016/J.CLINPH.2018.11.025

Malenka, R. C., & Nicoll, R. A. (1999). Long-Term Potentiation--A Decade of Progress? *Science*, *285*(5435), 1870–1874. https://doi.org/10.1126/science.285.5435.1870

Malleret, G., Alarcon, J. M., Martel, G., Takizawa, S., Vronskaya, S., Yin, D., Chen, I. Z., Kandel, E. R., & Shumyatsky, G. P. (2010). Bidirectional Regulation of Hippocampal Long-Term Synaptic Plasticity and Its Influence on Opposing Forms of Memory. *Journal of Neuroscience*, *30*(10), 3813–3825. https://doi.org/10.1523/JNEUROSCI.1330-09.2010

Marescaux, C., Vergnes, M., Kiesmann, M., Depaulis, A., Micheletti, G., & Warter, J. M. (1987). Kindling of audiogenic seizures in Wistar rats: An EEG study. *Experimental Neurology*, *97*(1), 160–168. https://doi.org/10.1016/0014-4886(87)90290-1

Matos, G., Tufik, S., Scorza, F. A., Cavalheiro, E. A., & Andersen, M. L. (2011). Sleep, epilepsy and translational research: What can we learn from the laboratory bench? *Progress in Neurobiology*, *95*(3), 396–405. https://doi.org/10.1016/J.PNEUROBIO.2011.09.006

McClelland, J. L., McNaughton, B., & O'Reilly, R. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102 3*, 419–457.

McCormick, D. A., & Contreras, D. (2001). On The Cellular and Network Bases of Epileptic Seizures. *Annual Review of Physiology*, *63*(1), 815–846. https://doi.org/10.1146/annurev.physiol.63.1.815

McGaugh, J. L. (2000). Memory--a Century of Consolidation. *Science*, *287*(5451), 248–251. https://doi.org/10.1126/science.287.5451.248

McIntyre, D. C., Poulter, M. O., & Gilby, K. (2002). Kindling: some old and some new. *Epilepsy Research*, *50*(1–2), 79–92. https://doi.org/10.1016/S0920-1211(02)00071-2

McNamara, J. O. (1989). Development of New Pharmacological Agents for Epilepsy: Lessons from the Kindling Model. *Epilepsia*, *30*, S13–S18. https://doi.org/10.1111/J.1528-1157.1989.TB05809.X

McNaughton, B. L., Barnes, C. A., & Andersen, P. (1981). Synaptic efficacy and EPSP summation in granule cells of rat fascia dentata studied in vitro. *Journal of Neurophysiology*, *46*(5), 952–966.

Meechan, C. F., Laws, K. R., Young, A. H., McLoughlin, D. M., & Jauhar, S. (2022). A critique of narrative reviews of the evidence-base for ECT in depression. *Epidemiology and Psychiatric Sciences*, *31*, e10. https://doi.org/10.1017/S2045796021000731

Meeter, M., Murre, J. M. J., Janssen, S. M. J., Birkenhager, T., & van den Broek, W. W. (2011). Retrograde amnesia after electroconvulsive therapy: A temporary effect? *Journal of Affective Disorders*, *132*(1–2), 216–222. https://doi.org/10.1016/j.jad.2011.02.026

Mendes, R. A. V., Zacharias, L. R., Ruggiero, R. N., Leite, J. P., Moraes, M. F. D., & Lopes-Aguiar, C. (2021). Hijacking of hippocampal–cortical oscillatory coupling during sleep in temporal lobe epilepsy. *Epilepsy & Behavior*, *121*, 106608. https://doi.org/https://doi.org/10.1016/j.yebeh.2019.106608

Metcalf, C. S., Huff, J., Thomson, K. E., Johnson, K., Edwards, S. F., & Wilcox, K. S. (2019). Evaluation of antiseizure drug efficacy and tolerability in the rat lamotrigine-resistant

amygdala kindling model. *Epilepsia Open*, *4*(3), 452–463. https://doi.org/10.1002/EPI4.12354

Mihály, I., Orbán-Kis, K., Gáll, Z., Berki, Á.-J., Bod, R.-B., & Szilágyi, T. (2020). Amygdala Low-Frequency Stimulation Reduces Pathological Phase-Amplitude Coupling in the Pilocarpine Model of Epilepsy. *Brain Sciences 2020, Vol. 10, Page 856*, *10*(11), 856. https://doi.org/10.3390/BRAINSCI10110856

Mody, I., & Heinemann, U. (1987). NMDA receptors of dentate gyrus granule cells participate in synaptic transmission following kindling. *Nature*, *326*(6114), 701–704. https://doi.org/10.1038/326701a0

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, *406*(6797), 722–726. https://doi.org/10.1038/35021052

Naik, A. A., Sun, H., Williams, C. L., Weller, D. S., Julius Zhu, J., & Kapur, J. (2021). Mechanism of seizure-induced retrograde amnesia. *Progress in Neurobiology*, *200*, 101984. https://doi.org/https://doi.org/10.1016/j.pneurobio.2020.101984

Navarro, V., Adam, C., Petitmengin, C., & Baulac, M. (2006). Toothbrush-Thinking Seizures. *Epilepsia*, *47*(11), 1971–1973. https://doi.org/10.1111/J.1528-1167.2006.00822.X

Neumann, A. R., Raedt, R., Steenland, H. W., Sprengers, M., Bzymek, K., Navratilova, Z., Mesina, L., Xie, J., Lapointe, V., Kloosterman, F., Vonck, K., Boon, P. A. J. M., Soltesz, I., McNaughton, B. L., & Luczak, A. (2017). Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats with chronic temporal lobe epilepsy. *Brain*, *140*(9). https://doi.org/10.1093/brain/awx179

Nguyen, P. v., Abel, T., & Kandel, E. R. (1994). Requirement of a Critical Period of Transcription for Induction of a Late Phase of LTP. *Science*, *265*(5175), 1104–1107. https://doi.org/10.1126/SCIENCE.8066450

Nicholls, R. E., Alarcon, J. M., Malleret, G., Carroll, R. C., Grody, M., Vronskaya, S., & Kandel, E. R. (2008). Transgenic Mice Lacking NMDAR-Dependent LTD Exhibit Deficits in Behavioral Flexibility. *Neuron*, *58*(1), 104–117. https://doi.org/10.1016/J.NEURON.2008.01.039

Nicoll, R. A. (2017). A Brief History of Long-Term Potentiation. *Neuron*, *93*(2), 281–290. https://doi.org/https://doi.org/10.1016/j.neuron.2016.12.015

Nikolin, S., Owens, K., Francis-Taylor, R., Chaimani, A., Martin, D. M., Bull, M., Sackeim, H. A., McLoughlin, D. M., Sienaert, P., Kellner, C. H., & Loo, C. (2022). Comparative efficacy, cognitive effects and acceptability of electroconvulsive therapies for the treatment of depression: protocol for a systematic review and network meta-analysis. *BMJ Open*, *12*(12), e068313. https://doi.org/10.1136/bmjopen-2022-068313

Noachtar, S., & Peters, A. S. (2009). Semiology of epileptic seizures: A critical review. *Epilepsy & Behavior*, *15*(1), 2–9. https://doi.org/10.1016/J.YEBEH.2009.02.029

Noebels, J. (2011). A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. *Epilepsia*, *52*(SUPPL. 1), 39–46. https://doi.org/10.1111/J.1528-1167.2010.02909.X

Olafsson, E., Ludvigsson, P., Gudmundsson, G., Hesdorffer, D., Kjartansson, O., & Hauser, W. A. (2005). Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. *The Lancet Neurology*, *4*(10), 627–634. https://doi.org/10.1016/S1474-4422(05)70172-1

Palop, J. J., Chin, J., Roberson, E. D., Wang, J., Thwin, M. T., Bien-Ly, N., Yoo, J., Ho, K. O., Yu, G.-Q., Kreitzer, A., Finkbeiner, S., Noebels, J. L., & Mucke, L. (2007). Aberrant Excitatory Neuronal Activity and Compensatory Remodeling of Inhibitory Hippocampal Circuits in Mouse Models of Alzheimer's Disease. *Neuron*, *55*(5), 697–711. https://doi.org/https://doi.org/10.1016/j.neuron.2007.07.025

Palop, J. J., & Mucke, L. (2016). Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nature Reviews Neuroscience*, *17*(12), 777–792. https://doi.org/10.1038/nrn.2016.141

Parra, J., Kalitzin, S. N., Iriarte, J., Blanes, W., Velis, D. N., & da Silva, F. H. (2003). Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception? *Brain*, *126*(5), 1164–1172. https://doi.org/10.1093/brain/awg109

Paschen, E., Elgueta, C., Heining, K., Vieira, D. M., Kleis, P., Orcinha, C., Häussler, U., Bartos, M., Egert, U., Janz, P., & Haas, C. A. (2020). Hippocampal low-frequency stimulation prevents seizure generation in a mouse model of mesial temporal lobe epilepsy. *ELife*, *9*, 1–57. https://doi.org/10.7554/ELIFE.54518

Paxinos, G., & Franklin, K. B. J. (2019). *Paxinos and Franklin's the mouse brain in stereotaxic coordinates*. Academic press.

Penfield, W. (1952). MEMORY MECHANISMS. *A.M.A. Archives of Neurology & Psychiatry*, *67*(2), 178–198. https://doi.org/10.1001/archneurpsyc.1952.02320140046005

Prince, D. A., & Connors, B. W. (1986). Mechanisms of interictal epileptogenesis. *Advances in Neurology*, *44*, 275–299.

Racine, R. J. (1972). Modification of seizure activity by electrical stimulation: II. Motor seizure. *Electroencephalography and Clinical Neurophysiology*, *32*(3), 281–294. https://doi.org/https://doi.org/10.1016/0013-4694(72)90177-0

Ramírez-Toraño, F., García-Alba, J., Bruña, R., Esteba-Castillo, S., Vaquero, L., Pereda, E., Maestú, F., & Fernández, A. (2021). Hypersynchronized Magnetoencephalography Brain Networks in Patients with Mild Cognitive Impairment and Alzheimer's Disease in down Syndrome. *Brain Connectivity*, *11*(9), 725–733. https://doi.org/10.1089/BRAIN.2020.0897/SUPPL_FILE/SUPP_FIG2.DOCX

Reid, I. C., & Stewart, C. A. (1997). Seizures, memory and synaptic plasticity. *Seizure*, *6*(5), 351–359. https://doi.org/https://doi.org/10.1016/S1059-1311(97)80034-9

Ribak, C. E., Shapiro, L. A., Yan, X.-X., Dashtipour, K., Nadler, J. V., Obenaus, A., Spigelman, I., & Buckmaster, P. S. (2012). Seizure-induced formation of basal dendrites on granule cells of the rodent dentate gyrus. *Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th Edition*.

Roullet, P., Vaiva, G., Véry, E., Bourcier, A., Yrondi, A., Dupuch, L., Lamy, P., Thalamas, C., Jasse, L., Hage, W. el, & Birmes, P. (2021). Traumatic memory reactivation with or without propranolol for PTSD and comorbid MD symptoms: a randomised clinical trial. *Neuropsychopharmacology 2021 46:9*, *46*(9), 1643–1649. https://doi.org/10.1038/s41386-021-00984-w

Ruan, Y., Xu, C., Lan, J., Nao, J., Zhang, S., Fan, F., Wang, Y., & Chen, Z. (2020). Low-frequency Stimulation at the Subiculum is Anti-convulsant and Anti-drug-resistant in a Mouse Model of Lamotrigine-resistant Temporal Lobe Epilepsy. *Neuroscience Bulletin*, *36*(6), 654. https://doi.org/10.1007/S12264-020-00482-X

Sanchez, P. E., Zhu, L., Verret, L., Vossel, K. A., Orr, A. G., Cirrito, J. R., Devidze, N., Ho, K., Yu, G.-Q., Palop, J. J., & Mucke, L. (2012). Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proceedings of the National Academy of Sciences*, *109*(42), E2895 LP-E2903. https://doi.org/10.1073/pnas.1121081109

Sasaguri, H., Nilsson, P., Hashimoto, S., Nagata, K., Saito, T., De Strooper, B., Hardy, J., Vassar, R., Winblad, B., & Saido, T. C. (2017). APP mouse models for Alzheimer's disease preclinical studies. *The EMBO Journal*, *36*(17), 2473–2487. https://doi.org/https://doi.org/10.15252/embj.201797397

Schwabe, L., Nader, K., Wolf, O. T., Beaudry, T., & Pruessner, J. C. (2012). Neural Signature of Reconsolidation Impairments by Propranolol in Humans. *Biological Psychiatry*, *71*(4), 380–386. https://doi.org/https://doi.org/10.1016/j.biopsych.2011.10.028

Shimada, T., & Yamagata, K. (2018). Pentylenetetrazole-induced kindling mouse model. *Journal of Visualized Experiments*, *2018*(136). https://doi.org/10.3791/56573

Silva, B. A., Astori, S., Burns, A. M., Heiser, H., van den Heuvel, L., Santoni, G., Martinez-Reza, M. F., Sandi, C., & Gräff, J. (2021). A thalamo-amygdalar circuit underlying the extinction of remote fear memories. *Nature Neuroscience 2021 24:7*, *24*(7), 964–974. https://doi.org/10.1038/s41593-021-00856-y

Simon, K. C. N. S., Gómez, R. L., & Nadel, L. (2018). Losing memories during sleep after targeted memory reactivation. *Neurobiology of Learning and Memory*, *151*, 10–17. https://doi.org/https://doi.org/10.1016/j.nlm.2018.03.003

Sitnikova, E., Grubov, V., & Hramov, A. E. (2020). Slow-wave activity preceding the onset of 10–15-Hz sleep spindles and 5–9-Hz oscillations in electroencephalograms in rats with and without absence seizures. *Journal of Sleep Research*, *29*(6), e12927. https://doi.org/10.1111/JSR.12927

Soeter, M., & Kindt, M. (2015). An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent. *Biological Psychiatry*, *78*(12), 880–886. https://doi.org/10.1016/J.BIOPSYCH.2015.04.006

Sparks, F. T., Liao, Z., Li, W., Grosmark, A., Soltesz, I., & Losonczy, A. (2020). Hippocampal adult-born granule cells drive network activity in a mouse model of chronic temporal lobe epilepsy. *Nature Communications 2020 11:1*, *11*(1), 1–13. https://doi.org/10.1038/s41467-020-19969-2

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–177. https://doi.org/10.1016/J.NLM.2004.06.005

SQUIRE, L. R., CHACE, P. M., & SLATER, P. C. (1976). Retrograde amnesia following electroconvulsive therapy. *Nature*, *260*(5554), 775–777. https://doi.org/10.1038/260775a0

Staley, K. J., & Dudek, F. E. (2006). Interictal Spikes and Epileptogenesis. *Epilepsy Currents*, *6*(6), 199–202. https://doi.org/10.1111/j.1535-7511.2006.00145.x

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature*, *437*(7063), 1272–1278. https://doi.org/10.1038/nature04286

Szűcs, A., Rosdy, B., Kelemen, A., Horváth, A., & Halász, P. (2019a). Reflex seizure triggering: Learning about seizure producing systems. *Seizure*, *69*, 25–30. https://doi.org/https://doi.org/10.1016/j.seizure.2019.03.019

Szűcs, A., Rosdy, B., Kelemen, A., Horváth, A., & Halász, P. (2019b). Reflex seizure triggering: Learning about seizure producing systems. *Seizure*, *69*, 25–30. https://doi.org/10.1016/J.SEIZURE.2019.03.019

Temkin, O. (1994). *The falling sickness: a history of epilepsy from the Greeks to the beginnings of modern neurology* (Vol. 4). JHU Press.

Teskey, G. C. (2020). Kindling. *Oxford Research Encyclopedia of Psychology*. https://doi.org/10.1093/ACREFORE/9780190236557.013.790

Tezer, F. I., Bilginer, B., Oguz, K. K., & Saygi, S. (2014). Musicogenic and spontaneous seizures: EEG analyses with hippocampal depth electrodes. *Epileptic Disorders*, *16*(4), 500–505. https://doi.org/https://doi.org/10.1684/epd.2014.0706

Thijs, R. D., Surges, R., O'Brien, T. J., & Sander, J. W. (2019). Epilepsy in adults. *The Lancet*, *393*(10172), 689–701. https://doi.org/10.1016/S0140-6736(18)32596-0

Trenite, D. G. A. K.-N., DiVentura, B. D., Pollard, J. R., Krauss, G. L., Mizne, S., & French, J. A. (2019). Suppression of the photoparoxysmal response in photosensitive epilepsy with cenobamate (YKP3089). *Neurology*, *93*(6), e559–e567. https://doi.org/10.1212/WNL.0000000000007894

van Erum, J., van Dam, D., & de Deyn, P. P. (2019). PTZ-induced seizures in mice require a revised Racine scale. *Epilepsy & Behavior*, *95*, 51–55. https://doi.org/https://doi.org/10.1016/j.yebeh.2019.02.029

van Luijtelaar, G., Hramov, A., Sitnikova, E., & Koronovskii, A. (2011). Spike–wave discharges in WAG/Rij rats are preceded by delta and theta precursor activity in cortex and thalamus. *Clinical Neurophysiology*, *122*(4), 687–695. https://doi.org/10.1016/J.CLINPH.2010.10.038

Velíšek, L., Velíšková, J., & Stanton, P. K. (2002). Low-frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. *Neuroscience Letters*, *326*(1), 61–63. https://doi.org/https://doi.org/10.1016/S0304-3940(02)00294-X

Wada, J. A. (1977). Pharmacological Prophylaxis in the Kindling Model of Epilepsy. *Archives of Neurology*, *34*(7), 389–395. https://doi.org/10.1001/ARCHNEUR.1977.00500190023003

Wagner, J. J., & Alger, B. E. (1996). Homosynaptic LTD and depotentiation: Do they differ in name only? *Hippocampus*, *6*(1), 24–29. https://doi.org/https://doi.org/10.1002/(SICI)1098-1063(1996)6:1<24::AID-HIPO5>3.0.CO;2-7

Whishaw, I. Q. (1987). Hippocampal, granule cell and CA3–4 lesions impair formation of a place learning-set in the rat and induce reflex epilepsy. *Behavioural Brain Research*, *24*(1), 59–72. https://doi.org/https://doi.org/10.1016/0166-4328(87)90036-2

Wieser, H. G. (1998). Seizure induction in reflex seizures and reflex epilepsy. In *Advances in neurology* (pp. 69–85).

Wilson, I. A., Gallagher, M., Eichenbaum, H., & Tanila, H. (2006). Neurocognitive aging: prior memories hinder new hippocampal encoding. *Trends in Neurosciences*, *29*(12), 662–670. https://doi.org/https://doi.org/10.1016/j.tins.2006.10.002

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, *265*(5172), 676–679. https://doi.org/10.1126/science.8036517

Winters, B. D., Tucci, M. C., & DaCosta-Furtado, M. (2009). Older and stronger object memories are selectively destabilized by reactivation in the presence of new information. *Learning & Memory*, *16*(9), 545–553.

Wolf, P. (2017). Reflex epileptic mechanisms in humans: Lessons about natural ictogenesis. *Epilepsy & Behavior*, *71*, 118–123. https://doi.org/https://doi.org/10.1016/j.yebeh.2015.01.009

Xue, L. Y., & Ritaccio, A. L. (2006). Reflex Seizures and Reflex Epilepsy. *American Journal of Electroneurodiagnostic Technology*, *46*(1), 39–48. https://doi.org/10.1080/1086508X.2006.11079556

Yang, M.-T., Lin, Y.-C., Ho, W.-H., Liu, C.-L., & Lee, W.-T. (2017). Everolimus is better than rapamycin in attenuating neuroinflammation in kainic acid-induced seizures. *Journal of Neuroinflammation*, *14*(1), 15. https://doi.org/10.1186/s12974-017-0797-6

Yassa, M. A., Stark, S. M., Bakker, A., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2010). High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment. *NeuroImage*, *51*(3), 1242–1252. https://doi.org/https://doi.org/10.1016/j.neuroimage.2010.03.040

Zeng, L.-H., Rensing, N. R., & Wong, M. (2009). The Mammalian Target of Rapamycin Signaling Pathway Mediates Epileptogenesis in a Model of Temporal Lobe Epilepsy. *The Journal of Neuroscience*, *29*(21), 6964. https://doi.org/10.1523/JNEUROSCI.0066-09.2009