Scoping review of relationship between alcohol, memory consolidation, and ripple activity: recompilation of mean methodologies to analyze ripples

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Abstract

Alcohol abuse is not only responsible for 5.3% of the total deaths in the world, but also has a substantial impact on neurological and memory disabilities throughout the population. One extensively studied brain area involved in cognitive functions is the hippocampus. Evidence in several rodent models has shown that ethanol produces cognitive impairment in hippocampal-dependent tasks and that the damage is varied according to the stage of development at which the rodent was exposed to ethanol and the dose. To the authors' knowledge, there is a biomarker for cognitive processes in the hippocampus that has not been evaluated in association with memory impairment by alcohol administration. This biomarker is called Sharp Wave Ripples which are synchronous neuronal population events that are well known to be involved in memory consolidation. Methodologies for facilitation or automatic identification of ripples and their analysis have been reported for a wider bandwidth than Sharp Wave Ripples. This review is focused on communicating the state-of-the art about the relationship between alcohol, memory consolidation and ripple activity as well as the use of the main methodologies to identify SWRs automatically.

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Short running title: Relationship between alcohol, memory consolidation and ripple activity.

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Abstract

Alcohol abuse is not only responsible for 5.3% of the total deaths in the world, but also has a substantial impact on neurological and memory disabilities throughout the population. One extensively studied brain area involved in cognitive functions is the hippocampus. Evidence in several rodent models has shown that ethanol produces cognitive impairment in hippocampal-dependent tasks and that the damage is varied according to the stage of development at which the rodent was exposed to ethanol and the dose. To the authors' knowledge, there is a biomarker for cognitive processes in the hippocampus that has not been evaluated in association with memory impairment by alcohol administration. This biomarker is called Sharp Wave Ripples which are synchronous neuronal population events that are well known to be involved in memory consolidation. Methodologies for facilitation or automatic identification of ripples and their analysis have been reported for a wider bandwidth than Sharp Wave Ripples. This review is focused on communicating the state-of-the art about the relationship between alcohol, memory consolidation and ripple activity as well as the use of the main methodologies to identify SWRs automatically.

Keywords: Alcohol, cognitive impairment, identification of ripples, memory consolidation, ripples, Sharp Wave Ripples

Abbreviations

CA Cornu ammonis

DG Dentate gyrus

EtOH Ethanol

HFOs High Frequency Oscillations

RMS Root mean square

SWRs Sharp wave-ripple complexes

This review has a total of 32 pages, four tables, and three figures.

Introduction

Memory is defined as the storage of a learned item and evidence suggests that a brain region called the hippocampus is active during its consolidation (Tulving and Markowitsch, 1998; Duff et al., 2020). Several biomarkers for cognitive operations in the hippocampus have been studied, including altered structure, functional connectivity, and volume of hippocampus (Feng et al., 2019); however, in this review; we concentrate on Sharp Wave-Ripple complexes (SWRs). SWRs are brief (50-100 ms), high-frequency (120-250 Hz), synchronous events that occur during non-rapid-eye movement sleep and "off-line" states of the brain associated with consummatory behaviors and memory consolidation (Buzsáki, 2015; Cowen et al., 2020; Oliva et al., 2020; Zhen et al., 2021; García-Pérez et al., 2022). In addition, the effect of alcohol on memory has been studied previously (Abrahao et al., 2017; Miyake et al., 2020; Hamel et al., 2022), however, to the authors' knowledge, SWRs have not been evaluated in association with memory impairment by chronic alcohol administration.

Moreover, effective identification of ripples may be performed visually by an expert, although it is a laborious and time-consuming work. Methodologies for facilitation or automatic identification of ripples and their analysis are more commonly reported for epilepsy than for SWRs. Epileptic patients present High Frequency Oscillations (HFOs), which are events with frequencies of 80-600 Hz (Burnos et al., 2014). As the bandwidth of SWRs is 120-250 Hz, which is in between the bandwidth of HFOs, the reported methodologies for HFOs may be used for the identification of SWRs. Different approaches for automatic detection of ripples are also reviewed in this article.

This review intends to communicate the state-of-the art about the relationship between alcohol, memory consolidation, and ripple activity, as well as the use of the main methodologies to identify SWRs automatically.

1. Alcoholism as a global problem of health and study models

Alcohol is a toxic and psychoactive substance that causes dependence and has been consumed as a socially acceptable drug for centuries (World Health Organization, 2018a). In 2016, 43% of the total population (15+ years) was current drinkers and 12.5% were former drinkers. Among drinkers, the record of alcohol per capita consumption was 15.1 liters per year (World Health Organization, 2018b). Alcohol consumption can progress to alcoholism, a condition characterized by a physical dependence on alcohol and the inability to stop or limit drinking (Wood, 2013). Globally, an estimated 237 million men and 46 million women suffer from alcohol use disorders (Härtl and Garwood, 2018). Beyond the significant social and economic losses to individuals and society, the harmful use of alcohol has important health consequences. The impact of alcohol consumption on chronic and acute health outcomes is determined by the total volume of alcohol consumed and the pattern of drinking (World Health Organization, 2018a).

Harmful use of alcohol is accountable for 7.1% and 2.2% of the global burden of disease for males and females, respectively (World Health Organization, 2018a). Twenty-five chronic diseases and conditions are entirely attributable to alcohol, including alcoholic fibrosis and sclerosis of the liver, alcoholic cardiomyopathy, and fetal alcohol syndrome. Additionally, alcohol is a risk component in certain cancers (e.g. mouth cancer, liver cancer, breast cancer, and nasopharynx cancer), mental and behavioral disorders (e.g. unipolar depressive disorders), neurological conditions (e.g. epilepsy), cardiovascular and circulatory diseases (e.g. hypertensive heart disease and ischemic heart disease), brain vascular diseases (e.g. ischemic stroke), and diabetes (Shield et al., 2013; Hendricks, 2020). Of all deaths attributed to alcohol in 2016, 28% were due to injuries, such as those from traffic crashes, self-harm, and interpersonal violence; 21% due to digestive disorders; 19% due to cardiovascular diseases, and the remainder due to infectious diseases, cancers, mental disorders, and other health conditions (Härtl and Garwood, 2018).

Accordingly, alcoholism is a global health problem that requires the study of the molecular and cellular mechanisms that produce different acute and chronic diseases. This can be assessed with animal models. At this respect, the resemblance in the anatomical organization, functional development, and effects of alcohol at the same concentrations (Table 1) between the human and rodent brain compels rodents as a commonly used animal model (Clark and Squire, 2013).

In addition, an accurate model of alcoholism requires the following criteria: a) alcohol must produce positive reinforcing effects, b) the animals must consume the alcohol for its pharmacological effects and not only for its caloric value, taste, or smell, c) the animal should orally self-administer ethanol (EtOH) under free-choice conditions, d) self-administration of EtOH must lead to pharmacologically relevant blood alcohol concentrations, e) the animals should be willing to work to obtain EtOH, f) chronic consumption of EtOH should lead to metabolic and functional tolerance, g) physical signs of withdrawal should develop following EtOH withdrawal after a period of chronic consumption, and h) the animal model easily demonstrates relapse drinking after a prolonged period of abstinence (McBride et al., 2014).

Alcohol models include different methods of ethanol administration like consumption of EtOH in the drinking water (Augier et al., 2014), ethanol-containing liquid diet, vapor inhalation, repeated intraperitoneal injections, intra-gastric infusions of EtOH, schedule-induced EtOH polydipsia, voluntary ethanol drinking

paradigm, and food restriction with alcohol as the only fluid available (Crabbe, 2014; Kliethermes, 2005; Tabakoff and Hoffman, 2000). A summary of the principal models is shown in Table 2.

2. Relationship between alcohol, memory consolidation, and hippocampus

Evidence in several rodent models has shown that ethanol produces cognitive impairment in hippocampal-dependent tasks and that the damage varies according to the stage of development at which the rodent was exposed to EtOH and the dose (Table 3) (White et al., 2000; Reid et al., 2020; Mira et al., 2020). As brain development persists during childhood and adolescence in mammals, alcohol consumption is not only risky during the prenatal stages, but adolescence as well (Table 3). Furthermore, adolescence is usually the age for the start of alcohol consumption and abuse in humans (Mira et al., 2020) due to social enhancement and coping motives (Kuntsche et al., 2005). On the other hand, alcohol-related alterations in adult rodents are not conclusive. However, some experiments have reported cognitive impairment in non-spatial and spatial tasks in the Morris water maze as well as behavioral flexibility impairment (Matthews et al., 2020; Ho et al., 2022).

In addition, several experimental evidences demonstrate that alcohol consumption during gestation, young, and adult rodents produce physical changes such as a reduction in neuronal cell number, brain size, density and volume (Klintsova et al., 2007; Lee et al., 2015; Livy et al., 2003), neurodegeneration (Bird et al., 2018), and decreased neurogenesis (Ieraci and Herrera, 2007) that may explain cognitive impairment (Table 4). However, further investigation is needed.

Memory consolidation is one of the principal processes altered in cognitive impairment produced by alcohol. Memory can be divided into short-term and long-term memory. Short-term memory, called working memory, maintains current, albeit transient, representations of goal-relevant knowledge obtained by verbal and visual-spatial information (Kumar et al., 2020). Short-term memory is converted into long-term memory by a process called memory consolidation, which is enhanced by repetition and by adding several sensory modalities or adding emotional context (Tonegawa et al., 2018; Klinzing et al., 2019; Girardeau and Lopes-dos-Santos, 2021). Figure 1 provides an overview of the subdivisions of memory.

In addition, memory consolidation requires both hippocampus-dependent and non-hippocampus-dependent processes, but we will focus on the role of the hippocampus structure (Kibble and Halsey, 2015; Klinzing et al., 2019). The hippocampus is a bilateral structure, meaning that the brain has two hippocampi, which are located deep in the innermost fold of the temporal lobe (Figure 2a,b) (Stimac, 2022). It has a seahorse-like shape formed by the cornu ammonis (CA), further divided into four zones, namely, CA1, CA2, CA3, and CA4 (Mira et al., 2020). The hippocampus forms the hippocampal formation, which also includes the dentate gyrus (DG) and the subiculum. Together, these structures play important roles in learning and memory, and considering that the DG is one of the two sites for neurogenesis in the mature brain (Sokolowski and Corbin, 2012; Abbott and Nigussie, 2019). Hippocampus in mammals has a five-layered structure, consisting mainly of pyramidal cells that have both apical and basal dendrites. In contrast, the DG has a three-layered structure consisting mainly of granule cells that have only apical dendrites. Interneurons are a minority of neurons in the hippocampal formation, making up only 10-20% of the total, but they play a crucial role in regulating circuit-level signaling within the hippocampus due to their dense axonal arborization (Bird et al., 2018).

The hippocampus plays a relevant role in memory consolidation. In this brain region, multimodal sensory and spatial information from the entorhinal cortex via its principal trisynaptic circuit is processed and integrated (Figure 3) (Chao et al., 2020; Park et al., 2021). In this circuit the axons of layer II neurons of the entorhinal cortex project through the perforant pathway into the granule cells of the DG. Granule cell axons, termed mossy fibers, are projected into the mossy fiber pathway to stimulate pyramidal cells in the CA3 region of the hippocampus. Finally, the CA3 axons, called the Schaffer collaterals, project through the Schaffer collateral pathway to make excitatory synapses on more proximal regions of CA1 pyramidal cell dendrites. The major output of the hippocampus is through the pyramidal neurons in the CA1 region, which project to the subiculum before extending back to the entorhinal cortex. Both, CA1 and the subiculum, have projections into the fornix, primarily to the septal nuclei and the mammillary bodies; moreover, in this

circuit backprojection pathways could serve to modulate information processing in

hippocampal CA1 (Xu et al., 2016; Martin, 2021).

As mentioned before, human and rodent brains have a resemblance in the anatomical organization and functional development, particularly in the hippocampal formation, which is illustrated in Figure 2. These similarities in memory function across mammalian species compel rodents as animal models (Clark and Squire, 2013). Furthermore, both humans and rodents manifest SWRs in the hippocampus when they are consolidating memory (Buzsáki, 2015).

3. Role of ripples on memory consolidation

SWRs are bursts (50-100 ms) of cell activity in the hippocampal local field during a pause in active exploration or while asleep. Sharp wave ripples encompass two distinct components, namely sharp waves and ripples, which collectively constitute this neural phenomenon. Sharp waves refer to brief, high-amplitude waveforms that are characterized by a rapid and synchronized depolarization followed by a slower, hyperpolarizing phase. On the other hand, ripples are fast oscillations that occur within the context of sharp waves. Ripples are high-frequency oscillations in the range of 100-250 Hz and are superimposed on the sharp wave waveform. Sharp wave ripples, as a whole, refer to the combined occurrence of these two phenomena. The timescale at which SWRs are presented aligns with the optimal window to induce synaptic plasticity, and therefore, they have been accepted as a definite biomarker for the encoding of memory fingerprints on synaptic weights (Buzsáki, 2015; Cowen et al., 2020; Evangelista et al., 2020; Oliva et al., 2020; Roumis and Frank, 2015). Brain rhythms, such as slow waves, ripples, and spindles, happen at approximately the same speed in mammals, irrespective of brain size (Buzsáki et al., 2013). Several electroencephalography traces of mammals from the literature and their reported characteristics have been summarized and compared by Buzsáki et al. (2013).

Studies suggest that the CA3 region is the source of SPW in the hippocampus, as the spatial distribution of spontaneous SPW closely resembles that of Schaffer collateral evoked responses (Buzsáki et al., 1983). Also, evidence demonstrates that the blockage of CA3 output of the trisynaptic hippocampal circuit impairs the consolidation of contextual fear memory and the CA1 ripples and the ripple-associated reactivation of experience-dependent firing patterns of CA1 neurons, underlie the importance of the trisynaptic circuit and SWR in the consolidation of hippocampus-dependent memory (Nakashiba et al., 2009). Similarly, the SWR are physiological events associated with replay (multifactorial event) that underlie memory consolidation in the trisynaptic hippocampal circuit and the organization of this replay is influenced by the brain state (Buszáki, 1989, 2015), then during replay, SWR are also influenced by other factors in the trisynaptic circuit, such as genetic, microcircuits and behavioral states. De la Prida (2020) analyzes, under scrutiny based on the evidence, some of these factors in the CA1 hippocampal region, such as cell-type and input-specific connectivity as well as radial expression of receptors and intrinsic properties that influence the replay.

Additionally, the behavior of CA3 cells can be compared to that of pacemaker cells, as they exhibit early firing during population events and recruit follower cells to fire (Wittner and Miles, 2007). As described before, these pyramidal cells have extensive axon collaterals that project to both CA3 and CA1 regions, and the synapses they form account for most connections within the hippocampus (Amaral and Witter, 1989). Although recent research has called into question the extent of connectivity in CA3 (Guzman et al. 2016).

A group of interneurons cooperate to coordinate temporally and spatially the spike content of SWRs to replay the awake neuronal sequence segments in a compressed manner (Buzsáki, 2015). The connections between these interneurons and the pyramidal neurons are organized in a precise and intricate manner to allow for the generation and propagation of SWRs (Buzsáki, 2015). Parvalbumin -positive basket cells and oriens lacunosum-moleculare cells form local inhibitory circuits within the hippocampus, with their axons forming perisomatic and dendritic synapses on pyramidal neurons, respectively. These inhibitory connections help to shape the spatiotemporal patterns of SWRs and regulate the timing and coordination of the network activity during SWRs (Klausberger and Somogyi, 2008). It has been demonstrated that parvalbumin -positive basket cells fire before oriens lacunosum-moleculare during multiple brain rhythms including ripples and theta waves (Varga et al., 2012).

Axo-axonic cells have been shown to preferentially fire just after the peak of the theta cycles and discharge transiently at the beginning of SWRs (Klausberger et al., 2003). Other interneurons, such as ivy cells, appear to be only weakly modulated by SWRs (Buzsáki, 2015). However, the exact mechanisms underlying SWRs are still an active area of research, and further studies are needed to fully understand the complex interplay of interneurons in SWR generation and propagation.

After a sharp wave event, there is a brief period during which hyperpolarization occurs, ending the wave and creating a refractory period (Buzsáki, 2015). Specific groups of active cells that encode a particular memory tend to be preferentially replayed during SWRs (Wilson and McNaughton, 1994). During SWR replay, newly obtained and previously known knowledge is merged to affect judgements, plan actions, and maybe inspire original ideas (Buzsáki, 2015).

SWRs have been shown to be critically involved in the process of episodic memory consolidation (Jadhav et al., 2012). Spatial learning requires remembering and choosing paths to goals (Shin et al., 2019). Disruption of SWRs impairs spatial memory (Buzsáki, 2015), which consolidation depends on the reactivation of hippocampal place cells that were active during recent behavior (Oliva et al., 2020). Continuous track of hippocampal-prefrontal ensembles throughout learning of a spatial alternation task demonstrated that during pauses between behavioral trajectories, reverse and forward hippocampal replay supports an internal cognitive search of available past and future possibilities and exhibits opposing learning gradients for prediction of past and future behavioral paths, respectively (Shin et al., 2019).

Examination of the role of SWRs during the consolidation of social memory—the ability of an animal to recognize and remember a member of the same species—revealed that CA2 pyramidal neurons that are active during social exploration of previously unknown conspecifics are reactivated during SWRs. This suggests that SWRs originating from different regions may have different functional roles: CA3 SWRs seem to be important for spatial memory, whereas consolidation of social memory requires SWRs arising in CA2 and object remapping dorsal CA1 and CA3 (Oliva et al., 2020).

Various changes in SWRs have been reported in different pathologies such as epilepsy (Mooij et al., 2022), models of Alzheimer's disease (Jones et al., 2019; Stoiljkovic et al., 2019; Prince et al., 2021; Caccavano et al., 2020), and aging (Cowen et al., 2020; Witton et al., 2014). However, little evidence has been reported on the effect of alcohol on SWRs and memory consolidation. According to a study by Krawczyk et al. (2016), increased duration and amplitude were observed in SPW waveforms when evaluating the effect of prenatal ethanol exposure on recordings from CA3 hippocampal pyramidal cells *in vitro* . A previous experiment was done by Mikaye et al. to analyze the effect of acute ethanol administration on the spike patterns of hippocampal cell populations. Their results suggested that ethanol does not significantly alter the frequency of hippocampal SWRs (Miyake et al., 2020). While these studies provide valuable insights into the effects of ethanol exposure on SPW waveforms, further investigations are warranted to fully elucidate the complex relationship between chronic alcohol use and SWRs. Advancing our knowledge in this area can have important implications for addressing alcohol-related cognitive impairments and developing targeted interventions.

Understanding the role of hippocampal ripples in memory consolidation is crucial for elucidating the mechanisms underlying alcohol-induced memory impairments. However, as have been revised, analyzing ripple activity can be challenging due to the complex and dynamic nature of these events, as well as the variability in the methods used to detect and quantify them.

To address these challenges, researchers have developed a range of analytical models and techniques aimed at improving the accuracy, reliability, and reproducibility of ripple analyses. The use of these analysis models is essential for understanding the functional significance of hippocampal ripples and their relationship with memory consolidation (Girardeau, 2021, Creery, 2022). As can be seen in the next section of this paper, by providing more accurate and reliable measures of ripple activity, these techniques can help to elucidate the neural mechanisms underlying memory processes and the effects of various factors, such as alcohol consumption, on these processes.

Moreover, these techniques can facilitate comparisons between different experimental conditions and bet-

ween different studies, thereby enhancing the generalizability and reproducibility of findings across different research contexts.

4. Principal methodologies to study and analyze ripples as a biomarker of memory consolidation

Studies of oscillations with frequencies above traditional electroencephalogram limits (greater than 40 Hz), have increased over the last decade due to increasing evidence that suggests that HFOs reflect a mechanism of epileptic phenomena and might serve as a biomarker of epileptogenesis and epileptogenicity. This has resulted in a growing interest in the detection and analysis of these events (Birot et al., 2013; Navarrete et al., 2016). The bandwidth of SWRs (120-250 Hz) (Buzsáki, 2015) falls between the one of HFOs (80-500 Hz) (Burnos et al., 2014), therefore, the methodologies for automatic identification of HFOs might be adapted to identify SWRs. In recent decades, there has been a substantial surge in the field of artificial intelligence, which has been extensively explored for enhancing the classification of HFOs. Although our subsequent discussion primarily focuses on conventional methodologies that do not utilize machine or deep learning, it is worth noting that readers may find the works of Wong et al., 2021 and Navas-Olive et al., 2020 intriguing in the context of HFO classification.

In general, HFO detection methods are classified in three main groups: manual review, supervised detection, and unsupervised detection. Manual review is a visual inspection performed by an expert. It is a time-consuming process and highly subjective to the perception of the reviewer; however, it is currently considered the gold standard when assessing the performance of automated algorithms for HFO detection. Supervised detection consists of methods with high sensitivity and low specificity detection, which is later reviewed manually to eliminate false positive events. On the other hand, unsupervised detection methods must have high sensitivity and high specificity, which is difficult to achieve (Birot et al., 2013; Navarrete et al., 2016).

In the last two decades, several methods for the automatic detection of HFOs have been developed. Broadly speaking, the supervised and unsupervised detection algorithms perform a series of common steps to identify the putative events. The first step is to emphasize the frequency of interest by filtering the raw signal. Then, a threshold handling detection method is implemented. This can be based on the energy, statistical or spectral characteristics of the filtered data. Finally, depending on the method, a supervised or unsupervised mechanism is implemented to distinguish the HFO from noise, artifacts, and spikes (Navarrete et al., 2016).

Staba et al. (2002) reported the first supervised method for the automatic detection of HFOs, which uses the root mean square (RMS) to calculate the threshold after applying a band-pass filter. The authors declared a sensibility of 84%. Later, other authors used the algorithm proposed by Staba et al. as the initial steps for theirs. For example, Burnos et al. (2014) decreased the number of standard deviations (SDs) established to classify the oscillation as an event of interest (EoI). Then, they utilized the instantaneous power spectra of the Fourier Transform representation to eliminate some false positive events. This methodology had a higher sensibility in 4 out of 5 accepted patients when compared to the methodology proposed by Staba et al (Burnos et al., 2014). Other authors that used the algorithm of Staba et al. as the initial steps of theirs include Crèpon et al. (2010), Ellenrieder et al. (2012), and Blanco et al. (2010).

Charupanit and Lopour (2017) reported a simple statistical detection method. The iterative algorithm uses an estimate of the amplitude probability distribution of the background activity to calculate the optimum threshold for identification of HFO. It described a sensitivity of 99.6%. Additionally, Shimamoto et al. (2018) computed an algorithm that uses independent component analysis to detect ripples. The events detected were further classified as true or false ripples by implementing a topographical analysis to the time-frequency plots. They declared a precision of over 91% and a sensibility of over 79%.

Another supervised algorithm to detect HFOs was implemented by Birot et al. (2013) . This algorithm uses the RMS amplitudes and a Fourier or Wavelet energy ratio to detect putative events. They implemented this algorithm in both human and animal datasets and had an area under the curve greater than 0.95. Another author that used wavelet entropy was Zelmann et al. (2010) with a reported sensitivity and specificity of 96%. Finally, Liu et al. (2021) computed in 2021 an algorithm that combines several reported features like Short-time Energy and Hilbert Transform with visual extracted features from the frequency spectrum. They

also evaluated this algorithm with datasets from both patients and animal models and reported a sensibility greater than 91%.

However, despite the increasing methodologies for effective automatic identification of HFOs, there is currently no gold standard other than visual examination. Therefore, we suggest that a global consensus of the identification of true ripple activity and its analysis must be reached to evaluate more accurately and compare properly under different experimental conditions. It has been proposed as a solution to implement different algorithms across similar datasets to reach a consensus about the one method that performs best in all contexts (Navarrete et al., 2016).

5. Perspectives

Despite the extensively reported negative impacts of alcohol on health, alcohol consumption persists at high rates worldwide. Alcohol abuse generates significant impairments in cognition, which have been demonstrated by rodent models. Morphological alternations of the hippocampus after exposure to ethanol may explain physiological impairments. To enhance memory consolidation, SWRs help transport compressed hippocampus representation to dispersed circuits. Selective disruption of SWRs interferes with memory. To the author's knowledge, there is no evidence of research where Sharp Wave Ripples are evaluated in association with memory impairment produced by chronic alcohol administration. The study of the effect of alcohol on SWRs as a memory consolidation biomarker may provide an opportunity for new forms of management to restore and improve cognitive impairment in alcoholism. This could be done by utilizing alcoholism animal models, such as rats exposed to chronic levels of alcohol, and recording their SWRs during "off-states". The detection and analysis of SWRs could be assisted by automatic detection algorithms that have been previously reported for HFOs. Out of all the algorithms reported here, the parallel implementation of several methodologies can potentially resolve false negative identification of events. Additionally, implementation of several methodologies on similar datasets is necessary to pinpoint a gold standard that performs best in all contexts with minimal adjustments.

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Figure captions

Figure 1. Subdivisions of the human memory and its associated brain regions. Reproduced and modified from (Kandel et al., 2013; Sweatt, 2003).

Figure 2. The anatomical features of the hippocampus.**(a)** and **(b)** illustrate the hippocampal formation of human and rodent brain, respectively, in relation to three structures: 1) the fornix, which represents one of its output pathways; 2) the entorhinal cortex, which serves as both an input and an output pathway; and 3) the mammillary body, a target that it projects to. The amygdala is located in the anterior part of the temporal lobe. The images are adapted and modified from Martin (2021) and Sokolowski and Corbin (2012).

Figure 3. Pathways in the hippocampus. Information arrives to the hippocampus from the entorhinal cortex through the perforant pathways and travels to the CA1 by both a direct (blue) and an indirect (red), also called Trisynaptic circuit of the hippocampus. Arrows denote the direction of impulse flow. Reproduced and modified from (Kandel et al., 2013).

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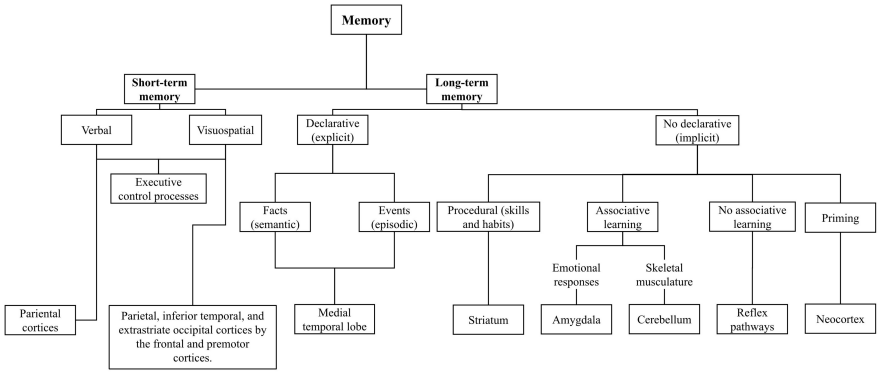

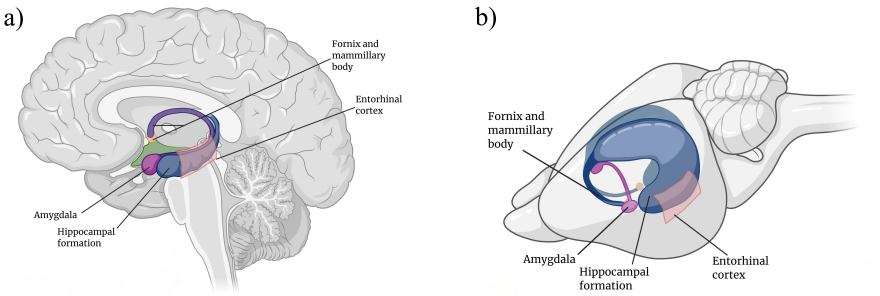

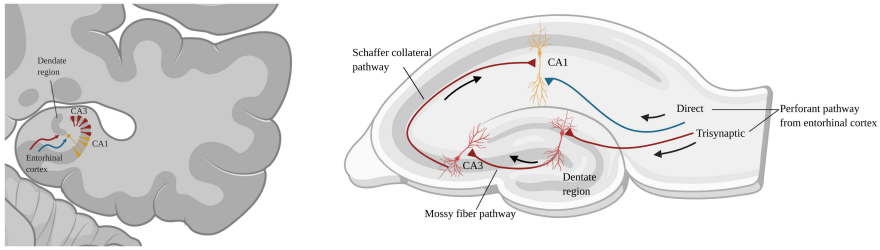

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