Neuroscience

Perspective

Epileptic seizures and link to memory processes

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Abstract: Epileptogenesis is a complex and not well understood phenomenon. Here, we explore the hypothesis that epileptogenesis could be "hijacking" normal memory processes, and how this hypothesis may provide new directions for epilepsy treatment. First, we review similarities between the hypersynchronous circuits observed in epilepsy and memory consolidation processes involved in strengthening neuronal connections. Next, we describe the kindling model of seizures and its relation to long-term potentiation model of synaptic plasticity. We also examine how the strengthening of epileptic circuits is facilitated during the physiological slow wave sleep, similarly as episodic memories. Furthermore, we present studies showing that specific memories can directly trigger reflex seizures. The neuronal hypersynchrony in early stages of Alzheimer's disease, and the use of anti-epileptic drugs to improve the cognitive symptoms in this disease also suggests a connection between memory systems and epilepsy. Given the commonalities between memory processes and epilepsy, we propose that therapies for memory disorders might provide new avenues for treatment of epileptic patients.

Keywords: epilepsy; memory consolidation; kindling; long-term potentiation; Alzheimer's disease; reflex epilepsy; extinction therapy

1. Introduction

During sleep and quiet wakefulness, memory patterns are frequently replayed to consolidate memories. For example, patterns of neuronal activity evoked during a behavioral task are later spontaneously replayed when an animal is resting or sleeping [1]. It has been proposed that epileptic

activity is "hijacking" those memory consolidation processes, where repetitive memory replay generates aberrant oscillatory network activity [2]. Our recent work provided new evidence for this hypothesis. Using chronic neuronal recordings in epileptic rats, we found that ictal activity patterns were similar to neuronal patterns occurring spontaneously between seizures [3]. This observation suggests that ictal activity could be a "memory pattern" which gets trapped in attractor-like dynamics (B.L. McNaughton personal communication).

Most seizures are spontaneous, meaning that they do not have any clearly identifiable trigger, and can occur at any time, including sleep [4–6]. However, in a subset of epileptic patients, spontaneous seizures are preceded by auras: a sensation of particular smell, lights, or certain thoughts [7,8], 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 [9–12]. For example, reflex seizures in some patients may be elicited by flickering lights, certain sounds, or specific activities [13]. A patient may experience both "spontaneous" and "reflex" seizures, suggesting the same underlying mechanisms [12]. It was also reported that performing a specific action (for example, toothbrushing) as well as just thinking about that action can induce seizures [14]. 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 [15].

In this perspective we present experimental and clinical studies to illustrate the close relationship between epileptogenesis and memory consolidation mechanisms. We begin by describing the interictal events, and how they relate to memory consolidation processes. Next, we describe kindling model used for seizure induction, and its relation to long-term potentiation (LTP), a model for memory formation [16]. We also discuss how cognitive decline in Alzheimer's disease has been related to the development of convulsive pathways [17]. Finally, we 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 perspective is that memory formation processes and epilepsy may be closely related, which could help in developing new therapies.

2.   Seizure related consolidation and memory related changes during sleep

Seizure related consolidation refers to the changes that occur in the neuronal activity after a seizure epoch, consisting of the 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 [18]. This selective modification of 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 preferentially strengthened [1,18]. Similarly, activity patterns during inter-ictal spiking (IIS) can be consolidated during the following sleep. [19]. 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 [20]. IIS propagation is seen to be promoted by sleep, with the non-rapid eye movement (NREM) period particularly conducive to greater spike production and propagation [21–23]. These studies provide evidence that seizure induced activity can be

consolidated in neuronal circuits using similar mechanism as employed by normal learning and memory functions [1].

Moreover, in childhood epilepsy the presence of IISs disturbs the spatiotemporal coupling mechanisms associated with sleep related memory consolidation [24]. 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 [25–30]. The interaction of hippocampal IIS with cortical spindles during NREM sleep has been associated with impaired memory consolidation [31]. Studies have shown that IISs disrupt memory and cognition in both animal models [32] and epileptic patients [33]. Recent studies indicate that this is possibly due to intrahippocampal IISs disrupting memory consolidation during sleep involving the hippocampal and cortical circuits [34,35]. Those results suggest that IISs could be "hijacking" and disturbing normal memory processes [36,37].

3.   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 [38]. SWRs reactivate the same sequential neuronal patterns, which were involved before in learning during wakefulness [1]. 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 [39,40]. The fast oscillations usually originate in the epileptogenic area [39,40]. The pathological HFOs are also associated with memory impairments [41] and were shown to disrupt the cognitive functionality of the hippocampus, especially when it is part of the epileptic circuit [42]. Although, pathological HFOs may involve distinct subnetworks of neurons as compared to SWRs [43], there is a strong overlap between the mechanisms underlying SWRs and pathological HFOs [44]. This leads to the suggestion that normal physiological processes which are involved in SWR can be "reused" to generate epileptic HFOs [2,45].

4.   Neuronal plasticity mechanisms in epilepsy and in memory processes

4.1. 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 [46]. The stimulation, which could be electrical, chemical, optogenetic, or sensory (for example, tactile or auditory) [46–50], recruit neurons to become part of the "kindled" circuit. The behavioral seizures occur later when the kindled activity spreads to the motor cortex [51]. 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 [52]. The neural changes induced by kindling are usually long lasting [53,54]. The resemblance of kindling to chronic focal epilepsy in human patients has resulted in using it as a common epilepsy model in animals [55–58].

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 [59]. As a result of those changes in NMDA receptors, granule cells produce long duration synaptic currents, leading to a burst spiking mode [60,61]. This increased activity then propagates into the CA3 area of the hippocampus from the dentate gyrus contributing to the developing epileptic circuits [60].

The lasting synaptic changes leading to convulsive behavior are akin to the physiological mechanisms forming memory engrams [53], which is mediated by LTP [62]. LTP increases the synaptic strength that can last for years [63,64] serving as a basis for memory at the cellular level [65,66]. The LTP can be experimentally induced by repetitive, high frequency stimulation of afferent connections [67], most widely studied in the Schaffer collaterals and the perforant pathway [68]. At the synaptic level, LTP is typically mediated by NMDA receptors [69], similarly as described above in the kindling model.

4.2. 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 [70–72]. In an in vitro study, LFS of Schaffer collaterals has been shown to reduce the epileptiform activity in a gradual and persistent fashion [73]. Likewise, in a study in young rat pups, 1 Hz LFS was shown to reduce after-discharges as well as behavioral seizures [74]. The main mechanism by which the LFS reduces the response of the stimulated pathways is LTD [75,76]. LTD is the opposing process to LTP, and it is implicated in the clearing of old memory traces [77,78]. Similarly, as kindling and LTP, the LFS and LTD is NMDA depended, as it can be blocked by a NMDA receptor antagonist [73]. 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).

5. 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 [79,80]. Alzheimer's disease leads to a hypersynchronous activity which was suggested to accelerate the progression of dementia [81]. Hypersynchronous activity, similar to ictal activity, was observed in both animal models of Alzheimer's disease and in clinical studies [82–84]. For instance, imaging studies using fMRI showed hyperactivity in the hippocampus, which was also accompanied by cognitive impairments affecting pattern separation [85]. Alzheimer's patients were also reported to have silent hippocampal seizures and epileptiform spikes during sleep [86]. Memory impairments and increase in the incidence of epilepsy and seizures is also commonly observed in normally aging animals, including humans ($\geq$ 60 years old) [87–91]. Importantly, antiepileptic drugs were shown to offer new therapeutic potential for memory impairments in elderly animals and humans [92,93], which provides strong support for common underlying neuronal circuit changes in epilepsy and in memory impairments.

6.   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 [94]. 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 [95,96]. Thus, the specific sensory stimulus may lead to over-activation in specific brain regions which can induce seizures in susceptible patients [97]. 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 [98]. 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 [99]. In another example, specific memories of music led to convulsive episodes [100–102]. This shows that memories have an ability to activate the epileptic pathways, similarly to sensory stimuli.

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 [103,104].

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 [105]. Similarly, in epileptic patients with spontaneous (non-reflex) seizures, increased slow wave activity was observed as compared to healthy controls [106–108]. 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.

7.   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 [109]. 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 [110]. Reactivation of memories makes them susceptible to modification [111,112]. Thus, by targeting specific memories during the reconsolidation processes it is possible to weaken those memory traces [113]. For example, reactivated fear memories coupled with protein synthesis inhibitors injected into the amygdala led to amnesia related to a fear inducing stimulus [111]. Similarly, beta-adrenergic receptor blocker propranolol has been shown to be effective in ameliorating post-traumatic stress disorder (PTSD) related memories [114,115]. Propranolol was shown to also interfere with memory reconsolidation processes when administered after exposure to stressful stimuli in animals [116] and in humans [117].

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 [118,119]. Thus, this type of exposure therapy has been proven to be a valuable option for fear memory extinction [120].

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. [121], 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 [18]. 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.

8. Conclusion

In only about two-thirds of patients, seizures can be controlled with medication [122]. 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 [123] 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 [20]. 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 [18]. 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 [124]. 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 [99,125]. Similarly, administrating memory reconsolidation blockers after a spontaneous seizure may weaken epileptic networks. In future, we plan to combine electrophysiology with behavioral experiments and modeling [126–130] to explore those ideas. In summary, 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.

Acknowledgements

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

Ritwik Das and Artur Luczak conceptualized this work and wrote this manuscript.

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