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Review

# From adagio to allegretto: The changing tempo of theta frequencies in epilepsy and its relation to interneuron function

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ABSTRACT

Despite decades of research, our understanding of epilepsy, including how seizures are generated and propagate, is incomplete. However, there is growing recognition that epilepsy is more than just the occurrence of seizures, with patients often experiencing comorbid deficits in cognition that are poorly understood. In addition, the available therapies for treatment of epilepsy, from pharmaceutical treatment to surgical resection and seizure prevention devices, often exacerbate deficits in cognitive function. In this review, we discuss the hypothesis that seizure generation and cognitive deficits have a similar pathological source characterized by, but not limited to, deficits in theta oscillations and their influence on interneurons. We present a new framework that describes oscillatory states in epilepsy as alternating between hyper- and hypo-synchrony rather than solely the spontaneous transition to hyper-excitability characterized by the seizures. This framework suggests that as neural oscillations, specifically in the theta range, vary their tempo from a slowed almost adagio tempo during interictal periods to faster, more rhythmic allegretto tempo preictally, they impact the function of interneurons, modulating their ability to control seizures and their role in cognitive processing. This slow wave oscillatory framework may help explain why current therapies that work to reduce hyper-excitability do not completely eliminate seizures and often lead to exacerbated cognitive deficits.

## 1. Introduction

Traditionally, epilepsy is defined by the seemingly spontaneous transition from normal inter-ictal activity to a state of hyper-excitability defined by electrographic and motor seizures. However, recent investigations of temporal lobe epilepsy (TLE) have made it increasingly evident that the transition is not spontaneous, nor is inter-ictal activity similar to that in healthy animals. In fact, the morphology of seizure onset patterns can be identified seconds before ictal spiking (Shiri et al., 2016) and the activity of individual neurons during the transition is inhomogeneous in rats (Avoli et al., 2016; Grasse et al., 2013b) and humans (Perucca et al., 2013). Specifically, multiple studies demonstrate that during the transition to seizures some neurons increase their firing rate while others decrease (Babb et al., 1987a; Bower and Buckmaster, 2008b; Bower et al., 2012; Grasse et al., 2013b; Jiruska et al., 2013; Karunakaran et al., 2016; Truccolo et al., 2011b) suggesting heterogeneous changes in firing rate rather than simple overall hyper-excitability. Studies from our lab and others (Arabadzisz et al., 2005b; Avoli et al., 2013; Behr et al., 2017; Broggini et al., 2016; Grasse et al., 2013b; Jefferys et al., 2012; Perucca et al., 2013) show that the critical factor in the transition to seizures is hyper-synchrony, as measured by increases in synchrony within local field potentials (LFPs), between units and LFPs (i.e. spike-field coherence) and between units, especially in the theta band. Therefore, we hypothesize that hyper-synchrony, rather than simple hyper-excitability, is a better marker of the likelihood of a network transitioning to ictal activity (Schwartzkroin and Haglund, 1986; Wyler et al., 1982).

While seizures may be the hallmark of TLE, the disease is also associated with several common co-morbidities including cognitive dysfunction and psychiatric disease (Avanzini et al., 2013; Chauviere et al., 2009; Dinkelacker et al., 2016; Farina et al., 2015; Giovagnoli et al., 2011, 2016; Karunakaran et al., 2016; Lee et al., 2017a; Parente et al., 2013; Semple et al., 2018; Xu et al., 2018). Interestingly, cognitive disability may also be associated with pathological oscillations,

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specifically characterized by hypo-synchrony, which can be defined as a lack of oscillations within a region (Chauviere et al., 2009), the lack of coherence of oscillations between electrodes (Sarnthein et al., 2005) or a lack of spike-timing (Karunakaran et al., 2016) or phase precesion between individual neurons and oscillations (Lenck-Santini and Holmes, 2008), in the theta band during interictal periods. This is important because theta oscillations play a key role in synaptic plasticity and cognition (Buzsáki, 2002; Wallenstein and Hasselmo, 1997). In fact, direct lesions of the medial septal nucleus (MSN) or the dorsal fornix reduce hippocampal theta oscillations and impair spatial memory performance (Chrobak et al., 1989; Givens and Olton, 1990a; Winson, 1978) in rodents. Moreover, a concomitant decrease in theta oscillations and impaired spatial learning can be observed in models of both traumatic brain injury (Fedor et al., 2010; Kumar et al., 2009; Lee et al., 2013) and epilepsy (Chauviere et al., 2009; Kitchigina et al., 2013a; Lee et al., 2017a). Similar to findings in rats, theta oscillations have been observed in humans across a variety of cognitive tasks, including recognition (Hsieh et al., 2011; Raghavachari et al., 2001), recall (Sederberg et al., 2003) and virtual spatial navigation tasks (Caplan et al., 2003; de Araujo et al., 2002; Kahana et al., 1999; Watrous et al., 2011, 2013a).

While there are clear epilepsy-related changes in synchrony that impair learning and memory, the effects of therapeutic interventions on cognition are often over-looked. Current anti-epileptic drugs (AEDs) reduce excitability by acting on specific cellular mechanisms, such as enhancing GABA-mediated chloride currents or reducing glutamate-mediated currents, sodium currents or voltage-gated calcium currents (primarily T-type)(Bromfield et al., 2006; Macdonald and Meldrum, 1995). Similarly, the three currently FDA-approved therapies involving electrical modulation (vagal nerve stimulation, deep-brain stimulation, and responsive neurostimulation) are also designed to lower excitability (Geller et al., 2017; Salanova et al., 2015). One consequence of lowering excitability, however, is that many patients experience enhanced cognitive impairments (Trimble, 1987) resulting in non-compliance due to unwanted side-effects (Buck et al., 1997; Hovinga et al., 2008). Therefore, we further hypothesize that while a tonic reduction in excitability does reduce hyper-synchrony and, therefore prevent or reduce seizures, it may also favor a hypo-synchronous state, which may explain the increased cognitive disability and additional reports of diminished quality-of-life.

To understand the cellular and network mechanisms that can, on the one hand, lead to hypersynchrony and seizures while, on the other, hyposynchrony and cognitive deficits, requires the development of a new framework that can account for both phenomena rather than hyper-excitability alone. This new framework could allow us to develop therapies, whether future drug development or neuromodulation paradigms, that are both highly efficacious yet with minimal side effects. In fact, understanding the mechanisms of epilepsy that span seizures and the comorbid impact on cognitive disorders could lead to the identification of treatment options that are more effective and for which patients are willing to be more compliant (Buck et al., 1997; Hovinga et al., 2008). There are certainly oscillations across multiple frequency bands, and potential oscillatory interactions that may contribute to ictogenesis (Levesque and Avoli, 2018), and certainly to arousal and cognitive function (Mizuseki and Miyawaki, 2017). However, we propose that theta frequency oscillations, and synchrony with these oscillations, play a key and specific role of theta oscillations to modulate seizures as well as learning and plasticity. Therefore, in this review, we will examine the evidence that pathological theta synchrony with interneurons, transitioning from a slow adagio tempo to faster allegretto explains both spontaneous seizures and cognitive decline (Fig. 1). Specifically, short and defined epochs of hyper-synchrony result in the generation and spread of seizures while extended periods of hypo-synchrony result in the reduced potential for plasticity and therefore cognitive disorders. Understanding these mechanisms may lead to therapies that can reduce the hypersynchrony while maintaining physiologic levels of synchrony that do not interfere with cogntivie processing.

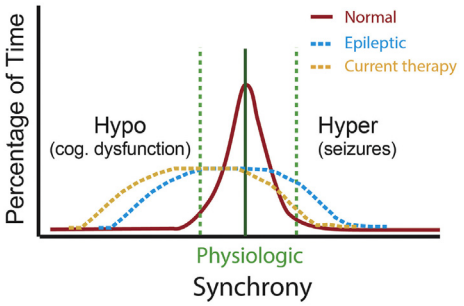


**Fig. 1.** Schematic of synchrony. We hypothesize that in epileptic patients, the septohippocampal circuit is disrupted, with periods of hypo- and hyper-synchrony that correspond to cognitive dysfunction and seizures respectively. We further hypothesize that standard care to treat seizures shifts the curve resulting in reduced hyper-synchrony but increasing hypo-synchrony.

## 2. Sources of hippocampal theta oscillations

Hippocampal theta (3–12 Hz) oscillations are dependent on multiple rhythm generators as well as intrinsic membrane properties of hippocampal neurons (Kocsis et al., 1999, Colgin 2013, Kirk et al. 1998, Montgomery et al. 2009, Watrous et al., 2013a,b, Vanderwolf 1969, Green & Arduni 1954, Buzsaki et al. 1986) (Pevzner et al., 2016). For example, entorhinal cortex cells projecting to the hippocampus (Klink et al. 1993, Alonso & Linas 1989, Alonso & Klink 1993, Quilchini et al. 2010, Dickson et al. 2000) have a natural theta resonance due to a mix of voltage-sensitive currents and the MSN displays intrinsic bursting in the theta range (Vinogradova et al., 1980). Within the hippocampal CA1 subfield these inputs set up a dipole between the distal dendrites and soma. Layer 3 entorhinal cortex (EC) and CA3 subfield connections with the distal dendrites of CA1 residing near the hippocampal fissure depolarize the dendrites (Konopacki et al. 1987, Bland, 1986, Alonso & Garcia-Austt 1987, Kocisis et al., 1999, Kamondi et al. 1998) and this dendritic depolarization can co-occur with somatic hyperpolarization, often related to inputs from the medial septum nucleus (MSN) (Green & Arduni 1954, Petsche et al. 1962, Vertes et al. 2004, Bland 1986). Inpusts from the MSN include projections from GABAergic, cholinergic and glutamatergic neurons and the sum of the activity of these neurons results in hippocampal theta (Tóth et al., 1997, Wang 2002, Cole & Nicoll 1984, Apartis et al. 1998, Vandercasteele et al. 2014, Fuhrmann et al. 2015, Smythe et al. 1992, Colom et al. 2005, Hajszan et al. 2004). In fact, GABAergic neurons have been suggested as the primary pacemakers of theta generation in CA1 as they disinhibit hippocampal interneurons (Wang 2002, Freund and Antal, 1988). MSN cholinergic and glutamatergic neurons modulate excitability in CA1 pyramidal cells. In turn, the CA1 projects back to the MSN resulting in further oscillatory modulation (Toth et al. 1992, 1993, Gaykema et al. 1991, Mattis et al. 2014, Manseau et al. 2008).

In addition to the EC and MSN modulating theta, there are intrinsic membrane properties within the neurons of the hippocampus that contribute to the theta oscillations (Leung and Yim, 1991). For example, in CA1 pyramidal cells, the result of the combined voltage gated and ionic currents results in rhythmicity. Specifically, depolarizations result in the activation of $I_M$ ($K^+$ current), which results in hyperpolarization. In turn, hyperpolarization activates $I_h$ (mix $Na^+$/ $K^+$ current), which depolarizes the cell, bringing the membrane potential closer to spike threshold. Finally, these alternating currents are occurring at the same time as a persistent $Na^+$ current ($I_{NAP}$) (Hu et al., 2002, Pike et al. 2000). Ultimately, the sum of these currents results in intrinsic modulation of the CA1 theta rhythm. In addition to CA1 pyrmaidal cells, hippocampal inhibitory interneurons (Maccaferri &

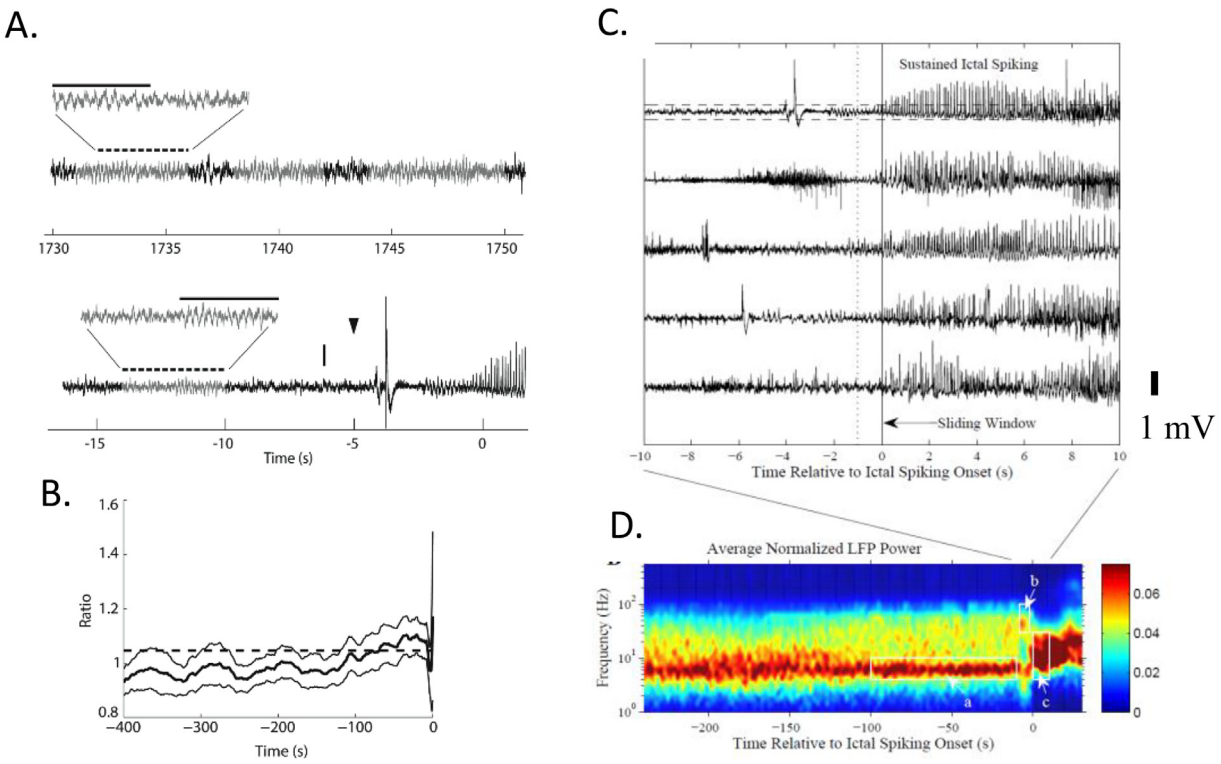


**Fig. 2.** Theta oscillations precede majority of seizures. A) Example of theta prior to seizure onset. B) Ratio of theta (4–10 Hz) power to summed power in delta (1–4 Hz) and alpha (10–20 Hz) bands during the transition to seizures averaged over all seizures for all animals (mean ± sem). Dashed line indicates the mean normalized power in the preictal (2 h) periods. C) Five examples of spontaneous seizures recorded from 5 different rats. Various diverse types of LFP activity are visible before the onset of sustained ictal spiking (0 s). Initial LFP spikes appear in the first, third and fourth seizure, with slow waves following in the first and fourth seizures.. LVF activity and high frequency oscillations are present to some degree or other in all seizures. Horizontal dashed lines in the first seizure symbolize the spike amplitude threshold used to determine the ictal spiking onset. Vertical lines indicate the final resting place of the reverse sliding window used for the same purpose. D) LFP power spectrogram, computed by estimating the power spectrum in consecutive 2 s bins for each seizure, normalizing to the total power in each bin, smoothing, and averaging over all seizures (n = 25). Events a, b, and c (arrows) represent dominant seizure related oscillations, not observed in the background average. White boxes indicate boundaries of time-frequency oscillation windows. A and B reporeinted from Karunakaran et al., 2016. C and D reprinted from Grase et al., 2012.

McBain 1996, Chapman & Lacaille 1999, Pike et al. 2000) (Cobb et al., 1995) also have a natural theta resonance due to a mix of voltage-sensitive currents.

In summary, hippocampal slow wave theta oscillations are modulated by a combination of inputs as well as the intrinsic firing properties of hippocampal pyramidal and interneurons. Each of the generators and modulators plays a critical role maintaining physiologic theta, and thus preventing extended epochs of hyper- or hypo-synchrony.When considering the effects of epilepsy on oscillations and synchrony, cell death or neuronal dysfunction at any level could contribute to pathological hyper- or hypo-synchrony in relation to the theta frequency. Therefore, the distributed anatomy that supports theta oscillation strengthens the case for considering a framework of theta synchrony to both explain, and to target for treatment, seizure and cognitive disorders related to TLE.

## 3. Pathological theta and relationship to interneurons pre-ictally

There is abundant evidence that high power theta oscillations are dominant during the transition to seizures (Fig. 2). For example, highly regular high-powered theta oscillations are the hallmark of hippocampal and septal EEG prior to ictogenesis in models of acute chemically induced seizures (Butuzova and Kitchigina, 2008a; Turski et al., 1983). More recently, studies have shown that theta oscillations are prevalent prior to the onset of spontaneous seizures (Broggini et al., 2016; Grasse et al., 2013b). In fact, a recent study reported that theta oscillations preceded a majority (81%) of spontaneous seizures in a rat model of tetanus toxin-induced TLE (Sedigh-Sarvestani et al., 2014). Moreover, these theta oscillations that precede seizures are different from those during interictal theta oscillations. For example, a narrowing of the theta frequency band from a broader 4–10 Hz to a more rhythmic or narrower 5–8 Hz band has been observed in the approximately 100 s period prior to ictal spiking onset (Grasse et al., 2013b). In sum, these studies emphasize a clear relationship between pathological theta oscillations and the transition from an inter-ictal state to seizures.

Unlike in epileptic animals, neuronal firing during theta oscillations in healthy animals has been widely studied (Buzsáki, 2002; Csicsvari et al., 1999), and both pyramidal cells and interneurons can be classified by their firing patterns in relationship to on-going theta oscillations. Studies in anesthetized animals identified two populations of interneurons whose firing rates were phase-related with theta oscillations. In one population, interneurons increased firirng rate in phase with theta oscillations (theta-on) compared to non-theta periods and another subtype whose firing rate decreased (theta-off cells) (Bland et al., 1999; Colom and Bland, 1987; Smythe et al., 1991). In addition, there are interneurons that don't seem to modulate firing rate in relation to theta. Specifically, within the CA3 there are a number of cells whose activity was not related to oscillations (Bland et al., 2005) and were termed non-theta related while roughly one-third of CA1 interneurons activity were deemed theta-independent (Czurko et al., 2011) Given that theta is the dominant oscillation during the transition to seizure, but also relevant for cognition, how these specific neuronal subtypes fire in relation to theta rhythms (i.e. varying levels of synchrony), might be the key for understanding the difference between

physiological and pathological oscillations.

Multiple studies show that during the transition to seizures, some neurons increase their firing rate while others decrease (Babb et al., 1987b; Bower and Buckmaster, 2008a; Bower et al., 2012; Truccolo et al., 2011a). To better understand this heterogeneity in activity, changes in the firing rates of different neuronal subtypes in the CA3 hippocampus, a common site of seizure initiation in pilocarpine-treated rats (Lévesque et al., 2011; Lévesque et al., 2012; Samiee et al., 2018; Toyoda et al., 2015b), were studied during the transition to seizure. Interestingly, the firing rate of pyramidal cells is typically slower prior to seizure onset than during interictal periods, regardless of theta cell type. In fact, pyramidal cells in the CA3 increase their firing rates after the onset of rhythmic LFP spiking (Grasse et al., 2013b; Toyoda et al., 2015a). Conversely, although in vitro studies have long supported an important role for interneurons during the transition to seizure, the relationship between interneuron firing patterns and seizures is more complex. Despite in vitro seizure-like-events not being spontaneous, they can mimic certain acute changes leading up to a spontaneous seizure, most commonly rhythmic ictal spiking. In vitro studies identified that activation of hippocampal (Fujiwara-Tsukamoto et al., 2010; Velazquez and Carlen, 1999; Ziburkus et al., 2006) and entorihinal (Avoli and de Curtis, 2011a; de Guzman et al., 2008; Gnatkovsky et al., 2008b; Jefferys et al., 2012; Panuccio et al., 2012; Uva et al., 2009; Uva et al., 2015) interneuron networks are potentially responsible for initiation of these seizure-like-events. For example, interneuron activity is maximal just before the onset of rhythmic ictal spikes in the local field of hippocampal slices. In addition, cortical pyramidal cells are recruited into the epileptiform event only after the failure of existing inhibitory restraint mechanisms (Aracri et al., 2018; Levesque et al., 2016; Trevelyan et al., 2007). However, it should be noted that this may be the case for low voltage fast-onset events only, whily hypersynchronous-onset discharges rely on the activation of pyramidal cells (Shiri et al., 2015). Induced seizures have also been studied in the intact brain preparation, where interneuron activity was also shown to be related to the generation of seizure-like-events (Bragin et al., 1997; Gnatkovsky et al., 2008a; Timofeev et al., 2002). These results suggest a complex role for interneurons in the generation of seizures that has recently been studied in-vivo prior to spontaneous seizure in both animals and humans.

In animal models of spontaneous seizures, approximately 40% of CA3 interneurons increase their firing rate at seizure onset (Grasse et al., 2013a), an increase predominately driven by theta-on interneurons (Karunakaran et al., 2016; Toyoda et al., 2015b) (Fig. 3). In the entorhinal cortex in both rats (Levesque et al., 2016) and humans (Elahian et al., 2018), only interneurons showed phase-locked relationship with on-going oscillatory activity in the 5-15 Hz range during the tonic phase. Recordings from the dentate gyrus, CA1 and subiculum found similar patterns of activity as in CA3, with interneurons showing an increase in firing rate in the seconds preceding an ictal event and the patterns of activity were highly consistent from event-to-event (Toyoda et al., 2015b). Here too there was evidence of cell-type specificity, with parvalbumin-positive basket cells and putative bistratified cells being more active pre-ictally, while interneurons in the oriens lacunosum moleculare were not (Toyoda et al., 2015b). Still, nearly a quarter of CA1 interneurons became inactive in the same period. These combined results suggest that identifying the roles of each neuronal subtype, as well the relationship between their firing pattern changes and ongoing theta oscillations, are critical to understanding the physiological mechanisms underlying the transition to seizures and for developing therapeutic interventions.

In addition to changes in individual firing rates of neuronal types during ictogenesis, there are more complex changes for the network to transition from inter-ictal to ictal spiking (Fig. 4), including changes in coherence, studied in the CA3 hippocampus. For example, during the narrowing of the theta frequency band in the 100 s period prior to ictal spiking onset there is a reliable and concomitant increase in synchrony between interneurons and the on-going theta (Grasse et al., 2013a,b). As seizure onset nears, there is an increase in gamma power. As a consequence, interneuron spiking switches its entrainment from the on-going theta to this gamma power increase (Grasse et al., 2013a,b; Lopez-Pigozzi et al., 2016; Toyoda et al., 2015b). Over the subsequent 10 s, interneurons make a final transition in their firing pattern coherence from the gamma oscillations to the emergent ictal spikes, with their firing rate dropping below baseline levels. This switch is unlikely to be due to the slowing of the gamma frequency that occurs as the level of excitation to interneurons decreases (Traub et al., 1996), since the firing rate of the interneurons remains high during this period. Moreover, the switch to a lower frequency is not a continual shift in frequency, but rather reflects the emergence of a separate oscillatory mode since gamma oscillations and ictal spiking coexist (Kopell et al., 2000). This switch could be due to a gradual alteration of a network parameter such as the accumulation of extracellular potassium (Shin et al., 2010), deficits in somatic or dendritic inhibitory efficacy (Cossart et al., 2001; Wendling et al., 2002), or changes in slow potassium currents (Kopell et al., 2000).

Detailed inspection of the enhanced coherence between interneurons and on-going oscillations reveals that these average increases in coherence are not the result of sustained increases, but rather originate from short bursts of coherence for each neuron (Grasse et al., 2013a,b). Typically, the higher the frequency, from theta to gamma, the shorter the interval. Moreover, the fraction of interneurons that show an increase in coherence in each of these oscillation windows is greater than during interictal periods. In summary, during the transition to seizures, not only are there changes in firing rates, but more interneurons show a higher level of phase-locking to the on-going dominant local field oscillations as compared to interictal periods.

As ictal oscillations emerge, they entrain both pyramidal cells and interneurons into a hypersynchronous state as demonstrated in CA3 (Grasse et al., 2013b; Toyoda et al., 2015a), CA1 (Toyoda et al., 2015a) and entorhinal cortex (Levesque et al., 2016). Early in this phase, pyramidal cell firing rates increase as interneuron firing rates drop, suggesting they are synchronous with different phases of the ictal spiking (Grasse et al., 2013a,b; Toyoda et al., 2015b). Together, these findings suggest a series of state transitions dominated by changes in entrainment of interneurons with the ongoing LFP, starting with theta, followed by a peak in gamma power and finally ictal spiking oscillations (Fig. 4). Therefore, a combination of changes in interneuronal activity (both increases and decreases) and spike-field synchrony play an important role in recruiting a network into ictal spiking.

This increased entrainment of interneuron activity to the underlying oscillations and spikes in the CA3 could be partly due to a dysfunction of normal entorhinal cortex operations (Bartolomei et al., 2005; Du et al., 1995; Herrington et al., 2015; Kispersky et al., 2010; Kumar and Buckmaster, 2006). For example, CA3 theta oscillations have been shown to be more locally synchronous when the entorhinal cortex is lesioned (Cappaert et al., 2009). Either alternatively to, or in conjunction with dysfunction of entorhinal driven theta, the medial septum is likely to play a part in the theta synchrony we observe. Highly rhythmic theta oscillations concurrent with rhythmic unit activity have been observed in the hippocampus and/or medial septum (Butuzova and Kitchigina, 2008b; Kitchigina and Butuzova, 2009; Popova et al., 2008) prior to seizures induced in the septum. This highly rhythmic theta activity was considered to be mechanistically different from native theta oscillations, which suppress interictal spikes (Colom et al., 2006). Regardless of an entorhinal or septal origin of the coherent activity, the result is likely to be increased synaptic plasticity, a process highly favored by theta rythmicity (Diamond et al., 1988; Huerta and Lisman, 1993; Larson et al., 1986; Natsume and Kometani, 1997). The resulting potentiation of synapses between small networks of cells in the hippocampus may create a pathologically interconnected network (Bragin et al., 2005).

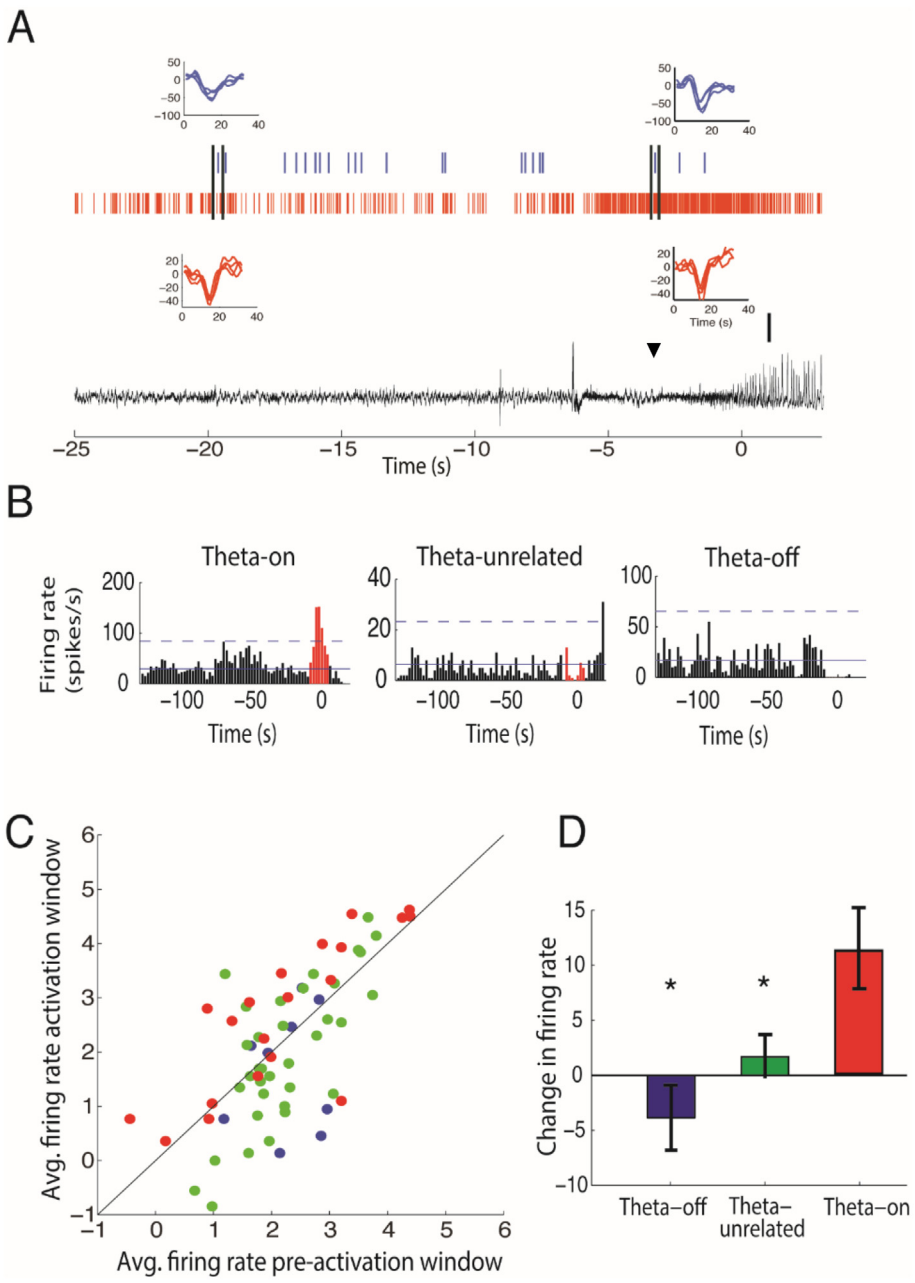


**Fig. 3.** A) LFP trace leading to an example seizure and raster plots of a pyramidal cell (blue) and interneuron (red) firing. Time 0 refers to the onset of rhythmic ictal spiking. Insets show waveforms of an action potential in 4 wires of the tetrode for each neuron in two time windows. Vertical scale bar indicates 5000 microvolts. B) Firing rates of example theta-on, theta-unrelated and theta-off interneurons in the 2 min around rhythmic ictal spiking onset. C) Firing rates of all interneurons during activation (−6 to 4 s) vs firing rate during previous 2 min (pre-activation window) color coded by theta-dependent firing. D) Average change in firing rates in the two windows compared across theta subtypes. Reprinted from Karunakaran et al., 2016. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 4. Pathological theta related decrease in neuronal activity interictally

While hyper-synchrony is the hallmark of epilepsy and transition to seizure, it is critical to consider which changes in inter-ictal neural activity may be connected to behavioral co-morbidities or even disease progression. For example, when comparing recordings from the CA3 of hippocampus between sham and epileptic rats, a reduction in theta power and a general slowing of theta rhythms, as well as the overall firing rate of cells recorded is observed (Karunakaran et al., 2016). Comparing neuronal activity from healthy controls and epileptic animals can help to identify the impact of epilepsy on neuronal firing patterns during ictal periods, explain the patterns observed at seizure onset (Karunakaran et al., 2016), as well as the comorbid decrease in cognitive function (Lopez-Pigozzi et al., 2016).

For both kainic acid (Arabadzisz et al., 2005a; Dugladze et al., 2007; Riban et al., 2002) and pilocarpine (Chauvière et al., 2009; Colom, 2006; Karunakaran et al., 2016; Lee et al., 2017b; Marcelin et al., 2009) models of TLE in rodents, a significant reduction of theta power follows both acutely induced status-epilepticus as well as chronic spontaneous and recurring seizures (Fig. 5). Changes in oscillatory power occur bilaterally, in the dorsal (Arabadzisz et al., 2005a; Colom, 2006; Dugladze et al., 2007; Karunakaran et al., 2016; Lee et al., 2017b; Marcelin et al., 2009) and ventral hippocampus (Arabadzisz et al., 2005a; Dugladze et al., 2007) as well as the medial septum (Arabadzisz et al., 2005a; Colom, 2006). Theta oscillations during interictal periods within hippocampal CA3 are also slower in epileptic animals compared to controls, consistent with observations in CA1 hippocampus of kainate-treated (Inostroza et al., 2013) or pilocarpine-treated (Marcelin et al., 2009) animals. The reasons for this decreased theta frequency could be a reduction in theta resonance (Marcelin et al., 2009). Alternately, significant neuronal loss in either the medial septum or the hippocampus, and in particular GABAergic cells (Kitchigina et al., 2013b) can lead to a diminished or altered theta directly or indirectly through reorganization of the surviving cells in these networks .

Along with changes in oscillations, the activity of both pyramidal

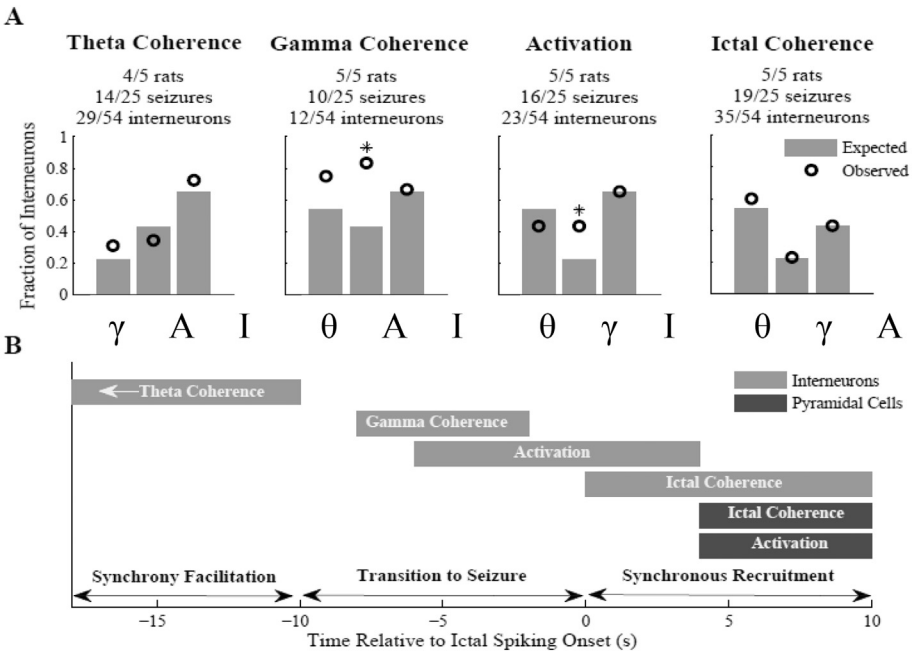


**Fig. 4.** A) Overlap of interneuron population exhibiting different behaviors. For each type of behavior, listed is the total number of rats and seizures for which this activity was present, along with the total number of interneurons which exhibited it. Of the neurons which exhibited each type of behavior, the fraction which also displayed a different type of behavior (circles) is plotted below (T: Theta Coherence, G: Gamma Coherence, A: Activation (increase in firing rate), I: Ictal Coherence). The expected fraction of neurons (bars) is based on the assumption of independence between different behavior types. (*) indicates the activity types are not categorically independent ($p < .01$). B) Summary of different types of observed neuronal behavior at approximate times of occurrence relative to the ictal spiking onset. During the synchrony facilitation stage (displayed truncated here, but −100 to −10 s) more interneurons are coherent with theta LFP and correlated to each other, while pyramidal cells are less correlated to each other. The transition to seizure stage (−10 to 0 s) contains high numbers of interneurons that are coherent with gamma LFP and have increased firing rates. Increased firing rates remain in the beginning of the synchronous recruitment stage, but begin to disappear as pyramidal cells increase activity. Both cell types are coherent with ictal spiking during this stage. Repreinted from Grasse et al., 2013.

cells and interneurons is reduced in the CA3 of epileptic animals compared to controls during the inter-ictal period (Karunakaran et al., 2016). Lateral septal neurons, a target of hippocampal glutamatergic neurons that play a key role in theta frequency modulation (Alonso and Kohler, 1982; Alonso and Frotscher, 1989; Jinno and Kosaka, 2002), also have lower firing rates in epileptic animals (García-Hernández et al., 2010), presumably due to reduced hippocampal feedback. This general decrease in activity that is consistent through preictal periods during both theta and non-theta epochs suggests that it may be mediated by anatomical or physiological alterations or long-term functional and synaptic changes (Cavalheiro et al., 1996; Curia et al., 2008).

There are two intriguing exceptions to the general reduction in activity. The first is that the firing rate of theta-off pyramidal cells is state dependent – it is pathologically low during theta epochs (Karunakaran et al., 2016) but not during non-theta periods. The impact of this is unclear, in part because the role of these cells is not well understood. However, since pyramidal cells are more inhibited during theta than in control animals, theta-off pyramidal cells in the epileptic CA3 are excessively inhibited during theta epochs, contributing to the ineffective transmission of information to downstream neurons.

The second is that the firing patterns (firing rate and entrainment) of theta-on interneurons are unchanged regardless of theta state (Karunakaran et al., 2016). It is possible that this cell type is functionally preserved in epilepsy or that there is minimal loss of these neurons. It has been reported that, in rat models of epilepsy, there is a selective preservation of hippocampal (Cossart et al., 2001; Ratte and Lacaille, 2006) and medial septum interneurons (Cossart et al., 2005; Garrido Sanabria et al., 2006; Majczynski Henryk and Urszula, 2005). Regardless, the critical observation is a relatively high firing rate of theta-on interneurons in the epileptic CA3 network compared to other cell types. Since CA3 interneurons are almost certainly inhibitory interictally, this exclusive maintenance of theta-on interneuron firing rate demonstrates higher levels of inhibition during theta compared to healthy controls.

## 5. Interneurons are more coherent with theta interically

As described above, firing rates of most neurons, except theta-on interneurons, are decreased in epileptic animals compared to healthy controls. Moreover, theta-off pyramidal cells decrease their firing rate compared to healthy controls during inter-ictal theta epochs but not during non-theta epochs. However, the effectiveness of synaptic barrages depends not only on the overall number of post-synaptic potentials, but also on their temporal pattern. To assess the impact of this reduction in firing rate during theta, the phase locking of neuronal activity during oscillations can be estimated by the coherence between the oscillation (field) and the single-neuron spike times (spike-field coherence). We investigated the relationship between those interneurons that modulate their firing rate with theta (theta-on and theta-off) as well as those that did not (theta-unrelated) and found that both theta-off and theta-unrelated interneuron subtypes, but not pyramidal cells, have increased theta band spike-field coherence interictally in CA3 of epileptic rats compared to controls (Karunakaran et al., 2016). Therefore, there are subtype-specific differences in both interictal firing rate and spike field coherence of interneurons but not pyramidal cells compared to control animals.

As hippocampal interneurons are the exclusive targets of medial septal GABAergic projections (Freund and Antal, 1988; Tóth et al., 1997), the increased coherence could be due to enhanced theta coherence between medial septum and hippocampus (Avoli and de Curtis, 2011b; Holtkamp et al., 2005; Towle et al., 1998) or hypersynchrony in superficial layers of upstream entorhinal cortex (Kobayashi et al., 2003; Kumar and Buckmaster, 2006; Kumar et al., 2007). Understanding the origins of the altered coherence, or potential targets for mediating coherence, is critical in both understanding critical mechanisms related to ictogenesis as well as potential therapeutic targets. For example, during interictal periods, this increased synchrony during theta could help to compensate for lower overall firing rates of interneurons and help to explain both the seemingly spontaneous occurrence of seizures and comorbid cognitive deficits. First, the coherent interneuron action potentials could be more effective due to temporal coincidence of their inhibitory postsynaptic potentials in downstream neurons compared to a similar number of non-coherent potentials. Second, for pyramidal cells embedded in a pathologically connected network, there is no such compensation and no opportunity for coherent excitation. Therefore, during interictal periods, the increased interneuron synchrony would be

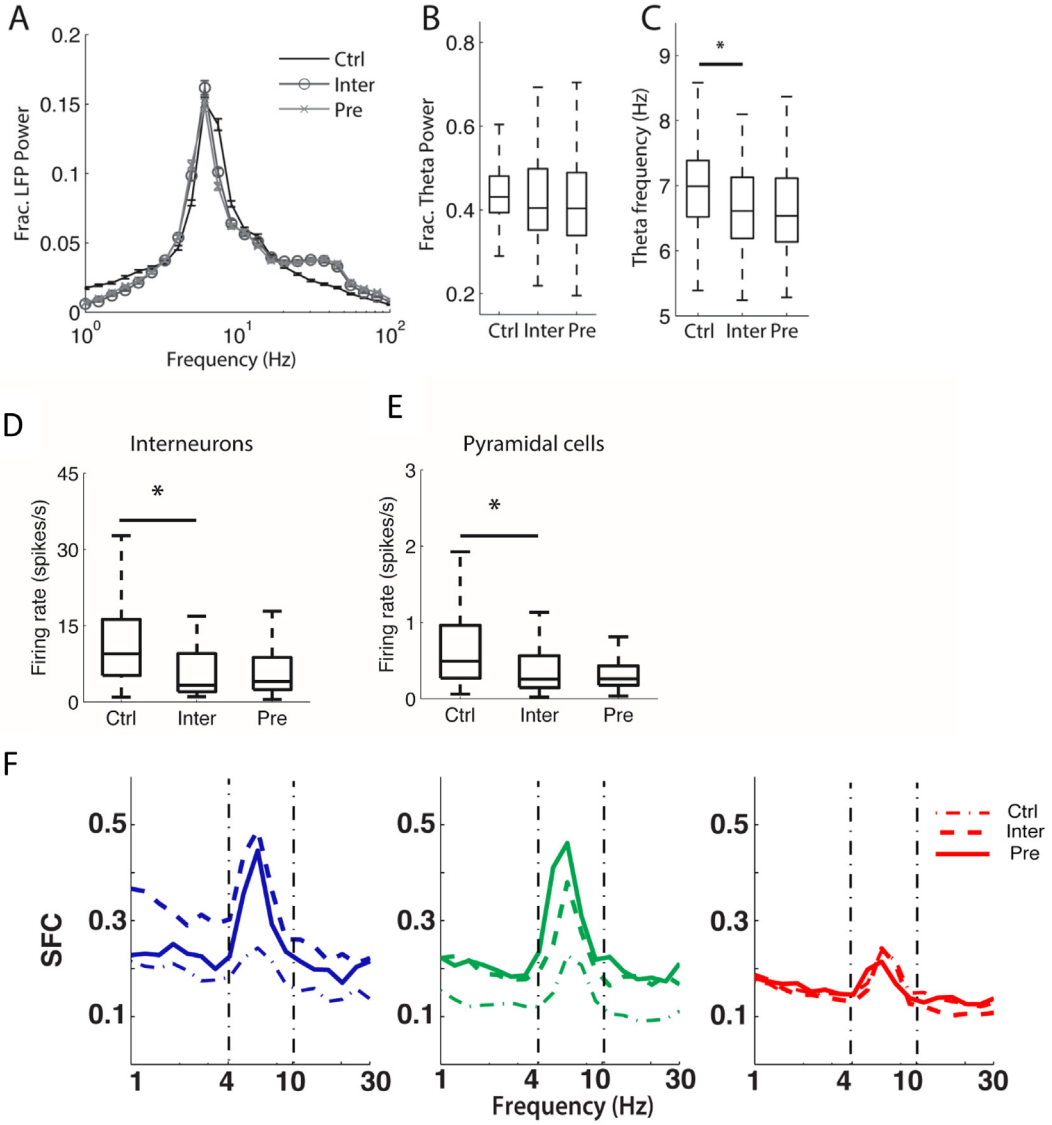


**Fig. 5.** A) Spectrum of fractional LFP power during theta oscillations in three groups – Ctrl - control, Inter – Interictal and Pre - preictal. B) Average fractional power in the theta frequency band (4–10 Hz) for the three groups. C) Theta frequency (median and interquartile ranges) for three groups. Theta frequency was significantly decreased in epileptic animals, during interictal periods, compared to controls. Average (average over time) firing rates of C) interneurons and D) pyramidal cell population are decreased intericatally. For both populations, average firing rates of neurons was decreased in the interictal group (Inter) compared to the control group (Ctrl). F) SFC spectrum for example interneurons of each subtype and group. Vertical dashed lines indicate frequency band of interest, 4–10 Hz.

sufficient to keep pyramidal cell firing in-check during theta so that networks prone to ictogenesis do not continuously transition to seizure. Moreover, this suppression of pyramidal activity could, in some animals, be overpowering and simultaneously induce cognitive deficits (see next). In support of our proposed framework, these findings demonstrate a pathological imbalance between excitation and inhibition in favor of synchronous inhibition during interictal theta oscillations that could account for both the seemingly spontaneous nature of seizures and comorbid cognitive deficits.

## 6. Pathological theta and reduced cognitive performance

There is considerable evidence that lesions to the hippocampus, and even the septohippocampal circuit, can lead to cognitive dysfunction (Dickerson and Eichenbaum, 2010). Some of these changes in behavior may be directly related to the inability to generate a memory (i.e. the loss of significant place cells). However, one other potential consequence of neuronal loss, is that the injury will result in altered oscillations, preventing the remaining intact circuit from functioning optimally (Mizumori et al., 1990). At the level of individual synapses, for example, there is evidence that timing high frequency bursts to the phase of theta results in the greatest amount of potentiation (Greenstein et al., 1988; Larson et al., 1986; Orr et al., 2001). Extending this idea into our proposed framework, the ability to form and recall memories requires the integration of activity and plasticity across multiple brain regions. The role of theta oscillations in synchronizing neural networks facilitating plasticity and learning have been well described in rodent models (Buzsaki, 2005). For example, theta oscillations facilitate the timing of neuronal activity across distal regions of the brain, thereby promoting learning and memory (Buzsaki, 2005; Harris and Gordon, 2015; Hasselmo, 2005; Siapas et al., 2005; Vertes and Kocsis, 1997). More specifically, there is evidence that oscillations play a role in coordinating activity between the hippocampus and prefrontal cortex (PFC), as evidenced by enhanced theta coherence during spatial working memory and decision-making tasks in the rat (Benchenane et al., 2010; Jones and Wilson, 2005). Importantly, pharmacological inactivation of the MSN using tetracaine results in diminished hippocampal theta and is correlated with deficits in tasks such as the Morris

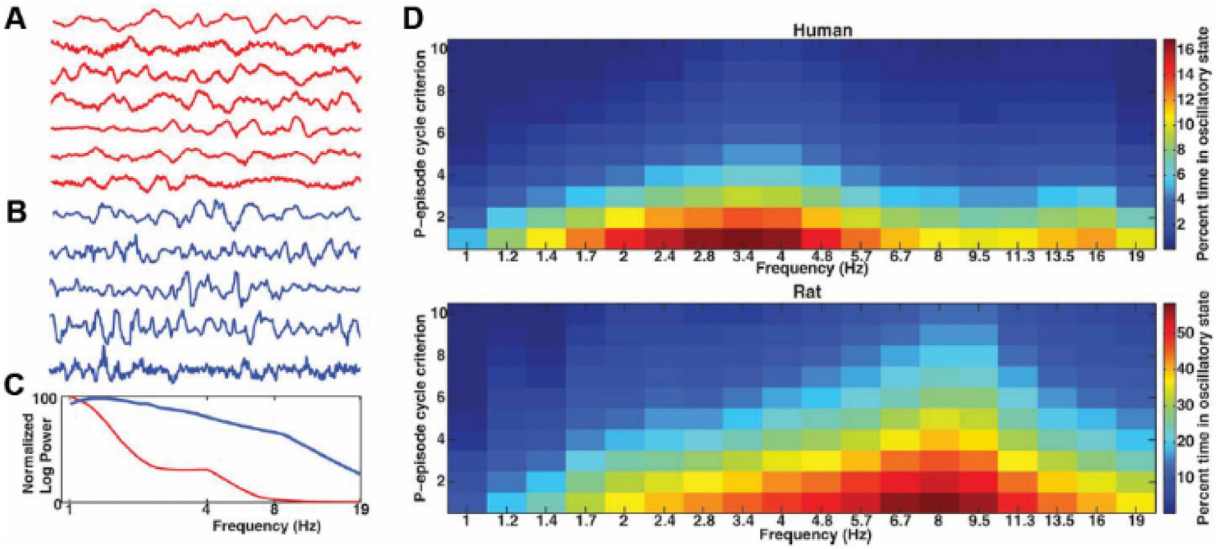


**Fig. 6.** Example traces from hippocampal depth electrodes in patients (A) performing a virtual reality spatial learning task and rats (B) performing the Barnes maze spatial learning task. A comparison of normalized log power (C) demonstrates that while theta oscillations are present during navigation in both human and rat, human theta oscillations have less power and occur at a lower frequency. Using the p_episode it is also clear that not only is the dominant theta frequency of theta oscillations in humans lower than in rat, but that there are also fewer consecutive cycles observed. Adapted from Watrous et al. 2013.

water maze (McNaughton et al., 2006). Similarly, injection of either muscimol or scopolamine into the MSN results in attenuated theta and impaired cognitive performance (Givens and Olton, 1994; Givens and Olton, 1990b). Akin to pharmacological manipulations, large lesions of the MSN result in reduced hippocampal theta oscillations and alter spatial learning. Similar lesions of the septum that do not result in altered theta oscillations do not affect spatial learning (Winson, 1978). Critically, models of neurological disease also can result in attenuated oscillations and cognitive dysfunction. For example, we, as well as others, have reported that both rats with traumatic brain injury (Lee and Heckman, 2013) and rats that have experienced status epilepticus (Lee et al., 2017b) or have chronic epilepsy (Chauvière et al., 2009; Kitchigina et al., 2013b) exhibit reduced hippocampal theta oscillations and impaired spatial learning (Fig. 6). Taken together, these pharmacological, lesion and disease-related data demonstrate the functional link between theta oscillations and cognitive function.

There is now mounting evidence from electrocorticography (ECoG) recordings in epilepsy patients that there is a similar relationship of theta oscillations with episodic memory and spatial navigation as has been observed in rodent models (Burke et al., 2014; Comper et al., 2017; Rzezak et al., 2017; Tramoni-Negre et al., 2017; Vaz et al., 2017; Viskontas et al., 2016; Watrous et al., 2013b; Young et al., 2018) (Fig. 6). Also consistent with rodent data, individual human hippocampal neurons phase-lock to theta oscillations (Jacobs et al., 2007), with optimal spatial performance during periods of high (as compared to low) theta power (Bohbot et al., 2017; Merkow et al., 2014). Finally, there is clinical evidence that individuals with diminished theta oscillations do not perform as well on spatial tasks (Cornwell et al., 2008a). For example, studies of healthy and depressed patients (Cornwell et al., 2008b; Kumar et al., 2009) demonstrate a clear correlation between diminished theta oscillations and poor spatial learning in a virtual water maze paradigm (Astur et al., 2002). In studies of aging, there was also a significant relationship between theta power and spectral coherence across age, with older subjects having both less theta and a decline in cognitive performance (Dias et al., 2015). At present, the role of theta oscillations in learning and the relationship of attenuated oscillations to cognitive dysfunction are well-accepted. However, there remain many questions related to the role of theta to cognitive processes, including the significance of specific oscillatory frequencies, coherence, spike timing, and cross-frequency coupling (Fig. 7).

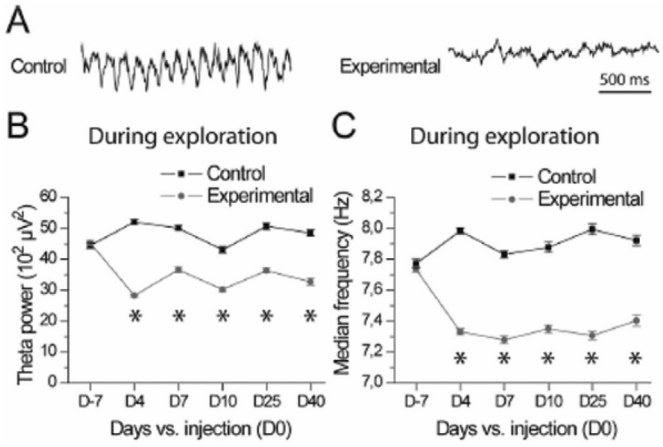


**Fig. 7.** Theta oscillations were recorded from the dorsal hippocampus over the first 7 weeks following administration of pilocarpine. Example EEG traces from control and epileptic rats (A) demonstrate clear differences in the frequency and amplitude of hippocampal oscillations. When observations were analyzed during exploration there was both a significant decrease in theta power (B) as well as the median frequency (C) of theta oscillations which corresponded with impaired spatial learning. Adapted from Chauviére et al. 2009.

## 7. Stimulation of theta reduces ictogenesis and attenuates cognitive dysfunction

While we have previously detailed how high-power theta oscillations precede ictal events, there is also evidence that stimulating theta oscillations can attenuate evoked seizures. For example, activating the cholinergic circuit either with microinjections of carbachol or electrical stimulation of the MSN in the range of 4–8 Hz evoke hippocampal theta oscillations and inhibit pentylenetetrazol-induced seizures (Miller et al., 1994). Similar microinjections of carbachol also induce theta oscillations and inhibit behavioral and electrographic seizures in acutely exposed pilocarpine rats (Colom, 2006). In addition, both spontaneous occurrences of theta and induced theta via tail pinch reduce markers of epileptiform activity (Colom, 2006).

While theta oscillations can prevent seizures, alternatively theta frequency stimulation may improve cognitive outcome in animals with

epilepsy. Early observations of theta oscillations in rats identified specific frequency bands related to navigating environment. For example, theta oscillations were of a relatively higher frequency (8–10 Hz) in rats exposed to a new environment as compared to a familiar environment. After animals had habituated to the environment theta would remain high in the start area, but would drop into the 6.5-to-8.5 Hz range as they explored the environment (Gray and Ball, 1970). Critically, doing a dose response curve looking at both frequency and amplitude, these authors demonstrated that 7.7 Hz theta stimulation of the MSN generated the highest power hippocampal theta oscillations for the least amount of input current (Ball and Gray, 1971; Gray and Ball, 1970). Subsequent evaluation of 7.7 Hz stimulation determined that, following tetracaine inactivation of the MSN, that the best treatment for restoring oscillations and behavior was replacing physiologic theta (McNaughton et al., 2006). Specifically the authors recorded from the intact supramamillary nucleus and used the EEG to trigger stimulation into the fornix superior. However, our concern was that, in the injured brain, there may not be physiologic theta. In that same paper the authors also demonstrated the fixed 7.7 Hz stimulation drove hippocampal oscillations and improved spatial learning performance. However, an irregular theta stimulation that resulted in an averge frequency of 7.7 Hz resulted in minimal rhythmicity and no behavioral improvement. Moreover, our own laboratory demonstrated that while these similar fixed 7.7 Hz oscillations could improve spatial learning in rats following TBI, that 100 Hz stimulation did not (Lee et al., 2015). Furthermore, we also demonstrated that following pilocarpine-induced status epilepticus there was a significant acute reduction in oscillatory power in the 6–10 Hz theta frequency band, accompanied by a significant increase in latency and the use of significantly worse search strategies in a Barnes maze (Izadi et al., 2019; Lee et al., 2017b). Stimulation of the MSN at 7.7 Hz, however, led to a significant decrease in latency to find the hidden escape box and a significantly improved search strategy. Interestingly, stimulation of sham rats with otherwise normal theta oscillations led to a significant decrease in object exploration and a trend toward worse performance on the Barnes maze as compared to non-stimulated shams (Lee et al., 2017b). Ongoing studies are currently evaluating the effect of deep brain theta stimulation of the MSN to improve cognitive function in chronically epileptic rats. Along with pharmacology, electrical neuromodulation shows promise to drive theta oscillations and test the framework that hypo-synchrony is related to depressed cognitive function in rodents and even, in some cases seizures.

## 8. Impact of an inclusive framework on treatment

Over 3.4 million people are currently diagnosed with epilepsy in the United States (Zack and Kobau, 2017), resulting in an estimated economic impact of over 9.5 billion dollars annually (Yoon et al., 2009). Partial onset epilepsies represent more than two-thirds of all cases, and TLE is the most prevalent subtype (Semah et al., 1998). Approximately 30–40% of patients with TLE are refractory to anticonvulsant medications, representing 80% of the total economic burden (Begley et al., 2000; Laxer et al., 2014). Most patients with intractable TLE experience persistent altered cognitive function due to recurrent seizures as well as drug-related side effects (Trimble, 1987). As previously described, the majority of interventions for epilepsy were designed to reduce hyper-excitability (Bromfield et al., 2006; Macdonald and Meldrum, 1995), not hyper-synchrony. AEDs significantly reduce the chance of hyper-excitability and also seizures (Nayak et al., 2017; Sohal and Huguenard, 2003; Sohal et al., 2003) but they also favor a hypo-synchronous state. Data from our labs and others demonstrate that hypo-synchronous activity is concomitant with cognitive dysfunction, which is consistent with other cognitive disorders. In fact, while ~60% of patients treated with AED become seizure free, many also report an increase in the prevalence of common co-morbidities such as cognitive dysfunction and depression (Alonso-Vanegas et al., 2013; Carreno et al., 2008; Mula, 2012) resulting in high rates of non-compliance (Buck et al., 1997; Cramer et al., 1989; Hovinga et al., 2008). Therefore, while eliminating hyper-excitability may prevent hyper-synchronous states that transition to seizures, this approach also induces a general state of hypo-synchrony that produces cognitive dysfunction. Moreover, there are no clinical interventions that employ specific anatomical targets and stimulation parameters that alleviate both seizures and cognitive impairments associated with TLE. Throughout this review we have demonstrated that periods of hyper-synchrony, including high power theta oscillations, increased theta coherence, and spike-frequency coherence in interneurons are associated with ictogenesis. We have also cited an extensive literature that suggests that hypo-synchrony, and specifically hypo-synchrony related to theta oscillations, is associated with cognitive dysfunction. We propose that this framework could help develop novel therapies, whether new anti-epileptic drugs or deep brain stimulation paradigms, to modulate theta synchrony, both within fields and between field and single neurons. This approach would allow for reduction of both seizures and epilepsy-related comorbidities, resulting in an overall improvement in behavioral and cognitive function.

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