Hypothesis

Sleep Links Hippocampal Propensity for Epileptiform Activity to Its Viscerosensory Inputs

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Sleep Links Hippocampal Propensity for Epileptiform Activity to Its Viscerosensory Inputs

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Abstract: Seizure development relies on two factors. One is the existence of an overexcitable neuronal network and the other is a trigger that switches normal activity of that network into a paroxysmal state. While mechanisms of local overexcitation have been the focus of many studies, the process of triggering remains poorly understood. We suggest that, apart from the known exteroceptive sources of reflex epilepsy – visual, auditory or olfactory, there is a range of interoceptive triggers, relevant for seizure development in Temporal Lobe Epilepsy (TLE). The hypothesis proposed here aims to explain the prevalence of epileptic activity in sleep and in drowsiness states and provide a detailed mechanism of seizure triggering by interoceptive signals.

Keywords: VNS; temporal lobe epilepsy; vagus nerve; interoception; hippocampus; medial septum

Wide prevalence of temporal lobe epilepsy

Temporal Lobe Epilepsy (TLE) is the most frequent form of focal epilepsy (60-70%) and constitutes around 24% of all cases of epilepsy (Semah et al., 1998, reviewed by Téllez-Zenteno & Hernández-Ronquillo, 2012). This is a type of focal epilepsy originating from hippocampus, amygdala and entorhinal cortex that relies on oversynchronization of activity of neuronal circuits in these areas, but often also includes structural and functional abnormalities in neocortical areas, especially limbic, lateral temporal and frontal cortices and the thalamus (Bernhardt et al., 2013). TLE has also the highest rate of pharmacoresistancy (75-89%) and only a moderate rate of successful surgical treatment at 65-70% (Fanselow & Dong, 2011; Téllez-Zenteno & Hernández-Ronquillo, 2012) and an estimated Standard Mortality ratio of treatment-resistant epilepsy at 2.54 (Mohanraj et al., 2006). Although local neuronal changes associated with TLE have been extensively studied, much less is known about the triggers of seizure activity and mechanisms related to that triggering. As frequency, severity, prodromal symptoms and patterns of occurrence across sleep-wake cycle vary between patients (Karoly et al., 2017, 2018; Lunardi et al., 2011) understanding the mechanisms that trigger TLE can provide substantial advantage to its prediction and treatment.

Vagal nerve stimulation: an unorthodox treatment for TLE

Vagal Nerve Stimulation (VNS) is a treatment option developed for pharmacoresistant cases of epilepsy that yields 37.5% seizure reduction in 6 months and 75.5% reduction in 10 years (Elliott, 2011). The side effects are generally mild and often decrease over time or after optimising the stimulation parameters individually for each patient (Sackeim et al., 2001). The antiepileptic effects

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of VNS were initially attributed to widespread cortical desynchronization (Zanchetti et al., 1952), but both synchronization and desynchronization have been observed with VNS in animal studies (Chase et al., 1966, 1967). EEG studies in human patients have also reported variable outcomes (Vonck & Larsen, 2018). The hypothesis involving modulation of noradrenaline pathways (Vonck & Larsen, 2018) was also met with criticism due to the relatively slow speed of the development of noradrenaline modulation. It could not explain the immediate effects of VNS, although it can potentially contribute to the long-term increase of the VNS efficiency over time (Dorr & Debonnel, 2006). Another contradiction is the lack of VNS-associated sleep disturbances usually caused by excessive noradrenaline levels. Slow effects of VNS in TLE might also be related to normalization of hippocampal activity during the treatment through possible neuronal development and growth, as well as changes in sensitivity to GABA. This may be because $GABA_A$ receptor density in hippocampus increases in patients responsive to VNS (Groves & Brown, 2005; Marrosu et al., 2003). VNS can also affect cytokine production, potentially controlling inflammation during long-term application (Majoie et al., 2011).

In summary, an explanation for the fast-acting component of vagal stimulation is lacking and the slow effects of VNS are also poorly understood. Thus, the method is currently used largely on an empirical basis (Yap et al., 2020; Groves & Brown, 2005). Such uncertainty leads to the current inability to predict the outcome of the intervention. This is an important issue, since not all patients benefit from VNS and this can only be established after the implantation. In addition, offering VNS to patients having serious side effects to pharmacological treatments and using VNS in paediatric practice will remain problematic until the neural mechanisms underlying the effects of VNS are adequately understood.

Novel model for action of VNS in TLE

We have recently proposed a new framework describing how the antiepileptic effect of VNS may arise from interruption of the resonant paroxysmal activity triggered by rhythmical interoceptive signalling (Pigarev et al., 2020). In the present paper, we discuss specifically the applicability of that hypothesis to TLE and TLE-comorbid conditions, with an emphasis on hippocampal connectivity and its functions.

Since approximately 80% of vagal fibres are afferent, VNS is expected to activate multiple brain areas due to the broad representation of the vagal input in subcortical and cortical structures; e.g., nucleus of the solitary tract, hippocampus, hypothalamus, thalamus, amygdala, as well as multiple cortical areas such as the insular, orbitofrontal, medial prefrontal and cingulate cortices and some somatosensory and motor cortical areas (Saper, 2002; Cechetto & Saper, 1987; Neafsey, 1990; Ongür et al., 1998; Ongür and Price, 2000; Nieuwenhuys, 2012; Azzalini et al., 2019).

Hippocampal functional connectivity and epilepsy - in sleep and when awake

Of the above listed brain areas potentially involved in VNS, hippocampus is the most seizure-susceptible structure in the brain (Green and Scheetz, 1964) and so warrants a close examination of its afferent and efferent projections. However, the susceptibility for seizures is not uniformly distributed across the hippocampus, but increases along its dorso-ventral axis in animals (corresponding to posterior-to-anterior axis in human), as consistently reported in kindling studies *in vitro* and *in vivo* (Bragdon et al., 1986; Elul, 1964, Strange et al., 2014; Isaeva et al., 2015.; Akaike et al., 2001). There is also a matching profile of $GABA_A$ receptor distribution along the same axis (Sotiriou et al., 2005). Human patients suffering from TLE also have greater structural atrophy in the anterior parts of the hippocampus in comparison to the posterior ones (Barnett et al., 2019). Furthermore, dorsal and ventral parts of the hippocampus have distinctly different connectivity with subcortical and cortical areas (Strange et al., 2014; Fanselow & Dong, 2010).

There is a specific smoothly changing pattern of connections along the above axis, which supports different goal-oriented behaviours. Dorsal hippocampus is engaged in cognitive functions including memory and spatial navigation, while ventral hippocampus is involved in emotional and affective behaviour, stress-related responses and autonomic regulation. For example, lesions of

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dorsal hippocampus in rodents impair spatial memory (Moser et al., 1995), while ventral hippocampus lesions produce changes in emotional behaviour and reactions to stress (Henke, 1990). In both rodents and primates, dorsal hippocampus is connected with cortical and subcortical structures that form a circuit organizing exploratory and foraging activity (Swanson, 2000).

Ventral hippocampus extensively connects with structures of visceral and emotional control: amygdala, insular cortex, infralimbic and prelimbic cortices and the areas of hypothalamus that control autonomic, endocrine and somatomotor activities supporting behaviours with strong emotional components, such as feeding, reproduction and defence (Dong & Swanson, 2006; Herman et al., 2005; Kishi et al., 2000; Petrovich et al., 2001; Fanselow & Dong, 2011; Castle et al., 2005). The outermost ventral portions of hippocampal CA1 and subiculum project to hypothalamic neuroendocrine motor neurons via lateral septum and bed nucleus of the stria terminalis, which is an important relay for hypothalamic-pituitary-adrenal axis of stress response (Dong & Swanson, 2006; Fanselow & Dong, 2011; Herman et al., 2016). Ventral C1A also projects to the shell of nucleus accumbens and shows responses related to expectation of food or receiving food reward (Vidyasagar, et al., 1991; Salzman et al., 1993). This emotions-related connectivity pattern of the ventral hippocampus may correspond to the high comorbidity of TLE and depression (Hermann et al., 2000). Human data regarding hippocampal dysfunction and volume loss also demonstrate association with other psychiatric conditions having an affective component, such as anxiety, bipolar and posttraumatic stress disorders (Frey et al., 207; Bonne et al., 2008). Note that VNS was confirmed to be effective and approved for using in depression as well (reviewed by Nemeroff et al., 2006), suggestive of possible commonality of the VNS mechanisms in both epilepsy and depression.

Ventral hippocampus also possesses connections with the regions of hypothalamus regulating sleep-wake cycle – suprachiasmatic and dorsomedial hypothalamic nucleus (Cenquizca and Swanson, 2007; Kishi et al., 2000; Krout et al., 2002; Saper et al., 2005). Interestingly, there are a number of factors related to sleep that could potentially play some direct role in TLE. The intrinsically photosensitive retinal ganglion cells (ipRGCs), a class of RGCs containing the photosensitive pigment, melanopsin, play an important role in circadian rhythm by causing the release of melatonin in the dark through a separate pathway that does not contribute to image formation (Mure, 2021). This is via their projection to the suprachiasmatic nucleus (SCN), which in turn can potentially send these signals on to the hippocampus.

Although hippocampus possesses its own mechanisms of circadian regulation that affect memory functioning over a sleep-wake cycle, suprachiasmatic nucleus functions as a "master clock", providing phase setting over the hippocampal circadian variations (Snider et al., 2018). This is conducted via both endocrinal and neuronal pathway-related mechanisms. The main endocrinal mechanism is the regulation of corticosterone production in the adrenal gland by SCN, and the dependence of hippocampal circadian phasing on corticosterone. The pathway directly affecting circadian phasing connects SCN with hippocampus via medial septum and modulates balance of excitation and inhibition in the hippocampus. It has been shown that both excitatory and phasic or tonic GABAergic inhibition modulated during sleep/wake cycle can affect hippocampal neural activity and even synaptic plasticity (Cirelli, 2013; Wu et al., 2022). Notably, vagal input into hippocampus is conducted via medial septum as well (Castle et al., 2005; Suarez et al., 2018). This pathway links the major brainstem input area receiving vagal afferentation – nucleus of the solitary tract (NTS) – to the hippocampus.

We described earlier increased propagation of visceral information to various cortical areas during sleep (Pigarev, 1994; Pigarev et al., 2013; Pigarev & Pigareva, 2014), and recently reported dramatic increase in the responsiveness of insular cells to visceral stimulation during sleep (Levichkina et al., 2021). Rembado and colleagues have also demonstrated substantial increase of VNS responses during slow wave sleep in multiple cortical areas in primates (Rembado et al., 2021). This indicates either more efficient or more prominent vagal inputs during sleep in comparison to wakefulness. Medial septum can be a structure that provides gating of the vagal input based on the information coming from SCN, increasing the propagation during the night when dark and attenuating it during daytime.

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It has been hypothesized that the role of hippocampus in assessing the current needs of an organism and supporting motivations with appropriate emotions extends to the need for sleep (Pigarev & Pigareva, 2013). Considering the influences of the above-described strong modulatory influences by SCN, it is likely that hippocampal activity might be affected by a wakefulness-to-sleep transition and sleep and be sensitive to sleep disturbances.

Paroxysmal activity during sleep and TLE

There is a strong prevalence of paroxysmal activity during slow wave sleep (SWS) and in drowsy states in contrast to wakefulness and REM. Roughly half of the seizures occur during SWS/drowsy states despite these states occupying less than a fourth of the whole sleep-wake cycle of 24 hours (e.g., Shouse et al., 1996; Herman et al., 2001; Dinner, 2002; Combi et al., 2004; Pavlova et al., 2004; Hofstra and de Weerd, 2009; Chokroverty & Nobili, 2017). The association between slow wave activity and epileptic discharges which share the same mechanisms has been highlighted (Beenhakker & Huguenard, 2009).

Epileptic activity is believed to occur in hyperexitable oscillatory networks (reviewed by Beenhakker & Huguenard, 2009). TLE, as a connectivity dysfunction, often manifests as events consisting of high amplitude spikes lasting for 50-100 ms duration followed by a slow wave lasting 200-500 ms. These are common in SWS, when they propagate to other areas more easily due to the increased slow wave synchronization (Mendes et al., 2019). Another stereotypical activity is a "sharp wave-ripple" complex consisting of ~100 ms wave followed by a high frequency ripple, initiated by synchronized activity of CA3 pyramidal neurons. These occur in hippocampus in both normal and epileptic conditions, but with an increase of the ripple frequency in epilepsy, causing the characteristic "fast ripples" (Staba et al., 2007; Maier & Kempter, 2017). Synchronous activity of CA3 cells is inhibited by adenosine, whose levels drop by 20% during SWS in comparison to wakefulness (Basheer et al., 2004). This increases the probability of CA3 neurons to ovesynchronize in SWS, since both ripples and fast ripples occur mostly during sleep.

Visceral triggers of hippocampal paroxysmal activity

The question arises what may facilitate the slow wave oversynchronization that is expected to drive susceptible ventral hippocampal circuits into paroxysmal activity? A highly plausible candidate that we propose is the afferent rhythmical signalling coming from visceral systems. Breathing, heart rate, gastric and intestinal activities are all rhythmical. Hippocampal breathing rhythm is a particularly well-known phenomenon, and the hippocampal sharp wave-ripple complex can be entrained by respiration (Liu, McAfee & Heck, 2017; Lockmann et al., 2016; Radna & MacLean, 1981; Bordoni et al., 2018). This breathing-associated rhythmic activity is also present in prefrontal cortex, especially in the areas connected with the olfactory system. This provides grounds for synchronization of large brain networks by breathing due to their extensive connections to the hippocampus. Frequency of the hippocampal breathing rhythm is different in different species, with the one reported in human epileptic patients being around 0.16-0.33 Hz (Zelano et al., 2016) while, in smaller animals, this rhythm is faster and can be mistaken for delta or theta activity (Lockmann et al., 2016). In a study focussed on the relationship between visceral events such as heart rate and breathing with hippocampal cell responses in human patients, a large proportion of neurons in hippocampus and amygdala were found to either synchronize with the heart rate itself (20%) or respond to changes in heart rate (23%), in addition to 15% of cells synchronised to the respiratory period (Frysinger & Harper, 1989).

When the activity in those with TLE falls roughly into the delta frequency range and seems to be correlated with cardiac activity, it raises a few issues. (i) In smaller animals with faster heart rates, higher frequency ranges would be expected to become oversynchronised, which may not be the case. (ii) In the over 50% of the cases where no correlation with cardiac or breathing activity is seen, is there another rhythmic activity that could provide the trigger?

Hippocampus is known to receive vagal input (Suarez et al., 2018; Castle et al., 2005), it is engaged in organization of feeding behaviour and was shown to receive signals from gastrointestinal

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tract, with neurons in the macaque hippocampus and parahippocampus showing food reward-related responses (Vidyasagar et al, 1991; Tamura et al., 1991; Salzman et al., 1993) and human PET experiments revealing hippocampal responses to gastric stimulation (Wang et al., 2006). Thus, there is a reason to believe that rhythmical gastrointestinal events could also lead to hippocampal rhythmical activity and potentially to triggering seizures. We propose that all the variants of TLE, including those where correlation or modulation with easily recordable visceral events such as breathing or heart rate are not observed, share essentially the same mechanism of being triggered by interoceptive slow waves. We suggest that networks susceptible to paroxysmal activity that include the ventral hippocampus may be triggered by afferent visceral signals, especially by those arising from the gastrointestinal tract.

Externally-driven seizure events are not uncommon and reflex epilepsy is a well-known example of the epileptiform activity triggered by sensory stimuli. Seizures in TLE can be provoked by rhythmical olfactory stimulation (Lunardi et al., 2016) due to the presence of strong projections from the olfactory system to hippocampus. Olfactory auras also occur in drowsy/dreaming states in 6% of TLE patients. TLE-associated, 'eating epilepsy' has been described as well (Nagaraja & Chand, 1984). Here, sight, smell or thought of food did not cause seizures and they only rarely occurred during eating itself. In the majority, it occurred at the end of a heavy meal, suggestive of gastrointestinal activity as the trigger, with partial control over seizures achieved simply by changing the eating habits.

Autonomic disturbances accompany TLE seizures in up to 75% of cases and are frequent during the aura period preceding a seizure (Buren & Ajmone-Marsan, 1960). Ictal autonomic changes include cardiorespiratory, gastrointestinal, vascular, urogenital and pupillary symptoms (Dütsch, Hilz & Devinsky, 2006). The most commonly reported seizure triggers relate to particular visceral states such as menstruation, sleep deprivation, fatigue, eating, fever, etc. or to stress and anxiety (Lunardi et al., 2011), indicating that such changes do not just accompany, but may also induce paroxysmal activity.

Mechanism of visceral trigger of TLE seizures

Slowing of EEG activity with irregular delta waves occurs in over 60% of TLE patients (Jan et al., 2014). Stimulation frequencies in a low range, such as 1 Hz, are used for pre-operative testing aimed to provoke epileptic seizure to define its source. This stimulation induces seizures when applied to the hippocampus and related structures of the hippocampal gyrus and propagate in ways that match seizure propagation (Corcoran & Cain, 1980; Munari et al., 1993; File et al., 2019). It seems likely that natural visceral activity occurring at comparable low frequencies, such as cardiac rhythms, can also initiate the same processes through resonance.

The frequency range of oscillatory activities, both normal and ictal, is determined by the biophysical properties of the morphological cell types of the oscillating cell assembly and the balance of excitation and inhibition on the cells of the assembly (Hutcheon and Yarom, 2000; Economo & White, 2012; Markram, et al., 2004). These cell assemblies, by virtue of the circuitry they are embedded in, would also have a resonant frequency that they are most susceptible to (Hutcheon and Yarom, 2000; Herrmann, 2001). This has been pointed out in the general context of communication through coherence between brain regions (Vidyasagar, 2013; Esghaei et al., 2022) and more specifically in its potential to trigger ictal activity (Pigarev et al., 2020; Sohanian & Markazi, 2019). Thus, when there is sufficient overlap between the frequency ranges of the interoceptive wave and the local hippocampal oscillatory activity to trigger the resonant frequency in the hippocampal circuit, a typical ictal oversynchronisation can potentially occur. Such overlap and oversynchronisation at the resonant frequency of the hippocampal circuit may be the result of a widening of the frequency bandwidth of one or both circuits, thanks to an abnormal hippocampal circuit from a lesion and/or a faster than normal visceral oscillation.

However, it is still remains to be explained how the slow interoceptive waves (mostly <1 Hz, e.g., breathing or gastrointestinal activity) lead to the ictal oversynchronisation that occur at higher frequencies and the spread of the seizure from the hippocampus to various cortical areas. For example, patients with TLE often have "sinusoidal" patches of ictal activity at frequencies of 5-10 Hz

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(Jan et al., 2014), and fast ripples occurring at very high frequencies (>150 Hz) are characteristic of hippocampal epileptiform activity (Foffani et al., 2007; Ogren et al., 2009).

One possibility is the occurrence of resonance at harmonics of the fundamental frequency, as was pointed out earlier (Pigarev et al., 2020). Thus, in a study of photosensitive epilepsy when photic stimulation was applied at 10-20 Hz, synchronized activity at harmonically related frequencies occurred within 30-120 Hz (Parra et al., 2003).

The other and likely more common mechanism is a cross-frequency coupling, which has been suggested as an efficient means of communication between brain areas (Canolty & Knight, 2010; Lisman & Jensen, 2013; Esghaei et al., 2022). CFC can be either amplitude-amplitude coupling, when the two frequencies are similar and oscillation in area A directly adds to the oscillation in its target area B, or phase-amplitude coupling, when the phase of lower frequency oscillation in area A modulates the amplitude of a local higher frequency oscillation in area B, coordinating spikes of its neurons. Normal hippocampal ripples are known to be entrained by breathing (Liu et al., 2017; Lockmann et al., 2016; Radna & MacLean, 1981; Bordoni et al., 2018; Nokia & Penttonen, 2022). As pathological fast ripples in the hippocampus have similar origin as the normal ripples (Foffani et al., 2007), it seems safe to assume that CFC-based entrainment by respiration or other low frequency visceral events can cause fast ripples as well.

That the visceral waves usually have a frequency range that barely overlaps with the theta, beta and gamma frequencies typically seen in most of the brain regions, including the hippocampus explains why seizures are not easily triggered, at least during waking hours when the vagal afferent activity from gastrointestinal tract is less (Pigarev, 1994; Pigarev et al., 2013; Rembado et al., 2021; Levichkina et al., 2021; Levichkina et al., 2022). However, we suggest that, with an altered abnormal hippocampal circuit, this protection is lost, especially during sleep, when the visceral oscillations are stronger.

The next question to address is the spread of activity from hippocampus to other brain regions, such as the frontal cortex, which receives a strong projection from the hippocampus (Barbas & Blatt, 1995; Thierry et al., 2000; Catenoix et al., 2011) sometimes leading to generalised convulsions. CFC-mediated spread of hippocampal seizure may be further augmented by the claustrum, consistent with the proposed function of the claustrum with a unique morphology and connectivity that enables it to enhance neural synchrony between brain areas (Vidyasagar & Levichkina, 2019: Madden et al., 2022). It has been pointed out that the claustral projections are uniquely organised to rapidly abort the enhanced neural synchrony between cortical areas (Vidyasagar & Levichkina, 2019). This could potentially explain why such augmentation of synchrony does not usually cause seizures and why claustral damage, on the other hand, can sometimes cause seizures (Maletti et al., 2017).

Putative mechanism of action of VNS and implications for therapy

The above account of the role of the vagus in transmitting the visceral signals to the brain, including the hippocampus, gives the basis for the efficacy of VNS in controlling seizures in many cases of pharmacoresistant epilepsy. VNS stimulation can potentially desynchronise the hippocampal network that is causing, or about to cause, a seizure (Pigarev et al., 2020). In that case, there is no need for VNS to desynchronize the whole cortex to be effective. From that point of view, both VNS and ventral hippocampus stimulation can be effective in seizure prevention, although VNS implantation has less risk and is, therefore, preferable in many cases.

In conclusion, we propose that TLE is largely a reflex type of epilepsy with visceral events serving as triggers, and these triggers are expected to be more effective in provoking resonant activity and oversynchronisation in the hippocampus in sleep. From that point of view, effectiveness of VNS relies on its ability to stop such oversynchronization of the networks involved in the analysis of visceral information.

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