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Review

Patterns of epileptic seizure occurrence

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ABSTRACT

Background: The occurrence of epileptic seizures in seemingly random patterns takes a great toll on persons with epilepsy and their families. Seizure prediction may markedly improve epilepsy management and, therefore, the quality of life of persons with epilepsy.
Methods: Literature review.
Results: Seizures tend to occur following complex non-random patterns. Circadian oscillators may contribute to the rhythmic patterns of seizure occurrence. Complex mathematical models based on chaos theory try to explain and even predict seizure occurrence. There are several patterns of epileptic seizure occurrence based on seizure location, seizure semiology, and hormonal factors, among others. These patterns are most frequently described for large populations. Inter-individual variability and complex interactions between the rhythmic generators continue to make it more difficult to predict seizures in any individual person. The increasing use of large databases and machine learning techniques may help better define patterns of seizure occurrence in individual patients. Improvements in seizure detection –such as wearable seizure detectors— and in seizure prediction –such as machine learning techniques and artificial as well as neuronal networks— promise to provide further progress in the field of epilepsy and are being applied to closed-loop systems for the treatment of epilepsy.
Conclusions: Seizures tend to occur following complex and patient-specific patterns despite their apparently random occurrence. A better understanding of these patterns and current technological advances may allow the implementation of closed-loop detection, prediction, and treatment systems in routine clinical practice.

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1. Introduction

One of the most disabling features of epilepsy is that seizures occur in a seemingly unpredictable pattern (Karoly et al., 2016). The apparent unpredictability of seizure occurrence leads to a sensation of loss of control and worsens the quality of life of patients and families (Jacoby, 1992; Kotwas et al., 2016). However, a growing body of literature demonstrates that seizures tend to occur in patterns (Karoly et al., 2016; Loddenkemper et al., 2011b; Quigg, 2000), making seizure prediction in the individual patient a potentially attainable goal in the future. In this review article, we summarize the evidence demonstrating a non-random pattern of seizure occurrence, the potential mechanisms that explain these cyclical patterns or rhythmicity, and the implications for seizure prediction and seizure treatment.

2. Results

2.1. Historical evolution of the concept of seizure non-randomness

Ancient civilizations conceptualized and explained epilepsy in various ways. Most recognized the influence of environmental factors and the cyclical nature of seizure occurrence (Chaudhary et al., 2011). The translation of a cuneiform text on epilepsy shows that Babylonians classified epilepsy into diurnal epilepsy or nocturnal epilepsy (Wilson and Reynolds, 1990). Aristotle also emphasized the relationship between sleep and epilepsy in his treatise "On sleep and waking" stating that "sleep is similar to epilepsy and in some way sleep is epilepsy" (Magiorkinis et al., 2010). Most ancient civilizations emphasized the influence of environmental factors such as food, physical exercise, or climate on seizure occurrence (Chaudhary et al., 2011). Additionally, some ancient societies suggested that menstruation or moon cycles had the power to disorder the mind (Eadie, 2012; Raison et al., 1999). In particular, full moon was associated with bouts of "insanity" and epilepsy (Raison et al., 1999). This association is still represented in the English language by the word "lunatic" –from "luna", the moon or the goddess of the moon— which refers broadly to mental disorders (Raison et al., 1999). Peaks of seizure occurrence during full moon are well documented in modern literature (Polychronopoulos et al., 2006), although they may be explained by increased nocturnal luminance and resultant decrease in sleep time (Baxendale and Fisher, 2008; Raison et al., 1999). After Edward Sieveking presented a paper on epilepsy and seizure clustering in women to the Royal Medical and Chirurgical Society in 1857, Sir Locock, obstetrician to the Queen Victoria, observed that potassium bromide successfully stopped epileptic seizures in all but one (n = 14 or 15) women whose seizure occurrence was exclusively during their menstruation period (Eadie, 2012). This is considered one of the earliest documented reasonably effective treatment of epilepsy as well as an early description of catamenial epilepsy. In summary, it is remarkable that the influence of environmental factors and their association with seizure cyclical patterns was recognized by most ancient cultures.

2.2. Chaos theory

Seizure occurrence appears random because seizure patterns are often too complex to be described by any simple intuitive model. Chaos theory aims to explain with mathematical models the behavior of systems that change or evolve with time –dynamic systems— and that appear to be random, such as the double pendulum trajectory, natural phenomena, or economy.

From a qualitative point of view, the two main characteristics of chaotic systems are: high sensitivity to initial conditions and order without periodicity depending on system stability. Due to high sensitivity to initial conditions, small variations at onset cause exponentially divergent outcomes, popularly known as the butterfly effect. Due to order without periodicity, sudden turns from order to chaos and vice versa happen often -for example, fractal geometry in nature-. As a result, long-term behavior predictions are challenging in chaotic systems.

To mathematically describe the sensitivity to initial conditions in systems with limited initial information –the most common situation- the Lyapunov exponent is used. This exponent measures the divergence between two starting and infinitesimally close conditions in a dynamic system in which all possible states are represented. Lyapunov exponent is represented by λ in the function $|\delta Z(t)| \approx e^{\lambda t}|\delta Z_0|$, where δZ_0 is the initial separation and t is the time. The number of Lyapunov exponents is equal to the number of dimensions of the system, that is, the rate of divergence. The maximal Lyapunov exponent (MLE) determines the predictability of the system, and a positive MLE indicates that the system is chaotic.

From a mathematical point of view, nonlinear systems follow sets of differential equations – a differential equation is a mathematical equation which connects a function with its derivatives-. To describe order without periodicity, each specific differential equation models specific systems –for instance, Navier-Stokes equations characterizes fluid dynamics; Lorentz laws, electromagnetics; Lorenz system, the atmospheric convection, among others-. Given the chaotic nature of brain neuronal activity, it should be possible to describe epileptic seizures through nonlinear differential equations, and then find a mathematical solution to seizure occurrence.

From a pragmatic point of view, brain neuronal activity could exemplify a chaotic system. Therefore, long-term EEG recordings could benefit from nonlinear analysis and provide clinically useful tools in the field of epilepsy (Elger et al., 2000; Iasemidis and Sackellares, 1996; Lehnertz, 1999). Three chaotic levels depending on the epileptic state have been discovered using nonlinear EEG analysis. The ictal state or seizure discharge corresponds to the lowest chaotic level (order); the postictal state corresponds to the highest chaotic level (chaos); and the pre-ictal state corresponds to an intermediate chaotic level. The intermediate chaotic level during the pre-ictal state reflects a spatiotemporal transition from chaos to a more predictable state (seizure discharge), probably underlying a synchronous neuronal discharge. Moreover, different levels of chaos are registered from the epileptogenic areas and non-epileptogenic areas during interictal states facilitating

the detection of seizure foci (Drury et al., 2003; Iasemidis and Sackellares, 1996). As a result, seizure location and prediction facilitated by the use of chaos theory may simplify epilepsy diagnosis, patient follow-up, treatment response monitoring and epilepsy pre-surgical planning (i.e. by reduced seizure detection time and accurate location) (Ferri et al., 2001; van der Heyden et al., 1999). Some preventive future interventions aim to move a step further from description and predict, warn, and treat patients prior to seizure onset (e.g., real-time tailored therapy through implanted devices capable of detecting pre-ictal state and delivering treatment in response) (Cook et al., 2013; Venkataraman et al., 2014).

2.3. Non-random patterns of seizures in the EEG

The pattern of seizure occurrence is not random. There is a relationship between seizure onset and certain prior EEG features which may permit seizure pattern predictions through mathematical models. For example, a cascade of electrophysiological events (long-term energy bursts) was recorded hours before the clinical seizure onset in a small number of patients with mesial temporal lobe epilepsy (Litt et al., 2001). In another study, 'forbidden ordinal patterns' during a peri-ictal stage (which are the missing ordinal patterns in deterministic dynamics) were recorded in intracranial EEG in a small number of patients with pharmaco-resistant focal epilepsy (Schindler et al., 2011). Likewise, other authors found that a reduction of sleep spindles could predict the occurrence of seizures and propensity of seizure generalization in focal epilepsy (Tezer et al., 2014). A relationship between changes in spike rate, both increased and decreased rate, and seizures onset has also been described in a study involving a small number of patients (Karoly et al., 2016). These authors suggested that a high spike rate inhibits seizures onset instead of promoting them or that a decreased spike rate is a secondary symptom of the brain approaching a seizure. They also concluded that patterns of spike and seizure occurrence were highly subject-specific and follow diurnal and nocturnal cycles with the same regulatory mechanisms. Recently, Cook et al. (2016) have suggested that focal seizures could be characterized by seizure groups of fixed duration and interval which signifies that seizures follow a predetermined path (Cook et al., 2016). Regarding the end of seizures, a study demonstrated that self-terminating seizures end through a common dynamical mechanism via a critical electrophysiological transition, in contrast to status epilepticus that does not cross the critical transition despite repeated approaches (Kramer et al., 2012). Concerning clinical applicability, a seizure advisory system has already been implanted in several patients with drug-resistant epilepsy and it demonstrated the ability to predict seizure likelihood (Cook et al., 2013). In conclusion, both onset and end of seizures can potentially be predicted through EEG with mathematical models.

2.4. Pathophysiological basis of seizure rhythmicity

The pathophysiological basis of seizure rhythmicity remains incompletely understood. However, the 24-h periodicity of epilepsy and its relation to sleep-wake cycles suggest that circadian and diurnal body systems may contribute to seizure rhythmicity (Hofstra and de Weerd, 2009; Kothare and Zarowski, 2011; Loddenkemper et al., 2011a).

The circadian system is a biological rhythm with an approximately 24-h period composed by one or more oscillators which receive inputs and provide outputs (Smolensky and Peppas, 2007). Components of the circadian system include:

Oscillator. An oscillator is a structure of an organism capable to produce a rhythmic output. The main oscillator is called **pacemaker** or biological clock since its rhythm is self-sustained in contrast to the **peripheral oscillators**, which require the pacemaker activity to work. The suprachiasmatic nucleus (SCN) –the human oscillator— is located inside the hypothalamus and each one of the two nuclei contains 8000–10000 neurons. These neurons are responsible for circadian periodicity in humans and other mammals by generating rhythmic electrical activity and producing synchronizing signals. The pacemaker activity may be explained due to 'core circadian clock genes', which generate auto-regulatory transcriptional-translational feedback loops (Bell-Pedersen et al., 2005). The SCN is connected with other brain areas – such as pineal body, thalamus, other hypothalamic nuclei, limbic system and retina- and it can be entrained by environmental inputs. Heart, lung, liver, pineal gland, kidney, fibroblast, testis and skeletal muscle are some examples of human peripheral oscillators or peripheral clocks activated by the SCN. Mutations in clock genes or irregularities in transcriptional-translational processes could cause circadian system dysfunction and, consequently, produce diseases related with circadian rhythmic disruption.

Inputs. An input is a signal coming from the external medium that allows SCN to entrain with the environment. The main input pathways to SCN are the retina, by the retino-hypothalamic tract, and the intergeniculate leaflet, by the geniculo-hypothalamic tract. The light-dark cycle is the main input signal coming from the retina, concretely from rods, cones and ganglion cells which contain rhodopsin, photopsin and melanopsin respectively, and all three required for optimal light entrainment (Panda et al., 2002). Many other input signals entrain the SCN, such as feeding, social interactions, and temperature.

Outputs. An output is an SCN efferent or a result from the oscillator's activity. SNC has efferents to many hypothalamic nuclei. It connects through ventral and dorsal subparaventricular zones and dorsomedial nucleus with the medial preoptic area, ventrolateral preoptic nucleus, paraventricular nucleus and lateral nucleus (Saper et al., 2005). SNC also connects with other brain areas, such as the pineal body, thalamus, and limbic system. These connections, together with cortico-thalamic connections, may represent part of the pathophysiological basis of specific seizure rhythmicity and epilepsy patterns, since these are involved in some epileptic networks (Loddenkemper et al., 2011a). The SCN, through its connections with different areas of the hypothalamus, regulates processes such as sleep, wakefulness, feeding, metabolism, corticosteroids secretion, and corporal temperature (Saper et al., 2005). Peripheral oscillators also modulate other physiological and biochemical functions. For example, the pineal gland regulates the melatonin release depending on the amount of darkness or light. Low melatonin levels increase alertness, heart rate, body temperature, and activate high-alpha frequency in the EEG. Another example may be cardiac features, including modulation of heart rate, blood pressure, vasodilation, and gene expression (Bell-Pedersen et al., 2005). All of the 24-h periodicity biological activity patterns are controlled through clock genes products which orchestrate gene expression, protein modifications and hormone secretion among others.

Another concept related to seizure rhythmicity is seizure clustering. On the one hand, seizure rhythmicity draws non-random cyclical patterns of seizure occurrence through the time - temporal distribution of epileptic seizures-. On the other hand, seizure clustering means acute and repetitive seizures during a defined period of time, despite the lack of consensus to define the period and the number of seizures included in it -closely grouped series of seizures- (Haut, 2015).

2.5. Non-random patterns of seizures based on seizure onset, semiology, and evolution

Circadian patterns in epilepsy, which correspond to diurnal / nocturnal cycles, have been well described (Quigg, 2000). Specifi-

cally, patient wakefulness and sleep cycles have shown to be a better predictor for seizures types than day / night cycling (Kaleyias et al., 2011; Loddenkemper et al., 2011b). The literature on seizure patterns is also summarized in Tables 1 and 2.

2.5.1. Seizure location (Fig. 1 and Table 1)

- **Frontal lobe epilepsy** (FLE). Seizures related to frontal lobe epilepsy occur more frequently during sleep (Herman et al., 2001; Kaleyias et al., 2011; Loddenkemper et al., 2011b) and overnight between 12 a.m.–6 a.m., with a peak in the very early morning (Loddenkemper et al., 2011b). A later study added that these results change depending on different age groups. Frontal lobe seizures occur more frequently during wakefulness in infants, but they happen more frequently during sleep in adolescents (Ramgopal et al., 2014a). These results suggest that changes in circadian rhythms might cause different seizure susceptibility depending on age group. In terms of the sleep phase involved, one study pointed out that focal seizures with onset during

Table 1
Distribution of seizure occurrence according to location of seizure onset in the brain. (See below-mentioned references for further information.)

	FLE	OLE	PLE	TLE	MTLE	NCTLE	XTLE	GEN	MTLOB
Quigg et al. (1998)					N = 64 (774) 15h				
Pavlova et al. (2004)				N = 15 (41) 15–19h			N = 11 (49) 19–23h		
Adults Durazzo et al. (2008)	N = 23 (132) 4–7h	N = 13 (83) 16–19h	N = 16 (77) 4–7h		N = 45 (217) 16–19h 7–10h	N = 34 (160) 13–16h			
Children Hofstra et al. (2009)				N = 13 (67) 5–17h			N = 63 (329) 11–17h		
Adults Hofstra et al. (2009)				N = 65 (241) 11–17h					
Children Kaleyias et al. (2011)				N = 31 (125) 9–12h, 15–18h			N = 35 (134) 6–9h		
Children Loddenkemper et al. (2011b)	N = 29 (118) 0–6h	N = 9 (10) 9–12h 15–18h	N = 9 (74) 6–9h	N = 29 (183) 21–9h				N = 67 (374) 6–12h	N = 91 (249)
Children Ramgopal et al. (2014a)	N = 41 (184) Ch: 21–3h Ad: 6–12h	N = 2 (13)	N = 11 (50)	N = 62 (271) In: 3–6h Ad: 12–15h				N = 109 (490) In: 6–15h Ch: 6–9h, 12–15h Ad: 6–9h, 18–21h	N = 165 (746) In: 9–12h, 15–18h Ch: 0–3h, 6–9h Ad: 6–9h

N: number of patients (and seizures) in the series. FLE: frontal lobe epilepsy. OLE: occipital lobe epilepsy. PLE: parietal lobe epilepsy. TLE: temporal lobe epilepsy. MTLE: mesial temporal lobe epilepsy. NCTLE: neocortical temporal lobe epilepsy. XTLE: extratemporal lobe epilepsy. GEN: generalized epilepsy. MTLOB: multilobar epilepsy. In: infants. Ch: children. Ad: adolescents. DS: Dyscognitive seizures. TS: tonic seizures. TCS: tonic-clonic seizures. CS: clonic seizures. AuS: automotor seizures. HMS: hypermotor seizures. AtS: atonic seizures. hmS: hypomotor seizures. MS: myoclonic seizures. ES: epileptic spasms. VS: versive seizures. GS: gelastic seizures. Abs: absence seizures.

Table 2
Distribution of seizure occurrence according to seizure semiology.

	DS	TS	TCS	Aura	CS	AuS	HMS	AtS	hmS	MS	ES	Others (VS, GS, Abs)
Children Hofstra et al. (2009)	(215) 11–17h	(107) 5–11h										
Adults Hofstra et al. (2009)	(265) 11–17h											
Children Loddenkemper et al. (2011b)	N = 24 (78) 9–12h 21–0h	N = 47 (201) 6–9h	N = 7 (24) 6–9h	N = 41 (152) 21–0h	N = 21 (91) 6–9h	N = 15 (82) 0–6h	N = 26 (118) 0–9h	N = 13 (55) 6–9h 12–15h	N = 17 (62) 9–12h	N = 22 (66) 6–12h	N = 12 (39)	VS: N = 12 (35) GS: N = 1 (5)
Children Generalized N = 77 (316) Zarowski et al. (2011)		(50)	(24)		(27) 6–9h 12–15h			(54) 12–18h		(70) 6–12h	(44) 6–9h 15–18h	Abs: (47) 9–12h 15–24h
Children Ramgopal et al. (2012a)											N = 51 (219) <3 y/o 9–12h 15–18h >3 y/o 6–9h	

N: number of patients (and seizures) in the series. FLE: frontal lobe epilepsy. OLE: occipital lobe epilepsy. PLE: parietal lobe epilepsy. TLE: temporal lobe epilepsy. MTLE: mesial temporal lobe epilepsy. NCTLE: neocortical temporal lobe epilepsy. XTLE: extratemporal lobe epilepsy. GEN: generalized epilepsy. MTLOB: multilobar epilepsy. In: infants. Ch: children. Ad: adolescents. DS: Dyscognitive seizures. TS: tonic seizures. TCS: tonic-clonic seizures. CS: clonic seizures. AuS: automotor seizures. HMS: hypermotor seizures. AtS: atonic seizures. hmS: hypomotor seizures. MS: myoclonic seizures. ES: epileptic spasms. VS: versive seizures. GS: gelastic seizures. Abs: absence seizures.

sleep often occur during NREM sleep, mainly in stage 2, and essentially never in REM sleep, which suggested that hypersynchrony of sleep could facilitate the onset of certain focal seizures (Herman et al., 2001). That is, sleep has a synchronizing effect on frontal lobe seizures.

- **Occipital lobe epilepsy** (OLE). In contrast, occipital lobe seizures occur more frequently during daytime, with peaks from 9 a.m. - noon and 3 p.m. – 6 p.m. (Loddenkemper et al., 2011b) and during wakefulness (Kaleyias et al., 2011).
- **Parietal lobe epilepsy** (PLE). Parietal lobe seizures occur more frequently during sleep, with a peak between 6 a.m. – 9 a.m. (Loddenkemper et al., 2011b).
- **Temporal lobe epilepsy** (TLE). Temporal lobe seizures happen mostly in wakefulness (Kaleyias et al., 2011; Loddenkemper et al., 2011b; Ramgopal et al., 2014a) and at night between 9 p.m. – 9 a.m., with an early morning seizure peak in some studies (Loddenkemper et al., 2011b), and during daytime in others (Kaleyias et al., 2011).
- **Multilobar seizures.** Multilobar seizures occur largely during sleep (Loddenkemper et al., 2011b).
- **Generalized epilepsy** (GEN). Generalized seizures happen mostly in wakefulness and daytime with a peak between 6 a.m. – 12 p.m. (Loddenkemper et al., 2011b; Ramgopal et al., 2014a). A study points out that occurrence of seizures at night increases in older patients (Ramgopal et al., 2014a). Idiopathic generalized epilepsy syndromes are more frequent in wakefulness, in contrast with symptomatic generalized syndromes, which do not show differences in wakefulness/sleep cycle (Zarowski et al., 2011).

2.5.2. Seizure semiology (Loddenkemper et al., 2011b; Zarowski et al., 2011) (Table 2)

- **Atonic seizures**, **hypomotor seizures** and **myoclonic seizures**. All three happen mostly in wakefulness and during daytime.
- **Automotor seizures** and **hypermotor seizures.** Both occur mostly during sleep and at night.
- **Gelastic seizures**, **dyscognitive seizures** and **auras.** All three happen more frequently in wakefulness than in sleep, without any clear differences in day or night cycle.
- **Epileptic spasms.** Epileptic spasms are more frequent in wakefulness than in sleep, without differences in day-night cycle, with the exception of one study that demonstrated a higher frequency during daytime (Ramgopal et al., 2012a). Furthermore, this study shows differences in daytime depending on patient age (younger patients have epileptic spasms mostly between 9 a.m. - noon and 3 p.m.–6 p.m., and older patients have epileptic spasms mostly during 6 a.m.–9 a.m.) (Ramgopal et al., 2012a).
- **Tonic seizures** and **tonic-clonic seizures**. Both happen mostly during sleep, without differences in day/night cycle. Tonic seizures show a peak around midnight and in the early morning hours.
- **Clonic seizures**. Clonic seizures occur mainly during daytime, without differences in wakefulness/sleep cycle.

2.5.3. Clinical evolution of seizures

Several studies suggest that the clinical evolution of seizures (specifically the clinical evolution from one semiological pattern into the next phase) also follows non-random patterns, and occurs at specific times, or at a particular time of the wakefulness/sleep cycle, independent of potential confounding factors (Ramgopal et al., 2012b; Sánchez Fernández et al., 2013). For example, a study focusing on this topic has shown that evolution into tonic seizures peaks between 9 p.m. - noon and during sleep; into automotor seizures peaks during wakefulness; into clonic seizures peaks between 0–3 a.m. and 6–9 a.m. and during sleep, and into generalized tonic-clonic seizures (GTC) seizures peaks during sleep (Sánchez Fernández et al., 2013). Another study focusing on the evolution into GTC seizures has shown that evolution into GTC seizures occurs more frequently between 12–3 a.m. and 6–9 a.m. Patients with generalized EEG onset have more frequent tonic-clonic evolution between 9 a.m. and 12 p.m., and patients with extratemporal focal seizures are more likely to evolve into GTC during sleep (Ramgopal et al., 2012b). In addition, this study suggests that increasing patient age and sleep are the main predictors of secondary generalization (Ramgopal et al., 2012b). Additionally, frontal lobe seizures present with less frequent secondary generalization during sleep compared with other focal seizures (Herman et al., 2001). In conclusion, seizures may follow non-random patterns.

2.6. Irregular patterns of seizure occurrence

The pattern of seizure occurrence is most often described over a 24 h period, and mainly influenced by time of day and sleep-wake stage (Loddenkemper et al., 2011b; Quigg, 2000). Detailed data from patients with intracranial monitoring devices show that the pattern of seizure occurrence may be more irregular and complex (Cook et al., 2016; Karoly et al., 2016). In a series of 15 patients with refractory focal epilepsy and an implanted intracranial device, the inter-seizure interval showed a cyclical pattern which was more complex than a simple circadian pattern (Cook et al., 2016). Furthermore, the seizure pattern occurrence was highly individual-specific (Cook et al., 2016). This series showed that patient-specific ultradian and infradian rhythms may also contribute to the distribution of seizure occurrence (Karoly et al., 2016). The mechanisms associated with ultradian and infradian rhythms are currently unknown but may shed light on the pathophysiology of seizure generation.

Studying complex distributions require numerous data points. As seizures occur relatively rarely in any given patient, deciphering the individual pattern of seizure occurrence might be challenging. Additionally, interictal epileptiform activity also follows a rhythmic pattern (Anderson et al., 2015) and the distribution of interictal epileptiform discharges often closely mimics that of the distribution of seizures (Karoly et al., 2016). Therefore, it is possible that the analysis of interictal epileptiform discharges may help elucidate patient-specific patterns of seizure occurrence in the future.

2.7. Non-random patterns of status epilepticus

In contrast to the large body of literature showing that seizures follow non-random patterns related to time of day and sleep-wakefulness cycles, little is known about the diurnal and nocturnal patterns of status epilepticus. The lack of literature on the 24 h variation of status epilepticus might be related to the population needed to address this question. Describing the 24 h distribution of seizure onset is an attainable goal in a single large epilepsy unit. In contrast, describing the 24 h distribution of status epilepticus onset is only attainable if a very large number of cases of status epilepticus are analyzed together. Large multicenter networks studying status epilepticus (Cock et al., 2011; Sánchez Fernández et al., 2014) or the use of large patient self-reported databases (Goldenholz et al., 2015) might provide answers in the near future. The distribution of status epilepticus over time may simply reflect the distribution of seizures over time or status epilepticus may have its individual 24 h distribution. Answering this question may provide insights into the mechanisms that lead from seizures to status epilepticus generation.

2.8. Perimenstrual non-random patterns and other triggers

Catamenial epilepsy refers to seizures that occur in relation to the menstrual cycle. This type of epilepsy follows an infradian rhythm which may be entrained by environmental infradian rhythms, such as lunar cycle. The menstrual cycle is divided into a follicular phase (day 1 to 14 of the cycle) and a luteal phase (day 15 to 28 of the cycle), which are separated by ovulation (day 14 or 15) and menstruation (which starts on day 1). These cyclical phases are associated with changes in hormonal levels, mainly an estradiol surge during the follicular phase followed by a pre-ovulatory luteinizing hormone (LH) peak, and a premenstrual decrease in progesterone levels. Based on the menstrual cycle, three catamenial seizure patterns have been described: C1 or perimenstrual pattern (seizure occurrence around menstruation, from three days before to three days later), C2 or peri-ovulatory pattern (seizure occurrence around ovulation, from four or five days before to one day later), and C3 pattern in anovulatory cycles (seizure occurrence around luteal phase, from four or five days before to three days later) (Herzog, 2015). The highest seizure likelihood during the menstrual cycle corresponds to day 1 and the lowest seizure likelihood corresponds to the mid-luteal day in ovulatory cycles. Estimating the prevalence of catamenial epilepsy is challenging due to heterogeneous study inclusion and exclusion criteria. A recent study estimates a prevalence of 44.2% among women with epilepsy (Herzog, 2015).

The pathophysiology of catamenial epilepsy is based on menstrual oscillations of the sexual hormones which have neuroactive properties and effects on epileptic substrates (Scharfman and MacLusky, 2006; Woolley and Schwartzkroin, 1998). Progesterone effect may protect from seizures. In contrast, estrogen effects may increase or decrease seizure susceptibility depending on estrogen levels, regulation of gene expression, duration of estrogen exposition (acute or chronic), estrogen species, seizure type, neurotransmitter system involved, and interaction with progesterone (Velísková, 2006; Velísková et al., 2010). Progesterone works mainly through its metabolite allopregnanolone, which is a potent modulator of $GABA_A$ receptor, and through changes in $GABA_A$ receptor subunit expression; on the other hand, estrogens are related to many complex excitatory and inhibitory mechanisms, involving both NMDA and non-NMDA receptors (Kalkbrenner and Standley, 2003).

Besides the perimenstrual non-random patterns, other non-random patterns have been described. Many patients relate the occurrence of their seizures to lack of sleep, higher self-reported stress and anxiety levels, weather variation –such as changes in temperature, humidity, wind force, light exposure, or seasonality-, among others, and their perceptions are being progressively corroborated (Gunn and Baram, 2017; Haut et al., 2007; Rakers et al., 2017; Rüegg et al., 2008).

2.9. Practical implications

2.9.1. Differential antiepileptic dosing

Approximately one-third of epilepsy patients continue to have seizures after two cycles of appropriately chosen and dosed antiepileptic drugs (Kwan and Brodie, 2000). The availability of multiple antiepileptic drug choices in the last years did not reduce the proportion of medically refractory epilepsy. Chronotherapy, based on the current understanding of chronobiology, seizure patterns and sleep-wake patterns, may be a promising approach, since seizure susceptibility patterns are often well defined in epilepsy (see previous sections) (Ramgopal et al., 2013). Chronotherapy aims to synchronize treatment to biological rhythms and disease patterns taking into account dynamic changes in both drug pharmacology and disease-related processes, with the objective of improving the effectiveness and reducing the toxicity of treatments. This type of therapy may be used in the form of differential dosing, as preparations designed to deliver sustained or pulsatile drug at times of greatest susceptibility, or in the form of 'zeitgebers' that reset endogenous rhythms. Chronotherapy is successfully used in many diseases with periodic endogenous rhythms in their pathogenesis, such as diabetes, cancer, cardiovascular diseases, asthma, and arthritis (Youan, 2004).

Differential antiepileptic dosing has been shown to be useful without increasing adverse effects in several series:

1. A study of 103 adults patients with more frequent tonic–clonic seizures at night and previous use of sub-therapeutic doses of phenytoin and carbamazepine found that administration of a higher percentage of the total daily antiepileptic dose in the evening improved seizure control and reduced side effects (Yegnanarayan et al., 2006).
2. In a series of 17 children with nighttime seizures were treated with differential dosing and it was found that 15 (88%) patients responded to treatment with $\geq$ 50% seizure reduction, 11 (65%) of these patients became seizure free, nine patients (53%) received monotherapy after dose modification, two patients complained of transient side effects (fatigue / somnolence) and none presented with worsening of seizures (Guilhoto et al., 2011).
3. In a recent study, 27 patients with a high proportion of seizures at nighttime (6 p.m. to 6 a.m.) were treated with clobazam differential dosing (> 50% of the total daily dose after 6 p.m.). Patients with differential dosing tolerated a higher median total clobazam dose as compared to controls. Additionally, differential dose patients exhibited a median seizure reduction of 75% as compared to 50% in controls, and patients with generalized seizures benefited the most (Thome-Souza et al., 2016).
4. Another study showed that patients tend to take their medication sooner or later than expected, which could mean that patients adapt these times to their morning or evening pattern (Hofstra et al., 2012).

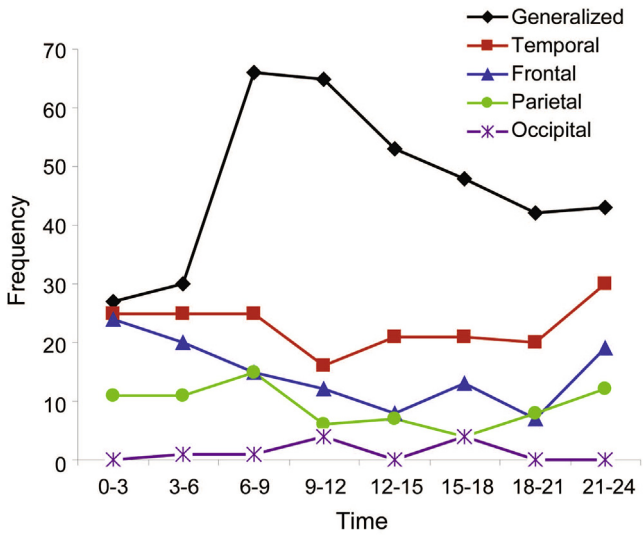

Fig. 1. Seizures patterns based on seizure onset. This figure represents seizures patterns depending on seizure onset throughout a 24-h time period. Each type of seizure reveals specific peaks. Generalized seizures peak at 6–12 h; temporal lobe seizures, at 21–9 h; frontal lobe seizures, at 0–6 h; parietal lobe seizures, at 6–9 h; and occipital lobe seizures, at 9–12 h and 15–18 h. (Reproduced with permission from Neurology/Wolters Kluwer Health and Loddenkemper et al. (Loddenkemper et al., 2011b)).

In terms of infradian rhythms, the first large-scale study about hormonal treatment in catamenial epilepsy supports benefits from adjuvant progesterone therapy during the luteal phase −200 mg TID from day 14 to 25 followed by decreasing dosage until finish it on day 28- in women whose seizures follow a strong perimenstrual exacerbation or C1 pattern -besides optimal antiepileptic treatment- (Herzog, 2015).

2.9.2. Big data, machine learning, and seizure prediction

Seizures tend to occur following patient-specific patterns (Cook et al., 2016; Karoly et al., 2016; Loddenkemper et al., 2011b). Seizure prediction has been an area of intense research for decades (Litt and Echauz, 2002; Mormann et al., 2007). Implanted intracranial devices in patients with focal refractory epilepsy have provided detailed data on the pattern of clinical and subclinical seizure occurrence (Cook et al., 2013; Morrell et al., 2011). The analysis of these patterns suggests that seizures do not occur randomly, but that they follow complex and patient-specific probability distributions (Cook et al., 2016; Karoly et al., 2016). Implantable intracranial devices have led the way towards seizure prediction and closed-looped systems of seizure detection and seizure treatment (Cook et al., 2013; Morrell et al., 2011). A series of 191 adults with refractory focal epilepsy were implanted with a neurostimulator that detected abnormal electrocorticographic activity (Morrell et al., 2011). Patients who were randomized to receive stimulation in response to abnormal electrocorticographic activity

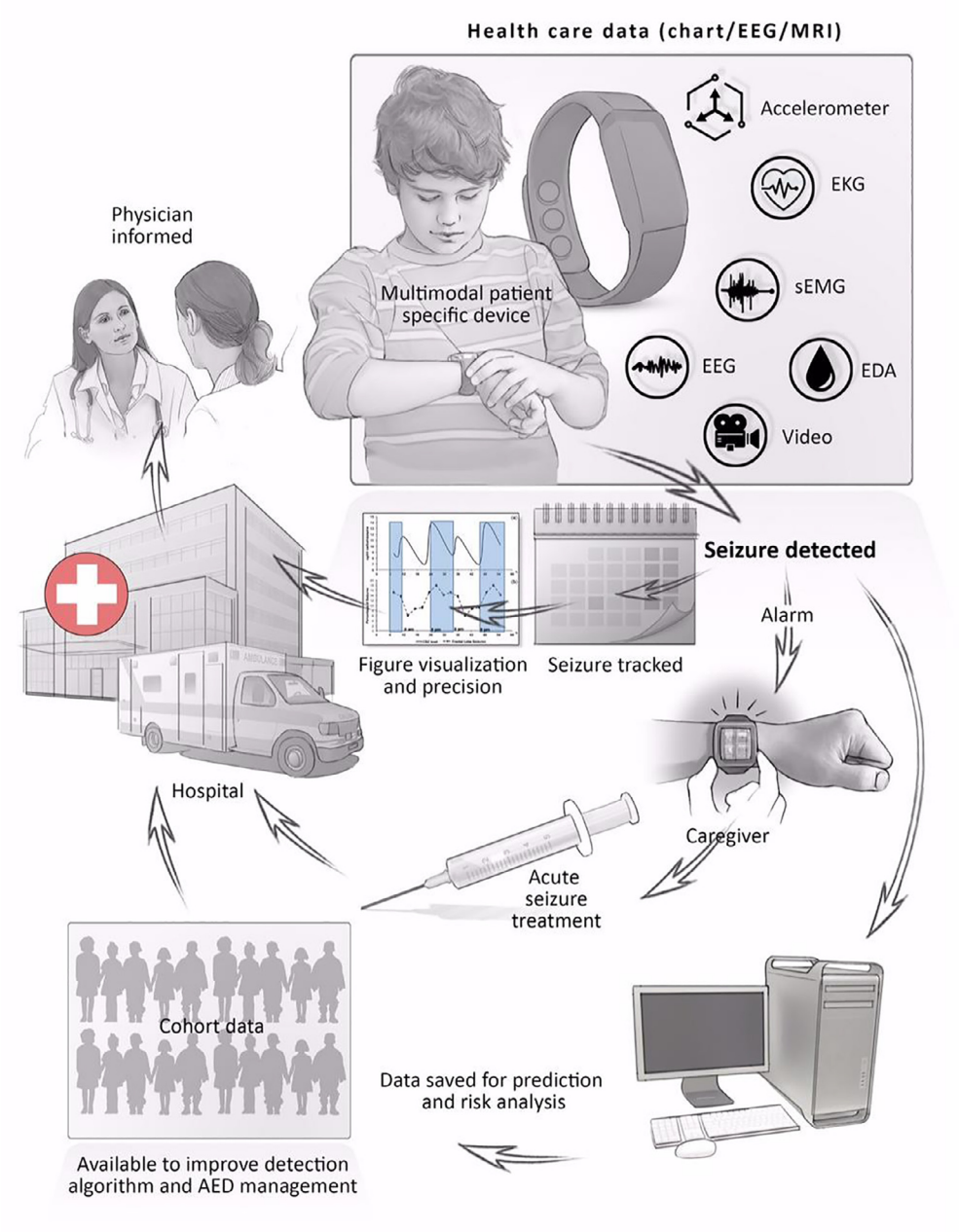

Fig. 2. Components of the closed-loop detection-treatment systems. The portable device has access to the patient's health care data and contains a combination of seizures detection modalities -accelerometer (ACM), electrocardiogram (EKG), surface electromyogram (sEMG), electroencephalogram (EEG), electrodermal activity (EDA) and video monitoring-. When a seizure is detected, it is registered in the patient's clinical chart – which gives information to the physician in order to improve the management of the patient – and general registers –which allow the improvement of detection algorithms and medication management from cohort data -. Furthermore, when a seizure is detected the caregiver is informed and this leads to a corrective response which could imply abortive pharmacotherapy, neurostimulation or a micro-pump that delivers medication, and transport to an emergency room if needed. (Reproduced with permission from Seizure/Elsevier and Ulate-Campos et al. (Ulate-Campos et al., 2016)).

presented with a much higher reduction in seizure frequency than patients randomized to no stimulation, with no difference in adverse events (Morrell et al., 2011). A series of 15 patients with focal refractory epilepsy demonstrated that seizure prediction is feasible, with prediction of seizure occurrence better than chance (Cook et al., 2013). However, two major aspects limit the application of these methods to the wider population of epileptic patients. First, the positive and negative predictive values of the detection algorithms are still far from what would be considered appropriate for clinically meaningful prediction. More importantly, prediction based on intracranial EEG data is only applicable to a minority of patients with epilepsy in whom the benefits of detecting seizures outweigh the risks of neurosurgery and of an implanted intracranial device.

As many seizures tend to occur in predictable patterns, these patterns may be amenable to detection based on the occurrence of clinical seizures. The recent more widespread use of electronic seizure diaries makes it feasible and relatively straightforward to collect large amounts of information on patients with epilepsy. Electronic seizure diaries provide the amount of data points that might allow identification of complex seizure patterns. The rapidly increasing size of clinical databases allows for development of more complex models that may improve treatment selection (Devinsky et al., 2016) and may refine seizure prediction models developed in databases of limited size (Hall et al., 2009). When the seizure number is sufficiently large, the possibility to predict seizure occurrence (Cook et al., 2016) and seizure counts (Tharayil et al., 2017) becomes more likely. The application of machine learning algorithms on clinical data may allow prediction of seizure occurrence (Sánchez Fernández et al., 2016). Simple learning algorithms like robust linear regression and random forests may be the building blocks of more complex approaches like deep learning. Once developed, these algorithms may be integrated in clinically applicable devices. Integration of learning algorithms into wearable detection devices may lead to closed-loop systems for seizure detection and prediction (Ulate-Campos et al., 2016).

2.10. Future directions: seizure detection and seizure prediction in the ambulatory setting

The quality of life of patients with chronic diseases and their caregivers is an often overlooked aspect in treatment. Patients with epilepsy may be better managed remotely by closed-loop detection-treatment systems and may benefit from reducing hospital appointments and EEG recordings. Patients with epilepsy, especially patients with uncontrolled epilepsy, are in urgent need of seizure susceptibility prediction devices (Schulze-Bonhage et al., 2010).

Technology to detect seizures using devices other than EEG is now available (Ramgopal et al., 2014b; van Andel et al., 2016). These devices are based on extra-cerebral signals. For example, accelerometers, gyroscopes, magnetometers and video recordings have proven useful in detecting movement of patients during seizures; electromyography may detect the tonic phase of seizures; electrocardiography or breathing/saturation sensors may detect changes in heart rate or respiration respectively, allowing seizure detection; and electrodermal activity could change due to sweating, meaning activation of the sympathetic nervous system. Depending on the seizure type, selected electrophysiological patterns or combinations of signals may work better for individual patients and seizure patterns (Ulate-Campos et al., 2016). Furthermore, this technology has already been integrated into portable devices which may facilitate detection of seizures in ambulatory settings (Fig. 2).

Some algorithms for detecting generalized tonic-clonic seizures have proven to be useful in clinical settings (van Andel et al., 2016), and work is ongoing to improve the detection of other seizure types. However, some technical difficulties in home settings –such as interferences and alarm fatigue, data privacy and high false positive rates – are aspects that leave room for future improvements (van Andel et al., 2016). Despite these issues, in the near future the development of these technologies in portable devices may modify the field of epilepsy, such as diagnostic methods, treatment and follow-up. In addition to improving quality of life, portable devices may also reduce morbidity and mortality in epilepsy due to rapid seizure detection and instant tailored treatment (Van de Vel et al., 2013).

In summary, implementing machine learning driven closed-loop detection, prediction, and treatment systems in routine clinical practice is the research prospect that promises to revolutionize the field of epilepsy.

3. Conclusion

Despite their apparently random occurrence, seizures tend to occur following complex and patient-specific probability distributions. A better understanding of these patterns -thanks to machine learning techniques and artificial as well as neuronal networks- may allow the development of closed-loop detection, prediction, and treatment systems that may change the field of epilepsy and drastically improve the quality of life of patients with epilepsy.

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ETHICS

This study complied with biomedical research ethical standards.

FUNDING

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DECLARATION OF INTEREST

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Tobias Loddenkemper serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council (and as Vice President) of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for Seizure, and as an Associate Editor for Wyllie’s Treatment of Epilepsy 6th edition. He is part of pending patent applications to detect and predict seizures and to diagnose epilepsy. He receives research support from the Epilepsy Research Fund, the American Epilepsy Society, the Epilepsy Foundation of America, the Epilepsy Therapy Project, PCORI, the Pediatric Epilepsy Research Foundation, CURE, HHV-6 Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Acorda, and Pfizer. He serves as a consultant for Zogenix, Upsher Smith and Lundbeck. He performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children’s Hospital and affiliated hospitals and bills for these procedures and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies including the AAN, AES and ACNS, and for grand rounds at various academic

centers. His wife, Dr. Karen Stannard, is a pediatric neurologist and she performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures and she evaluates pediatric neurology patients and bills for clinical care.

The authors report no potential conflicts of interest.

CONTRIBUTORS

Marta Amengual-Gual participated in drafting and revising the manuscript for content, including medical writing for content, in study concept and design, and study supervision.

Iván Sánchez Fernández participated in including medical writing for content, in study concept and design, and study supervision or coordination.

Tobias Loddenkemper participated in medical writing for content, in study concept and design, and study supervision or coordination.

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