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Pharmaco-resistant seizures: self-triggering capacity, scale-free properties and predictability?

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Abstract

Relevant and timely questions such as regarding the predictability of seizures and their capacity to trigger more seizures remain the subject of debate in epileptology. The present study endeavors to gain insight into these dynamic issues by adopting a non-reductionist approach and via the use of mathematical tools. Probability distribution functions of seizure energies and inter-seizure intervals and the probability of seizure occurrence conditional upon the time elapsed from the previous seizure were estimated from prolonged recordings from subjects with pharmaco-resistant seizures, undergoing surgical evaluation, on reduced doses of or on no medications. The energy and inter-seizure interval distributions for pharmaco-resistant seizures, under the prevailing study conditions, are governed by power laws ('scale-free' behavior). Pharmaco-resistant seizures tend to occur in clusters and the time to the next seizure increases with the duration of the seizure-free interval since the last one. However, characteristic size energy probability density functions were found in a few subjects. These findings suggests that: (i) pharmaco-resistant seizures have an inherent self-triggering capacity; (ii) their time of occurrence and intensity may be predictable in light of the existence of power law distributions and of their self-triggering capacity; and (iii) their lack of typical size and duration (scale-free), features upon which their classification into ictal or interictal is largely based, may be inadequate/insufficient classifiers.

Introduction

The temporal behavior and other dynamic aspects of human epilepsy, such as the probability distributions of seizure duration and intensity, remains an underdeveloped area in epileptology. This is largely due to the fact that seizure diaries do not record subclinical events or quantify severity and under-estimate the number of clinical seizures, particularly when they occur in clusters (Blum *et al.*, 1996; Hoppe *et al.*, 2007). These limitations hinder the characterization of the dynamics of epilepsy; efforts to control it may prove futile without this knowledge.

Fundamental questions remain unanswered, such as: Can the dynamics of epilepsy be adequately characterized without taking inventory of subclinical/electrographic seizures? Are seizures independent of each other? Are seizure energies correlated with the length of the preceding or of the subsequent seizure-free interval? Do seizures have the inherent capacity to trigger seizures? These questions remain more than 100 years after Gowers' observation that 'seizures beget seizures' (Gowers, 1901). This dearth of knowledge, concerning the dynamics of seizures, may account in part for the fact that, despite attempts spanning nearly two decades, worthwhile prediction of seizures remains elusive (Osorio *et al.*, 2001; Lai *et al.*, 2002, 2003; Harrison *et al.*, 2005; Mormann *et al.*, 2007).

The present study aims to gain insight into the dynamics (Milton, 2003) of localization-related pharmaco-resistant seizures by adopting a large-scale (non-reductionist) approach to its study using simple but powerful mathematical tools that have proven useful in fields that investigate the behavior of complex systems, such as the brain.

Methods

Three tools were used to investigate the dynamics of pharmaco-resistant seizures: (i) probability density or distribution functions of seizure 'energy' and of inter-seizure intervals; (ii) superposition ('stacking') analysis of seizures; and (iii) empirical estimation of the probability of seizure occurrence conditioned upon the time elapsed from the previous seizure.

A probability density function of a given variable (e.g. the 'energy' or power of a seizure) is obtained by integration (summing) of the values of the variable of interest over an interval, providing an estimate of the probability that the variable will fall within that interval. Loosely defined, a probability density function of a variable may be regarded as a 'smoothed-out', normalized version of a histogram or as the relative frequencies of event (seizure) occurrences. Moreover, probability density functions can provide constraints and guidelines to identify the underlying mechanisms of the behavior of complex systems (Sornette, 2006), such as the epileptic brain.

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Conditional probability is the probability of some event A, given the occurrence of some other event B. Conditional probability is written $P(A|B)$, and is read 'the probability of A, given B'.

Superposition analysis orderly 'stacks' a variable using a 'marker' to ensure alignment. In the present analysis, seizures are the variables and their onset and termination times are the 'markers' that allow their precise alignment.

With approval from the Human Subjects Committee and also with approval from the University of Kansas Medical Center Human Subjects Committee and the understanding of each subject (signed consent form obtained according to the Declaration of Helsinki), quantitative analyses were performed on 16 032 automated seizure detections in prolonged (several days' duration) intracranial recordings from 60 human subjects with mesial temporal and frontal lobe pharmaco-resistant seizures, on reduced doses or off medications, and undergoing evaluation for surgery at the University of Kansas Medical Center (1996–2000). The large majority of these seizures lacked behavioral manifestations and were classified as subclinical. Using a validated detection algorithm (Osorio *et al.*, 1998, 2002) seizure onset and end times, duration, peak intensity and site of origin were obtained. Seizures were defined as the sudden increase in a particular weighted frequency band (8–42 Hz) reaching a threshold value, T , of at least 22 and remaining at or above it for at least 0.84 s (duration constraint, D) as previously described elsewhere (Osorio *et al.*, 1998, 2002). A dimensionless ratio is continuously calculated in moving windows of the electrocorticogram (ECoG) signal by dividing the present (2-s window) by the past (30-min window) seizure content. Based on detailed and rigorous analyses of long time series recorded from humans with epilepsy (Osorio *et al.*, 1998, 2002), the probability that a dimensionless ratio of 22 (referred to herein as threshold $T = 22$) is indicative of seizure onset has been estimated at >90%. This value of T has been chosen to optimize sensitivity, specificity and speed of detection.

Two key variables were derived from the output of the detection algorithm: (i) 'energy' (E), defined as the product of each seizure's peak intensity and its duration (in seconds) and (ii) inter-seizure intervals defined as the time (in seconds) elapsed between the onset of two consecutive seizures. Seizure energy and inter-seizure intervals were chosen as they adequately describe a seizure time series.

To characterize the statistical distribution of seizure energy and inter-seizure intervals of clinical and subclinical seizures, pooled values (all subjects, irrespective of site of seizure origin) of these two variables were used to construct plots with logarithmic scales on the x - and y -axes. For this, the number of seizures of a given energy and the number of inter-seizure intervals of a given duration were used to construct histograms whose bins were geometrically spaced (by powers of 2) and made to span the entire range (from the smallest to the largest value) of the data. The number of seizures in each bin was then normalized by the bin's width and plotted on a log–log scale.

The temporal evolution of the probability of being in seizure as a function of time before the onset and following the termination of a given seizure was investigated as follows. (i) The state of being in seizure was assigned a value of 1 and the non-seizure state a value of 0. (ii) Seizure onsets were 'time-locked' to all onsets and seizure ends to all other ends. (iii) The state values (0, 1) overlaid in this manner were then averaged to compute the empirical probability, $P(t)$, of being in seizure at a relative time, t , in reference to the onset and termination of another seizure. (iv) The resulting probability curves for each subject were then normalized by the subject's total fraction of time spent in seizure and averaged across all subjects.

The existence of correlations between seizure energy and the lengths of the preceding and following seizure-free intervals (inter-seizure

intervals) was probed using the two-dimensional Kolmogorov–Smirnov test (Press *et al.*, 1992). The distribution of the original time series for all subjects was compared against 100 surrogate time series obtained by randomizing the temporal order of seizure energies to eliminate any such dependencies, if present. Statistically significant differences between the original and randomized distributions are interpreted as indirect evidence of correlation between seizure energy and the lengths of the preceding and/or immediately following seizure-free intervals.

The Kolmogorov–Smirnov test (Press *et al.*, 1992) is one of the most useful and general non-parametric methods for comparing two samples, as it is sensitive to differences in both the location and the shape of the empirical cumulative distribution functions of the samples. This test, which was chosen because the distribution of inter-seizure intervals is non-Gaussian, quantifies the 'distance' between the original and the randomized inter-seizure interval distributions. In the two-sample case, the distribution of this statistic is calculated under the null hypothesis that the samples are drawn from the same distribution.

Results

Seizure energy distribution

For all subjects, the probability of a seizure (irrespective of site of origin) having energy larger than x is proportional to $x^{-\beta}$, where $\beta \approx -2/3$ (Fig. 1) (β refers to the exponent of the survival distribution; the exponent of the probability density function is $1 + \beta$), i.e. seizure energy is inversely correlated with the probability of its occurrence: the higher the energy, the lower the probability of occurrence. The slight deviation from linearity (Fig. 1, red curve, 'arrows') is due to the presence of characteristic scales in the probability density function of seizure energy of 9/60 subjects (Fig. 1); exclusion of these nine subjects eliminated the 'shoulder' (Fig. 1, light green curve).

Temporal distribution of the probability of seizure occurrence

In these subjects, there was an increased probability of seizure occurrence in the window beginning 30 min before a seizure and ending 30 min later (Fig. 2). That is, seizures in these subjects and under the conditions studied had a tendency to cluster. This clustering has a clear ramp-up before and a ramp-down after a seizure, suggesting a quantitative statistical precursory diagnostic of impending seizures.

Distribution of inter-seizure intervals

The probability density function estimates for inter-seizure intervals, defined as the time elapsed from the onset of one seizure to the onset of the next, were also calculated using histogram-based estimation methods. The probability density function of inter-seizure intervals (Fig. 3) in these subjects approximately follows a power-law distribution characterized by $\beta \approx 0.5$. This distribution encompasses very short and long inter-seizure intervals, consistent with seizures clustering and prolonged seizure-free intervals in this population.

Statistically significant differences were found between seizure energy/inter-seizure interval pairs and the 100 temporally randomized data surrogates, when either the preceding inter-seizure intervals ($\alpha_{KS} < 7.2e-5$, $P = 0.01$) or immediately following inter-seizure intervals ($\alpha_{KS} < 0.013$, $P = 0.01$) were used.

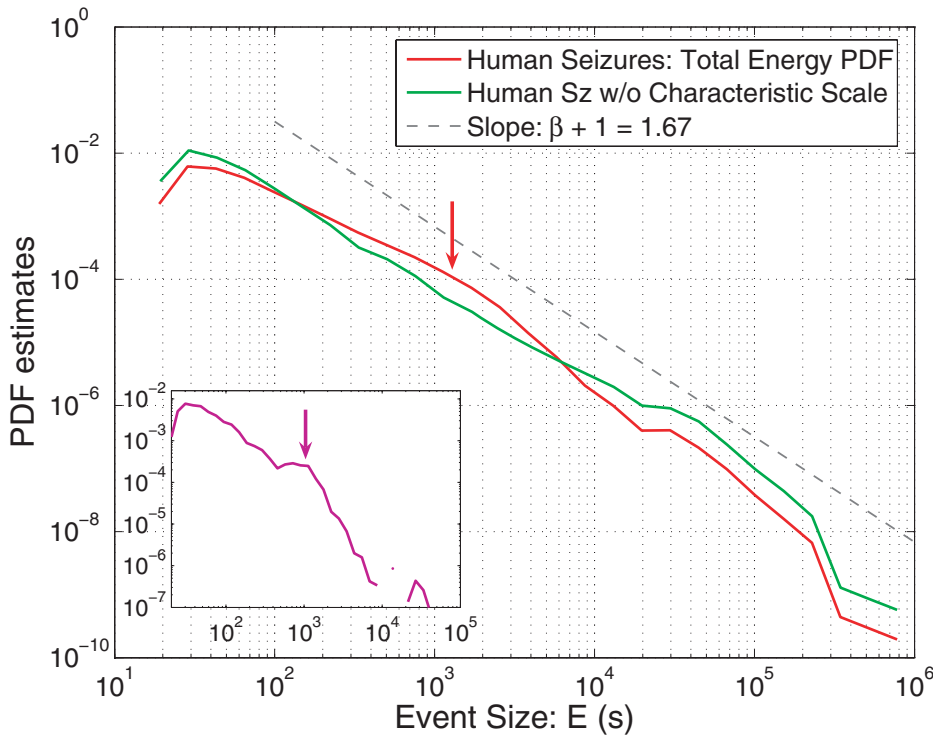


FIG. 1. Probability density function (PDF) estimates of seizure energies E (E = peak intensity \times duration) of 60 human subjects (red curve). Seizures originated in these subjects from mesial temporal and frontal lobe regions. This probability density function's power law exponent is ~ -1.67 ; the slight deviation from linearity manifesting as a 'shoulder' in the red curve (see arrow) disappears (light green curve) with the exclusion of 9/60 subjects whose probability density function of seizure energies had characteristic sizes [see inset; the linear regime in 51/60 subjects (light green curve) spans more than four decades on both axes]. x -axis: seizure energy, E (logarithmic scale); y -axis: number of seizures (logarithmic scale) with energy E . Inset: probability density function of seizure E of one subject with characteristic scale as evidenced by the prominent 'shoulder' (see purple arrow) that destroys linearity.

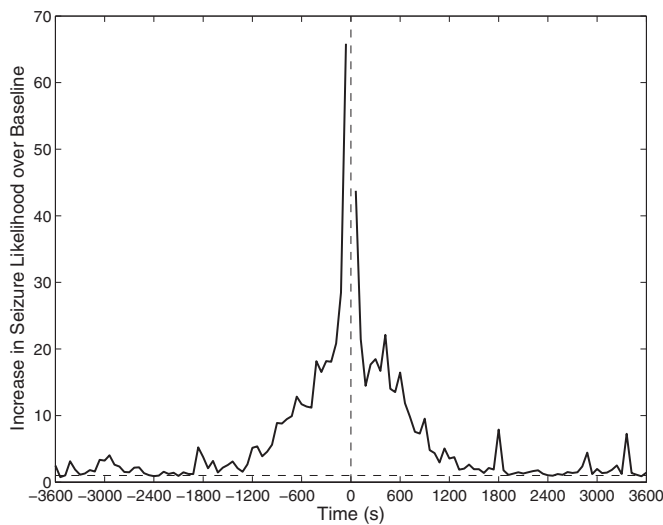


FIG. 2. Empirical probability (0–1; y -axis) of being in seizure as a function of time elapsed (x -axis) before onset and after termination of a seizure. The curve to the left of the vertical dashed line (at time zero) depicts the probability before onset and the one to the right of this line depicts the probability after seizure termination. The empirical probability of being in seizure increases approximately 1200 s before onset and returns to baseline 1200 s after termination of a given seizure. This behavior is indicative of a strong clustering tendency.

Paradox of conditional expected waiting time to next seizure

The prediction derived from the heavy tail structure of the inter-seizure interval distributions between successive events (Fig. 3) that 'the longer it has been since the last event, the longer the expected time until the next' (Sornette & Knopoff, 1997), was tested. The results confirmed that for seizures the dependence of the average conditional additional waiting time until the next event, denoted $\langle \tau|t \rangle$, is directly proportional to the time t already elapsed since the last event (Fig. 4). For short inter-seizure intervals, $\langle \tau|t \rangle$ is smaller than the average

(unconditional) waiting time $\langle \tau \rangle$ between two events (reflecting the phenomenon of clustering), and then increases until it becomes significantly larger than $\langle \tau \rangle$ as t increases (reflecting the phenomenon of intermittency, which is the other 'face' of clustering). This means that the longer the time since the last seizure, the longer it is expected to be until the next.

Discussion

The dynamics of seizures originating from discrete brain regions in these subjects (under post-operative conditions and on reduced doses of or off anti-seizure medications) may be partly described by laws, more specifically by power laws. The probability density function of seizure energy, a power law, differs from a Gaussian or normal probability density function in its skewness (to the right), reflecting the presence of very large ('extreme') events (corresponding in this study to clinical seizures) that occur with low probability (compared with subclinical seizures) that is nonetheless many orders of magnitude larger than would be predicted by the Gaussian probability density function fitted to these data. In other words, these 'extreme' events lie many standard deviations away from the 'mean', which would correspond to nearly zero probability of occurrence according to a Gaussian probability density function.

The finding that the probability density function of seizure energy (the product of peak intensity and duration) and inter-seizure intervals follow power laws indicates that the epileptic brain may behave non-linearly and/or be subject to stochastic multiplicative (parametric) noise. Non-linear, noisy systems have extreme events (clinical seizures in this case) that for practical purpose control their dynamics. Furthermore, systems with power-law probability density functions with an exponent < 2 (the seizure energy probability density function exponent is ~ 1.67) do not follow the central limit theorem, which means that unlike normal (Gaussian) distributions, the distributions of seizure energy and inter-seizure intervals are not determined by the mean and/or variance.

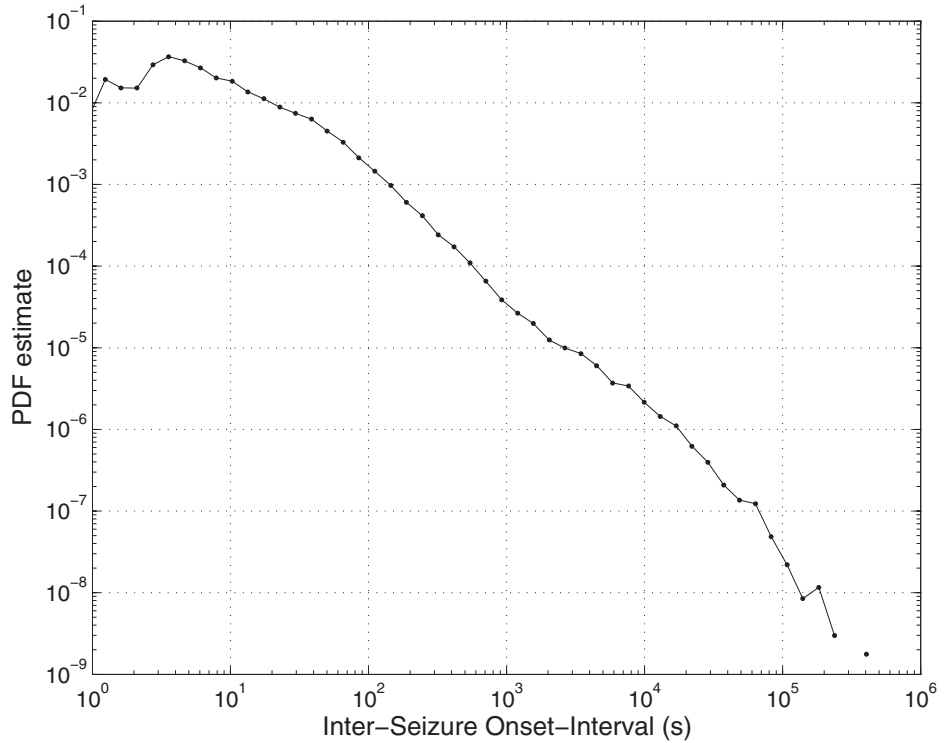


FIG. 3. The probability density of pooled (all subjects) inter-seizure intervals approximately follows a power law characterized by the exponent $\sim -1/2$ [as in Fig. 1, the exponent of the probability density is $-(1 + \beta)$]. x-axis: inter-seizure interval (logarithmic scale); y-axis: number of inter-seizure intervals (logarithmic scale) with length L .

Another important practical implication of the power-law distribution of inter-seizure intervals derives from the fact that its non-exponential (non-Poisson) probability density function contains information that improves the estimate of the probability of occurrence (prediction) of seizures in a given time interval. The rejection of the null hypotheses (that distributions of seizure energy/inter-seizure intervals are indistinguishable from temporally randomized data surrogates) strengthens this argument and provides indirect evidence

for the presence of correlations or dependencies between seizures and length of preceding and immediately following seizure-free intervals.

Power laws, which are ubiquitous in nature, have the property of ‘self-similarity’ or ‘scale-invariance’. This means that the shape of the distributions of physical quantities such as seizure energy and inter-seizure intervals are ‘scale-free’ or insensitive to changes (increases or decreases) in the scale at which they are observed. Consequently, there is no typical seizure energy or inter-seizure interval, only a ‘contin-

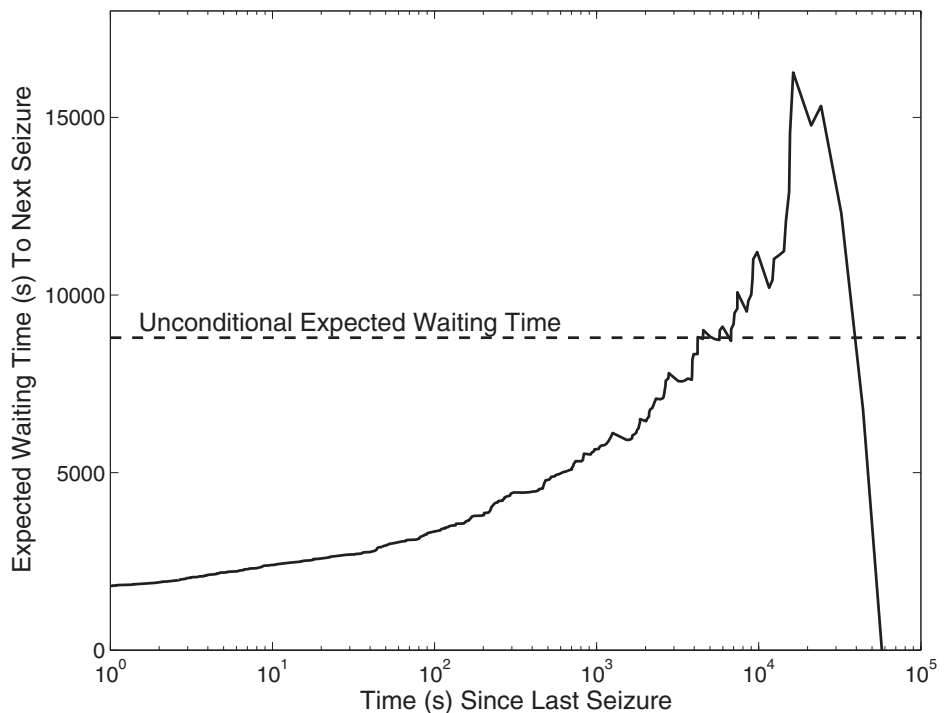


FIG. 4. The expected time to next seizure (y-axis) increases as a function of time elapsed since the last (previous) seizure (x-axis). That is, the longer since the last seizure the longer until the next seizure or vice versa.

uum' of energy ('sizes') and waiting times between events. The clinical implication of this scale invariance is that intensity or duration may not be fundamental to defining seizure properties. That is, and contrary to the universally sanctioned practice in basic and clinical epileptology, intensity and/or duration may not be dynamically relevant or sufficient criteria to classify certain abnormal neuronal activity as either ictal (seizure) or interictal epileptiform activity.

The structural and functional substrate to support the scale-free behavior observed in these seizure time series is in place: the brain is an assembly of coupled, mainly non-linear oscillators (neurons) with labile and unstable dynamics (Friston, 2000) and the length, density/clustering and patterns of neuronal interconnectivity have fractal or 'self-similar' properties that are repeated across a vast hierarchy of spatial scales (Sporns & Zwi, 2004; Breakspear & Stam, 2005; Sporns, 2006; Honey *et al.*, 2007)

That in certain subjects the probability density function of seizure energy had characteristic scales is indicative of the coexistence of more than one dynamic regime in the epileptic brain. The probability density function of event energies in systems composed of interacting relaxation threshold oscillators such as the brain is shaped in part by the strength of coupling among these oscillators (neurons in this case): increases in excitatory inter-neuronal coupling above a certain level cause the seizure power law regime to become coextensive with a characteristic scale regime. The size of spontaneous electrical discharges ('avalanches') of cultured neurons maintained under physiological condition also follows a power-law exponent ($-3/2$) which is different from that estimated for pharmaco-resistant seizure energy ($-2/3$). However, addition to the culture of the convulsant strychnine (which enhances excitatory coupling) destroyed the power law, rendering the event size probability density function bimodal or with characteristic sizes (Beggs & Plenz, 2003).

The increased probability of subclinical and clinical pharmaco-resistant seizures occurring in clusters (Fig. 2), an observation previously made for clinical seizures only (Taubøll *et al.*, 1991), and the decreased probability of seizure occurrence with increasing time from the last one (Fig. 4) may be interpreted as: (i) reflecting the inherent capacity of seizures to trigger seizures, thus supporting [at least over short time scales (minutes to tens of minutes)] Gowers' assertion that 'seizures beget seizures' (Gowers, 1901), and of others (Morrell & deToledo-Morrell, 1999; Hauser & Lee, 2002; Ben-Ari, 2006) whose claims are in line with those of Gower; (ii) indicative of some form of seizure interdependency or plasticity ('memory') in the system, as recently proposed (Sunderam *et al.*, 2007; and references therein); and (iii) a harbinger of predictability, but without specifying the probability or ease of success. That seizures may be predictable is in itself a valuable finding for which no factual support had been sought, as those working in this field presumed predictability 'a priori'. Although at this juncture neither seizure 'predictability' nor the tendency to cluster nor the alleged self-triggering capacity may be generalized to out-of-hospital, non-surgical conditions and to properly medicated subjects, these findings justify and foster not only renewed efforts in the field of prediction, but also different approaches from those applied to date. In particular, and at a minimum, the monitoring of observables should be expanded from the local (epileptogenic zone) to the global/systems scale and encompass both clinical and subclinical seizures, including their severity and the system's history (Osorio *et al.*, 2008).

The uncovering of 'laws' governing the temporal behavior of seizures and of their energy distribution may be illuminating. This work's research direction may provide much needed impetus for the development of new or the refinement of existing theories and tools for the eventual control or prevention of pharmaco-resistant seizures and the mitigation of its potentially devastating psycho-social impact.

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