Sleep Medicine Reviews xxx (2017) 1–9

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

TECHNICAL REVIEW

Nonlinear dynamical analysis of sleep electroencephalography using fractal and entropy approaches

Yan Ma [a, *], Wenbin Shi [b], Chung-Kang Peng [a], Albert C. Yang [a, c, d, **]

[a] Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[b] State Key Laboratory of Hydroscience and Engineering, Department of Hydraulic Engineering, Tsinghua University, Beijing, China
[c] Department of Psychiatry, Taipei Veterans General Hospital, Taipei City, Taiwan
[d] School of Medicine, National Yang-Ming University, Taipei City, Taiwan

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form
31 December 2016
Accepted 19 January 2017
Available online xxx

Keywords:
Electroencephalography
Brain activity
Nonlinear
Sleep medicine
Sleep stages
Fractal
Entropy
Complexity

SUMMARY

The analysis of electroencephalography (EEG) recordings has attracted increasing interest in recent decades and provides the pivotal scientific tool for researchers to quantitatively study brain activity during sleep, and has extended our knowledge of the fundamental mechanisms of sleep physiology. Conventional EEG analyses are mostly based on Fourier transform technique which assumes linearity and stationarity of the signal being analyzed. However, due to the complex and dynamical characteristics of EEG, nonlinear approaches are more appropriate for assessing the intrinsic dynamics of EEG and exploring the physiological mechanisms of brain activity during sleep. Therefore, this article introduces the most commonly used nonlinear methods based on the concepts of fractals and entropy, and we review the novel findings from their clinical applications. We propose that nonlinear measures may provide extensive insights into brain activities during sleep. Further studies are proposed to mitigate the limitations and to expand the applications of nonlinear EEG analysis for a more comprehensive understanding of sleep dynamics.

Background

Sleep, in contrast to wakefulness, is characterized by reduced awareness and responsiveness. A basic model of sleep homeostasis is based on the concept of sleep-wake transition [1]. Conventionally, sleep stages in humans are classified as wake, rapid eye movement (REM) sleep, and an approximate continuum of depth during non-REM (NREM) sleep based on electroencephalographic patterns, which comprises about 80% of the entire sleep [2]. This cycling model of wake/NREM/REM sleep switches has been the primary focus of sleep research for decades. However, this reductionist type of approach is over-simplified and has limitation in understanding pathophysiological mechanisms in sleep disorders.

Sleep is not simply a succession of human invented stages, but a delicate and sophisticated nonlinear symphony played by the brain in a democratic and mutual interaction with the rest of the body [2]. Real sleep stages are dynamic transitions between multiple physiological states swinging between the dual condition of stability and instability to warrant environmental adaptations and achieve physical and mental restoration [3].

Quantification of sleep stages via the analysis of electroencephalography (EEG) signal has been a challenge for years. Conventional visual sleep stage scoring is arbitrary and does not fully capture intrinsic EEG activity [4]. Fourier-based spectral analysis can quantify frequency compositions in EEG signals and is the most commonly used EEG analysis; however, it has intrinsic limitations to capturing underlying dynamics of the brain oscillations. First, fast Fourier transform (FFT)-based analysis assumes that complex oscillations embedded in the EEG signal are comprised of sine waves with different frequencies [5]. In this context, EEG signal can be decomposed into frequency components such as beta, alpha, theta, or delta frequency bands. However, it has long been known that brain oscillation is not a linear combination of these arbitrary frequency components, a property called “nonlinearity” [6]. Second, FFT-based spectral analysis assumes that none of these frequency components change in amplitude or shape as time evolves, which is clearly against what has been observed in complex brain oscillations, a property called “nonstationarity” [5].

* Corresponding author.
** Corresponding author. Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA.
E-mail addresses: dr.yan.ma@gmail.com (Y. Ma), cyang1@bidmc.harvard.edu (A.C. Yang).

http://dx.doi.org/10.1016/j.smrv.2017.01.003
1087-0792/

Abbreviations

ApEn	approximate entropy
AS	active sleep
CAP	cyclic alternating pattern
CD	correlation dimension
DFA	detrended fluctuation analysis
ECG	electrocardiography
EEG	electroencephalography
ESES	electrical status epilepticus during slow-wave sleep
FD	fractal dimension
FFT	fast Fourier transform
fMRI	functional magnetic resonance imaging
H	Hurst exponent
MSE	multiscale entropy
N1	nonrapid eye movement sleep stage 1
N2	nonrapid eye movement sleep stage 2
N3	nonrapid eye movement sleep stage 3
NREM	nonrapid eye movement
OSA	obstructive sleep apnea
PD	Parkinson disease
PSG	polysomnography
QS	quiet sleep
REM	rapid eye movement
SampEn	sample entropy
SWS	slow-wave sleep

It has long been observed that physiologic output of human body is nonstationary and nonlinear. Controls of physiological systems and outputs such as heartbeat, respiration, and brain wave oscillations are extraordinary complex [7]. Such complexity is believed to arise from nonlinear interactions among multiple control nodes in different physiological body systems that operate at multiple time scales. It has been hypothesized that the complexity of a biological system should be related to the system's capacity to adapt and function in an ever changing environment [7]. Conventionally, scientists employ a reductionist approach to disassemble the complex system into constituent pieces, examine each component, and, finally, reassemble them to recreate the original entity. However, this approach is often unrealistic. In most circumstances, we can observe only the macroscopic output of physiological functions, such as an EEG, heart rate, or respiration. In the language of complex systems, the composite behavior cannot be fully understood by “adding up” the components. Instead, one needs new approaches to measuring a system's integrative behavior. Thus, the understanding of the complex dynamics of the physiologic output, such as changes in EEG dynamics observed across different sleep stages, will be improved by applying nonlinear dynamical approaches to the analysis of EEG signal.

Nonlinear analysis of sleep EEG

The term *nonlinear* applies to systems in which components interact non-additively [8]. One example of the non-additivity is brain electrical activity that reflects combinations of excitatory and inhibitory postsynaptic potentials in apical dendrites of pyramidal neurons in the superficial layers of the cortex [9]. To understand the nonlinear feature of the EEG signal, in 1985, Rapp et al. pioneeringly performed a chaos analysis of spontaneous neural activity in monkeys [10], and Babloyantz et al. examined the correlation dimension (CD) of human sleep EEG [11]. At the early stages (1985–1990) and since 1990, nonlinear EEG analysis was mainly referred to low-dimensional chaotic dynamics and surrogate data testing, respectively [3]. In the late 1990s, phase synchronization and generalized synchronization became widely used. Recently, the concepts and methods originated from the chaos theory or complexity science has attracted considerable attention. Nonlinear approaches are suggested to be superior to traditional linear methods in understanding EEG dynamics [12]. In addition, the nonlinear approaches provide clearer insights into dynamical nature and variability of the brain signal and have shown their ability to surpass traditional spectral techniques, such as tracing epileptic changes in the EEG signal [13].

Quantification of the nonlinear features of sleep physiology is very important in two aspects: 1) for evaluating dynamical models of sleep homeostasis and 2) for clinically monitoring alteration/degradation of normal sleep physiology with aging and pathological conditions [8]. In the last two decades, novel approaches derived from concepts of nonlinear dynamics and statistical physics theories have been developed and applied to probe generic features of complex systems. These approaches revealed that the fluctuations in the outputs of these systems contain important information about the underlying mechanisms of system controls. For instance, robust fractal/scale-invariant, multifractal, and time irreversibility were observed in healthy physiologic systems (indicating complex physiological control) and the alterations of these nonlinear statistical properties are associated with aging and pathological states [8,14]. Moreover, certain generic features exist in a various number of physiological systems (e.g., similar scale-invariant correlations in heartbeat fluctuations, motor activity, gait, respiration, and brain wave oscillations), indicating a universal “rule” in the underlying mechanisms of nonlinear interactions in physiological systems. These universal features of different physiological systems provide an important guidance for building physiologically meaningful models of integrative physiological systems.

Nonlinear dynamics theory provides new opportunities for the understanding of sleep EEG behavior [15], and increasing amount of studies have used nonlinear methods to investigate the characteristics of brain activities during sleep. In this article, we therefore present the most commonly used nonlinear analyses of sleep EEG signal, such as fractal or entropy methods, and review their applications to sleep studies. This review intends to inspire future sleep studies to understand the complex nature of sleep physiology, particular the dynamical changes in brain activity during sleep.

Fractal-based methods

Mandelbrot [16] introduced the *fractal* theory, which can be expressed by two phenomenon: self-similarity and fractional dimensionality. Fractal theory has been used for explaining natural landscapes, modeling temporal dynamics of a time series, and predicting extreme events or human behavior [17]. Therefore, fractal analysis has potential to describing the dynamics of brain electrical activities under physiological and pathological conditions. To quantify fractal scaling behavior in a time series, several methods have been developed to quantify the fractal dimension, including the CD, Hurst exponent (*H*), and detrended fluctuation analysis (DFA).

Correlation dimension

The correlation dimension (CD, or D_2 in certain literature) [18] describes the fractional dimensionality of an underlying process in relation to its geometrical reconstruction in embedded phase

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space. The values of the CD range between zero and the value of embedding dimension and can be used to quantify the complex dynamics of the brain activity [19]. In a chaotic system, the CD usually shows a non-integer value larger than 1, indicating an increased complexity of system dimensionality.

In the analysis of sleep EEG recorded from healthy adults, the CD has been consistently reported to decrease from wake to sleep stages N1−N3 and increase during REM [11,15,20–24]. Furthermore, studies of neonatal EEG suggested that CD during active sleep tends to be higher than that during quiet sleep, whereas CD during indeterminate sleep is at the midpoint of the range between active and quiet sleep states [25]. This trend of changes in the values of the CD between different sleep stages may be associated with the sleep depth [15,20]. Studies have reported that the CD of the sleep EEG in N2 stages was significantly lower in the first half of the night than that in the second half of the night, indicating an association of sleep EEG complexity with the restoration effect of the sleep [26,27]. For healthy subjects under total sleep deprivation, EEG in sleep-deprived states yields lower CD values than that in normal states, suggesting that sleep deprivation results in the decrease of the brain signal complexity [28].

Compared to healthy subjects, CD was lower during stage 2 and REM sleep in unmedicated schizophrenic patients [29] while CD was found to be decreased during slow-wave sleep (SWS) in depression [30]. In contrast, CD derived from resting-state awake EEG of schizophrenic patients was not distinguishable from healthy volunteers while CD was found to be lower in schizophrenic patients under arithmetic test [31]. These alterations in the nonlinear dynamical properties of EEG in sleep/wake and task conditions indicate that brain's ability to process information may be disturbed in depression and schizophrenia [29,30]. In the studies of neurological disorders, CD in SWS was lower in narcoleptic patients than that in healthy subjects, indicating a lower degree of complexity in the sleep-wake regulation among narcoleptic patients [32].

Hurst exponent

The Hurst analysis is an important method derived from chaos theory to quantify the long-term memory processes of a time series [33]. The biological time series often exhibits long-range dependence which refers to dependence structures that decay slowly with increasing distance, such as a power-law decay [34]. The value of the Hurst exponent (H) ranges between 0 and 1. Based on H, a time series can be classified into three categories: a) $H = 0.5$, indicating the presence of uncorrelated randomness; b) $0 < H < 0.5$, indicating an anticorrelated process; and c) $0.5 < H < 1$, indicating a long-range correlation process with characteristics of 1/f power spectrum.

Although H has been applied in many studies to distinguish brain signal dynamics from different states or pathological conditions [35], it was less frequently used in sleep EEG studies compared with other nonlinear approaches. Results reported from existing studies are inconsistent. In Acharya's et al. study, H values were higher in wake and REM sleep, but lowest in stage 3 and 4 [15]. While in Weiss's et al. studies, H was higher in NREM stage 4 than stage 2 and REM period [36,37], suggesting that sleep EEG signals may be less fractal during SWS [36]. However, the discrepancy in studies using Hurst exponent indicates a need for a comprehensive comparison of different approaches and careful evaluation of the fractal property.

Detrended fluctuation analysis

DFA, originally introduced by Peng et al. [38], is a widely used method for quantifying the long-range correlation of the physiological time series, such as heart beat time series, respiratory signals, and EEG recordings [39–41]. The scaling exponent (α) derived from the DFA method represents the long-range correlation properties of the signal: $\alpha = 0.5$ indicates the presence of uncorrelated randomness; $\alpha < 0.5$ suggests the presence of anti-correlated process; $0.5 < \alpha < 1$ represents the existence of long-range correlations in the time series and $\alpha = 1$ resembles 1/f noise. When $\alpha > 1$ and approaches to 1.5, a Brownian noise is indicated, which is the integration of the white noise.

In healthy subjects, the values of DFA scaling exponent increase beyond 1 with increased depth of sleep stages [39,42], suggesting that the dynamics of the sleep EEG is more like a Brownian noise process in deeper sleep stages [39]. Studies of obstructive sleep apnea (OSA) [39,43] have reported that patients with OSA exhibited a similar trend of the DFA exponent in different stages of NREM sleep, but their DFA exponent values were lower than those from healthy subjects [39].

In depression-related sleep disturbance, a study reported that the DFA scaling exponents were lower in patients with major depression during stage 2 and SWS; the authors suggested that these findings might be related to the sleep fragmentation and instability observed in major depressive disorders. Another study found that DFA exponents of sleep EEG in depressed patients were higher than those from healthy controls [37]. This study also identified a significant correlation between the severity of depression and DFA exponent [40], suggesting that the sleep EEG under the depressive state exhibits a slower decay of long-range temporal correlations which is associated with the severity of depression [40].

Implications of fractal-based methods

Based on aforementioned literature (Table 1), both the values of the CD and DFA exponent change in accordance with the advancement of NREM sleep stages (Fig. 1a). Consistent across three different fractal-based methods, sleep EEG in awake status is more compatible with 1/f noise, an important characteristic of nonlinear dynamics, and EEG signals in NREM stages become more ordered with reduced fractal dimensional complexity. There has been increasing evidence that the activity of brain circuit becomes more coherent and ordered as sleep stage goes deeper [44,45], which may contribute to the reduced complexity found in EEG signals during NREM sleep. Collectively, this evidence suggests that fractal-based EEG markers may be of use to track sleep stages, and the degree of changes in fractal-based EEG markers between awake and NREM stages may be of help to distinguish between healthy sleep and pathologic sleep conditions, such as insomnia. In addition, fractal-based EEG markers show a significant difference between wake and REM period [46], despite these two conditions involve intense brain activities, the importance of this finding remains elusive but worth further studies.

Future studies with incorporation of latest neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), may also help address several unsolved questions, including: which brain circuit or network (i.e., measured by brain connectivity) is associated with loss of fractal complexity of the sleep EEG in NREM stage? Is loss of sleep EEG fractal complexity associated with memory or cognitive functions? Is brain circuit involved in REM sleep different with those in awake period? Importantly, findings in these fractal-based literature may be useful in developing and testing mathematical models of sleep wake regulations [39].

Entropy-based methods

In information theory, entropy measures the uncertainty about the information source and the probability distribution of the samples drawn from it, thus the estimates of entropy can be an indicator of a system's complexity. Complexity analysis of the

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Table 1
Applications of fractal-based methods*.

Citations	Study subjects	Main finding(s)
Correlation Dimension		
Roschke, *et al.* 1992 [21]	12 healthy males, 20-31 y; sleep under lorazepam versus placebo	SWS depicts a much smaller dimensionality than light or REM sleep; lorazepam does not alter the EEG's dimensionality except in stage 2 and REM sleep.
Roschke, *et al.* 1994 [30]	9 depressive and 11 schizophrenic inpatients compared to healthy controls	Altered nonlinear brain dynamics mainly during slow wave sleep in depression and during REM sleep in schizophrenia.
Achermann, *et al.* 1994 [24]	11 healthy males, 23-32 y	CD was high in REM sleep, declined progressively within each NREM sleep episode, and reached a low level at times when SWS was dominant.
Fell, *et al.* 1996 [22]	12 healthy males, 23-36 y	Nonlinear measures yield additional information, which improves the ability to discriminate sleep stages and which may in general improve the ability to distinguish different psychophysiological states.
Pereda, *et al.* 1998 [20]	9 healthy males and females, mean age 27.3 y	EEG exhibits random fractal structure with $1/f^{-\beta}$ ($1 < \beta < 3$) and a negative linear correlation between CD and fractal exponent (β) in all states except during SWS.
Ferri, *et al.* 1999 [32]	9 narcoleptic patients, male and female, 20–55 y	CD was higher in normal controls than in narcoleptic patients.
Kobayashi, *et al.* 2000 [27]	1 healthy male, 22 y	CD decreased from wake to sleep stage 1 to 3, and increased for REM sleep.
Kobayashi, *et al.* 2000 [26]	10 healthy males, mean age 23.6 y	CD significantly decreased from wake to sleep stage 1, 2, 3 and increased during REM sleep. The mean CD of the sleep EEG in the second half of the night was significantly higher than those in the first half of the night.
Jeong, *et al.* 2001 [28]	20 healthy male volunteers, 23.4±1.9 y. A 24-hour schedule of sleep deprivation began on morning awakening following a normal sleep night.	The sleep-deprived states had lower CD values at three channels (P4, O2, and C3) than normal states.
Kobayashi, *et al.* 2001 [90]	9 male subjects, 21–24 y, in good health and with no history of alcoholism. PSG was recorded on baseline night (no ethanol) and on study night when ethanol (0.8 g/kg) was given 15 minutes prior to sleep study.	The mean CD of EEG during sleep stage 2 and those for the second sleep cycle on the ethanol night were significantly higher than those on the baseline night (no ethanol). The changes in CD between sleep cycles were reduced on ethanol night as compared to baseline night.
Ferri, *et al.* 2001 [89]	5 children with ESES, males and female, 6.5-10 y	In NREM sleep, the possible presence of low-dimensional chaos could be suspected. EEG without ESES could not be distinguished from linearly filtered noise.
Acharya, *et al.* 2005 [15]	8 healthy Caucasian, males and females, 21-35 y	CD decreases from wake to sleep stages 1-4 and then increases during REM sleep.
Scher, *et al.* 2005 [91]	116 EEG recordings in 55 neonatal subjects (28-43 wk gestational age)	For full-term infants, CD between AS and QS was significantly different. A positive correlation between CD and increasing conceptional age was noted.
Janjarasjitt, *et al.* 2008 [25]	50 healthy neonates (22 male) with postmenstrual age of 28-42 wk.	CD during AS is higher than during QS, and CD during indeterminate sleep is virtually at the midpoint between them. The birth status (preterm or full-term) of the neonate has an influence on CD.
Bell, *et al.* 2012 [88]	54 subjects with histories of coffee-induced insomnia, male and female, mean age 20 y	Both *Coffea cruda* 30c and *Nux vomic* 30c increased CD in SWS in the post-remedy night.
Hurst Exponent		
Acharya, *et al.* 2005 [15]	8 healthy Caucasian, males and females, 21-35 y	*H* values were higher in wake and REM sleep, indicating higher self-similarity, but were lowest in stage 3 and 4.
Weiss, *et al.* 2009 [36]	10 healthy subjects, male and female, 17–53 y	Higher *H* values during stage 4 compared to stage 2 and REM sleep in all electrodes.
Weiss, *et al.* 2011 [37]	22 healthy subjects	Highest *H* values emerged frontally during all sleep stages, while the minimum was found during REM in the central zone.
Detrended Fluctuation Analysis		
Lee, *et al.* 2002 [43]	17 PSG data in MIT/BIH database	The mean scaling exponents of EEG is discriminated according to NREM, REM and wake, and gradually increased from stage 1 to stage 2, 3 and 4.
Lee, *et al.* 2004 [39]	The sleep EEGs of six healthy males (30–35 y) and six sleep apnea EEGs (slp02a, slp14, slp16, slp37, slp61, and slp66; aged 32–39 years; all of them were males) from MIT/BIH PSG database.	The mean scaling exponents increased from wake to sleep stage 1, 2, 3 and 4, but decreased during REM sleep. The scaling exponents of the apnea were lower than those of the healthy subjects for all the stages.
Ferri, *et al.* 2005 [95]	5 healthy subjects, male and female, 20–32 y	Higher levels of interregional synchronization during CAP sleep than during non-CAP with a small but significant difference between its A and B phases. Only the first DFA exponent showed different values during the different sleep stages.

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Table 1 (*continued*)

Citations	Study subjects	Main finding(s)
Lee, *et al.* 2007 [40]	11 unmedicated unipolar depressed patients and 11 non-depressed, age-matched controls.	All the scaling exponents in depressed patients and healthy controls were between 0.5 and 1.0. The scaling exponents of depressed patients have relatively higher values in whole brain regions compared to healthy controls, with significant differences at F3, C3, T3, T4 and O1 channels. A significant linear correlation was observed between the severity of depression and the scaling exponent over most of the channels, except O2.
Leistedt, *et al.* 2007 [41]	10 unmedicated inpatients with acute major depression, and 14 normal controls	The median values of alpha were lower in patients during sleep stage 2 and SWS.
Leistedt, *et al.* 2007 [94]	10 untreated depressed men in full to partial remission (42.43+/-5.62 y) and 14 healthy subjects (42.8+/-8.55 y)	Significant difference and deviation of the scaling exponents between the two groups were not observed during targeted three sleep stages (stage 2, SWS and REM).
Dumont, *et al.* 2007 [93]	24 patients with sleep apnea-hypopnea syndrome (12 moderate-to-severe and 12 severe subjects respectively), and 12 normal controls; mean age 44 y	For all sleep bands, the fluctuations of the synchronization between sleep EEG and heart activity appear scale free and the scaling exponent is close to one as for 1/f noise. We could not detect any effect due to sleep apnea-hypopnea syndrome.
D'Rozario, *et al.* 2013 [92]	8 untreated OSA patients and 13 non-OSA controls	DFA scaling exponent and power spectra biomarkers significantly correlated with simultaneously tested performance and self-rated sleepiness across the testing period in OSA patients and controls. Baseline DFA scaling exponent were markers of impaired simulated driving after 24-h extended wakefulness in OSA. OSA patients had a higher scaling exponent and delta power during wakefulness than controls.

* Only methods introduced in the review are listed in the table. Some studies included more than one method.
Abbreviations: AS, active sleep; BIH, Beth Israel Hospital; CAP, cyclic alternating pattern; CD, correlation dimension; DFA, detrended fluctuation analysis; EEG, electroencephalography; ESES, electrical status epilepticus in sleep; *H*, Hurst exponent; MIT, Massachusetts institute of technology; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PSG, polysomnography; QS, quiet sleep; REM, rapid eye movement; SWS, slow wave sleep.

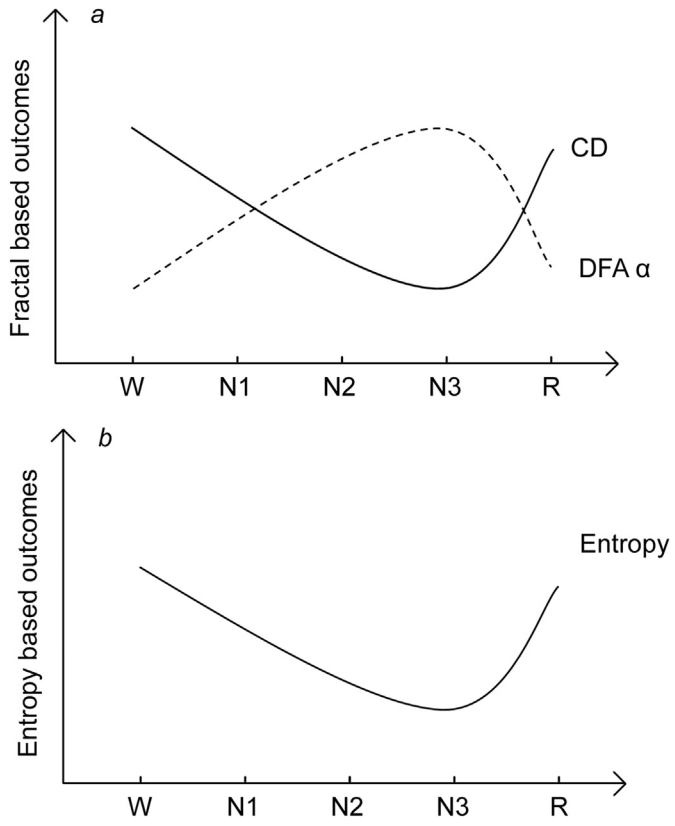

Fig. 1. Reported trends of fractal- and entropy-based outcomes for different sleep stages.

physiological time series has revealed the fundamental mechanisms of the human physiologic system [47]. Aging and illness have been shown to exhibit a progressive loss of physiologic complexity [8,14], reflecting the reduced adaptability of physiologic system to intrinsic or extrinsic stimuli. Several entropy analyses have been introduced in sleep literature, including Shannon entropy [48], permutation entropy [49], spectrum entropy [50], approximate entropy (ApEn) [51], sample entropy (SampEn) [52], and multiscale entropy (MSE) [53,54]. Three of commonly used analyses (ApEn, SampEn, and MSE) are detailed below. In contrast with fractal-based measures, these entropic-based analyses tend to measure similar physical properties (e.g., irregularity), thus we outline their applications to sleep EEG signals in a single section "Applications of entropy-based methods".

Approximate entropy

ApEn was introduced to assess the irregularity of the time sequence data [51]. Two input parameters, a pattern length *m* and tolerance factor *r*, are specified to compute ApEn. Increased value of ApEn indicates increased irregularity of the time series data and has been used extensively to characterize the degree of randomness in studies of physiologic time series [55,56].

Sample entropy

SampEn was developed to solve the shortcomings of ApEn, in which the precise estimate of ApEn requires substantial lengths of the data and lack of relative consistency (e.g., if the ApEn of one data set is higher than that of another, then it should, but often does not, remain higher under all parameters tested) [52]. Similar to ApEn, a higher value of SampEn indicates increased irregularity in the time series. SampEn has been found to be more consistent and less vulnerable to the constraint of time series length than the ApEn algorithm [57].

Multiscale entropy

MSE analysis was introduced based on SampEn to quantify the entropy over different time scales [53,54]. The motivation of MSE is

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that increased entropy is not *always* associated with increased dynamical complexity. For example, an uncorrelated randomness (such as irregular heart rate seen in atrial fibrillation) has high entropy but did not convey physiologically meaningful complexity [8]. MSE method measures the entropy of a time series over different time scales, enabling a dimensional view of complexity that differentiates true complex dynamics from regularity and uncorrelated randomness. For example, a regular time series would exhibit low entropy in all time scales, whereas a random time series could show a high entropy in short time scale and the entropy decades as scale factor increases [53].

Applications of entropy-based methods

For healthy adults, the entropy of sleep EEG signals gradually decreases from wake to sleep stages N1, N2, to N3 (or stage 3 + 4), and increases during REM [50,58–62] (Fig. 1b). The results are consistent regardless of the different entropic methods used in the literature. Nonetheless, inconsistency was found in the comparison between the entropy of REM and other sleep stages. Some studies found entropy of REM EEG was between that of wake and N1 [50,59], whereas others reported to be between N1 and N2 [50,58,61,62]. The similar trend of entropy change is also present in children (wake > REM sleep > NREM sleep) [60] and in newborns (active sleep > quiet sleep) [63].

The entropy of sleep EEG signals may be of help to assess the trajectory of brain maturation in newborns. For example, a study in newborns (age 25–60 wk) reported that entropy of EEG increased during both active sleep and quiet sleep before approximately 42 wk in age but ceased to increase in quiet sleep and even decreased in active sleep after newborns reached term age [63].

In pathological conditions such as Parkinson's disease (PD), sleep stage-specific increased MSE was observed during NREM sleep in PD patients, compared with non-PD controls, and the difference was significant at high time-scale factors, which might reflect a compensatory mechanism for early defects in neuronal network control machinery in PD [64].

Implications of entropy-based methods

In general, findings from the sleep EEG studies using entropy-based methods are relatively consistent (Table 2), compared to those using fractal-based analyses. Although entropy and fractal-based methods have very different physical definitions, the ubiquitous principle among different complexity analyses is to quantify how the variability (or temporal dynamics) of the time series changes with different time scales [65], and the properties of regularity and randomness captured by these methods is interchangeable. Using methods of nonlinear dynamics, sleep EEG signals become less complex (i.e., toward regularity) as sleep stage advances, suggesting that brain activity during sleep becomes more coherent and periodic compared to the wake or REM period.

One limitation of the most existing studies is that complexity was not measured at multiple time scales. The EEG signal apparently contains multiple frequency components; each operates at distinct time scales [66]. Thus, investigation of complexity changes across different time scales in EEG signals may be of help to identify specific mode of brain activity that is related to sleep-wake regulation.

Discussion

Our review of recent studies deduced that the findings of nonlinear approaches are somehow related and consistent regardless of the particular methods. From a fractal perspective, a fractal component decreases from wake to sleep stages N1–N3 and increases during REM sleep, and DFA scaling exponents increase from wake to stages N1–N3 and decrease during REM sleep. From the entropy perspective, the complexity of sleep EEG decreases from wake to sleep stages N1–N3 and increases during REM.

Efficient sleep is supposed to be restful and restorative [2]. Nonlinear features exhibit a pattern of gradual change through sleep stages, which is consistent with NREM sleep stages approximately paralleling a depth-of-sleep continuum, with arousal thresholds generally lowest in N1 and highest in N3.

Sleep and wakefulness are influenced by different neurotransmitter signals in the brain. Neurons in the brainstem produce neurotransmitters such as serotonin and norepinephrine that keep some parts of the brain active while we are awake. Other neurons, which begin signaling when we fall asleep, appear to "switch off" the signals that keep us awake [67]. Neural models of information processing have suggested that both the degree of synchrony and time scale determine the maximum information transfer between neurons [68]. Overall, the cortex may become more inactive as a person proceeds through one stage to the next deeper stage until N3 [44]. As sleep is getting deeper, the reason why entropy, CD, and *H* decrease, could be that fewer neurons are available for processing information, or that the neurons are better synchronized to generate brain waves with less complexity [45]. In REM sleep, the brain becomes highly active again and can nearly attain the level of someone who is awake. In addition, cerebral blood flow and metabolism decreases in deep sleep, and remains about the same during REM sleep as in wakefulness, which reflects that cerebral synaptic activity levels are lower in deep sleep but higher in REM as in wake [69]. The cortex becomes more active and it is possible that additional neurons are available or neurons are desynchronized for processing information [70]; consequently, entropy, the CD, and *H* increase.

Both conventional spectral analyses and nonlinear measures have certain advantages. For example, nonlinear measures more effectively discriminated between N1 and N2, whereas the spectral measures were superior in separating N2 and SWS [22]. We believe that the dynamic complexity of sleep EEG is influenced by both linear and nonlinear features and can be effectively interpreted using comprehensive approaches including nonlinear measures of brain activity; furthermore, studies have proven that using nonlinear measures can yield valuable information compared to conventional linear measures such as Fourier transforms [71,72].

In recent years, progresses have been made in advancing nonlinear methods. Examples of latest developments include 1) substituting a fuzzy membership function for the Heaviside function in SampEn to improve the consistency [73], 2) using symbolic series instead of the continuous variables to improve the robustness to outliers [74], and 3) measuring the distribution of inter-vector distances in order to mitigate the dependence on input parameters [75]. Other than the above reviewed fractal and entropy based methods, another widely-used methods, such as recurrence quantification analysis [76], are also capable of measuring complexity for non-stationary data including sleep EEG [77]. Of note, this review focuses mainly on the analysis of brain signal in temporal dimension using fractal or entropy methods. In recent years, there has been an increasing interest in applying graph theory to study the complexity of brain networks in spatial dimension [78–80] using various correlative methods to assess inter-dependency of brain signal among different brain regions [72,81–86].

Nonlinear analysis of EEG signal can serve in the understanding or as consistent descriptors of sleep dynamics and potentially assist in automatic sleep classification. All existing findings encourage using nonlinear approaches as additional aids to visual or automated sleep staging. Furthermore, they may help in assessing pathologic conditions [87].

Please cite this article in press as: Ma Y, et al., Nonlinear dynamical analysis of sleep electroencephalography using fractal and entropy approaches, Sleep Medicine Reviews (2017), http://dx.doi.org/10.1016/j.smrv.2017.01.003

Table 2
Applications of entropy-based methods*.

Citations	Study subjects	Main finding(s)
Approximate Entropy		
Acharya, *et al.* 2005 [15]	8 healthy Caucasian, males and females, 21-35 y	In sleep stage 4, the ApEn was the lowest due to the very low variation in the EEG signal. In REM sleep, the variation is slightly more and as a result the ApEn increases.
He, *et al.* 2005 [50]	8 healthy subjects, 21-35 y	ApEn declined from wake to each NREM sleep episode progressively, and reached a low level at times when SWS was dominant. ApEn in REM sleep is higher than in than SWS.
Burioka, *et al.* 2005 [59]	8 healthy males, 23-26 y	ApEn of EEG was significantly lower during sleep stage 4 and higher during wake and REM sleep.
Lee, *et al.* 2013 [60]	6 adults, 19-25 y; 6 children, 11-13 y.	ApEn trends for both age groups: wake > REM sleep > NREM sleep. Adults had significantly larger ApEn values than children during wakefulness.
Sample Entropy		
Zhang, *et al.* 2009 [63]	168 newborns with postmenstrual age ranging from 25 to 60 wk	SampEn of EEG during AS is higher than that during QS. SampEn increases during both AS and QS before about 42 wk in PMA while it ceases its increase in QS and even decreases in AS after newborns reaching term age. A distinct decrease in the interquartile range of SampEn is found with increasing PMA (25-50 wk), followed by maintenance of low fluctuation in SampEn curves.
Chouvarda, *et al.* 2010 [62]	10 healthy subjects, male and female, 25-45 y	SampEn values are related to both the sleep stages and the subtype of CAP. Complexity features can serve as consistent descriptors of sleep dynamics and can potentially assist in the classification of sleep stages
Chouvarda, *et al.* 2011 [58]	10 healthy subjects, male and female, 25-45 y	SampEn declined from wake to each NREM sleep episode. SampEn in REM sleep is higher than in SWS. For CAP sleep, A3 presented a quite similar complexity independently of the sleep stage, while A1 and A2 showed higher complexity in light sleep than during deep sleep.
Chouvarda, *et al.* 2012 [97]	11 healthy subjects, male and female, 25-45 y	Based on the nonlinear properties of the EEG at transition points of the sequences that build the CAPs, EEG signal present significant differences between activations and non-activations in the SampEn.
Chouvarda, *et al.* 2012 [98]	11 healthy subjects, mean age 32.7 y, and 10 subjects diagnosed with primary insomnia, mean age 32.5 y, male and female	As regards the deep sleep building phases defined by CAP, more irregular activation-deactivation patterns, with larger deactivation time, i.e., distance between consecutive activation events, and appearing with higher EEG complexity in deactivation. A longer duration of desynchronization phases, with increased EEG complexity and more irregular patterns.
Mendez, *et al.* 2015 [96]	10 healthy adult subjects (5 males), 25-45 y, mean age 32.7 y	When define an onset window containing the first two seconds of the A-phase of CAP, SampEn showed statistical differences between the two consecutive no overlapped windows with duration of 2 seconds before the onset window, as well as between two windows after the onset window. On the other hand, the SampEn measure shows a different behavior during the onset.
Multiscale Entropy		
Bell, *et al.* 2012 [88]	54 college students with histories of coffee-induced insomnia, male and female, mean age 20 y	MSE results indicate significant, remedy-specific directional effects, especially later in the night (*Coffea cruda*: remedy night increases and post-remedy night decreases in MSE at multiple sites for both stage 3 and 4 in both REM cycles; *Nux vomica*: remedy night decreases and post-remedy night increases).
Chung, *et al.* 2013 [64]	9 patients with PD, (mean age 78.2 y) and 11 non-PD controls (mean age 61.2 y); male and female	Sleep stage-specific increased MSE was observed in patients with PD during NREM sleep. The difference was more marked and significant at higher time scale factors.
Shi, et al. 2016 [66]	4 healthy male subjects (27-38 yrs with mean age 32.0 ±4.6yrs)	Entropy is higher during wakefulness and increasing time scales at small scales (<0.04 s). In contrast, entropy is higher during deep sleep and lower with increasing time scales at large scales (0.25–2 s).

* Only methods introduced in the review are listed in the table. Some studies included more than one method.
Abbreviations: ApEn, approximate entropy; AS, active sleep; CAP, cyclic alternating pattern; EEG, electroencephalography; MSE, multiscale entropy; NREM, non-rapid eye movement; PD, Parkinson's disease; PMA, postmenstrual age; QS, quiet sleep; REM, rapid eye movement; SampEn, sample entropy; SWS, slow wave sleep.

Nonlinear approaches are promising and worth further investigation; however, some limitations must be mentioned. First, high-quality studies with well-designed experimental conditions and large samples are scant. Nearly all existing studies are based on the conventional definition of sleep stages. Therefore, the full advantages of nonlinear approaches have yet to be determined. Regarding the clinical use, it seems difficult to define the norm for sleep EEG by using nonlinear methods, because these methods themselves involve signal pre-processing and multiple parameters to be defined within the algorithm. In addition, the neurophysiologic mechanisms behind the complex oscillations of brain signals remain poorly understood. We suggest to evaluate a wide range of nonlinear measures in the large-scale sleep database, and to develop practical applications of nonlinear approaches to understanding the sleep EEG dynamics in healthy and pathological conditions.

Conclusion

EEG is critical for extending the knowledge of sleep and revealing its fundamental mechanisms. Studies have shown that nonlinear analyses of sleep EEG signal can distinguish sleep stages as well as normal and pathological conditions. Both nonlinear and linear measures have certain advantages and disadvantages that

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are complementary to each other. Because of the nonlinear and nonstationary properties of brain activity, nonlinear approaches to sleep EEG are more appropriate for researching the physiologic and pathologic features of the brain activity during sleep. Nonlinear approaches using fractal or entropy methods may facilitate automatic sleep classification, but more importantly, additional studies are encouraged to mitigate the limitations toward expanding the application of nonlinear approaches to comprehensively understand sleep dynamics.

Practice points

1) Sleep is not simply a succession of human invented stages, but a delicate and sophisticated nonlinear symphony played by the brain in a mutual interaction with the rest of the body.
2) Nonlinear approaches are potentially promising because electrobiophysiological signals like EEG are typically nonlinear and non-stationary.
3) Nonlinear analyses of sleep EEG signals are able to differentiate sleep states and distinguish pathological sleep conditions form healthy states.
4) There are limitations in existing literature. Full advantages of nonlinear approaches have yet to be determined. Future studies are encouraged to investigate sleep neurophysiology by nonlinear approaches.

Research agenda

This review has addressed a number of important approaches and findings in nonlinear analyses for sleep EEG, and proposed some research questions warranting consideration in future studies for better understanding of sleep:

1) Can nonlinear methods help to delineate critical and hidden dynamical properties of sleep?
2) What are the biological mechanisms of changes in nonlinear indices during sleep?
3) Can nonlinear approaches assist in automatic sleep scoring and classification?
4) Can nonlinear approaches help to differentiate normal and pathologic conditions during sleep?

Conflicts of interest

The authors report no conflict of interest in this review.

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* The most important references are denoted by an asterisk.

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