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Review

Chaos in the brain: a short review alluding to epilepsy, depression, exercise and lateralization

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Abstract

Electroencephalograms (EEGs) reflect the electrical activity of the brain. Even when they are analyzed from healthy individuals, they manifest chaos in the nervous system. EEGs are likely to be produced by a nonlinear system, since a nonlinear system with at least 3 degrees of freedom (or state variables) may exhibit chaotic behavior. Furthermore, such systems can have multiple stable states governed by "chaotic" ("strange") attractors. A key feature of chaotic systems is the presence of an infinite number of unstable periodic fixed points, which are found in spontaneously active neuronal networks (e.g., epilepsy).

The brain has chemicals called neurotransmitters that convey the information through the 10^{16} synapses residing there. However, each of these neurotransmitters acts through various receptors and their numerous subtypes, thereby exhibiting complex interactions.

Albeit in epilepsy the role of chaos and EEG findings are well proven, in another condition, i.e., depression, the role of chaos is slowly gaining ground. The multifarious roles of exercise, neurotransmitters and (cerebral) hemispheric lateralization, in the case of depression, are also being established. The common point of reference could be nonlinear dynamics.

The purpose of this review is to study those nonlinear/chaotic interactions and point towards new theoretical models incorporating the oscillation caused by the same neurotransmitter acting on its different receptor subtypes. This may lead to a better understanding of brain neurodynamics in health and disease.

Keywords: Chaos (nonlinear dynamics); Brain; Epilepsy; Depression; Neurotransmitters; Exercise; (Cerebral) hemispheric lateralization

1. Introduction

Electroencephalograms (EEGs) reflect the electrical activity of the brain. Even when they are analyzed from healthy individuals, they manifest chaos in the nervous system [1,2]. A comprehensive review of quantified EEG or qEEG is available in Gevins [3].

EEGs are likely to be produced by a nonlinear system. The basis for this conjecture is that a nonlinear system with at least 3 degrees of freedom (or state variables) may exhibit chaotic behavior. As an example of chaotic activity, the waxing and waning of α-EEG activity in alert subjects may be considered. Albeit α-EEG activity closely resembles a sine wave, it is (i) certainly not periodic (i.e., does not repeat itself after a period T), (ii) is bounded (i.e. amplitudes are generally confined up to 100 μV) and (iii) is too regular to qualify as a noise. Therefore, it is more likely to be chaotic.

A key feature of chaotic systems is an infinite number of unstable periodic fixed points. Similar points are present in spontaneously active neuronal networks in epilepsy [4]. Oscillations in hippocampal theta rhythm are also characteristic of chaos [5–7]. Similarly typical EEGs are also found in the thalamus [8–10]. Skarda and Freeman [11] have demonstrated that chaos can be generated in a model of the olfactory system. The model incorporates a feedback loop among the "neurons" and a delay in responsive times. Similar observations were also made by Kay et al. [12] who postulated that preafferent input from the limbic system can serve to bias the landscape in such a way as to facilitate the capture of the system by a basin of an attractor corresponding to the goal of the intended observation.

When bathed in artificial cerebrospinal fluid containing excess potassium (K^+), the brain exhibits spon-

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taneous bursts of synchronized neuronal activity, which can trigger seizure-like discharges in the neighboring region. However, controlling these bursts to make them more periodic may actually increase the seizure activity. Alternately, by "anticontrol" of chaos, the system can be kept away from low period orbits [13–15].

Chaotic dynamics offer many functional advantages. These dynamics operate under a wide range of conditions and are therefore adaptable and flexible (i.e., plastic). This plasticity allows systems to cope with the exigencies of an unpredictable and changing environment. The stochastic chaotic activity has certain benefits, like, (i) continuous aperiodic activity needed by neurons to stay fit, (ii) exhibit rapid state transition without "ringing" attending departures from limit cycle attractors, (iii) contains broad spectrum carrier waves, (iv) minimizes tendencies to parasitic phase locking and (v) is a source of unstructured activity for driving Hebbian synapses during learning, so as to create new basins of attraction instead of reinforcing existing attractors in complex landscapes [16–18].

The nervous system may show loss of variability and the appearance of pathological periodicities in many disorders like epilepsy, Parkinsonism (pill-rolling tremor) and manic depressive psychosis [19]. Thus the study of nonlinear dynamics is useful in understanding their pathophysiology and thereby modifying the treatment.

In the three subsequent sections we discuss (i) the present use of EEG, (ii) the present methods of quantifying EEG and (iii) the future prospects.

1.1. Present use of EEG

The domain of EEG, with all of its related fields, covers clinical medicine, psychophysiology, neurophysiology, general electrophysiology and certain areas of basic EEG research. Now there seems to be a gap between the "classical EEG" and the "sophisticated, modern, 21st century oriented EEG". But classical EEG has not become obsolete as long as this clinical method is carried out with proper technique, a good training background and some ingenuity. Evoked potentials (EP), event-related EEG changes are now seen in a broad view that practically integrates EEG and EP approaches. In the highest degrees of sophistication, these methods are now playing a major role in neurocognitive research — though in hot competition with fMRI (functional magnetic resonance imaging) and PET (positron emission tomography) scanning. It is now fair to state that the psychophysiologic orientation of Hans Berger (founder of human EEG) has successfully been revived and promises a better comprehension of neurocognitive functions [20]. However, a detailed description of the various applications of EEG is beyond the scope of this review.

1.2. Present methods of quantifying EEG

There are two contradictory conjectures for the generation of EEG signals. The most well known conjecture has been that the EEG is a very complex-looking, virtually unpredictable signal; therefore, it must be produced by a very complex system [2]. The statistical pattern recognition [21] for complex system analysis has been based on extraction of quantitative features from EEG intervals. These features are supposed to be representative of the test segment and usually include parameters related to the frequency content of the signal. The second conjecture is that the EEG is a very complex-looking, virtually unpredictable signal; therefore, it must be produced by a relatively simple, nonlinear system [2]. The second conjecture will be dealt with in Section 2.

Nearly 200 years ago Joseph Fourier (contemporary of Galvani, Volta, Euler and Bernoullis) defined the Fourier Series as an expansion of a periodic function into sinusoid (i.e., sine and cosine waves) functions according to a rule. The Fourier series is a special case of Fourier Transform. The EEG signal can be considered as a function as it is composed of numerous waveforms. By this method, the original signal (amplitude as a function of time) is converted to an amplitude spectrum — a graph of amplitude as a function of frequency. Usually the amplitude values are squared to give rise to "Power (Density) Spectra" [22,23]. It may be a continuous spectrum in which the graph is a continuous line over a range of frequencies or a discrete spectrum (sometimes known as a line spectrum) in which only specific frequencies are present and their amplitudes are represented by vertical lines at those points on the frequency axis. This is the DFT (discrete Fourier transform) of the signal.

Cooley and Tukey [24] presented an algorithm for the computation of DFT applicable when **N** is a composite number (product of two or more integers) and called it FFT (fast Fourier transform) algorithm. Presently FT can be done with the help of a personal computer using the FFT algorithms [25]. The advantages of spectra are their transparency and reversibility (by inverse DFT the original signal can be regained). A sinusoidal function $X(t)$ is completely described by three parameter-amplitude A, frequency f and the phase ϕ as $X(t)=A\sin(2ft+\phi)$, where t is time. Spectral analysis is a method of calculating the amplitude A_n and phase ϕ_n corresponding to each frequency component f_n that is contained in the EEG epoch. The power spectrum of the EEG is a measure of the relative magnitudes of the $A_n^2 s$, with no account taken of the phase information. In the case of a complete direct evaluation of an N-point DFT, $4N^2$ real multiplications and $(4N^2-2N)$ real additions are required. For the direct computation of the DFT, the amount of computation, and thus the computation time, is approximately proportional to N^2 and can become very great for large values of N. The basic principle is decomposing the computation of

the DFT of a sequence of length N into successively smaller DFTs. It may be either decimation-in-time, where the sequence $X(t)$ is decomposed into successively smaller subsequences or decimation-in-frequency, where the DFT coefficient $X(k)$ is decomposed into smaller subsequences. The decimation-in-time algorithm is best applicable when N is an integral power of 2 i.e., $N=2^r$.

FFT is not superior to time-domain transforms, rather it is more informative than the conventional analog recordings which are still preferred by clinicians. Any transform, being derived from the original signal, is always likely to lose some information. However, frequency domain processing makes the findings more objective (quantified) and hence, observer independent. Power density spectra measurement is a form of quantitative EEG (qEEG), albeit not the only one. Duffy [26] discusses the role of quantified EEG or quantified neurophysiology (qNP) or neurometrics or BEAM (Brain Electrical Activity Mapping) which gives color coded topographical representation of the FFT values in different regions of the brain. The darker sides of it are that controlling the artifacts are quite difficult, huge data sets have to be managed, classic EEG and multivariate statistics are essential for proper inferences.

Another tool for the analysis of signals like EEG, "bispectrum" [27], is the Fourier Transform (FT) of the Third Order Cumulant (TOC) sequence generally used (a) to extract information in the signal pertaining to deviations from Gaussianity and (b) to detect the presence of nonlinear properties and quadratic phase coupling. Since TOC and bispectrum are both zero for a stationary Gaussian process, bispectrum purveys a natural measure of Gaussianity. Also, bispectrum can detect phase coupling (i.e., presence of quadratic nonlinearity) and the degree of phase coupling can be quantified using the bicoherence index, i.e., a normalized bispectrum. Bispectra have been computed to detect phase coupling in the cortical and hippocampal EEG of rat during various vigilance states. For EEG recordings from the hippocampus, significant phase coupling was obtained during REM sleep between the frequency components at 6–8 Hz associated with θ rhythm. During slow wave sleep (SWS), EEGs from frontal cortex or hippocampus exhibit a larger deviation from Gaussian distribution than those of quiet waking and REM sleep. So, bispectral analysis yields extra information not obtainable from the power spectrum.

Another type of quantification has been done with cepstrum (power spectrum of the logarithmic power spectrum) and bicepstrum analyses of EEG [28,29].

Apart from these, an approach to visual evaluation of long-term EEG recordings has been based on multichannel adaptive segmentation, subsequent feature extraction, automatic classification of acquired segments by fuzzy cluster analysis (*fuzzy c-means* algorithm) and on distinguishing of the segments so identified by color directly in the EEG record [30].

The Lyapunov spectrum of EEG has also been analyzed [31]. The FFT dipole approximation algorithm has been applied for localizing the sources of various EEG waves [32]. Another approach to measure the scalp potentials due to dipole sources has been a finite-element modeling of the human head [33].

ANNs (Artificial Neural Networks) are also now being used to automatically recognize EEG patterns in various sleep states [34,35]. One may question the need of automated diagnosis from EEG recordings. The answer lies in the following. EEG paper recordings have not only great inter-observer variations, but also a lot of intra-observer variations. Unlike ECG (electro-cardiography for heart), it is not very specific either. For a long time, qEEG has been trying to overcome these problems. However, we shall limit this article only to the nonlinear analysis of qEEG, and specific to the topics mentioned in the title.

1.3. Future prospects

In the subsequent sections we are going to discuss the role of chaos theory in providing physiological insights, examples of EEG changes that satisfy chaotic conditions, changes in epilepsy, exercise, depression, neurotransmitters, and changes in (cerebral) hemispheric lateralization.

It should be investigated whether all the results obtained from studies (described below) of nonlinear or chaotic dynamics can be correlated with clinical and behavioral changes in depression, especially with reference to hemispheric lateralization. Also, whether or not the changes in exercise and depression are inversely related, deserves investigation. Moreover, nonlinear modeling on the basis of cellular neurotransmitter changes may be able to predict our behavior more correctly, especially in cases of depression.

2. EEG as a product of nonlinear systems

EEG signals are assumed to be the output of a deterministic system of relatively simple complexity but containing non-linearities [2]. In many models of neural networks processing nonlinear wave pulse functions, the nonlinear characteristic is approximated by a linearized version, especially when the input signals have a small range of amplitude. However, such oversimplification may ignore essential nonlinear properties of the system, like the generation of higher harmonics. Actually these networks can be described by a number of coupled nonlinear differential equations as a function of time and space. These sets of equations may purvey the knowledge of genesis of any EEG activity [36–38]. An interesting point is that all nonlinear dynamic systems with more than 2 degrees of freedom can display unpredictable (chaotic) behavior over a prolonged period. Such

systems can have multiple stable states governed by "equilibrium", "limit cycle" or "chaotic" ("strange") attractors. Whether the system will find itself in any stable state depends on the system's parameters and input conditions.

The human brain is a rather superior information processor compared to any artificial system devised so far. Brain modeling comprises detailed study of different processes involved in biological neural computation and to incorporate the facts so learnt into more realistic models of brain function and make them more "intelligent", in comparison with presently available systems in performing cognitive tasks. There have been artificial neural networks of excitatory–inhibitory neural pairs exhibiting chaotic behavior in certain parameter regions [39]. Hence a complete knowledge about the domains of subharmonic behavior and chaos in the parameter space is very important [40]. Chaotic systems are more flexible than nonchaotic ones since the attractor spans a large volume of the state space, and, with proper control, one can rapidly switch among many different behaviors [41]. Using variable feedback control, the networks have been made to converge to any possible periodic pattern. On withdrawal of the control signal, the network reverted to the chaotic state [42]. Similarly, the phenomenon of state synchronization among elements of a coupled chaotic network has also been studied, emulating the neural basis of "attention" [42].

Since EEG signals may be considered chaotic, Nonlinear Dynamics and Deterministic Chaos Theory may supply effective quantitative descriptors of EEG dynamics and of underlying chaos in the brain. Karhunen–Loeve (KL) decomposition of the covariance matrix of the EEG signal has been used to analyze EEG signals of four healthy subjects, under drug-free condition and under the influence of diazepam. KL-complexity of the signal differs profoundly for the signals registered in different EEG channels, from about 5–8 for signals in frontal channels up to 40 and more in occipital ones. But no consistency in the influence of diazepam administration on KL-complexity is observed. The embedding dimension of the EEG signals of the same subjects was estimated, which turned out to be between 7 and 11, thereby supporting the presumption about the existence of a low-dimensional chaotic attractor. Therefore nonlinear time series analysis can be used to investigate the dynamics underlying the generation of EEG signals. This approach does not seem practical yet, but deserves further study [43,44].

EEG signals have been considered to be generated by nonlinear dynamic systems exhibiting chaotic behavior. The system may behave as a deterministic chaotic attractor. The complexity of the attractor can be characterized by the correlation dimension that can be computed from one signal generated by the system. The nonlinear properties of biological neural networks are the threshold for spike generation and saturation phenomena. Also, these populations interact by means of feedback loops with time delays. For calculating the correlation dimension, the EEG signal to be analyzed comprises a set of samples x_n, defined from $n=1,\ldots,N+k$. From this series, one can construct m-dimensional vectors (in an N-dimensional space) $V_m(i)$ with $i=1,\ldots,N$, defined by:

$$V_m(i)=(x(i+k_0),\ x(i+k_1),\ldots,x(i+k_{m-1})) \tag{1}$$

using a fixed set of delays k_l with $0\leq k_l\leq k$ ($l=0,\ldots,m-1$) and $k_l\neq k_p$ if $p\neq 1$. The correlation integral $C(r,m)$, where r is the radius of a sphere with center $V_m(i)$ in R^m may be defined as

$$C(r,m)=1/N^2\sum_{i=1}^{N-1}\sum_{j=i+1}^{N} h(r-d)(V_m(i),V_m(j)) \tag{2}$$

where h is the Heaviside or step function ($h(x<0)=0$, $h(x\geq 0)=1$), and d is the distance between 2 vectors, for which one may use the largest difference between the corresponding components.

If an attractor is present in the time series, then, the values $C(r,m)$ should satisfy, for small r and large m and N: $C(r,m)\propto r^{D_2}$ where D_2 is the correlation dimension of the attractor and is given by the slope of the plot of $\log C(r,m)$ vs $\log(r)$ [45]. $C(r,m)$ is calculated as per Grassberger and Procaccia [46]. During epileptic seizures D_2 is found to be low (between 2 and 4) [47].

2.1. Role of chaos theory in providing physiological insights

Complex bodily rhythms are ubiquitous in living organisms. These rhythms arise from stochastic, nonlinear and biological mechanisms interacting with a fluctuating environment. Disease often leads to alteration from normal to pathological rhythm [48]. Mathematical and physical techniques combined with physiological and medical studies are transforming our understanding of the rhythms of life [49,50]. Chaotic dynamics might be easier for the body to control than stochastic dynamics [51].

Electrical stimulation of complex dynamics in cardiac and neural systems using chaos-control techniques has led to the regularization of complex rhythms [14].

There is a wide spectrum of dynamical behavior associated with both normal and pathological physiological functioning. Extremely regular dynamics are often associated with disease, including periodic (Cheyne–Stokes) breathing, certain abnormally rapid heart rhythms, cyclical blood diseases, epilepsy, neurological tics and tremors. However, regular periodicity can also reflect healthy dynamics — for example in the sleep–wake cycle and menstrual rhythms. Finally, irregular rhythms can also reflect disease. Cardiac dysrhythmias such as atrial fibrillation and frequent ectopy, and neurological dis-

orders like post-anoxic myoclonus, are often highly irregular. The term "dynamical disease" captures the notion that abnormal rhythms, which could be either more irregular or more regular than normal, arise owing to the modifications in physiological control systems that lead to bifurcations in the dynamics. What is more important in distinguishing health from disease is that there is a change in the dynamics from what is normal, rather than regularity or irregularity of dynamics [48].

3. Examples of EEG changes that satisfy chaotic conditions

3.1. Changes in epilepsy

The theoretical models of epileptogenesis have assumed oscillations in a network of neurons. Such models analyze the trajectories in the phase plane whose coordinates are the potential and its first derivative. A nonlinear system that goes into stable oscillation even after the input stimulus has ceased will produce a closed trajectory in the phase plane; i.e., a limit cycle. Models attempting a precise waveform fit with recorded EEG activity have been simulated [52–55]. Recently attempts have been made to combine the local (internal) and the global (scalp EEG) levels within a synthetic theoretical framework [56,57]. However, proper interpretation of nonlinearity in EEG is still not foolproof [58–60].

Because of its high versatility, nonlinear time series analysis has already gone beyond the physical sciences and, at present, is being successfully applied in a variety of disciplines, including cardiology, neurology, psychiatry, and epileptology. However, it is well known that different influencing factors limit the use of nonlinear measures to characterize EEG dynamics in a strict sense. Nevertheless, when interpreted with care, relative estimates of, e.g., the correlation dimension or the Lyapunov exponents, can reliably characterize different states of normal and pathologic brain function. In epileptology, extraction of nonlinear measures from the intracranially recorded EEG promises to be important for clinical practice. In addition to an immense reduction of information content of long-lasting EEG recordings, previous studies have shown that these measures enable (a) localization of the primary epileptogenic area in different cerebral regions during the interictal state, (b) investigations of antiepileptic drug effects, (c) analyses of spatio-temporal interactions between the epileptogenic zone and other brain areas, and (d) detection of features predictive of imminent seizure activity. Nonlinear time series analysis provides new and supplementary information about the epileptogenic process and thus contributes to an improvement in presurgical evaluation [61]. Now nonlinear analysis of EEG is being used for prediction of seizures too [62,63].

Silva et al. [64] calculated correlation dimension maps for 19-channel EEG data from 3 patients with a total of 7 absence seizures. The signals were analyzed before, during and after the seizures. Phase randomized surrogate data was used to test chaos. In the seizures of two patients two dynamical regions on the cerebral cortex could be distinguished, one that seemed to exhibit chaos whereas the other seemed to exhibit noise. The pattern shown is essentially the same for seizures triggered by hyperventilation, but differ for seizures triggered by light flashes. The chaotic dynamics that one seems to observe are determined by a small number of variables and have low complexity. On the other hand, in the seizures of another patient no chaotic region was found. Before and during the seizures no chaos was found either, in all cases. The application of non-linear signal analysis revealed the existence of differences in the spatial dynamics associated to absence seizures. This may contribute to the understanding of those seizures and be of assistance in clinical diagnosis.

3.2. Changes in exercise

Regularly performed exercise is associated with diminished cardiovascular responses to environmental stress, even in animals [65]. However, there is a paucity of information regarding the potential mechanism(s) by which exercise training might blunt the response of stress. Exercise increases slow wave sleep [66], which, in turn, is associated with elevated mood. Again, how does exercise increase SWS and how does SWS alleviate depression — these are yet to be properly understood. Some evidence [67] suggests that physical training can alter β_1 and β_2 adrenoceptor population and reduce α-adrenergic responsiveness. Cross sectional studies based on national surveys done in the USA and Canada have shown a positive association between physical activity and affect (mood, depression, anxiety). The association seems to be most positive for self-reported and transient changes in affect and also of self-esteem [67].

Moore [68] has studied the effects of exercise on body-image, self-esteem and mood, in Australian female college students, testing with "Profile of Mood States" (and Levenson Locus of Control) scales. Exercisers reported a higher quality of life, better mood states, greater concentration and reduced confusion. Hays [69] advocates the use of exercise (in accordance with the need and capacity of the subject) in psychotherapy.

Schlicht [70], performing a meta-analysis of 20 studies published between 1980 and 1990, has observed 22 effect-sizes based on 1306 subjects. The age of the subjects served as a weakly moderating variable. For middle-aged (31–50 years), the relation between physical exercise and anxiety was closer than for younger adults. The marginal moderating effect of age correlated

also with meta-analytical results of relationship between physical exercise and mental health.

The interactions of physical activity and fitness with anxiety and depression have been stressed as an integral part of health [71].

3.3. Changes in depression

Depression is a psychosomatic (psychobiosocial) disorder, which affects every aspect of human physiology. Yet under-diagnosis and under-treatment in general medical practice is all pervasive [72].

Nandrino et al. [73] reported a decrease of complexity in EEG as a sign of depression. Nonlinear methods can predict major depression because of the reduced complexity. In healthy systems, there is a high level of complexity in the dynamics. The diminished complexity of brain function, in depression, may be due to a low level of environmental interaction. Later they found that first episode and recurrent patients strongly differ in their dynamical response to therapeutic interventions [74].

Vogel et al. [75] had surmised "REM sleep deprivation" as the mechanism of action of most of the antidepressant drugs. Oniani et al. [76] had speculated that during active wakefulness (it can logically be extrapolated to exercise) and REM sleep, other neurobiological brain processes (particularly on the level of the forebrain) also proceed similarly, thus making these two states competitive. The impression is created that, on the one hand, episodes of forced wakefulness/activity restrict the formation of a biological need for REM sleep during SWS, and on the other, they can utilize the REM need already formed thereby reducing the depressive tendency. Heart rate variability of sinus rhythm in healthy individuals has characteristics suggestive of low-dimensional chaos-like determinism, which is modulated but not eliminated by inhibition of autonomic tone or by exercise. The dominant Lyapunov exponent characterizes heart rate variability independent of other investigated measures [77].

The theory of dynamical systems allows one to describe the change in a system's macroscopic behavior as a bifurcation in the underlying dynamics. From the example of depressive syndrome, the existence of a correspondence between clinical and electro-physiological dimensions and the association between clinical remission and brain dynamics reorganization (i.e., bifurcation) can be shown. On the basis of this experimental study, such results concerning the question of normality vs pathology in psychiatry and the relationship between mind and brain have been discussed [78,79].

3.4. Changes due to neurotransmitters

There are various chemicals called neurotransmitters that convey the information to be passed and processed through the 10^{16} interconnections between the 10^{10} neurons in our brain. However, each of the several (many perhaps yet to be discovered) neurotransmitters act through various receptors and their numerous subtypes. So much so that the same neurotransmitter acting through a different receptor subtype may have opposing actions. To cite an example, serotonin or 5-HT (5-hydroxytryptamine) receptor subtype $5HT_4$ increases a "second messenger" adenylate cyclase (AC), thereby modulating cognition and causing anxiety. On the other hand, $5HT_{1A}$ receptor subtype reduces AC activity, thus leading to antidepressant and anxiolytic action. Most of the antidepressant medications utilize this property and are called SSRI or Selective Serotonin Reuptake Inhibitors. Therefore, the same chemical serotonin, acting through a different receptor subtype, can both produce and reduce anxiety. It is this sort of interaction that causes chaotic oscillations in the brain. Now, there are also other neurotransmitters. Another group of drugs, with relative selectivity for the neurotransmitter norepinephrine's transporter molecule, also have antidepressant property, as they too reduce AC activity. To continue with the conundrum, a medicine to reduce high blood pressure (hypertension), reserpine, blocks vesicular monoamine transporter, and therefore, simultaneously depletes brain levels of serotonin, norepinephrine and dopamine and, in the process, gives rise to depression. We also have neuropeptides, colocalized in neurons that also contain classic neurotransmitters, other neuropeptides or both. One such neuropeptide, neurotensin, is found in neurons containing the dopamine synthetic enzyme tyrosine hydroxylase. Therefore, reserpine causes a decrease in both neurotensin and dopamine, albeit not in human and non-human primates [80]. So, many of the psychotropic drugs exert their therapeutic effects through various neurotransmitters, mainly through their several specific receptor subtypes.

3.5. Changes in (cerebral) hemispheric lateralization

Interestingly, there are greater right sided (non-dominant hemispheric) EEG abnormalities in depression due to impaired cerebral lateralization [81–83]. Thus, females are more prone (because of earlier cerebral lateralization) and males are less predisposed to depression. Therapeutically too, better antidepressant results are obtained with nondominant unilateral electroconvulsive shock [84].

Shagass et al. [85], testing "eyes open" and "eyes closed" awake EEGs, in 12 leads, in different psychiatric patients, found that depressives, like the personality disorder group, had a low level of EEG activation. Later, they [86] performed time series analysis of amplitude, frequency and wave symmetry. Differences between eyes open and closed were adjusted for "eyes closed" values to obtain measures of reactivity. These reactivity measures yielded the main difference between the

unmedicated and non-patients. Depressives were more reactive. Reactivity differences were eliminated or reversed in medicated patients. The EEGs of unmedicated depressives were over-reactive and with medication, EEG reactivity declined.

Nyström et al. [87] had chosen 5-s epochs from 5-min awake-EEG recordings and averaged to a total of 60-s recordings. In primary major depressive disorder (MDD), they found an increase in 'δ' amplitude and in retarded MDD, increased 'δ' and 'θ' amplitude along with EEG variability. In cases of recurrent unipolar MDD, a reduction of total alpha symmetry was found. Symmetry was measured by left/right ratio in amplitude values (mean amplitude=square root of power). The number of former depressive episodes was positively correlated with 'β' amplitude and negatively correlated with EEG symmetry for 'δ'.

It is generally claimed that "affect" processing is a right hemisphere (RH) function. It is also claimed that RH dysfunction is characteristic of depressive illness. Both these claims are controversial and it has been found that the relationship between affect processing and affective illness, in terms of intra- and inter-hemispheric role play, is not straight forward. There is an exchange of information and action between the two hemispheres (inter-hemispheric, i.e., between left and right; intra-hemispheric i.e., between anterior and posterior; and also cross-hemispheric coupling i.e., similarities among the left anterior and right posterior quadrants) [83,88]. Summarily, sad mood is a function of positive coupling (stimulation) of left posterior and right anterior areas and/or negative coupling (depression) of left anterior and right posterior areas of the brain. Interestingly, in Alzheimer's disease, significant nonlinear changes in the left hemisphere (O_1 lead of EEG) has been found in qEEG [89].

The electrophysiological measures of MEG (magnetoencephalography) consisting of 6 spectral band measures together with spectral edge frequency and spectral entropy, plus the time-domain-based entropy of amplitudes (ENA) and the nonlinear measures correlation dimension D2 and Lyapunov exponent L1 has been measured during cognitive tasks. The results indicate a pronounced task-dependent difference between the anterior and the posterior region, but no lateralization effects. Though the nonlinear measures ranged in the middle field compared to the number of significant contrasts, they were the only ones to be partially successful in discriminating the mental tasks from each other [90].

Neuroimaging studies of memory have consistently shown that episodic retrieval is associated with right frontal activation, whereas semantic retrieval is associated with left frontal activation. Various hypotheses have been proposed to account for this lateralization in terms of underlying psychological processes. Alternatively, this lateralization may reflect the complexity of information retrieved: retrieval of complex, contextual information accompanying episodic retrieval invokes right-lateralized processes preferentially. This hypothesis was tested by manipulating the type and complexity of information retrieved. Initial increase in complexity of both episodic and semantic information was associated with right inferior frontal activation; further increase in complexity was associated with left dorsolateral activation. That implies that frontal activation during retrieval is a non-linear function of the complexity of retrieved information [91].

Whether a correct lateralization of the primary epileptogenic area by means of neuronal complexity loss analysis can be obtained from interictal EEG recordings using semi-invasive foramen ovale electrodes has been investigated. In a previous study with recordings from intrahippocampal depth and subdural strip electrodes it was shown that the dynamics of the primary epileptogenic area can be characterized by an increased loss of neuronal complexity in patients with unilateral temporal lobe epilepsy (TLE). In this study [92] neuronal complexity loss analysis was applied. This analysis method is derived from the theory of nonlinear dynamics and provides a topological diagnosis even in cases where no actual seizure activity can be recorded. Interictal EEG recorded intracranially from multipolar foramen ovale electrodes in 19 patients with unilateral TLE undergoing presurgical evaluation was examined. The primary epileptogenic area was correctly lateralized in 16 of the 19 investigated patients. The misclassification of the side of seizure onset in three patients might be attributed to the larger distance between the foramen ovale electrodes and the mesial temporal structures as compared to intrahippocampal depth electrodes. These results confirm the previous findings and provide further evidence for the usefulness of nonlinear time-series analysis for the characterization of the spatiotemporal dynamics of the primary epileptogenic area in mesial temporal lobe epilepsy.

4. Summary and conclusions

In general, definitive evidence has hardly been found for the existence of nonlinear determinism in EEG signals except for those recorded during epileptic seizures. So, a given neuronal network may present essentially different modes of activity (different dynamics) depending on specific conditions. For some values of control parameters, a neuronal network may change its dynamical mode of activity, e.g., instead of a random noisy state, a limit cycle or even a chaotic attractor may occur. This is called a bifurcation — representing a qualitative change and depends on a set of control parameters that define the operating regime of the system. It can be hypothesized that the main difference between a

normal and epileptic brain is that the operating regimen of a neuronal network in the epileptic brain is much closer to a bifurcation point than the normal brain, leading to a low-dimensional chaotic mode of behavior. In other words, in an epileptic neuronal network, the distance between operating and bifurcation points is so small that the system may easily switch from a stable equilibrium to a chaotic attractor despite a very weak (undetectable) stimulus. Therefore, in case of epilepsy, the basic question is which factors are responsible for the change in the operating point of the involved neuronal networks. This nonlinear behavior has been identified at neuronal level [93] where apparently chaotic oscillation was observed near transition from sub-threshold to bursting oscillations in thalamic neurons.

All the facts depicted in this article make us aware of our far from complete knowledge and understanding of definitive diagnostic and prognostic values of EEG especially with reference to depression and the role of nonlinear activities of the brain. Even today the textbooks of medicine, neurology and psychiatry do not attach as much importance to EEG as they do regarding the ECG or electrocardiogram. The EEG is considered to be quite nonspecific except in a few cases of epileptic disorders. Moreover the same recording elicits a different interpretation not only from different experts (inter-observer variations), but also from the same expert (intra-observer variations) at different times. On the other hand, the journals, specialized textbooks and reference books on EEG are stressing the various new computer-aided (quantitative or qEEG) methods for analysis.

As yet there is no consensus on the appropriate mathematical analysis. Each method has its inherent advantages and disadvantages. A neuropsychiatrist is less likely to afford the time to learn all of those techniques. In the near future, that may lead to laboratory dependent qEEG diagnosis. Initially what had started with the aim of simplifying and standardizing the EEG interpretations, have, with time, grown into a much more complex and over expanding exercise. However, without these computations, we could not have known the finer details of EEG and brain functions.

First [94] has discussed potential applications of computer technology to diagnostic assessment and two basic design axioms for computerized assessment. The first axiom: given the current state of computer technology, a human clinician must remain a necessary component of diagnostic procedure to ensure a sufficiently high level of diagnostic validity. The second axiom, for a successful diagnostic computer program, is that the clinician must understand completely the strengths and the limitations of the computer-assisted assessment procedure. Two basic approaches are the use of computers as an expert-system and the use of computers to collect data directly from patients by administering a diagnostic interview or questionnaire. Butcher [95] believes that computer-generated procedures for psychiatric assessment remove subjective bias from the interpretation process. However, computerized assessments (CAs) can also lead clinicians to make serious errors unless the potential problems are recognized and avoided. The CAs can encourage a passive stance in clinical evaluation, mystify the assessment process and may lend an unwanted aura of scientific precision to test interpretations through impressive printouts. Also, it may not be specific or sensitive for each patient or disease. It should be considered as raw test data or hypothesis and not as final clinical evaluation. Clinical acumen and automated diagnostic decision support systems are not mutually exclusive; rather they reinforce each other [96,97].

Sarbadhikari [35] has shown that automated differentiation of qEEG (power density spectra) is possible in case of depression and exercise, albeit it is not entirely unambiguous. Moreover, because of the inherent nonlinearities in EEG, the fractal nature of self-similarity can be usefully employed in EEG signal compression for transmission [98].

Another report [99] reviews and compares all therapies that have shown efficacy in depression and Parkinson's disease, although some are not in current use and others are at the experimental stage. They include pharmacological modification of neurotransmitter pathways, electroconvulsive therapy (ECT), sleep deprivation, psychosurgery, electrical stimulation through cerebral electrodes, and transcranial magnetic stimulation. Stemming from a pathophysiological model that stresses the brain as an open, complex, and nonlinear system, all therapies have been attributed a common mechanism of action. This report suggests that the therapeutic isomorphism is related to their ability to help the CNS (central nervous system) deactivate cortical-subcortical circuits that are dysfunctionally coupled. These circuits are self-organized among neurons of their informational subsystem (rapid conduction) and modulating subsystem (slow conduction). Finally, this report extends the analysis and comparison of these therapies to some cardiac arrhythmias.

Neuropharmacological investigations aimed at understanding the electrophysiological correlates between drug effect and action potential trains have usually been carried out with the analysis of firing rate and bursting activity. In this study [100], a selective alteration of neural circuits providing inputs to ventral tegmental area dopaminergic neurons has been produced, and the corresponding electrophysiological correlates have been investigated by nonlinear dynamical analysis. The nonlinear prediction method combined with Gaussian-scaled surrogate data has been used to show the chaotic structure in the time-series corresponding to the electrical activity of ventral tegmental area dopaminergic neurons, extracellularly recorded in vivo. A decrease in chaos of ventral tegmental area dopaminergic neurons was found

in a group of rats lesioned with 5,7-dihydroxytryptamine, a neurotoxin, which selectively destroys serotonergic terminals. The chaos content of ventral tegmental area dopaminergic neurons in the control group and the decrease of chaos in the lesioned group cannot be explained in terms of standard characteristics of neuronal activity (firing rate, bursting activity). Moreover, in the control group a positive correlation has been found between the density–power-spectrum of the interspike intervals and the chaos content measured by nonlinear prediction S score; this relation was lost in the lesioned group. It is concluded that the impaired serotonergic tone induced by 5,7-dihydroxytryptamine reduces the chaotic behavior of the dopaminergic cell firing pattern, while retaining many standard interspike interval characteristics. The functional role of this behavior in a neuronal coding problem context and the implications for the pathophysiology of some mental disorders are discussed in the paper [100].

However, some pitfalls still remain. Jeong et al. [101] have raised a suspicion that the determinism in the EEG may be too high-dimensional to be detected with current methods.

To sum up, whether the complex dynamics are an essential feature or if they are secondary to internal feedback and environmental fluctuations is not known [48]. Because of the complexity of biological systems and the huge jump in scale from a single ionic channel to the cell to the organ to the organism, for the foreseeable future all computer models will be gross approximations to the real system.

Despite that shortcoming, better theoretical models incorporating the oscillation caused by the same neurotransmitter acting on its different receptor subtypes may lead to a better understanding of brain neurodynamics. Therefore, we can hopefully look forward to some reliable nonlinear techniques for evaluating qEEG, in health and disease, in the near future.

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