Review

Complexity and Irregularity in the Brain Oscillations of Depressive Patients: A Systematic Review

Alejandro de la Torre-Luque[†], Xavier Bornas

Abstract

Associations between brain oscillations and depressive disorders have been studied for many years, leading to the development of prominent theories (e.g., the frontal EEG asymmetry). The brain, however, is a complex nonlinear system, and tools from the Nonlinear Dynamic Systems (NDS) theory are increasingly used to better understand its complex rhythms. This scientific review aimed at gathering relevant evidence on the use of nonlinear measures (those derived from the NDS) to identify biomarkers hidden under the brain oscillations of depressive patients. Thus, electroencephalographic (EEG) and magnetoencephalographic (MEG) studies which aimed either to compare depressives and healthy controls' oscillations (diagnostic studies) or to examine the efficacy of interventions to ameliorate depressive symptomatology (intervention studies) on those oscillations were selected. As a result, 12 diagnostic studies and nine intervention studies were reviewed. Diagnostic studies essentially examined the brain oscillations in the broad frequency band and reported larger complexity or irregularity in depressives, as shown by the fractal dimension measures and informational measures. Regarding the intervention studies, the larger the decrease in brain complexity (e.g. in fractal dimension) the higher the amelioration of depressive symptomatology. The increased complexity found in brain oscillations of depressives may probably be related to deficits in cortical inhibition control mechanisms. Further research should be conducted to determine the features of antidepressant interventions in order to get efficient cost-benefit treatments. Much more research in this field is required, but the use of NDS based concepts and tools may promise a less reductionistic understanding of the complex brain oscillations in health and disease.

Keywords:

EEG, Complexity, Depression, Irregularity, Brain

Introduction

The brain perpetually generates rhythms and scientists have been trying to understand the meaning of these rhythms for a hundred years, ever since Hans Berger discovered the EEG in the early 1920s. Perhaps the most common approach to the study of resting EEG oscillations has been frequency analysis. Based on the mathematical assumption that any complex oscillation is made up of oscillations at specific frequencies, the highly complex fluctuations in the brain were divided into several narrow bands (e.g. delta, theta, alpha, beta and gamma), ranging from the slowest to the fastest waves. This band-based approach has provided valuable knowledge but the significance of each frequency band oscillation is far from clear despite extensive research [1]. In addition to (or superimposed onto) the band-based approach, researchers looked for specific meanings of oscillations depending on the cortical lobes where they were recorded. Thus, one of the most valuable theories

nowadays concerning depression is frontal brain alpha asymmetry [2,3]. Even though "one should not view it [the frontal cortex] as the only 'location' of the complex neuronal processes associated with the depressive state" [4].

The brain, nevertheless, is perhaps the best example of a complex system, and it should be noted that complex systems cannot be fully understood by breaking them down into simpler components (e.g. frequency bands). In the last decade or so, efforts have been made to apply concepts and techniques from the Nonlinear Dynamical Systems (NDS) theory to the study of brain rhythms (i.e. the EEG). As pointed out by Freeman [5], nonlinear brain dynamics (what he called a new scientific field at that time) allowed us "to recognize these patterns as manifestations of chaos, which looks like noise but has hidden order and the capacity for rapid and widespread changes, just us our thoughts do" (p. 9). In a similar vein, the theory of self-organised criticality [6] suggests that the brain operates at a near critical state [7-10], so that quick reorganisation of neural networks during processing demands would be possible by the critical state dynamics of spontaneous oscillations [11,12].

It is beyond the scope of this review to explain the characteristics of complex systems. However, a brief mention of those that have been researched in EEG studies may be helpful. Among the essential properties of complex systems is the sensitivity to initial conditions, popularly known as the butterfly effect. Depending on the value of the control parameters regulating the behaviour of the system, very small changes in the initial values of system variables will lead to large changes in system trajectory over time. The sensitivity of a system to initial conditions is estimated by means of the largest Lyapunov exponent (LLE) and positive values of this exponent reveal said sensitivity (chaos). Complex systems are less predictable than simpler ones and, consequently, predictability has been considered a measure of the complexity of a system. When a dynamical system generates a lot of new information, predicting its future behaviour becomes highly difficult or impossible, whereas systems that do not generate new information (e.g. a sinus wave) are highly predictable. The rate of new information a system generates is called "entropy" in information theory. Hence, high entropy values characterise unpredictable (complex) systems. Closely related to entropy measures, the Lempel-Ziv complexity (LZC)

of finite sequences [13] accounts for how new elements are encountered along a time series (for instance, an EEG epoch). Based on a symbolic dynamics approach, the more new information found, the stronger the evidence of complexity. Long-range temporal correlations (LRTC) in electroencephalographic oscillations [11,14] are usually evaluated by means of the so-called scaling exponent, calculated using detrended fluctuation analysis (DFA). DFA was introduced by Peng, *et al.* [15] as a method to quantify scaling, i.e. the "scale-invariant (fractal) correlation property" in healthy heartbeat fluctuations. Several algorithms have been used to estimate the fractal dimension (FD) of the EEG system (e.g. Katz's or Higuchi's algorithms). Finally, there are geometric techniques. For instance, recurrence plots quantify the times when a system's trajectory visits roughly the same area in the phase space (the abstract mathematical space that includes all the possible states of a system).

Along with the use of nonlinear, complex tools to better understand healthy human brain rhythms, there is a growing willingness to study EEG recordings from people suffering psychiatric disorders using these complexity tools. In fact, scaling in resting-state EEG has been suggested as a biomarker for pathophysiology in neurodevelopmental disorders [16-18]. In more general terms, the search for nonlinear biomarkers of emotional diseases has seen fast growth in recent years [19], although a specific review on depression and nonlinear EEG studies has yet to be conducted. The main hypothesis underlying all this research is that diseased systems would show decreased complexity. However, due to the large number of measures used to quantify complexity, the exact meaning of "decrease" is unclear. For instance, random systems may show complexity indices as high as those for complex systems, but randomness is not the same as complexity. This question will be discussed after reviewing the studies undertaken to evaluate the brain oscillations of depressive individuals.

This study aims at gathering EEG-based empirical evidence derived from nonlinear measures in the brain oscillations of depressive patients. As we will see, most studies have focused on the EEG broad band over narrower bands, thus attempting to better understand the complexity of brain oscillations. Moreover, large cortical areas seem to be involved in depressive states beyond lobe-specific characteristics (e.g. asymmetries). In this regard, Lee, *et al.* [20]

and Morillas-Romero, *et al.* [21] reported complexity decreases in large cortical areas as being associated with the severity of depression and negative (depressive) emotional regulation strategies, respectively. As a second aim, this study reviews the effects of interventions to ameliorate depressive symptomatology on the complexity of EEG oscillations.

Methods

Firstly, searches in scientific databases were carried out. The consulted databases were: Cochrane Plus Database; databases provided by EBSCOhost server (FRANCIS, PsycInfo, PsycARTICLES, CINAHL, and e-Journals); databases provided by OvidSP server (Ovid NursingDatabase, all OVID journals, and NASW Clinical Register); PubMed; PubPsych; Scopus and Web of Science. Search queries were made by means of crossing keywords related to depression and depressive disorders (dysthymia, depressive episode, etc.) with keywords derived from the NDS framework [19]. The database search was conducted between October and November 2016.

Articles included in this review had to be comparative studies published in scientific literature in English and at least include a group of individuals (humans not animals) with a depressive diagnosis (not subclinical samples). In order to meet our study aims, two types of empirical studies were selected: diagnostic studies, operationalised as studies in which EEG oscillations of depressed individuals were compared with those from healthy controls, and intervention studies, conceptualised as studies where a treatment aimed at ameliorating depressive symptomatology was delivered, where either pre-/posttest or between-group (clinical vs. control group), or responder analysis (intervention responders vs. non-responders) comparisons were reported. The outcomes in both categories of studies were to be extracted from the EEG-based oscillations (in waking time) by means of nonlinear measures. These measures were classified into categories [22]: statistical, geometrical, informational, energetic and invariant.

Results

In total, twelve diagnostic studies were selected from the scientific literature review and nine studies (four of which also selected as diagnostic studies) focused on intervention delivery. The main features of all of these studies are summarised in the Appendix. Half of these studies were published from 2010 onwards and conducted in European research centres (41.67% were run in Asian laboratories and only one study in an American laboratory).

Diagnostic studies

The twelve studies focused on identifying distinctive profiles of EEG oscillations comparing depressive and control patients. A total of 215 patients took part in these studies as well as 183 healthy control participants. A relatively similar proportion of men and women were observed across the studies, with the exception of the study by Bachmann, *et al.* [23], whose sample exclusively comprised women. All the studies involved adult populations.

Nonlinear measures of broad band oscillations

The majority of the studies (83.33%) extracted nonlinear measures from broad band EEG. Protocols and findings differed among studies **(Table 1)**. Thus, three studies extracted nonlinear measures from a broad band up to 50 Hz [24-26]. Acharya, *et al.* [24] studied the EEG oscillations from both brain hemispheres separately, from a sample of 15 depressive patients in comparison to 25 healthy controls, under resting conditions (with closed and open eyes). Recordings lasted five minutes and geometric, informational and invariant measures were calculated. As a final aim, they intended to classify depressive and control individuals by means of a depression diagnosis index. In terms of recurrence plot measures (geometric measures), Acharya, *et al.* found that participants with depression showed higher values than control participants. These findings pointed to a more rhythmic, predictable pattern of oscillations in both hemispheres not considering different power bands. Entropy-related measures were used in the informational domain (for instance, sample entropy) and healthy controls were found to show higher levels of entropy than their clinical counterparts. Finally, the DFA exponent α, the FD, and the LLE were extracted as invariant measures. In this regard, the DFA α of depressed individuals was higher compared to control individuals, although exponents from both groups were lower than 1, reflecting the presence of LRTC. Conversely, control individuals showed greater LLE and FD in both hemispheres. Lee, *et al.* [20] observed

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Table 1: Main findings derived from nonlinear dynamics of EEG brain oscillations (Diagnostic studies).

Diagnostic studies

Frequency bands	Bandwidth	Study	Studied areas	Nonlinear measures	Main findings
Broadband	Up to 30 Hz	Nandrino *et al.*, 1994	Frontal, central and parietal	Informational (correlation coefficient ρ)	↑EG
		Pezard *et al.*, 1996	Frontal, central and parietal	Informational (Information index S_0), invariant (Kolmogorov-Sinai entropy)	↑EG when comparing with first-episode depressives and no differences between controls and patients with recurrent MDD, nor between the depressive groups
	Up to 40 Hz	Mendez *et al.*, 2012	All áreas	Informational (LZC)	↑EG
	Up to 50 Hz	Acharya *et al.*, 2015	Frontal, central, parietal and temporal	Geometric (recurrence plot measures), informational (BiEnt, EntPh, SampEn) invariant (Lacasa FD, Hurst exponent, LLE)	↑EG for DFA and recurrence plot measures. ↑CG for FD, informational measures and LLE
		Akar *et al.*, 2015a	Frontal, central, parietal and temporal	Informational (KC, LZC, Shannon entropy), invariant (Higuchi FD, Katz FD)	↑EG in frontal, central and parietal areas under resting. ↑EG in frontal and parietal areas under music stage for invariant measures and LZC. ↑EG in frontal and parietal areas under noise stage for invariant measures, KC and LZC
		Lee *et al.*, 2007	Frontal, central, temporal and occipital	Invariant (DFA α)	↑EG (except in C4). DFA < 1 for both groups
		Li *et al.*, 2008	All áreas	Informational (LZC)	↑EG across study stages but no differences in frontal areas under the emotion induction task
	Up to 60 Hz	Akar *et al.*, 2015a	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	↑EG
	Up to 70 Hz	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	↑EG in frontal areas
		Bachmann *et al.*, 2013	All áreas	Invariant (Higuchi FD, Katz FD)	↑EG in all areas, but no differences in frontal regions
Slow oscillations	δ	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	↑EG in frontal areas, globally and in the left hemisphere
		Akar *et al.*, 2015b	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	↑EG
	θ	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	No between-group differences
		Akar *et al.*, 2015b	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	No between-group differences
		Linkenkaer-Hansen *et al.*, 2005	Occipitoparietal and temporocentral	Invariant (DFA α)	↑EG
α	8-12 Hz	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	No between-group differences
		Akar *et al.*, 2015b	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	No between-group differences
		Arns *et al.*, 2014	Frontal and occipital	Informational (LZC) and invariant (LLE)	No between-group differences
		Linkenkaer-Hansen *et al.*, 2005	Occipitoparietal and temporocentral	Invariant (DFA α)	No between-group differences
Fast oscillations	β	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	↑EG
		Akar *et al.*, 2015a	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	↑EG
		Linkenkaer-Hansen *et al.*, 2005	Occipitoparietal and temporocentral	Invariant (DFA α)	No between-group differences
	γ	Ahmadlou *et al.*, 2012	Frontal	Invariant (Higuchi FD, Katz FD)	↑EG (but not in the right hemisphere)
		Akar *et al.*, 2015a	Frontal and parietal	Invariant (Higuchi FD, Katz FD)	↑EG

Note: Nonlinear measures: BiEnt = Bispectrum entropy; DFA = Detrended fluctuation analysis; EntPh = Bispectrum phase entropy; FD = Fractal dimension; KC= Kolmogorov complexity index; LLE = Largest Lyapunov exponent; LZC = Lempel Ziv complexity index; MSE = Multiscale entropy; SampEn = Sample entropy.
↑ CG refers to higher values in a definite index for a control group in comparison to clinical one. ↑ EG refers to higher values in a definite index for a clinical group in comparison to a healthy control one.

similar higher levels of DFA across EEG areas in depressed compared to control participants.

Akar, *et al.* [25] conducted a study in which EEG oscillations of depressive patients and control participants were recorded under closed-eyes resting conditions and under emotion induction tasks (listening to pleasant Turkish music and listening to noise, appraised as inducing unpleasant emotions). These authors made use of the Kolmogorov index, LZC and Shannon entropy (informational measures), and the fractal dimension calculated as per the Higuchi and Katz algorithms. As a result, they found no discriminating power for Shannon entropy between the groups. Conversely, the fractal dimension and LZC values were significantly higher for depressives in frontal, central and parietal areas under resting conditions, but only in frontal and parietal areas under the emotion induction stages. In turn, the Kolmogorov index was significantly higher in depressive patients when analysing EEG oscillations in central areas under resting conditions and in frontal areas during the noise stage. Li, *et al.* [26] found similar higher LZC along the scalp (even in occipital locations) in depressives with psychotic symptoms under closed-eyes resting conditions, as well as during a stress induction stage. However the differences were not significant between the groups in frontal areas for this stage.

A more limited broad band was analysed in three studies [12, 27,28]. Mendez, *et al.* [27] studied brain oscillations by means of resting-state magnetoencephalography in a bandwidth from 1.5 to 40 Hz, looking at anterior, lateral, central and posterior areas. They observed higher LZC in older participants. Moreover, depressive patients showed greater LZC in all brain regions. Nandrino, Pezard and their colleagues [12,28] utilised a tone detection attention task to analyse the basal levels of depressive and control participants, as well as the effect of pharmacotherapy on EEG-based oscillations. The bandwidth taken ran from .08 to 30 Hz. Focusing on the diagnostic test, i.e. the first EEG recording (when entering the hospital for treatment), the depressive samples (patients with an initial depressive episode as well as recurrent-episode patients) showed higher information index S_0 and correlation coefficients of the predicted reconstructed curve of performance with the observed series than control participants. Additionally, Kolmogorov-Sinai entropy, a measure of invariance, was also higher for depressive than for control

participants. No differences were shown among depressive participants.

Other studies calculated nonlinear measures on wider broad band oscillations. Akar, *et al.* [29] explored the fractal dimension in frontal and parietal areas under closed-eye resting states looking at brain oscillation broad band from 1 to 60 Hz. They found a higher fractal dimension for depressives in comparison to control participants in both areas. Bachmann, *et al.* [23] obtained similar results but without any difference in frontal areas when using a broad band from .30 to 70 Hz. Conversely, Ahmadlou, *et al.* [30], focusing on frontal areas and looking at the same width of broad band oscillations, showed a higher fractal dimension for depressives when integrating the oscillations from both hemispheres. Between-group differences disappeared when each hemisphere was considered independently.

■ Nonlinear measures of band-specific brain oscillations

Several studies analysed EEG activity looking at nonlinear dynamics for specific frequency band oscillations. Ahmadlou, *et al.* [30] studied the fractal properties of frontal EEG oscillations in the frequency bands α, β, δ, γ, and . As a result, they found that the fractal dimension of β and γ oscillations was higher in depressives when compared to control participants in the frontal area, considered globally, but also in the left hemisphere. For the right hemisphere, only the fractal dimension of the β rhythm was significantly higher for depressives. Akar, *et al.* [29] observed a similar higher fractal dimension in β and γ frequency bands for frontal and parietal areas. Arns, *et al.* [31] aimed to study the informational properties of the α rhythm in frontal and occipital areas by means of LZC. No between-group differences were found.

Finally, Linkenkaer-Hansen, *et al.* [11] aimed to shed light on the presence of LRTC in depressive patients exploring occipitoparietal and temporo-central areas. Concretely, they looked at LRTC hidden in α, β, and θ magnetoencephalographic rhythms. The DFA exponent was found to be higher in control participants when looking at the θ oscillations in both studied areas. The DFA exponent was between .50 to 1, thus confirming the presence of LRTC for both study groups. Moreover, a negative correlation was observed between the severity of depressive symptomatology and the DFA exponent in the θ band: the more depressed the patient, the less

autocorrelation of the amplitude fluctuations in the theta-frequency band. Furthermore, there was a small, albeit significant, positive correlation between exponents and depression scores for alpha oscillations detected over the occipitoparietal region.

■ **Intervention studies**

Nine studies evaluated the role of nonlinear dynamics in EEG brain oscillations as a biomarker for treatment effectiveness when an intervention was delivered to ameliorate depressive symptomatology (Table 2). A total of 261 patients took part in these studies, with a relatively similar proportion of men and women. Three studies followed a cross-sectional design based on responder analysis (comparing intervention responders vs. non responders). A further three studies provided pre-/posttest comparisons. One study compared two conditions with different doses of the same intervention [32]; and two studies, with pre-/posttest comparisons, also included a group of quasi-control into its design [12,28]. Most studies evaluated changes in the EEG broad band oscillations and only one study [31] focused on the nonlinear dynamics of oscillations in the α frequency band (see Appendix).

■ **Studies with Electroconvulsive Therapy (ECT)**

The changes produced in nonlinear dynamics of EEG oscillations after undergoing ECT were analysed in 44.44% of studies. Gangadhar, *et al.* [33] studied a sample of depressive patients who were randomly assigned to different bilateral ECT delivery according to the number of weekly sessions (one or three) and the dose stimulus (threshold dose or higher). For analysis, the authors did not take into consideration group assignment. As a main aim, Gangadhar and colleagues intended to examine how the fractal properties of the frontal EEG oscillations (measured at F3 and F4) were able to predict the efficacy of the treatment two weeks later. Thus, the fractal dimension based on Katz's algorithm was calculated from the early-, mid- and post-seizure EEG stage across the first session of ECT. Moreover, the depressive symptomatology measurement was taken two weeks after starting the ECT and showed 62.50% of the sample remitted in symptoms (responders). With regard to how the fractal dimension was related to symptomatology reduction, it was observed that smaller post-seizure dimensions increased the cumulative probability of being a responder.

In this vein, Jagadisha, *et al.* [34] examined EEG fractal properties for depressives in the first week of ECT in early (42.50% of sample) or late responders. They delivered right-unilateral ECT with 50-pulse/s or 200-pulse/s frequency, three times a week. All participants received attendant threshold stimulus. EEG recordings were taken in the second and third ECT sessions in frontal and temporal areas, and attempted to relate the fractal dimension of the EEG seizures across the ECT session with symptom reduction. As a result, they found that participants who responded to ECT earlier (reductions of symptomatology in the second week) showed a significantly lower post-seizure fractal dimension than late responders. Moreover, there was a significant correlation between the percentage of symptom amelioration and the post-seizure fractal dimension.

Two studies analysed the effects of ECT on brain oscillation nonlinear dynamics in pre-/posttest designs. Thomasson and Pezard [35] monitored a depressive patient who underwent ECT sessions (three times a week) to ameliorate depression. No further details were reported regarding the intervention. An EEG recording was conducted every two days, the last one taking place on day 14. The Kolmogorov entropy was extracted from the multichannel integrated oscillation (31 electrodes distributed along the scalp) after using the spatial embedding method. As a result, a reduction of entropy was seen as ECT sessions were delivered. Additionally, a positive correlation between the ameliorations in symptomatology and the decrease in entropy was reported. Okazaki et al. [36] opted for a similar design with three depressives who received bilateral ECT. However, they utilised multiscale entropy (MSE), an entropy-like measure which considers complexity/irregularity at multiple time scales. As a result, all three patients showed a decrease in MSE, especially relevant in MSE factor scales 1 to 5, corresponding to γ frequency band oscillations.

Finally, Motreja, *et al.* [32] compared the effects of ECT, delivered bilaterally with a frequency of 125 pulse/s, with a frequency of one or three sessions a week. In this instance, participants were assigned to a group who received either a concomitant threshold stimulus (110 mC on average) or a higher dose (from 240 mC). The fractal dimension of the EEG post-seizure was evaluated and as a result, no significant differences were found between groups regarding these nonlinear properties.

■ Pharmacotherapy and other studies

A total of three studies analysed the effects of pharmacotherapy on the nonlinear properties of EEG oscillations. All of them examined brain oscillations in the broad band taking 40 Hz as an upper band [27]. Thus, Nandrino, Pezard and their colleagues [12,28] analysed the effects of pharmacotherapy in patients with depressive episodes in a hospital. They used a tone detection attention task to examine the broad band (up to 30 Hz) informational and fractal properties. Participants in an initial depressive episode were treated with clomipramine, as were recurrent-episode participants, although some were also treated with fluoxetine during the ten first days after admission. As a result, participants saw reduced levels of informational (correlation coefficient ρ and Kolmogorov complexity) and invariant properties (Kolmogorov-Sinai entropy).

Mendez, *et al.* [27] examined how the informational properties of brain oscillations changed after a 6-month course of mirtazapine. They found a marginal but non-significant decrease in LZC in anterior areas after treatment. However, they observed that this effect was moderated by age. Due to this reason, they analysed LZC reductions according to age and observed that younger participants showed a significant decrease in this nonlinear property, reaching similar levels as control participants.

Finally, the study by Arns, *et al.* [31] is worth noting, where the effect of an intervention delivering repetitive transcranial magnetic stimulation (rTMS) plus psychotherapy on the nonlinear properties of α-band oscillations was analysed. Transcranial stimulation was applied unilaterally in the dorsolateral prefrontal cortex. On average, participants underwent 21 sessions of rTMS and concomitant psychotherapy (no indications was given regarding the psychotherapy in the manuscript). Arns and colleagues conducted a responder analysis and found that intervention responders showed a decrease in LZC in frontal and occipital areas but no changes were shown regarding invariant properties (LLE levels).

Discussion

After discovering important dynamic, complex features in EEG brain oscillations, empirical research has increased substantially in the search for potential nonlinear markers of EEG

among psychiatric patients. In fact, psychiatric disorders can be understood as dynamic diseases. Recently, Hosenfeld, *et al.* [37] considered major depressive disorder to be a nonlinear dynamic system with a two-state pattern characterising its time course in many patients [38]. Many studies have been conducted with the aim of identifying the EEG profile of depressives in comparison to control participants, in addition to examining the effect of interventions to ameliorate depressive symptomatology [39,40]. However, the scattered pieces of evidence in this field needed to be collected together.

This review aimed to extract relevant conclusions from the findings of empirical comparative studies in the search for EEG nonlinear biomarkers of depressives (diagnostic studies). Moreover, its secondary aim was to study the effects of interventions to ameliorate depressive symptoms on EEG nonlinear properties. As a result, a sample of 12 empirical studies was reviewed as diagnostic studies, with nine being intervention studies.

Diagnostic Evidence

The findings across studies point to an increase in complexity in patients with depression. Moreover, the larger the decrease in complexity in EEG oscillations, the greater the symptom amelioration. This could well be the main conclusion derived from this up-to-date review. However, as it does appear to be at odds with the belief that diseased systems are less complex than healthy ones, some important issues and clarifications should be made.

Studies analysing broad band (up to 50Hz) EEG oscillations highlighted a pattern of higher complexity in depressives, in terms of informational measures and FD measures [25,27,30]. As an exception, it is noteworthy to mention the study by Acharya, *et al.* [24]. This found a pattern of higher complexity and less rhythmicity in healthy control participants when compared to depressives. This study examined EEG brain oscillations under resting conditions with open and closed eyes. It is known that different brain processes are detected when EEG recordings are conducted under open-eyes and closed-eyes resting conditions [41,42]. For this reason, the comparability of this study with the rest of those reviewed is quite limited since the recording conditions were from resting closed-eyes or from tasks eliciting emotional reactivity.

Results are less conclusive when the upper limit of the broad band is 70 Hz and the γ rhythm can be better recorded. Thus, studies by Ahmadlou, *et al.* [30] and Bachmann, *et al.* [23] showed contradictory findings in the FD properties of the frontal areas. We should state that these results were found when individuals were exposed to attention and emotion induction tasks.

Consequently, what is the meaning of the increased complexity that would characterise the EEG profile of depressive patients? As stated in a previous study [19], some deficits in inhibition control mechanisms may lead to a heightened neuronal firing and this excessive cortical excitability would explain the higher complexity. In this regard, a decrease in GABAergic activity, as well as the increased functional connectivity between cortical areas in depressives, would support this speculation [43-45]. This more variable, irregular profile of functioning may be related to areas involved in emotional processing, strongly linked to anterior insula and cingulate cortical activity [46,47]. Conversely, a more irregular functioning would not always relate to healthier functioning, especially when irregularity turns into randomness [38,48]. Unfortunately, extensively used measures like LZC do not distinguish complex systems from random, albeit simple, systems. Diagnostic studies so far do not allow conclusions in terms of randomness in brain oscillations to be extracted. As previously recommended [19], more sensitive measures under more clearly defined states (e.g., closed-eyes resting), such as DFA scaling exponents, should be taken into consideration in future research.

Traditional EEG frequency band analysis often constitutes a useful approach to contextualise brain correlates of depressive symptomatology [47,49]. In terms of nonlinear properties, diagnostic studies showed higher FD in δ, β, and γ oscillations of depressive participants. It is known that EEG δ oscillations, especially in frontal areas, are linked to autonomic regulation and reacting to motivationally salient stimuli [50]. Some symptoms, such as anhedonia or psychological pain, have been linked with increased δ activity in frontal and parietal areas. This activity would be associated with circuits stemming from the rostral anterior cingulate cortex [51,52]. Moreover, changes in physiological systems (e.g., cardiac system) in depressive participants [19,53] might also show a neural correlate in this activity. This speculation should be contrasted in future research.

A lower scaling exponent in θ rhythms in posterior brain areas was reported for depressive participants by Linkenkaer-Hansen, *et al.* [11]. A lower exponent would point to lower LRTC among depressive patients and support some evidence in favour of the existence of random-like patterns within brain dynamics. Neural θ tendency to randomness in posterior areas might be involved in the lower long-range phase synchronisation between anterior and posterior areas observed in depressives, as a marker of emotional processing [54-57].

The lack of a distinctive profile in α oscillation in depressives may point to a low sensitivity of NDS measures to detect depression-related changes in this rhythm, changes found with frequency-domain or cordance measures [4,45,58,59].

With regard to fast oscillation rhythms, studies highlighted a higher FD in both β and γ frequency bands for depressive participants [29,30]. These results point to more complexity in brain oscillations related to these frequency bands in frontal and parietal areas. For the β rhythms, this complexity seems approximate to LRTC in depressive participants as reported by Ahmadlou, *et al.* [30]. It has been suggested that increased β connectivity mediates a top-down control mechanism for emotional regulation [60-62]. Further research should be conducted to test the relationship between nonlinear measures and specific emotion regulation strategies [21]. Similar to β, γ oscillations, especially in frontal areas, have been associated with the processing of emotional stimuli, for instance in emotional face recognition tasks [54,55]. A higher FD for depressives in the γ frequency band was reported by Ahmadlou, *et al.* [30] and Akar, *et al.* [29]. Hence, nonlinear measures provide useful evidence that might be linked with the emotional processing biases of depressives. Further research should test hypotheses in this regard.

■ Intervention outcomes and practical implications

Results from studies aimed at ameliorating depressive symptomatology were in line with some findings from the diagnostic studies: complexity reductions in broad band brain oscillations point to symptomatology ameliorations or better response to treatment [34,36]. Studies were basically focused on electroconvulsive therapy and pharmacological interventions **(Table 2)**. Thus, a lower FD in EEG post-seizure in the first session of ECT predicted early response to treatment [34].

Moreover, a decreasing pre-/posttest pattern of informational complexity in responders to ECT was also reported [35,36].

Studies with pharmacotherapy also reported decreasing patterns of complexity as a marker of symptom amelioration. However, some important issues must be taken into consideration, such as the history of depressive episodes, as well as the age of patients [12,27]. Tricyclic antidepressants showed a decrease in complexity for first-episode depressive patients in an attention task [12,28]. An intervention with a selective norepinephrine and serotonin reuptake inhibitor (NSRI), mirtazapine, showed a decreasing complexity in anterior areas although only for younger participants [27]. NSRI treatment is recommended for depressive syndromes due to its lower toxicity effects [63-65]. Findings provided from nonlinear measures would endorse the use of these interventions due to the changes observed in symptom amelioration.

Finally, further research should be performed to gather some relevant conclusions. It would be very interesting to analyse the effects of psychological interventions on EEG oscillations in treatment responders. The role of nonlinear biomarkers for treatment response in several physiological systems has already been highlighted in other mental disorders, such as anxiety disorders [66-69] or bipolar disorders [70]. Many components of psychotherapy lead to symptomatology ameliorations and valuable findings could be gained by adding nonlinear measures in the study of EEG oscillations in depressive patients.

Conclusions and Future Suggestions

Due of its high temporal resolution, the EEG is ideally suited to the study of nonlinear dynamics of brain waves. Many different metrics have been used to quantify the complexity of those dynamics and the studies reviewed here addressed the question of whether EEG dynamics were more or less complex in

Table 2: Main findings derived from nonlinear dynamics of EEG brain oscillations (Intervention studies).

Intervention studies

Frequency bands	Bandwidth	Study	Type of treatment	Studied areas	Measure	Main findings
Broadband	No reported	Gangadhar et al., 1999	ECT	Frontal	Invariant (Katz FD)	No differences between intervention responders and no-responders in the post-seizure EEG FD. However, the post-seizure FD was the closest predictor of the intervention benefits
		Jagadisha et al., 2003	ECT	Frontal and temporal	Invariant (Katz FD)	Early intervention responders showed lower post-seizure EEG FD than late responders
		Motreja et al., 1998	ECT	Frontal	Invariant (Katz FD)	No between-group differences in the post-seizure EEG FD
		Thomasson and Pezard, 1999	ECT	All areas	Informational (Kolmogorov entropy)	A decreasing entropy from prettest to posttest (high correlations with symptomatology reductions)
	Up to 30 Hz	Nandrino et al., 1994	Pharmacotherapy	Frontal, central and parietal	Informational (correlation coefficient ρ)	First-episode depressives exhibited similar levels than controls after the intervention
		Pezard et al., 1996	Pharmacotherapy	Frontal, central and parietal	Informational (Information index S_0), invariant (Kolmogorov-Sinai entropy)	First-episode depressives exhibited similar levels than controls after the intervention
	Up to 40 Hz	Mendez et al., 2012	Pharmacotherapy	All areas	Informational (LZC)	Decreasing complexity in anterior areas only significant for younger participants
	Up to 120 Hz	Okazaki et al., 2013	ECT	All areas	Informational (MSE)	Lower MSE (especially in lower scale factors)
α	7-12 Hz	Arns et al., 2014	rTMS + PSY	Frontal and occipital	Informational (LZC)	Decreasing complexity after the intervention (changes LZC correlating negatively with symptomatology reductions)

Note.

ECT = Electroconvulsive therapy; PSY = Psychotherapy; rTMS = Repetitive transcranial magnetic stimulation.

Nonlinear measures: DFA = Detrended fluctuation analysis; FD = Fractal dimension; LZC = Lempel Ziv complexity index; MSE = Multiscale entropy;

depressive patients compared to healthy control participants. Nonetheless, this is a tricky issue since the word "complexity" does not have a single, unique meaning [19,71]. Specifically, many studies that used informational measures (e.g. entropy or LZC) reported increased complexity in depressive patients' EEGs, but one should be aware of the fact that random (and not necessarily complex) systems may show high values in that domain measure. Therefore, EEG dynamics for depressive patients appear more complex but may be more random than the dynamics of healthy non-depressed individuals. Studies on connectivity point in this direction. For instance, Fingelkurts, *et al.* [4] reported increased structural synchrony in EEGs of depressed outpatients and associated this finding with the complexity results reported by Pezard, Nandrino, and colleagues in studies that we have reviewed here **(Table 1)**. Somehow, increased connectedness (or functional connectivity, i.e. temporal correlation between spatially remote neurophysiological events) can be a sign of disorganisation that may be reflected in the increased EEG complexity/randomness reported in most of the studies reviewed here. In fact, one of the main goals of the research in this field in coming years should be to link studies on nonlinear features of brain oscillations with studies on brain functional connectivity.

Finally, future research should pay special attention to two topics. The first concerns frequency bands. We have seen that most studies focused on the so-called broad band whereas few studied fluctuations in traditional narrow bands. Interesting insight has been provided by both approaches to brain oscillations and they should continue, but agreement concerning the limits of each band is highly recommendable to increase comparability for reported findings. The second topic concerns brain areas. It is clear that researchers have moved beyond old localisationist theories and many findings (especially from broad band research) stress widespread complexity alterations, i.e. these alterations are rarely specific (e.g. parietal or temporal) and, on the contrary, changes in complexity have been found across wide cortical areas. Therefore, it seems to be the brain oscillation system as a whole that is affected in depression, rather than more specific brain areas or lobes. However, the role of slow waves or fast waves in different cortical regions deserves further research too.

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