Iran J Psychiatry 2023; 18: 4: 493-502

Review Article

Brain Complexity and Psychiatric Disorders

Ronald Miguel Hernández[1*], Jacqueline Cynthia Ponce-Meza[2], Miguel Ángel Saavedra-López[3], Walter Antonio Campos Ugaz[4], Roxana Monteza Chanduvi[5], Walter Campos Monteza[6]

Abstract

Objective: In recent years, researchers and neuroscientists have begun to use a variety of nonlinear techniques for analyzing neurophysiologic signals derived from fMRI, MEG, and EEG in order to describe the complex dynamical aspects of neural mechanisms. In this work, we first attempted to describe different algorithms to estimate neural complexity in a simple manner understandable for psychiatrists, psychologists, and neuroscientists. Then, we reviewed the findings of the brain complexity analysis in psychiatric disorders and their clinical implications.
Method: A non-systematic comprehensive literature search was conducted for original studies on the complexity analysis of neurophysiological signals such as electroencephalogram, magnetoencephalogram, and blood-oxygen-level-dependent obtained from functional magnetic resonance imaging or functional near infrared spectroscopy. The search encompassed online scientific databases such as PubMed and Google Scholar.
Results: Complexity measures mainly include entropy-based methods, the correlation dimension, fractal dimension, Lempel-Ziv complexity, and the Lyapunov exponent. There are important differences in the physical notions between these measures. Our literature review shows that dementia, autism, and adult ADHD exhibit less complexity in their neurophysiologic signals than healthy controls. However, children with ADHD, drug-naïve young schizophrenic patients with positive symptoms, and patients with mood disorders (i.e., depression and bipolar disorder) exhibit higher complexity in their neurophysiologic signals compared to healthy controls. In addition, contradictory findings still exist in some psychiatric disorders such as schizophrenia regarding brain complexity, which can be due to technical issues, large heterogeneity in psychiatric disorders, and interference of typical factors.
Conclusion: In summary, complexity analysis may present a new dimension to understanding psychiatric disorders. While complexity analysis is still far from having practical applications in routine clinical settings, complexity science can play an important role in comprehending the system dynamics of psychiatric disorders.

Key words: *Brain; Complexity Analysis; Neuropathology; Psychiatric Disorders*

1. Universidad Privada Norbert Wiener, Lima, Perú.
2. Universidad Privada del Norte, Lima, Perú.
3. Universidad Continental, Huancayo, Perú.
4. Universidad Nacional Pedro Ruiz Gallo, Lambayeque, Perú.
5. Universidad Católica Santo Toribio de Mogrovejo, Chiclayo, Perú.
6. Universidad de San Martin de Porres, Lima, Perú.

***Corresponding Author:**
Address: Mz B1, Lt 39, Urbanización Los Molinos, Carabayllo, Postal Code: 15121.
Tel: +51980561224, Email: ronald.hernandez@outlook.com.pe

Article Information:
Received Date: 2023/02/21, Revised Date: 2023/03/14, Accepted Date: 2023/03/16

Psychiatric disorders are typically considered complex conditions, not only for relatively difficult diagnosis issues that are related to the psychopathology of patients, but also for comprehensive integrated management of such patients that require psychological, biological, and social care due to the multidimensional nature of psychiatric illnesses (1, 2). However, some researchers suggest that the complexity of psychiatric disorders may be comprehended through investigating the dynamics of psychical functioning. Indeed, they applied the principles of physics and physical models to explain the relationship between psychical energy and the human mind (3). Although such an approach to mental illnesses appears attractive and interesting, lack of strict analysis techniques made the processes of psychodynamics understanding vague and ambiguous (4). Over time, research on brain functioning had become an appealing interdisciplinary field with no longer any restrictions to neuroscience, neurology, and psychiatry. Various relevant principles from physics and mathematics with the aid of computer science are growingly employed to study the human brain and, subsequently, the abnormalities and neuropathologies related to the mental illnesses (5, 6). In fact, computational psychiatry and computational neuroscience approaches utilize these nonmedical concepts to explore the complex behaviors and symptoms in patients with different psychological conditions (7, 8). Nonlinear analysis and the concept of complexity is one of these important disciplines that has been used in the last few decades to inform us about complex pathological mechanisms in brain functioning resulting from various psychiatric conditions (9). The dynamical time-dependent nature of psychiatric disorders, such as autism, schizophrenia, depression, and bipolar disorder, which are characterized by pathological variations of neurotransmitter levels and lead to chaotic and unpredictable patterns of neural activities, support this idea that complexity science and nonlinear dynamics analysis of the brain function can provide more insights into complex behavioral manifestations in psychiatric patients (10).

The approaches based on this complexity concept have provided potentials in quantifying the behavioral symptoms or disease course of different mental illnesses (11). For instance, patients with schizophrenia have been shown to have more regular behaviors with less complexity compared to healthy individuals in a cognitive task (12). Patients with bipolar disorder have more predictable patterns compared to healthy individuals in a daily record of mood (3). Given the highly complex nature of the human brain, this informative concept has been widely utilized for the analysis of neurophysiological signals such as BOLD, MEG, and EEG. The nonlinear and chaotic nature of such biological signals supports the use of complexity analysis to quantify important hidden patterns of neural activity (13). Traditionally, both time and frequency analyses of neurophysiological data have been used to infer the function of the neurons and identify their pathologic conditions (14, 15). However, the knowledge derived from such methods is limited, because we deal with a huge network of millions of neurons, axons, and synapses that are linked in a hierarchical and highly organized manner by nonlinear dynamic processes. Thus, in recent years, researchers and neuroscientists have begun to use a variety of nonlinear techniques for analyzing neurophysiologic signals derived from fMRI, MEG, and EEG in order to describe the complex dynamical aspects of neural mechanisms. Researches in various fields of science have indicated that nonlinear methods can more accurately model complex systems (16). Since 1985, when Rapp *et al.* (17) and Babloyantz *et al.* (18) first applied chaos theories to analyze EEG data, several nonlinear analytic methods were introduced and considerable advances were made in the field of biological signal processing with the advancement of mathematical and computer science (19). In this work, we first attempted to describe different algorithms used to estimate neural complexity in a simple manner understandable for psychiatrists, psychologists, and neuroscientists. Then, we reviewed the findings on brain complexity analysis in psychiatric disorders and their clinical implications.

Complexity measures

Over the years, different complexity measures have been introduced and utilized to investigate psychiatric disorders based on various neurobiological data, as depicted in Table 1. These measures include entropy-based methods, the correlation dimension, fractal dimension, Lempel-Ziv complexity, and the Lyapunov exponent. It is important to note that there are notable differences in the physical notions among these measures. For instance, the Lyapunov exponent and correlation dimension are formulated based on chaos theory, whereas Lempel-Ziv measure is an algorithmic complexity that operates based on symbolizing the oscillations of a time series (20). Each measure has its own important prerequisites and considerations that should be taken into account during analysis and interpretation to avoid incorrect observations and interpretations. Generally, complexity estimators can be categorized into indices of regularity and predictability. Estimators of predictability measure the temporal (e.g., fractal dimension and detrended fluctuation analysis) or spatial (e.g., correlation dimension and Lyapunov exponent) dimensionality of a dynamical system, whereas estimators of regularity measure the complexity of the output of a dynamical system on single- (e.g., approximate/sample/fuzzy entropy and Lempel-Ziv complexity) or multi-scales (e.g., multiscale entropy). In the following sections of this paper, we reviewed various findings of original studies on the complexity analysis of neurobiological signals in psychiatric disorders.

Table 1. Brief Description and Main Consideration of Some Important Complexity Measures Applied to Neurophysiological Signals

Complexity measure	Brief description	Main consideration
Lyapunov exponent	The Lyapunov exponent (LE) examines the dynamic aspects of the trajectory and describes the chaotic nature of a system. LEs calculate the mean exponential convergence (negative exponents) or divergence (positive exponents) of trajectories of the attractor starting at adjacent initial conditions in the phase space. In fact, LE measures the changes in the final data with respect to changes in initial conditions and, naturally, it is a function of time; and as a result, it indicates the sensitive dependence on initial conditions.	It requires a large quantity of data and stationary and noise free time series.
Correlation dimension	Correlation dimension as a widely utilized measure is the complexity or the degrees of freedom to explain the dynamics by determining the distribution of points in the phase space.	It requires a large quantity of data and stationary and noise free time series.
Fractal dimension	Fractal dimension is a statistical indicator of complexity based on details in the pattern changes with the scale to quantify the self-similarity of time series.	It is sensitive to the noise level, amplitude and density of the sampled oscillations.
Lempel-Ziv complexity	Lempel-Ziv is an algorithmic complexity that works based on symbolizing the oscillations of a time series. It enumerates the number of separate substrings and their recurrence rate along a finite time series.	It is sensitive to the bandwidth of the time series spectrum and the probability density function of the time series.
Approximate entropy	Approximate entropy is an information theory-based algorithm for quantifying the amount of randomness in a time series by measuring the logarithmic probability of patterns runs that are close for adjacent observations that stay close on subsequent comparisons.	It depends on the data length and uniformly and provides underestimations for short-length data. It also lacks relative consistency.
Sample entropy	Sample entropy is the modified version of approximate entropy to assess the complexity of biological signals that works based on the negative natural logarithm of the conditional probability of the sequences of data vectors.	It provides more regularity than the real value due to its formulation. It is sensitive to its parameters and also noise level.
Multiscale entropy	Multiscale entropy is an information theory-based algorithm for quantifying the amount of randomness in a time series at several temporal scales through a coarse-graining method. Randomness at every temporal scale is estimated using sample entropy.	It is sensitive to its parameters and also noise level.

Dementia

Given the high prevalence of dementia and its high cost and burden for the healthcare system and society, effective prevention approaches, such as the early reliable identification of its biomarkers, are paramount to address this critical health issue (21). Late-onset Alzheimer's disease (AD) is responsible for most cases of dementia which impacts memory as well as cognitive and executive functions seriously, and thus a great portion of the literature in the field of nonlinear complexity analyses is devoted to AD (22). EEG, MEG, and BOLD (captured from fMRI or fNIRS) signals recorded from AD patients in resting-state and task-related conditions have been extensively subjected to the complexity analysis through various complexity measures such as entropy algorithms, Lempel-Ziv complexity, and fractal dimension (21, 23-34). In general, these studies demonstrated that the neurophysiological signals from AD patients exhibit more predictable oscillations and less complexity compared to healthy individuals, mostly in the right frontal, temporal, occipital, and left parietal regions. This finding is relatively consistent among studies, which derived from the complexity of different frequencies and temporal scales. This important observation may indicate the presence of distinct dynamical systems in the brain affected by AD, supporting the disconnection syndrome hypothesis underpinning the neuropathology of AD and

providing further insights into abnormal neural connectivity in this disease (35). In addition to AD, other types of dementia have also been investigated in terms of brain complexity. For example, Nicastro *et al*. showed that patients with frontotemporal dementia had a reduced MRI complexity in the cingulate regions, insula, paracentral gyrus, and orbitofrontal cortex compared to healthy peers. Moreover, this reduced complexity was correlated with cognitive function impairments, especially language and memory impairments, in patients with frontotemporal dementia (21).

Autism

Autism is a neurobiological developmental illness characterized by serious social problems, language and cognitive dysfunctions, atypical motor and sensory functioning, and repetitive behaviors (36). Abnormal neural connectivity (both structural and functional) is the main neuropathological mechanism that is associated with autism symptoms (37). Over the past two decades, several studies have utilized complexity measures, especially multiscale entropy, to better understand the neuropathological mechanisms underlying autism, mostly using EEG signals (38-42). These studies almost consistently suggest that autistic brains exhibit reduced complexity compared to normal brains in the occipital and temporo-parietal areas across all ages. There is an accumulating consensus suggesting that this reduced complexity is associated with aberrant neural connectivity in autism. For instance, Ghanbari *et al*. found that increased functional connectivity was significantly correlated with decreased complexity in children with autism, probably due to inhibitory dysregulation in their cortical circuits (40). Furthermore, it has been shown that the amount of complexity reduction is associated with the severity of autistic symptoms, such that severe autistic patients manifest significantly greater reduction in complexity than autistic patients with mild symptoms (41). Remarkably, Kang *et al.* demonstrated that a 10-session anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex can significantly shift the brain electrical activity of autistic patients to randomness and increase EEG complexity towards normal patterns (43).

Schizophrenia

Schizophrenia is a severe mental illness with a broad variety of clinical symptoms, such as paranoia, delusion, and hallucination, as well as cognitive impairments. Schizophrenia has been conceptualized as a disconnection syndrome from a computational and theoretical perspective with disruptions in several constraint organizations within and between neurological subsystems in the brain (44). Indeed, growing evidence suggests the presence of functional and structural abnormal neural connectivity among patients with schizophrenia (45). Complexity measures have been widely employed in schizophrenia research to elucidate the neuropathological mechanisms involved in this illness (46-58). Compared to dementia and autism, previous studies inconsistently reported decreased or increased complexity during rest, sleep, or cognitive functioning in schizophrenia. These contradictory reports can be attributed to several important factors. Firstly, previous studies showed that the neurophysiologic recording protocol (i.e., in resting-state condition or during cognitive tasks) affects complexity patterns. For instance, Kirsch *et al.* found no difference between patients with schizophrenia and healthy controls in terms of EEG complexity in resting-state; however, different complexity behaviors were observed between patients and controls during cognitive tasks (55). Secondly, the condition and course of the disease may affect brain complexity patterns. For instance, schizophrenic patients with positive symptoms showed different EEG complexity patterns compared to those with negative symptoms (54). Lastly, medication and age have been shown to be important factors affecting brain complexity patterns in schizophrenia. Younger patients with schizophrenia showed increased complexity compared to older counterparts (12). Moreover, it has been shown that increased EEG complexity in patients with schizophrenia shifts toward more predictable patterns comparable to healthy subjects after treatment with antipsychotics (47). In general, it appears that drug-naïve, young patients with positive symptoms (highly symptomatic) tend to show aberrantly increased complexity compared to their healthy peers. A recent computational study suggested that an imbalance in the ratio of excitation to inhibition in cortical neuronal populations is a possible cause of this abnormally greater brain complexity in schizophrenia (59). However, further studies are required to systematically investigate multiple complexity measures using different neuroimaging modalities to provide more conclusive and consistent results and clarify the neuropathological processes underlying schizophrenia.

Depression and bipolar disorder

After early efforts to investigate the relationship between depressive disorders and brain fluctuations, which led to important theories such as frontal EEG asymmetry (60), the use of complexity measures for diagnosing depression and assessing its brain abnormalities, as well as evaluating treatment progress, has expanded over the last two decades. Few studies have used neuroimaging modalities to examine the complexity of different brain regions in depression (61), and most studies have used EEG and MEG data (49, 62-67). Entropy-based measures and fractal dimension are the most common complexity measures employed in these studies. Such studies consistently suggest that brain complexity is increased in depressive disorders, especially in the frontal region, probably due to impairments in the mechanisms of cortical inhibition control. Furthermore, they reported that the complexity of neurophysiologic signals recorded from patients with depressive disorders shifts toward a normal range after different treatments such as psychopharmacology and electroconvulsive therapy. In fact, the greater the reduction in complexity (i.e., the more

the pattern of brain activity complexity resembles the normal pattern), the greater the reduction in depressive symptoms (63, 66, 68). In addition, very few studies have investigated the brain complexity of bipolar disorder as an affective illness with distinct underlying neuropathological mechanisms, such as impaired gray matter volume and deficits in the frontal cortex (69). The results of these studies almost consistently indicate that the brain complexity of patients with bipolar disorder is increased in the middle temporal gyrus and middle frontal gyrus. Notably, this abnormal complexity pattern in brain activity has been shown to be associated with the clinical symptoms and cognitive functions of bipolar disorder (70-72).

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric conditions in children and adolescents, affecting 4-10% of the pediatric population worldwide (73). Thus, the majority of studies investigating brain complexity in ADHD have been conducted on pediatric populations. Many electrophysiological and neuroimaging studies have been conducted on ADHD and linked different neuropathological mechanisms to the core symptoms of the disorder, such as inattention and impulsivity (74, 75). Some of these neuropathological mechanisms were later used as criteria for the diagnosis of ADHD as well as in neuropsychological treatments such as neurofeedback. The most famous of these measures is the theta-to-beta ratio, which has been extensively studied in ADHD (76). Additionally, fronto-striatal impairment has emerged as a definitive pathophysiological characteristic in ADHD (77). However, few studies have attempted to investigate brain complexity through nonlinear dynamic analysis in ADHD. Interestingly, this limited number of studies yielded remarkable findings regarding patterns of brain complexity in ADHD using EEG, MEG, fMRI, and fNIRS modalities. All studies involving ADHD children consistently reported increased brain complexity, particularly in the right frontal lobe, compared to normal children (5, 19, 78, 79). Meanwhile, Sohn *et al.* in their study of adolescents with ADHD showed reduced complexity in the right frontal region during a cognitive task, but not at rest, compared to healthy adolescents (80). In contrast, all studies focusing on adults with ADHD showed reduced brain complexity in frontal and occipital regions compared to healthy peers (81, 82). In summary, it seems that the disturbance in the complexity pattern of brain activity in ADHD is affected by age, changing from lower complexity values in childhood to higher complexity values in adulthood (Figure 1). However, further research is needed to prove such a finding in different conditions.

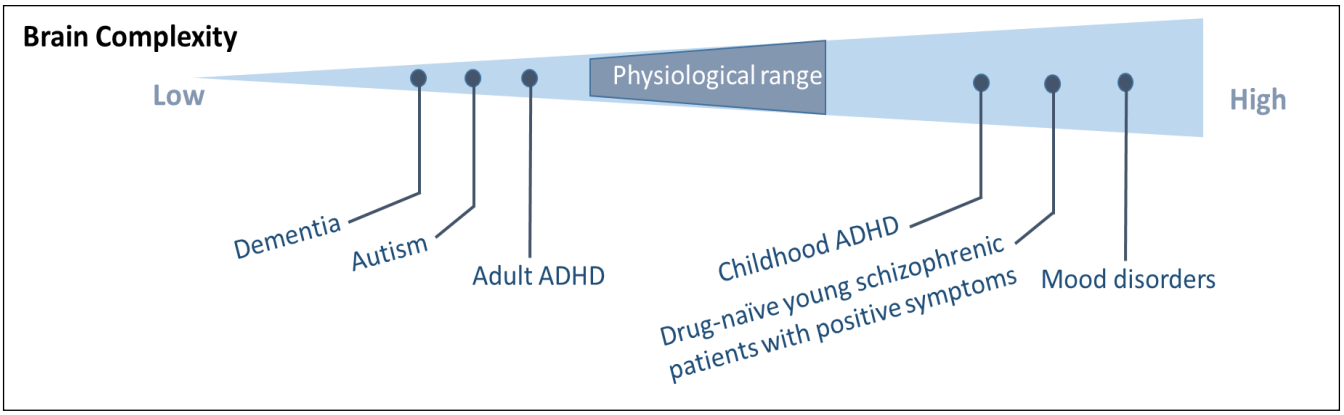

Figure 1. Overview of Changes in Brain Complexity with Psychiatric Disorders

Other psychiatric disorders

Other psychiatric disorders have also been investigated through complexity measures, mainly using EEG signals, including obsessive compulsive disorder (OCD) (83-86), dissociate disorder (87), social anxiety disorder (88), panic disorder (89), anorexia nervosa (90), and post-traumatic stress disorder (PTSD) (91). In general, all these studies report lower brain complexity in patients compared to healthy peers. Furthermore, some of these studies have found a significant relationship between this impaired complexity pattern and core symptoms of the respective disorders, suggesting that the reduced brain complexity may be associated with deficits in neural integration in these psychiatric illnesses. For instance, Aydin *et al.* found reduced EEG complexity in the prefrontal and right fronto-temporal regions in patients with OCD. They concluded that these abnormal complexity patterns in OCD are similar to those neuroimaging studies that categorize OCD as a subgroup of anxiety disorders (86). However, it should be noted that complexity studies focusing on these psychiatric disorders are so rare, and more research is needed to confirm these findings and make a definitive conclusion.

Discussion

The human cerebral cortex is a highly organized complex system characterized by its tremendous dynamical neural communications and connectivity across functionally

specialized areas, which underlies various functions such as perception, language, learning, action, and cognition (92). Many efforts have been made to understand this complex neural network and its impairments employing complexity analysis in different conditions, especially mental illnesses. In this review, we aimed to present a general picture of the patterns of brain complexity in psychiatric disorders. However, it should be noted that the interpretation of changes in complexity measures must be done with extreme caution. This is because healthy mental function is naturally complex and can be influenced by different health conditions such as sleep, resting state, and cognitive/executive functions (9). Meanwhile, it is worth noting that both extremely random (irrational or impulsive behaviors) or ordered (stereotyped or repetitive behaviors) patterns are not desirable. Observed psychopathology in daily practices follow a pattern of randomness and order. Indeed, healthy mental functions are complex in a normal physiological range and may deteriorate into two different pathological paths: randomness and order. From a macroscopic perspective, children with ADHD usually show impulsive behavior that has a sense of randomness, while autistic patients exhibit repetitive behaviors that have a sense of order. Comparable implications can be expanded to thought, cognition, speech, emotion, and symptomatic behaviors such as apathy, delusion, and irrational behavior. The main question is whether these macroscopic psychopathologies can be linked to microscopic phenomena such as neural connectivity. From a systems view, complexity refers to the ability of a system to adapt to the continuously altering environment (93). Such adaptation is generally affected by psychiatric disorders, generating either random or ordered behavioral patterns. Considering the brain as the organ of the mind, the adaptability of mental functions should result from the underpinning neuroplasticity (94), which may be reasonably quantified through complexity measures at the microscopic level. However, lots of effort is needed to determine the associations between microscopic alterations in the neural dynamics within the brain and macroscopic behaviors.

Over the last two decades, multiple analytical approaches have been utilized to estimate brain complexity in psychiatric disorders using neurophysiologic signals. Such approaches have been employed to understand the underlying neuropathological mechanisms of mental disorders, as well as diagnose and evaluate patients during the treatment process (95). However, the results of complexity patterns have remained relatively inconsistent in some disorders (e.g., schizophrenia and ADHD) due to a number of factors including (i) technical issues, (ii) large heterogeneity in psychiatric disorders, and (iii) interference of typical factors. First, it should be recognized that any measure of complexity based on its physical principles may contain information that is not necessarily comparable to another measure. For example, entropy-based measures are based on information theory, randomness, and system regularity, whereas the Lyapunov exponent and correlation dimension are based on the physical concepts of chaos (96). Furthermore, as mentioned in Table 1, each complexity measure has its own technical considerations for obtaining reliable results, including data length, noise level, artifacts, and algorithm parameterization. Second, most psychiatric illnesses are heterogeneous in their neuropathological mechanisms and clinical symptoms. As an example, the neuropathological backgrounds associated with positive symptoms and negative symptoms in schizophrenia are quite different (44). Finally, the pattern of complexity in normal aging and development should be considered when investigating neuropathology. Previous studies have reported that brain complexity increases from childhood to adulthood and afterwards decreases from adulthood to senility (9, 10).

Challenges and future direction

We must keep in mind that our goal of complexity analysis is to gain knowledge of the system (the brain) by observing its output signals, such as EEG, MEG, etc. However, this approach has its own limitations and relies on many assumptions about the system that may not be true. For example, different assumptions lead to different values of complexity, hence it is crucial to avoid generalizing the terminology of a specific measure. For example, some studies assume that randomness makes a system more complex. However, consider a simple white noise generator which is fully random and has a high degree of entropy (in all definitions of entropy) without being an example of a complex system. Moreover, certain studies assume that a periodic system is not complex, while we can find many complex systems with periodic behaviors, such as the Vander-Pole oscillator, Lorentz system, etc. To summarize, we must first provide a precise definition of complexity and what we want to measure. With this in mind, researchers may use the terms randomness, predictability, and complexity with more care and caution. As mentioned previously, factors such as data length and noise level are crucial in selecting a complexity measure. For example, accurate values of complexity with Lyapunov exponent and correlation dimension can be difficult to obtain due to their basic assumptions of long time series and high signal-to-noise ratio, as these assumptions may not be realistic in clinical settings. Conversely, Lempel-Ziv complexity may be a more robust measure for noisy short time series. In addition, while entropy-based measures such as approximate entropy and sample entropy are the most widely used methods, they actually represent irregularity statistics rather than the complexity of a system. Moreover, approximate entropy and sample entropy are sensitive to their computational parameters (96). Therefore, it is recommended to use fuzzy-based entropy measures, which utilize a fuzzy function instead of a single value of parameter. Furthermore, one of the issues that may be discussed in the article is hyper-parameters. Most comparative methods for complexity estimation

have some hyper-parameters that can significantly change the results. For example, estimating the embedding dimension in the Lyapunov exponent and correlation dimension is a challenging task that is easily neglected in most psychiatric studies.

Limitation

Due to the vastness of the subject under discussion, it was not possible to carry out a systematic review. However, the authors tried to retrieve and review most of the studies in this field using a comprehensive search and their experience in this field. Moreover, there were limitations in some of the original studies, such as not meeting basic assumptions for measures of complexity, which are discussed in this article.

Conclusion

The lack of biomarkers in psychiatry has always made it a second-class field in medicine. Despite many attempts, the causes of most mental illnesses remain unknown, and even the precise classification of such disorders has been challenging. Complexity analysis may present a new dimension to understanding psychiatric disorders. While complexity analysis is still far from having practical applications in routine clinical settings, complexity science can play an essential role in comprehending the system dynamics of psychiatric disorders.

Acknowledgment

The authors thank the institutions where they work for encouraging the development of research.

Conflict of Interest

None.

References

1. Marín O. Developmental timing and critical windows for the treatment of psychiatric disorders. Nat Med. 2016;22(11):1229-38.
2. Mohammadi MR, Ahmadi N, Khaleghi A, Mostafavi SA, Kamali K, Rahgozar M, et al. Prevalence and Correlates of Psychiatric Disorders in a National Survey of Iranian Children and Adolescents. Iran J Psychiatry. 2019;14(1):1-15.
3. Yang AC, Tsai SJ. Is mental illness complex? From behavior to brain. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:253-7.
4. Leichsenring F. Are psychodynamic and psychoanalytic therapies effective?: A review of empirical data. Int J Psychoanal. 2005;86(Pt 3):841-68.
5. Mohammadi MR, Khaleghi A, Nasrabadi AM, Rafieivand S, Begol M, Zarafshan H. EEG classification of ADHD and normal children using non-linear features and neural network. Biomedical Engineering Letters. 2016;6:66-73.
6. Khaleghi A, Zarafshan H, Mohammadi MR. Visual and auditory steady-state responses in attention-deficit/hyperactivity disorder. Eur Arch Psychiatry Clin Neurosci. 2019;269(6):645-55.
7. Khaleghi A, Mohammadi MR, Shahi K, Nasrabadi AM. Computational Neuroscience Approach to Psychiatry: A Review on Theory-driven Approaches. Clin Psychopharmacol Neurosci. 2022;20(1):26-36.
8. Xiao W, Manyi G, Khaleghi A. Deficits in auditory and visual steady-state responses in adolescents with bipolar disorder. J Psychiatr Res. 2022;151:368-76.
9. Lau ZJ, Pham T, Chen SHA, Makowski D. Brain entropy, fractal dimensions and predictability: A review of complexity measures for EEG in healthy and neuropsychiatric populations. Eur J Neurosci. 2022;56(7):5047-69.
10. Fernández A, Andreina MM, Hornero R, Ortiz T, López-Ibor JJ. [Analysis of brain complexity and mental disorders]. Actas Esp Psiquiatr. 2010;38(4):229-38.
11. Paulus MP, Braff DL. Chaos and schizophrenia: does the method fit the madness? Biol Psychiatry. 2003;53(1):3-11.
12. Fernández A, Gómez C, Hornero R, López-Ibor JJ. Complexity and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:267-76.
13. Khaleghi A, Birgani PM, Fooladi MF, Mohammadi MR. Applicable features of electroencephalogram for ADHD diagnosis. Research on Biomedical Engineering. 2020;36:1-11.
14. Khaleghi A, Mohammadi MR, Moeini M, Zarafshan H, Fadaei Fooladi M. Abnormalities of Alpha Activity in Frontocentral Region of the Brain as a Biomarker to Diagnose Adolescents With Bipolar Disorder. Clin EEG Neurosci. 2019;50(5):311-8.
15. Moeini M, Khaleghi A, Mohammadi MR. Characteristics of Alpha Band Frequency in Adolescents with Bipolar II Disorder: A Resting-State QEEG Study. Iran J Psychiatry. 2015;10(1):8-12.
16. Maksimenko VA, Pavlov A, Runnova AE, Nedaivozov V, Grubov V, Koronovslii A, et al. Nonlinear analysis of brain activity, associated with motor action and motor imaginary in untrained subjects. Nonlinear Dynamics. 2018;91:2803-17.
17. Rapp P, Zimmerman I, Albano A, Deguzman G, Greenbaun N. Dynamics of spontaneous neural activity in the simian motor cortex: The dimension of chaotic neurons. Physics Letters A. 1985;110(6):335-8.
18. Babloyantz A, Salazar J, Nicolis C. Evidence of chaotic dynamics of brain activity during the sleep cycle. Physics letters A. 1985;111(3):152-6.
19. Zarafshan H, Khaleghi A, Mohammadi MR, Moeini M, Malmir N. Electroencephalogram complexity analysis in children with attention-

deficit/hyperactivity disorder during a visual cognitive task. J Clin Exp Neuropsychol. 2016;38(3):361-9.
20. Breakspear M. Dynamic models of large-scale brain activity. Nat Neurosci. 2017;20(3):340-52.
21. Nicastro N, Malpetti M, Cope TE, Bevan-Jones WR, Mak E, Passamonti L, et al. Cortical Complexity Analyses and Their Cognitive Correlate in Alzheimer's Disease and Frontotemporal Dementia. J Alzheimers Dis. 2020;76(1):331-40.
22. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002;16(4):203-12.
23. Wang B, Niu Y, Miao L, Cao R, Yan P, Guo H, et al. Decreased Complexity in Alzheimer's Disease: Resting-State fMRI Evidence of Brain Entropy Mapping. Front Aging Neurosci. 2017;9:378.
24. Perpetuini D, Chiarelli AM, Cardone D, Filippini C, Bucco R, Zito M, et al. Complexity of Frontal Cortex fNIRS Can Support Alzheimer Disease Diagnosis in Memory and Visuo-Spatial Tests. Entropy (Basel). 2019;21(1):26.
25. Perpetuini D, Chiarelli AM, Filippini C, Cardone D, Croce P, Rotunno L, et al. Working Memory Decline in Alzheimer's Disease Is Detected by Complexity Analysis of Multimodal EEG-fNIRS. Entropy (Basel). 2020;22(12):1380.
26. Perpetuini D, Bucco R, Zito M, Merla A. Study of memory deficit in Alzheimer's disease by means of complexity analysis of fNIRS signal. Neurophotonics. 2018;5(1):011010.
27. Sun J, Wang B, Niu Y, Tan Y, Fan C, Zhang N, et al. Complexity Analysis of EEG, MEG, and fMRI in Mild Cognitive Impairment and Alzheimer's Disease: A Review. Entropy (Basel). 2020;22(2):239.
28. van Cappellen van Walsum AM, Pijnenburg YA, Berendse HW, van Dijk BW, Knol DL, Scheltens P, et al. A neural complexity measure applied to MEG data in Alzheimer's disease. Clin Neurophysiol. 2003;114(6):1034-40.
29. Yoshimura M, Isotani T, Yagyu T, Irisawa S, Yoshida T, Sugiyama M, et al. Global approach to multichannel electroencephalogram analysis for diagnosis and clinical evaluation in mild Alzheimer's disease. Neuropsychobiology. 2004;49(3):163-6.
30. Escudero J, Abásolo D, Hornero R, Espino P, López M. Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy. Physiol Meas. 2006;27(11):1091-106.
31. Park J-H, Kim S, Kim C-H, Cichocki A, Kim K. Multiscale entropy analysis of EEG from patients under different pathological conditions. Fractals. 2007;15(04):399-404.
32. Czigler B, Csikós D, Hidasi Z, Anna Gaál Z, Csibri E, Kiss E, et al. Quantitative EEG in early Alzheimer's disease patients - power spectrum and complexity features. Int J Psychophysiol. 2008;68(1):75-80.
33. Jelles B, Scheltens P, van der Flier WM, Jonkman EJ, da Silva FH, Stam CJ. Global dynamical analysis of the EEG in Alzheimer's disease: frequency-specific changes of functional interactions. Clin Neurophysiol. 2008;119(4):837-41.
34. Mizuno T, Takahashi T, Cho RY, Kikuchi M, Murata T, Takahashi K, et al. Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy. Clin Neurophysiol. 2010;121(9):1438-46.
35. Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? Neuropsychol Rev. 2003;13(2):79-92.
36. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. Nat Rev Dis Primers. 2020;6(1):5.
37. Ecker C, Schmeisser MJ, Loth E, Murphy DG. Neuroanatomy and Neuropathology of Autism Spectrum Disorder in Humans. Adv Anat Embryol Cell Biol. 2017;224:27-48.
38. Bosl W, Tierney A, Tager-Flusberg H, Nelson C. EEG complexity as a biomarker for autism spectrum disorder risk. BMC Med. 2011;9:18.
39. Catarino A, Churches O, Baron-Cohen S, Andrade A, Ring H. Atypical EEG complexity in autism spectrum conditions: a multiscale entropy analysis. Clin Neurophysiol. 2011;122(12):2375-83.
40. Ghanbari Y, Bloy L, Christopher Edgar J, Blaskey L, Verma R, Roberts TP. Joint analysis of band-specific functional connectivity and signal complexity in autism. J Autism Dev Disord. 2015;45(2):444-60.
41. Hadoush H, Alafeef M, Abdulhay E. Brain Complexity in Children with Mild and Severe Autism Spectrum Disorders: Analysis of Multiscale Entropy in EEG. Brain Topogr. 2019;32(5):914-21.
42. Liu T, Chen Y, Chen D, Li C, Qiu Y, Wang J. Altered electroencephalogram complexity in autistic children shown by the multiscale entropy approach. Neuroreport. 2017;28(3):169-73.
43. Kang J, Cai E, Han J, Tong Z, Li X, Sokhadze EM, et al. Transcranial Direct Current Stimulation (tDCS) Can Modulate EEG Complexity of Children With Autism Spectrum Disorder. Front Neurosci. 2018;12:201.
44. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. JAMA Psychiatry. 2020;77(2):201-10.
45. Harrison PJ, Lewis DA, Kleinman JE. Neuropathology of schizophrenia. Schizophr. 2010:372-92.
46. Lee SH, Choo JS, Im WY, Chae JH. Nonlinear analysis of electroencephalogram in schizophrenia patients with persistent auditory hallucination. Psychiatry Investig. 2008;5(2):115-20.
47. Takahashi T, Cho RY, Mizuno T, Kikuchi M, Murata T, Takahashi K, et al. Antipsychotics reverse abnormal EEG complexity in drug-naive

schizophrenia: a multiscale entropy analysis. Neuroimage. 2010;51(1):173-82.
48. Kikuchi M, Hashimoto T, Nagasawa T, Hirosawa T, Minabe Y, Yoshimura M, et al. Frontal areas contribute to reduced global coordination of resting-state gamma activities in drug-naïve patients with schizophrenia. Schizophr Res. 2011;130(1-3):187-94.
49. Li Y, Tong S, Liu D, Gai Y, Wang X, Wang J, et al. Abnormal EEG complexity in patients with schizophrenia and depression. Clin Neurophysiol. 2008;119(6):1232-41.
50. Fernández A, López-Ibor MI, Turrero A, Santos JM, Morón MD, Hornero R, et al. Lempel-Ziv complexity in schizophrenia: a MEG study. Clin Neurophysiol. 2011;122(11):2227-35.
51. Fernández A, Ríos-Lago M, Abásolo D, Hornero R, Alvarez-Linera J, Paul N, et al. The correlation between white-matter microstructure and the complexity of spontaneous brain activity: a difussion tensor imaging-MEG study. Neuroimage. 2011;57(4):1300-7.
52. Irisawa S, Isotani T, Yagyu T, Morita S, Nishida K, Yamada K, et al. Increased omega complexity and decreased microstate duration in nonmedicated schizophrenic patients. Neuropsychobiology. 2006;54(2):134-9.
53. Sabeti M, Katebi S, Boostani R. Entropy and complexity measures for EEG signal classification of schizophrenic and control participants. Artif Intell Med. 2009;47(3):263-74.
54. Raghavendra BS, Dutt DN, Halahalli HN, John JP. Complexity analysis of EEG in patients with schizophrenia using fractal dimension. Physiol Meas. 2009;30(8):795-808.
55. Kirsch P, Besthorn C, Klein S, Rindfleisch J, Olbrich R. The dimensional complexity of the EEG during cognitive tasks reflects the impaired information processing in schizophrenic patients. Int J Psychophysiol. 2000;36(3):237-46.
56. Kotini A, Anninos P. Detection of non-linearity in schizophrenic patients using magnetoencephalography. Brain Topogr. 2002;15(2):107-13.
57. Jin SH, Na SH, Kim SY, Ham BJ, Lee DH, Lee JH, et al. Hemispheric laterality and dimensional complexity in schizophrenia under sound and light stimulation. Int J Psychophysiol. 2003;49(1):1-15.
58. Na SH, Jin SH, Kim SY, Ham BJ. EEG in schizophrenic patients: mutual information analysis. Clin Neurophysiol. 2002;113(12):1954-60.
59. Khaleghi A, Mohammadi MR, Shahi K, Motie Nasrabadi A. Possible Neuropathological Mechanisms Underlying the Increased Complexity of Brain Electrical Activity in Schizophrenia: A Computational Study. Iran J Psychiatry. 2023; 18(2):127-133.
60. Allen JJ, Reznik SJ. Frontal EEG Asymmetry as a Promising Marker of Depression Vulnerability: Summary and Methodological Considerations. Curr Opin Psychol. 2015;4:93-7.
61. Pei-Shan H, Chemin L, Guan-Yen C, Ho-Ling L, Chih-Mao H, Tatia Mei-Chun L, et al. Complexity analysis of resting state fMRI signals in depressive patients. Annu Int Conf IEEE Eng Med Biol Soc. 2017;2017:3190-3.
62. Thomasson N, Pezard L, Allilaire J-F, Renault B, Martinerie J. Nonlinear EEG changes associated with clinical improvement in depressed patients. Nonlinear Dynamics Psychol Life Sci. 2000;4:203-18.
63. Méndez MA, Zuluaga P, Hornero R, Gómez C, Escudero J, Rodríguez-Palancas A, et al. Complexity analysis of spontaneous brain activity: effects of depression and antidepressant treatment. J Psychopharmacol. 2012;26(5):636-43.
64. Akdemir Akar S, Kara S, Agambayev S, Bilgiç V. Nonlinear analysis of EEGs of patients with major depression during different emotional states. Comput Biol Med. 2015;67:49-60.
65. Akar SA, Kara S, Agambayev S, Bilgic V. Nonlinear analysis of EEG in major depression with fractal dimensions. Annu Int Conf IEEE Eng Med Biol Soc. 2015;2015:7410-3.
66. Arns M, Cerquera A, Gutiérrez RM, Hasselman F, Freund JA. Non-linear EEG analyses predict non-response to rTMS treatment in major depressive disorder. Clin Neurophysiol. 2014;125(7):1392-9.
67. Ahmadlou M, Adeli H, Adeli A. Fractality analysis of frontal brain in major depressive disorder. Int J Psychophysiol. 2012;85(2):206-11.
68. Okazaki R, Takahashi T, Ueno K, Takahashi K, Higashima M, Wada Y. Effects of electroconvulsive therapy on neural complexity in patients with depression: report of three cases. J Affect Disord. 2013;150(2):389-92.
69. Khaleghi A, Sheikhani A, Mohammadi MR, Moti Nasrabadi A. Evaluation of Cerebral Cortex Function in Clients with Bipolar Mood Disorder I (BMD I) Compared With BMD II Using QEEG Analysis. Iran J Psychiatry. 2015;10(2):93-9.
70. Zhang N, Niu Y, Sun J, An W, Li D, Wei J, et al. Altered Complexity of Spontaneous Brain Activity in Schizophrenia and Bipolar Disorder Patients. J Magn Reson Imaging. 2021;54(2):586-95.
71. Xiang J, Tan Y, Niu Y, Sun J, Zhang N, Li D, et al. Analysis of functional MRI signal complexity based on permutation fuzzy entropy in bipolar disorder. Neuroreport. 2021;32(6):465-71.
72. Guan S, Wan D, Zhao R, Canario E, Meng C, Biswal BB. The complexity of spontaneous brain activity changes in schizophrenia, bipolar disorder, and ADHD was examined using different variations of entropy. Hum Brain Mapp. 2023;44(1):94-118.
73. Mohammadi MR, Zarafshan H, Khaleghi A, Ahmadi N, Hooshyari Z, Mostafavi SA, et al. Prevalence of ADHD and Its Comorbidities in a Population-Based Sample. J Atten Disord. 2021;25(8):1058-67.
74. Kasparek T, Theiner P, Filova A. Neurobiology of ADHD From Childhood to Adulthood: Findings of Imaging Methods. J Atten Disord. 2015;19(11):931-43.
75. Slater J, Joober R, Koborsy BL, Mitchell S, Sahlas E, Palmer C. Can

electroencephalography (EEG) identify ADHD subtypes? A systematic review. Neurosci Biobehav Rev. 2022;139:104752.
76. Arns M, Conners CK, Kraemer HC. A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. J Atten Disord. 2013;17(5):374-83.
77. Mehta TR, Monegro A, Nene Y, Fayyaz M, Bollu PC. Neurobiology of ADHD: a review. Curr Dev Disord Rep. 2019;6:235-40.
78. Fernández A, Quintero J, Hornero R, Zuluaga P, Navas M, Gómez C, et al. Complexity analysis of spontaneous brain activity in attention-deficit/hyperactivity disorder: diagnostic implications. Biol Psychiatry. 2009;65(7):571-7.
79. Gu Y, Miao S, Han J, Zeng K, Ouyang G, Yang J, et al. Complexity analysis of fNIRS signals in ADHD children during working memory task. Sci Rep. 2017;7(1):829.
80. Sohn H, Kim I, Lee W, Peterson BS, Hong H, Chae JH, et al. Linear and non-linear EEG analysis of adolescents with attention-deficit/hyperactivity disorder during a cognitive task. Clin Neurophysiol. 2010;121(11):1863-70.
81. Sokunbi MO, Fung W, Sawlani V, Choppin S, Linden DE, Thome J. Resting state fMRI entropy probes complexity of brain activity in adults with ADHD. Psychiatry Res. 2013;214(3):341-8.
82. Akdeniz G. Complexity Analysis of Resting-State fMRI in Adult Patients with Attention Deficit Hyperactivity Disorder: Brain Entropy. Comput Intell Neurosci. 2017;2017:3091815.
83. Yazdi-Ravandi S, Mohammadi Arezooji D, Matinnia N, Shamsaei F, Ahmadpanah M, Ghaleiha A, et al. Complexity of information processing in obsessive-compulsive disorder based on fractal analysis of EEG signal. Excli j. 2021;20:462-654.
84. Altuğlu TB, Metin B, Tülay EE, Tan O, Sayar GH, Taş C, et al. Prediction of treatment resistance in obsessive compulsive disorder patients based on EEG complexity as a biomarker. Clin Neurophysiol. 2020;131(3):716-24.
85. Tan S, Aydin S. Electroencephalographic complexity and decreased randomness in drug-naive obsessive-compulsive patients. Dusunen Adam. 2017;30.
86. Aydin S, Arica N, Ergul E, Tan O. Classification of obsessive compulsive disorder by EEG complexity and hemispheric dependency measurements. Int J Neural Syst. 2015;25(3):1550010.
87. Bob P, Golla M, Epstein P, Konopka L. EEG complexity and attentional processes related to dissociative states. Clin EEG Neurosci. 2011;42(3):175-9.
88. Al-Ezzi A, Al-Shargabi AA, Al-Shargie F, Zahary AT. Complexity analysis of EEG in patients with social anxiety disorder using fuzzy entropy and machine learning techniques. IEEE Access. 2022;10:39926-38.
89. Bob P, Kukleta M, Riecansky I, Susta M, Kukumberg P, Jagla F. Chaotic EEG patterns during recall of stressful memory related to panic attack. Physiol Res. 2006;55 Suppl 1:S113-s9.
90. Tóth E, Kondákor I, Túry F, Gáti A, Weisz J, Molnár M. Nonlinear and linear EEG complexity changes caused by gustatory stimuli in anorexia nervosa. Int J Psychophysiol. 2004;51(3):253-60.
91. Chae JH, Jeong J, Peterson BS, Kim DJ, Bahk WM, Jun TY, et al. Dimensional complexity of the EEG in patients with posttraumatic stress disorder. Psychiatry Res. 2004;131(1):79-89.
92. Mohammadi MR, Khaleghi A. Transsexualism: A Different Viewpoint to Brain Changes. Clin Psychopharmacol Neurosci. 2018;16(2):136-43.
93. Churruca K, Pomare C, Ellis LA, Long JC, Braithwaite J. The influence of complexity: a bibliometric analysis of complexity science in healthcare. BMJ Open. 2019;9(3):e027308.
94. Hamilton GF, Rhodes JS. Exercise Regulation of Cognitive Function and Neuroplasticity in the Healthy and Diseased Brain. Prog Mol Biol Transl Sci. 2015;135:381-406.
95. Takahashi T. Complexity of spontaneous brain activity in mental disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:258-66.
96. Gao J, Hu J, Tung WW. Complexity measures of brain wave dynamics. Cogn Neurodyn. 2011;5(2):171-82.