Review

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Is EEG Entropy a Useful Measure for Alzheimer's Disease?

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Abstract

Background: The number of individuals diagnosed with Alzheimer's disease (AD) has increased, and it is estimated to continue rising in the coming years. The diagnosis of this disease is challenging due to variations in onset and course, its diverse clinical manifestations, and the indications for measuring deposit biomarkers. Hence, there is a need to develop more precise and less invasive diagnostic tools. Multiple studies have considered using electroencephalography (EEG) entropy measures as an indicator of the onset and course of AD. Entropy is deemed suitable as a potential indicator based on the discovery that variations in its complexity can be associated with specific pathologies such as AD.

Methodology: Following PRISMA guidelines, a literature search was conducted in 4 scientific databases, and 40 articles were analyzed after discarding and filtering.

Results: There is a diversity in entropy measures; however, Sample Entropy (SampEn) and Multiscale Entropy (MSE) are the most widely used (21/40). In general, it is found that when comparing patients with controls, patients exhibit lower entropy (20/40) in various areas. Findings of correlation with the level of cognitive decline are less consistent, and with neuropsychiatric symptoms (2/40) or treatment response less explored (2/40), although most studies show lower entropy with greater severity. Machine learning-based studies show good discrimination capacity.

Conclusions: There is significant difficulty in comparing multiple studies due to their heterogeneity; however, changes in Multiscale Entropy (MSE) scales or a decrease in entropy levels are considered useful for determining the presence of AD and measuring its severity.

Keywords

entropy; Alzheimer's disease; dementia; electroencephalography; biomarkers

Introduction

As of 2021, it was estimated that approximately 55 million individuals were living with dementia. Among them, between 60 and 70% were diagnosed with Alzheimer's disease (AD), making it the most common form of dementia. It is estimated that by 2030, the number of individuals diagnosed with dementia will increase to 78 million and by 2050 to 152 million [1]. The annual costs of the disease in the United States were approximately 1 trillion dollars in 2019, a figure expected to double by 2030 [1,2]. Therefore, AD represents a significant public health problem, underscoring the need to reach a consensus for the development of biological and neurophysiological markers that support its diagnosis.

The international classification systems, International Classification of Diseases 11th Revision (ICD-11) [3] and Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) [4], have the highest level of dissemination worldwide [5,6]. Additionally, more specific criteria proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) have been designed for clinical practice [7] and are endorsed by various management guidelines [8–10]. Other diagnostic criteria are exclusively used in clinical research [11,12] and involve biomarkers such as β-amyloid deposits, pathological tau proteins, and the presence of neurodegeneration.

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Table 1. Main complexity measures used in Alzheimer's disease studies with EEG.

Complexity measure	Abbreviation	Description
Approximate Entropy	ApEn	Measures the regularity of the data by examining similar epochs of time-series data. Higher values correspond to greater complexity in the data [28].
Fuzzy Entropy	FuzzyEn	Determines a fuzzy measure of similarity between two vectors based on their shapes [28].
Sample Entropy	SampEn	An improved algorithm over ApEn that avoids the bias caused by self-matching [29].
Permutation Entropy	PE	A method that computes entropy based on permutation patterns. Suitable for analyzing arbitrary real-world data, especially chaotic time series [27].
Multiscale Entropy	MSE	Provides a sample entropy estimation over multiple time scales [31].
Spectral Entropy	SpectEn	A measure of unpredictability and disorder associated with the spectrum of a signal. Higher values indicate greater complexity [26].
Shannon Entropy	ShE	Quantifies the diversity, uncertainty, or randomness of an equilibrium system [30].
Tsallis Entropy	TsE	Explores the properties of a probability distribution among non-equilibrium systems [19].
Transfer Entropy	TE	A theoretical information measure that quantifies statistical coherence between evolving systems in time [25].
Correlation Dimension	D2	A measure of the independent variables is required to define the complexity of the dynamics precisely [19].
Fractal Dimension	FD	Measures the change in signal amplitude as the signal is sampled at successively longer intervals [26].
Lempel-Ziv Complexity	LZC	Reconstructs the original time series into a binary sequence [19].
Hurst Exponent	HE	Used primarily to measure the fractal dimension of a time series [19].
Lyapunov Exponent	LLE	A metric for assessing the randomness of finite sequences [19].

Note. Source: Own elaboration. EEG, electroencephalography.

AD is characterized by physiopathological and clinical heterogeneity, particularly in late-onset presentations, leading to diagnostic challenges. In patients clinically evaluated and monitored over the years, purely clinical diagnostic criteria exhibit diagnostic accuracy with a sensitivity and specificity ranging between 70 and 80% when compared to neuropathology [13]. Hence, there is a need to develop more precise, accessible, and non-invasive diagnostic and screening tools for early identification in at-risk populations [14]. For this purpose, various modalities for evaluating the central nervous system (CNS), such as electroencephalography (EEG), have been employed.

EEG involves monitoring the electric fields generated in the brain through electrodes placed on the scalp. These fields result from the activity of pyramidal neurons in the cerebral cortex, where the synchronous activity of groups of neurons functions as micro-dipoles, allowing EEG to record activity. EEG's advantages as a diagnostic tool include its ability to be easily conducted, its temporal resolution in milliseconds, its non-invasive nature, and its cost-effectiveness, which may facilitate widespread use. Moreover, automated processing methods developed in recent decades have enhanced data robustness and enhanced evaluation [14,15].

Prior studies have shown EEG's utility for early screening of AD by detecting: (1) signal slowing (characterized by an increase in the energy of low-frequency signals and a decrease in the energy of high frequencies), (2) changes in synchrony (a feature of neuronal connectivity), and (3) reduced complexity (more regular patterns in AD patients). The latter parameter can be evaluated by entropy analysis [14].

Interactions among physiological variables that enable adaptation processes, alongside mechanisms that regulate them, are typically nonlinear and susceptible to be analyzed under chaos theory-based approaches. These processes are known to be complex. From this perspective, it is assumed that: (1) A system's complexity reflects its ability to adapt to changing environments; (2) Physiological processes operate across multiple temporal and spatial scales, and its complexity is multiscale; (3) In aging or disease states, adaptability diminishes, thus reducing the system's complexity [16,17].

In time series analyses, entropy is defined as a complexity measure that studies system organization [18,19]. If a system is more predictable, it will produce signals with lower entropy measures. Despite the existence of a certain degree of stability in organisms, there must be room for variations that allow them to adapt adequately to environmental demands [19,20]. From a biological standpoint, it is generally accepted that healthier systems exhibit greater complexity and, consequently, higher entropy lev-

Table 2. Search terms, descriptors, and search equations.

	MeSh		**Unrestricted**	**DeCS**
Terms	· Alzheimer Disease · Entropy · Signal Processing, Computer-Assisted		• Alzheimer • Entropy	• Alzheimer • Entropy
Search Strategies				
-Selected MeSh Terms: Alzheimer's disease, Entropy, Computer-Assisted, Signal processing -Unrestricted: Alzheimer, Entropy				
Database	**Scopus**	**PubMed**	**Lilacs**	**SciElo**
Final Search Equation	*alzheimer* AND *entropy* AND (EXCLUDE (DOCTYPE, *"cp"*)) AND (LIMIT-TO (DOCTYPE, *"ar"*)) AND (LIMIT-TO (LANGUAGE, *"English"*))	(Alzheimer Disease [MeSH]) AND (entropy) *Filters applied: English, spanish.*	("alzheimer") AND ("entropy") AND (db:("LILACS"))	("alzheimer") AND ("entropy")
Results	544	166	1 (language Portuguese)	1 (Portuguese), 1 (Spanish).

The bold text indicates the types of terms or the databases in which the search was conducted.

els [17,21]. These measurements vary depending on the systems and the algorithms used, so both increases and decreases in entropy have been reported for different pathologies [14,22,23].

The various measures used to quantify the complexity of records and images include fractal dimension, correlation dimension, Lempel-Ziv complexity, Hurst exponent, Lyapunov exponent, and entropy-based measures [24]. The latter are the most commonly used, as they require less data for analysis, are less sensitive to signal interference, and can be processed using simple algorithms [19]. Table 1 (Ref. [19,25–31]) summarizes the main measures used.

Therefore, this paper reviews the evidence regarding EEG entropy measures for evaluating AD patients. Our purpose is to contribute to the understanding of these tools' potential as biomarkers and outline their limitations.

Methodology

In April 2024, a literature search was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols [32]. Documents published between 2000 and 2023 were included. The databases searched were *PubMed*, *Scopus*, *Scielo*, and *Lilacs*. An exhaustive search was conducted using the main terms and MeSH/DeCs terms: *Entropy*, *Alzheimer's Disease*, *Signal Processing*, and *Computer-Assisted*, as well as free search terms for the equation with the highest sensitivity (Table 2).

After combining the search terms by applying filters by language (including Spanish and English), type of publication (original articles only) and areas of knowledge (excluding those other than biosciences), 713 articles were obtained. Subsequently, duplicate articles were removed using the bibliographic manager. The selection criteria considered were population (patients with Alzheimer's disease), measurement (entropy in EEG records), and results (clinical evaluation), adapting the population, intervention, comparison and outcomes (PICOT) criteria [33]. Four researchers independently determined that each of the studies met the selection criteria. Studies on populations with other mental disorders or Mild Cognitive Impairment (MCI) were excluded. Furthermore, studies that calculated complexity exclusively with measures different from those based on entropy were also excluded (Fig. 1).

Results

A total of 40 articles (Table 3, Ref. [20,25–28,30,31,34–66]) published between 2000 and 2023 using entropy measures were included (Fig. 2). Some studies utilized solely entropy-based measures [20,25,34–36], while others combined entropy analysis with additional complexity measures [37–39], spectral measures [26,38], time-frequency analysis measures [40], and relative power measures [41].

Studies that included AD patients matched with healthy controls (HC) [26,27,34,36–38,42–46,48–50,60,61,66] revealed lower entropy values, except for one study that used Spectral Entropy (SpectEn) [44]. This decrease in entropy levels in AD patients was observed in frontal

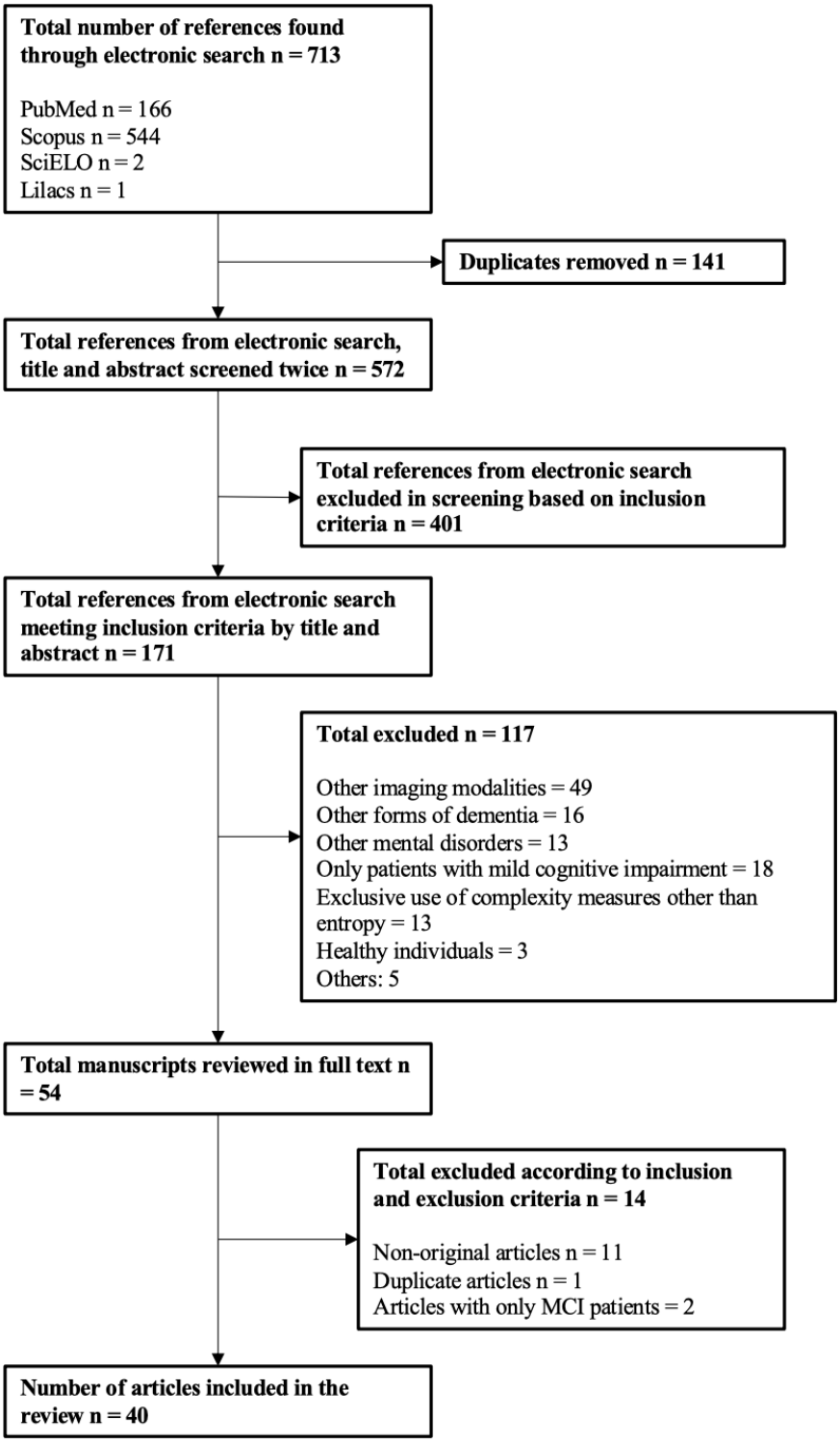

Fig. 1. Search tree diagram. *Note.* Source: Own elaboration. MCI, Mild Cognitive Impairment.

[27,46], temporal [47,48], parietal [42,43,48–51], central [27], and occipital [28,42,43,49,50] areas. A recent study showed that the best differentiation between HC and probable AD was obtained using delta waves [52].

Another study evaluated the potential of multiscale fluctuation dispersion entropy (MFDE) in awake and sleep EEG as a biomarker for AD in its early stages. The results suggested that the slow-to-fast-activity ratio of entropy

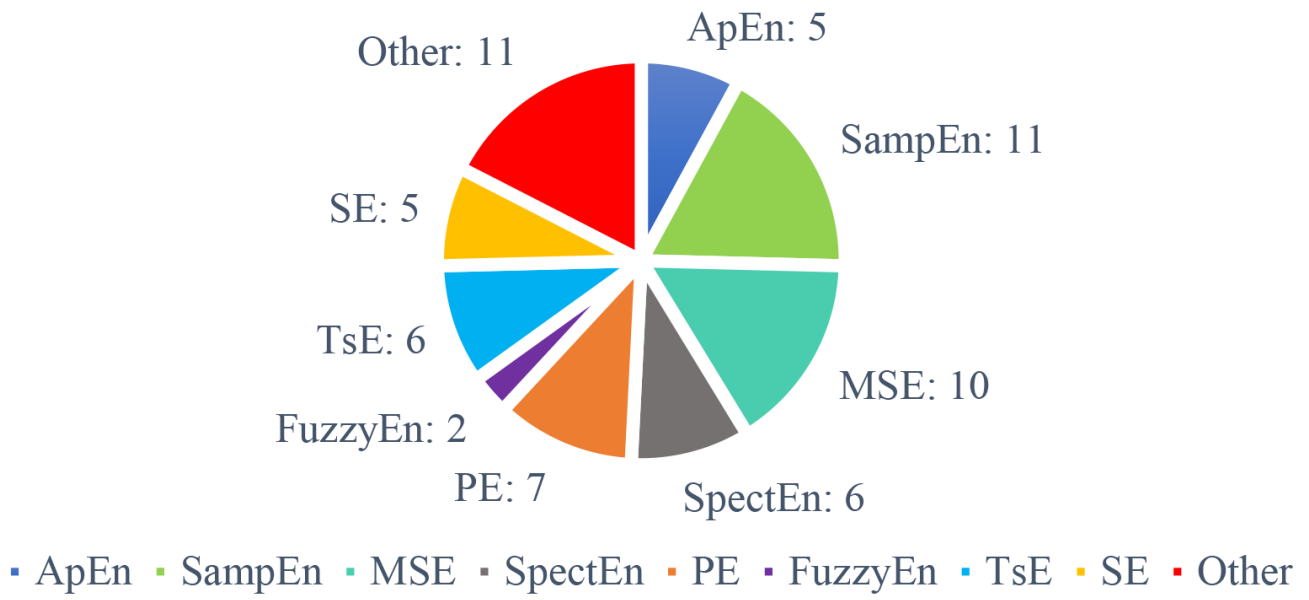

Fig. 2. Entropy-based measures used in the evaluated studies. *Note*. Source: Own elaboration. ApEn, Approximate Entropy; SampEn, Sample Entropy; MSE, Multiscale Entropy; SpectEn, Spectral Entropy; PE, Permutation Entropy; FuzzyEn, Fuzzy Entropy; TsE, Tsallis Entropy; SE, Shannon Entropy.

(SFAR-entropy) on rapid eye movement (REM) sleep could differentiate dementia from MCI and HC, especially in temporal and occipital regions. Furthermore, higher SFAR-entropy during REM sleep correlated with worse performance on the Montreal Cognitive Assessment, suggesting a link between increased SFAR-entropy and more severe cognitive impairment [53].

Multiscale Entropy (MSE) analysis divides the signal into data sets of different sizes. Scale 1 corresponds to the entropy analysis using the original signal, while a scale of 10 corresponds to the entropy analysis of the result of averaging 10 contiguous data points. Short-time scales in MSE are thus more susceptible to rapid or abrupt signal changes. As the scale increases, rapid changes are averaged out, and entropy becomes more sensitive to changes produced on longer time scales. In the case of EEG, entropy in short scales is more susceptible to high-frequency signals, while longer scales are more sensitive to low-frequency signals. Several studies have found a decrease in short time scales and an increase in long time scales in frontal, temporal, central, and occipital areas in patients with AD [29,43,54–56]. This means there is a decrease in the entropy of high-frequency signals (alpha and beta bands) and an increase in the entropy of low-frequency band signals (theta and delta). However, one of the studies did not show a correlation between entropy and the level of cognitive decline [43], and another only found a correlation between them in short timescales [56].

A recent study evaluated brain response to musical stimulation in AD patients with different degrees of dementia by employing Sample Entropy (SampEn), Permutation Entropy (PE), and Lempel-Ziv Complexity (LZC). According to the results, mild to moderate AD patients displayed higher brain entropy than severe AD patients during and after the stimulus compared to pre-stimulus [57]. On the other hand, two studies that employed Shannon entropy (SE) and Tsallis entropy (TsE) yielded discordant results. One study found that the level of cognitive decline in frontal and temporal areas is associated with an increase in entropy [55], while the second reported a decrease [30].

The association between entropy changes and emotional and behavioral symptoms in AD was reported in two studies that calculating MSE [29,31] and applying the Neuropsychiatric Inventory (NPI). One study showed a correlation between lower MSE values on short scales and the domains of depression, anxiety, aberrant behavior, and sleep changes [29]. The other study suggested this exact correlation for the domains of irritability, aberrant behavior, and sleep changes [31]. The concordant findings between the studies were for the domains of aberrant behavior and sleep changes.

Machine learning-based approaches have been successfully applied to discriminate AD patients from HC, MCI subjects, and individuals with Subjective Cognitive

Table 3. Articles included in the review.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
1	Abásolo *et al*. [50], 2005	Evaluate the use of entropy as a diagnostic biomarker for AD.	Patients = 10 Controls = 8	ApEn	Significantly decreased ApEn values were found in occipital and parietal areas.
2	Abásolo *et al*. [42], 2006	Evaluate the use of entropy as a diagnostic biomarker for AD.	Patients = 11 Controls = 11	SampEn, SpectEn	Decrease in SampEn in occipital and parietal areas. No differences in SpectEn were found.
3	Abásolo *et al*. [49], 2008	Evaluate the use of entropy as a diagnostic biomarker for AD.	Patients = 11 Controls = 11	ApEn	Decrease in ApEn in occipital and parietal areas.
4	Abazid *et al*. [58], 2021	To use EpEn to brain network assessment and demonstrate its effectiveness with different graph parameters for AD diagnosis.	Patients AD = 28 Patients MCI = 28 Patients SCC = 22	EpEn	Effectiveness of Support Vector Machine (SVM) algorithm for analyzing the brain network in patients with different stages of cognitive dysfunction. Statistical modeling of EEG signals with EpEn allows a better differentiation between SCC, MCI and AD stages.
5	Al-Nuaimi *et al*. [45], 2015	Evaluate the use of entropy as a diagnostic biomarker for AD.	Patients = 20 Controls = 32	TsE	Statistically significant decrease in TsE in AD patients.
6	Amezquita-Sanchez *et al*. [40], 2021	A new EEG-based methodology is presented to differentiate MCI, AD and healthy subjects using DWT, DEI, a recently proposed nonlinear measurement by Rostaghi and Azami, and a fuzzy logic-based classification algorithm.	AD Patients = 45 MCI Patients = 45 Controls = 45	IDE DWT	The EEG signals measured in patients with mild cognitive impairment, and AD does not present significant visual differences compared to those obtained in healthy subjects.
7	Ando *et al*. [46], 2021	Understanding the alteration of EEG dynamics in AD.	AD Patients = 16 HC = 18	MSE MF	MSE and MF analyses showed reduced EEG complexity in AD patients. The classification accuracy is better when combining MSE and MF analyses than when applying each individually.
8	Azami *et al*. [53], 2023	To evaluate the potential of multiscale fluctuation dispersion entropy analysis of EEG during sleep as a physiological biomarker for the early clinical stages of Alzheimer's disease.	Patients MCI-AD = 23 Patients = 19 Controls = 35	SFAR-entropy	The average SFAR-entropy across the entire brain during REM sleep significantly differentiated individuals with dementia—AD from those with mild cognitive impairment probable AD and HC. Additionally, brain regional differences in SFAR-entropy during REM sleep were more pronounced in the temporal and occipital regions for dementia. During REM sleep, SFAR-entropy in the occipital region was significantly correlated with lower MoCA scores.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
9	Cao *et al.* [36], 2015	Using entropy as a biomarker in the EEG and machine learning software and its accuracy to distinguish HC from patients.	Patients = 20 Controls = 20	ApEn, SampEn, fApEn fSampEn	The four entropies were statistically decreased in AD patients in temporal and parietal areas; the software could distinguish the traces between the two groups with the four entropies. However, fSampEn had the highest accuracy at 88.1%.
10	Coronel *et al.* [55], 2017	Using EEG complexity measures as a biomarker of AD severity.	Patients = 79	SE, TsE, SpectEn, MSE	Statistically significant decrease in SpecEn and MSE in frontal and temporal areas and these measures were correlated with lower MMSE scores. The increase in SE and TsE was correlated with lower MMSE scores.
11	Das & Puthankattil [61], 2022	To analyze the relation between functional connectivity and complexity by modeling the MCI-AD condition with the help of the Kuramoto model.	Patients = 13 Controls = 15	FDispEn LZC HFD	In real EEG signals, FDispEn values were significantly lower in the anterior and central regions for patients with MCI-AD. No significant differences in FDispEn were reported in simulated signals from patients compared to controls. The simulation comparison showed a tendency toward reduced FDispEn in the central and posterior regions for cases with impaired connectivity.
12	Deng *et al.* [27], 2015	Evaluate the use of entropy as a diagnostic biomarker for AD.	Patients = 14 Controls = 14	WPE	Statistically significant decrease in PE and WPE in all areas of the theta band, frontal and occipital in the delta band, along with the frontal and central in the beta band.
13	Deng *et al.* [47], 2017	Compare the advantage of multi-scale weighted permutation entropy (MMSWPE) over multi-scale permutation entropy (MMSPE).	Patients = 14 Controls = 14	WPE, PE	The efficacy of MMSWPE is validated by simulated and experimental signals. The simulation results demonstrate that MMSWPE retains the advantages of WPE and the multiscale multivariate method and can distinguish the system with different complexity, but MMSPE works unsatisfactorily.
14	Escudero *et al.* [43], 2006	Use of entropy as a diagnostic EEG biomarker and its relationship to the level of cognitive impairment.	Patients = 11 Controls = 11	MSE	Significant decreases in MSE at short time scales in frontopolar, frontal, and posterior regions. There was no correlation between MMSE scores and MSE at long time scales.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
15	Fan *et al.* [31], 2018	Characterize the functional brain activities at different time scales that best discriminate the severity levels of AD groups from normal controls in terms of EEG complexity. Profile the topographic map of EEG biomarkers for various AD severities and investigate the multivariate correlation patterns with cognitive dysfunctions.	Patients = 108 Controls = 15	MSE	A classification accuracy of approximately 80% was found between severe AD cohorts and normal controls. In the long run, the complexity of EEG signals decreases with the severity of AD.
16	Fide *et al.* [66], 2023	To evaluate the level of complexity differentiation driven by medication status and the relationship between the complexity levels and the global cognitive status of the participants.	Patients AD de novo = 26 Patients with cholinergic therapy = 24 Patients with combined therapy = 20 Controls =27	PE	AD participants had reduced total PE values.
17	Garn *et al.* [30], 2015	To investigate which quantitative electroencephalographic marker or combination of markers correlates best with the severity of AD, as measured by the MMSE.	Patients with probable AD = 79 Patients with possible AD = 39	TsE, ShE	The data indicates that specific quantitative electroencephalogram (QEEG) markers related to slowing, synchrony, and complexity are closely associated with the severity of AD in patients with MMSE scores between 15 and 26 points.
18	Houmani *et al.* [35], 2018	(I) Develop a method to automatically discriminate patients with possible AD from patients with SCC. (II) Automatically discriminate possible AD patients from MCI patients and MCI patients from other pathologies.	SCC Patients = 22 AD Patients = 49 MCI Patients = 58 Patients with other pathologies = 40	EpEn, BM	The study reveals that Alzheimer's disease induces a reduction in the complexity of the EEG and an increase in its synchrony in the theta band compared to patients with MCI, who are considered in this work as control subjects.
19	Hsu *et al.* [56], 2020	Test the performance of ALD to differentiate patients with moderate to severe AD from healthy subjects.	Mild AD Patients = 69 Mod-Sev AD Patients = 15 Controls = 15	MSE ALD	The use of only a few MSE features as input to ALD provides high classification performance in distinguishing healthy subjects from AD patients.
20	Labate *et al.* [44], 2013	Use of entropy as a biomarker in EEG in AD and MCI patients.	Not specified	PE, SampEn	Multiscale multivariate PE entropy can distinguish between subjects from the three categories in all brain areas and across all scales. SampEn is able to distinguish AD records from HC but has inconsistent results in MCI patients.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
21	Maturana *et al.* [20], 2019	Determine the relationship between EEG signal complexity and degree of cognitive impairment among five groups of subjects with different severity of AD.	MCI Patients = 51 Mild AD Patients = 51 Moderate AD Patients = 50 Severe AD Patients = 50 Controls = 51	MSE RMSSE	A high correlation between AD severity and analysis in MSE and RMSSE. Combining both measures can achieve better values.
22	McBride *et al.* [25], 2015	Evaluate the diagnostic utility of different machine learning software using spectral methods and complexity measures to distinguish between AD, mild cognitive impairment, and HC.	AD Patients = 15 MCI Patients = 16 Controls = 15	TE	Changes in transfer entropy in AD and MCI patients performed well for the algorithm to discriminate between groups. For the MCI vs. HC group, the records had an accuracy between 87.1% and 93.6%; for the AD vs. HC group, the records had an accuracy between 87.5% and 93.8%; and for the AD vs. MCI group, the records had an accuracy between 81.8% and 90.9%.
23	McBride *et al.* [38], 2014	Evaluate the diagnostic utility of different machine learning software using spectral methods and complexity measures to distinguish between AD, mild cognitive impairment, and HC.	AD Patients = 15 MCI Patients = 16 Controls = 15	SampEn, SpectEn	Changes in spectral measures and decreased complexity in AD and MCI patients performed well for the algorithm to discriminate between groups. For the MCI vs. HC group, the records had an accuracy between 83.9% and 96.8%; for the AD vs. HC group, the records had an accuracy between 71.9% and 96.9%; and for the AD vs. MCI group, the records had an accuracy between 87.9% and 90.9%.
24	Mizuno *et al.* [54], 2010	Use of entropy as a diagnostic biomarker and its relationship with level of cognitive impairment.	Patients = 15 Controls = 18	MSE	Statistically significant decrease in MSE at short time scales in frontal regions in all AD patients and a significant increase in MSE at long time scales globally in brain regions for severe AD patients; this increase correlated with measures of cognitive impairment.
25	Nobukawa *et al.* [34], 2020	Evaluate functional connectivity and complexity measures in the EEG of AD patients using machine learning software and its accuracy to distinguish HC from patients.	Patients = 16 Controls = 18	MSE	There was a significant decrease in MSE at short time scales in frontal, temporal, and parietal areas. There was an increase in MSE at long time scales, but this was not significant. The software distinguished patients from controls based on functional connectivity and entropy with an accuracy of 100% and 73.5%, respectively.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
26	Perez-Valero *et al.* [64], 2022	To Evaluate the potential of a fully self-driven approach for multiclass discrimination of Alzheimer's disease based on a commercial EEG acquisition device and automated processing.	Patients = 12 Controls = 9	SE	There is no specific mention of entropy analysis.
27	Polat [62], 2022	To evaluate a new approach based on the 'complextrogram' used to represent EEG signals in a way that enhances the performance of deep neural networks for the automatic diagnosis of Alzheimer's disease using EEG data.	Patients = 24 Controls = 24	PeEn	For beta oscillations, the PeEn complexity distributions showed greater variance in AD.
28	Puri *et al.* [63], 2022	To evaluate and develop a robust and efficient method for the early detection of Alzheimer's disease using EEG signals, which could help delay neuronal degeneration.	Patients = 12 Controls = 11	ShE TsE ReEn	There is no specific mention of entropy analysis.
29	Puri *et al.* [59], 2023	To evaluate the potential of a dual decomposition technique that combines DWT and VMD with multiscale permutation entropies (ShE, TsE, and ReEn) to detect AD.	Patients AD = 59 Patients MCI = 7 Controls = 102	ShE TsE ReEn	Three different entropy features, ShE, TsE, and ReEn, were calculated for both binary and three-way classifications. All three features exhibit high discriminative capability.
30	Ruiz-Gómez *et al.* [37], 2018	Evaluate the diagnostic utility of different machine learning software using spectral methods and complexity measures to distinguish between AD, mild cognitive impairment, and HC.	AD Patients = 37 MCI Patients = 37 Controls = 37	SampEn, FuzzyEn, SpectEn	AD patients had significantly reduced values of all complexity measures compared to HC, and MCI patients showed intermediate values between the other two groups. The algorithm accurately distinguished HC from all of 78.43% and AD from all of 76.47%.
31	Santos Toural *et al.* [41], 2021	Evaluate the performance of a method for simultaneous classification between healthy, MCI, and AD using EEG signals.	MCI Patients = 9 AD Patients = 15 HC = 17	SampEn PE WT MSE MF	The results suggest that the Wavelet entropy has the best features for use in a Healthy-MCI-AD classifier for sample and permutation entropies.
32	Şeker *et al.* [60], 2021	To develop a 3-way diagnostic classification using EEG complexity in detecting MCI/AD in clinical practice.	MCI Patients = 85 AD Patients = 85 HC = 85	PE	The distribution of the measured PE shows that EEG complexity is lower in the AD group and higher in the control group. The MCI group is observed as an intermediate form due to heterogeneous values. Classification of Controls from both patient groups is best achieved. The eyes open state increases the discrimination of MCI and AD.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
33	Sharma *et al.* [39], 2019	To investigate whether selected EEG and cognitive biomarkers can classify mild cognitive impairment (MCI), dementia, and healthy subjects using a support vector machine classifier in four scenarios: eyes closed, eyes open, finger tapping test, and continuous performance test.	MCI Patients = 16 AD Patients = 15 Controls = 13	SpectEn HFD DSP Obliquity K SK Spectral asymmetry FCS	Good sensitivity and specificity were found for differentiating between AD patients and controls, MCI and AD patients, and between AD and MCI patients, mainly using the finger tapping and continuous performance tests analyzed by combining various measures. In all groups, SpectEn was present.
34	Simons *et al.* [28], 2015	Demonstrate that QSE can provide more robust entropy estimates than SampEn.	AD Patients = 11 Controls = 11	SampEn ApEn QSE KSE	The QSE method is more robust than SampEn, on which it is based. It can highlight differences in AD patients and controls for a variety of input parameters beyond what is currently accepted with SampEn or ApEn.
35	Simons *et al.* [48], 2018	Evaluate FuzzyEn to identify differences between AD patient signals vs. Healthy.	AD Patients = 11 Controls = 11	ApEn SampEn FuzzyEn	AD patients had significantly lower FuzzyEn values than control subjects and had higher diagnostic accuracy than ApEn and SampEn.
36	Staudinger & Polikar [26], 2011	Use of spectral features and complexity measures of signals as biomarkers in EEG through the use of machine learning software.	Patients = 79 Controls = 82	HFD SpectEn	There was a significant decrease in Higuchi fractal dimension and SpectEn in frontal and temporal lobes. The use of the above features resulted in a diagnostic accuracy of 78% in distinguishing between patients and controls.
37	Tsai *et al.* [65], 2015	Test whether some features of the MSE analysis of EEG data can be associated with the efficacy of AChE inhibitor therapy in AD patients.	AD Patients = 17	MSE SampEn	MSE analysis of EEG recordings can show both short—and long-term features and provides a potential tool for predicting the efficacy of AChE inhibitors in AD, mainly at scales of 6–20.
38	Vicchietti *et al.* [52], 2023	To evaluate the automatic detection of Alzheimer's disease based on six methods commonly used in the literature, C, F, Q, E, D, and I, according to the corresponding *p* values and AUC's.	Patients = 160 Controls = 24	QE	There is no specific mention of entropy analysis.

Table 3. Continued.

N°	Year	Objective	N	Entropy measures	Complexity analysis in the patient group
39	Wang *et al*. [51], 2019	Detect the differences between healthy subjects and AD patients, combining SampEn and the surrogate data method.	AD Patients = 14 Controls = 20	SampEn	There were significant differences between healthy subjects and AD patients. Higher SampEn was significant in healthy subjects, mainly in c3, f3, o2, and p4 recordings, and in surrogate data, it was significant in c3 and o2.
40	Wu *et al*. [57], 2022	To evaluate whether there are differences in brain response to musical stimulation in AD patients with different degrees of dementia, which could provide a theoretical basis for music therapy in Alzheimer's disease.	Patients with mild to moderate AD = 17 Patients with severe AD = 16 Controls = 16	SampEn PmEn LZC	Entropy values were higher during and after stimulus in patients with mild to moderate AD and lower in patients with severe AD.

Note. Source: Own elaboration. AD, Alzheimer's disease; EEG, Electroencephalography; MMSE, Mini-Mental State Examination; SpectEn, Spectral Entropy; ApEn, Approximate Entropy; HFD, Higuchi Fractal Dimension; MF, Multifractal Entropy; MSE, Multiscale Entropy; fApEn, Fuzzy Approximate Entropy; SampEn, Sample Entropy; fSampEn, Fixed Sample Entropy; TsE, Tsallis Entropy; FuzzyEn, Fuzzy Entropy; PmEn/PeEn/PE, Permutation Entropy; WPE, Weighted Permutation Entropy; ShE/SE, Shannon Entropy; RMSSE, Refined Multiscale Spectral Entropy; EpEn, Epoch-Based Entropy; LZC, Lempel-Ziv Complexity; ReEn, Rényi Entropy; Q, Quadratic Entropy; QSE, Quadratic Sample Entropy; MCI, Mild Cognitive Impairment; SCC, Subjective Cognitive Complaint; TE, Transfer Entropy; DSP, Power Spectral Density; K, Kurtosis; SK, Spectral Kurtosis; FCS, Spectral Crest Factor; DWT, Discrete Wavelet Transform; IDE, Dispersion Entropy Index; WT, Wavelet Transform; KSE, Kolmogorov-Sinai Entropy; AChE, Acetylcholinesterase; BM, Bump Model; SFAR-entropy, slow-to-fast-activity ratio of entropy; FDispEn, Fluctuation-based Dispersion Entropy; C, Wavelet coherence; F, Fractal dimension; E, Wavelet energy; I, Visibility graphs; D, Quantile graphs; AUC, area under the curve; VMD, Variational mode decomposition; HC, healthy controls; DispEn, dispersion entropy; QE, quadratic entropy.

Complaint (SCC) (Table 4, Ref. [20,25,26,34–40,58,59,61–64]). These studies have also found significantly lower entropy values in AD than in HC and a high discriminative capability [20,25,36,37,40,58,59,62,63]. Some studies revealed that MCI patients have intermediate entropy values between AD patients and those in HC [37,60]. Furthermore, one study reported significantly lower entropy in anterior and central regions in patients with MCI-AD [61].

Among the machine learning tools, there is Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis (QDA), Multilayer Perceptron (MLP), the Fuzzy Logic Classifier (FLC), time-frequency complexity maps (complextrogram) [62], algorithms based on Support Vector Machines (SVM), which are the most frequently used. Sensitivity values for diagnosis have been found between 64.7%–100%, specificity 64.7%–100%, and accuracy 71.9%–96% (Table 4). However, there are some limitations in these studies, as the use of EEG signals captured from all channels increases the computational complexity and data redundancy [63]. The wide range of values could be influenced by the great heterogeneity in the studies regarding the type of measures (or a combination thereof), the type of patients (with MCI or Subjective Cognitive Complaint (SCC)), and the algorithm used. These characteristics make it difficult to compare studies directly [37,60].

Finally, a recent study using a fully self-driven machine learning approach based on a portable EEG successfully discriminated AD patients from MCI patients [64].

Regarding entropy as a predictor of response to cholinesterase inhibitor treatment, a study is available with a limited sample of AD patients treated with donepezil for 12 months. The Mini-Mental State Examination (MMSE) and associated characteristics were calculated in the participants, including the slopes for 1–5 time scales and 6–20 scales [65]. Based on MMSE scores, patients were classified as responders and non-responders, the former were those whose scores were equal to or greater than their initial score one year after treatment; the latter were those who obtained lower scores. It was found that entropy displayed a more pronounced decrease in non-responding patients on the 6–20 scale. Another study found that acetylcholinesterase inhibitor (AChE-I) treatment was superior to dual therapy (AChE-I + memantine**)** in its effect of increasing cognitive scores and normalizing EEG complexity levels [66].

Discussion

The present work explores the contribution of entropy-based EEG measures to the assessment of AD patients. A wide heterogeneity was found in the reviewed studies, both in the methodology and the entropy-based measures used; MSE is one of the most frequently used. A consistent finding suggest reduced entropy values in patients compared to controls. In addition, decreased levels of entropy are associated with a greater level of cognitive decline, as well as with the presence of behavioral symptoms. This reduction in EEG complexity is consistent with the perspective that the neuropathological alterations of AD generate losses of effective brain connectivity, thus creating a disconnection of afferent and efferent pathways between brain areas [67,68].

Entropy as a Discriminator of Disease and Severity

Regarding its usefulness in differentiating between patients and controls, it has been found that when using different time scales, such as in MSE, the values in AD patients are lower on short time scales and higher on long time scales compared to those in HC. Studies provide evidence that MSE is also a potential biomarker of disease severity, as a decrease in short time scales and an increase in long time scales correlate with cognitive decline measures. Therefore, as cognitive decline increases, a greater number of alterations in EEG signals are evidenced.

The increased complexity in long time scales of MSE could be related to possible compensatory mechanisms in the brain that are activated upon neuronal death or synaptic loss in a specific area. Gaubert *et al*. [69] (2019) described this finding. In their study, early neurodegeneration (measured in amyloid beta load) appeared to be modulated by an increase in spectral frequency [69]. However, the pathophysiological mechanism of these findings in MSE is not yet fully understood.

From a mathematical perspective, MSE short scales are more sensitive to high-frequency bands. Therefore, a reduction in entropy on these scales indicates less variability in high frequencies (Beta and gamma). On the other hand, long scales are more sensitive to low-frequency bands. Consequently, an increase in entropy on longer scales translates into greater complexity in lower frequencies [69].

Alternatively, observed changes in entropy may be due to a redistribution in the spectral power of EEG signals [14], that is, to the change in the relative intensity of high- and low-frequency waves [19,60]. In this scenario, the de-

Table 4. Sensitivity, Specificity, and Accuracy for differentiating Alzheimer's disease (AD) patients from those with SCC, MCI and HC using entropy-based measures.

Study	Method	Classifier	Class	Sensitibity	Specificity	Accuracy
Abazid *et al.* [58], 2021	EpEn+ functional connectivity measures	SVM	AD vs SCC	85.1–96.4%	84–96%	84.0–96.0%
			MCI vs SCC	92.8–96.4%	77.2–96.4%	88.94%
			AD vs MCI vs HC	91.0%	87.0%	82.6–86.9%
Amezquita-Sanchez *et al.* [40], 2021	DEI + DWT	FLC	AD vs MCI vs HC	91.0%	87.0%	82.8–89.9%
Cao *et al.* [36], 2015	ApEn	SVM	AD vs HC	81.5%	81.5%	81.4%
	SampEn			86.1%	84.0%	85.0%
	fApEn			86.8%	84.1%	85.3%
	fSampEn			90.1%	85.6%	88.1%
Das & Puthankattil [61], 2022	LZC + HFD + FDispEn	NR	MCI-AD vs HC	NR	NR	NR
Houmani *et al.* [35], 2018	EpEn	SVM	AD vs SCC	87.8%	100%	91.6%
Maturana *et al.* [20], 2019	MSE	QDA	AD vs HC + MCI	81.8%	58.5%	69.7%
			HC vs AD	88.8%	52.3%	79.1%
McBride *et al.* [25], 2015	TE	SVM	AD vs HC	82.4–100%	86.7–100%	87.5–93.8%
			AD vs MCI	88.2–100%	64.7–93.8%	81.8–90.9%
			MCI vs HC	87.5–100%	86.7%	87.1–93.6%
McBride *et al.* [38], 2014	SampEn + SpectEn + LZC + Other spectral mesures	SVM	AD vs HC	64.7–100%	80.0–88.2%	71.9–96.9%
			AD vs MCI	82.4–88.2%	87.5–100%	87.9–90.9%
			MCI vs HC	93.8–100%	73.3–100%	83.9–96.8%
Nobukawa *et al.* [34], 2020	MSE	SVM	AD vs HC	NR	NR	73.5%
Perez *et al.* [64], 2022	RP + HjC + SE	MLP	MCI vs mild AD + HC	NR	NR	NR
Polat [62], 2022	PE + Complexogram	MobileNet	AD + HC	45%–100%	48–100%	48–100%
Puri *et al.* [63], 2022	ShE + TsE + ReEn, K	EBT	AD + HC	90.49%	97.50%	96.20%
		SVM		89.35%	96.50%	93.80%
		KNN		86.69%	96.75%	93.10%
Puri *et al.* [59], 2023	ShE + TsE + ReEn + DWT + VMD	DT + SVM + EBT + KNN + NN	AD vs HC	96.06%	99.50%	97.70%
			AD vs MCI	89.35%	100%	94.70%
			AD vs MCI vs HC	91.25%	99.75%	95.20%
Ruiz-Gómez *et al.* [37], 2017	SpectEn + SampEn + FuzzyEn + LZC+ AMI + Other non- linear measures	LDA	HC vs AD + MCI	82.3%	64.7%	76.4%
			AD vs HC + MCI	82.3%	64.7%	74.5%
		QDA	HC vs AD + MCI	79.4%	76.4%	78.4%
			AD vs HC + MCI	64.7%	79.4%	74.5%
		MLP	HC vs AD + MCI	82.3%	70.5%	78.4%
			AD vs HC + MCI	70.5%	79.4%	76.4%
Staudinger & Polikar [26], 2011	SpectEn + HFD + SC + ZCR	SVM	AD vs HC	NR	NR	78.0%

Table 4. Continued.

Study	Method	Classifier	Class	Sensitibity	Specificity	Accuracy
Sharma *et al.* [39], 2019	SpectEn + FD	SVM	AD vs HC	82.0%	82.0%	82.0%
			AD vs MCI	83.0%	63.0%	73.4%
			MCI vs HC	86.0%	81.0%	84.1%

Note. Source: Own elaboration. Sensitivity is the ability to correctly detect individuals who do have the condition or disease. Specificity is the ability to correctly identify individuals who do not have the condition or disease, and accuracy is the overall ability of the test to correctly classify all individuals, both healthy and sick. A test is considered more useful the higher its sensitivity and specificity, which are related through accuracy. EpEn, Epoch-based Entropy; DEI, Dispersion Entropy Index; DWT, Discrete Wavelet Transform; MSE, Multiscale Entropy; SpectEn, Spectral Entropy; SampEn, Sample Entropy; FuzzyEn, Fuzzy Entropy; LZC, Lempel-Ziv Complexity; AMI, Auto-Mutual Information; ApEn, Approximate Entropy; fApEn, Fuzzy Approximate Entropy; TE, Transfer Entropy; HFD, Higuchi Fractal Dimension; SC, Spectral Centroid; ZCR, Zero-Crossing Rate; SVM, Support Vector Machines; FLC, Fuzzy Logic Controller; QDA, Quadratic Discriminant Analysis; LDA, Linear Discriminant Analysis; MLP, Multilayer Perceptron Neural Network; SCC, Subjective Cognitive Complaint; MCI, Mild Cognitive Impairment; HC, healthy controls; NR, Not Reported; HjC, Hjorth Complexity; K, Kurtosis; FDispEn, Fluctuation-based Dispersion Entropy; VMD, Variational Mode Decomposition; EBT, Ensemble Bagged Tree; PE, Permutation entropy; TsE, Tsallis entropy ; KNN, k-nearest neighbors; NN, neural network; RP, relative power; DT, decision tree.

crease in entropy on short scales stems from a reduction of the signal's spectral component in the highest frequencies concerning the spectral element for lower frequencies [37].

Entropy and Machine Learning

The use of machine learning algorithms for analyzing biological signals has several advantages: reviewing large volumes of data to detect specific patterns or trends, having the possibility of continuous improvement, and being good at handling multi-dimensional data in dynamic environments [70]. Studies that used these algorithms to classify patients with AD versus individuals without AD diagnoses showed, in some cases, high values of sensitivity, specificity, and accuracy. However, the wide range of values could be influenced by the great heterogeneity in the studies, which involves different measures, algorithms, and inclusion criteria (e.g., patients with MCI or SCC). These characteristics make it difficult to compare studies directly [37,60]. In addition, algorithms require a large amount of high-quality data, and their development and interpretation require highly qualified professionals in the field [70], which poses some challenges and always requires a cost-effectiveness evaluation [64].

Conclusions

In conclusion, we found that the reduction of MSE is a complexity indicator that consistently detects AD and its severity. However, it is necessary to reproduce these findings by standardizing the measurement processes and building normative variability values to apply these measures in clinical practice. The latter may facilitate the evaluation process, especially in cases where clinical diagnostic criteria are insufficient or the presentation is atypical.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MAZ, ÁAG, JCRC, MÁUL, and DABR conceptualized and designed the review. MAZ, ÁAG, MCMB, MPVR, and BIF performed the search and data acquisition. MAZ, ÁAG, JCRC, BIF, MCMB, and MPVR analyzed and synthesized the data. ÁAG, JCRC, and MÁUL provided supervision. All authors contributed to drafting or making significant editorial changes to the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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