Chapter 16
Fractal Dimension Analysis in Neurological Disorders: An Overview

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Abstract Fractal analysis has emerged as a powerful tool for characterizing irregular and complex patterns found in the nervous system. This characterization is typically applied by estimating the fractal dimension (FD), a scalar index that describes the topological complexity of the irregular components of the nervous system, both at the macroscopic and microscopic levels, that may be viewed as geometric fractals. Moreover, temporal properties of neurophysiological signals can also be interpreted as dynamic fractals. Given its sensitivity for detecting changes in brain morphology, FD has been explored as a clinically relevant marker of brain damage in several neuropsychiatric conditions as well as in normal and pathological cerebral aging. In this sense, evidence is accumulating for decreases in FD in Alzheimer's disease, frontotemporal dementia, Parkinson's disease, multiple sclerosis, and many other neurological disorders. In addition, it is becoming increasingly clear that fractal analysis in the field of clinical neurology opens the possibility of detecting structural alterations in the early stages of the disease, which highlights FD as a potential diagnostic and prognostic tool in clinical practice.

Keywords Brain tumors · Complex systems · Cognition · Clinical neurology · Fractal dimension

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A. Di Ieva (ed.), *The Fractal Geometry of the Brain*, Advances in Neurobiology 36,
https://doi.org/10.1007/978-3-031-47606-8_16

16.1 Introduction

Fractals are geometric objects that are self-similar at distinct scales and can be found widespread in nature, appearing in many research domains, including dynamical systems, physics, biology, and behavioral sciences [61]. In recent years, fractal analysis has emerged as a powerful tool for characterizing irregular and complex patterns found in the nervous system. Specifically, the concept of fractal geometry objectively analyzes and quantifies the intricate structures conforming the topological and functional patterns of the human brain, elucidating how it works at a system's level. Fractal analysis has thus become a promising method to aid physicians and scientists in the diagnosis of certain neurological conditions, prediction of clinical outcomes, classification between pathological states, and detection of disease progression in the brain, with the ultimate goal of aiding novel therapeutic strategies and preventative medicine.

In the field of neuroscience, fractal analysis is used to measure the scaling properties inherent to neurological systems (e.g., neuroanatomical structures at the micro, meso-, and macroscale) and is typically applied by estimating the fractal dimension (FD), a scalar index that describes the topological complexity of the object under investigation. A wide range of neural structures—from neurons to complex networks—can be characterized as structural or dynamical fractals to quantify their intrinsic complexity. In this sense, the spatial properties of irregular components of the nervous system, both at the macroscopic and microscopic levels, may be viewed as geometric fractals, while temporal properties of neurophysiological signals should be interpreted as dynamic fractals [14, 15]. This chapter provides an updated overview of the applications of fractal analysis in human neuroimaging and neurodiagnostics, with a particular focus on clinical neurology.

16.2 Geometric Fractal Analysis Applied to Neuroscience

The convoluted structure of the cerebral cortex poses the problem of how to characterize its morphological complexity quantitatively [19]. Several methods and tools are available for the quantitative measurement of brain volume [34, 62, 66]. However, different factors including the type of MRI machine, brain volume artifacts, clinicopathological conditions, and variability among the standardized protocols may yield important variations in volume estimates [3]. As the field of neuroscience evolves, significant efforts have been made to develop new techniques to analyze the brain and to complement the existing ones, providing crucial knowledge on functionality as well as information surrounding the structural alterations, like those seen in neurological diseases. In this sense, one of the most promising indices is the fractal dimension (FD), a measure that has long been applied to estimate the topological complexity of natural structures [42] and that has been employed to evaluate brain complexity across multiple scales [17, 25, 45].

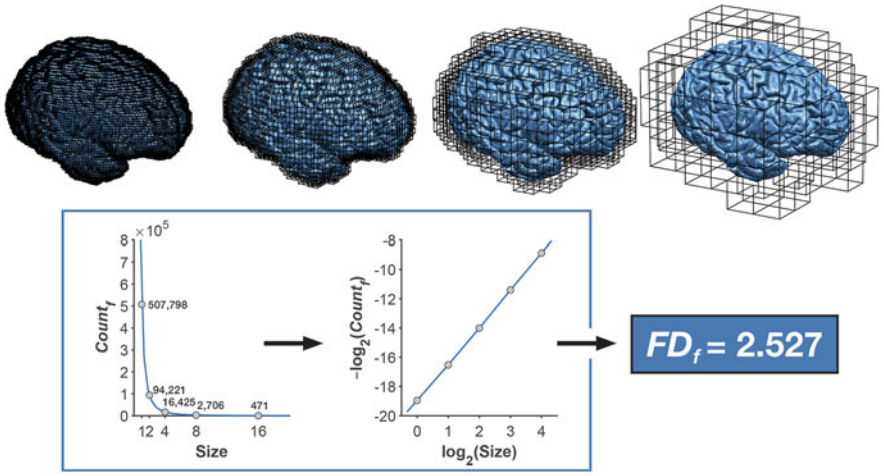

Fig. 16.1 Illustration of the box-counting method of calculating fractal dimensionality. Top: visualization of the number of boxes necessary to contain the brain structure across different box sizes. Bottom: Plot of the power-law relationship between the number of boxes (count) and box size, followed by a conversion to log–log space. The slope of line for this count-size relationship in log–log space represents the fractal dimensionality estimate of the structure. (Figure reprinted from Madan [36] with permission)

Given its sensitivity for detecting changes in brain morphology, FD has been explored as a clinically relevant marker of brain damage in several neuropsychiatric conditions as well as in normal and pathological cerebral aging [40, 55]. There are several different methodologies to compute the FD index empirically from structural MRI data. One of the most commonly applied methods is the box-counting algorithm, which is suitable to study the cerebral cortex [25, 38] and is illustrated in Fig. 16.1. Nonetheless, other approaches to measure cortical complexity through FD include techniques based on the Fourier transform, surface dilation, and spherical harmonic reconstructions [6, 18, 39, 46, 65]. In this sense, significant efforts to elucidate how much FD is related to other indices such as thickness and gyrification are of special interest to characterize the potential value of this measure for new insights into cortical architectural features [38, 53]. It is worth highlighting that several studies reported FD estimates as sensitive to multiple aspects related to data acquisition and processing, which may cause these research outcomes to be heterogeneous and therefore not directly comparable [45]. Nonetheless, formal evaluations have provided evidence that FD has higher test–retest reliability than conventional measures of brain structure [39], as well as is more robust to head motion-related artifacts [35]. This chapter reviews and summarizes recent literature on the application of FD to describe cortical brain complexity in healthy and clinical individuals, as well as to outline future lines of research in this field.

16.3 Relationship Between Fractal Dimension and Healthy Subjects

16.3.1 Aging and Development

A wide range of computational methods for calculating FD have been used to perform different experiments involving age, development stage, and clinical condition, among others. Generally, these research analyses focus on how cortical complexity varies during development and aging in nonpathological situations. For example, in addition to the studies described in Esteban et al. [17], Reishofer et al. [55] concluded that alterations of WM complexity can be reliably measured with fractal analysis in a large cohort of healthy aging subjects. This outcome suggests that FD may be considered a valuable biomarker for identifying WM structural changes in the human brain. More recently, Marzi et al. [43] conducted machine learning models for individual age prediction in two large datasets of healthy individuals. Their findings showed that the selections of the interval of spatial scales were relevant for a more suitable characterization of fractal properties of the cerebral cortex, as well as for a more accurate estimation of FD. Moreover, this work reported a monotonic reduction in structural complexity of the cortex with age during almost all the lifetime. Furthermore, an overall reduction in FD with age is reported in several studies that analyzed this index in healthy adults and elderly subjects [22, 28, 31, 32, 37, 38, 40, 43, 44]. Interestingly, a negative association between age and FD has been described at different spatial levels, including the whole brain [38, 40, 43, 44], the left dorsolateral prefrontal cortex [32], and in the posterior wall of the right central sulcus [28]. A comparative FD analysis was performed by [22] in different age groups, where altered values of FD were observed between young adults (<45 years), middle adults (45–60 years), and old adults (>65 years); more precisely, FD decrease was reported from young to middle age in the bilateral frontal, left frontal, and right limbic lobes, while from middle to old age, the FD reduction was observed in the bilateral temporal, parietal, and left limbic lobes, respectively. Nevertheless, an increase in FD estimates of the left middle orbitofrontal cortex region was highlighted from young to middle age and of the occipital lobe area from middle to old age groups.

Furthermore, two longitudinal studies yielded similar results, observing a negative relationship between FD and age ([31, 37]; reviewed in [45]). In comparison to other cortical measures, such as cortical thickness or gyrification index, FD appears to be more sensitive to age-related differences. Last, regarding gender differences, two studies reported that the reduction in FD was faster and more significant in males than in females [22, 28]. Similarly, one study in a large sample from the UK Biobank observed differential patterns of age-related changes in cortical FD according to sex, with relatively more age-affected regions in males [48].

16.3.2 Cognition

With respect to cognitive functioning, as reported by Meregalli et al. [45], several studies [20, 24, 31, 44, 47] have established that higher FD values were related to better cognitive performance, except for Lu et al. [32], who did not find any relationship between FD and scores derived from the Mini-Mental State Examination (MMSE). Im et al. [20] reported a positive relation between FD of the whole brain and years of education, as well as between FD of the right hemisphere and IQ in a group of healthy young individuals. More recently, Liu et al. [31] analyzed the association of FD values and cognition in subjects ranging from 70 to 90 years old and reported significant correlations between FD and global cognition in distinct brain areas, including the bilateral temporal lobe, left occipital lobe, and several subcortical structures, in line with the results previously obtained by Mustafa et al. [47] for whole-brain fractal analysis. Additionally, Kinno et al. [24] observed positive correlations between FD of several frontotemporal brain areas and memory function in a cohort of older subjects (over 75 years old), assessed by using the scores obtained in the Wechsler Memory Scale-Revised (WMS-R). On the other hand, McDonough and Madan [44] evaluated the association among FD, brain activity, and cognitive functioning in middle-aged and older subjects who were at risk of dementia. Their findings yielded that decreased FD was linked to higher brain activity during memory retrieval in several posterior brain areas and that this pattern was related to cognitive dysfunction.

Finally, Aguillard et al. [1] investigated patterns that emerged in brain signals in response to external stimulating image regimes recorded in a sample of young adults (18–22 years) that were analyzed using nonlinear techniques. Their results showed that subjects who were visually stimulated by a series of mixed images (a randomized set of neutrally or negatively arousing images) exhibited a significantly higher fractal dimension compared to subjects visually triggered by pure images (an organized set of either all neutral or all negatively arousing images). In addition, their findings also revealed that subjects who performed better on memory recall showed higher fractal dimension computed from the electroencephalogram.

16.4 Fractal Analysis and Neurological Disorders

Recent studies have started to compare differences in FD values between healthy control participants and patients with neurological or psychiatric conditions. Here, we summarize some relevant researches carried out in this field, in addition to the investigations outlined in Esteban et al. [17]. Overall, only a few have been conducted so far in these conditions and, therefore, the results obtained are limited and heterogeneous. However, the great majority reported the presence of global or regional FD changes in the clinical population, highlighting the sensitivity of fractal analysis across a wide spectrum of neuropsychiatric disorders [45].

16.4.1 Alzheimer's Disease (AD)

Different studies showed a general decrease in FD in patients with AD in comparison to healthy individuals. In particular, Villamizar et al. [63] performed a comparative analysis between the FD of neuroimages from healthy control subjects and AD patients. Their results showed lower general FD values in AD patients related to neurodegeneration. Also, Nobukawa et al. [50] applied Higuchi's fractal algorithm to evaluate specific temporal fractal properties. Their work established a comparison between the values of the temporal scale-specific FD of AD patient and healthy control groups. Their findings demonstrated that the AD group displayed reduced fractality at both slow and fast temporal scales; furthermore, they were able to correlate fractality at fast temporal scale with cognitive decline, which may be used as a basis for a useful methodology to characterize temporal neural dynamics in AD or other neurodegenerative diseases.

On the other hand, Nicastro et al. [49] and Ruiz de Miras et al. [57] characterized FD using spherical harmonic reconstruction, both reporting a decrease in whole-brain FD in AD patients. Regarding regional specificity, both studies showed reduced FD values in AD patients when compared to healthy subjects, particularly in areas embracing the insula, the temporal medial lobe, and the posterior cingulate cortex. In this line, Ruiz de Miras et al. [57] also observed differences in this index in the temporal pole, whereas Nicastro et al. [49] identified FD values variances between AD patients and controls in the precentral and postcentral gyri.

Moreover, Ruiz de Miras et al. [57] also assessed FD in patients presenting mild cognitive impairment (MCI), detecting that subjects who would develop manifest AD in the following 4 years exhibited lower white matter FD values than non-converter MCI subjects, particularly in the medial frontal lobe. By contrast, McDonough and Madan [44] calculated FD in subjects at risk for dementia without associated cognitive impairment and reported no relation between FD values and AD risk.

Finally, Nicastro et al. [49] and Ruiz de Miras et al. [57] also revealed positive correlation analyses regarding FD and cognitive performance, such that higher cognitive impairments were associated with lower FD estimations.

16.4.2 Frontotemporal Dementia

One of the main studies assessing FD in patients with frontotemporal dementia (FTD) was performed by Nicastro et al. [49], showing an FD decrease in patients when compared to healthy controls, both on the whole-brain level and in areas such as the insula, posterior cingulate cortex, and precentral and post-central gyri. They also conducted correlation analyses, detecting an association between memory, language, and fluency impairment, and decreased FD in the left insula, inferior temporal, and medial orbitofrontal gyri. Likewise, Sheelakumari et al. [59]

investigated FD in two subtypes of FTD: behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA). An overall reduction in FD was observed in both subtypes when compared with healthy individuals. In addition, whereas PPA appeared to be characterized by low FD in the left hemisphere of the brain, bvFTD was associated with an FD decrease in the right hemisphere, potentially linked to the behavioral manifestation of FTD. This hypothesis was supported by the identification of a negative correlation between the FD of the right hemisphere of bvFTD patients and their score on the frontal system behavior scale, which showed that less complexity was related to worse clinical status. Finally, Ziukelis et al. [68] provide a systematic review of fractal analysis in neurodegenerative diseases and dementia.

16.4.3 Multiple Sclerosis

Apart from the studies highlighted in Esteban et al. [17], research by Roura et al. [56] applied cortical FD as calculated by the box-counting method for the prediction of disability worsening in a cohort 146 of subjects suffering from relapsing-remitting multiple sclerosis (RRMS) with up to 5 years of clinical follow-up. Fractal analysis of the brain structures was conducted to evaluate whether significant differences exist between RRMS patients and healthy controls. Their findings unveiled that whole brain, cortical and deep grey matter FD, and whole brain, cortical and white matter FD lacunarity differed between the two cohorts. Furthermore, a longitudinal analysis assessing the 5-year follow-up revealed a significant reduction in fractal dimension and an increase in lacunarity. The authors applied linear mixed models that fitted the distribution of the annual variations in the FD and lacunarity of the brain areas under study in order to evaluate the changes that may appear in brain fractal geometry in relation to the duration of the disease. The models exhibited significant changes in the cortical and white matter FD and for cortical, grey matter, and white matter lacunarity in association with the disease duration. In particular, a decrease in the cortical FD, white matter FD, and grey matter FD was found. Last, a multivariate analysis was performed considering the relationship between brain volume and the presence of lesions with disability worsening, and results indicated a higher risk for disability worsening for cortical FD when adjusting for the presence of lesions and a trend for higher risk of disability worsening when adjusting for grey matter volume. To sum up, their results showed that cortical FD identified a subset of patients with brain damage who were at a higher risk of disease progression in short- to mid-term. The comparison of the risk based on cortical and grey matter fractal geometry yielded cutoffs associated with a higher risk of disability accumulation on several disability scales. Fractal geometry was thus pictured as a complementary measure that may represent a biomarker for disease monitoring and prognosis in patients with multiple sclerosis, even though multicenter validation studies in prospective cohorts will be required to confirm these findings.

16.4.4 Parkinson's Disease (PD)

As outlined in Meregalli et al. [45], two main studies are worth noticing regarding the application of fractal analysis in PD. First, Li et al. [29] described decreased values of FD in patients suffering from the disease in different brain areas, such as left precentral and postcentral cortex, left superior frontal cortex, left caudal middle frontal cortex, bilateral superior parietal cortex, and right superior temporal cortex. Additionally, a lower FD value in the left postcentral cortex was associated with a longer duration of the disease under study. By contrast, Kubera et al. [26] did not discover changes in FD in association with PD, despite the significant thinning of the cortex. However, it should be considered that the number of samples analyzed in the latter work was low, what may have limited statistical power.

16.4.5 Epilepsy

In addition to the research described in Meregalli et al. [45], two recent studies have extended this field of research. Lu et al. [33] used two indicators, Sample Entropy (SampEn) and Higuchi's Fractal Dimension (HFD) to identify epileptic signals characterized as being chaotic and nonlinear. By applying a support vector machine (SVM) classifier to these features, they were able to automatically classify the most EEG signal segments with an accuracy of 89.8%. Although preliminary, their results may provide theoretical guidance for the recognition or prediction of epileptic EEG signals in clinical practice.

Moreover, Malekzadeh et al. [41] proposed a new method for early identification of epileptic seizures in EEG signals by applying nonlinear features based on FD and a deep learning model and using Bonn and Freiburg datasets to perform empirical analyses. Their findings yielded that the proposed methodology achieved an accuracy of 99.736% and 99.176% in the automatic diagnosis of epileptic seizures in EEG signals for the Bonn and Freiburg datasets, respectively.

16.4.6 Autism Spectrum Disorder (ASD)

In addition to the articles described in Esteban et al. [17], two recent studies have addressed the study of FD in autistic individuals. Zhao et al. [67] measured FD values of the right and left cerebellar cortex in male children with autism spectrum disorder (ASD) and typically developing peers, identifying a decrease in FD estimates in the right cerebellar cortex of autistic children. Moreover, they detected a significant positive correlation in the ASD group regarding the FD values and the difference between performance and verbal IQ. On the other hand, Radhakrishnan et al. [54] investigated EEG signals of ASD using Higuchi Fractal Dimension

(HFD). These authors analyzed brain responses for auditory/visual stimuli in typically developing children and children with autism through EEG, attempting to characterize brain dynamics with HFD. Since one of the key parameters implicated in the computation of HFD is the time interval parameter "k," most researchers arbitrarily fix the value of "k" in the range of all channels to estimate the degree of nonlinearity in an EEG signal. As a result of their research, they ultimately proposed an algorithm to estimate the optimal value of the time parameter for each channel. Their statistical analysis revealed that a difference of 30% was observed between autistic and TD children.

16.4.7 Attention Deficit Hyperactivity Disorder (ADHD)

Avelar et al. [4] hypothesized that the dynamics of exploratory movements may predict differences in the use of information by children with ADHD when compared to their typical development (TD) peers. Their findings supported this hypothesis, suggesting that ADHD patients exhibit deficits in dynamic touch that may be crucial for the organization of effective, task, and context-sensitive movement patterns, which manifested as reduced sensitivity to mechanical information supporting perception of object properties by wielding. Importantly, they reported significant differences between children with and without ADHD related to temporal correlations (degree of fractality), particularly how the fractality of exploratory movements of the rod and hand moderated children's emphasis on the first principal moment of inertia (I1). In TD children, lower hand fractality and greater rod fractality were related to increased emphasis on I1. By contrast, children with ADHD increased emphasis on I1 when the exploratory movement was characterized by greater hand fractality and lower rod fractality. Generally, their study suggested that this result may be taken to reflect differences in the coordination of multiscale processes involved in information sampling and use, although further research on this topic is required. On the other hand, Wang and Kamata [64] proposed a novel classification approach using 3D fractal dimension complexity map (FDCM) for ADHD automatic diagnosis. By calculating the Hausdorff fractal dimension of grey matter density data extracted from structural MRI information, they designed a 3-dimensional convolutional neural network that allowed to estimate features from FDCM and discerning between ADHD children and typically developing peers. Additionally, Dawi et al. [7] analyzed the fractal dimension and sample entropy of EEG signals to investigate the changes in EEG signals' complexity, concretely the decrease in attention and memory of patients with ADHD with respect to normal subjects while playing a serious game. Their findings exhibited a reduction in FD and sample entropy of EGG signals for ADHD individuals, which may reflect their lower attention. They concluded that the decrease in attention and memory in ADHD patients could be mapped on the reduction of complexity and memory of their EEG signals. Last, Sho'ouri [60] looked for differences in eye movements in patients with ADHD and healthy people while performing an attention-related task.

The two groups were classified using the vector derived from the calculation of two features, approximate entropy (ApEn), and Petrosian's fractal dimension (Pet's FD) of electrooculogram (EOG) signals, along with support vector machine (SVM) and neural gas (NG) as another two classifiers. Their findings described that the values of both features were significantly lower in the ADHD group compared to the control group. Furthermore, the SVM classifier was more successful in separating the two groups than the NG. In conclusion, the reduction in ApEn and Pet's values in the EOG signals of the ADHD patients group explained that their eye movements were slower than the control group and this difference was due to their attention deficit.

16.4.8 Brain Tumors

Di Ieva et al. [8, 9, 10, 11, 12, 16] showed that the fractal dimension is an objective parameter to characterize brain tumors on neuroimaging and histopathology, offering a new prognostic, diagnostic, and therapeutic biomarker.

Moreover, fractal parameters can be used as morphometric and radiomic parameters to differentiate different types of brain tumors, as demonstrated by Jang et al. [21], Karsy et al. [23] and Petrujkic et al. [52].

Benson et al. [5] proposed a robust method for MR brain image classification based on FD. Their methodology assumed that brain tumors may increase the intracranial pressure (ICP), thus changing its normal structure and that those alterations could be effectively characterized by using fractal analysis. Their findings showed that the presence of tumors can cause significant changes in the fractal dimension of grey matter and white matter and used this variation in FD for the classification of MR brain images into two groups: with and without tumor. More recently, Sánchez and Martín [58] also explored morphological and fractal properties of brain tumors; they hypothesized that parameters extracted from the tumor interface fluctuations would allow for the characterization of the particular growth model, which could be relevant for an appropriate diagnosis and the correspondent therapeutic strategy. In this sense, they analyzed these fluctuations to determine generalized FD. Their results showed that tumor-interface FD, along with other parameters, may help to discriminate between gliomas and meningiomas or schwannomas.

16.4.9 Vascular Disease

A recent study conducted by Aminuddin et al. [2] explored the potential use of FD as a marker in cerebral small vessel disease (CSVD) and correlation with clinical sequalae of CSVD. Their findings revealed that asymptomatic CSVD subjects (from the incidental MRI finding of the presences of low white matter hyperintensity (WMH) burden) had significantly lower FD in comparison to the control subjects,

suggesting that FD may serve as a promising vascular neuroimaging biomarker for asymptomatic CSVD subjects from the presence of low WMH burden, since FD is an index that measures the complexity of a self-similar and irregular structure, such as circle of Willis and its tributaries. Previously, Pantoni et al. [51] evaluated changes in FD between healthy subjects and patients with small vessel disease (SMD) and mild cognitive impairment (MCI). By calculating white and grey matter FD changes, the authors observed a decrease in whole-brain white matter FD in individuals suffering from SVD. Moreover, their findings also reported a positive correlation between FD values and cognitive performance, such that a reduction in white matter FD was related to worse cognitive outcomes.

On the other hand, Lemmens et al. [27] conducted a systematic review of FD in the retinal vasculature to explore its role in neurodegeneration and stroke. The literature suggested that, overall, the central pathology is related to a reduction in FD as a measure of microvascular network complexity and considered this index as a promising noninvasive and cost-effective biomarker for the diagnosis of neurodegenerative and cerebrovascular disease. Similarly, Liew et al. [30] applied fractal analysis to estimate the branching complexity and density of the retinal vessels and its relationship with long-term stroke mortality. They reported that a decrease in retinal vascular FD, that is, a sparser vascular network, may be associated with cerebral tissue hypoxia and an increased risk of long-term stroke mortality. Nevertheless, further analyses should be conducted to validate FD performance as a neurodegeneration biomarker in clinical practice.

Di Ieva et al. [13, 14] have introduced a novel methodology to characterize the geometrical complexity of the arteriovenous malformations' (AVM) vascular nidus, proposing the nidus' FD as a promising angioarchitectural parameter predicting the response to gamma knife radiosurgery.

16.5 Conclusion

Overall, evidence is accumulating for decreases in FD across a variety of neuropsychiatric disorders, including AD, FTD, PD, and MS, and many other neurological diseases. It is becoming increasingly clear that fractal analysis in the field of neurodegenerative disorders opens the possibility of detecting structural alterations in the early stages of the disease, which highlights FD as a potential diagnostic and prognostic tool in clinical practice. In addition, FD alterations were also found to be linked to clinical worsening in different neurological conditions. Thus, further research is warranted to evaluate the association between topological complexity and specific clinical parameters and to assess the reliability of the different methodologies employed to calculate FD, with the objective of specifying the most appropriate techniques for the respective research questions. In conclusion, this overview shows that fractal analysis represents a valuable tool to describe brain complexity in healthy populations and to identify morphological alterations related to developmental or pathological conditions. Nonetheless, the present chapter also

revealed a lack of longitudinal studies in the existing FD literature, which will be of great relevance to better understand the prognostic role of fractal analysis in different neurological conditions and disease stages.

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