Review

Fractals in the Neurosciences, Part II: Clinical Applications and Future Perspectives

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Abstract
It has been ascertained that the human brain is a complex system studied at multiple scales, from neurons and microcircuits to macronetworks. The brain is characterized by a hierarchical organization that gives rise to its highly topological and functional complexity. Over the last decades, fractal geometry has been shown as a universal tool for the analysis and quantification of the geometric complexity of natural objects, including the brain. The fractal dimension has been identified as a quantitative parameter for the evaluation of the roughness of neural structures, the estimation of time series, and the description of patterns, thus able to discriminate different states of the brain in its entire physiopathological spectrum. Fractal-based computational analyses have been applied to the neurosciences, particularly in the field of clinical neurosciences including neuroimaging and neuroradiology, neurology and neurosurgery, psychiatry and psychology, and neuro-oncology and neuropathology. After a review of the basic concepts of fractal analysis and its main applications to the basic neurosciences in part I of this series, here, we review the main applications of fractals to the clinical neurosciences for a holistic approach towards a fractal geometry model of the brain.

Keywords
brain, electroencephalography, fractal analysis, fractal geometry, neuroanatomy, neuroimaging, self-similarity, tumors

Fractals in the Neurosciences, Part II: Clinical Applications and Future Perspectives

Speculations on fractal geometry of nature, introduced by Benoit Mandelbrot (1983), have been extended over the last decades into a universal approach for the analysis of the biomedical sciences. The analysis of the complexity of natural objects, including the biological systems that exhibit self-similar patterns and scaling properties, has led to the study of fractal geometry of life. In addition to other subdisciplines such as genomics, proteomics, and metabolomics (the suffix “-omics” refers to the concept of “wholeness”), the new field of fractalomics has been introduced (Losa 2009). The fractal dimension (FD), according to Mandelbrot’s (1975) definition, has been “injected” into several fields, and the natural evolution of the field has led to the introduction of fractal analysis in neuroscience, a field that could be defined as “neurofractalomics.”

The concepts derived from fractal theory and described in the first article of this series (Di Ieva and others in press) have been demonstrated as useful in characterizing the neurological systems, from simple cells to complex networks. The different types of fractals appearing in the life sciences have been applied to general physiology and pathology (West 2010) and to clinical neurosciences. As we describe below, the spatial properties of irregular structures making up the nervous system, such as the brain, the cerebellum, or the cerebral vasculature, can be interpreted as geometric fractals, while the temporal or dynamic properties of nervous system signals can be viewed as dynamic fractals. Fractal analysis has been applied to both macroscopic (i.e., anatomic) and microscopic (i.e., histological) images as well as high-resolution radiological imaging (i.e., MRI) to quantify the developmental complexity of the human cerebral cortex; the alterations occurring in the brain of patients with epilepsy, schizophrenia, stroke, multiple sclerosis, and cerebellar degeneration; and the morphological differentiation

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of the peripheral nervous system (Esteban and others 2009; King and others 2010). The alterations of fractal properties that underlie these diseases have clinical implications for diagnosis and for the potential prediction of patients’ outcomes (Thamrin and others 2010).

**Fractal Analysis in Neurological Disease**

The FD, the estimate of the topological complexity of an object, has been proposed as a potential surrogate marker of the degree of brain damage in several psychiatric and neurological alterations because of its sensitivity in detecting brain changes, including those observed in normal and pathological cerebral aging. The FD (computed by means of the box-counting method) of white matter (WM), segmented from MRI scans of the brain, has been shown to be significantly lower in older patients when compared to young adults, while conventional volumetric measurements for brain atrophy did not detect any changes with age (Zhang and others 2007). Using a similar approach, Mustafa and others (2012) have shown individual differences in the FD of the cerebral WM that were significantly associated with lifelong cognitive changes, independent of sex and WM volume. In addition, using a novel approach, the FD of the cortical ribbon showed greater distinction between normal controls and patients with mild Alzheimer disease (AD) compared to cortical thickness or gyrification index measures (King and others 2010).

The structural alterations underlying other cognitive and mental disorders have also been detected by fractal analysis of MRI scans of the brain. Using the “fractal information dimension” (FID) as a robust geometric measure, abnormalities of prefrontal cortical gyrification complexity have been detected in children showing attention deficit hyperactivity disorder (Li and others 2007). These authors showed that higher cortical convolution complexity results in a greater FID value (which is scale free by self-normalization), thus avoiding the effect of brain size related to commonly used measures such as cortical volume and thickness (Fig. 1). In dyslexic adolescents, volumetric structural changes have been detected in both gray matter (GM) and WM of the brain. Further measurements such as the ratio of GM/WM and the FD of the GM-WM boundary contour were proposed as markers of vulnerability to dyslexia because changes in these parameters, particularly in the left hemisphere, were also detected (Sandu and others 2008b). Using a similar FD estimation approach, some of these authors also found anomalies of structural cortical folding in patients with schizophrenia, which was not observed with traditional MRI morphometric analysis methods (Sandu and others 2008a).

Fractal analysis has been widely applied to investigate cerebral vascularization in its entire physiopathological spectrum. The spatiotemporal complexity of cerebral hemodynamics has been studied by means of fractal characterization (Herman and others 2001; Panerai 2009). The highly complex microcirculation of the human brain...
can be assessed by means of three-dimensional (3D) morphometric analyses (Minnich and others 2001). Several studies have been performed for the quantitative analysis of such results (Cassot and others 2006; Heinzer and others 2006; Lauwers and others 2008). Also, the FD has been applied to estimate the structural vascular complexity in MRI scans obtained from patients with arteriovenous malformations (AVMs) (Reishofer and others 2012; Di leva and others, in press). In fact, AVMs are related to the risk of morbidity and mortality due to intracerebral hemorrhaging and/or seizures. The angiostructural and dynamic properties of AVMs provide the basis for diagnosis and further intervention. Thus, the FD, as determined by application of the box-counting method and the Minkowski dimension, captures the emergent complexity of AVMs because of the increased number of feeding arteries. In addition, the FD was strongly correlated to physiological parameters such as the contrast media transit and the vessels’ nidus size, providing a simple and robust technique that can be automatically assessed to characterize this vascular disorder of the brain (Reishofer and others 2012). The FD of the AVMs’ nidus is an angiarchitectural quantitator as well as a potential image biomarker for predicting the successful obliteration of the nidus after γ knife radiosurgery treatment (Di leva and others, in press). Fractal-based analyses have also been used for the quantification of retinal microvascular changes as potential markers of stroke and other vascular-related diseases of the brain (Cavallari and others 2011; Cheung and others 2013; Doubal and others 2010; Jiang and others 2013; Kawasaki and others 2011; Ong and others 2013; Talu 2011).

In regards to other neurological diseases, the application of fractal analysis of MRI scans has provided results of potential clinical diagnostic significance. It has been demonstrated that changes in both WM (Esteban and others 2007) and GM (Esteban and others 2009) are well characterized by the FD in MRI scans that appear normal (i.e., without the characteristic cerebral lesions) in early stages of multiple sclerosis. This approach has been proposed as a useful early diagnostic biomarker of the disease and therefore could potentially be used in clinical decision making. In addition, some of these authors also detected changes in the FD of the brain in premature infants with a prenatal diagnosis of severe intraterine growth restriction (IUGR) when compared to premature infants without IUGR and full-term controls. These changes were related to neurodevelopmental functional disorders (Esteban and others 2010). In multiple system atrophy of the cerebellar type (MSA-C), which is a degenerative neurological disease of the central nervous system, the FD analysis of MRI scans using the box-counting method has been demonstrated to be superior to conventional volumetric methods (i.e., fractal analysis produces smaller variances and less gender effect); patients with MSA-C exhibited significantly lower FD values in both cerebellar WM and GM, suggesting a degeneration of the cerebellar structure (Wu and others 2010). Finally, a lower FD value, indicating less WM complexity, has been detected in the affected hemisphere of patients with stroke. Greater WM complexity was associated with better motor function of the affected upper extremity, while no significant correlations were observed when motor function was related to lesion volume (Zhang and others 2008). The authors also proposed the FD as a potential useful clinical parameter for monitoring the level of the residual WM structure or any accompanying neural plastic changes after stroke to guide future therapeutic interventions.

Alternatively to “static” fractal analysis, the different approaches used to characterize dynamic or temporal fractals have been shown as useful tools in quantifying time series and determining the nonlinear dynamic properties of nervous signals in an attempt to distinguish between healthy and diseased individuals. High accuracies of 90% and 99.3% were obtained for the diagnosis of autism and AD, respectively, when classifying Katz’s (1988) FD of electroencephalography (EEG) (Ahmadlou and others 2010, 2011). Higuchi’s method (1988) was selected for estimation of the EEG FD with the aim of analyzing the influence of lorazepam, a benzodiazepine drug with strong anxiolytic effects, on brain activity, confirming the hypothesis that this drug decreases the complexity of α bands and increases the complexity of β bands (Michail and others 2010). Moreover, Katz’s FD values of actigraphy data were significantly lower during the night in patients with dementia (including AD) and aggressive behavior when compared to controls (Besthorn and others 1996; Etcher and others 2012), thus detecting changes in the circadian rest-activity system motor in altered neurological conditions. A differential box counting–based approach has also recently been presented as a new detection method of epileptic seizures from multi-channel long-term EEG signals (Yuan and others 2012), which provides much higher sensitivity and a lower false detection rate when compared to other methods for EEG seizure detection.

**Fractal Analysis in Neuroimaging**

Because of the complex processes of gyrogenesis and sulcogenesis, the human brain’s cortex is highly folded, with a great part of its surface buried within the folds (Armstrong and others 1995). As in many other biological objects, the cerebral cortex is not a perfect mathematically fractal structure because the brain is not strictly self-similar (Zhang and others 2007). However, the model can still be usefully applied to the quantification of cortical complexity (Blanton and others 2001) (Fig. 2).
Hofman (1991) showed that the whole brain cortex has fractal features, as confirmed by further studies (Free and others 1996; Kiselev and others 2003; Majumdar and Prasar 1988).

Fractal analysis has been shown to be appropriate for the analysis of MRI scans (Swarnakar and others 1996) and for the automatic segmentation and identification of differently shaped lesions (Iftekharuddin and others 2011; Lahmiri and Boukadoum 2012). Fractal-based morphometric analysis has been shown as a robust and highly reproducible approach for characterizing the structural complexity of the human brain’s GM and WM structures (Goñi and others 2013) as well as for cortical surface folding complexity (Yotter and others 2011) (Fig. 3).

As previously reported, fractal analysis has been applied in several neuroimaging research contexts with clinical applications. The FD has been shown to be more accurate than other methods (i.e., volumetric voxel-based morphometry) for the detection of WM changes in several diseases and for identifying different clinical phenotypes such as amyotrophic lateral sclerosis (Rajagopalan and others 2013) (Fig. 4), AD (King and others 2010), multiple sclerosis (Esteban and others 2007, 2009), and epilepsy (Lin and others 2007). In addition, it has been used for investigating brain development and age-related changes (King and others 2009; Li and others 2011; Mustafa and others 2012; Zhang and others 2007). In the connectomics era, the traditional diffusion tensor models have also benefited from new computational fractal-based approaches for the characterization and measurement of water molecule diffusion in vivo (Jian and others 2007).

Fractal analysis has also been used to quantify the spatial heterogeneity of receptor distribution in PET or single-photon emission computed tomography (SPECT) studies of the brain (Kuikka and Tiihonen 1998). Along with other results, this application of fractal analysis has made it possible to confirm functional hemispheric lateralization (Tiihonen and others 1997). A quantitative fractal-based PET study aimed at assessing the heterogeneity of cerebral glucose metabolism in relation to age has shown increased heterogeneity in nine brain regions in elderly versus young patients (Lee and others 2004). Brain perfusion heterogeneity has been quantified by means of the FD in SPECT studies in simulation models and in patients with subarachnoid hemorrhage (Modzelewski and others 2012; Mustonen and others 2006), confirming FD as a valid descriptor of the overall complexity of cerebral perfusion in evaluating microvascular function. In patients with acute subarachnoid hemorrhage, brain perfusion heterogeneity was shown to be higher than in controls (Mustonen and others 2006). Nagao and others (2004, 2006) showed that SPECT perfusion heterogeneity, quantified by means of fractal analysis, was able to discriminate patients affected by AD from patients affected by frontotemporal lobar degeneration. Furthermore, within an elderly group of patients affected by AD, it was able to discriminate between patients with very early or early onset of symptoms. For a systematic review on the application of fractal analysis in radiological and nuclear medicine perfusion imaging, see Michallek and Dewey (2013).

In addition, fMRI allows for investigation of the amplitude of activation in neural networks of the brain. Indeed, fMRI time series have been analyzed by means of fractal analysis, demonstrating the ability of such an analysis to quantify the dysregulation of dynamic interactions between different limbic system regions in healthy adults in states of increased anxiety (Olejarczyk 2007). Fractal properties and applications of fractal analysis to fMRI can be found in the literature (Bullmore and others 2004; Li and Huang 2013; Rubin and others 2013).

**Fractal Analysis of Brain Tumors**

Tumor growth exhibits complex geometry characterized by apparent irregularities in cell spatial distribution, tumor-host interface width, vascularity, and even tumor time progression. Fractal geometry appropriately describes these irregularities and has been proved as a useful tool for the morphometric characterization of...
**Figure 3.** Changes in cortical thickness (horizontal axis) and gyrification index (vertical axis) of the brain (coronal slice from a control subject seen in the box) affect the fractal dimension (indicated by the number below the slice) of the cortical ribbons. Reprinted from King and others (2009), with permission from Springer.

**Figure 4.** Three-dimensional rendering of white matter skeleton image in a typical (A) control subject, (B) amyotrophic lateral sclerosis (ALS) patient with dementia, (C) ALS patient with corticospinal tract hyperintensity, and (D) ALS patient without corticospinal tract hyperintensity. The fractal dimension has been shown to be more sensitive than volumetric voxel-based morphometry in detecting changes of white matter. Reprinted from Rajagopalan and others (2013), with permission from the publisher.
cancer dynamics. In particular, the FD has been shown to be a tumor-specific index (Sedivy 1996; Waliszewski 1997).

In the case of brain tumors, the FD has been used for tumor classification, therapy follow-up, and grading (Di Ieva 2012; Iftekharuddin and others 2003; Martin-Landrove and others 2007; Pereira and others 2000). Contrast-enhanced (Pereira and others 2000; Martin-Landrove and others 2007) or susceptibility-weighted MRI scans (Iftekharuddin and others 2003; Di Ieva and others 2013a) were typically used for all of these applications because they exhibit all the noise and randomness that can be associated with tumor lesions. Martin-Landrove and others (2007) obtained clear differences in the FD between malignant and benign brain tumors. Iftekharuddin and others (2003) proposed three modified box-counting algorithms for fractal geometry analysis of MRI scans, which have been widely used for brain tumor detection and estimation of the FD. The most commonly used method, the piecewise–threshold–box-counting method (Iftekharuddin and others 2003), uses a threshold in the pixel intensity values (Pereira and others 2000; Martin-Landrove and others 2007). Other methods have also been proposed (Iftekharuddin and others 2003) including the improved piecewise–modified–box-counting and piecewise–triangular–prism–surface-area methods. In both methods, pixel intensity is treated as a third dimension, making them very suitable for fractal analysis of texture. Di Ieva and others (2012b) performed a preliminary study on fractal geometry analysis of susceptibility-weighted 7-Tesla MRI scans to evaluate the neuroradiological follow-up of brain tumors for monitoring the effects of antiangiogenic therapies in vivo (Fig. 5) as well as for brain tumor (gliomas) grading (Di Ieva and others 2013a) (Fig. 6B). Their findings comprise a range for FDs of intratumoral susceptibility-weighted imaging from a mean value of $1.682 \pm 0.278$ for grade II gliomas to $2.247 \pm 0.358$ for grade IV gliomas, with a statistically significant difference ($P = 0.013$) between histopathological groups (Di Ieva and others 2013a). Gazit and others (1995) showed, by means of fractal analysis, that the tumor vascular architecture is determined by the heterogeneous cellular interaction with the extracellular matrix rather than by simple gradients of diffusible angiogenic factors. They showed that the neoplastic microvasculature may fill the tissue space in a specific way, following

Figure 5. The 7-T MRI scans in a patient affected by the recurrence of glioblastoma multiforme undergoing serial susceptibility-weighted imaging (SWI) (every two weeks, in $T_0$, $T_1$, and $T_2$), showing the increase in the fractal dimension of SWI. Reprinted from Di Ieva and others (2012b), with permission from Elsevier.
a random, locally determined process rather than the globally optimized process found in healthy tissue (Gazit and others 1997).

A combined fractal and scaling analysis has recently been proposed for the characterization of in vitro tumor growth and sectional resected tumors (Brú and others 1998, 2003, 2008) (Fig. 7), showing that the tumor contour exhibits “super-rough” fractal geometry parameterized by a local roughness exponent, $\alpha_{loc}$, which relates the scale-averaged width, $W$, of the tumor-host interface to the scale of growth, given by the arc length, by power-law behavior (Brú and others 1998, 2003, 2008):

$$W(l,t) \sim l^{\alpha_{loc}}.$$  \hspace{1cm} (1)

This analysis has also been applied in vivo to brain tumors using contrast-enhanced MRI (Martín-Landrove and Pereira 2008; Torres Hoyos and Martín-Landrove 2012), showing similar power-law behavior. The FD and the local roughness exponent are related in a general way (Barabasi and Stanley 1995); that is, their sum is always equal to the Euclidean dimension of the embedding space, a fact that can be used as an alternative method for calculating the FD in solid tumors rather than using growth model parameterization. Box-counting FDs comprise a mean range from 2.09 ± 0.10 for glioblastoma multiforme to 2.32 ± 0.03 for benign tumors such as meningiomas and vestibular schwannomas, while local

$W$ is given by the following (Brú and others 1998):  

$$W(l,t) = \left\{ \frac{1}{L} \sum_{x,y} \left[ r_x(t) - \langle r_x \rangle_l \right]^2 \right\}^{1/2}. \hspace{1cm} (2)$$

Figure 6. Vascular trees (human brain vasculature) cast using red latex (A) and botanic tree (D) show similar arborization patterns, which can be analyzed and quantified by means of fractal analysis. The vascular patterns and the "microvascular fingerprinting" of brain tumors can be analyzed by means of fractal analysis in vivo (7-T susceptibility-weighted MRI scans in panel B) and in vitro (histopathological slides of CD34 immunohistochemically positive microvessels of brain tumors in panel C). Panel B reprinted from Di leva and others (2013a), with permission from Springer-Verlag. Panel C reprinted from Di leva and others (2012a), with permission from Nature Publishing Group.
roughness exponents range from a mean $0.90 \pm 0.04$ to $0.67 \pm 0.10$, respectively (Barabasi and Stanley 1995). Risser and others (2007) investigated normal and tumorous 3D microvascular networks in primate and rat brains and performed fractal and power spectrum analysis on high-resolution synchrotron tomography images. Scale-invariant fractal properties were present in a range from 1.4 µm up to 40 to 65 µm for normal vascular networks, and a wider range was expected for tumor vascular networks. The FD was estimated by two methods: box-counting and sandbox (Tél and others 1989). Box-counting FDs of normal vascular networks varied from 1.55 to 1.7, while sandbox FDs ranged from 1.55 to 1.9. In the case of tumor vascular networks, the ranges were from 1.9 to 2.2 (box-counting method) and from 1.9 to 2.4 (sandbox method), showing a clear-cut difference between normal and tumor vascular networks. Di Ieva and others (2012a) applied a fractal-based image analysis technique to quantify the microvascularity in histological specimens of World Health Organization grade II and III gliomas (Fig. 6C). The statistical analysis showed that the fractal-based indexes are the most discriminant parameters to describe the microvessels. The local box-counting FD (loc bcD) that is estimated in a scale range from 1 µm to 1000 µm, and the microvascular FD (mvFD), which is the monofractal dimension of the microvascular pattern of the whole specimen in a standardized scale range, were used to characterize fractal geometry of the vascular network. Figure 6C shows the correlation between the angioscore, assigned by the neuropathologist via observation of each tissue section, and the fractal-based variables, loc bcD and mvFD. Similar results for the mvFD have been obtained in glioblastoma multiforme, indicating that the mvFD is the most reliable morphometric parameter for the quantification of microvascularity in histological specimens of brain tumors (Di Ieva 2010). Furthermore, microvascular network complexity, expressed through the FD parameter, was correlated to the uptake of (11)C-methionine assessed by PET in glioblastoma multiforme in a pilot study by Di Ieva and others (2010). By means of these findings, fractal analysis has been proposed as a potentially valid tool for proving the hypothesis of “microvascular fingerprinting,” namely, that each different type and subtype of tumor has its own specific microvascular architecture (Di Ieva 2012; Di Ieva and Tschabitscher 2012).

Fractal Analysis of Time Series in Neurophysiology

Biosignals including EEG, magnetoencephalography (MEG), or heart rate variability (HRV) contain information about “dynamics,” the changes in the activity of different parts of the nervous system caused by physiological and pathological processes. Indeed, EEG and MEG are electromagnetic signals generated by the brain and registered on the scalp surface. They provide information about functioning, in particular about various dysfunctions of the brain (e.g., changes due to epilepsy) and about changes of the state of the brain due to anesthesia or during different sleep stages (Klonowski 2007a). The human heart is controlled by both the sympathetic (activating) and parasympathetic (inactivating) branches of the autonomic nervous system (ANS). Analysis of HRV obtained via electrocardiogram signals gives information about ANS activity and thus about many disease conditions. Some of these conditions are very elusive and not easily detectable with other diagnostic methods (Pierzchalski and others 2011).

Until the 1980s, biosignals were considered as continuous functions of time. Moreover, EEG was registered on paper tape. The introduction of computers changed this perspective. Now, biosignals are probed with some frequency and analyzed by a computer in the form of time series. Fractal analysis of physiological time series provides an exciting example of the use of fractal methods in neuroscience for obtaining physiological (i.e., dynamic) and not just morphological (i.e., static) information.

Linear methods of time series analysis obtained a boost with the introduction of computer programs for discrete fast Fourier transform (FFT) and further extensions of FFT-like wavelet transform. Linear methods are
simple and quick but may lead to erroneous results (Klonowski 2009). Moreover, they fail to provide the exact location of events in time (RajendraAcharya and others 2006). In principle, linear methods such as FFT are applicable only to stationary signals. Real biosignals, however, are nonstationary. Nonstationarity refers to statistical characteristics of the time series, in particular its mean value as well as standard deviation or correlation function, which are not constant but rather change with time. Nonlinear methods of time series analysis, including fractal methods, still remain misunderstood. Nonlinear methods are generally thought to demand very long input signals and are very sensitive to noise; the truth, however, is often the exact opposite (Klonowski 2009). The term “FD” has many different meanings depending on the context. One example is the FD of a geometric object that quantifies its geometric complexity in space. In this case, the FD quantifies the structural characteristics of the object. Another kind of FD, such as the correlation FD, is calculated in the “phase space” of a dynamic system. To calculate the correlation FD (e.g., with the Grassberger-Procaccia method), the analyzed physiological time series first has to be “embedded” in a properly chosen phase space using the time-delay method, which requires a long time series (Stam 2005). Another type of FD is obtained by estimating the frequency domain. The time series is transformed using FFT, and if the power spectrum of such a series in the frequency domain behaves like frequency to a certain negative power \( \beta \), then the FD of the considered series is equal to \( (1 - \beta) \). Because FFT only works properly for stationary series, however, this is not the proper method for calculating the FD of physiological time series.

Finally, the FD may be calculated directly in the time domain, without transforming the time series to the frequency domain and without embedding data in a phase space. Despite the fact that the frequency domain and phase-space methods are often used in biomedical research, it seems that time domain–based FD algorithms are more effective than frequency domain–based algorithms (Phothisonothai and others 2013). There exist several algorithms for calculating the FD of a time series in the time domain. Higuchi’s (1988) method is one of the most used because of its simplicity and easy interpretation (Klonowski 2007a). The FD, calculated by Higuchi’s method, denoted by \( HFD \), has obvious lower and upper limits, equal to 1 and 2, respectively, because \( (HFD - 1)*100 \) signifies the percentage of the 2D plane that is “occupied” by the curve representing the given time series as a function of time. Simple curves have a Euclidean dimension equal to 1, and so \( HFD = 1 \), while a curve representing pure noise fills up practically 100% of the plane, and so its \( HFD = 2 \). Any time series, regardless of whether it represents a deterministic, stochastic, or “really chaotic” system, may be characterized by \( HFD: 1 < HFD < 2 \).

Klonowski (2007a, 2007b) has used analysis of Higuchi’s (1988) method of EEG for several medical issues such as monitoring the depth of anesthesia and sedation, sleep staging, bright light therapy and seasonal affective disorder, analysis of posturography signals, evoked EEG and photostimulation, and influence of electromagnetic fields generated by cellular telephones. It has been found that HFD may be quite insensitive to artifacts; for example, analysis of the raw sleep EEG signal gives practically the same results in sleep staging as analysis of the same signal from which artifacts had been removed by a specialist (Klonowski 2008).

Results of linear Fourier analysis of EEG signals can be compared with those obtained by fractal analysis using Higuchi’s (1988) method with the following example. Several companies offer devices, called neutralizing protective devices (NPDs), which promote decreased adverse effects of the electromagnetic fields generated by cellular telephones. Using linear Fourier analysis, Bardasano and others (2005) found statistically significant differences in the spectral power of slow EEG waves (\( \delta \) and \( \theta \)) in 16 people (when the cellular telephone was “on”) as compared with the power of the same waves in basal EEG (i.e., when the cellular telephone was “off”). When the telephone was equipped with the NPD, these differences were much smaller. Using Higuchi’s method to analyze the same data, only 1 in 8 people tested by Klonowski (2007b) using Higuchi’s FD showed clear differences in recorded EEG signals when no NPDs were used as compared to basal EEG recordings or with NPDs used (Fig. 8). Thus, according to analysis of Higuchi’s method, only about 15% of the population may belong to a “high-risk” (hypersensitive) group of cellular telephone users. The above-mentioned fractal method may serve for quick and easy assessment of individual susceptibility to electromagnetic fields used in mobile communication as well as for testing of different cellular telephone models for their certification by appropriate institutions.

It has also been shown that MEG signals from patients with AD have lower HFD values than control subjects’ recordings (Gómez and others 2009). The highest accuracy (87.8%) was achieved when the mean HFD over all 148 MEG channels was analyzed, suggesting that spontaneous MEG rhythms are less complex in patients with AD than in healthy control subjects, indicating abnormal dynamics in AD.

Wavelet decomposition of MEG time series, as well as neuroimaging, has also shown that the functional networks of the brain are characterized by small-world properties, implying a scale-invariant or fractal small-world topological organization (Gallos and others 2012) made
up of an anatomic network of functionally connected hubs (Bassett and others 2006; Sporns 2006) (Fig. 9). Moreover, fractal analysis has been proposed as a reliable nonlinear method to study the trend of intracranial pressure, above all in patients with severe traumatic brain injuries (Di Ieva and others 2013b).

**Conclusion**

The nervous system, like other anatomic systems, is a complex system consisting of a number of hierarchical levels of anatomic organization that interrelate differently with each other to form networks of growing complexity. Brain networks are increasingly understood as one of a large class of information processing systems that share important organizational principles including the property of a modular community structure. The brain can be seen as a network of interconnected components whose architecture supports the emergence of adaptive behavior and cognition. The recently introduced concept of fractal geometry has been demonstrated to be a powerful means of quantifying the spatial complexity of real, irregularly shaped objects, which is able to overcome the intrinsic limits of Euclidean geometry. The application of complex network and fractal geometry tools to neuroscience and neuroimaging datasets has recently led to major advances.
in understanding the way the brain works at a systems level. Physical geometry of the brain’s modularity remains to be elucidated completely. Brain regions belonging to the same topological module are often anatomically colocalized. In the brain, like in many other biological systems, self-similarity is statistical rather than exact, so the modular community structure of brain networks is approximately (not perfectly) invariant over a finite number of hierarchical levels. Fractal analysis and other nonlinear techniques also have roles in shedding light on the complexity of cerebral circulation. Normal brain parenchyma has a highly complex microvascular structure that undergoes remodeling in the presence of a tumor, and fractal analysis seems to be a promising tool for the quantification of the microvascular fingerprint of brain tumors. Fractal analysis is a suitable method for quantifying heterogeneity in radiological and nuclear medicine perfusion images under a variety of conditions and in different organs, including the brain. High-resolution 3D reconstructions of GM and WM structures of the human brain can be characterized by quantifying aspects of their shape, volume, and topological complexity. In particular, methods based on fractal analysis have been applied in neuroimaging studies to quantify the structural complexity of the brain in both healthy and pathological conditions. The findings are valuable for defining appropriate parameter configurations when studying changes in fractal descriptors of the human brain structure, for instance, in studies of neurological diseases that do not allow repeated measurements or for disease-course longitudinal studies. The search for fractal patterns has occupied numerous investigators in neuroscience, as in many other fields of science. The application of theories and approaches, including fractal geometry, chaos, and nonlinear dynamics, strongly challenges comprehension of the brain structure and its behavior. The FD has been shown to be a potential surrogate and/or neuroimaging biomarker with several clinical applications.

Fractal geometry is a mathematical model introduced as a new speculative paradigm. Its application to clinical neurosciences as a powerful computational tool requires a research paradigm shift as well as further investigations to be confirmed useful from bench to bedside.

**Note**

All the authors are members of the web community “The Virtual Fractal Lab” at www.fractal-lab.org.

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