Applications of fractal analysis techniques in magnetic resonance imaging and computed tomography for stroke diagnosis and stroke-related brain damage: a narrative review

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Abstract

The fractal analysis technique has emerged as a novel and promising method in mathematical analysis, providing valuable insights across various fields of neuroimaging. The fractal analysis technique allows for the quantitative characterization of complex geometric structures that traditional Euclidean geometry-based morphometric methods fail to describe adequately. This review provides an overview of the principles, characteristics, and main applications of the fractal analysis technique, focusing on its applications and perspectives in stroke diagnosis based on neuroimaging data. In stroke research, the fractal analysis technique has been used to characterize brain tissue, pathological foci, and the vascular network, providing critical diagnostic and prognostic information. Researchers have applied the fractal analysis technique to brain lesions resulting from ischemic strokes to conduct geometric analyses of lesion shapes, indicating its diagnostic and prognostic values. Fractal properties have been used to study the texture of lesions, healthy tissue, and penumbra zones, which is essential for determining the presence and boundaries of damaged brain tissue. Additionally, fractal analysis of intracerebral hemorrhages has shown that hemorrhage geometry is correlated with prognosis and survival rates. This method has been used to assess cortex and white matter configurations in stroke patients, highlighting brain remodeling and compensatory changes. It has also been proven effective in detecting morphological alterations in brain structures during transient ischemic attacks. Moreover, fractal analysis of the brain vasculature revealed changes associated with ischemic stroke and hemorrhage. Overall, the fractal analysis technique in brain magnetic resonance imaging and computed tomography is an informative and sensitive imaging analysis method that, with further development, can significantly improve stroke diagnosis and prognosis on the basis of neuroimaging data.

Key words: brain; fractal analysis technique; fractals; hemorrhage; infarction; magnetic resonance imaging and computed tomography; neuroimaging; neuroscience technology; stroke; technology

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INTRODUCTION

Stroke remains one of the leading causes of disability and mortality worldwide. For example, stroke was the second leading cause of death and the third leading cause of death and disability combined in 2019.[1, 2] These alarming statistics underscore the urgent need for innovative approaches to improve stroke diagnosis, treatment, and rehabilitation.

Neuroimaging, particularly brain magnetic resonance imaging (MRI) and computed tomography (CT), has revolutionized the assessment of stroke-related brain damage by providing detailed structural and functional insights. MRI is generally considered more sensitive and, therefore, the preferable diagnostic method in acute stroke, as some lesions identified by MRI remain invisible on brain CT.[3-6] However, both methods are widely used in clinical practice, and CT retains its diagnostic value.[6]

Despite clear diagnostic criteria and the ability to visualize brain morphology, including the identification of brain lesions, the assessment of neuroimaging data in some cases remains challenging. These cases include but are not limited to differentiating between acute and chronic ischemic lesions,[7, 8] diagnosing transient ischemic attacks and hyperacute strokes often invisible on conventional MRI and CT,[9-11] determining the ischemic penumbra zone and differentiating it from infarcted zones and unaffected tissue,[12, 13] developing prognostic criteria on the basis of neuroimaging data,[14-16] and distinguishing strokes from conditions mimicking stroke lesions.[17-19]

The analysis of MRI and CT data in clinical practice is mainly descriptive and qualitative, with a focus on identifying and assessing brain stroke lesions. The quantitative evaluation of neuroimaging data typically includes morphometric measurements of the lesion, such as volumetry.[20, 21] Recent studies have indicated that lesion geometric parameters, specifically shape characteristics, may differ across different stroke types and are associated with varying prognostic outcomes.[22-24] Therefore, the development of geometric analysis methods for evaluating lesion shape and characterizing brain structures in stroke-related brain damage is highly needed.

Typically, the geometric analysis of brain lesions and structures is limited to methods rooted in Euclidean geometry. Euclidean geometry uses simple geometric measurements (linear dimensions, area, volume, and derivative characteristics) and allows for precise characterization of objects with geometrically simple shapes. However, the shapes of brain structures and lesions are often too irregular to be comprehensively characterized via these methods.

An alternative geometric analysis method, fractal analysis, rooted in mathematical concepts introduced by Benoît Mandelbrot, allows for the examination of irregular, fragmented shapes that traditional Euclidean geometry cannot adequately describe.[25-27] Fractal analysis techniques have emerged as a powerful tool for quantifying the complex, self-similar patterns observed in brain structures and lesions. The brain and its structures are considered fractals.[27-32] Therefore, fractal analysis techniques seem to be a promising method for analyzing neuroimaging data in different stroke subtypes. This method has shown promise in enhancing the detection, characterization, and quantification of brain structures, providing novel metrics that correlate with clinical outcomes.[29]

This review aims to explore the application of fractal analysis techniques in neuroimaging, focusing on brain MRI and CT in stroke-related brain damage. This section discusses the principles of fractal analysis techniques, their implementation in neuroimaging studies, and the potential clinical implications of this approach. By integrating findings from recent research, this article seeks to highlight the strengths and limitations of fractal analysis techniques and propose directions for future studies to improve stroke diagnosis and prognosis.

Search Strategy

The search was conducted in Scopus, Google Scholar, and PubMed for research papers published in English via the keywords "fractal," "fractal analysis," "fractal dimension," "stroke," "infarction," "intracerebral hemorrhage," and "transient ischemic attack." Additional search terms included "MRI," "CT," "neuroimaging," "vasculature," and "vessels." Relevant papers on the application of fractal analysis techniques in neuroimaging for stroke diagnosis and prognosis were selected and reviewed. Additional papers were also identified from the reference lists of these selected studies. Given that fractal analysis is a relatively new technique in stroke research, the timeline of the reviewed papers was not restricted. This narrative review also includes papers that provide essential information on the principles of fractal geometry and fractal analysis techniques in neuroimaging.

Fractal Analysis Techniques and Fractal Dimension: Brief Overview

Fractal geometry and fractals

Fractal geometry is a relatively young field of mathematics that has been applied in virtually all branches of the natural and technical sciences over the past few decades. The founder of fractal geometry and the originator of the term "fractal" is the French and American mathematician Benoît Mandelbrot (1924–2010), who outlined the foundations of fractal geometry.[25-27] The core concept of fractal geometry is the self-similarity of nature, and the geometric objects (mathematical sets) that exhibit this property are broadly termed fractals.[25-27, 33, 34] The fractal can be considered a mathematical set or object characterized by the following features: self-similarity and self-repetition (a part of the object partially or entirely, precisely or approximately, repeats the structure of the whole object); scale invariance (the structure of the object at different scales is similar; increasing the scale does not change the complexity of the spatial organization of the fractal); and the metric dimension of the fractal does not coincide with its topological dimension; the fractal is geometrically irregular (nonuniform) and thus cannot be adequately described via traditional geometric methods.[25-27, 33, 34]

Fractal dimension

Topological and metric dimensions are used to characterize fractals and other geometric figures quantitatively. The topological dimension assigns integer values to geometric objects. Specifically, these values can be only 1, 2, or 3, corresponding to the minimal number of parameters (or coordinates) required to uniquely specify any point within the object's space.[36, 37] For example, consider a line: a one-dimensional object. To identify a particular point on this line, only one coordinate is necessary. This reflects its topological dimension of 1. In contrast, a plane, which is a two-dimensional object, requires two coordinates to determine a specific point within it. This is indicative of its topological dimension being 2. Similarly, a three-dimensional object, such as a volumetric figure or cube, necessitates three coordinates to pinpoint a location within it, thereby assigning it a topological dimension of 3.[36, 37]

The metric dimension of ideal geometric figures (such as a line, plane, or cube) coincides with their topological dimension: the metric dimension of a straight line is one, that of a plane (surface) is two, and that of a filled cube is three. Such structures fill the entire available space within their respective coordinate systems: one-dimensional, two-dimensional, or three-dimensional.[36, 37] However, the metric dimension of structures with geometrically irregular shapes and fractal properties does not coincide with their topological dimension. For example, fractal properties can be inherent to irregular curves **(Figure 1B).** The topological dimension of linear structures, such as this curve, is one. However, if we examine **Figure 1**, we can see how different objects occupy space. A straight line (**Figure 1A**) fills the entire available one-dimensional space; thus, its metric dimension is one. A square, or plane (**Figure 1C**), fills the entire available two-dimensional space and therefore has a dimension of two. Consequently, the metric and topological dimensions of these simple geometric figures are identical. However, if we look at the irregular curve (**Figure 1B**), we observe that it fills more space than a straight line does but does not occupy the entire two-dimensional space like a plane does. Therefore, the metric dimension of such a curve will range between 1 and 2. On this basis, we can conclude that the metric dimension of such irregular linear objects can have values between 1 and 2.[33, 38] thus, the metric spatial dimension can be not only an integer but also a fractional number. This dimension is referred to as fractal or fractional (from the Latin fractus – broken, fractional).[25-27, 33, 34, 38] The fractal dimension allows for a quantitative assessment of the degree to which a certain geometric object fills space and characterizes the complexity of its spatial configuration.

Fractal structures

Therefore, which structures of the human brain and organism as a whole exhibit fractal properties, and for which structures would fractal dimension be particularly informative?

These structures include irregular curves and surfaces (**Figure 2**).[27, 33, 34] Examples of irregular curves and surfaces include the cerebral cortex, its pial surface, and the boundary between the cortex and white matter.[30-32] Additionally, the contours of various structures and pathological foci, including ischemic brain lesions, hemorrhages, and tumors, appear as irregular curves. These curves can be self-similar and self-repeating, with the complexity of their configuration depending on the number of "waves" (e.g., gyri and contour protrusions) and the degree of their complexity: the more intricate the configuration of the irregular curve or surface is, the more space it occupies.

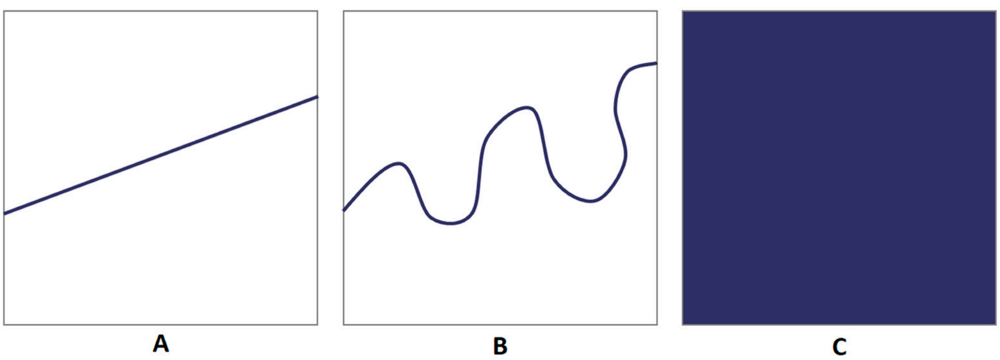

Figure 1: Geometric figures with different space-filling capacities.
Note: (A) A straight line filling all available one-dimensional space, with a metric dimension equal to one. (B) An irregular curve that fills more space than a straight line but less than a plane, with a metric dimension between one and two. (C) A plane (square) filling all available two-dimensional space, with a metric dimension equal to two. Created with Microsoft PowerPoint.

The second group of fractal objects includes tree-like and network structures (**Figure 3**).[27, 33, 34] These include vascular networks,[39, 40] the dendritic tree of neurons, and the arborized processes of glial cells,[41-44] as well as the white matter of the cerebellum.[45] Typically, these structures branch out in a tree-like manner and/or form complex networks. Tree-like structures are also self-replicating; larger branches consist of smaller branches that mimic their shape. The more extensively a fractal tree branches and the more branches it has, the more complex its spatial configuration and the more space it occupies.

The third group of natural fractals comprises cluster fractals: groups of structures often of simple shape but with a fractal and self-replicating organization pattern. Smaller clusters group into larger clusters (**Figure 4**).[33] Cluster fractals include the spatial distribution of cells,[46] including the arrangement of neuronal bodies in the brain (cytoarchitecture), clusters of nuclei in the brain and spinal cord, multiple brain lesions from stroke, amyloid plagues[47] and specific image texture properties: the distribution of darker or lighter pixels, corresponding to particular brain tissue characteristics, can exhibit a fractal clustering pattern. The fractal dimension of fractal clusters depends on the number and size of objects within the clusters, the number and size of the clusters themselves, and the density and uniformity of the object and cluster distribution relative to one another.

Fractal analysis

Fractals can be classified into artificial (mathematical fractals) and natural fractals (quasifractals). Artificial fractals are defined via mathematical algorithms, and their fractal dimensions are known in advance. In contrast, natural fractals exhibit distinct fractal properties but lack a defined mathematical algorithm for their formation, making their fractal dimensions unknown a priori.[25-27, 33, 34] Fractal analysis is employed to determine the fractal dimension of these natural structures.

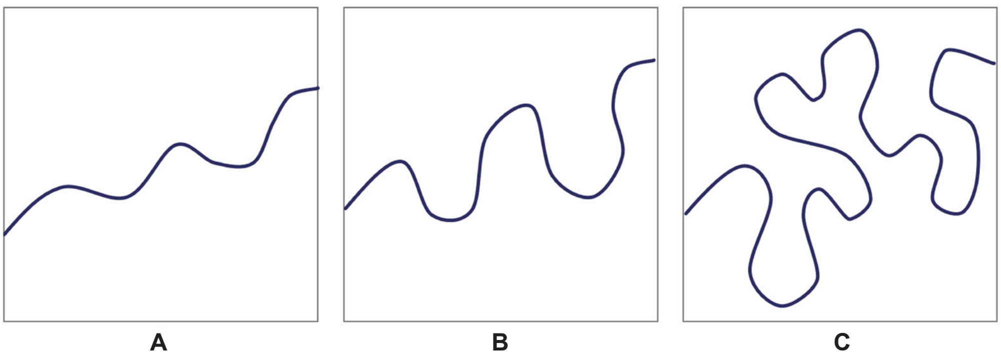

Figure 2: Fractal irregular curves with different degrees of spatial complexity (resulting from varying degrees of tortuosity and convolutedness) and space-filling capacities: low (A), medium (B), and high (C).
Note: Created with Microsoft PowerPoint.

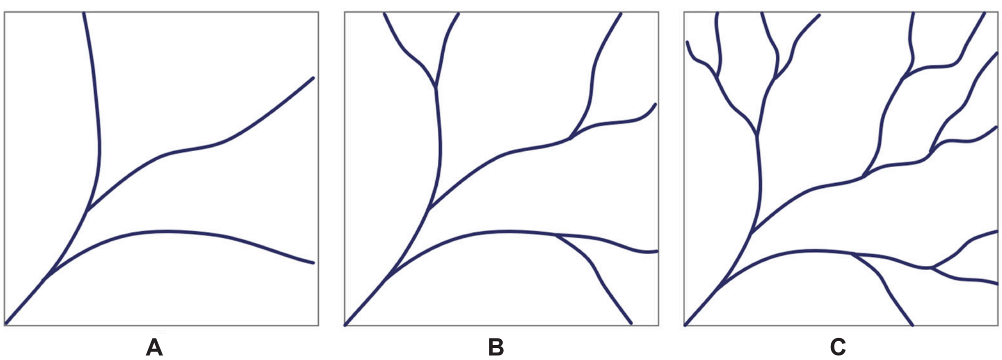

Figure 3: Fractal irregular tree-like branched structures with different degrees of spatial complexity (resulting from varying degrees of branching) and space-filling capacities: low (A), medium (B), and high (C).
Note: Created with Microsoft PowerPoint.

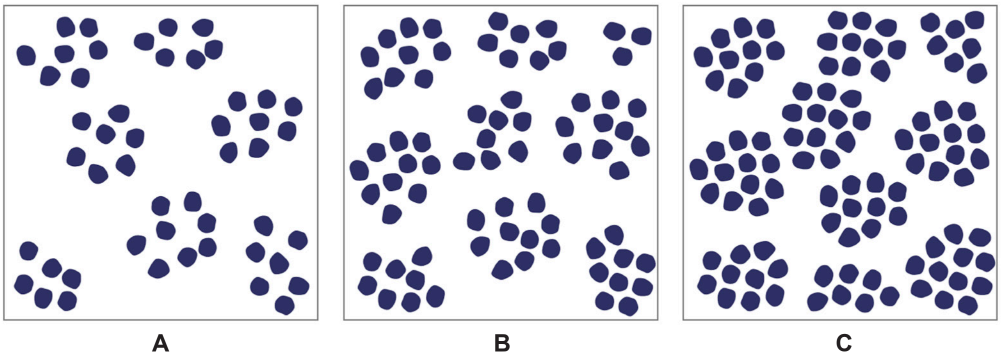

Figure 4: Fractal clustering structures with different degrees of spatial complexity (resulting from varying numbers of structures within clusters, numbers of clusters, and different patterns of object and cluster distributions) and space-filling capacities: low (A), medium (B), and high (C).
Note: Created with Microsoft PowerPoint.

There are several techniques of fractal analysis, among which the most commonly used methods in morphology and medicine include the box-counting method, Richardson's method, dilation and pixel dilation methods, the cumulative intersection method, and the mass-radius method.[41, 42, 48, 49] The "gold standard" method in fractal analysis is the box-counting method due to its simplicity, universality, and accuracy.[50-52] This method is predominantly used in medicine and neuroscience for fractal analysis. Therefore, what is the underlying principle?

For fractal analysis, a rectangular (often square) region of interest from an image is selected and divided into smaller boxes. As shown in **Figure 5A**, an irregular curve is placed within a square, with each side divided into two parts, resulting in a box size of 1/2. The grid is then overlaid on the image, and the number of boxes containing parts of the curve, denoted as N, is counted. In this case, N equals four, as all four boxes contain fragments of the curve.

In the next stage (**Figure 5B**), the box size is reduced by dividing each side of the initial square by four, yielding a box size of 1/4. The fractal grid now consists of 16 boxes, with N recalculated. Here, only 8 of the 16 boxes contain parts of the structure, so N equals 8. This process continues in subsequent stages, with the box size further reduced (**Figure 5C**) to 1/8, resulting in 64 smaller boxes, and N equals 21, as 21 of these boxes contain curve fragments. The number of iterations in fractal analysis depends on the structure's characteristics and the desired accuracy. The fractal dimension (FD) is then calculated via the natural logarithms of N and the inverse of the box size (1/box size). A linear regression equation, $y=bx+a$, is computed, where LN(1/Box size) is the independent variable (x) and LN(N) is the dependent variable (y). The FD corresponds to the slope (coefficient b) of the regression line. In the example provided, the FD was found to be 1.1962 (**Figure 6**).

The fractal dimension determined from two-dimensional images typically ranges from 1 to 2 and does not exceed the dimensionality of the image, which is two. The described box counting method can also be applied in a three-dimensional space. Instead of analyzing a rectangle (square), a rectangular prism (most often a cube) containing the studied structure is used. The cube is then subdivided into smaller cubes, analogous to how a square is subdivided into smaller squares. When the three-dimensional version of fractal analysis is used, the values of the fractal dimension can vary within a broader range – from 1 to 3 (usually between 2 and 3, depending on the object under study) – but cannot exceed 3, the dimensionality of the three-dimensional image being analyzed.

The counting of filled boxes (N) and the subsequent determination of the fractal dimension can be performed manually or with the aid of computer software, among which ImageJ is one of the most popular tools.[53, 54]

In addition to the fractal dimension, the lacunarity or lacunarity index is often calculated. It is computed via a similar principle to the fractal dimension, but instead of counting the "filled" boxes containing the studied structure, the number of "empty" boxes corresponding to the background is counted.[55-57]

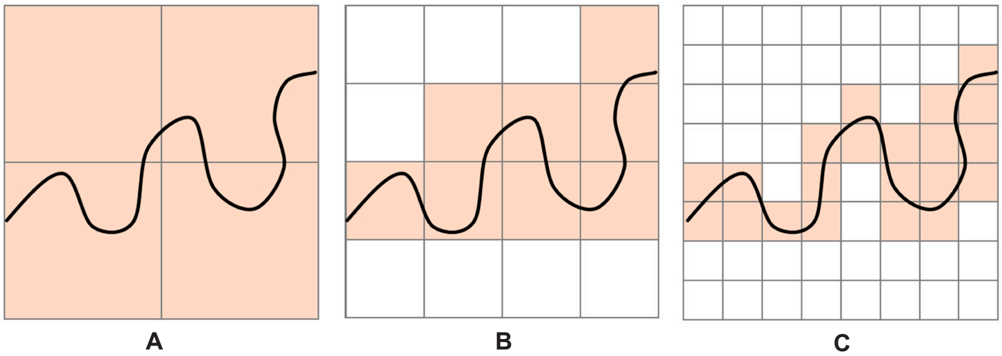

Figure 5: Fractal analysis algorithm: box counting method.
Note: (A) In the 1st stage (iteration) of fractal analysis, the box size is 1/2, and the number of filled boxes (N) is 4. (B) In the 2nd stage of fractal analysis, the box size is 1/4, N = 8. (C) In the 3rd stage of fractal analysis, the box size is 1/8, N = 21. Created with Microsoft PowerPoint.

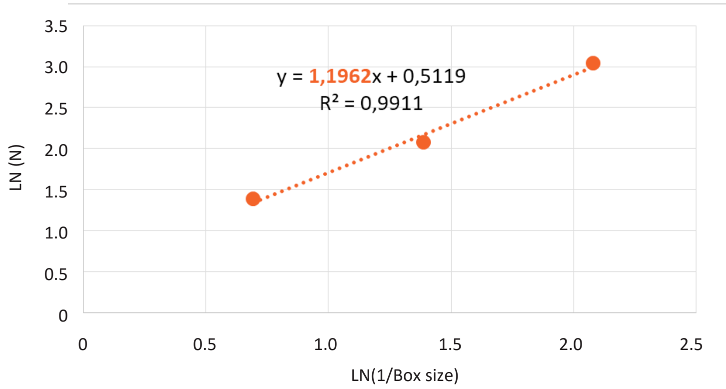

Figure 6: Determining fractal dimension via the box counting method of fractal analysis.
Note: The regression equation $y = bx + a$ is computed (using example data from **Table 1**), where LN(1/Box size) is the independent variable (x), and LN(N) is the dependent variable (y); the fractal dimension is the coefficient b, which represents the estimated slope of the regression line, whereas the coefficient a represents the estimated intercept. In this example, the fractal dimension is equal to 1.1962. Created with Microsoft PowerPoint.

Table 1: Data for calculating the fractal dimension via the box counting method

Stage of fractal analysis	Box size	1/Box size	LN(1/Box size)	N	LN(N)
1	1/2	2	0.693	4	1.386
2	1/4	4	1.386	8	2.079
3	1/8	8	2.079	21	3.045

Note: Box size: size of fractal grid boxes at each stage of fractal analysis; N: number of boxes that intercept the studied structure.

Fractal Analysis Techniques in Neuroimaging: Main Approaches and Applications

Fractal analysis is employed for interpreting and analyzing brain images obtained through neuroimaging techniques. This section describes the application of fractal analysis in general clinical neuroscience, focusing on the main subjects of study and the sensitivity and informativeness of fractal analysis in revealing and characterizing different diseases. Since fractal analysis is not yet widely used in stroke and stroke-related brain damage, this section draws upon work in nonstroke research to demonstrate the possibilities and broad range of fractal analysis applications in general clinical neuroscience. The specific applications of fractal analysis in stroke and the studied objects are described in the next section (Fractal analysis in stroke and stroke-related conditions).

The subjects of study can include brain structures such as tissue (cortex and white matter of cerebral hemispheres and cerebellum) or vascular networks, as well as pathological areas such as tumors, gliosis regions, and, in the case of strokes, ischemic lesions or hemorrhages in brain tissue.[29]

Fractal analysis techniques for the cerebral hemispheres

The cerebral hemispheres are the most frequently studied objects in fractal analysis within neuroimaging research. MRI images are typically utilized for fractal analysis of brain tissue. Prior to performing fractal analysis, preprocessing of images is conducted, including segmentation, which involves creating a binary mask corresponding to the studied structure (**Figure 7A–H,** image A for the segmentation sample is sourced from the database "A paired dataset of T1- and T2-weighted MRI at 3 Tesla and 7 Tesla" https://doi.org/10.6084/m9.figshare.c.6485272.v1[58]). This segmentation can be applied to two-dimensional images or three-dimensional reconstructions. Various structures and components of brain tissue can be segmented: the overall brain tissue[59] (**Figure 7B**), the cortical ribbon[30, 59-67] (**Figure 7C**), and the white matter[63-70] (**Figure 7D**).

These segmented images represent silhouettes that reflect the degree of space filled by these structures – be it the entire brain tissue, the cortex, or the white matter. The fractal dimension of surfaces, such as the pial surface of the cortex (**Figure 7E**)[59, 60, 63, 71, 72] and the outer surface of the white matter (which is also the inner surface of the cortex–gray–white matter interface)[60, 68-70] (**Figure 7F**), can also be determined. To achieve this goal, contour tracing is typically utilized to reveal the studied surface or contour. Additionally, skeletonization of silhouette images can be performed, producing either the digital skeleton (images obtained through a special processing algorithm – skeletonization, which creates a linear branching framework within the structure) of the overall brain tissue[73] (**Figure 7G**) or the white matter silhouette[68-70] (**Figure 7H**).

Different approaches to image preprocessing and various segmentation options allow for the analysis of different aspects of brain configuration. Fractal analysis of the cortex and its outer surface (the outer contour of the cortex in two-dimensional images) can characterize the number and shape of gyri and sulci. The fractal dimension of the pial surface mainly depends on the configuration of the surface of the brain and its gyri and sulci, whereas the fractal dimension of the cortical ribbon is significantly influenced by its thickness in addition to the aforementioned factors.[59-67, 71, 72] The white matter and its outer surface also exhibit complex geometric shapes; studies of the white matter surface configuration in three-dimensional space and digital skeletons of the white matter have proven informative for quantitatively characterizing the spatial complexity of the cerebral hemisphere shape.[63-70] Investigating cerebral hemisphere tissue as a whole and skeletonized images allows for the assessment of the overall brain configuration and simplifies the image segmentation procedure.[59, 74]

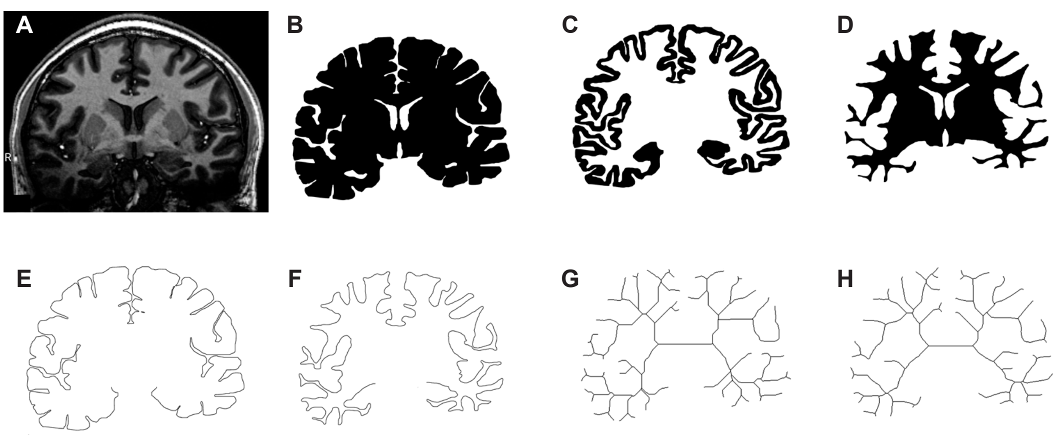

Figure 7: Variants of preprocessing (segmentation) techniques for brain MRI images for fractal analysis.
Note: (A) MRI T1-weighted 7T image (sourced from the database[58]). (B) Binary mask of the overall cerebral tissue. (C) Binary mask of the cerebral cortex. (D) Binary mask of the cerebral white matter. (E) Contour tracing of the pial surface of the cerebral cortex. (F) Contour tracing of the outer surface of the cerebral white matter (gray–white matter interface). (G) Skeletonized image (digital skeleton) of the overall cerebral tissue (Figure 7B is used for skeletonization). (H) Skeletonized image (digital skeleton) of the cerebral white matter (Figure 7D is used for skeletonization). Segmentation was performed using Adobe Photoshop (B–F); skeletonization (G, H) was performed via the "skeletonize" tool of ImageJ software. MRI: Magnetic resonance imaging.

The primary applications of fractal analysis for structures of the cerebral hemispheres encompass several significant areas. First, fractal analysis has proven informative for characterizing brain development and normal aging processes.[59, 62, 65, 68, 69, 72] Notably, in the context of brain development, Im et al.[71] reported a positive correlation between the fractal dimension values of the cortical surface and intelligence quotient (IQ) scores. Fractal analysis has also demonstrated utility in diagnosing developmental brain disorders, making it a valuable tool for identifying and characterizing certain malformations.[74]

With respect to the detection of age-related atrophic changes in the brain during normal aging, several studies have reported a decrease in the fractal dimensions of the cortex and its surface, as well as the overall brain tissue and its skeletonized images, with age; however, the reduction in the fractal dimension of white matter was less pronounced.[59, 62, 65, 68, 69, 72] These changes can be attributed to the smoothing of the brain surface, simplification of the gyral configuration, deepening and widening of sulci, and cortical thinning. These alterations lead to changes in brain structure configurations, resulting in lower fractal dimension values.

Beyond normal aging, fractal analysis has been informative in identifying changes associated with neurodegenerative diseases and related conditions that involve degeneration of nervous tissue. These include Alzheimer's disease,[60, 61] multiple sclerosis,[75-77] cognitive impairment associated with leukoaraiosis,[66] and small vessel disease.[67] Additionally, fractal analysis has proven useful in studying acute traumatic brain injury,[78] indicating its potential applicability for detecting and characterizing acute brain injuries in stroke.

Another important application of fractal analysis is in identifying changes related to mental disorders. Alterations in the fractal dimension of the cerebral cortex (both decreases and increases) have been observed in patients with schizophrenia,[79] auditory verbal hallucinations,[80] bipolar disorder,[81] anorexia nervosa and bulimia,[82] autism spectrum disorder with attention deficit hyperactivity disorder.[83]

Fractal analysis techniques for the cerebellum

Fewer studies have used fractal analysis to examine cerebellar structures than to investigate cerebral hemispheres.[84-89] Similar to cerebral hemisphere research, the fractal dimensions of the cerebellar cortex,[84-86] white matter,[85-88] and skeletonized images of cerebellar white matter[89] have been determined. Research on the cerebellar cortex facilitates the quantitative characterization of the morphological complexity of the cerebellum, whereas investigations of the white matter and its digital skeletons provide insights into the branching and complexity of the cerebellar white matter.

Some scholars have identified changes in the fractal dimensions of the cerebellar cortex and white matter in conditions such as autism spectrum disorder,[84] multiple system atrophy of the cerebellar type,[85] spinocerebellar ataxia type 2,[86] and Chiari malformation.[87, 88]

Fractal analysis techniques for the brain vasculature

Visualizing brain vessels via various angiographic techniques, including MRI and CT, allows for the fractal analysis of vascular images. The fractal dimension of vessels can be used to evaluate their branching complexity and quantify the degree of space filled by the vessels.[40] Typically, silhouette images of vessels are studied, or digital skeletonization is performed.[90] For example, a comprehensive study by Aminuddin et al.[90] investigated the role of brain vessels in small vessel disease via segmented and skeletonized MRI images. The study revealed that the fractal dimension of vessels was reduced in asymptomatic individuals with small vessel disease, suggesting its potential as a biomarker for diagnosing this condition. In another study, angiograms were analyzed for moyamoya disease,[91] and no changes in the fractal dimension were observed compared with those in healthy individuals. Fractal analysis has also proven informative in examining microvessels in malignant brain tumors.[92] Typically, these studies utilize MRI in the vascular mode. Given the diagnostic potential of fractal analysis in brain diseases with a vascular component in their etiopathogenesis, it can be inferred that fractal analysis of the vascular network may be particularly informative for diagnosing and predicting strokes.

Fractal analysis techniques for pathological foci within brain tissue

Among pathological brain lesions, fractal analysis is most frequently used to detect and characterize tumors on MRI and CT images.[93-97] In identifying pathological lesions, fractal analysis can be applied to the entire lesion, its contours (for example, the more complex the contour configuration, the more pronounced the tumor invasion into surrounding tissues might be), or the texture of the lesion. This type of analysis can also be applied to ischemic infarcts or intracerebral hemorrhages, allowing for the characterization of the lesion's shape, texture, and boundaries, as well as the differentiation of stroke lesions from other pathological brain lesions.

Fractal Analysis Techniques in Stroke and Stroke-Related Conditions

As discussed in the previous sections, fractal analysis encompasses a broad range of approaches that can characterize various aspects of brain tissue anatomy and pathological changes, pathological lesions within it, and the vascular network. In this section, we explore examples of the application of fractal analysis in neuroimaging of strokes, including ischemic types (such as acute ischemic stroke, the recovery period following a stroke, and transient ischemic attacks, which may precede strokes and require differentiation) and hemorrhagic types (including intracerebral and subarachnoid hemorrhages). The main fields, aims and applications of fractal analysis in stroke and stroke-related brain damage are depicted in **Figure 8**, and a brief summary of the reviewed works is presented in **Table 2**.

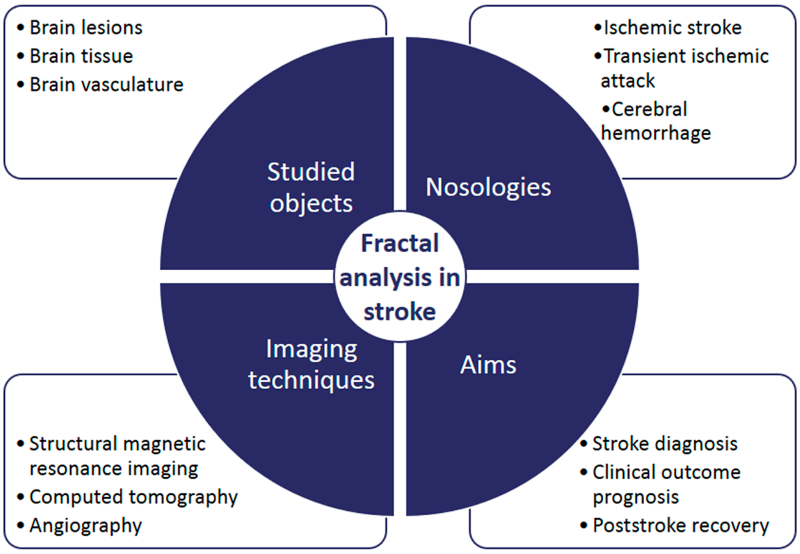

Figure 8: The main fields, aims and applications of fractal analysis in studies regarding stroke and stroke-related brain damage.
Note: Created with Microsoft PowerPoint.

Table 2: Studies on the application of fractal analysis in stroke and stroke-related brain damage

Study	Studied object	Nosology	Aim	Imaging technique
Frindel et al.[24]	Ischemic lesion	Ischemic stroke	Prognosis of clinical outcome	MRI
Karthik et al.[98]	Ischemic lesion	Ischemic stroke	Stroke diagnosis	MRI
Mandeep et al.[99]	Ischemic lesion	Ischemic stroke	Stroke diagnosis	CT
Maryenko and Stepanenko[100]	Ischemic lesion, penumbra	Ischemic stroke	Stroke diagnosis	MRI
Karaca et al.[101]	Ischemic lesion	Ischemic stroke	Stroke diagnosis, stroke classification	MRI
Zhang et al.[102]	White matter	Ischemic stroke	Poststroke recovery assessment	MRI
Lu et al.[103]	Cortex	Ischemic stroke	Poststroke recovery assessment	MRI
Liu et al.[104]	Cortex	Ischemic stroke	Poststroke recovery assessment	MRI
Lv et al.[105]	Cortex	Transient ischemic attack	Stroke diagnosis	MRI
Kliś et al.[106, 107]	Intracerebral hemorrhage	Hemorrhagic stroke	Prognosis of clinical outcome	CT
Krzyżewski et al.[108]	Intracerebral hemorrhage	Hemorrhagic stroke	Prognosis of clinical outcome	CT
Deshpande et al.[109]	Brain vasculature	Ischemic stroke	Stroke diagnosis and assessment	CT and MRI angiography
Deshpande et al.[110]	Brain vasculature	Ischemic stroke	Stroke diagnosis and assessment	MRI angiography
Wu and Zhao[111]	Brain vasculature	Ischemic stroke	Experiment	Autoradiography
Mustonen et al.[112]	Brain vasculature	Hemorrhagic stroke	Stroke diagnosis and assessment	SPECT

Note: CT: Computed tomography; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography.

Acute ischemic stroke: diagnosis

Research on the neuroimaging data of acute brain infarcts has focused primarily on direct fractal analysis of the lesion area, as well as the surrounding region, known as the ischemic penumbra.[98-101] Studies have demonstrated its utility in distinguishing between normal and infarcted brain tissues, particularly through parameters such as fractal dimension, lacunarity, and texture analysis.[98-100] This approach has proven effective in early stroke detection[99] and in characterizing ischemic penumbra boundaries.[100] Additionally, fractal analysis has been used to develop a stroke classification system that enhances diagnostic accuracy by incorporating detailed geometric and textural features of lesions.[101]

In the study conducted by Karthik et al.,[98] the focus was on the analysis of cerebral hemispheric stroke lesions via MRI data compared with unaffected cerebral tissue. Researchers have evaluated several parameters for lesions, including the average fractal dimension, fractal dimension deviation, and lacunarity. Their observations revealed a significant distinction in the feature values between normal and abnormal brain tissues.

Another study focused on the texture of lesion areas in ischemic stroke of the cerebral hemispheres via CT images.[99] The authors selected five regions of interest from areas potentially affected by ischemic stroke and five from unaffected areas. They identified 22 texture parameters, including fractal features. The proposed texture analysis algorithm proved to be effective and sufficiently sensitive for the early detection of ischemic stroke lesions on CT images.

In a study focusing on acute cerebellar infarction, T2-weighted MRI images of the stroke foci, adjacent areas (hypothetical ischemic penumbra), and unaffected areas of the cerebellar vermis were analyzed. The fractal dimensions were determined on the basis of pixel intensity: in the range of 0–100 for the whole cerebellar tissue and 0–90 for the cerebellar cortex contour. A two-dimensional variant of the pixel dilatation method was used for fractal analysis. The results indicated that the fractal dimension values of the whole cerebellar tissue and the outer contour of the cerebellar tissue in the area of the cerebellar ischemic infarction foci were significantly lower than those in the control group. There was no significant difference between the fractal dimension values of the cerebellar vermis or areas adjacent to infarction foci in patients with cerebellar infarction and the vermal fractal dimension values of the control group.[100] This study highlights the potential of fractal analysis in distinguishing between affected and unaffected brain regions and determining ischemic penumbra boundaries on conventional structural MRI images.

In addition to characterizing cerebral infarct lesions, Karaca et al.[101] proposed a classification system for strokes on the basis of the image features of the lesions, including the fractal dimension. The described stroke types included no stroke/transient ischemic attack; large vessel, small vessel, or cardioembolic; and multiple coexisting, cryptogenic, dissection, and other conditions (such as moyamoya, fibromuscular dysplasia, heredity, coagulopathy, vasculitis, and other rare conditions). To characterize the texture of stroke lesions, the authors applied fractal approaches, specifically using the box-counting dimension and wavelet transform modulus maxima. This classification system aims to increase the accuracy of stroke diagnosis and the understanding of various stroke etiologies by incorporating detailed geometric and textural analysis.

Acute ischemic stroke: prognosis of clinical outcomes

In addition to the assessment of stroke lesions for the purpose of stroke diagnosis, the assessment of lesion geometry has proven useful for determining the clinical outcomes of ischemic stroke patients.[24]

In the study by Frindel et al.,[24] the geometric shape of lesions in acute anterior circulation ischemic stroke was analyzed via diffusion-weighted imaging data. The authors employed a comprehensive approach, determining the fractal dimension of the lesions alongside several other parameters: the ratio between the lesion surface and lesion volume, the ratio between the volume of the bounding box and the volume of the lesion, the number of connected components, and the ratio of the size of the largest component to the smallest one. The box-counting method with a three-dimensional approach was used for fractal analysis. Furthermore, the study compared acute and final infarct volumes in patients who received and did not receive thrombolytic therapy. The authors concluded that the lesion shape contains significant predictive information. This insight underscores the potential of geometric shape analysis to predict the clinical outcomes of ischemic stroke patients on the basis of lesion morphology.

Postischemic stroke recovery

Several studies have focused on analyzing MRI images of the brain in patients during ischemic stroke recovery, examining the relationships between the fractal dimensions of different brain structures and stroke outcomes.[102-104] Unlike studies regarding stroke diagnosis and prognosis, where fractal analysis has been employed to characterize stroke lesions directly,[24, 98-101] research during stroke recovery has focused on brain structures such as white matter[102] and the cortex.[103, 104] These studies demonstrated the rearrangement of cerebral structures following a stroke, revealing intricate, lifelong brain changes that result from poststroke brain modifications.

Zhang et al.[102] conducted a study on fractal analysis of white matter in the brain via MRI data. Researchers have determined the fractal dimensions of digital skeletons of white matter in cerebral hemispheres through two-dimensional images via the box-counting method. They primarily observed a decrease in the fractal dimension of white matter in the hemisphere affected by stroke. This reduction can be attributed to changes in white matter configuration due to the formation of the ischemic infarction, leading to alterations in the digital skeleton configuration and the loss of regions corresponding to the lesion. Conversely, regions adjacent to the infarcted area within the affected hemisphere presented higher fractal dimension values than did those in the nonaffected hemisphere. The study did not find significant differences in fractal dimension values between cortical and subcortical lesions. Additionally, a correlation was identified between fractal dimension values and motor function, suggesting that a more complex white matter structure in nonaffected areas is associated with better motor function in patients with right-cortical lesions.

Lu et al.[103] focused on assessing the fractal dimensions of the cerebral cortex during ischemic stroke recovery. The authors performed voxel-based and surface-based morphometry analysis, determining fractal dimensions along with several additional parameters: gray matter volume, cortical thickness, gyrification index, and sulcus depth. This study specifically analyzed the contralesional hemisphere and revealed that stroke patients exhibited significant gray matter loss and cortical morphological changes in this hemisphere. These changes are correlated with sensorimotor functions and daily living abilities, highlighting the impact of stroke on cortical structure and its functional implications.

Liu et al.[104] also investigated MRI data in patients who had experienced ischemic stroke, particularly those with moyamoya disease. The study involved three-dimensional fractal analysis of T1-weighted MRI images to determine cortical fractal dimensions. The authors identified a substantial reduction in fractal dimensions in the left hemisphere with right-sided infarction, particularly in the superior temporal, inferior frontal, and insula regions. Additionally, the postcentral gyrus, superiorand inferior parietal gyri showed significant differences. Changes in fractal dimensions in the right hemisphere with left-sided infarction were confined to the precuneus and cingulate isthmus. The authors hypothesized that the reduction in cortical complexity could be due to long-term ischemic states in both hemispheres caused by chronic stenosis or occlusion of the internal carotid artery and/or middle cerebral artery, which is characteristic of moyamoya disease.

Transient ischemic attack

Fractal analysis has also proven its informativeness in transient ischemic attack. This application is particularly valuable for distinguishing changes in transient ischemic attacks and hyperacute ischemic stroke from nonaffected brain tissue and diseases accompanied by minor changes in brain tissue that may mimic ischemic lesions.

Lv et al.[105] conducted a study utilizing fractal analysis of MRI data to investigate transient ischemic attack. Although it is generally believed that transient ischemic attack does not involve significant morphological changes, fractal analysis allows researchers to detect subtle alterations. This study measured the fractal dimension of the cerebral cortex alongside other parameters that characterize cortical configuration, including cortical thickness, the gyrification index, and sulcal depth. The findings revealed a reduction in regional cortical thickness in patients with transient ischemic attack, which was associated with a decrease in the fractal dimension and gyrification index. The authors suggested that these changes reflect impaired morphological connectivity. The study demonstrated high sensitivity and specificity in differentiating patients with transient ischemic attack from healthy controls.

Cerebral hemorrhages: prognosis of clinical outcomes

In addition to studies on ischemic brain infarctions, fractal analysis has proven informative and specific for characterizing intracerebral hemorrhages. Similar to studies of ischemic brain infarctions,[24, 98-101] fractal analysis in hemorrhagic stroke has been applied directly to pathological foci, such as intracerebral hemorrhages.[106-108] These studies focused primarily on the prognosis of clinical outcomes, revealing that the fractal properties of the hemorrhage shape are associated with either better or worse prognoses.

Specifically, a series of works by Kliś et al.[106, 107] and Krzyżewski et al.[108] employed fractal analysis to examine hemorrhage lesions via brain CT data. In the study by Kliś et al.,[106] the fractal dimension was independently associated with a higher risk of poor treatment outcomes. The study by Kliś et al.[107] involved a retrospective analysis of 48 patients with spontaneous intracerebral hemorrhage. The authors calculated the fractal dimension, compactness, Fourier factor, and circle factor for each patient. The study revealed that the irregularity of the hemorrhage shape, indicated by the number of appendices, could predict intracerebral hemorrhage growth, with the size of the appendices also being significant. Shape roughness was found to better reflect the severity of brain tissue damage and the patient's overall condition. In the study by Krzyżewski et al.,[108] the authors extracted the contour and visual representation of the intracerebral hemorrhage. The analysis of the extracted contour included factors such as compactness, fractal dimension, Fourier factor, and circle factor. They discovered that higher fractal dimensions were independently associated with a higher risk of 30-day mortality among patients with larger hemorrhage volumes.

Fractal analysis techniques of the brain vasculature in stroke

Given the critical role of circulatory disturbances in the development of various types of strokes, the study of vascular networks via fractal analysis can be particularly informative and sensitive. Some researchers have revealed an increase in the fractal dimension of the brain vasculature,[109, 110] whereas other studies have reported a decrease in the fractal dimension in the studied region.[111, 112] The studies involved both ischemic[109-111] and hemorrhagic[112] stroke types.

In the study by Deshpande et al.,[109] a fractal analysis was conducted on the vascular network in stroke patients compared with age-matched healthy subjects. The authors combined Hessian-based probabilistic vessel-enhancing filtering with an active contour-based technique to segment MRI and CT angiograms. They subsequently extracted vessel centerlines and diameters to calculate the geometrical properties of the vasculature. They reported that, compared with healthy individuals, stroke patients had higher fractal dimension values of their blood vessels. The authors additionally studied the changes in vascular features with respect to aging and imaging modality. The observed differences between features as a result of aging were not significant.

In a subsequent study by Deshpande et al.,[110] the authors conducted a fractal analysis of MRI angiograms focusing on aging, strokes, and Alzheimer's disease. They reported an increase in fractal complexity with aging, as well as in both stroke and Alzheimer's disease cases.

An experimental study by Wu et al.[111] conducted on rats with middle cerebral artery occlusion applied fractal analysis to autoradiographic images. The fractal dimension of the blood vessels on the affected side was significantly lower than that on the opposite hemisphere, experimentally confirming the sensitivity of the fractal dimension to circulatory disorders.

In the study by Mustonen et al.,[112] patients with subarachnoid hemorrhage were analyzed via perfusion single-photon emission computed tomography data for fractal analysis. The study revealed that the fractal dimension was significantly reduced in patients with hemorrhage.

Applications of fractal analysis techniques in stroke treatment via different neuroimaging techniques

Fractal analysis can be utilized in stroke diagnosis via data obtained via different neuroimaging techniques. The most prevalent imaging methods used in stroke diagnosis are MRI and CT. MRI is preferred because of its greater sensitivity to ischemic changes in brain tissue, making it more commonly used for the diagnosis and characterization of brain infarctions. MRI has been instrumental in detailing ischemic stroke lesions,[24, 98, 100, 101] assessing poststroke recovery,[102-104] and evaluating transient ischemic attacks.[105] In contrast, CT has been employed less frequently for ischemic lesions, with only one study focusing on this application.[99] Nonetheless, the methodologies used in this study were sufficiently sensitive to facilitate early detection of ischemic lesions.

In regard to intracerebral hemorrhages, CT is predominantly utilized. Studies have demonstrated that CT is highly effective in visualizing hemorrhage foci and delineating their boundaries, which enhances the accuracy and ease of fractal analysis using this imaging modality.[106-108]

Research into fractal analysis of the brain vasculature has involved various imaging techniques, including MRI,[109, 110] CT,[109] autoradiography,[111] and single-photon emission computed tomography.[112] Notably, Deshpande et al.[109] conducted a comparative study using both CT and MRI angiograms. Although the primary findings were consistent across the imaging modalities, the study highlighted a significant discrepancy in the number of vascular branches identified, demonstrating that different imaging techniques can yield varied results.

In summary, while MRI remains the preferred method for analyzing ischemic changes and poststroke conditions because of its detailed imaging capabilities, CT is essential for studying intracerebral hemorrhages and provides valuable information for fractal analysis of the brain vasculature.

Discussion

Over the past few decades, fractal geometry and fractal analysis have garnered significant attention from researchers across various fields of natural sciences, including medicine and neuroscience.[28, 29] Fractal geometry approaches enable the quantitative characterization of objects with complex geometric shapes that are difficult or impossible to describe via conventional morphometric methods derived from Euclidean geometry.[25-27] The application of fractal analysis has significantly expanded the capabilities of MRI and CT imaging of the brain.[29]

In recent decades, fractal analysis techniques have been increasingly applied in clinical neuroscience. **Figure 9** shows the timeline for fractal analysis development and application in studies regarding stroke and stroke-related brain damage. Currently, relatively few studies have directly addressed the use of fractal analysis in neuroimaging research for stroke and stroke-related brain damage[24, 98-112] because of the relative novelty of the fractal approach. However, these studies have confirmed the diagnostic capability of fractal analysis for detecting and characterizing brain lesions in stroke patients and have outlined the main directions for the development of fractal approaches in neuroimaging research for different types of stroke.

The primary application of fractal analysis in stroke is the characterization of the lesions themselves: determining the fractal dimension of the lesions as a whole, their surfaces (contours), or texture features.[24, 98-101] An ischemic brain lesion can be considered a natural cluster fractal figure because of its self-similar and complex configuration. The shape of infarct lesions is often complex, with several lesions merging into one or more large lesions having protrusions and indentations on the surface, complicating their configuration. The fractal dimension of the lesion as a fractal structure and its contours can provide valuable information about the geometric configuration of the lesion. As earlier studies have shown, the shape of the stroke lesion has prognostic significance,[22-24] and characterizing it via fractal analysis can help predict the disease course. Hypothetically, strokes with more complex lesion configurations may be caused by the occlusion of larger arterial branches, resulting in infarctions in the supply areas of several smaller branches, whereas smaller strokes may have a simpler shape corresponding to the supply area of smaller arterial branches. The ability of fractal analysis to capture the complexity of stroke lesions provides a significant advantage over traditional morphometric methods. By quantifying the geometric features of lesions, fractal analysis can offer deeper insights into the pathophysiology of stroke. This information could be critical for predicting patient outcomes and tailoring treatment strategies. Additionally, the use of fractal dimensions to characterize lesion complexity can help differentiate between various types of strokes and their underlying causes, potentially leading to more targeted and effective interventions.

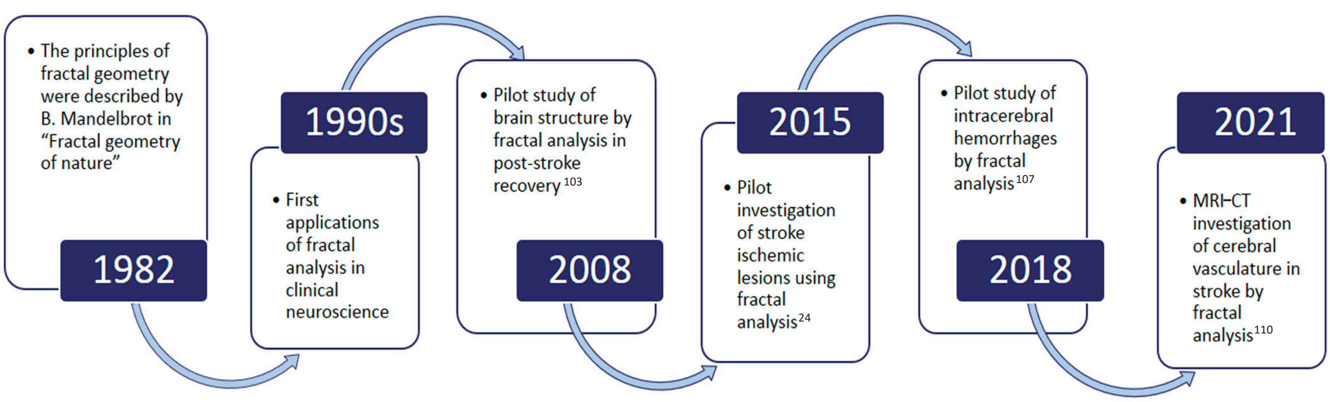

Figure 9: Timeline for fractal analysis development and application in studies regarding stroke and stroke-related brain damage.
Note: Created with Microsoft PowerPoint. CT: Computed tomography; MRI: magnetic resonance imaging.

Moreover, identifying and characterizing the boundary between damaged tissue, the penumbra, and undamaged tissue is crucial.[100] A more complex interface configuration between healthy and damaged tissue may indicate a more complicated course, whereas clearly demarcated areas may indicate that the stroke has fully developed.

Similarly, studies of intracerebral hemorrhage contours have shown that a greater number of protrusions and appendices on the hemorrhage surface are associated with hemorrhage growth and a worse prognosis.[106-108] Thus, increased complexity in the configuration of such lesions (increased fractality) indicates either multiple lesions or an ongoing process complicating the lesion's configuration.

Therefore, although relatively few studies on fractal analysis of stroke lesions exist, research in other areas of fractal analysis in neuroscience suggests that fractal analysis of different lesions could have significant diagnostic and prognostic value by indicating ongoing, progressive, or complex genesis of the lesions. This approach aligns with findings from other fields, such as oncology, where fractal measures have proven useful in characterizing tumor behavior: increased surface complexity indicates invasion into surrounding tissues.[93-97] These observations suggest that fractal analysis could offer significant diagnostic and prognostic value by revealing complex or progressive lesion characteristics. By providing a detailed assessment of the interface between damaged and healthy tissue, fractal analysis can improve the accuracy of stroke assessments and prognosis. The potential for fractal analysis to provide insights into the complexity and evolution of stroke lesions underscores its value as a diagnostic and prognostic tool.

The texture of stroke lesions and undamaged tissue can be considered fractal, as various textures exhibit self-similarity, self-repetition, and scaling invariance, i.e., similarity at different scales. The presence of such fractal properties allows the use of fractal analysis to characterize image textures. This approach also enables differentiation between healthy tissue and stroke lesions and identifies characteristics specific to different types of strokes.[98, 101] This method can be used in the early stages after a stroke when it is challenging to delineate the lesion boundaries, but it is necessary to determine the presence of brain tissue damage. For certain brain regions, such as the cerebellum, which has a highly heterogeneous appearance, this approach could become predominant.[100] The application of fractal analysis to texture characterization offers a promising approach for early stroke detection and differentiation. By capturing the self-similarity and scaling properties of textures, fractal analysis can provide insights into the nature and extent of brain damage. This is particularly important in heterogeneous regions where traditional methods may fall short. The ability to analyze texture at multiple scales allows for a more comprehensive understanding of tissue damage and can facilitate earlier and more accurate diagnosis.

In addition to characterizing the lesions themselves, it is also possible to evaluate brain structures, such as the cortex, white matter, digital skeleton, and brain tissue as a whole. This approach has been used to characterize brain anatomy after a stroke and in transient ischemic attacks.[102-105] By assessing changes in fractal dimensions, researchers can gain insights into how strokes impact brain anatomy and function over time. This approach can help identify patterns of brain remodeling and atrophy, providing important information for understanding stroke recovery and progression. In these cases, changes in the fractal dimension can be associated with two factors. First, the presence of brain lesions leads to the "loss" of cortex or white matter areas, thus changing their spatial configuration. Second, general changes in brain structures due to both brain remodeling after a stroke (compensatory increase in the fractality of certain areas) and general causes lead to atrophic, degenerative changes. For example, acute and/or chronic blood circulation disorders associated with strokes can cause atrophic changes in the brain cortex, resulting in decreased fractal dimensions. There are relatively few studies on fractal analysis during stroke recovery,[102-104] but many studies characterize the age dynamics of fractal dimensions of various brain tissue components during normal aging.[59, 62, 65, 68, 69, 72] This enables the use of these data as age normative criteria and the comparison of fractal dimension values of different brain structures in stroke patients with the age norm. Further research in this direction will provide important data on the dynamics of brain remodeling after a stroke, the compensatory capabilities of the brain, and the prediction of clinical outcomes, allowing timely selection and correction of therapy. Additionally, comparing fractal dimensions with age-related normative data can enhance our ability to distinguish between normal aging processes and stroke-related changes, leading to better-informed treatment strategies.

Another important and promising direction is fractal analysis of the brain vasculature.[110-113] Vascular networks exhibit pronounced fractal properties and can be considered natural tree-like fractals, making fractal analysis one of the most suitable morphometric methods for the comprehensive characterization of micro- and macrocirculation in brain structures.[40] The vascular component plays a crucial role in stroke genesis, so determining the fractal dimension of blood vessels is important for assessing a stroke that has already occurred and predicting its clinical course (to evaluate preserved blood flow) and for predicting the occurrence of strokes and identifying patients vulnerable to stroke, allowing for the prevention of the disease. Fractal analysis has shown sensitivity to small vessel disease, which often precedes a stroke.[90] Therefore, early diagnosis and assessment of the vascular network (preferably before a stroke occurs) are particularly important. Currently, fractal analysis is widely used to characterize retinal vessels in strokes.[113, 114] The rapid improvement and widespread implementation of MRI and CT in vascular modes make it possible to conduct similar in vivo studies directly on brain blood vessels. The continued development of imaging technologies and fractal analysis methods will enhance our ability to monitor and predict vascular health, ultimately contributing to more effective stroke prevention and management strategies.

Limitations and Future Directions

Despite these promising results, several limitations need to be addressed in future research. The variability in imaging modalities and analysis techniques can affect the reproducibility and generalizability of findings. Standardization of fractal analysis methods and the development of robust algorithms are essential for consistent application across studies. On the other hand, the development of new and diverse fractal analysis and preprocessing algorithms is needed for the development and selection of the most sensitive and informative approaches and algorithms. Additionally, larger and more diverse patient cohorts are needed to validate the clinical utility of fractal analysis in different stroke populations. Future studies should also explore the integration of fractal analysis with other advanced imaging techniques and machine learning algorithms to enhance diagnostic and prognostic capabilities.

Conclusion

Fractal analysis techniques represent a powerful tool for quantifying the complexity of brain structures, stroke lesions and vascular networks in stroke research. As the field advances, the integration of fractal analysis into clinical practice could improve the diagnosis, classification, and prognosis of stroke, as well as the assessment of poststroke recovery, ultimately leading to better patient outcomes.

Author contributions

NIM performed the literature search and data analysis, wrote the manuscript, and approved the final manuscript.

Conflicts of interest

The author declares no conflicts of interest.

Data availability statement

Not applicable.

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