



REVISTA DE LA FACULTAD DE CIENCIAS DE LA SALUD

Vol. 29(2):208-219, May - August 2026
i-ISSN 0123-7047 e-ISSN 2382-4603



Original article

Study of an integrated model for the identification of patients with Alzheimer's disease dementia

Estudio de un modelo integrado para la identificación de pacientes con demencia tipo Alzheimer

Estudo de um modelo integrado para a identificação de pacientes com demência do tipo Alzheimer

Manuel Alejandro Mejía-Ordúz  

manuel.l.mejia@ucp.edu.co 

Universidad Católica de Pereira. Pereira, Colombia.

Dúwamg Alexis Prada-Marín  

duwamg.prada@correo.uis.edu.co - duwamg.prada@ieom.edu.co

Universidad Industrial de Santander. Bucaramanga, Santander, Colombia.

Institución Educativa Oriente Miraflores

Edward Leonel Prada-Sarmiento  

edward.prada@upb.edu.co

Universidad Pontificia Bolivariana. Bucaramanga, Colombia.

Javier Villamizar  

javier.villamizar@outlook.es

Universidad Pontificia Bolivariana. Bucaramanga, Colombia.

Fabián Orlando Rojas-Delgado  

fabian.rojas@upb.edu.co

Universidad Pontificia Bolivariana. Bucaramanga, Colombia.

Germán Camilo Morantes-Gómez  

camilo.morantesg@gmail.com

Universidad Autónoma de Baja California. Mexicali, México.

Alexander Reyes-Lobo  

areyeslo@uis.edu.co

Universidad Industrial de Santander. Bucaramanga, Santander, Colombia.

Ara Mercedes Cerquera-Córdoba  

aramercedescerqueracordoba@gmail.com

Universidad Industrial de Santander. Bucaramanga, Colombia.

Rubén Avilés-Reyes  

ruben.aviles.reyes@uabc.edu.mx

Universidad Autónoma de Baja California. Mexicali, México.

ARTICLE INFORMATION:

Article received: May 31, 2025

Article accepted: February 27, 2026

DOI: <https://doi.org/10.29375/01237047.5025>



How to reference. Mejía-Ordúz MA, Prada-Marín DA, Prada-Sarmiento EL, Villamizar J, Rojas-Delgado FO, Morantes-Gómez GC, et al. Study of an integrated model for the identification of patients with Alzheimer's disease dementia. MedUNAB [Internet]. 2026;29(2):208-219. doi: <https://doi.org/10.29375/01237047.5025>

VIGILADA MINEDUCACIÓN

Author Contributions

MAMO. Methodology, validation, formal analysis, data curation, drafting of the original manuscript, review, and editing. **DAPM.** Conceptualization, methodology, software, validation, formal analysis. **ELPS.** Conceptualization, methodology, supervision, project management, fundraising, review, and editing. **JV.** Software, validation, formal analysis, resources, data curation. **FORD.** Conceptualization, methodology, research. **GCMG.** Methodology, research. **ARL.** Methodology, validation, formal analysis. **AMCC.** Conceptualization, methodology, project management, fundraising. **RAR.** Methodology, validation.

ABSTRACT

Introduction. Alzheimer's disease dementia represents a progressive cognitive impairment resulting from a brain pathology that impacts autonomy and functionality. Therefore, this study aimed to evaluate an integrating model combining cerebral, autonomic, and cognitive indicators to support the detection of Alzheimer's disease cases. **Methodology.** This observational study consisted of 14 older adults (controls) and 14 individuals diagnosed with dementia (Alzheimer's disease), selected and examined using purposive sampling. Participants were assessed using the Montreal Cognitive Assessment, magnetic resonance imaging ((MRI; fractal dimension derived from axial and coronal slices), and cardiac reactivity to an orthostatic tolerance test. **Results.** Differences were identified in cognitive, cerebral, and autonomic indicators between the two groups (*t-test*). Binomial logistic regression analysis indicated that the Montreal Cognitive Assessment and minimum heart rate constituted a model that explained the diagnosis in 75.55% of cases (adjusted R^2). The brain fractal dimension in axial ($r = -0.38$, $p = 0.046$) and coronal ($r = -0.42$, $p = 0.026$) slices correlated significantly with the Montreal Cognitive Assessment. **Discussion.** These findings were compared with studies that address the potential of integrating cognitive and autonomic measures in dementia diagnosis. In addition, the usefulness of brain fractal dimension as a magnetic resonance imaging derived indicator was discussed. **Conclusions.** Integrating cognitive and autonomic indicators explained the diagnosis to a greater extent than individual variables. Furthermore, brain fractal dimension showed potential utility, as it was associated with cognitive functioning as measured by the Montreal Cognitive Assessment.

Keywords:

Dementia; Alzheimer Disease; Fractals; Magnetic Resonance Spectroscopy; Mental Status and Dementia Tests; Orthostatic Intolerance; Heart Function Tests; Diagnostic Techniques and Procedures.

RESUMEN

Introducción. La demencia por enfermedad de Alzheimer representa una afectación cognitiva progresiva derivada de una patología cerebral que impacta en la autonomía y funcionalidad, por tanto, se planteó estudiar un modelo que integró indicadores cerebrales, autonómicos y cognitivos orientados a contribuir a la detección de casos con Alzheimer. **Metodología.** Estudio observacional conformado por 14 adultos mayores (controles) y 14 con diagnóstico de demencia (Alzheimer), seleccionados y examinados de manera intencional. Evaluación a través del examen cognitivo de Montreal, examen de resonancia magnética (dimensión fractal de cortes axiales y coronales), y la reactividad cardíaca ante una prueba de tolerancia ortostática. **Resultados.** Se identificaron diferencias en indicadores cognitivos, cerebrales y autonómicos entre ambos grupos (prueba t). Un análisis de regresión logística binomial reveló que el examen cognitivo de Montreal y la mínima frecuencia cardíaca constituyeron un modelo que explicó el diagnóstico en un 75.55% (R^2 ajustado). La dimensión fractal cerebral de cortes axiales ($r = -0.38$, $p = 0.046$) y coronales ($r = -0.42$, $p = 0.026$) se correlacionó significativamente con el examen cognitivo de Montreal. **Discusión.** Los resultados se contrastaron con estudios que abordan el potencial de integrar medidas cognitivas y medidas autonómicas en el diagnóstico de las demencias; adicionalmente, se abordó la utilidad de la dimensión fractal cerebral como indicador derivado de la resonancia magnética. **Conclusiones.** La integración de indicadores (cognitivo y autonómico) explicó

en mayor medida el Demencia; Enfermedad de Alzheimer; Fractales; Espectroscopía de Resonancia Magnética; Pruebas de Estado Mental y Demencia; Intolerancia Ortostática; Pruebas de Función Cardíaca; Técnicas y Procedimientos Diagnósticos.

Palabras clave :

Demencia; Enfermedad de Alzheimer; Fractales; Espectroscopía de Resonancia Magnética; Pruebas de Estado Mental y Demencia; Intolerancia Ortostática; Pruebas de Función Cardíaca; Técnicas y Procedimientos Diagnósticos.

RESUMO

Introdução. A demência por doença de Alzheimer representa um comprometimento cognitivo progressivo decorrente de uma patologia cerebral que impacta a autonomia e a funcionalidade; por tanto, propôs-se estudar um modelo que integrou indicadores cerebrais, autonômicos e cognitivos, orientados a contribuir para a detecção de casos de Alzheimer. **Metodologia.** Estudo observacional composto por 14 pessoas idosas (grupo controle) e 14 com diagnóstico de demência (Alzheimer), selecionadas e examinadas de forma intencional. As pessoas participantes foram avaliadas através do teste de Avaliação Cognitiva de Montreal

(MoCA), de uma ressonância magnética (dimensão fractal em cortes axiais e coronais) e da reatividade cardíaca frente a um teste de tolerância ortostática. **Resultados.** Foram identificadas diferenças nos indicadores cognitivos, cerebrais e autonômicos entre os dois grupos (teste t). Uma análise de regressão logística binomial revelou que o Teste Cognitivo de Montreal e a frequência cardíaca mínima constituíram um modelo que explicou o diagnóstico em 75.55% (R^2 ajustado). A dimensão fractal cerebral de cortes axiais ($r = -0.38$, $p = 0.046$) e coronais ($r = -0.42$, $p = 0.026$) correlacionou-se significativamente com o teste cognitivo de Montreal. **Resultados.** Foram identificadas diferenças nos indicadores cognitivos, cerebrais e autonômicos entre os dois grupos (teste t). Uma análise de regressão logística binomial revelou que a Avaliação Cognitiva de Montreal e a frequência cardíaca mínima constituíram um modelo que explicou o diagnóstico em 75.55% (R^2 ajustado). A dimensão fractal cerebral em cortes axiais ($r = -0.38$; $p = 0.046$) e coronais ($r = -0.42$; $p = 0.026$) correlacionou-se significativamente com a Avaliação Cognitiva de Montreal. **Discussão.** Os resultados foram comparados com estudos que abordam o potencial de integrar medidas cognitivas e autonômicas no diagnóstico das demências; adicionalmente, foi analisada a utilidade da dimensão fractal cerebral como indicador derivado da ressonância magnética. **Conclusões.** A integração de indicadores (cognitivos e autonômicos) explicou o diagnóstico em maior medida do que as variáveis isoladas. Além disso, demonstrou-se o potencial da dimensão fractal cerebral, uma vez que revelou uma associação com o funcionamento cognitivo, representado na Avaliação Cognitiva de Montreal.

Palavras-chave:

Demência; Doença de Alzheimer; Fractais; Espectroscopia de Ressonância Magnética; Testes de Estado Mental e Demência; Intolerância Ortostática; Testes de Função Cardíaca; Técnicas e Procedimentos Diagnóstico.

Introduction

Alzheimer's disease is a condition that generally manifests itself through cognitive, behavioral, and emotional changes, which are the result of a brain disorder. These changes affect functioning and are not a normal part of aging. They fall under the category of neurocognitive disorders (NCDs), as defined in the Diagnostic and Statistical Manual of Mental Disorders (1).

A 2021 report by the World Health Organization (WHO) indicates that approximately 57 million people worldwide had dementia, with annual projections of an increase of 10 million new cases. Alzheimer's disease accounted for between 60 and 70% of all cases of dementia (2). As for the situation in Colombia, we can refer to a retrospective study conducted by Guerrero-Barragán et al. (3). Using data from the 2015 Survey on Health, Well-being, and Aging (SABE, for the Spanish original), they analyzed results from a version of the Mini-Mental State Examination administered to 23,694 participants, revealing a prevalence of cognitive impairment without dementia of 8.9%. This was in contrast to the dementia identified in 10.8% of those evaluated (3), a figure that should serve as a warning to national public health authorities, due to the cognitive and functional impact associated with this disease.

If we consider that the WHO (4) continues using the term "dementia" to refer to Alzheimer's disease and that, since ICD-11 (International Classification of Diseases) (5) defines it as a cerebral syndrome characterized by a decline in cognitive functioning with impairment in two or more domains, which impacts activities of daily living, it is not surprising that special attention is initially given to cognitive assessment in a rigorous diagnostic approach, followed by an evaluation of both clinical and psychiatric

indicators in establishing a differential diagnosis. This may also be accompanied by a neurological examination supported by brain imaging.

In addition to what was described above regarding the diagnostic criteria for this condition, it should be noted that it requires a multidisciplinary approach (clinical psychology, psychiatry, neuropsychology, neurology, etc.), as reflected in the integration of multiple diagnostic indicators. Because of this, there is a growing interest in researching new variables that could serve as potential diagnostic indicators, as well as in analyzing models that integrate this diversity of components (cognitive, behavioral, clinical, physiological, neurological, etc.) to expand our understanding of the course and impact of the condition and improve diagnostic practices.

Taking into account the potential diagnostic indicators, this section discusses the scope of various indicators in the study and proposes a multicomponent model to aid in diagnosing Alzheimer's disease-related dementia. The impact on cognitive processes in Alzheimer's disease is clear. These processes involve memory, along with impairments in orientation, abstract thinking, language, judgment and reasoning, calculation and constructive skills, attention, and executive functioning (6–8). It must specifically be noted that the onset of cognitive decline begins to interfere with daily activities, functionality, and even the individual's social relationships, with mild cognitive impairment (MCI) observed as the first stage in a significant proportion of cases. This progressively worsens into the pathological cognitive impairment characteristic of Alzheimer's disease.

In clinical practice, the dementia-focused cognitive assessment is supplemented by a neurological examination

and brain imaging tests, including MRI. In this regard, systematic reviews of more than 20 studies involving over 2,000 participants, such as the one conducted by Lombardi et al. (9) revealed that hippocampal volume is one of the indicators commonly considered in the early diagnosis of Alzheimer's disease-related dementia. Furthermore, among the key findings of studies, such as the one mentioned above, is the observation that a single test, such as an MRI, may not be accurate for the early diagnosis or prognosis of Alzheimer's disease-related dementia, leading to the suggestion that future diagnostic approaches should not rely on a single method but rather on models that integrate various indicators (9).

In this regard, alternative methods of analyzing MRI images have been proposed in recent years, including the calculation of cerebral fractal dimension, described as a measure of structural complexity, which, in theory, has the potential to measure subtle distortions not visible to the naked eye. It could become a biomarker that is sensitive to the anatomical and morphological changes resulting from Alzheimer's disease, which affect brain tissue, given the progressive apoptosis that characterizes the course of this disease (10,11). In this regard, it has been suggested that the fractal dimension may be related to the anatomical and morphological properties of the brain, such as the patterns of similarity represented by the folds of the cortex. This type of complexity could be quantified and represented by a value corresponding to the aforementioned fractal dimension (11,12). Studies have been conducted to analyze the ability of algorithms to distinguish cases of Alzheimer's disease from control subjects based on the calculation of the fractal dimension of brain images obtained via magnetic resonance imaging to train artificial intelligence (AI) systems (13).

In addition, biological markers in the management of Alzheimer's disease focus on brain activity (primarily cortical), as they aim to explain the cognitive, behavioral, and emotional changes that characterize this type of dementia. To a lesser extent, significance is given to peripheral physiological markers, such as cardiac and vascular activity and their association with the aforementioned changes and even with the course of dementia (14). However, there has been an increase in studies focusing on neurological changes in brainstem nuclei associated with Alzheimer's disease (15–19), which are linked to decreased levels of serotonin and acetylcholine. This is why non-cognitive symptoms are becoming increasingly important. In fact, authors such as Simic et al. (15) have even proposed and discussed the possibility that Alzheimer's disease begins with changes in the brainstem, manifesting its initial phase through alterations in the sleep-wake cycle, mood, or the functioning of the autonomic nervous system. These symptoms would go unnoticed in clinical practice due to

the focus on cognitive deficits, which are assumed to stem from cortical abnormalities. The above is the rationale for studies that address cardiovascular reactivity as an indicator capable of distinguishing patients with mild cognitive impairment and even dementia through autonomic tests, such as orthostatic intolerance tests (15,16).

In this regard, studies such as those conducted by Omoya et al. (18) reveal that patients with Lewy body dementia exhibit lower cardiac reactivity during the aforementioned orthostatic intolerance test, along with slower early recovery compared to healthy controls (18). In addition, the study by Mellingsæter et al. (19) demonstrated divergent cardiac responses in both patients with mild cognitive impairment and those with Alzheimer's dementia during this standing test, revealing a reduction in cardiac reactivity manifested as a low sympathetic response. This has led to the conclusion that this autonomic test may identify early neuropathological processes at the subcortical level that affect autonomic control in patients with dementia (19).

Therefore, this study focused on developing a model that integrated cognitive, neurological, and autonomic indicators, represented respectively by performance on the Montreal Cognitive Assessment (MoCA), the calculation of cerebral fractal dimension in magnetic resonance imaging, and cardiac reactivity variables in autonomic tests. These were used to analyze the probability of detecting cases of Alzheimer's disease, since the results may provide evidence to support the proposal of alternative protocols for diagnosing dementia.

Methodology

Participants: An observational case-control study involving a sample of 28 volunteer older adults 65 and older, who were selected through purposive sampling due to the limitations on access to the sample in a clinical setting. A control group of participants (70.9 ± 7.2 years) was formed, consisting of 12 women and 2 men, taking into account the following: 1) No history of neurological, psychiatric, or psychological conditions, as indicated in their medical records; 2) No uncorrected visual or hearing impairments; 3) A minimum level of education of elementary school, with reading and writing skills; 4) Full independence according to the Lawton and Brody Index (20) and the Barthel Index (20, 21); 5) A MoCA score of 18 or higher, indicating the absence of cognitive impairment associated with dementia (22). For the group of volunteers with Alzheimer's dementia (72.1 ± 6.6 years), consisting of 10 women and 4 men, the following was considered: 1) Diagnosis of Alzheimer's dementia made by the neurology and psychiatry departments; 2) an absence of uncorrected visual and hearing impairments; 3) a minimum level of education of elementary school, with reading and writing

skills; 4) a mild or moderate level of impairment according to the Global Deterioration Scale (GDS) (23); 5) A MoCA score below 18, indicating cognitive impairment associated with dementia (22).

The following section describes the methods and materials used to collect data on cognitive, autonomic (physiological), and brain indicators, which were subsequently used in the multicomponent model analysis.

Montreal Cognitive Assessment (MoCA): a test used to assess overall cognitive function and identify performance patterns associated with mild cognitive impairment (24). The test consists of 19 items that assess cognitive domains, such as executive functions and visuospatial skills, as well as naming, memory, attention, language, abstraction, delayed recall, and orientation. For this study, a cutoff score of less than 18 was used to identify cognitive impairment associated with dementia (22). It should be noted that the test has adequate psychometric properties in the Colombian population (25). This study used a version validated for the Colombian context (26).

Regional orthostatic intolerance test: The PowerLab PL3508–8/35 (ADInstruments®) was used to record cardiac activity. The test was performed using the second lead of the electrocardiogram (ECG) and was recorded at a sampling rate of 200 Hz and a bandwidth of 0.05–150 Hz. For the orthostatic intolerance test, participants remained seated in a comfortable position provided by an armchair with a backrest and armrests (seated position) for approximately 10 minutes. Once they reached an average heart rate of 65 to 75 beats per minute for about 30 seconds, they were asked to suddenly change to a standing position, remaining upright for about two minutes. This test is known as the active standing test, which has proven to be sensitive in distinguishing autonomic differences between individuals with and without cognitive impairment (17–19). The cardiac activity analyzed in this study included the average, maximum, minimum, and range of heart rates recorded during the standing period as indicators of autonomic reactivity.

MRI settings and images: A GE (General Electric) Healthcare SIGNA (3.0 T) MRI scanner was used. Images were acquired at resolutions of 256×256 and 512×512 pixels using T1 and T1 FSPGR sequences, yielding 376 axial and 150 coronal slices, each 1.00 mm thick. Additionally, the selected axial segments ranged from -6.16 mm to -4.22 mm (images 180–184), while the selected coronal segments ranged from 2.28 mm to 4.75 mm (images 75–77).

Image preprocessing and fractal dimension estimation: The images were segmented using FreeSurfer software (27), which facilitated calculating the fractal dimension

associated with a cortical ribbon indicator in brain slice segments containing the hippocampus, through a motion correction process combined with intensity normalization aimed at removing outlier voxels. In turn, the gray matter was segmented from the white matter using an approach based on intensity differences and structural geometric differences between these two types of tissue (28).

It should be noted that image processing was carried out in two stages: first, the target structure was detected through a preprocessing step in which the image's black and white values were inverted. Subsequently, the target areas of the image were estimated using the Canny method (29). For detailed information on this preprocessing, we recommend consulting the document describing the operation of the fractal dimension algorithm used in this study (30).

When it comes to the algorithm used to estimate the fractal dimension, the Box Counting method was chosen due to the self-similarity patterns associated with brain tissue. This method is based on image analysis that examines the relationship between the length of the variable within an analysis grid, which covers the selected image, to calculate the number of boxes in that image. The Box Counting method is based on a linear regression between the number of boxes in the image and grid size, which is estimated by the following equation:

$$D = \frac{\ln(N)}{\ln(k)^r}$$

Where N is the finite number of subfigures, k is congruent to the numerical value $r = 1/k$, and r corresponds to a contraction factor. The iteration is represented by the number of equally sized cells in the grid covering the image, which increases as the size of the cells decreases. By repeating this process as the length decreases, more boxes are used to cover the analyzed image (Figure 1).

The authors of this study demonstrated the effectiveness of this algorithm in distinguishing cases from controls using fractal dimension, by analyzing magnetic resonance images obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<https://adni.loni.usc.edu/>), as shown in the study by Villamizar et al. (30).

Procedure: Participants without a diagnosis were recruited from an institutional project at Universidad Pontificia Bolivariana (UPB) aimed at characterizing older adults. These participants were evaluated by both a psychologist and a neuropsychologist, who ruled out the presence of clinically significant depressive symptoms and confirmed the absence of global cognitive impairment, in addition to confirming a level of full autonomy and functionality, in accordance with the protocol described above. Participants

diagnosed with Alzheimer's disease-related dementia were referred from the neurology department at Hospital Internacional de Colombia (HIC) following a consensus

diagnosis reached by specialists in neurology, radiology, and psychiatry.

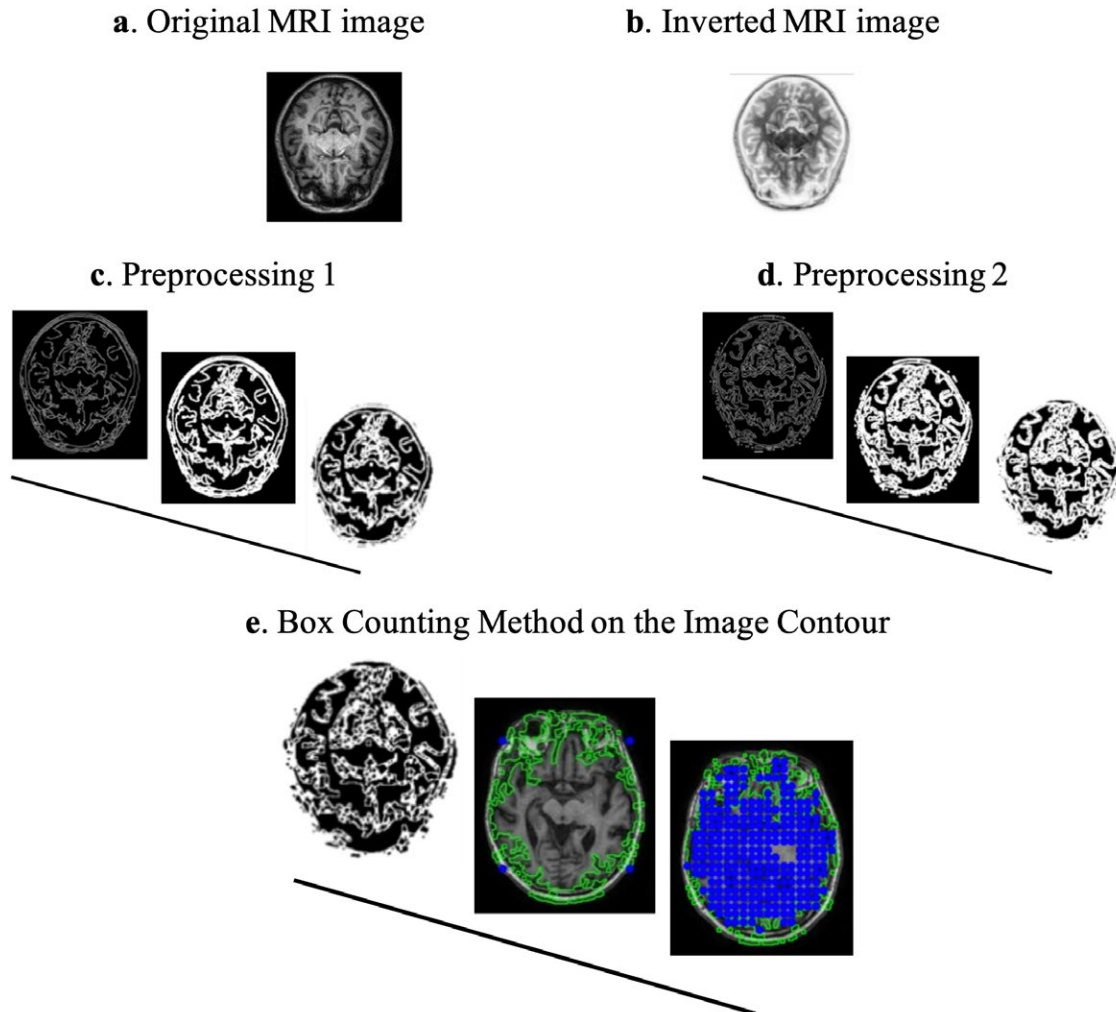


Figure 1. Illustration of the calculation of the fractal dimension in an axial brain slice using the Box Counting algorithm used in this study

a. The original MRI image that was uploaded is then inverted, as shown in **b**. This inverted image is then processed in **c** and **d** using edge detection (Canny), dilation (Diamond Kernel), and Floodfill. Next, in **e**, the image contour detection and the application of the Box Counting method for estimating the fractal dimension are shown.

Source: prepared by authors.

The MRI scan was performed by the radiology department at HIC, and the active standing test was conducted by psychology professionals with advanced degrees specializing in psychophysiology. In addition, it should be noted that all participants in the study voluntarily agreed to participate, and their participation did not begin until they had signed the informed consent form. The study was conducted in accordance with the ethical guidelines

set forth in Resolution 8430 of the Colombian Ministry of Health and was approved by the UPB Ethics Committee (Minutes: CE_A_46 of 2019).

Statistical analysis: A Student's t-test was performed to analyze potential differences in cognitive, brain, and physiological indicators between participants diagnosed with Alzheimer's dementia and the respective controls. Based on the results of these comparative analyses, the

variables that significantly distinguished the two groups of participants were included in a binomial logistic regression model, which was performed using the stepwise method, with an alpha value of > 0.05 serving as the criterion for variable exclusion. Subsequently, the probability of the event/diagnosis occurring (fits) was estimated using the variables that made up the model, and the participants were classified based on a probability value, which allowed calculating the percentages of true positives and true negatives. Finally, results were reported regarding correlations (Pearson's rho) between the cognitive indicator (MoCA) and cerebral fractal dimension, as well as with autonomic variables (heart rate). The software used to perform the analyses was Minitab 19.

Results

A binary logistic regression analysis was conducted to develop a model capable of integrating multiple factors that contribute to detecting cases of Alzheimer's disease. To this end, the various variables considered predictors were initially examined and their scores were compared between participants with and without a diagnosis of dementia using Student's t-test or the Mann-Whitney U test, depending on whether the data followed a normal distribution. In turn, a probability of error of less than 5% was considered as the criterion for statistical significance ($p < 0.05$). These results are shown in Table 1.

Table 1. Comparisons of cognitive, brain, and physiological indicators between participants with and without a diagnosis of Alzheimer's dementia

	Cognitive	Cerebral		Physiological (autonomic)		
	MoCA	FD. Coronal	FD. Axial	Average HR	Maximum HR	Minimum HR
Without AD Diagnosed Average + SD $n = 14$	22.92+5.29	1.42 + 0.14	1.48+0.02	84.41+12.35	93.30+15.86	79.38+11.84
With AD Diagnosed Average+SD $n = 14$	12.00+5.26	1.54+ 0.04	1.50+0.02	72.18+8.52	78.66+10.26	67.79+7.67
<i>t value</i>	-5.59	-3.01	-3.38	-3.18	-3.03	-3.20
<i>p value</i>	<0.001*	0.006*	0.002*	0.004*	0.006*	0.004*

AD: Alzheimer's Dementia, SD: Standard Deviation, FD: Fractal Dimension, HR: Heart Rate, * statistically significant difference ($p < 0.05$)

Source: prepared by the authors

It was found that participants diagnosed with Alzheimer's dementia scored lower on the MoCA. Furthermore, these participants exhibited lower autonomic reactivity during the active standing test, as reflected in the three analyzed heart rate indicators. Regarding differences in brain indicators, the fractal dimension of the coronal and axial slices was "higher" in participants with a diagnosis. However, the interpretation should be the opposite - lower brain fractality in cases of Alzheimer's dementia, since these fractality values have an inverse relationship

according to the preprocessing of the MRI images (see the fractal dimension estimation in the methodology section).

Since the aforementioned variables revealed significant differences between the participant groups, all of them were included as potential predictors of the outcome (diagnosis of dementia) in the binomial logistic regression model, which was run using a stepwise method with inclusion and exclusion criteria set at an alpha level of 0.05. Table 2 shows the resulting model with the variables provided by the explanatory indicators.

Table 2. Binomial regression analysis aimed at identifying the occurrence of a diagnosis of Alzheimer's dementia

Stepwise Method	Step 1		Step 2	
	<i>p-</i>	<i>value</i>	<i>p-</i>	<i>value</i>
Constant	8.35		34.0	
MoCA	-0.500	0.013	-0.749	0.034
Minimum HR			-0.295	0.045
R ²	56.75%		80.70%	
Adjusted R ²	54.17%		75.55%	

HR: Heart Rate.

Source: prepared by the authors

Based on the described results and the method used for the binomial regression analysis, the variables related to cerebral fractal dimension were excluded (because the error probability values in the model were greater than 5%: $p > 0.05$), maintaining a cognitive indicator corresponding to the MoCA and an autonomic indicator represented by the minimum heart rate during the standing period, which allowed identifying the event - the diagnosis of dementia - in 75.5% of participants (adjusted R^2). Based on these two

variables, the probability of the event occurring (fits) was estimated for each participant. Those with a probability greater than 70% were subsequently classified as positive. The data derived from this process was used to create a 2×2 contingency table, which facilitated estimating true positives and true negatives based on the classification performed according to the model, in contrast to the participants' diagnostic status (Table 3).

Table 3. Contingency table comparing classification probabilities from the model with participants' self-reports

	WITH diagnosed	Estado civil
WITH diagnosis according to model	13	1
Percentage	TP: 92.8%	7.1%
WITHOUT diagnosis according to model	1	13
Percentage	7.1%	TN: 92.8%

As can be seen in the contingency table (Table 3), both the true positive rate and the true negative rate are around 93%. Moreover, taking into account the average values and standard deviations in each group of participants for the variables that made up the model (MoCA and minimum heart rate), the model's predictive ability for the diagnosis of dementia was calculated, yielding an adjusted probability of 0.99 (95% confidence interval [CI]: (0.51–0.99) to identify the diagnostic condition based on the two mentioned variables.

Finally, although brain fractal dimensions did not emerge as predictive variables in the binomial regression analysis,

these brain indicators were found to show significant correlations with MoCA scores, both for the fractal dimension of axial sections ($r = -0.38$, $p = 0.046$) as well as for the fractal dimension of coronal sections ($r = -0.42$, $p = 0.026$). In addition, this last coronal fractal dimension was associated with the autonomic cardiac variables derived from the standing test: average heart rate (HR): average ($r = -0.47$, $p = 0.011$), maximum HR ($r = -0.53$, $p = 0.004$), and minimum HR ($r = -0.45$, $p = 0.017$). The following figures show the Pearson correlations between the cognitive indicator (MoCA) and brain fractal dimensions (Figure 2).

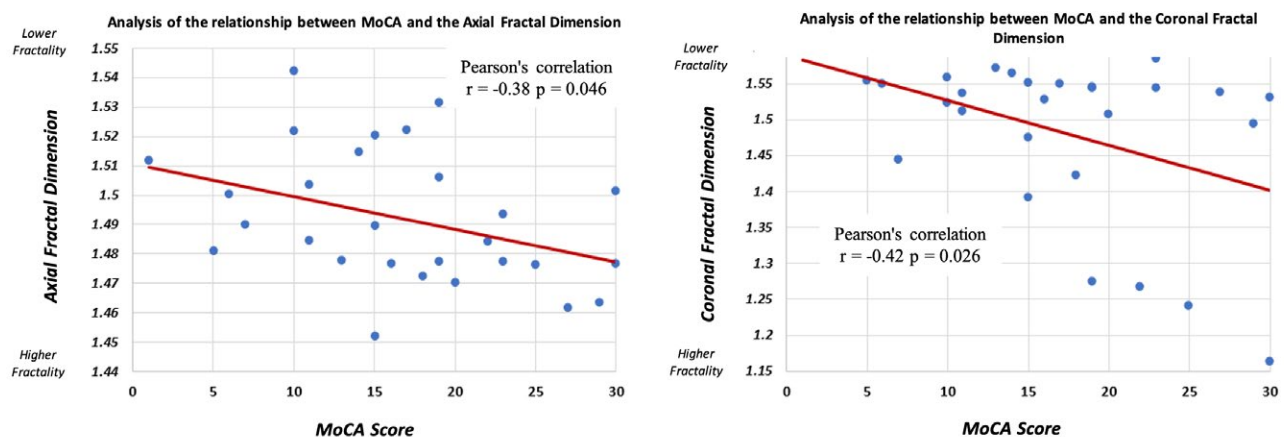


Figure 2. Pearson correlation analysis between MoCA scores and values of cerebral fractal dimensions from axial and coronal sections

Source: prepared by authors.

Discussion

Since this study analyzed a model that integrated cognitive, neurological, and autonomic indicators aimed at detecting cases of Alzheimer's disease, it was noted that initial comparative analyses revealed that volunteers diagnosed with Alzheimer's disease exhibited lower overall cognitive performance, lower cerebral fractality, and lower cardiac reactivity during an active standing test. Although this initially led to including all the aforementioned variables in the binomial logistic regression analysis, the best predictive model identified in the stepwise analysis consisted of MoCA scores and minimum heart rate, accounting for the occurrence of a dementia diagnosis in 75.5% of the participants in this study.

The results highlighted the importance of the global cognitive performance indicator in the diagnostic evaluation of dementia, as reflected in the use of cognitive screening tools, such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). These are designed to aid in detecting MCI and dementia in various neurological conditions (31). The latter test reports good psychometric reliability and validity properties, along with a sensitivity of 87% and a specificity of 100% for Alzheimer's dementia, based on a cutoff score of less than 18 (24). However, systematic reviews, such as the one conducted by Davis et al. (32), report that an internationally standardized cutoff point below 26 points has been associated with a high false-positive rate in just over 40% of cases, leading to recommendations to adjust the cutoff point and the need to integrate other approaches that increase diagnostic accuracy (32). This scenario favors considering a multicomponent approach.

In addition to the above, it is important to consider autonomic indicators, as it has been found that patients with mild cognitive impairment exhibit smaller changes in heart rate variability, an indicator associated with possible sympathetic dysfunction, along with lower systolic blood pressure upon standing. This has been linked to a deficit in the autonomic nervous system's response, known as dysautonomia (16,18,19), as a consequence of the deterioration of subcortical structures at the level of the brainstem in conditions such as Alzheimer's disease (15). In addition to this, there are reviews such as the one conducted by Forte et al. (17), who show that a decrease in heart rate variability resulting from increased sympathetic activity and a decrease in parasympathetic activity have been associated with poorer cognitive performance, particularly in terms of overall cognitive performance and executive function (17).

On the other hand, although the anatomical-cerebral indicator represented by the fractal dimensions derived from the analysis of axial slices did not emerge as a variable that contributed to the model, this result should not lead us to rule out the use and potential utility of cerebral fractal

dimensions. In fact, traditional MRI indicators, such as hippocampal volume, are also not 100% reliable in the diagnostic assessment of dementia, as systematic reviews have revealed a false-negative rate of approximately 27%. This finding was derived from 81 individuals in whom the potential diagnosis was missed and who were among 300 patients with MCI who later developed dementia due to Alzheimer's disease. Similarly, an erroneous prognosis for this type of dementia was made in 29% of cases, resulting from the identification of 203 false positives among 700 patients considered to have MCI (9).

In addition to the above, there has been discussion regarding the sensitivity of brain volume (volumetry) in the differentiation and identification of neuropathologies over the past decade. At the same time, other indicators have been studied and proposed, such as tissue viscoelasticity (magnetic resonance elastography), which have identified microstructural differences in brain tissue associated with cognitive performance in both young and older adults (33).

Another finding worth highlighting, which justifies further study of the cerebral fractal dimension, is that the present study demonstrated that cerebral fractal dimension, in both axial and coronal sections, was significantly associated with cognitive performance as assessed by the MoCA. This result was consistent with the results of the study by King et al. (34), who demonstrated that the fractal dimension of cortical thickness was associated with cognitive decline in participants diagnosed with Alzheimer's disease, as assessed using the ADAS (Alzheimer's Disease Assessment Scale-Cognitive) (34).

In addition, other studies have confirmed the correlation between fractal dimension and the areas of the gyri, cortical thickness, and cortical curvature (11,12). Therefore, as a method that incorporates cortical thickness measures, it could be effective in detecting morphological changes resulting from neurodegeneration, potentially distinguishing healthy individuals from patients with Alzheimer's disease. However, the evidence supporting these claims still requires further research (10,13,34).

Finally, for future research that aims to study Alzheimer's disease-related dementia using a model that integrates multiple indicators, it is recommended to consider assembling a sample that reflects diversity in the severity of the symptoms of dementia, as well as potential comorbidities that represent clinical reality. This would prevent statistical biases by promoting variability in data distribution, thereby enabling the identification of correlations between variables and, in turn, the development of multivariate models. Furthermore, the study on cerebral fractal dimension suggests the possibility of analyzing the sensitivity and specificity of indicators of this dimension derived from various structures associated with the cerebral atrophy characteristic of dementia for future research. Among these, in addition to cortical thickness, the study

proposes the size of the ventricles and changes in cortical sulci, such as the lateral fissure.

Conclusions

This study revealed that the integration of cognitive indicators (as measured by the MoCA) and autonomic indicators (derived from cardiac reactivity to an orthostatic intolerance test) allowed more accurately identifying the diagnosis than when the variables were considered in isolation, using a logistic regression model (adjusted $R^2 = 75.6\%$). Although the cerebral fractal dimensions from axial and coronal sections did not meet the statistical criteria for inclusion in the model, the potential utility of the cerebral fractal dimension was demonstrated, as it was found to be associated with the indicator of cognitive functioning corresponding to MoCA scores through statistically significant correlations.

Acknowledgments

The authors would like to thank the participating older adults and their families for their willingness to participate and their interest. We appreciate the collaboration and institutional support provided by the Ministry of Science, Technology and Innovation (MinCiencias, for the Spanish original), Universidad Pontificia Bolivariana (UPB), and Hospital Internacional de Colombia (HIC) – Fundación Cardiovascular de Colombia (FVC).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

This study was conducted as part of the project registered under Code 125-0120-3100 at the Universidad Pontificia Bolivariana, funded through MinCiencias Call for Proposals No. 844 – 2019.

Ethical responsibilities

Protection of people: This study is considered risk-free due to its nature. It was approved by the Institutional Ethics Committee.

Confidentiality of data: The authors declare they have followed their work center's protocols on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the informed consent of patients and/or

subjects mentioned in the article. This document is in the possession of the corresponding author referred to in the article.

References

1. Asociación Americana de Psiquiatría. Manual diagnóstico y estadístico de los trastornos mentales DSM – 5 [Internet]. Ciudad de México; Panamericana; 2015. Available from: <https://www.federaciocatalanatdah.org/wp-content/uploads/2018/12/dsm5-manualdiagnosticoyestadisticodelostrastornosmentales-161006005112.pdf>
2. World Health Organization. Demencia [Internet]. Ginebra: WHO; 2025. Available from: https://www.who.int/es/news-room/fact-sheets/detail/dementia?utm_source=chatgpt.com
3. Guerrero-Barragán A, Lucumí-Cuesta DI, Gómez IE, Lawior B. Análisis situacional del deterioro cognitivo en Colombia. Notas de Política [Internet]. 2023;45:1-3. Available from: <https://repositorio.uniandes.edu.co/server/api/core/bitstreams/32cc0920-573a-4b68-a8e3-0ca6b4c35804/content>
4. World Health Organization (WHO). The top 10 causes of death [Internet]. Ginebra: OMS; 2020. Available from: <https://www.who.int/es/news-room/fact-sheets/detail/the-top-10-causes-of-death>
5. Organización Mundial de la Salud. Salud mental de los adultos mayores [Internet]. Ginebra: OMS; 2025. Available from: <https://www.who.int/es/news-room/fact-sheets/detail/la-salud-mental-y-los-adultos-mayores>
6. Mestas L, Rincón S. Demencia o trastorno neurocognitivo mayor. En: Cerezo-Huerta K. Trastornos neurocognitivos en el adulto mayor: evaluación, diagnóstico e intervención neuropsicológica. Ciudad de México: Manual Moderno; 2019. p. 67-80.
7. Bartolini L, Russo MJ, Mesa-Morteo M, Iturri M, Román F, Sevlever G. Manejo inicial en deterioro cognitivo. En: Allegri R, Roqué M. Deterioro cognitivo, Alzheimer y otras demencias. Formación Profesional para el Equipo Socio-Sanitario [Internet]. Buenos Aires: UNLaM-Ministerio de Desarrollo Social; 2015. Available from: <https://www.algec.org/biblioteca/Deerieroro-cognitivo-Alzheimer.pdf>
8. Petersen RC. Mild cognitive impairment or questionable dementia? Arch Neurol [Internet]. 2000;57(5):643-4. doi: <https://doi.org/10.1001/archneur.57.5.643>
9. Lombardi G, Crescioli G, Cavedo E, Lucenteforte E, Casazza G, Bellatorre AG, et al. Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. Cochrane Database Syst Rev [Internet]. 2020;3:CD009628. doi: <https://doi.org/10.1002/14651858.CD009628.pub2>

10. Ziukelis ET, Mak E, Dounavi ME, Su L, O'Brien JT. Fractal dimension of the brain in neurodegenerative disease and dementia: A systematic review. *Ageing Res Rev* [Internet]. 2022;79:101651. doi: <https://doi.org/10.1016/j.arr.2022.101651>
11. Im K, Lee JM, Yoon U, Shin YW, Hong SB, Kim IY, et al. Fractal dimension in human cortical surface: Multiple regression analysis with cortical thickness, sulcal depth, and folding area. *Hum Brain Mapp* [Internet]. 2006;27(12):994-1003. doi: <https://doi.org/10.1002/hbm.20238>
12. Jiang J, Zhu W, Shi F, Zhang Y, Lin L, Jiang T. A robust and accurate algorithm for estimating the complexity of the cortical surface. *J Neurosci Methods* [Internet]. 2008;172(1):122-30. doi: <https://doi.org/10.1016/j.jneumeth.2008.04.018>
13. Di Marco N, Di Palma A, Frosini A. A study on the predictive strength of fractal dimension of white and grey matter on MRI images in Alzheimer's disease. *Ann Math Artif Intell* [Internet]. 2024;92:201-14. doi: <https://doi.org/10.1007/s10472-023-09885-8>
14. De Vilhena-Toledo MA, Junqueira LF Jr. Cardiac autonomic modulation and cognitive status in Alzheimer's disease. *Clin Auton Res* [Internet]. 2010;20(1):11-7. doi: <https://doi.org/10.1007/s10286-009-0035-0>
15. Simic G, Stanic G, Mladinov M, Jovanov-Milosevic N, Kostovic I, Hof PR. Does Alzheimer's disease begin in the brainstem? *Neuropathol Appl Neurobiol* [Internet]. 2009;35(6):532-54. doi: <https://doi.org/10.1111/j.1365-2990.2009.01038.x>
16. Nicolini P, Ciulla MM, Malfatto G, Abbate C, Mari D, Rossi PD, et al. Autonomic dysfunction in mild cognitive impairment: Evidence from power spectral analysis of heart rate variability in a cross-sectional case-control study. *PLoS One* [Internet]. 2014;9(5):e96656. doi: <https://doi.org/10.1371/journal.pone.0096656>
17. Forte G, Favieri F, Casagrande M. Heart rate variability and cognitive function: A systematic review. *Front Neurosci* [Internet]. 2019;13:710. doi: <https://doi.org/10.3389/fnins.2019.00710>
18. Omoya R, Miyajima M, Ohta K, Suzuki Y, Aoki A, Fujiwara M, et al. Heart rate response to orthostatic challenge in patients with dementia with Lewy bodies and Alzheimer's disease. *Psychogeriatrics* [Internet]. 2021;21(1):62-70. doi: <https://doi.org/10.1111/psyg.12625>
19. Mellingsæter MR, Wyller TB, Ranhoff AH, Bogdanovic N, Wyller VB. Reduced sympathetic response to head-up tilt in subjects with mild cognitive impairment or mild Alzheimer's dementia. *Dement Geriatr Cogn Disord Extra* [Internet]. 2015;5(1):107-15. doi: <https://doi.org/10.1159/000375297>
20. Colombia. Ministerio de Salud y Protección Social. Anexo: Instrumentos de valoración para la ruta de promoción y mantenimiento de la salud [Internet]. Bogotá: Minsalud; 2018. Available from: <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/PP/anexo-instrumentos-valoracion-ruta-promocion.pdf>
21. Barrero SCL, García AS, Ojeda MA. Índice de Barthel (IB): un instrumento esencial para la evaluación funcional y la rehabilitación. *Plast Rest Neurol* [Internet]. 2005;4(1-2):81-5. Available from: https://www.medigraphic.com/pdfs/plasticidad/prn-2005/prn051_2l.pdf
22. Loureiro C, García C, Adana L, Yacelga T, Rodríguez-Lorenzana A, Maruta C. Uso del test de evaluación cognitiva de Montreal (MoCA) en América Latina: revisión sistemática. *Rev Neurol* [Internet]. 2018;66(12):397-408. doi: <https://doi.org/10.33588/rn.6612.2017508>
23. Custodio N. Validación y precisión de la Escala de Deterioro Global (GDS) para establecer severidad de demencia en una población de Lima. *CES Med* [Internet]. 2017;31(1):14-26. doi: <https://doi.org/10.21615/cesmedicina.31.1.2>
24. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* [Internet]. 2005;53(4):695-9. doi: <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
25. Pedraza OL, Salazar AM, Sierra FA, Soler D, Castro J, Castillo PC, et al. Confiabilidad, validez de criterio y discriminante del Montreal Cognitive Assessment (MoCA) test, en un grupo de adultos de Bogotá. *Acta Médica Colombiana* [Internet]. 2016;41(4):221-8. doi: <https://doi.org/10.36104/amc.2016.693>
26. Gil L, Ruiz-de-Sánchez C, Gil F, Romero SJ, Pretelt-Burgos F. Validation of the Montreal Cognitive Assessment (MoCA) in Spanish as a screening tool for mild cognitive impairment and mild dementia in patients over 65 years old in Bogotá, Colombia. *Int J Geriatr Psychiatry* [Internet]. 2015;30(6):655-62. doi: <https://doi.org/10.1002/gps.4199>
27. Fischl B. FreeSurfer. *NeuroImage* [Internet]. 2012;62(2):774-81. doi: <https://doi.org/10.1016/j.neuroimage.2012.01.021>
28. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* [Internet]. 2000;97(20):11050-5. doi: <https://doi.org/10.1073/pnas.200033797>
29. Canny JA. Computational approach to edge detection. *IEEE Trans Pattern Anal Mach Intell* [Internet]. 1986;8(6):679-98. doi: <https://doi.org/10.1109/TPAMI.1986.4767851>
30. Villamizar J, Uribe L, Cerquera A, Prada E, Prada D, Alvarez M. Fractal analysis of neuroimaging: Comparison between control patients and patients with the presence of Alzheimer's disease. *J Phys Conf Ser* [Internet]. 2022;2159(1):012011. doi: <https://doi.org/10.1088/1742-6596/2159/1/012011>

31. Gómez-Moreno SM, Cuadrado ML, Cruz-Orduña I, Martínez-Acebes EM, Gordo-Mañas R, Fernández-Pérez C, et al. Validación de la versión española de la Escala Cognitiva de Montreal (MoCA) como herramienta de cribado de deterioro cognitivo asociado a la esclerosis múltiple. *Neurología* [Internet]. 2022;37:726-34. doi: <https://doi.org/10.1016/j.nrl.2019.11.006>
32. Davis DHJ, Creavin ST, Yip JLY, Noel-Storr AH, Brayne C, Cullum S. Montreal Cognitive Assessment for the detection of dementia. *Cochrane Database Syst Rev* [Internet]. 2021;7:CD010775. doi: <https://doi.org/10.1002/14651858.CD010775.pub3>
33. Schwarb H, Johnson CL, Daugherty AM, Hillman CH, Kramer AF, Cohen NJ, et al. Aerobic fitness, hippocampal viscoelasticity, and relational memory performance. *NeuroImage* [Internet]. 2017;153:179-88. doi: <https://doi.org/10.1016/j.neuroimage.2017.03.061>
34. King RD, Brown B, Hwang M, Jeon T, George AT. Alzheimer's Disease Neuroimaging Initiative. Fractal dimension analysis of the cortical ribbon in mild Alzheimer's disease. *NeuroImage* [Internet]. 2010;53(2):471-9. doi: <https://doi.org/10.1016/j.neuroimage.2010.06.050>