

Fractal Dimension as an Index of Brain Cortical Changes Throughout Life

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Abstract. *The fractal dimension (FD) of the cerebral cortex was measured in 93 individuals, aged from 3 months to 78 years, with normal brain MRI's in order to compare the convolutions of the cerebral cortex between genders and age groups. Image J, an image processing program, was used to skeletonize cerebral cortex and the box counting method applied. FDs on slices taken from left and right hemispheres were calculated. Our results showed a significant degree of lateralization in the left hemisphere. It appears that basal ganglia development, mainly in the left hemisphere, is heavily dependent upon age until puberty. In addition, both left and right cortex development equally depends on age until puberty, while the corresponding right hemisphere convolutions continue to develop until a later stage. An increased developmental activity appears between the ages of 1 and 15 years, indicating a significant brain remodelling during childhood and adolescence. In infancy, only changes in basal ganglia are observed, while the right hemisphere continues to remodel in adulthood.*

The study of gross appearances of the human brain cortex has been carried out in the past *via* post-mortem techniques and by the 19th century differences in brain weight and volume between males and females and at different ages had been recorded (1). Histological studies on autopsy material also revealed changes which may account for differences observed in brain morphology throughout life (2).

The introduction of magnetic resonance imaging (MRI) has enabled *in vivo* studies of healthy individuals and patients; since ionizing radiation is not involved children have also been included in such studies. Automated morphometric methods were applied on MRI's for the estimation of brain volume (3, 4), gray matter (GM) morphology (5-7) and as diagnostic tools for schizophrenia

(8), Alzheimer's disease, frontotemporal lobe degeneration (9, 10), Huntington's disease (11) and multiple sclerosis (12).

Age and gender differences in brain morphology were also demonstrated with volumetric studies in MRIs of healthy subjects at various ages (13-16).

The concept of fractal geometry introduced by Mandelbrot in 1982 (17) has been applied in biology and medicine (18) and has been used for the description of patterns of normal (19) and pathological tissues (20), radiological images (21, 22) and for differential diagnosis between normal, dysplastic and neoplastic tissue (23) the study of early cellular changes during proliferation and apoptotic cell death (24), and in the evaluation of tumor prognosis (25) and response to anticancer therapy (26).

Hofman (27) showed the fractal structure of human brain which was confirmed by a subsequent study (28). The fractal dimension (FD) of MRI's has been used for differential diagnosis between normal and pathological conditions. In the relatively few studies on the brain reported so far, FD was applied to identify early stage atherosclerosis (29), in the detection of brain tumors (30), in evaluation of age-related microstructural changes of white matter (WM) (31), in estimation of senile brain atrophy (32) and in patients with frontal lobe epilepsy (33), schizophrenia and manic-depression (34). It was also used for the investigation of hemispheric asymmetry between normal individuals aged 18-77 years (35).

To our knowledge FD, throughout the human life-span has not been reported. In this study, we applied FD in a cohort of 93 people with normal brain MRI's, the youngest being 3 months old and the oldest 78 years old. The aim was to compare the fractal dimension of cerebral cortex between genders and age groups of normal people including infants and to investigate whether any of the differences found occur at a steady rate, or begin to accelerate at a particular age.

Patients and Methods

Study participants. During a three-year period, sagittal images were taken from all patients submitted to brain investigation for various causes at the Heraklion University Hospital, Department of Radiology. Ninety-three people, 56 males and 37 females, aged 3

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Table I. Age distribution of participants.

Age (years)	Males Number	Females
0-1	8	6
1-9	20	7
10-19	15	12
20-29	5	3
30-39	3	5
40-49	3	
50-59	1	3
60+	1	1
Total	56	37

months to 78 years, (mean 16.6 ± 16.6 SD) selected as having no brain pathology on MRI, were enrolled in the study. Psychiatric patients and patients with epilepsy or dementia were not included. The age distribution of study participants is presented in Table I.

MRI. All subjects underwent MR on 1.5 T MR system (Magnetom/Vision Plus, Siemens, Erlangen, Germany) using standard quadrature RF head coil apparatus. A 3D multi-slice-single-echo GRE sequence endorsed with magnetization prepared prepulses (TR/TE/FA: 9.7 ms/4 ms/12°) was used. One single sagittal 3D slab (160 mm thickness) with 64 partitions was obtained, thus giving 64 2D sagittal slices of 2.5 mm effective thickness and no interslice gap. A rectangular field of view (FOV) covering an area of 270x236 mm² was used. The image reconstruction matrix was 256x224 pixels respectively to the FOV dimensions, corresponding to a pixel matrix with square pixel dimensions 1.05x1.05 mm. One signal average and a small receiver bandwidth (195 Hz/pixel) were utilized. All 64 images (12-bit grayscale, DICOM-3 format) were transferred to a PC workstation where a 8-to-12-bit dynamic range compression using a best histogram equalization algorithm was performed for each image separately. Images were then stored utilizing the standard 8 bit BMP format.

Image analysis. Image J, an image processing program developed at the National Institute of Health, Washington, USA, was used to skeletonize cerebral cortex. Using the program, surrounding structures of the cerebral cortex were removed and the contour of the brain surface was outlined. Left and right cerebral anatomy was recognized and manually extracted using standard contouring algorithms from a series of selected left and right cerebral parasagittal slices. An automatic threshold technique using a pixel value range (0-127) as 0 and a pixel value range (128-255) as 1 was applied in order to perform a series of 2-bit black and white images (Figure 1 a,b).

An exact calculation of the brain contour is impossible since it is dependent on the magnification used. FD, independent of the scale of magnification when dealing with biological images, is best calculated by the box-counting method. The dimension derived by this method is the box-counting dimension and is calculated by first covering the object (MRI) with squares or "boxes" with a side length of δ . If N is the number of boxes of size δ that completely cover the object, then the box-counting dimension is calculated by the equation:

Table II. Analysis of the 2D fractal dimension of MRI data.

	Minimum	Maximum	Mean	Standard deviation
LA	1.487	1.756	1.587	0.057
LB	1.495	1.763	1.593	0.058
LC	1.396	1.731	1.598	0.061
RA	1.478	1.734	1.609	0.058
RB	1.436	1.773	1.596	0.070
RC	1.487	1.764	1.587	0.062

L: left hemisphere; R: right hemisphere; A: outer margin; B: middle margin; C: inner margin.

$$D_B = \lim_{\delta \rightarrow 0} \frac{d(\log(N))}{d(\log(1/\delta))}$$

which is in the form of a graph of log (N) against log (1/ δ). The gradient of the best-fit line through the points gives an estimate of the box-counting FD of the object.

A standard box-counting method was utilized using the black and white images. The software repeatedly covers the image with squares (boxes) of varied δ of 1, 2, 4, 8, 16, 32, 64, 128, 256 and 512 pixels. The number of "boxes" (N) for each of the above box sizes that completely cover the image, are counted and the values inserted into the afore-mentioned equation in order to calculate the box-counting dimension. The gradient of the best-fit line through the points gives an estimate of the box-counting fractal dimension of the object.

The fractal dimension was calculated for each image. An average FD value obtained from the series of left and right cerebral parasagittal slices was also calculated and utilized for inter subject comparisons.

Results

The basic statistical data of the analysis of the 2D fractal dimension of MRI data are given in Table II.

Analysis of data reveals a significant degree of lateralization (*t*-test 2.51, *p*<0.03) in the left outer margin (LA) as compared to the right outer margin (RA) of the external slices. In contrast, middle and inner slices were not significantly different between the right and left hemispheres. In addition, ANOVA showed a slight dependence of brain convolution on gender (only in LA slice, *p*<0.04), while a significant dependence of brain fractal dimension with age was found (*p*<0.02).

Further analysis of dependence of brain convolution with age is presented in Table III. Here, data were divided into four distinct categories: infants (age <1 year), children (aged 1-10 years), peripubertals (aged 10-15 years) and adults (aged >25 years). Left hemisphere inner slice (as represented by slice LC) is heavily dependent upon age until puberty, while the corresponding right hemisphere (RC)

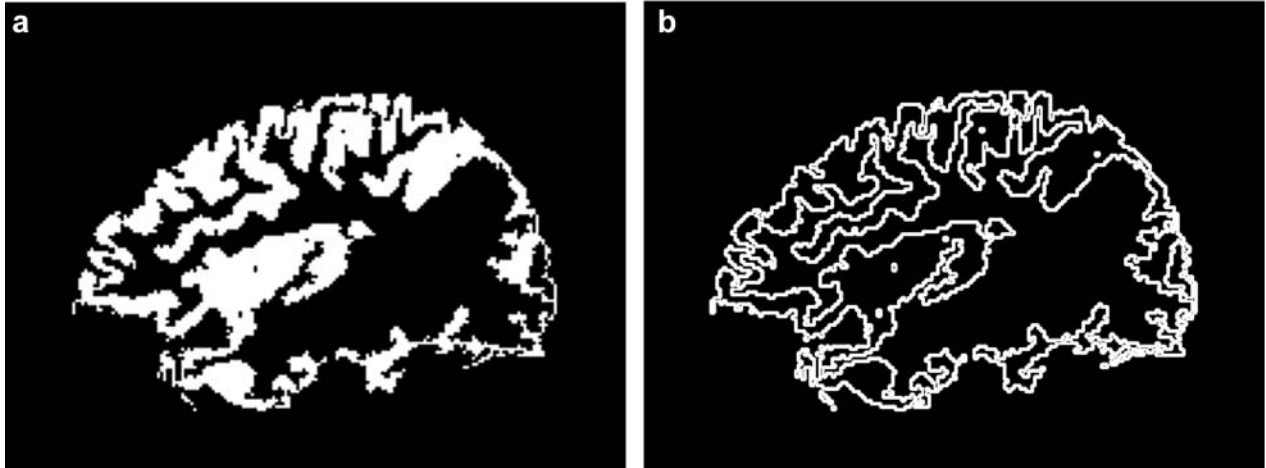


Figure 1. Binary black and white images generated by the application (a) of an automated threshold technique and (b) an automated edge detection algorithm depicting a parasagittal slice positioned at the outer margin of the orbit for the left hemisphere of a 12-year-old subject.

Table III. Analysis of dependence of brain convolution on age.

Age (years)	N	LA		LB		LC		RA		RB		RC	
		r_s	p	r_s	p	r_s	p	r_s	p	r_s	p	r_s	p
<1	14	-0.420	0.067	-0.083	0.389	-0.497*	0.035	-0.099	0.368	-0.411	0.072	-0.367	0.098
1-9	43	-0.369**	0.007	-0.387**	0.005	-0.312*	0.021	-0.354**	0.01	-0.479**	0.001	-0.277*	0.036
10-15	61	-0.449**	0	-0.444**	0	-0.316**	0.007	-0.272*	0.017	-0.468**	0	-0.232*	0.036
>15	35	-0.217	0.106	-0.193	0.133	-0.062	0.363	-0.286*	0.048	-0.382*	0.012	-0.188	0.14

L: left hemisphere; R: right hemisphere; A: outer margin; B: middle; C: inner margin.

Spearman's rho. r_s : correlation coefficient; p : Sig. (1-tailed); *correlation is significant at the 0.05 level (2-tailed); **correlation is significant at the 0.01 level (2-tailed).

slice shows a significant but lower dependence with age. In addition, both left (LA) and right external slices (RA) equally depend on age until puberty, while the corresponding right hemisphere convolutions continue to develop until a later stage

Discussion

FD serves as an index of cortical surface characteristics such as sulcal and gyral shape, and convolution, and is useful for intersubject comparative studies.

In our results from all measurements a mean FD of 1.59 ± 0.061 was found. In the few studies reported so far a wide range of FDs was given. Fractal analysis of the boundary between white matter and cerebral cortex in psychiatric patients and normal controls gave a mean FD 1.4 (34). Cook and colleagues (33), investigating cerebral cortical patterns in 16 patients with frontal lobe epilepsy, found a FD of 1.45 ± 0.6 in a control group of normal

subjects. Extrapolation of this planar FD from two (2FD) to three dimensions (3FD) gave a value of 2.45 (28) Majumdar and Prasad (36) found a 3FD of 2.60 after extrapolation of the 2FD value while Free *et al.* found a 3FD of 2.30 (37). In six subjects Kiselev *et al.* (28) obtained a 3FD value of 2.80 and Lee *et al.* (35) a 3FD of 2.40 to 2.42 in normal adults. The above variations may be due to the variety of methods applied. In studies in which a 3FD value was reported, images obtained after removing surrounding structures of the cerebral cortex are 2D and this may result in errors in the 3D computation.

In our results, extrapolation of the mean 2FD found to a 3FD gave a value of 2.68 which is in the range of the values reported in previous papers.

Analysis of sulcal variability by measuring the FD of six post-mortem brains by Thomson *et al.* (38) showed no significant hemispheric variability, while Lee *et al.* (35) found a significantly greater FD for the right than the left hemisphere on MRIs of normal adults.

Our results only showed a significant degree of lateralization in the left hemisphere as compared to right of the slices taken from the external margin of the orbit.

As shown, basal ganglia development mainly in the left hemisphere (as represented in inner slice), is heavily dependent upon age until puberty, compared to corresponding right hemisphere slice. In right hemisphere a significant but lower dependence with age is observed. In addition, both left (LA) and right cortex (RA) development equally depend on age until puberty. Comparing age dependence of brain convolutions, it is interesting to note an increased developmental activity at ages between 1 and 15 years, indicating significant brain remodelling during childhood and adolescence. In infancy, only changes in basal ganglia are observed, while in adulthood, the right hemisphere continues to remodel. This may be due to the fact that brain cortex gray matter (GM) (visualized by external slices) develops more rapidly than basal ganglia, shown in middle and internal MRI slices.

Apart from our finding of the above difference between the left and right side, we also found a significant difference in lateralization (left hemisphere) with gender and correlations of left hemisphere differences with age.

Cerebral anatomical asymmetries of the brain cortex were found in studies in which morphometrical methods were applied.

Good *et al.* (39) examined human brain asymmetry in normal adults. They observed significant differences with increased leftwards asymmetry in males. They did not find any significant interaction between asymmetry and handedness nor any main effect of handedness. This is not in accordance with recent observations of Herve *et al.* (40). In their study, a comparison between right- and left-handed young males revealed significant effects of handedness of anatomical asymmetry in frontal regions, with right-handed subjects being more leftward asymmetric. In a study in which MRI data from normal subjects and schizophrenic patients were compared, hemispheric asymmetry indices did not differ significantly with gender, hand preference or diagnosis (41).

Luders *et al.* (42) analyzed hemispheric differences in regional GM thickness in young healthy adults. Their results revealed differences between the two hemispheres with a generally thicker cortex in the left hemisphere. Asymmetry profiles were similar in both genders but hemispheric differences appeared slightly pronounced in males. In another study from the same group of investigators (43), a significantly greater cortical thickness was found in women compared with men.

Handedness was not recorded in our material retrieved from hospital records but in view of the aforementioned studies this parameter may play a role in our observed cortical changes.

So far brain development has been studied by volumetric methods with which changes of GM and WM volume were

estimated. Pfefferbaum *et al.* (44) in a study which includes ages from 3 months to 70 years showed that intracranial volume increased by about 300 mL from 3 months to 10 years. The same patterns of change in volume were seen in both sexes: cortical GM volume peaked around age 4 years and decreased thereafter; cortical WM volume increased steadily until about age 20 years. Brain volumes were statistically adjusted for normal variation in head size and revealed the following pattern: GM volume decreased, showing an average volume loss of 0.7 mL/y, while WM volume remained constant during the five decades, complementary to the cortical GM decrease.

In a morphometric quantitative study on MRIs from healthy subjects aged 4-18, years males had a larger cerebral volume which did not change significantly across the examined age range. The cerebral hemispheres and caudate showed a highly consistent right greater than left asymmetry (13).

Brain mapping was used to identify changes and revealed differences in the development of cortical regions. Blanton *et al.* (45) mapped cortical asymmetry and complexity patterns in 24 normal children aged 6-11 years. They analysed cortical variation and complexity in three dimensions and revealed significant age-associated changes in frontal regions. A significant gender with age interaction was found in the left superior frontal and right inferior frontal regions with complexity increasing with age in females. They also found significant age effects, primarily in the left hemisphere in the measurements of individual sulcal parameters.

Sowell *et al.* (46) studied brain development using MRI's from normal children scanned twice between the ages of 5 and 11 years. They quantitatively mapped cortical thickness and revealed regional specific brain growth and cortical gray matter thickness changes.

Brain mapping using volumetric methods can give detailed information on development and differences of various regions of the cerebral cortex. This was not within the scope of this study.

We demonstrated differences in two dimensional FD between ages and genders, possibly related to brain development. In our opinion the 2FD suffices for the comparisons made in this study. Interpretation of two dimensional pictures is common in everyday medical practice and measurement of two dimensional FD can easily be used since it does not need complicated volumetric methods and can indicate a threshold between normal as well as pathological changes.

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