Artículo original

Cambios corticales asociados al envejecimiento normal en imágenes FLAIR-MR: valores de tendencia central versus dispersion

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Resumen

El envejecimiento normal conduce a una reducción del volumen cerebral, adelgazamiento de la materia gris cortical y alteraciones en la intensidad de las señales de resonancia magnética (MRI). Se requieren mayores esfuerzos en la descripción de lo que es el envejecimiento cerebral normal y cuáles parámetros usar pare ello. El objetivo del presente estudio es usar los valores de tendencia central y de dispersión de los perfiles de intensidad de la señal T2-FLAIR-MRI de las cortezas frontal, parietal, occipital y cingulada y correlacionarlos con la edad y el género. Se evaluaron imágenes de resonancia de un total de 88 sujetos sanos (22-80 años de edad, 58 femeninos, 30 masculinos) obtenidos mediante secuencias T2-FLAIR en 1.5T, se calcularon la media y el coeficiente de variación (CV) de las intensidades de señal a partir de perfiles lineales de cada corteza, realizándose análisis de correlación y regresión de los mismos con la edad y por género. La media de la señal FLAIR se correlacionó negativamente mientras el CV positivamente con la edad en las cortezas frontal, parietal y occipital. La corteza cingulada no mostró cambios significativos. Los cambios fueron mas intensos para el sexo femenino y para el hemisferio izquierdo. El envejecimiento normal reduce los valores medios de intensidad de la señal T2-FLAIR pero incrementa la dispersión de la misma. Las ecuaciones de regresión obtenidas pueden ser usadas para detectar cambios corticales anormales dependientes de la edad.

Palabras clave: *Corteza cerebral, envejecimiento, MRI, FLAIR, dispersión*

Age related FLAIR-MRI brain cortical changes in normal aging: central tendency versus dispersion values

Original article

Abstract

The normal aging leads to a decrease in brain volume, gray matter cortical thinning and altered signal intensity on MRI. Efforts are needed to describe what normal brain aging is and which parameter to use. The aim was to use central tendency and dispersion values of T2-FLAIR-MRI signal intensity profiles from frontal, parietal, occipital and cingulate cortices and correlate them with age and gender. Images from a total of 88 healthy subjects (22-80 years old, 58 females, 30 males) were evaluated with 1.5T MRI FLAIR sequences obtaining mean and coefficient of variation (CV) signal intensities values from linear profiles of frontal, parietal, occipital and cingulate cortices. Correlation and regression analysis were performed between age and gender. FLAIR signal mean was negatively while CV was positively related to age for frontal, parietal and occipital cortex. Cingulate cortex did not show significant changes. These changes were more intense for females and for left hemisphere. Normal aging impacts inversely mean and CV values from cortical FLAIR MRI image. The regression equations obtained could be used to detect abnormal age-related cortical changes.

Key words: *Brain cortex, aging, MRI, FLAIR, dispersion*

Introduction

It is known that normal aging leads to a decrease in total brain volume, thinning of cortical gray matter, enlargement of the ventricles and altered signal intensity on magnetic resonance images (MRI) expressed by a decrease of T1-MRI signal in cortical gray matter[1,2]. Changes in different signal properties of the neural tissue have been demonstrated to be associated to aging[3] such as a gradual contrast decrease on MRI T1, SD and T2 sequences for both gray and white matter[4].

The high complexity of brain cortex based on the high folding structure of sulci and gyri hinders the exact and accurate measurement of the cortical gray matter and the underlying white matter image properties. In the abundant literature on brain changes that occur during normal aging, there are numerous studies of different cortical gray matter and underlying white matter regions in both hemispheres describing changes about e.g., loss of volume or thickness of different cerebral cortices[5-12], visual cortex[3,9-11], hippocampus[11,13-15] as well as those that report gender and age differences[16,17]. Several of those reports were obtained by different techniques based on manual delimitation of regions of interest (ROIs), semi or automated segmentation forms[18-21] including voxel-based[16,22]

and surface-based morphometry[23-25]. Moreover, cross-sectional studies show large inter-individual variability while longitudinal designs are difficult to complete if extended in time because it depends on the state of health of patients but also on improvements of the scanner that could affect the volumetric estimates[26-27]. Additionally, fractal dimension analysis applied to measure the gray/white matter folding complexity in MRI sequences, has shown a decrease of this parameter with age[28,29] not evenly distributed through the cerebral hemispheres or gender[30].

The carefully review of previously cited reports strongly suggests that variability of results is a common factor in all of them, but what if this variability or data dispersion is not only a merely statistical result from sample size and/or from the measurement technique precision but an actual intrinsic property of the human brain cortex which deserves to be evaluated. The present study aims to evaluate cross-sectional subject changes in terms not only of central tendency values but also of variability or dispersion values of the cortical gray and the white matters that occur during aging in healthy subjects.

Methods

This study was approved by the Institutional Bioethics Committee of the Research and Intellectual Production Office of the Health Sciences Faculty. After an informed consent, MRI images from a total of 88 subjects were evaluated. Patient's data such as age, gender, height, weight, and clinical history were collected.

Inclusion criteria

Subjects requesting a cranial MRI study at the Imaging Unit of San Rafael's Clinic were included in the study if they were conscious, asymptomatic, self-recognized such in good health, older than 20 years old, of any gender, with or without microvascular abnormal image patterns, with or without drug treatment.

Exclusion Criteria

Were excluded subjects with a clinical history of ischemic or hemorrhagic events, tumor brain lesions, vascular malformations, moderate to severe head trauma, unconscious, cystic lesions of any etiology, mental illness such as schizophrenia or psychosis, dementia, drug abuse including alcohol or tobacco, congenital malformations and subjects who have not been reporting these criteria but with abnormal MRI images.

MRI Imaging

We use T2 FLAIR MRI sequence of a routine clinical studies to display a good contrast between cortical gray, sub cortical white matters and cerebrospinal fluid (CSF) allowing a precise delimitation of their boundaries[31,32]. Following international protocol to conduct a clinical MRI study, in a low-stress environment, the subject was informed on how the study will be conducted and safety measures, thereafter, lying down on the resonator table, the subject's head was adjusted by a harness to reduce movement artifacts during image acquisition. A 1.5 Tesla, calibrated General Electric MRI (signa excite™) system was used to obtain 5 mm axial sections from base to vertex of the brain with 2.5 mm gap between successive sections in all instances. T2 FLAIR sequences at TR: 8002 ms, TE: 95.19 ms, flip angle: 90, slice tnk: 5 mm, DFOV: 240 mm were acquired using the same scanner gain for all studies, and finally stored on the hard disk of the device computer in native DICOM (.DIF) format.

Two-dimensional morphometry

The images in its original raw DICOM format were post- processed using the ImageJ software[33]. A 256 gray levels densitometry (T2 FLAIR MR signal intensity) profile was obtained with values from white (255) to black (0). It was selected the axial

section just above the corpus callosum to visualize frontal, parietal, occipital and cingulate cortices in the same single slice. One neuroradiologist, one neurophysiologist (each with 30 years of experience in neuroimaging) and one image technologist (with 15 years of experience in neuroimaging) jointly decided the correct axial section and drew freehand regions of interest (ROIs) such as that previous reported[34] using Image J software. For a systematic morphometry of MRI signal intensity, a series of digital reference lines were superimposed on the image (*figure 1*). Four transverse lines from anterior to posterior plane divide the image in three segments (frontal, parietal and occipital), then, FLAIR cortical density profiles were obtained from every segment and hemispheres (lines 1 to 8 in *figure 1*). In this way frontal, parietal, occipital and cingulate profiles were generated for right (profiles 2,4,6 and 8) and left (1,3,5 and 7) hemispheres respectively (*figure 1*). Measuring profile were obtained from straight lines across cortical sulci and gyri i.e., gray and immediate white matters.

Statistics

Cortical profile values of FLAIR signal intensity were analyzed by the arithmetic mean (x) of every cortical area. Gray/white matter interface from cortical sulci and gyri was evaluated by the standard deviation (SD) and coefficient of variation (CV). Intra and interhemispheric cortical lobar values were compared by non-parametrical Kruskal-Wallis test complemented by Mann-Whitney pairwise test. CV differences were tested by two different methods: a) Standalone value such as other else parameters (with Kruskal-Wallis test, see above) and b) Fligner-Kileen (F-K) test. Spearman correlation and regression analysis with linear and non-linear curve fitting were performed between age and FLAIR signal intensity parameters. The correlation intensity was evaluated by the coefficient of determination (R^2 x 100) expressed as percentage. Significant regressions were presented with their corresponding curve fitting. The level of statistical significance for all tests was set at $P<0.05$. PAST statistical software was use[35].

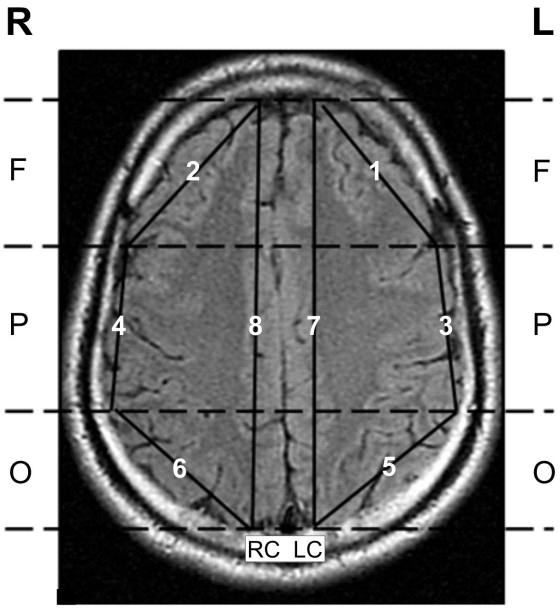

Figure 1. FLAIR MRI image with horizontal reference anatomical landmarks (dash lines) and measurement lines (black) where MR signal intensity profiles were obtained. F: frontal; P: parietal; O: occipital; RC: right cingulate; LC: left cingulate. 1,3,5,7 for measuring lines on left and 2,4,6,8 for right hemisphere.

Results

A total of 88 subjects were evaluated, 66% females (n=58) and 34 % males (n=30) with an age range from 22 to 80 years old. Two age groups were analyzed: young (under 40 years old; n=22; 25%) and old (over or equal to 40 years old; n=66; 75%).

Correlation between age and cortical FLAIR intensity values.

FLAIR signal intensity decreases with the age i.e., cortical and subcortical areas turn darker with the age. *Table 1* presents the linear regression

analysis of age and FLAIR signal intensity mean from cortical areas in each hemisphere for all subject's sample. 75% of all regression coefficients were statistically significant negative except the cingulate cortex from both hemispheres which were also negative but non-significant. The aging was associated to a progressive lowering of cortical FLAIR intensity by a percentage between 4.3 for right occipital, to 20.1% for right frontal cortex. Correlation coefficients from age and each cortical areas parameter (mean and CV) were pairwise compared and no significant differences were found among these coefficients. Despite these significant associations, no differences were found between correlation coefficients neither for means nor CVs i.e., they display similar curve slopes.

Cortical area		R	R^2	F	P	Equation
Right	Frontal	-0.33	20.1	10.9	0.001	-0.5397x+273.9
	Parietal	-0.26	7.1	6.6	0.01	-0.3945x+254.3
	Occipital	-0.21	4.3	4.2	0.05	-0.3535x+244.4
	Cingulate	-0.19	3.5	3.2	ns	ns
Left	Frontal	-0.26	7.0	6.5	0.01	-0.4177x+269.1
	Parietal	-0.32	9.9	9.5	0.003	-0.3842x+271.1
	Occipital	-0.31	9.9	9.4	0.003	-0.4475x+268.4
	Cingulate	-0.12	1.4	1.2	ns	ns

Table 1. Linear regression analysis of FLAIR signal intensity mean from cortical areas and each hemisphere against patient age.

Scatter plots for cortical FLAIR signal intensity mean values (arbitrary units) and subject age presented in *figure 2* show in all evaluated cortical areas the mean intensity reducing effect of age which contrast to the increasing effect on the dispersion signal intensity at the same cortical areas (*figure 3*). These effects were more intense for frontal areas than for cingulate ones. It is to be noted that age-related increase of CV values is not a statistical consequence of a reduced sampling of old subjects as can be seen in *figure 3*.

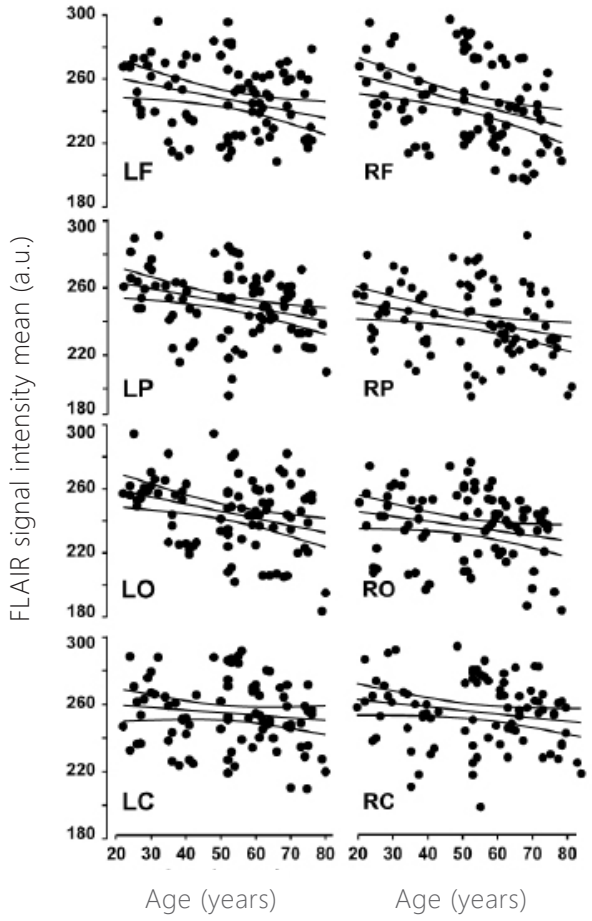

Figure 2. Scatter plots for cortical FLAIR signal intensity mean values (arbitrary units) from left frontal (LF), right frontal (RF), left parietal (LP), right parietal (RP), left occipital (LO), right occipital (RO), left cingulate (LC) and right cingulate (RC) cortical areas versus subject age. n=88 subjects; Linear regression curve and 95% CI are shown; R^2 are presented on *Table 1*.

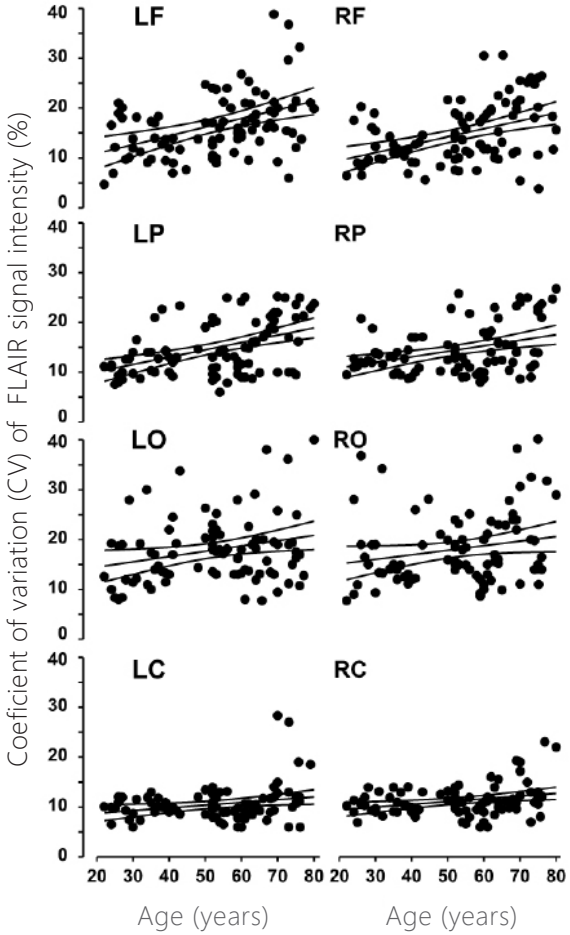

Figure 3. Scatter plots for cortical FLAIR signal intensity CV values (%) from left frontal (LF), right frontal (RF), left parietal (LP), right parietal (RP), left occipital (LO), right occipital (RO), left cingulate (LC) and right cingulate (RC) cortical areas versus subject age. n=88 subjects; Linear regression curve and 95% CI are shown; R^2 are presented on *Table 1*.

FLAIR signal intensity measures of cortical areas

Right-left cortical homologous areas comparison shows significant differences for parietal (233.5±23.9 vs 250.8±19.6; p < 10-6) and occipital cortex (225.8±27.3 vs 244.8±22.9; p < 10-6). CV values were not statistically different among the four tested cortical areas.

Age groups and FLAIR signal intensity measures of cortical areas

Two age groups: young (under 40 years old) and old (over or equal 40 years old) were compared for overall but also for homologous cortical areas in both hemispheres potential differences, showing statistical significant lower mean intensity signal for the healthy older group than for the younger group in the overall cortical area screening (242.0±26.4 vs 250.8±22.3 a.u. respectively; t: 4.17; P<0.00003). CV values were also significantly higher for older group than the younger group (15.9±6.7% vs. 12.9±4.8%; t: 5.8; P<10-8 and F-K test: z: 2.8; P<0.002). There is significant lower mean signal intensity for right occipital and cingulate areas and left frontal and parietal areas in the older than in the younger group being more accentuated in left frontal area. The variability of dispersion signal intensity of left cingulate and occipital cortices were lower than the values in other brain cortices for both age groups (*figure 4*). Left occipital and cingulate cortices shows lower CV values and left frontal and parietal cortices display higher CV values than contralateral homologous areas (*figure 4*).

Gender and FLAIR signal intensity measures of cortical areas

Table 2 presents linear regression analysis of mean signal intensity from cortical areas and each hemisphere against age in female subjects. All evaluated cortical areas, except cingulate cortex of both hemispheres, show significant negative regression coefficients with age and without significant differences between them. The age influenced the mean of signal intensity from 20.3% (left parietal) to 8.5% (left occipital).

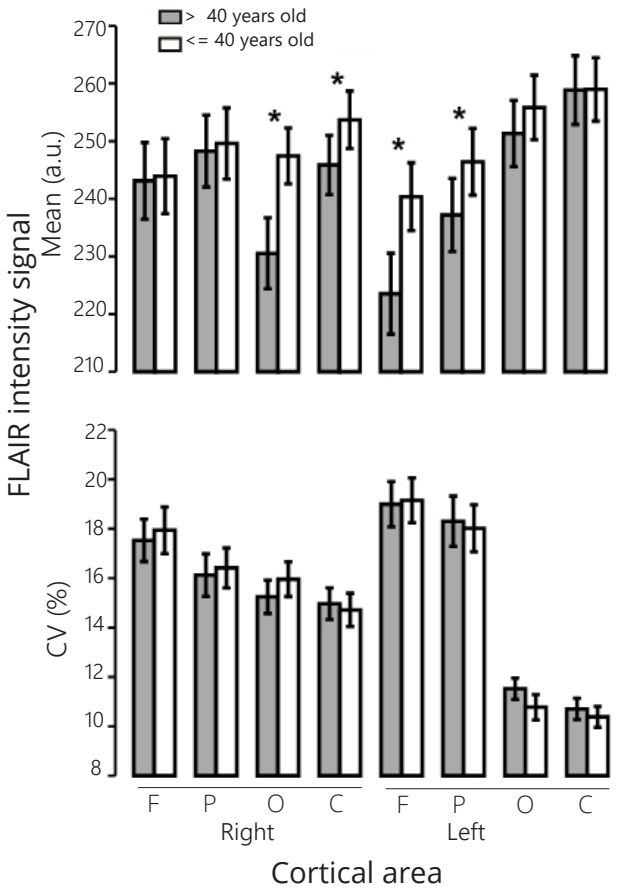

Figure 4. Cortical FLAIR signal intensity mean (arbitrary units) of right (R) or left (L) hemisphere and frontal (F), parietal (P), occipital (O) or cingulate (C) areas (upper panel) from subjects with more than 40 years old (grey bars) and with 40 or less years old (clear bars), compared by ANOVA test. * P<0.0005. Bottom panel CV values of the same age groups and cortical areas.

Table 2. Linear regression analysis of FLAIR signal intensity mean from cortical areas and each hemisphere against age in female patients.

Cortical area		R	R^2	F	P	Equation
Rigth	Frontal	-0.58	16.4	10.9	0.001	-.0.58x+284.1
	Parietal	-0.34	11.4	7.2	0.009	-0.44x+262.5
	Occipital	-0.32	10.1	6.3	0.01	-0.38x+253.5
	Cingulate	-0.24	5.4	3.18	ns	ns
Left	Frontal	-0.31	9.4	5.8	0.01	-0.50x+279.6
	Parietal	-0.45	20.3	14.3	0.0004	-0.43x+278.2
	Occipital	-0.29	8.5	5.2	0.02	-0.35x+268.6
	Cingulate	-0.09	0.8	0.45	ns	ns

n=88 patients; ns: no significant

Table 3 show linear regression analysis of CV signal intensity from cortical areas and each hemisphere against age in female subjects. All evaluated cortical areas, except cingulate cortex of both hemispheres, show significant positive regression coefficients with age and without significant differences between them. The age influenced the CV of signal intensity from 26.7% (left parietal) to 7.0% (left occipital). Linear regression analysis of mean signal intensity from cortical areas and each hemisphere against age in male subjects is presented in *Table 4*. None of the evaluated right cortex was associated to the subject age and for the left hemisphere only the occipital area shows a significant association to age with a 15.1%, while for CV values frontal and cingulate cortex from both hemispheres were associated to age (*Table 5*).

Table 3. Linear regression analysis of FLAIR signal intensity CV from cortical areas and each hemisphere against age in female patients.

Cortical area		R	R^2	F	P	Equation
Rigth	Frontal	0.45	20.0	14.0	0.0004	0.21x+4.16
	Parietal	0.40	16.4	11.0	0.002	0.11x+8.37
	Occipital	0.36	12.8	8.19	0.006	0.12x+10.35
	Cingulate	0.11	1.2	0.71	ns	ns
Left	Frontal	0.37	13.9	9.0	0.004	0.18x+6.8
	Parietal	0.52	26.7	20.4	0.00003	0.17x+6.0
	Occipital	0.26	7.0	4.2	0.04	0.12x+11.07
	Cingulate	0.18	3.2	1.84	ns	ns

n= 88 patients; ns: no significant

Table 4. Linear regression analysis of FLAIR signal intensity mean from cortical areas and each hemisphere against age in male patients.

Cortical area		R	R^2	F	P	Equation
Rigth	Frontal	-0.28	7.7	2.4	ns	ns
	Parietal	-0.17	2.8	0.8	ns	ns
	Occipital	-0.13	1.6	0.45	ns	ns
	Cingulate	-0.14	2.0	0.57	ns	ns
Left	Frontal	-0.19	3.7	1.1	ns	ns
	Parietal	-0.18	3.2	0.9	ns	ns
	Occipital	-0.39	15.1	4.9	0.03	-0.62x+267.3
	Cingulate	-0.17	2.9	0.85	ns	ns

n=88 patients; ns: no significant

Table 5. Linear regression analysis of FLAIR signal intensity CV from cortical areas and each hemisphere against age in male patients.

Cortical area		R	R^2	F	P	Equation
Rigth	Frontal	0.44	19.5	6.8	0.01	0.11x+12.44
	Parietal	0.31	9.5	2.9	ns	ns
	Occipital	0.04	0.2	0.05	ns	ns
	Cingulate	0.51	25.7	9.7	0.004	0.13x+4.30
Left	Frontal	0.52	27.4	10.6	0.003	0.15x+8.88
	Parietal	0.29	8.3	2.54	ns	ns
	Occipital	0.19	3.8	1.11	ns	ns
	Cingulate	0.40	15.8	5.27	0.03	0.08x+6.10

n=88 patients; ns: no significant

Gender and age (old and young) differences in cortical mean signal intensity of all evaluated cortical areas are presented in *figure 5*. Systematically, and independently to age significant lower values for signal intensity were observed in male than in female cortical areas (*figure 5*), cingulate cortex in the less than 40 years old group is an exception to this because no gender difference was observed.

Dispersion values of signal intensity of all cortical areas evaluated by gender and age are presented on *figure 6*, showing CV percentages from 10 to 20% for all cortical area. It was found that left occipital cortex at any age, shows the higher gender differences, while the overall CV values were higher for the older group and more accentuate in right frontal and occipital and left occipital cortical areas.

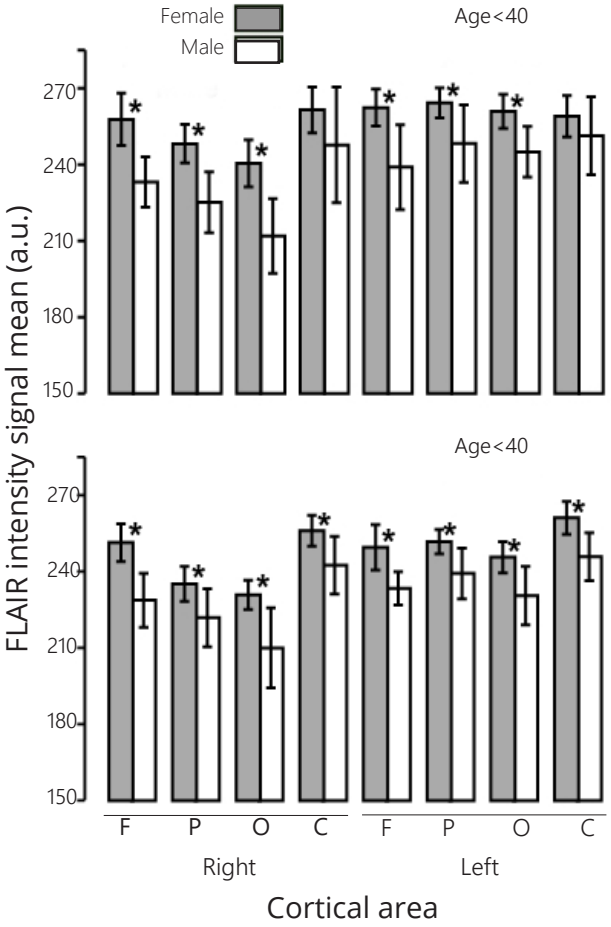

Figure 5. Gender differences in cortical FLAIR signal intensity mean (arbitrary units) of right or left hemisphere and frontal (F), parietal (P), occipital (O) or cingulate (C) areas from subjects with less than 40 years old (upper panel) and with 40 or less years old (bottom panel), female (grey) and male (clear) groups. Arithmetic mean±standard error; *= P<0.005.

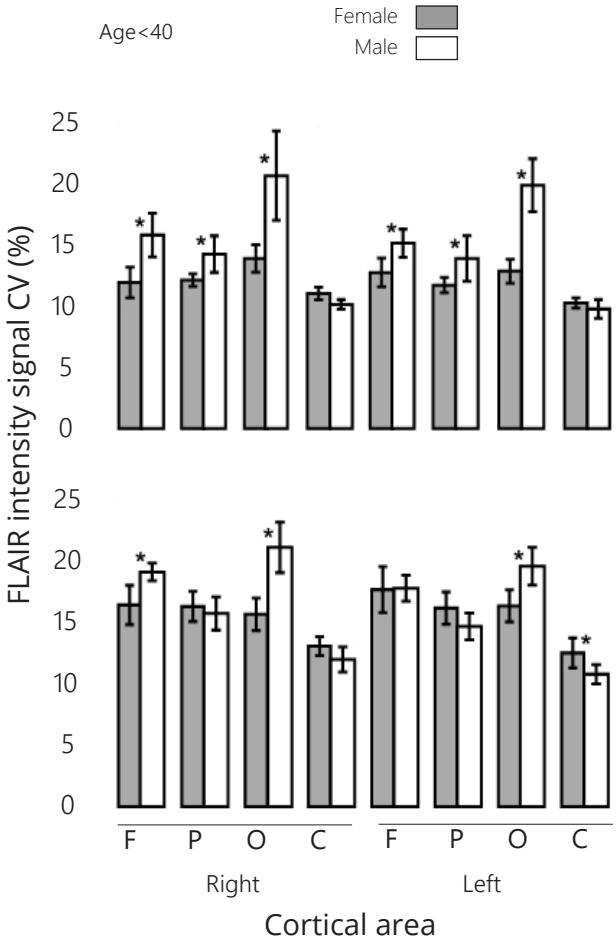

Figure 6. Gender differences in cortical FLAIR signal intensity CV (%) of right or left hemisphere and frontal (F), parietal (P), occipital (O) or cingulate (C) areas from subjects with less than 40 years old (upper panel) and with 40 or less years old (bottom panel), female (grey) and male (clear) groups. Arithmetic mean±standard error; *= P<0.005.

Discussion

In the present study, conventional 1.5T FLAIR MRI signal intensity profiles from frontal, parietal, occipital and cingulate cortical areas of both brain hemispheres were evaluated in subjects with healthy conditions looking for age-related changes and gender differences in both central tendency values such as arithmetic mean and dispersion values such as the coefficient of dispersion. Almost all tested cortical areas displayed age related changes with decreasing mean intensity but increasing dispersion values.

Our measurement method uses a straight line crossing cortical sulci and gyri combines anatomical parameters such as cortical thickness but also intra- and inter-cortical FLAIR signal intensity differences between gray and white matters from gyri and sulci. The known cortical age related atrophy modifies the thickness but also the signal density as observed in aging ex vacuo hydrocephalus thus, modifying density value. This high integrative measure was able to detected the age related decrease in the cortical intensity signal (darkening) for frontal, parietal, occipital and cingulate cortex. Interestingly, the dispersion (CV) of the FLAIR intensity measurements shows a consistent age-related increase in all these areas which is not a statistical artifact due to the distribution tail n-reduction of subject sampling, but probably to an intrinsic cortical aging characteristic instead, which could be estimated following the regression equations presented in *Table 6*. These estimations of mean or CV described in the present study would be used to detect abnormal age related cortical changes.

The findings reported here are consistent with the progressive decrease in signal intensity of the gray and white matter during aging[4] but also to an equivalent age-related increase in T1 signal intensity on frontal and occipital white matters with a decrease on cortical gray matter[36]. However, T1 signal intensity of cortical gray increases by about 53% and subcortical frontal white matters by 47%, with lower percentage in the occipital white matter and no gender differences reported[37]. In contrast, we found that all cortical areas except the cingulate cortex, were associated to aging by 4 to 20%, this agrees to decreasing signal intensity of frontal, temporal and parietal white matters, but less evident in the occipital white matter described in other report[38]. These differences probably reflect differential sensitivity between T1 and T2 sequences to detect gray/white matters density, but at the same time T1 sequence analysis was not able to detect age-related changes in other cortical areas than frontal or occipital suggesting perhaps high specificity for T1 signal but high sensibility for T2 sequences or T2-related sequence such FLAIR for better detection.

The fact that these age changes were different for right or left hemisphere support the notion that hemispheric specialization also must be taken into account to evaluate differential age related cortical changes[39] and drive to analyze differences between homologous cortex instead cortical pools of data from both hemispheres. These results constitute new insights to the well-known neuroimaging, cognitive, behavioral, and genetic human brain lateralization[40] and support the notion that brain hemispheres could be differentially affected by age[41].

Previous studies[2,8,12,42] report an anterior-posterior gradient decline where the frontal and parietal cortex are more affected at the left hemisphere. This is related to the hypothesis ("last in, first out") where these last regions shown less age sensitivity during development ripen early such as the occipital visual cortex. Instead frontal and parietal cortex mature later but are the first to be affected, showing volume loss and MRI signal intensity alteration of

cortical gray but also the white matters in healthy and pathological aging. Our findings agree in the sense that left frontal and parietal areas show age-related changes but suggest that they are differentially expressed on each hemisphere, with occipital and cingulate areas affected in the right hemisphere[40].

The fact that FLAIR signal intensity mean of left frontal and parietal areas was lower than all other cortical areas strongly suggests the structural association to the cognitive, neuromuscular coordination and attention processing age-related impairment.

Combined transverse and longitudinal studies[40] showed a decrease in cortical volume of older than young people. According to a review of 56 longitudinal MRI studies[41], a stable brain volume is shown for the period between 18-35 years old, a mild decrease (0.2-0.5%) from 35 to 65 years old, but over 0.5% after 60 years[13,42]. This age-related volume changes show an anterior-posterior cortical gradient with more impact on association than primary cortical areas[43,44]. White matters loss shows also an annual decline up to 0.23%[45] which was clinically associated to a proportional cognitive dysfunction[46,47].

Gender differences in cortical FLAIR signal intensity mean were found in both hemispheres, in all tested cortical areas and in all ages, resulting in significant lower mean values for male than female subjects, but when the aging effect for females is analyzed then we found a progressive decrease in FLAIR signal intensity in frontal, parietal and occipital cortices in each hemisphere being more accentuated in left frontal and parietal cortex for the female group. The cingulate cortex was preserved in this group. For the male group, only the left occipital cortex showed a negative age-related FLAIR signal intensity mean. These results agree with those reporting a greater age-related thickening of the parietal and temporal gray matter cortices on women[44] or age-related cortical thinning in men[27]. However, other studies did not report gender differences of these cortical parameters related to age[13,17] probably due to the use of less sensitive detecting technique. It is known that age and gender influence the brain iron concentration by decreasing its subcortical concentrations in females over 50 year old compared to younger women or males[45,47].

Cortical structural complexity was also evaluated in the present study by measuring the coefficient of variation (CV) of the FLAIR signal intensity profile. Despite the fact that comparison of CV values from similar cortical areas between old and young subject group did not found significant differences, the regression analysis was able to detect clearly the increasing effect of aging on this parameter.

In the present study, variability of the FLAIR signal was considered such as measure of complexity, however, its value could be increased by a reduction of the sample size which normally occurs at the tail of samples. Our data did not display such situation; hence the age-related CV increase is probably generated intrinsically in the cortex as a product of aging in all tested cortex.

These results contrast widely to reports where restricted cortical complexity evaluated by the fractal dimension decrease with age[29,30]. However, our results express the fact that CV is more sensible to gray and white matters transitions which in the progressive age-related enlargement of sulci results in large signal intensity changes within the same cortical area leading to greater CV values. Hemispheric lateralization on cortical CV values was also found when left frontal and parietal cortices shows the highest and that left occipital and cingulate cortices the lowest

CV values than contralateral homologous areas. Manual segmentation on MRI is considered the gold standard in different brain areas i.e., for hippocampal volumetry, moreover, this method could make easy comparisons across different studies and outcomes of clinical trials[34,48].

In the present study MRI FLAIR sequences were analyzed using a manual traced segmentation performed by 3 neuroimaging experts similar technique has been successfully applied and used for validation and certification procedures[34,48,49,50].

Most of the reported cortical and subcortical changes in the MRI signal intensity may correspond to an increased accumulation of brain iron deposits, loss of neurons, alterations in synapse, increased water content and degradation of myelin fibers occurring during healthy aging[51] which also could explain the cognitive, memory disorders and related psychomotor retardation associated to normal aging but more intense for dementia[52,53].

Evaluation of 3T and 7T MRI FLAIR sequences[54] reported hypo-intensities in the motor cortex due to excessive accumulation of iron in microglial cells, this report agrees to the present study in the sense that the mean value of FLAIR signal intensity decreases with age, more interesting, this effect in cortical gray and the underlying white matters was stronger in the left hemisphere than the right. Similar hemispheric lateralization has been reported of higher iron accumulations in basal ganglia and frontal white matter of the left hemisphere compared to the right hemisphere[55].

Despite to well-known evidence of global and specific regional differences between the two cerebral hemispheres such as more cortical thickening in the left hemisphere[15,25], increased volume in the left parietal and temporal lobes[56,57], greater volume in the left frontal and parietal cortices and left parietal white matter[58], significant age-related differences between the two hemispheres were not described previously.

Although numerous studies have based their findings on the use of MRI gradient echo fast sequences, 3D volumetric and sub millimeter, semi and automatic morphometry techniques, our study was performed with T2 FLAIR conventional MRI and ROIs performed manually, obtaining new image insights about aging brain.

Conclusions

An age-related decrease in the cortical signal intensity mean was found in left frontal and parietal cortices and occipital and cingulate cortices for the right hemisphere. Coefficient of variation shows an age-related overall cortical increase. These changes were more intense for females and for left hemisphere. Conventional T2-FLAIR MRI with manual delimited ROIs for signal intensity profiles evaluated by center tendency values (mean) and variation values (CV) can detect contrasting cortical differences and could be an alternative method for clinical MRI evaluations of normal and abnormal age-related cerebral cortical changes.

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