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Global fractional anisotropy and mean diffusivity together with segmented brain volumes assemble a predictive discriminant model for young and elderly healthy brains: a pilot study at 3T

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Summary

Several parameters of brain integrity can be derived from diffusion tensor imaging. These include fractional anisotropy (FA) and mean diffusivity (MD). Combination of these variables using multivariate analysis might result in a predictive model able to detect the structural changes of human brain aging.

Our aim was to discriminate between young and older healthy brains by combining structural and volumetric variables from brain MRI: FA, MD, and white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) volumes.

This was a cross-sectional study in 21 young (mean age, 25.71±3.04 years; range, 21–34 years) and 10 elderly (mean age, 70.20±4.02 years; range, 66–80 years) healthy volunteers. Multivariate discriminant analysis, with age as the dependent variable and WM, GM and CSF volumes, global FA and MD, and gender as the independent variables, was used to assemble a predictive model.

The resulting model was able to differentiate between young and older brains: Wilks' $\lambda = 0.235$, $\chi^2(6) = 37.603$, $p = .000001$. Only global FA, WM volume and CSF volume significantly discriminated between groups. The total accuracy was 93.5%; the sensitivity, specificity and positive and negative predictive values were 91.30%, 100%, 100% and 80%, respectively.

Global FA, WM volume and CSF volume are parameters that, when combined, reliably discriminate between young and older brains. A decrease in FA is the strongest predictor of membership of the older brain group, followed by an increase in WM and CSF volumes. Brain assessment using a predictive model might allow the follow-up of selected cases that deviate from normal aging.

Keywords: aging, brain, diffusion tensor imaging, discriminant analysis, volume, white matter

Introduction

An approach that integrates structural and volumetric biomarkers could be adopted in an attempt to explain some of the discrepancies in the current literature on the aging process of the human brain (Abe et al., 2008); for example, it is known that white matter (WM) changes exceed gray matter (GM) changes during aging (Allen et al., 2005), meaning that human WM is more vulnerable than GM, especially in late-myelinating regions such as the frontal and temporal lobes. Gender has also been associated with the brain aging process: cortical GM declined more steeply with age in men than women, but cortical WM volumes remained stable across the adult age span in both genders (Sullivan et al., 2004). Knowledge of the parameters of brain aging is essential in order to understand what underlies the cognitive declines associated with normal aging and how these deficits differ from those related to pathological conditions such as mild cognitive impairment (MCI) or Alzheimer's disease (AD).

Diffusion tensor imaging (DTI) allows the calculation of several biomarkers of structural integrity of brain tissue (Vernooij et al., 2008). These include fractional anisotropy (FA) and mean diffusivity (MD) (Abe et al., 2008; Hsu et al. 2008). Previous studies have proved the usefulness of a global (whole-brain) approach when using DTI-derived biomarkers in the detection of GM and WM changes (Kochunov et al., 2011). A lower FA value represents a decrease in diffusion directionality due to a loss of microstructural integrity (Vernooij et al., 2008); this is thought to correspond to a decrease in water movement along (the same) axonal tracts. Age-related changes in FA and MD should be presented using a global rather than a regional approach, as a global approach allows a comprehensive quantitation of a tract or group of tracts and not only a partial measurement of fibers (as is the case when using a regional, or structure-based, approach). Previous studies using a regional approach showed: that FA in the temporal and occipital regions was not correlated with age (Hsu et al., 2008); that FA was negatively correlated in the frontal and temporal WM regions (Abe et al., 2008); that FA measurements did not reveal significant differences, with aging, between the temporal and posterior WM regions (Salat et al., 2005). They also showed the existence of significant differences in FA between cross-sectional normal WM tracts (Nusbaum et al., 2001; Roldan-Valadez et al., 2012). Furthermore, correlations between FA and MD reportedly change depending on the brain region considered: lower FA and higher MD values have been found in the WM of older versus younger subjects, while basal ganglia FA and MD measurements were higher in older than in younger subjects (Pfefferbaum et al., 2010). These variations might be due to methodological differences in image analyses or acquisition, selection and placement of regions of interest, and/or study populations (Jenkinson et al., 2012).

The primary aim of this study was to evaluate global measures of diffusion (i.e. global FA and MD), selected volumes of WM, GM and cerebrospinal fluid (CSF), and gender, assembling a model that allows us, through a multivariate analysis, to discriminate between normal younger and normal older brains. This global approach offers an integrative model that allows quantitative depiction of normal aging using a series of biomarkers that have previously been used separately in the diagnosis of other neurological diseases, but not as an integrative model of normal brain aging.

Materials and methods

Subjects

A cross-sectional study was performed in right-handed healthy volunteers, divided into young adults and elderly persons. The young subjects were consecutively recruited from a group of medical residents; the elderly subjects were recruited from the Geriatric Unit at Medica Sur Clinic & Foundation, in the period from July 2011 to August 2012. The young adults underwent detailed health examinations performed by a general practitioner; the elderly subjects underwent complete physical and geriatric examinations performed by a board certified geriatrician. Participants were excluded if they had a history of major neurological, psychiatric or cardiovascular disease. The local institutional review board approved the study (protocol #2011.043), and all the participants gave their written informed consent.

MRI scans showing structural abnormalities, such as tumors or stroke, anatomical variations (e.g., mega cisterna magna, cavum septum pellucidum), or technical artifacts, were excluded. WM hyperintensities, as observed on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images, were rated by a radiologist using the age-related WM changes (ARWMC) score (Wahlund et al., 2001). We excluded elderly subjects with regional ARWMC scores higher than 1. For all participants a preliminary neuropsychological evaluation included the Wechsler Adult Intelligence Scale-III intelligence quotient (IQ) test validated for Mexican patients (considering an average IQ of 100 and a standard deviation of 15) (Wechsler, 1997), and a validated, modified version of the Mini-Mental State Examination (MMSE) in Spanish, adjusted for age and level of education (a score of 25 points or more was taken as normal) (Reyes-de-Beaman et al., 2004). Elderly participants with MCI or AD were excluded on the basis of diagnostic criteria established in accordance with the diagnostic guidelines of the National Institute on Aging-Alzheimer's Association work groups (Albert et al., 2011; McKhann et al., 2011).

Brain image acquisition

MRI evaluations of the brain were performed using a 3.0T Signa HDxt scanner (GE Healthcare, Waukesha, WI) and a high-resolution eight-channel head coil (Invivo, Gainesville, FL). Contraindications to MRI were the presence of a pacemaker or metallic implant and claustrophobia. All participants were included.

The examination included standard clinical sequences: sagittal T1-weighted FLAIR (TE/TR = 9.9/2500 ms) with a 5/3-mm slice thickness/gap and 24 × 24 cm field of view (FOV); axial fast spoiled gradient-echo (FSPGR) (TE/TR = 3.9/9.4 ms) with a 1.3/0-mm slice thickness/gap and FOV of 24 × 18 cm; coronal T2-weighted fast spin-echo (TE/TR = 164.1/2617 ms) with a 3/0-mm slice thickness/gap and FOV of 22 × 16 cm; and axial FLAIR (TE/TR = 115.8/11002 ms) with a 5/1-mm slice thickness/gap and FOV of 22 × 22 cm. The DTI sequence resulted in 50 axial slices covering the entire brain and brainstem with 1.7 × 1.7 × 3.0 mm^3 voxel size, acquired with 25 non-collinear diffusion directions with a b-value of 1,000 s/mm^2, and one with a b-value of 0 s/mm^2.

Volumetric data analysis

MRI data of the T1-weighted FSPGR sequence were transferred to a Linux-based workstation. Individual brain atlas-based volumetry was performed using the IBASPM software version 1.0 (Alemán-Gomez et al., 2006), a toolbox for structure segmentation of structural MRI images implemented in MATLAB 7.0 (MathWorks, Natick, MA). This software uses the spatial normalization and segmentation routines of the Statistical Parametric Mapping software version 2 (SPM2) (Roldan-Valadez et al., 2012). A description of the method for volume measurement was recently published elsewhere (Roldan-Valadez et al., 2013).

DTI analysis and global MD and FA measurements

We used the *dcm2nii* software (Rorden et al., 2011) (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html) and tools from the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl) version 4.1.9 (Smith et al., 2004), as follows. DTI images were extracted using the Brain Extraction Tool (BET) version 2.1 (Smith, 2002). Eddy currents were corrected using the Diffusion Toolbox version 2.0; the Reconstruct Diffusion Tensor (DTIFIT) and the fslmaths tool generated the eigenvector and eigenvalue maps for each tensor metric. The fslstats tool calculated the scalar measures (mean values) of global FA and MD. Evidence of the clinical application of global DTI-derived tensor metrics for brain imaging has recently been published (Roldan-Valadez et al., 2014).

Statistical analysis

Sample size Considering that this was a pilot/feasibility study, in accordance with the considerations and recommendations of others we chose to include at least 10 subjects per group (Hertzog, 2008), and to have a minimum overall sample size of 30 (Lancaster et al., 2004). The statistical analysis was focused on the calculation of 95% confidence intervals (CIs) according to contemporary definitions (Pfister and Janczyk, 2013); a boot strapping method with bias corrected and accelerated confidence estimates was performed with 1000 bootstrap resamples (Henderson, 2005). Differences between groups (normal young and normal older brains) for each variable were tested using the Mann-Whitney U test; the value of z was used to calculate an approximate value of r as a measure of effect size (r = z/square root of N where N = total number of cases); effect sizes of 0.1, 0.3 and 0.5 were termed small, medium and large, respectively (Cohen, 1988).

Multivariate discriminant analysis Multivariate discriminant analysis (DA) (Tabachnik and Fidell, 2013) included continuous and categorical variables to identify specific volumetric and structural attributes in young and older brains. The dependent variable (DV) was age group, with subjects classified as young adults or healthy elders. The independent variables (IVs) comprised: three volumes (cm^3): GM, WM and CSF; two DTI-derived measurements: MD (mm^2s^{-1}) and FA (dimensionless number), and one categorical variable (gender: male or female). The effect-size measure for DA was calculated using the squared canonical correlation as the equivalent of the R^2 in regression. By convention, effect sizes of 0.02, 0.15 and 0.35 were termed small, medium and large, respectively (Cohen, 1988).

Diagnostic model evaluation The cross-validated contingency table generated by the DA was used to evaluate the diagnostic performance of the DA model; we reported values of sensitivity and specificity, positive and negative likelihood ratios, and positive and negative predictive values, with their corresponding CIs. Statistical significance was indicated by a p-value < 0.05.

Software DA analyses were carried out using the IBM® SPSS® Statistics software (version 22.0.0.0, IBM Corporation, Armonk, NY, USA). Diagnostic performance was assessed using MedCalc® (version 14.8.1 MedCalc Software bvba, Mariakerke, Belgium). Reporting of diagnostic performance tests followed the STARD initiative (Bossuyt et al., 2003).

Results

Subjects

The study was conducted in 31 subjects: 23 females and eight males, distributed in two age groups: 21 young adults (mean age, 25.71 ± 3.04 years; range, 21–34 years) and 10 healthy elders (mean age, 70.20 ± 4.02 years; range, 66–80 years). Table I shows the gender distribution in each age group.

Table I

Gender distribution between the young and older brains.

Group	Gender	n	%
Young brain	Male	5	16.13
	Female	16	51.61
Older brain	Male	3	9.68
	Female	7	22.58
Total		31	100.00

FA values were higher in younger than in older brains, with a significant difference and a large effect size: U = 17.0, z = −3.719, p < .001, r = .66. Significantly lower volumes of CSF were found in young versus older brains, this finding also showed a large effect size: U = 136.0, z = −32.916, p = .004, r = .52. No significant differences between the groups were found for MD (p = .186), GM volume (p = .087) and WM volume (p = .072). Table II presents the mean values, SD and CI for each age group.

Table II

Mean values, standard deviations and confidence intervals of the structural and volumetric biomarkers in each age group.

Variable	Young brains (20–35 years)				Older brains (60–85 years)			
	Mean	SD	95% CI		Mean	SD	95% CI	
			Lower	Upper			Lower	Upper
GM volume (cm^3)	638.166	69.102	606.377	666.678	591.725	62.345	549.884	628.896
WM volume (cm^3)	382.034	33.501	367.440	395.757	414.978	49.903	386.179	447.963
CSF volume (cm^3)	359.397	68.103	331.930	389.319	477.271	105.053	414.772	543.323
MD (mm^2/s)	0.001224	0.000082	0.001191	0.001262	0.001272	0.00014	0.001183	0.001360
FA (dimensionless)	0.294860	0.012442	0.289698	0.299928	0.266776	0.015586	0.257207	0.276734

Abbreviations: GM=gray matter; WM=white matter; CSF=cerebrospinal fluid; MD=mean diffusivity; FA=fractional anisotropy; SD=standard deviation; 95% CI=bootstrap 95% confidence intervals.

Discriminant analysis

The DA was performed by entering the measurements of the six IVs for each of the 31 brains — five continuous (WM, GM and CSF volumes; FA and MD) and one categorical (gender) — for a total of 186 measurements. DA revealed one discriminant function. The assumption of homogeneity of variance-covariance matrices was interpreted as non-significant (Box's M value = 62.335, p = 0.002), assuming the covariance matrices between the groups were equal (Huberty and Petroskey, 2000). This discriminant function significantly differentiated the young and older brains: Wilks' λ = 0.235, χ^2 (6) = 37.603, p = .000001. By indicating the significance of the discriminant function, Wilks' λ explained a low proportion (only 23.55%) of the total variability not explained by the model. A canonical correlation of .8743 suggested that the model explains 76.45% of the variance in the final model.

Summary of discriminant functions

The tests of equality of group means provided statistical evidence of significant differences between means of the groups (young adult and elderly) for only three of the IVs (FA, WM and CSF volumes) with FA producing the highest F-test variance ratio value (Table III).

Table III

Multivariate analysis showing the statistical effect of each independent variable included in the analysis.

Variable	Wilks' Lambda	F ratio	p-value
Fractional anisotropy	.497	29.330	< .001
Cerebrospinal fluid volume	.671	14.210	.001
White matter volume	.859	4.753	.038
Gray matter volume	.899	3.247	.082
Mean diffusivity	.953	1.437	.240
Gender	.996	.127	.724

Standardized canonical discriminant function coefficients provided an index of the importance of each predictor of diagnosis with the sign indicating the direction of the relationship. A significant decreased value for FA was the strongest diagnostic predictor of older brains, while a significant increase in CSF volume was next in importance. The variables with large coefficients stand out (for these data) as those that strongly predict allocation to the young or elderly group. On the basis of these coefficient scores the rest of the variables were decreasingly strong as diagnostic predictors (Table IV A).

Table IV

Independent variables included in the discriminant analysis.

A **Standardized canonical discriminant function coefficients**		**B** **Structure matrix**		**C** **Canonical discriminant function coefficients**	
Variable	Function		Function		Function
1		Variable 1		Variable 1	
MD	−918	FA	−558	MD	−8842.143
FA	−956	CSF volume	.388	FA	−70.806
GM volume	.019	WM volume	.225	GM volume	.000281
WM volume	.506	GM volume	−186	WM volume	.012860
CSF volume	1.264	MD	.124	CSF volume	.015526
Gender	.570	Gender	−037	Gender	1.262

Abbreviations: MD=mean diffusivity; FA=fractional anisotropy; GM=gray matter; WM=white matter; CSF=cerebrospinal fluid

A) ordered by their standardized canonical discriminant function coefficients (variables with larger coefficients stand out as those that strongly predict allocation to each diagnosis). B) Within-groups correlation matrix depicts the participant variables ordered by absolute size of correlation (Pearson coefficients) within function. A value of 0.30 is considered the cut-off between important and less important variables. C) Unstandardized coefficients used to create a discriminant function operating just like a regression equation. Coefficients indicate the partial contribution of each variable to the discriminate function controlling for all other variables in the equation.

The structure matrix table provides another way of indicating the relative importance of the diagnostic predictors by showing the correlations (Pearson's coefficients) of each variable with each discriminate function. Many researchers consider structure matrix correlations more accurate than standardized canonical discriminant function coefficients (Field, 2009). By identifying the largest loadings for each discriminate function it is possible to see a different pattern of variables. Here we have FA (a unitless structural measurement) and CSF (measured in cm^3), which account for the largest loadings for the functions that discriminate between the young and elderly groups. A value of 0.30 is taken as the cut-off between important and less important variables (Field, 2009) (Table IV B).

The canonical discriminant function coefficients table shows the unstandardized coefficients (b) that are used to create the discriminant function (equation), operating just like a regression equation. In this study we observed:

$$D = 17.601(\text{Constant}) - (8,842.143 \times MD) - (70.806 \times FA) + (0.000281 \times GM) + (0.012860\,WM) + (0.015526 \times CSF) + (1.262 \times \text{Gender})$$

The categorical variable gender was classified as: male = 1 and female = 2. The discriminant function coefficients (b) indicate the partial contribution of each variable to the discriminate function controlling for all other variables in the equation (Table IV C).

Group centroids table: we also described each group in terms of its profile, using the group means of the predictor variables called centroids. The mean of the two centroids is considered the cut-off value; if the discriminant score of the function is less than or equal to the cut-off, the case is classed as 1 (young brain), whereas if it is above, it is classed as 2 (older brain). In our study, young brains had a mean of −1.203 while elder brains produced a mean of 2.526 (Table V).

Table V

Means of the predictor variables (centroids) used to describe each group in terms of its profile.

Age group	Functions at group centroids
Young adults (20–35 years)	−1.203
Elders (> 60 years)	2.526
Cut-off value	.060

The cut-off value is considered the mean of the two centroids; if the discriminant score of the function is less than or equal to the cut-off a new case can be classed as 1 (young adult), whereas if it is above, it is classed as 2 (elderly).

We finished the DA by performing a classification phase, using the cross-validated set of data to present the power of the discriminant function. The classification results revealed that 93.5% of the patients were classified correctly in the “young adult brain” or “older brain” groups, this value corresponded to the overall predictive accuracy of the discriminant function; additional results of diagnostic tests are presented in table VI. The average D scores for each group and the group centroids help us to see the effectiveness of the discriminant function. Histograms and box plots of the average D scores for each group were used as visual demonstrations of the power of the discriminant function, the absence of overlap of the plots revealed an excellent discriminant function (Fig. 1).

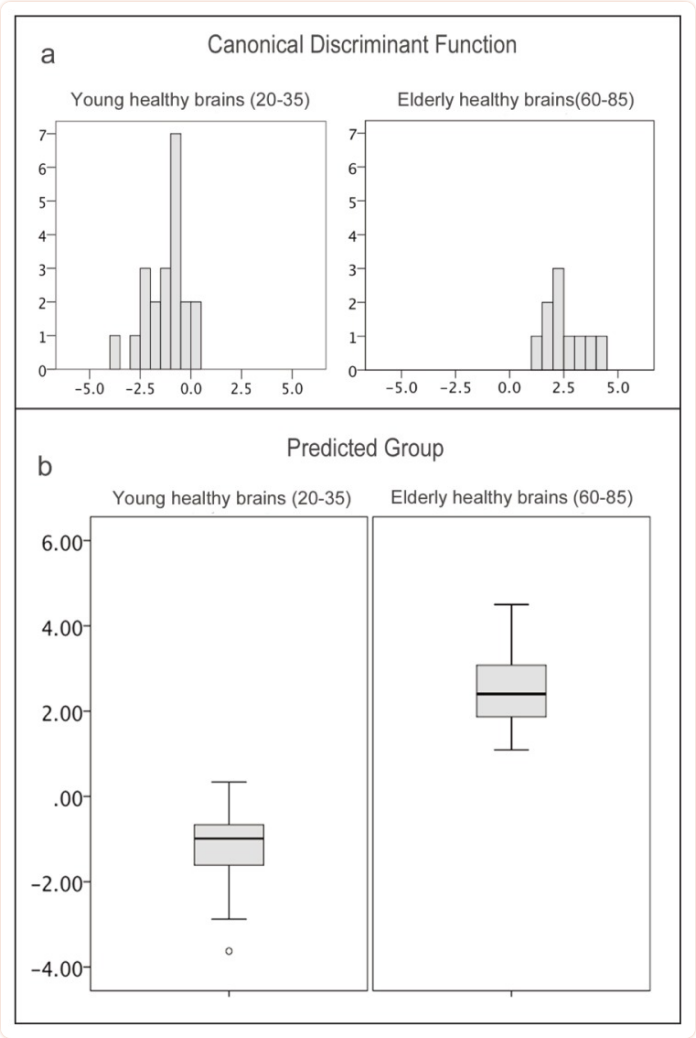

Fig. 1

Visual demonstration of the effectiveness of the discriminant function.

a) histograms showing the distribution of discriminant scores for young and older brains. b) box plots of the average D scores. Both illustrate the distribution of the discriminant function scores for each group. The absence of overlap between groups constitutes a visual demonstration of excellent discrimination.

Table VI

Results of diagnostic tests of the discriminant model.

Test	Value (%)	95% CI
Sensitivity	91.30	71.96–98.93
Specificity	100.00	63.06–100.00
+ likelihood ratio	-	-
– likelihood ratio	0.09	0.02–0.33
+ predictive value	100.00	83.89–100.00
– predictive value	80.00	44.39–97.48

Discussion

There is cumulative evidence showing that brain aging is a complex and heterogeneous process characterized by a pattern of age-related preservation and selective loss and associated with a high degree of inter-individual variability (Gunning-Dixon et al., 2009). In this study we investigated whether global (whole-brain) measures of MD and FA, together with segmented WM, GM and CSF volumes and gender, are able to document microstructural brain changes during normal aging.

Our assembled model showed 93.5% accuracy for discrimination between young and elderly brains, with FA topping the ranking of significant discriminant variables, followed by CSF volume and WM volume; such a ranking of MRI global parameters as part of a predictive model has not previously been reported in clinical settings to the best of our knowledge.

Surprisingly, MD, GM volume and gender were not significant parameters for classifying between groups even though they have been reported in the literature as biomarkers of the brain aging process.

In our view the clinical importance of this study lies in the assembling of a multivariate predictive model, which combines global (whole-brain) measures of MD and FA (which are easier to calculate and understand) with segmented WM, GM and CSF volumes and gender, and allows the building of a profile of the healthy elderly brain in normal aging. The adoption of a predictive model might supplement the assessment of brain structure and function in different circumstances: when brain measures in a new patient deviate from the expected parameters of normal aging, as well as in the follow-up of selected cases. Although radiologists and researchers have previously used and reported these parameters separately, the literature lacks a model that integrates them and is able to document microstructural brain changes during normal aging on a day-to-day basis.

Our evidence pointing to decreased FA as the best biomarker for classification of young vs older brains is in agreement with the findings of a previous study in normal aging (Michielse et al., 2010). FA values for WM continue to increase until the third to fourth decade of life, but they start to decline during aging (after 40 years of age) (Kochunov et al., 2011). These findings further support the idea that decreased FA might be interpreted as an expression of degeneration of the axonal myelin sheath (demyelination) and/or replacement of axonal fibers with other cells (gliosis) (Smith et al., 2006), and that it may precede atrophy in many regions of the brain (Hugenschmidt et al., 2008).

On the other hand, MD reflects the physicochemical properties of the nervous system (e.g., viscosity and temperature) as well as its structural components (macromolecules, membranes, and intracellular organelles) (Di Paola et al., 2010). In our study, MD depicted the smallest correlation and its values were not significant for discriminating between groups.

A possible explanation for this apparent difference with previous findings is that in our study we used a global measure of MD instead of a local or regional measure, and it seems that MD changes remarkably depending on the brain region considered. This may suggest that MD is a weak global biomarker of normal aging. Further research on aging and its related bio-markers should focus on FA rather MD, however we acknowledge that MD might still have important applications outside of the aging process.

Gender had a non-significant influence as a biomarker in our study, a finding that agrees with the equivalent disruption of regional WM microstructure between men and women found by Sullivan et al. (2001). It is possible, therefore, that the pattern of transition from the young to the older brain in men and women is equivalent.

An additional interesting finding in this study was that increased WM volume significantly predicted membership of the older brain group; this finding is in line with the continued production of ‘redundant myelin’ that has been observed in human adults (Allen et al., 2005; Salat et al., 2009) and suggested to be a compensatory mechanism for myelin degeneration.

The observed decrease in GM volume in elderly brains was non-significant, in contrast to earlier findings of a gradual linear decrease of GM, 5% per decade of age, from early adulthood (Smith et al., 2007). These findings suggest that GM loss progresses gradually, whereas WM loss starts later and progresses more precipitously (Raz et al., 2005); these findings might indirectly explain the significant increase in CSF volume in the older brains in our study and its key role in the model. This interplay between segmented WM, GM and CSF volumes remains unclear and could be investigated in further studies including ratios of WM, GM and CSF instead of absolute values. Our model follows the recommendation of Abe et al. (2008) to assess FA and brain volumes together, as complementary indices of brain aging. Despite the non-significant participation of MD and GM volume in our model, we recommend keeping track of their changes during follow-up studies, and also of changes in the other structural and volumetric biomarkers (FA, CSF and WM volumes), until more evidence helps validate their role in integrative models.

Several limitations in our study need to be addressed: our DA model, represented by an equation, behaves like a regression model and is strictly valid only within the range of the observed data on the explanatory variables. Our sample size, although small, was statistically valid for evaluating the diagnostic performance of the predictive model (Cortez-Conradis et al., 2013); this study is a starting point for a research line focused on MRI biomarkers of aging in the normal brain and in degenerative brain diseases. Further studies could increase the homogeneity of the sample in terms of gender, as well as the number of subjects, thus increasing the statistical power for generalizing the findings.

Segmentation algorithms and intensity thresholds of GM, WM and CSF may differ across laboratories, producing variable results. We acknowledge that alternative software like Freesurfer (Han et al., 2006) allows the calculation of surface-based cortical thickness measures. We did not use that software because our aim was to limit the computational costs of our study; also, we aimed to choose variables (brain volumes) which we could compare with previous studies. We believe it is necessary to reach a consensus of standardized software algorithms and measurements able to guarantee that all measurements are conducted within the same algorithms in all patients; in this way, variations in the results would be a reflection only of the distribution of the selected biomarkers. For example, a recent study has proposed the use of machine learning, albeit in a younger age group (8–22 years) (Erus et al., 2015). Despite the initially steep learning curve of the open-source software packages used in this study, they are suitable for use on a day-to-day basis in MRI units, for example those supporting geriatric or family medicine studies, and not only in clinical research. We acknowledge that further studies examining the changes, with age, in the biophysical properties of the DTI signal are necessary, as well as the inclusion of additional brain volume correlates; both groups of variables could supplement the study of neurodevelopment, healthy aging and brain disorders (Roldan-Valadez et al. 2014, 2015).

The increased availability of open source software in MRI units around the world would allow these measurements to become low-cost and commonly used biomarkers. By calculating multivariate discriminant models, further studies will help to rank the influence of these parameters in physiological brain aging. Eventually, similar reports would lead to the generalization and acceptance of multivariate-integrative models by clinicians (geriatricians, neurologists, psychiatrist, neuroscientists, etc.).

In summary our study shows that FA, CSF volume and WM volume are reliable imaging parameters that can depict microstructural changes during normal brain aging by using a global and integrative approach.

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