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Age related T2-FSE-MRI basal ganglia and inter-nuclei changes in normal aging

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ABSTRACT

To evaluate clinically easy to obtain parameters such as area and T2 MR signal intensity (SI) profiles from right and left caudate, putamen and thalamus nuclei and to describe age-related and inter-nuclei changes in both genders in healthy subjects, 71 healthy subjects (22–80 years old, 52 females) were evaluated with 1.5 T MRI conventional axial T2-Fast axial spin echo sequences obtaining SI and cross-sectional areas from caudate, putamen and thalamus nuclei using manually defined ROIs. Regression analysis were performed between age and MR parameters for inter-nuclei, gender and hemisphere side. Male basal ganglia show lower SI than those from females. Aging was differentially associated to a progressive lowering of basal nuclei SI in both genders. Male basal ganglia show SI changes following a positive quadratic function. Aging modifies differentially SI from all nuclei pair combination in both genders, showing mainly negative quadratic function. Age-related reduction of female caudate and a right lateralization for caudate nucleus SI in both genders were found. Healthy age-related nonlinear changes in SI from basal ganglia were defined for both genders. Basal ganglia show differential age-related changes. These results can be helpful to differentiate normal from abnormal aging changes.

1. Introduction

Healthy and pathological aging induces brain changes affecting both the cortical gray matter and deep gray matter. Basal ganglia and thalamus are the main subcortical nuclei which include vital parts of the sensorimotor system i.e., dorsal striatum, caudate and putamen nuclei involved in the extrapyramidal motor control as well as in executive functions, behavior, learning, emotions, and motivation among others. All these functions are related to many neural pathways that connect these nuclei to specific cortical areas in frontal lobe but also forming an intra- and inter-nuclei complex neuronal network (Obeso, Rodriguez-Oroz, Stamelou, Bhatia, & Burn, 2014). The thalamus is a large complex nucleus being a large sensorimotor relay and processing center that connects to and from well-defined cortical areas (Herrero, Barcia, & Navarro, 2002).

Magnetic resonance imaging has made it possible to detect *in vivo* changes occurring in the different brain areas, such as tissue water content, edema, demyelination, necrosis and increased iron accumulation not only in brain cortex but also in deep gray matter. Some of these alterations have been linked to neuro-degenerative diseases such as Alzheimer, Parkinson and Huntington. However, clinical neuroimagers face a frequent dilemma to decide whether a brain image change is consequence of normal or abnormal aging. So, more knowledge is needed to improve the use MRI techniques, especially for those clinically available, in order to detect early changes attributable to aging and to differentiate them from those attributable to disease even before the manifestation of symptoms.

Reported age-related changes of deep gray matter nuclei are a rather contrasting issue. The caudate nucleus has a shrinkage of its volume with increasing age (Jernigan et al., 1991; Jiji, Smitha, Gupta, Pillai, & Jayasree, 2013; Walhovd et al., 2005). Putamen also shows decreased volume (Raz et al., 2003; Wang, Xu, & Zhang, 2010) and the thalamus can show a linear age-associated volume decrease (Fleischman et al., 2010; Raz et al., 2005; Sussman, Leung, Chakravarty, Lerch, & Taylor, 2016; Wang et al., 2010) or no-changes (Bergfield et al., 2010; Grieve, Clark, Williams, Peduto, & Gordon, 2005; Jernigan et al., 1991). Age-related volume changes and lateralization have been reported for caudate nucleus (Gunning-Dixon, Head, McQuain, Acker, & Raz, 1998; Peterson et al., 1993; Yamashita et al., 2011), putamen (Bergfield et al., 2010; Lu et al., 2016; Peterson et al., 1993) and thalamus (Lu et al., 2016; Peterson et al., 1993; Szabó et al., 2006). Gender differences for such a change seems to plays also a role for caudate nucleus, putamen (Abedelahi, Hasanzadeh, Hadizadeh, & Joghataie, 2013; Brabec, Kraseny, & Petrovicky, 2003; Király et al.,

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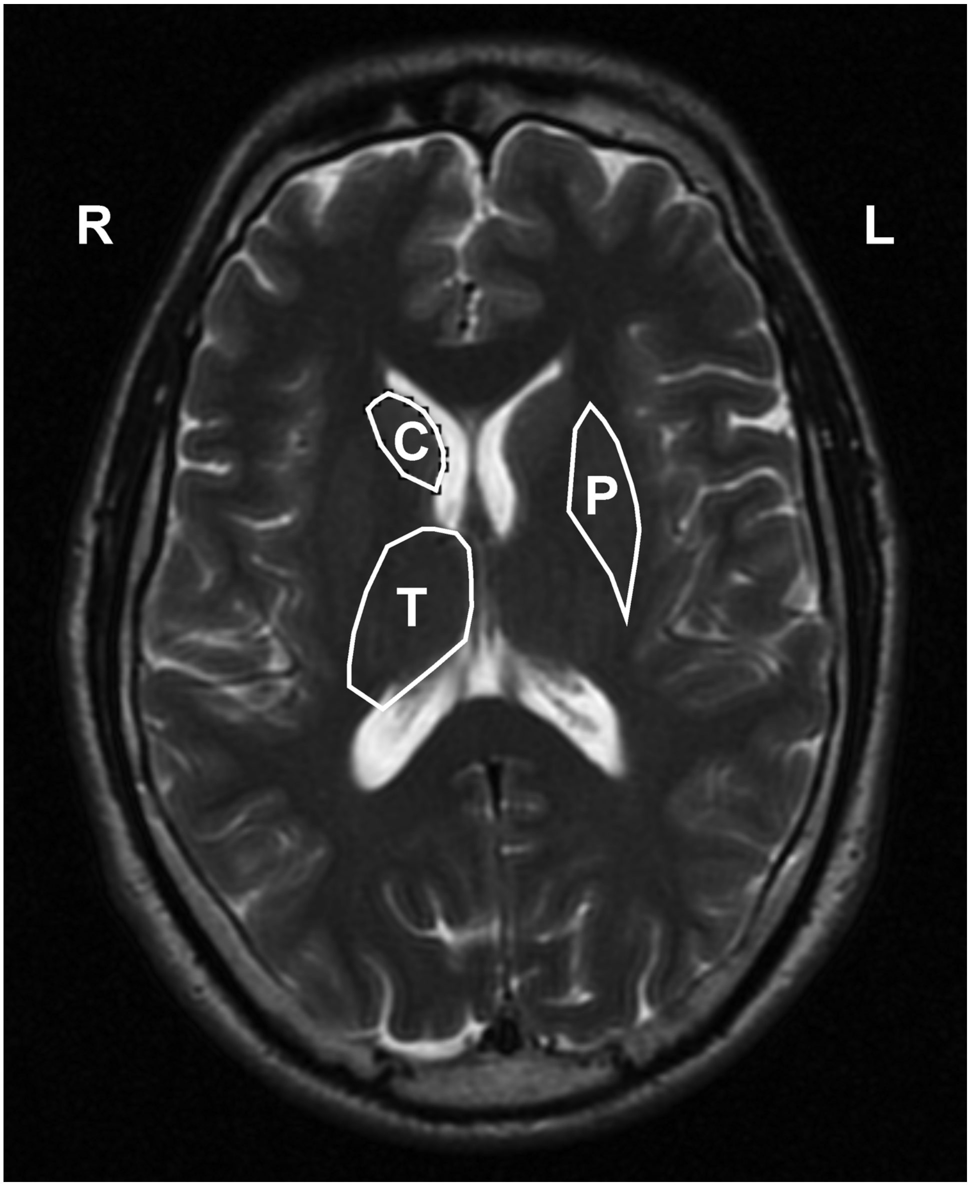

Fig. 1. Axial T2-Fast axial spin echo sequences displaying a good contrast between different subcortical gray matter nucleus, anterior and posterior limb of the internal capsule and cerebrospinal fluid. Basal nuclei are outlined and measured for area and signal intensity in both hemispheres. Caudate (C); putamen (P) and thalamus (T) nuclei; left side (L); right side (R).

Table 1
Age- and gender-related changes in median area (mm^2) from caudate, putamen and thalamus nuclei evaluated by regression analysis.

Females (n = 52)	R^2 (%)	F	P	Equation
Caudate	11.4	9.7	0.002	−0.033Age + 12.19
Putamen	5.3	2.5	ns	ns
Thalamus	1.1	0.4	ns	ns
Males (n = 19)				
Caudate	27.1	3.1	ns	ns
Putamen	2.0	0.2	ns	ns
Thalamus	11.7	1.2	ns	ns

ns: no significant.

2016; Schröder, Hopf, Lange, & Thörner, 1995; Wierenga et al., 2014) and thalamus (Király et al., 2016; Peterson et al., 1993; Wierenga et al., 2014) however reports are not consistent (Wierenga et al., 2014). Moreover, the possible relationship among age-related changes that take place in a basal nucleus respect to another is unknown.

The aim of the present study is to evaluate clinically easy to obtain parameters such as area and T2 MRI signal intensity profiles from caudate, putamen and thalamus nuclei and to correlate them with age, gender, hemisphere lateralization, but also for inter-nuclei age-related changes in healthy subjects.

2. Materials and methods

This study was approved by the Institutional Bioethics Committee of the Research and Intellectual Production Office of the Health Sciences Faculty and was performed according to the Declaration of Helsinki. Informed consent was obtained from each participant. MRI images were selected from the institutional database according to inclusion and exclusion criteria. Images from a total of 71 subjects were evaluated. Anonymous subject's data such as age, gender, and clinical history were collected.

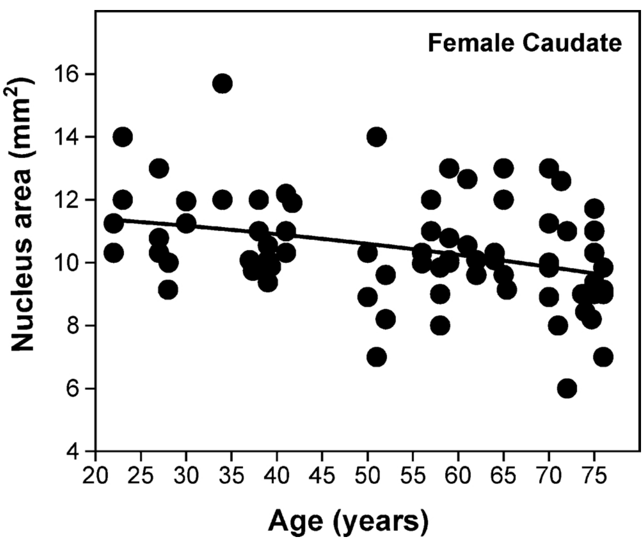

Fig. 2. Scatter plot of age-related changes of female caudate nucleus area showing a progressive decrease of the nucleus cross-section with age. Linear curve fitting is shown on Table 1.

Table 2
Age- and gender-related changes in median T2-MRI signal intensity (AU) from caudate, putamen and thalamus nuclei evaluated by regression analysis.

Females (n = 52)	R^2 (%)	F	P	Equation
Caudate	9.6	8.13	0.005	− 0.365Age + 235.2
Putamen	15.0	6.6	0.002	+ 0.029Age^2-2.83Age + 249
Thalamus	13.0	5.6	0.005	+ 0.018Age^2-1.62Age + 233.3
Males (n = 19)				
Caudate	30.4	3.7	0.045	+ 0.079Age^2-7.75Age + 386
Putamen	60.5	13.0	0.0003	+ 0.106Age^2-10.3Age + 455.6
Thalamus	83.1	43.0	10^{-7}	+ 0.18Age^2-18.24Age + 643.7

ns: no significant.

2.1. Inclusion and exclusion criteria

MRI image T2 sequences were included in the study, from conscious, without known disease, any gender, age 20 and older, with or without microvascular image pattern i.e., as small, sharply demarcated areas of high-signal intensity, located in the gray matter, white matter and basal ganglia, who attended the Imaging Unit of the San Rafael Clinic requesting a MRI brain study between November 2015 and February 2016. Images from subjects with a history of ischemic or hemorrhagic encephalic events, tumor brain lesions, intracranial vascular malformations, head trauma, unconscious, cystic lesions of any etiology, mental illness i.e., schizophrenia or psychosis, congenital malformations of the central nervous system and also from subjects who did not report these events but displayed abnormalities in their MRI images were excluded from the study. Additionally, patient under prescribed permanent medication were also excluded.

2.2. MRI imaging

In a low-stress environment, the subject was instructed about the MRI study then, lying down on the table resonator the subject's head was fixed by a harness to reduce movement and artifacts during image acquisition. A 1.5 T, General Electric MRI (Signa Horizon™) device was used to obtain axial Sections 5 mm of thickness from the base to the vertex brain. Clinical routine axial T2-Fast axial spin echo sequences at TR: 5000 ms, TE: 112.88 ms, Flip Angle: 90°, Slice Tnk: 5 mm, DFOV: 240 mm sequences were collected to display a good contrast between different subcortical gray matter nucleus, anterior and posterior limb of the internal capsule and cerebrospinal fluid allowing a precise delimitation of their boundaries and iron deposition (Aquino et al., 2009). Acquired images were store on the hard disk of the device computer in DICOM (.DIF) format.

2.3. Two-dimensional morphometry

The images in its original DICOM format were post- processed using the freely available Image J (NIH, USA) package (Schneider, Rasband, & Eliceiri, 2012). For a systematic morphometry of MRI signal intensities, the axial section just at the basal ganglia level was selected to bilaterally visualize the head of caudate, putamen, and thalamus in the same slice (Fig. 1). 256 gray level densitometry (T2-frSE-MR signal intensity) profiles were obtained within a scale of white (value of 255) to black (value 0). One neuroradiologist and one neurophysiologist (each with 30 years of experience in neuroimaging) jointly drew free-hand regions of interest (ROIs) such as that previous reported (Aquino et al., 2009). ROIs were measured in both hemispheres for the nucleus cross-sectional area (calibrated in mm^2) and signal intensity median (arbitrary density units) within the nucleus outline. Manual and automatic defined ROI methods proved to be equally valid (Aquino et al., 2009).

2.4. Statistical analysis

Median T2-frFSE-MRI signal intensity and area nuclei values were analyzed. This central tendency measure was selected due to its relative immunity to outlier values. Intra- and inter-hemispheric nuclear values were compared by non-parametrical Kruskal-Wallis test with Mann-Whitney post hoc test. Nuclear asymmetries were pairwise compared by non-parametrical Mann-Whitney test (MW). To evaluate age-related left-right nuclear asymmetries, the inter-hemispheric asymmetry index (IAI) for cross-sectional area and T2 signal intensity was calculated, dividing the values of each right nucleus by the corresponding left value. Values > 1 suggest right predominance and values < 1 left predominance. Correlation and regression analysis with linear and non-linear curve fitting were performed between age and area or signal intensity for each nucleus, and the coefficient of determination (r^2x100) expressed as percentage was calculated to measure the intensity of association between age and each of these parameters. Association of T2 signal intensity or cross-sectional area between any possible nuclei pair combination measured at the same subject was also evaluated. The level of statistical significance was set at $P < 0.05$. The statistical package PAST v.3.19 was used (Hammer, Harper, & Ryan, 2001).

3. Results

The institutional MRI image database included 157 patients from which 86 (548%) were excluded due to pathological images (tumors, ischemia, infarct, hematoma, atrophy, arterio-venous malformations), 2 patients were excluded due to MRI slice misalignment. Normal or pathological MRI images were blindly confirmed by 2 different radiologists with more than 25-year clinical MRI expertise. A total of 71 subjects with normal MRI images were included in the study. In this sample, the patient´s reasons for imaging evaluation were 96.1% due to cephalea and the rest due to a general periodic health check and initial job/insurance requirements. Females were the majority 73.2% (n = 52) over 26.8% males (n = 19). The age range of the sample was 22 to 79 years old. Age comparison between female (54.4 ± 17.2 years) and male (53.1 ± 11.0 years) subjects was not statistically significant (MW; z = -0.14; p = 0.15).

3.1. Effects of age and gender on the area of basal nuclei

Female subjects showed statistically significant age-related size reduction of caudate nucleus with 11.4% association between both

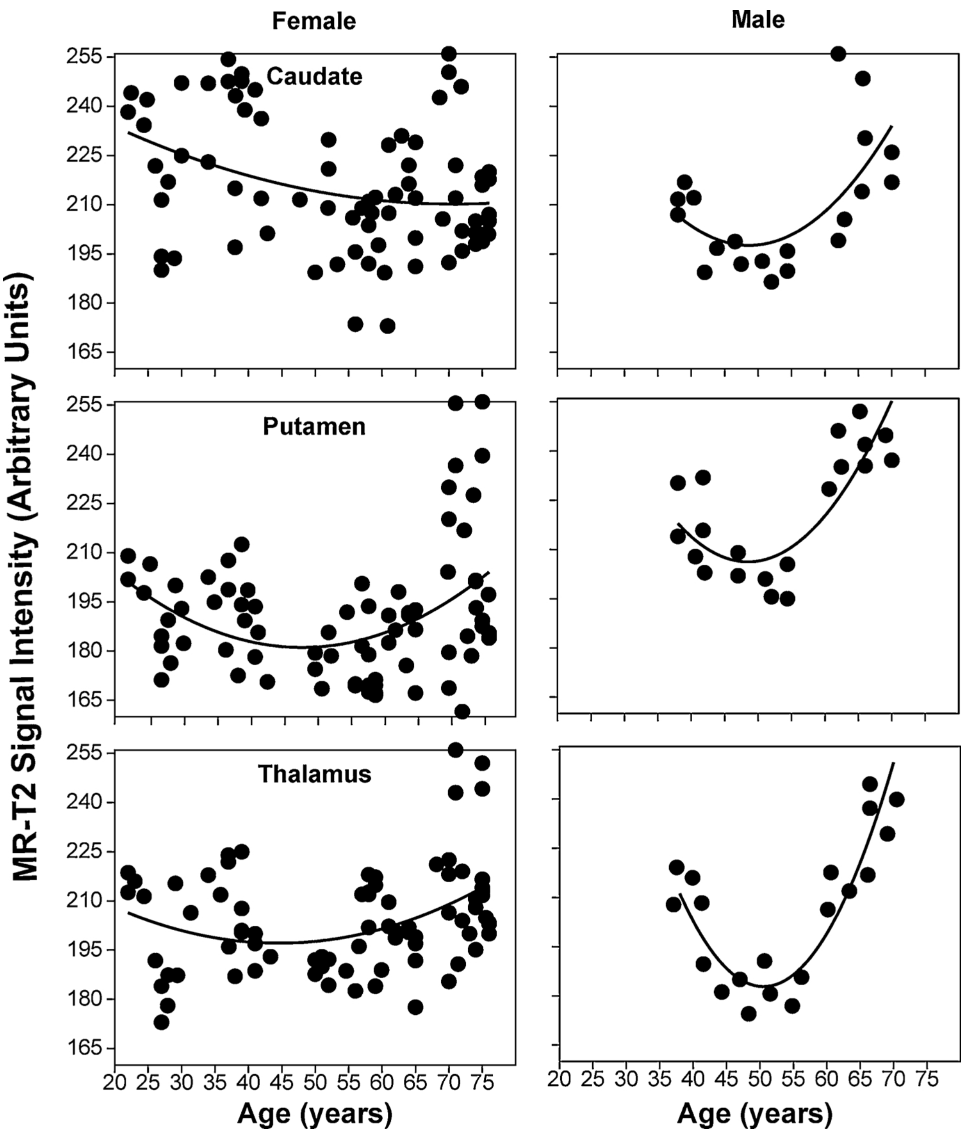

Fig. 3. Scatter plots and curve fittings of statistically significant age-related changes of T2 signal intensity for caudate, putamen and thalamus in female and male healthy subjects. See Table 2 for curve fitting equations.

Table 3
Gender differences in T2 signal intensity (median AU) from caudate, putamen and thalamus nuclei in female (n = 52) and male (n = 19) groups.

Basal Nuclei	Md (AU)		Δ (%)	z	p
	Female	Male			
Caudate	258.8	239.7	−7.9	3.3	0.0009
Putamen	238.0	221.2	−7.0	2.8	0.005
Thalamus	224.9	205.9	−8.4	3.2	0.001

Mann-Whitney *U* test AU: arbitrary units. Md: Median values.

variables. This size reduction follows an inverse linear curve fitting (Table 1 and Fig. 2). This change was not observed neither for putamen and thalamus nuclei nor for any of the male nuclei (Table 1).

3.2. Effects of age and gender on basal nuclei T2 MRI signal intensity

Female aging was significantly associated to a progressive lowering of T2 signal intensity in basal nuclei by a percentage between 9.6% for caudate to 15.0% for putamen nucleus which follow inverse linear curve fitting (Table 2 and Fig. 3). Thalamus shows significant changes (Table 2 and Fig. 3) with intermediate values. All three evaluated male nuclei showed statistically significant age-related changes in their T2 MRI signal intensity following a positive quadratic curve fitting with different age association intensities i.e., thalamus with the highest percentage of association and caudate with the lowest (Table 2 and Fig. 3).

3.3. Gender and T2 signal intensity measures

T2 MRI signal intensity median values from each basal nucleus were compared between genders. It was found a significant lower values (darker) for the three nuclei in males compared to those measured in females (Table 3). No age differences were found between genders in the subject sample *vide supra*.

3.4. Age-related inter-nuclei changes

A highly significant proportional age-related association of T2 signal intensity changes was found in both genders among all nuclei pair combinations (Table 4). Regression fitting curve for all male nuclei combination were negative quadratics with high R^2 coefficients whereas for female nuclei combinations were all linear, significant but

Table 4
Association of cross-sectional area or T2 signal intensity changes among any nuclei pair combination evaluated after gender.

Males *Cross-sectional area* Nuclei Pair	p	R^2(%)	Regression
Caudate - Putamen	0.089	ns	ns
Caudate - Thalamus	0.323	ns	ns
Putamen - Thalamus	0.187	ns	ns
T2 Signal Intensity			
Caudate - Putamen	0.001	54.5	$-0.0187C^2 + 8.79C\text{-}792.1$
Caudate - Thalamus	10^{-8}	85.1	$-0.0334C^2 + 15.36C\text{-}1534$
Putamen - Thalamus	10^{-7}	83.1	$-0.0237P^2 + 11.49P\text{-}1169$
Females			
Cross-sectional area			
Caudate - Putamen	0.145	ns	ns
Caudate - Thalamus	0.476	ns	ns
Putamen - Thalamus	0.191	ns	ns
T2 Signal Intensity			
Caudate - Putamen	10^{-7}	30.6	$0.538C + 75.1$
Caudate - Thalamus	0.006	9.4	$0.248C + 150.8$
Putamen - Thalamus	10^{-10}	42.5	$0.541P + 100.9$

C and P in regression equations are T2 signal intensity values (arbitrary units) of putamen and thalamus nuclei.

with less intense association (Fig. 4). No significant association was found among nuclei cross-sectional areas neither in females nor in males (Table 4).

3.5. Basal ganglia interhemispheric asymmetry

The inter-hemispheric asymmetry index (IAI) for basal nuclei shows a significant right predominance in T2 signal intensity for the caudate nucleus (mean: 262.8 vs 247.0, z: 4.46, p: 0.007; Table 5). No significant differences were observed for putamen or thalamus nuclei neither for cross sectional area nor for signal intensity (Table 5) in any of the genders. Regression analysis between age and IAI values from each basal nucleus did not show any statistically significant association (not shown).

4. Discussion

In the present study, conventional T2-FSE-axial 1.5 T MRI cross sectional area and signal intensity profiles from caudate, putamen and thalamus nuclei of both brain hemispheres were evaluated in healthy subjects looking for age-related changes, gender differences and inter-hemispheric nuclear asymmetries using manual defined anatomical nuclei ROIs obtaining their cross-sectional areas and T2 signal intensity. This simple method, which could be applied for routine clinical evaluations using standard and most frequent 1.5 T equipment, was able to detect age-related signal intensity changes and size in basal ganglia.

4.1. Age-related changes in basal nuclei T2 signal intensity

The fact that T2 signal intensity showed a progressive darkening effect with age for almost all tested basal ganglia could be due to a progressive iron accumulation into the brain deep gray matter (Bartzokis & Tishler, 2000; Bartzokis, Tishler, Shin, Lu, & Cumming, 2004; Acosta-Cabronero, Betts, Cardenas-Blanco, & Yang, 2016; Keuken et al., 2017) which is an intrinsic condition of aging. However, the signal intensity changes follow a positive quadratic function i.e., progressive darkening (decreasing values) from 20 to 50 years age followed by increasing values (lightening effect) towards the 80th year of age. The behavior at late decades was more intense for male nuclei contrasting to the mild increase observed in females, and could be expression of an unbalance between neuronal loss (Daugherty & Raz, 2016; De Jong et al., 2008; Fleischman et al., 2010) and iron deposition (Bartzokis & Tishler, 2000; 2004; Acosta-Cabronero et al., 2016; Keuken et al., 2017). These results give both original insight about a gender difference in structural age decay of basal nuclei and detailed mathematical characterization. These age-related changes affect both genders but the decay was more accelerated after 50 years of age for male subjects, which as a group and independent of age, show significantly lower values ranging from 7 to 8.4% (darker images) than females. This gender difference does not depend on group age because no significant age difference between gender groups was found, and probably depends on direct gender related causes. However, the female majority of the sample could introduce gender bias to the results however this bias (if exists) match to the higher incidence of neurodegenerative diseases such Alzheimer in females.

It is known that the highest levels of brain iron are found in the basal ganglia and that excessive accumulation of iron causes cellular damage by oxidative free radical reactions (Bartzokis & Tishler, 2000; 2004; Aquino et al., 2009; Acosta-Cabronero et al., 2016; Daugherty & Raz, 2016). Our results show that the association between age and T2 signal intensity was higher for male than for female nuclei which supports the notion that iron deposition and/or neuronal susceptibility predominates in males but pathological response predominates in females as in the cases of Alzheimer and Parkinson's diseases (Bartzokis et al., 2004). Despite that iron deposition plays a relevant role for T2 signal intensity, other factors such as neuronal and/or myelin lost, water content, local edema, brain interfaces and magnetic field inhomogeneities should be also taken into account to interpret the signal intensity results

detected by conventional or advanced MR imaging (Bartzokis & Tishler, 2000; Nunnemann et al., 2009; Daugherty & Raz, 2016; Keuken et al., 2017), therefore a quadratic age-related changes in T2 signal intensity could express that for late decades of life, an accelerated neuronal lost (Manza et al., 2015) together to a constant and in most of normal aging, slow iron deposition (Aquino et al., 2009) take place within the nuclei.

Aquino et al. (2009) reported a progressive increase of iron deposition at the putamen with no saturation but with a high variability after age 50 years and maximum value at the 6^{th} decade of life but, interestingly they reported a slight decrease in the curve within the 5^{th} decade of life. In the same study, a nearly flat curve of iron deposition for the caudate nucleus was reported concluding that this process is scarce and very slow which could reflect an attenuating effect of mixing both genders data. In our study, both genders show different patterns, mainly with a positive quadratic effect for the three nuclei, exception should be made for female caudate with a slow linear darkening. These results suggest gender differential age-related changes in the T2 signal intensity which were characterized in the present study by their regression equations for normal aging. Similar age-related quadratic relationship for T2 signal intensity was reported for subcortical white matter (Jernigan et al., 1991) which suggests that basal ganglia and connecting white matter could share age-related changes perhaps interdependent each other. The age-related quadratic changes in T2 signal intensity seem to be similar to those reported for T1 weighted signal intensity in different cortical areas (Westlye et al., 2010) and could express a general brain aging characteristic.

4.2. Age-related changes in basal nuclei size

We found significant size changes in the female caudate nucleus, agreeing with previous reports (Brabec et al., 2003; Jernigan et al., 1991) despite that only 33% of the healthy subjects show a significant volume loss of this nucleus (Jiji et al., 2013). Decrease in caudate nucleus size showed a heterogeneous age change which followed a linear relationship, this agrees to other report (Walhovd et al., 2005). In the present study, the curve fitting of this regression was by far better for linear than for a quadratic function, however, a quadratic decrease for

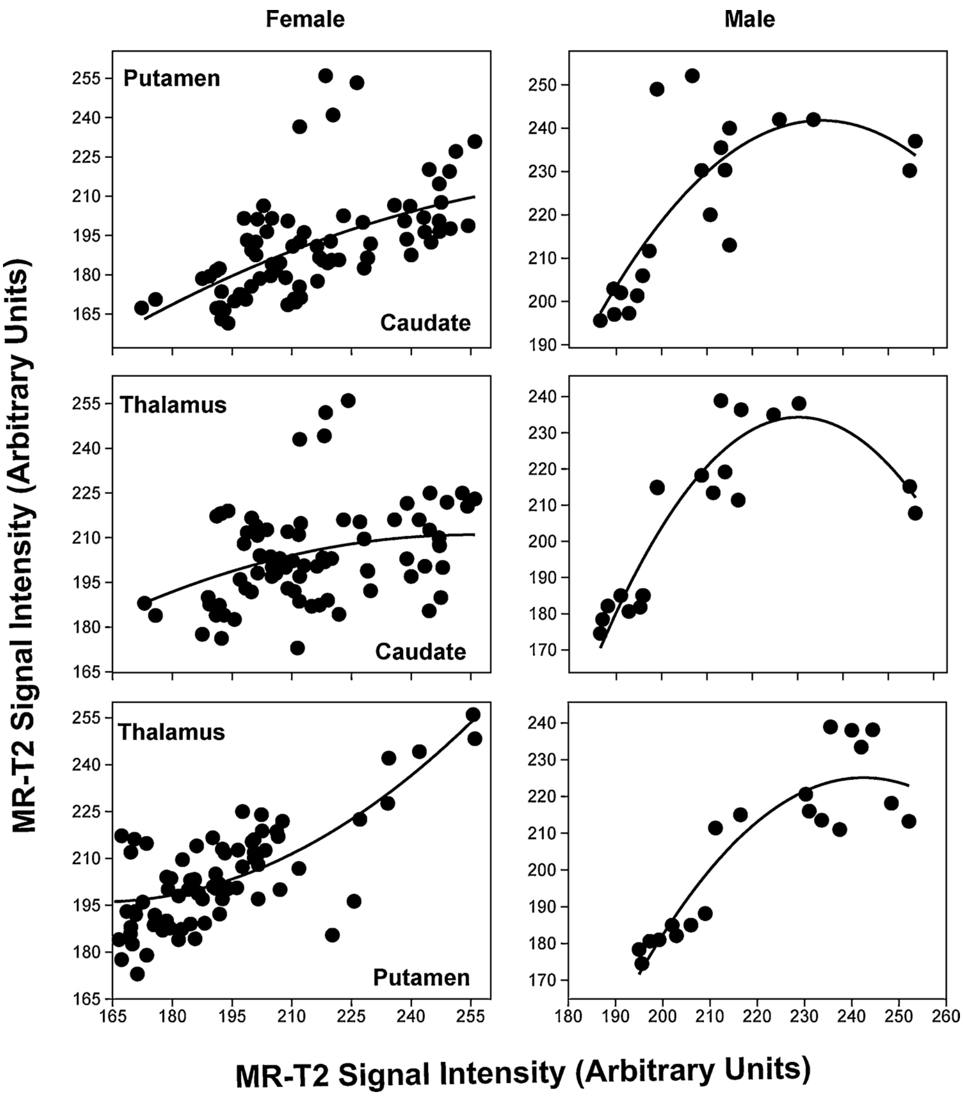

Fig. 4. Scatter plots and curve fittings of statistically significant age-related association of T2 signal intensity changes among all nuclei pair combination for caudate, putamen and thalamus in female and male healthy subjects. See Table 3 for curve fitting equations.

Table 5
Interhemispheric asymmetry index (IAI) for each cross-sectional area and T2 signal intensity for basal nuclei for all subjects.

Nucleus	IAI Area	p	IAI Signal Intensity	p
Caudate	0.96	0.16	1.04	0.007*
Putamen	1.01	0.48	0.75	0.55
Thalamus	0.99	0.70	1.00	0.93

Mann-Whitney test, * significant.

the caudate with greater atrophic changes over the 60 years of age, was reported by (Pfefferbaum et al., 2013). Likewise, a study carried out during childhood and adolescence showed a decrease in the size of the caudate nucleus with age but for the thalamus, a small age-dependent increase during childhood followed by a slight decrease in the volume of the thalamus (Wierenga et al., 2014). Taken together, these results support the notion that basal ganglia show changes of maturation and decay throughout the life.

All other nuclei in males and females did not show age-related changes in their cross-sectional size which agrees to the notion of no gender-dependent volume difference (Peterson et al., 1993). The lack of difference may be attributable to the fact that we do not use an overall brain volume correction to maintain the simplicity of the calculation and due to the actual possibility to detect nuclei size difference without volume correction (Dennison et al., 2013; Ostby et al., 2009; Wierenga et al., 2014). However, it is most probably that such differences could be better detected by techniques such as diffusion tensor imaging (Goodro, Sameti, Patenaude, & Fein, 2012) or comparing results from large longitudinal and cross-sectional studies (Raz et al., 2003).

4.3. Interhemispheric asymmetry

Several studies have shown higher levels of brain iron content in the left hemisphere (frontal region), putamen and thalamus suggesting a left lateralization (Xu, Wang, & Zhang, 2008). These asymmetries are related to the motor system and with some emotional, motivational, associative and cognitive functions, so these areas would be more vulnerable to changes in their signal intensity and/or cross-sectional areas during healthy aging and more probably in basal ganglia neuro-degenerative diseases. In the present study, higher T2 signal intensity of the right caudate nucleus complements other asymmetry reports about it for nucleus volume (Peterson et al., 1993; Yamashita et al., 2011) and caudate head (Szabó et al., 2006). Additionally, this result shows that caudate nucleus asymmetry did not change with age thus, both sides suffer the same process and impact. The fact that no other asymmetries for nucleus size or T2 signal intensity may reflect homogeneous age-related changes specially when contrasting reports exist (Gunning-Dixon et al., 1998; Lu et al., 2016; Peterson et al., 1993).

The advantages shown by the methodology used in the present study are that the simplicity of measurements avoid accumulation of errors that arise from aggressive multi-step post-processing of the data and that is freely available. The reference values of normal basal ganglia aging could give to clinicians more decision-making information facing normal versus abnormal MRI evaluation. More advanced method to quantify iron accumulation in deep gray nuclei had been described such as quantitative susceptibility mapping (QSM) but it still shows susceptibility to reconstruction problems and is not used for clinical routine studies (Langkammer et al., 2012). Further research should be addressed to evaluate contribution to these results by using less frequently available 3 T MRI devices.

4.4. Longitudinal versus cross-sectional study

Intrinsic difficulties to perform longitudinal large subject sample support the notion to apply cross-sectional design studies to solve this specific issue (Pfefferbaum et al., 2013) specially for a wide clinical conventional use. The substantial age-related diversity reported for different basal ganglia conforms a confusing clinical scenario to differentiate between normal and abnormal images of these structures using strictly structural parameters such as nucleus volume and MR signal intensity. Further research is needed to contrast these results from normal subjects to values from Alzheimer or Parkinson disease as well as other neurodegenerative patients.

4.5. Limitations of the study

The easy but time consuming measuring method applied in the present study rise the need for an automatic supervised or unsupervised algorithm to obtain the measures. Gender bias of the sample could reduce precision when applying these results to male patients. Regional patient imaging data base and general application of curve fitting for diagnostics could depends on local, genetics population characteristics

5. Conclusions

Inter-nuclei changes of basal ganglia were evaluated by T2-FSE-MRI in 71 healthy subjects. Aging modifies differentially parameters from all nuclei pair combinations. Age-related inter-nuclei signal intensity changes follow quadratic functions. Healthy age-related nonlinear changes in basal ganglia occurs for both genders. These results can be helpful to differentiate normal from abnormal aging changes.

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Conflict of interest

The authors declare no conflicts of interest.

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