MRI based morphometry of caudate nucleus in normal persons

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ABSTRACT

Because of continuous changing of anatomy, function and metabolism of the human brain, age-related change is a major risk factor in most prevalent neurodegenerative diseases, including Parkinsons and Huntingtons disease. Therefore, knowing patterns of age-related atrophy of brain tissue can identify causes and possible role of diseases in decreasing brain function with age. The aim of this study was to determine the age, sex, and hemispheric differences in volume of the human neostriatum (striatum) nucleus in right-handed healthy humans. This study was performed on 120 normal human subjects (60 males, 60 females) 15–65 years old that was divided into young (<40 years) and old (≥40 years) groups. The sectional brain images obtained via magnetic resonance imaging (MRI) was analyzed and processed using the Image-J software and the caudate volume was calculated using the Cavalieri's principle. The analyses revealed bilateral age-related changes in the caudate volume of both sexes and the caudate nucleus was significantly smaller in older than younger subjects ($P<0.001$). There were statistically significant volume differences between males and females ($P<0.05$) and there was a significant negative correlation between age and volume of the caudate nucleus. Our results provide useful baseline data on age and gender-related changes of caudate volume in neurodegenerative diseases such as Parkinsons and Huntingtons, which has the potential to diagnose neurodegenerative disease before the appearance of typical clinical symptoms.

Keywords: Caudate nucleus; Neostriatum; MRI; Morphometry

INTRODUCTION

The caudate nucleus plays an important role in planning, control of movement and execution [1, 2]. These functions alter during aging and age- related changes of this nucleus led to increasing prevalence neurodegenerative diseases, including Parkinsons and Huntington's disease [3, 4]. These changes have laded to an increased need to understand the normal aging brain. Therefore morphometry and analysis of caudate nucleus in normal persons essential to monitor clinical outcomes of neurodegenerative diseases. Two approaches of postmortem and imaging techniques studies has utilized to analysis of age-related changes in brain tissue including caudate nucleus. The postmortem studies for several limitations, such as fixation artifacts and volume shrinkage are not reliable for volumetric studies of caudate nucleus. In contrast, imaging studies strongly MRI because of better tissue contrast and non-invasive method increases the accuracy of the morphometric measurements [5-7]. In addition, MRI morphometric studies beside of software techniques have been developed recently that could prove useful information for measurement of caudate volume. Volumetric studies have been showed negative correlation between age and brain tissue includes caudate nucleus [6-9].

However, these studies have been showed different reduction patterns in different regions of the brain tissue. The study of Smith et al. reported age-related atrophy in volume of brain tissue which this reduction was different in the brain nuclei [7]. However, Cherubini *et al*. was observed age related changes in deep gray nuclei only in the thalamus, putamen and caudate nucleus [8]. Gender is another important factor in morphologic changes of brain tissue. A number of MRI studies have demonstrated effects of sex on age-related changes in brain structure [9-12]. Xu *et al*. reported more age-related changes of volume in the posterior part of the right frontal lobe, the middle part of the right temporal, the left cerebellum and basal ganglia in men compared to women [9]. Riello and colleagues also concluded that age-related atrophy occurs faster in men [13]. Although Chen *et al*. showed that the gender-related changes occur in middle aged healthy men and women brain [14]. Only, a few imaging studies have examined effects of age on caudate nucleus and fundamental questions about differences in gender and age-related changes in caudate nucleus remain unanswered yet. Because different disease can cause different age-related changes in caudate structure. Therefore, it is important to study the age and gender- related changes of the caudate nucleus in normal individuals that is an appropriate method for assessing age-related changes. Among many fundamental questions concerning age and gender-related changes in healthy human striatum, this study was specially designed on the elucidation of questions, whether there are any age-related changes in human caudate nucleus and whether these age-related changes are sex dependent or not.

This study can provide new information about age and gender-related changes in caudate volume and provide a reference data to be used in compare studies with samples of neurodegenerative diseases.

MATERIAL AND METHODS

Subjects

One hundred and twenty healthy volunteers (sixty men, sixty women) with ages between 15 and 65 years recruited from the Babak imaging center were randomly selected. Each subject had a complete neuropsychiatric and physical examination and no risk factors for stroke, such as hypertension, diabetes, cardiovascular disease. Subjects were divided into young (<40) and old groups (≥40) which were 30 men (age 27.10 ± 7.25 years) and 30 women (27.23 ± 8.03 years) in the young group and 30 men (age 50.27 ± 6.35 years) and 30 women (52.40 ± 8.10 years) in the old group. There was no significantly difference in age between men and women. The study was approved by the Ethics Committee of the Iran University of Medical Sciences and from all the subjects of this study after providing complete information about the procedure and outcome of study, a written consent was recorded.

MRI acquisition

Brain images were obtained using a 1.5 Tesla Gyroscan-Philips intra system at the Babak imaging center (Tehran, Iran). The subject's head was aligned along the midline or the canthomeatal line at 0˚ degrees using head support. All the scans used for the volumetric analysis were (axial and coronal) T_2-weighted spin-echo images with the following parameters: TE=100*msec*, TR=2800*msec*, slice thickness=2.5*mm*, inter-slice gap=0.3*mm*, repetition=1, mutation angle=90°, FOV=220*mm*, acquisition matrix=352×512. The axial and coronal T_2-weighted images are highly sensitive to local pathology and provided good demarcation of the CSF-containing spaces which results to high-spatial-resolution images with excellent gray-white matter contrast, to be used for measurement by means of manual tracing of striatum nucleus structure.

MRI processing

The brain images were transferred to a PC workstation (27-inch video monitor screen with standard brightness and contrast) using the *Image-J* software (Version 1.34, National Institutes of Health) that provides a reliable morphometry and manual tracing. The volumes of the caudate nucleus were calculated using the Cavalieri's theorem of systemic sampling and was computed by multiplying the summed slice area by slice thickness and volumes were presented in cubic centimeters (cm^3).

Delineation of the Caudate Nucleus

The volume of the caudate nucleus was estimated from 20 axial (Fig. 1.A-C) and coronal (Fig.1.D-F) slices according to standard anatomical brain atlases. Caudate nucleus were segmented and measured by two investigators (anatomist) to reduce measurement variability and to establish measurement reliability that limited error percentage. The caudate nuclei appeared firstly in the rostral section, the stria-terminalis and terminal vein constituted the ventral boundary. The caudate was traced on each section until it was no longer visible. The lateral ventricle and the anterior limb of the internal capsule represented the medial and lateral boundaries, respectively. The dorsal boundary of the caudate was surrounded by white matter. On more anterior sections of the caudate nucleus, the accumbens nucleus featured as the ventral border and the accumbens nucleus was included in the total caudate volume.

Statistical Analysis

All analysis was performed by *SPSS 15* (SPSS/PC Inc., Chicago, IL). All the data were presented as Mean (SD). Dependence of caudate nucleus on age in each sex group was tested using linear regression. Differences between male and female groups were tested by including sex × age interaction in the regression models and Analysis of variances (*ANOVA*) and Welch robust tests following by Tukey and Games-Howell testes. Differences were considered significant at the confidence interval level of 95% ($P<0.05$).

RESULTS

Effect of age on striatum volume

The results of the statistical analysis on age-related changes for both sides of the caudate and putamen volumes are shown in Table 1. There exist significant negative correlations between age and caudate volume in male group (right side: r=-0.718, $P<0.001$; left side: r=-0.721, $P<0.001$). In female group, there exist significant negative correlations between age and caudate volume (right side: r=-0.627, $P<0.001$; left side: r=-0.569, $P<0.001$). In male group, the negative association between age and the volumes of caudate nucleus were stronger than female group ($P< 0.01$). However, there were significant differences between age groups in the volumes of caudate. Men in the young group had significantly larger total volumes for the caudate nucleus than the old group (8.92 *vs* 7.12cm^3 respectively, $P<0.001$) .In comparison to old group, men in the young group had larger measured volumes of right (4.55 *vs* 3.63cm^3 respectively, $P<0.001$) and left (4.37 *vs* 3.49cm^3 respectively, $P<0.001$) caudate nucleus. In women between two age groups, the young group had significantly larger total measured volumes for caudate (8.42 *vs* 6.79cm^3 respectively, $P<0.001$). Besides, measured volumes of right caudate (4.34 *vs* 3.47cm^3 respectively, $P<0.001$), left caudate (4.09 *vs* 3.32cm^3 respectively, $P<0.001$) was larger in the young group.

Effect of sex on striatum volume

The descriptive statistics for the volume of the right or left caudate nucleus by *age×sex×group* are presented in Table 1. The older men had larger right (3.63 *vs* 3.47cm^3 respectively, $P=0.63$) and left (3.49 *vs* 3.32cm^3 respectively, $P=0.55$) caudate volumes than the older women. Across the two age groups, there were no statistically significant volume differences between the two sexes for the right and left caudate nucleus ($P>0.05$). Furthermore, the rate of reduction of the striatum volume (*age×sex*) was used to assess the degree of volume shrinkage with a span between 15 and 65 years old. For this region, there was a significant age-related decrease in the volumes of caudate for men and women. The observed volume reduction rate by age and sex for men were 4.9% and 4.5% and for women were 3.3% and 2.9% for the right and left caudate, respectively (Fig. 2, 3). Overall rate of decrease was less for women than men and interaction of gender with age was significant (for caudate $P=0.036$ and for putamen $P=0.008$) suggesting that the rates of caudate and putamen volume decrease with age are different between two sexes.

Table 1. Age distribution of the subjects, mean volumes, index asymmetry of caudate nucleus in men and women

	Male (mean ± SD)		**Female (mean ± SD)**	
	Young	**Old**	**Young**	**Old**
Age	27.10±7.25	50.27±6.35	27.23±8.03	52.40±8.10
Caudate				
Right	4.55±1.01	†3.63±0.52	4.34±0.78	†3.47±0.53
Left	4.37±0.92	†3.49±0.47	4.08±0.78	†3.32±0.44
Total	8.92±1.05	†7.12±0.85	8.42±1.40	†6.79±0.87

†Mean of old groups significantly different than mean of young groups (P<0.001)
‡The index of asymmetry significantly higher than young groups (P<0.05)

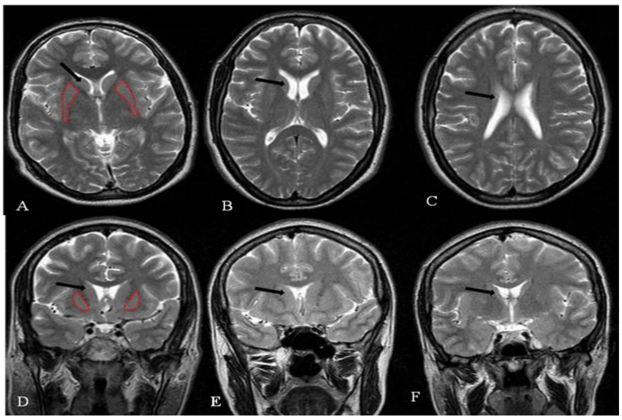

Figure 1. Segmentation method: example for caudate nucleus on a T_2-weighted MRI scan. (A-C) in the axial section and (D-F) in coronal section, the border of the putamen nucleus is traced on every slice and saved as an object mark (in red). The volume of the segmented object map is calculated in cubic centimeters for the right and left sides. Noted caudate nucleus in cross-sectional image (arrow).

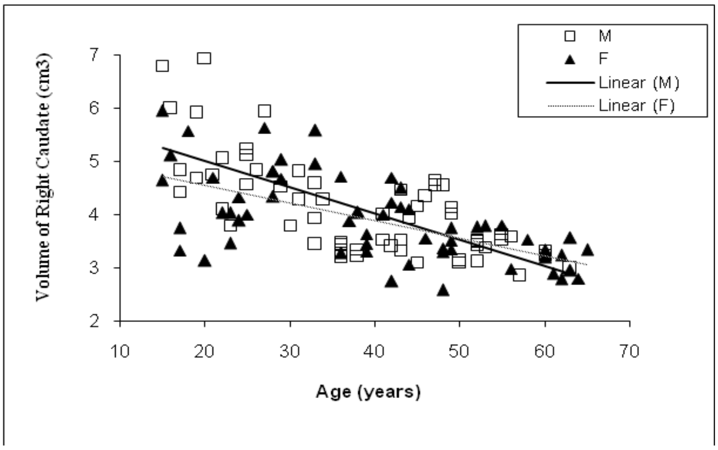

Figure 2. Scatter-plots and linear regression showing the negative relation between age and Right Caudate nucleus in men (open squares, solid regression line) and women (filled triangles, solid regression line).

DISCUSSION

In this study, we measured age- and gender-related changes of caudate nucleus volume in healthy subjects aged 15-65 years. Quantitative analysis of this study indicated that the volume of caudate nucleus was decreased with aging in both sexes. We also observed that age-related decrease in volume of caudate nucleus was steeper in men; on the other hand the shrinkage of caudate volume during aging in men was greater than women. Age was negatively correlated with caudate volume and bilateral atrophies of caudate nucleus with aging were found in both sexes. In accordance with our finding, Gunning- Dixon *et al*. showed an age-related decline of the head of the caudate [15] whereas; in this study the total volume of caudate nucleus calculated. This result showed higher correlation between age and the volume of caudate nucleus in men than women; on the other hand, men had a greater age-related reduction of caudate volume. The results of this study is consistent with results of kokkalainen *et al*, who indicated an age- related decrease in the all striatum volume but the volume decrease was not uniform [11]. In contrast to the study of Brabec *et al*, there were gender- related volume differences in caudate volume [16]. The precise etiology of age-related decline in the caudate volume is not entirely clear. The reduction in caudate volume such could be mediated by several processes, including neuronal and glial cell death especially dopaminergic neurons, restrict blood flow and progressive iron deposition [8, 17-20]. Pikrell *et al* showed that the striatum such as caudate nucleus is sensitive to defects in neuronal oxidative phosphorylation and has been associated with a variety of neurodegenerative diseases, including Parkinson's and Huntington's disease [17].

Cherabini *et al* suggests the possibility of free radical reactions catalyzed by iron deposition and contributing to neurodegenerative and volume decrease of striatum during life span [8]. Matochik *et al* suggested the striatum volume atrophy could result from age-related changes in the integrity of dopaminergic system and the dense dopaminergic input to the striatum [18]. According to this idea, they demonstrated the globus pallidus, which receives less dopuminergic input than the striatum, should show less volume reduction [18]. Raz *et al*. didn't found volume decline in the globus pallidus with age, too [12]. In another research, Yu ZQ *et al*. indicated that the dopamine content decreased in striatum of elderly rats and induces degeneration and death of neurons, which may offset the motor coordination ability observed in the elderly [19]. Unfortunately, MRI studies are unable to identify the mechanisms that are responsible for volume reduction, but they can provide complementary information into possible mechanisms for age-related decline in the volume of striatum. MRI studies in combination with advanced software and histological and biochemical examinations may improve prediction of aging in striatum related to disrupted motor function and balance in elderly. However the age–related decline was more rapid in men. Such accelerated age-related decline in men is thought to be contributed to more frequent and earlier onset of the motor abnormalities such as Parkinson's disease [21]. To our knowledge, there are few published reports on gender differences on the age- related changes in caudate. In our study, the effects of age on caudate atrophy were comparable for men and women; there were significant gender-related changes in the striatum volume. The accuracy and reliability of the current study might be due to wide range of age, embedding equal number of males and females in groups, large sample size and relatively small section thickness. The cause of gender differences in striatum atrophy with aging is still unclear and might be attributed to external and internal factors [9, 14]. Sex hormones may be more important on brain structure. For example, intranasal administration of progesterone and testosterone increased dopamine level and enhances the dopaminergic activity in neostriatum of male rats [22, 23].

CONCLUSION

In conclusion, our results confirmed age-related decline of the caudate nucleus. These data from normal subjects provide useful information to interpret changes in caudate structure in neuron degenerative conditions and understanding the behavioral changes with aging.

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