Article

# Age-Related Changes In Female and Male Cerebral Volumes

## A Study of Whole-Brain Tissue Using the Stereological Method

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**ABSTRACT**

The stereological techniques based on the Cavalieri methods are used in many studies to estimate volumes of anatomical structures in an unbiased fashion. This is a rapid, inexpensive approach that provides a correct volumetric calculation using magnetic resonance (MR) brain images. We investigated and age-sex-related volumetric changes in human brain using Cavalieri method. Three-dimensional MR imaging was obtained 120 healthy volunteers to 10 people from each age and gender-decade group. The Cavalieri method of modern design stereology was used to measure the cerebral volumes. To estimate this volume, the point counting approach was preferred. In our study, it was found that significant decreases in whole-brain volume (p<0.05) emerge progressively with increasing age. The most remarkable alteration was observed in older people's brain volume. There was significant volumetric effect of gender on normalized brain volumes. Furthermore, both women and men showed statistically significant asymmetries in hemisphere volume. This quantitative volumetric study demonstrated a possible normal increase and then decrease in brain volume from age 0 to 60 years in healthy subjects. The differences in the brain sizes between the male and female subjects may be mainly attributable to the differences in total brain volume. A better understanding of this process may help to distinguish normal age-related alterations from neurodegenerative diseases.

**Key Words:** brain volume, stereology, MR images, age-sex-related volumetric changes, developmental change

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## 1. Introduction

The quantitative assessment of brain volume is an increasingly important consideration in clinical studies and the treatment of diseases such as Alzheimer's, multiple sclerosis, and schizophrenia. For this reason, magnetic resonance imaging (MRI) technology has been used to perform morphometric studies on the brain (Odaci *et al.*, 2003; Elfaki *et al.*, 2011). Age-related changes in brain volume in healthy adult brains have also been of great interest in recent years, because the determination of normal age-specific brain volume values is very important when it comes to evaluating both pathological conditions and the normal aging process (Biegon*et al.*, 1994). The estimated results from such analyses have shown that age-related brain loss may vary in different brain regions, as well as according to hemisphere (Miller *et al.*, 1980; Coffey *et al.*, 1992) and sex (Xu *et al.*, 2000). Human cerebral volume estimation via stereological methods is based on MRI. One of these methods is Cavalieri method, which is a sampling technique used to generate mathematically unbiased estimates of the geometric objects of three-dimensional structures based on two-dimensional slices of the object. One of the most important quantitative parameters is volume, which represents important data in many research areas (Unal *et al.*, 2010a). The stereological method has been mathematically validated, and this method should be used to determine the volumetric effects of histopathologic materials.

In humans, normal aging can affect brain volumes in as life progresses (Drayer,

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1988). T2-weighted MRI measured brain volume decreases with increasing age, while sex differences affect human brain volume during progressive life; a decrease in brain volume correlates well with impaired cognitive function (Coffey *et al.*, 1998). However, the structural alterations that cause the development and progression of brain atrophy are not yet fully understood (Good *et al.*, 2001). Many studies have suggested that cerebral hemispheric symmetry or asymmetry of brain volume is related with an interaction between brain function and morphology (Watkins *et al.*, 2001). The aim of the present study was to investigate possible brain volume changes via stereological methods in normal adults and adolescents divided into 23 groups according to age and gender using MRI. In addition, we also compared age-dependent brain volumes in both hemispheres.

## 2. Materials and Methods

### *MRI*

A total of 120 subjects who visited the hospital for a personal health-screening program participated in this study. MRI (1,5-T MRI unit, Magneton Impact, Siemens Medical Systems) was obtained for 10 healthy volunteer visitors in each group (decade 1: age 0–10, decade 2: age 10–20; decade 3: age 20–30;decade 4: 30–40 age, decade 5:50–50; and decade 6:50–60). We used the turbo spin echo technique (TR 4,600 ms, TE 90 ms, FOV 201 x 230 mm, matrix 132 x 256.3 mm thick slices with a 1-2 mm gap, and three acquisitions) to obtain MRI whole-brain images, which thickness was approximately 5-6 mm. In this way, we obtained 15–16 images for each patient's whole brain. All measurements and estimations were performed on these images (Fig. 1).

### *MRI Stereological Estimations*

We used the Cavalieri method in modern design-based stereology to measure cerebral volumes. To perform the estimation, the point counting approach was preferred. Firstly, detailed systematic series of axial MRI (T1-weighed, TR/TE 400/10 msec) of 5 mm thickness were obtained throughout the whole brain of subjects. Secondly, to magnify the images, all MRI were projected on a screen using a projection machine, and then the images were evaluated with the point counting method (Gundersen, 1986; Gundersen *et al.*, 1988; Cruz-Orive and Weibel, 1990). We used the serial and parallel section techniques with a known distance of these images to estimate the considered objects' volumes correctly; this method is first important rule for stereology (Gundersen, 1986; Gundersen *et al.*, 1988; Cruz-Orive and Weibel, 1990). We performed a pilot study before beginning the study to set both the coefficient of error (CE) and variation, as well as to modify our approach using the imaging technique according to stereological principles and determine the slice thickness from considered object. We applied the systematic Random Sampling, while the samples were chosen and all interest object images were evaluated using stereological methods (Mackay *et al.*, 1999).

Images obtained from the objects considered were projected onto a screen using a projector (Braun Paxiscope 650) (Figure 1). A point grid was employed for cerebral volume estimations, and the grid points were equally spaced (0.5 cm) both across and down. The grid point density was determined as a serial MRI number, which was taken as the CE. The CE was calculated according to formula of Gundersen and Jensen, and 13–15 cerebral images were used to measure cerebral volumes.

The point grid was randomly placed on the MRI to measure the area of interest and count how many points hit the region of interest according to the constant rule. The results were then used to compute the volume (Fig. 2).

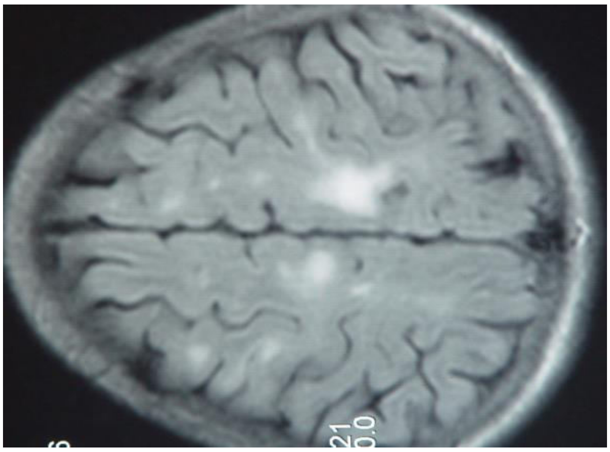

**Figure 1.** Images of interest were projected onto a screen using a projector

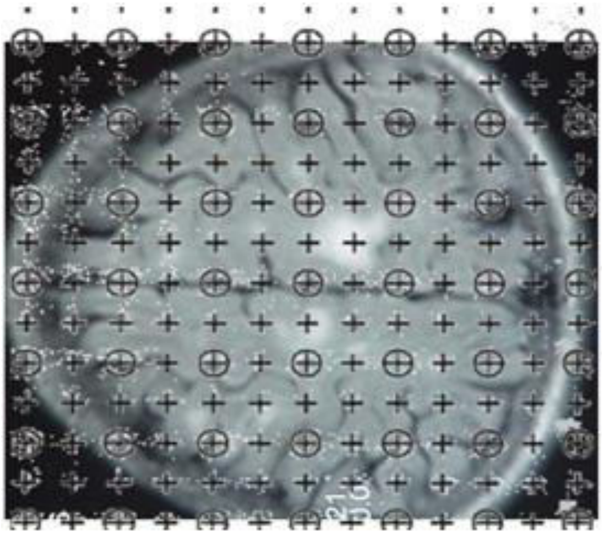

**Figure 2.** Estimation of the area of the slice using a transparent point grid

The test point of grid area was *a* cm² and the size was *k* cm² (*a* cm² = *k* x *k* cm²). We calculated the MRI and overhead projector magnifications, and then multiplied by the magnification of the calculated values (cm²):

$$\text{Volume} = t\ (\text{cm}) \times a/p\ (\text{cm} \times \text{cm}) \times ((\sum P)\ \text{cm}^3$$

Here, V is the volume of the object of interest object in one section plane, t is the section thickness, a/p is the inter point area, and ΣP is the number of points touching the area of interest in that section (Gundersen *et al.*, 1988). The volumes for each section were estimated by the above formula and the sum of total brain volumes was estimated by the formula given below:

$$\text{Total Volume} = V_1 + V_2 + ... + V_n$$

The CE of the volume was estimated due to the combined effects of sectioning and point counting (GundersenandJensen, 1987). The formula for CE estimation is as follows:

$$Noise = 0.0724 \times (b/\sqrt{a}) \times \sqrt{n \times \sum P}$$

Here, Noise represents the sample section near-surface reflection data, $b/\sqrt{a}$ denotes the average length of the boundary divided by the square root of the average area of the boundary, n is the number of slices of interest, and ΣP is thetotalnumber of points hitting the object of interest.

$$Var_{SRS}(\sum_{i=1}^{n} a) = (3 \cdot (A - Noise) - 4 \cdot B + C)/12$$

SRS in this equation stands for systematic random sampling. Here,

$$Var_{SRS}(\sum_{i=1}^{n} a)$$

is the variation in total area. These data gave us information about what number of slices would be sufficient. A, B, and C are shown in the columns in Table 1.

$$TotalVar = Noise + Var_{SRS}$$

$$CE(\sum P) = \frac{\sqrt{Total\ Var}}{\sum P}$$

$$Noise = 0.0724 \times (b/\sqrt{a}) \times \sqrt{n \times \sum P}$$

$$= 0.0724 \times 5 \times \sqrt{227 \times 10} = 17.25$$

$$Var_{SRS}(\sum_{i=1}^{n} a) = (3 \times (A - Noise) - 4 \times B + C)/12$$

$$= (3 \times (5251 - 17.25) - 4 \times 4783 + 4371)/12 = 78.35$$

$$Total\ Var = Noise + Var_{SRS} = 17.25 + 78.35 = 95.6$$

$$CE(\sum P) = \frac{\sqrt{Total\ Var}}{\sum P} = \frac{\sqrt{95.6}}{227} = 0.043$$

$$\text{Volume} = t \times a/p \times ((\sum P) - (1/2))$$

$$= 1 \times 3.642 \times (289.3 - 16) = 995.48 cm^3$$

## *Statistical Analyses*

For statistical analysis, differences between the decades were tested by the analysis of variance (ANOVA) and paired samples test using SPSS 17.0 for Windows XP (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was considered significant.

## 3. Results

In this study, the brain volumes of healthy men and women in all age-decade groups were shown in Table 2.

Firstly, the average cerebral volumes of subjects' of the same age and gender were compared with those of older groups of the same gender for all age-decade groups. The same comparison was applied to both sexes (Table 3). With the exception of the last comparison for males, the pairs of comparisons showed a statistically significant difference ($p<0.05$).

Secondly, age-dependent average cerebral volume in the same group was compared by gender. The average brain volume difference was 6.36% for males; all pairs of comparisons were shown in Table 4.

When the right and left hemisphere volumes were compared in groups from the same decade, the pair of group comparisons and the results were seen in Table 5. When the male and female right and left hemispheres volumes were compared according to gender, all comparisons except males in decade 6 and females in decade 1 showed a statistically significant difference; the comparisons were seen in Table 5.

**Table 1.** In this study, estimates of brain volumes were generated according to the sampling strategy procedure.

| Section No | $P_i$ | $P_i$ x $P_i$ | $P_i$ x $P_{i+1}$ | $P_i$ x $P_{i+2}$ |
|---|---|---|---|---|
| 1 | 20 | 400 | 440 | 460 |
| 2 | 22 | 484 | 506 | 528 |
| 3 | 23 | 529 | 552 | 667 |
| 4 | 24 | 576 | 696 | 600 |
| 5 | 29 | 841 | 725 | 725 |
| 6 | 25 | 625 | 625 | 525 |
| 7 | 25 | 625 | 525 | 425 |
| 8 | 21 | 441 | 357 | 441 |
| 9 | 17 | 289 | 357 | 0 |
| 10 | 21 | 441 | 0 | 0 |
| | **227** | **5251** | **4783** | **4371** |

**Table 2.**Male and female average brain volumes.

| | Female (N:10) | Male (N: 10) |
|---|---|---|
| **1st decade** | 1404.358 $cm^3$ | 1415.296 $cm^3$ |
| **2nd decade** | 1592.826 $cm^3$ | 1613.766 $cm^3$ |
| **3th decade** | 1650.087 $cm^3$ | 1769.144 $cm^3$ |
| **4th decade** | 1423.788 $cm^3$ | 1505.39 $cm^3$ |
| **5th decade** | 1282.099 $cm^3$ | 1452.987 $cm^3$ |
| **6th decade** | 1267.135 $cm^3$ | 1409.906 $cm^3$ |

**Table 3.**Comparison of female and male cerebral volume in older groups.

| Group | Difference One Way ANOVA |
|---|---|
| **1st decade / 2nd decade female** | (P<0.05) |
| **2nd decade / 3th decade female** | (P<0.05) |
| **3th decade / 4th decade female** | (P<0.05) |
| **4th decade / 5th decade female** | (P<0.05) |
| **5th decade / 6th decade female** | (P>0.05) |
| **1st decade / 2nd decade male** | (P<0.05) |
| **2nd decade / 3th decade male** | (P<0.05) |
| **3th decade / 4th decade male** | (P<0.05) |
| **4th decade / 5th decade male** | (P<0.05) |
| **5th decade / 6th decade male** | (P>0.05) |

In this study, we also investigated the difference between the total cerebral right hemisphere volumes by gender; the difference was 8.20% in favor of the male right hemisphere. The groups comparisons are shown in Table 6.Similar results were obtained from comparisons of the total cerebral left hemisphere volumes by gender; the difference was 3.68% in favor of the male left hemisphere. The group comparisons are shown in Table 7.

**Table 4.** Comparison of the same age groups' total brain volumes by sex.

| Group | Difference – **One way ANOVA, *all p value*** |
|---|---|
| **1st decade male/ 1st decade female** | 0.06% (on behalf of male. P>0.05) |
| **2nd decade male/ 2nd decade female** | 1.30% (on behalf of male. P<0.05) |
| **3th decade male/ 3th decade female** | 7.23% (on behalf of male. P<0.05) |
| **4th decade male/ 4th decade female** | 5.74% (on behalf of male. P<0.05) |
| **5th decade male/ 5th decade female** | 13.35% (on behalf of male. P<0.05) |
| **6th decade male / 6th decade female** | 11.44% (on behalf of male. P<0.05) |

When female subjects' age-dependent cerebral left hemisphere volumes were compared to those of the older female groups, all groups were statistically significantly different from one another (one-way ANOVA, p<0.05).The group comparisons are shown in Table 8.When female age-dependent cerebral right hemisphere volumes were compared to the older female groups, all groups comparisons except decade 5/decade 6 comparisons were statistically significantly different from each other (one-way ANOVA, p<0.05).The group comparisons are shown in Table 9.

In the same way, male cerebral left hemispheres were compared to those of the older male groups. All group comparisons except decade 5/decade 6 were statistically significantly different from the other group comparisons (one-way ANOVA, p<0.05). The group comparisons are shown in Table 10.When male subjects' right hemispheres were compared to those of males in the older groups, all comparisons except decade 5/decade 6 were statistically significantly different (one-way ANOVA, p<0.05). The group comparisons are shown in Table 11.

**Table 5.** Comparison of male and female cerebral volumes by hemisphere volumes.

| Group | Left | Right | Difference |
|---|---|---|---|
| 1st decade female left/right | 701.199 $cm^3$ | 703.159 $cm^3$ | 0.28% (on behalf of right hemisphere. P>0.05) |
| 2nd decade female left/right | 817.745 $cm^3$ | 775.081 $cm^3$ | 5.28% (on behalf of left hemisphere. P<0.05) |
| 3th decade female left/right | 833.285 $cm^3$ | 816.802 $cm^3$ | 1.98% (on behalf of left hemisphere. P<0.05) |
| 4th decade female left/right | 721.605 $cm^3$ | 702.183 $cm^3$ | 2.7% (on behalf of left hemisphere. Test. P<0.05) |
| 5th decade female left/right | 653.991 $cm^3$ | 628.108 $cm^3$ | 3.96% (on behalf of left hemisphere. P<0.05) |
| 6th decade female left/right | 641.456 $cm^3$ | 625.679 $cm^3$ | 2.46% (on behalf of left hemisphere. P<0.05) |
| 1st decade male left/right | 699.651$cm^3$ | 715.645 $cm^3$ | 2.28% (on behalf of right hemisphere. P<0.05) |
| 2nd decade male left/right | 797.374$cm^3$ | 816.392 $cm^3$ | 2.38% (on behalf of right hemisphere. P<0.05) |
| 3th decade male left/right | 876.575$cm^3$ | 892.569 $cm^3$ | 1.82% (on behalf of right hemisphere. P<0.05) |
| 4th decade male left/right | 743.757 $cm^3$ | 761.633 $cm^3$ | 2.4% (on behalf of right hemisphere. P<0.05) |
| 5th decade male left/right | 718.944 $cm^3$ | 734.043 $cm^3$ | 2.1% (on behalf of right hemisphere. P<0.05) |
| 6th decade male left/right | 699.767 $cm^3$ | 710.139 $cm^3$ | 1.48% (on behalf of right hemisphere. P>0.05) |

**Table 6.** Comparison of the same age groups' right hemisphere by sex.

| Group | Difference<br>Paired Samples Test. One way ANOVA |
|---|---|
| 1st decade male right/female right brain volume | 1.75% (on behalf of male right hemisphere. P<0.05) |
| 2nd decade male right/female right brain volume | 5.07% (on behalf of male right hemisphere. P<0.05) |
| 3th decade male right/female right brain volume | 8.49% (on behalf of male right hemisphere. P<0.05 |
| 4th decade male right/female right brain volume | 7.81% (on behalf of male right hemisphere. P<0.05) |
| 5th decade male right/female right brain volume | 14.44% (on behalf of male right hemisphere. P<0.05) |
| 6th decade male right/female right brain volume | 11.9% (on behalf of male right hemisphere. P<0.05) |

**Table 7.**Comparison of the same age groups' left hemisphere by sex.

| Group | Difference<br>Paired Samples Test. One way ANOVA |
|---|---|
| 1st decade female left /1st decade male left brain volume | 0.22% (decreased left hemisphere volume on behalf of female. P>0.05) |
| 2nd decade female left / 2nd decade male left brain volume | 2.55% (decreased left hemisphere volume on behalf of female. P<0.05) |
| 3th decade female left /3th decade male left brain volume | 4.94% (increased left hemisphere volume on behalf of male. P<0.05) |
| 4th decade female left /4th decade male left brain volume | 2.98% (increased left hemisphere volume on behalf of male. P<0.05) |
| 5th decade female left /5th decade male left brain volume | 9.94% (increased left hemisphere volume on behalf of male. P<0.05) |
| 6th decade female left /6th decade male left brain volume | 8.34% (on behalf of male left hemisphere. P<0.05) |

**Table 8.** Comparison of female left cerebral hemispheres in older groups.

| Group | Difference |
|---|---|
| 1st decade female left/2nd decade female left brain volume | 16.62% (increased volume on behalf of older age group. P<0.05) |
| 2nd decade female left/3th decade age female left brain volume | 1.9% (increased volume on behalf of older age group P<0.05) |
| 3th decade female left/4th decade female left brain volume | 13.41% (decreased volume on behalf of older age group. P<0.05). |
| 4th decade female left/5th decade female left brain volume | 9.37%(decreased volume on behalf of older age group P<0.05). |
| 5th decade female left/6th decade female left brain volume | 1.92% (decreased volume on behalf of older age group. P<0.05) |

**Table 9.** Comparison of female right cerebral hemispheres in older groups.

| Group | Difference |
|---|---|
| 1st decade female right/2nd decade female right brain volume | 10.23% (increased volume on behalf of older age group. P<0.05) |
| 2nd decade female right/3th decade female right brain volume | 5.38% (increased volume on behalf of older age group. P<0.05) |
| 3th decade female right/4th decade female right brain volume | 16.32% (decreased volume on behalf of older age group. P<0.05). |
| 4th decade female right/5th decade female right brain volume | 11.20% (decreased volume on behalf of older age group. P<0.05). |
| 5th decade female right/6th decade female right brain volume | 0.49% (decreased volume on behalf of older age group. P>0.05) |

**Table 10.** Comparison of male left cerebral hemispheres in older groups.

| Group | Difference |
|---|---|
| 1st decade male left/2nd decade male left brain volume | 12.26% (increased volume on behalf of older age group. P<0.05) |
| 2nd decade left/3th decade male left brain volume | 9.04%(increased volume on behalf of older age group. P<0.05) |
| 3th decade male left/4th decade left brain volume | 17.85% (decreased volume on behalf of older age group. P<0.05). |
| 4th decade male left/5th decade male left brain volume | 3.45% (decreased volume on behalf of older age group. P<0.05). |
| 5th decade male left/6th decade male left brain volume | 2.75% (decreased volume on behalf of older age group. P>0.05) |

**Table 11.** Comparison of male right cerebral hemispheres in older groups.

| Group | Difference, One way ANOVA |
|---|---|
| 1st decade male/2nd decade male right brain volume | 14.07% (increased volume on behalf of older group. P<0.05) |
| 2nd decade male/3th decade male right brain volume | 9.33% (increased volume on behalf of older group. P<0.05) |
| 3th decade male /4th decade male right brain volume | 14.66% (decreased volume on behalf of older group. P<0.05) |
| 4th decade male /5th decade male right brain volume | 3.62% (decreased volume on behalf of older group. P<0.05) |
| 5th decade male /6th decade male right brain volume | 3.25% (decreased volume on behalf of older group. P>0.05) |

## 4. Discussion

In this study, we measured both male and female cerebral volumes in healthy subjects aged 0–60 years and evaluated the data by age, sex, and hemisphere. The results showed patterns of age-related changes in male and female brain volumes via the Cavalieri method (Table 2). The female brain volume results can be summarized as follows: A regular and constant increase was observed in cerebral volumes from decade 1 to decade 4, but cerebral volume started to decrease from decade 4 to decade 6. All group differences were statistically significant ($p<0.05$). In male subjects, brain volumes constantly increased in decade 1 to decade 3, but decreased from decade 4 to decade 6. Except for decade 5/decade 6, all group comparisons exhibited statistical significance ($p<0.05$) (Table 3). In some research, while brain volume and weight have been found to change according to age and gender, brain ventricles are expanded (Anderton, 1997; Anderton, 2002). We found similar results in our study, but the decade 5 and decade 6 groups exhibited decreased brain volumes. In addition, the brain volumes increased to decade 3, then decreased by small amounts ($p>0.05$).

Some researchers have tried to clarify whether neuronal pigmentation and granulovascular degeneration are related to brain volume changes (Ball, 1977). One stereological study found that total brain volume was increased by 15% and myelination nervous fibrils were increased by 17% in adolescents when compared to adult subjects (Tang *et al*., 1997).The findings from the study showed a linear decrease of 0.31% of total brain volume per year in subjects at an average age of 73 years (Ikram *et al*., 2008). A parallel decrease of 0.3% per year was reported in the population-based WHICAP cohort of people aged an average of 80 years (Brickman *et al*., 2008). Some related studies have shown that the myelination of nervous fibrils decreased at 30% with increasing age, but this alteration showed differences between sexes (Marner *et al*., 2003).Sex-dependent degenerative changes affected female subjects less than male subjects; the reason for this is that female gonadal hormones have a neuroprotective effect on the nervous system (Unal *et al*., 2010b). Our study results are in accordance with these findings.

One stereological study reported that investigated the cerebrum (cortex, basal ganglions, thalamus, and white matter), cerebellum, and lateral ventricle volumes of 32 female and 32 male subjects aged 74–87 over four years. It was shown that cerebral volumes decreased 2.1% per year, lateral ventricles volumes expanded 5.6% per year, and the progression of cerebral atrophy was statistically significant by sex (Tang *et al*., 2001). In our study, brain volumes showed a linear increase with age in adolescents, and then a decrease that was stronger in men than in women. The linear decrease of brain volume has also reported in other studies (DeCarli *et al*., 2005).

Researchers have been trying to clarify the differences between the male and female cortical functions for decades. Therefore, the present study investigated the relationship between hemispheric asymmetries and morphological changes between sexes (Harshman and Remington, 1976; Shaywitz *et al*., 1995; Hirnstein *et al*., 2010). The relationship between hemispheresis linearly is positive, because hemispheric asymmetries originate in better cognitive processing. However, the experimental data supporting this concept are mixed, and the statistical methods to analyze this relationship have been assessed. When the brain's morphological structure was evaluated in relation to sexual dimorphism, sexual dimorphism was found in the corpus callosum, or splenium, and this asymmetry appeared in the decade 4 and older age groups (Dubb *et al*., 2003); the male brain volumes decreased to a lesser extent than those of females in adult subjects(Gur *et al*., 2002). These findings showed that degenerative changes varied by sex (Kertesz *et al*., 1990). Sex-dependent degenerative changes did not appear in early adolescence, however, and the study indicated that male and female brain volumes begin to change at the age of 10 years (Giedd *et al*., 1997). The brain volume changes between the sexes observed in the present study might be the result of hormonal activity in the body. In our study, we found similar results, where in the male and female subjects' brain volumes started to change at 10 years old. Compared to decade 1total brain volumes by sex, no statistically significant difference was determined in groups between the sexes. However, the male and female brain volume difference increased in relation to increasing age.

Age-dependent male and female brain volumes have been reported to be different from each other, and male brain volumes have been found to be higher than female brain volumes in many studies (Giedd *et al*., 1997). This finding is in accordance with our results, where in male and female brain volumes exhibited a statistically significant difference in favors of male.

As far as hemispheric asymmetries are concerned, according to our method, the brain showed volumetric differences by hemisphere as well as sex. While male right hemisphere volumes were higher than left hemisphere volumes, female left hemisphere volumes were higher than right hemisphere volumes. Although some studies support this notion (Gur *et al*., 1991), others have reported results that are contrary to our findings (Sullivan *et al*., 2001; Gur *et al*., 2002).

## 5. Conclusion and Outlook

This quantitative volumetric study demonstrated a possible normal increase followed be a decrease of brain volume across adult life, from 0–60 years, in healthy subjects. The volume changes in different decades indicate that brain volume increase occurs in a linear pattern starting from early adolescence (0–10 years), whereas brain volume decrease occurs in early adulthood (30–40 years). These alterations illustrate processes of both brain maturation and aging during adult and adolescent life, and they may be taken as targets in evaluating pathological conditions such as atrophy with increasing age. Differences in brain sizes between male and female subjects may be mainly attributable to differences in total brain volume. A better understanding of this process may help to distinguish normal age-related alterations from neurodegenerative diseases.

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