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ORIGINAL ARTICLE

Volumetric evaluation of the relations among the cerebrum, cerebellum and brain stem in young subjects: a combination of stereology and magnetic resonance imaging

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Abstract The Cavalieri estimator using a point grid is used to estimate the volume of three-dimensional structures based on two-dimensional slices of the object. The size of the components of intracranial neural structures should have proportional relations among them. The volume fraction approach of stereological methods provides information about volumetric relations of the components of structures. The purpose of our study is to estimate the volume and volume fraction data related to the cerebrum, cerebellum and brain stem. In this study, volume of the total brain, cerebrum, cerebellum and brain stem were estimated in 24 young Turkish volunteers (12 males and 12 females) who are free of any neurological symptoms and signs. The volume and volume fraction of the total brain, cerebrum, cerebellum and brain stem were determined on magnetic resonance (MR) images using the point-counting approach of stereological methods. The mean (±SD) total brain, cerebrum and cerebellum volumes were 1,202.05 ± 103.51, 1,143.65 ± 106.25 cm^3 in males and females, 1,060.0 ± 94.6, 1,008.9 ± 104.3 cm^3 in males and females, 117.75 ± 10.7, 111.83 ± 8.0 cm^3 in males and females, respectively. The mean brain stem volumes were 24.3 ± 2.89, 22.9 ± 4.49 cm^3 in males and females, respectively. Our results revealed that female subjects have less cerebral, cerebellar and brain stem volumes compared to males, although there was no statistically significant difference between genders ($P > 0.05$). The volume ratio of the cerebrum to total brain volume (TBV), cerebellum to TBV and brain stem to TBV were 88.16 and 88.13% in males and females, 9.8 and 9.8% in males and females, 2.03 and 2.03% in males and females, respectively. The volume ratio of the cerebellum to cerebrum, brain stem to cerebrum and brain stem to cerebellum were 11.12 and 11.16% in males and females, 2.30 and 2.31% in males and females, 20.7 and 20.6% in males and females, respectively. The difference between the genders was not statistically significant ($P > 0.05$). Our results revealed that the volumetric composition of the cerebrum, cerebellum and brain stem does not show sexual dimorphism.

Keywords Brain · Cerebellum · Brain stem · Magnetic resonance imaging · Stereology · Cavalieri principle · Point-counting

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Introduction

Several studies focused on the determination of brain compartments and their gender differences [2, 3, 6, 9] There are some of studies showing that the volume of intracranial neural structures do not show sexual dimorphism [4, 21].

However, a huge amount of study revealed that the volumes of neural structures are bigger in males than females [1, 6, 15, 19]. The main reason for the sexual dimorphism is the males have bigger body size than the females. In the light of this available knowledge, we can say that the brain size of a subject is closely related to the body size of subject. However, proportional relations of the volume of neural structures may have a constant value which are independent of the body size of the subjects.

The volume and volume fraction approach of stereological methods provides information about volumetric relations of the components of structures [5, 13, 29]. The requirement for the application of this method is an entire set of two-dimensional slices through the object, provided they are parallel, separated by a known distance, and begins randomly within the object, criteria that are met by standard MR imaging and CT scanning techniques [27, 30].

We presume that the size of the components of intracranial neural structures should have proportional relations among them. However, we have not been able to find any study evaluating the volume relation among the intracranial neural structures. In the present study we evaluated the volume relation of cerebellum, brain stem, cerebrum and total brain volume (TBV) using the volume and volume fraction approach of modern stereological methods.

Materials and methods

Estimation of volume by the Cavalieri principle

It is known that the volume of regular-shaped objects (i.e., prism, cube, cylinder) can be estimated by the following formula [22, 32]:

$$V = t \times a, \tag{1}$$

where (t) is the height and a is the base area of the object. Similar to this approach, using the Cavalieri principle, an unbiased estimated volume of an object of arbitrary shape and size may be obtained efficiently and with a known precision [19]. The method requires sectioning of the structure with a series of parallel planes. To avoid bias, the first section must be placed at a uniform and random position in a constant interval of length, and the series of sections must encompass the object entirely. Thus, an unbiased estimate of volume can be obtained by multiplying the total area of the section-cut surfaces by the mean section thickness.

The formula could be rewritten for the radiological studies regarding the reduction ratio of the printed films and point density of the grids as follows:

$$V = t\left[\frac{\mathrm{SU} \times d}{\mathrm{SL}}\right]^2 \sum P \tag{2}$$

where t is the sectioning interval for n number of consecutive sections, SU is the scale unit of the printed film, d is the distance between the test points of the grid, SL is the length of the scale printed on the film and $\sum P$ is the total number of points hitting the section cut surface areas.

The coefficient of error (CE) of volume estimations was done using the formula that is reported by Gundersen and Jensen [10]. The coefficient of variation (CV) of volume was calculated using the approach that is described in the literature [11, 23, 34]. All calculations and other related data were obtained as a spreadsheet using Microsoft Excel. After initial setup and preparation of the formulas, the point counts, formulas and other data were entered for each subject and the final data were obtained automatically.

Volume fraction

The volume of biological structures can be estimated by combining the sectional radiological imaging techniques with the Cavalieri principle of stereological volume estimation as described in the previous studies [22, 31, 32]. The human brain does, however, vary widely in size [14]. To date, scientists have documented several factors that contribute to this variation. Factors related to brain growth, such as gender and physical size, are thought to influence the maximal size of an individual's brain [24, 33]. The volume fraction of a component within a reference volume is a simple and very widely used parameter in biomedical science [12, 17, 18]. Thus it is used to express the proportion of a phase or component within the whole structure. The volume fraction of an X phase within a Y reference volume is simply expressed as follows:

$$V_V(X, Y) = \frac{\text{Volume of } X \text{ phase in } Y \text{ reference space}}{\text{Volume of } Y \text{ reference space}} \tag{3}$$

where the V_V (X,Y) indicates volume fraction of X phase within the Y reference volume. Using this approach, V_V (hippocampus, brain), V_V (alveoli, lung) and V_V (tumor, liver) can be estimated. Volume fraction ranges from 0 to 1 and is often expressed as a percentage [21].

The volume fraction of a phase can be estimated by means of the Cavalieri principle on radiological images using point-counting approach [20]. The volume fraction formula with the combination of Cavalieri principle can be written as follows:

$$V_V(X, Y) = \frac{V_X = t \times [((\mathrm{SU}) \times d)/\mathrm{SL}]^2 \times \sum P_X}{V_Y = t \times [((\mathrm{SU}) \times d)/\mathrm{SL}]^2 \times \sum P_Y} \tag{4}$$

where 't' is the sectioning interval for n consecutive sections, SU is the scale unit of the printed film, d is the distance between the test points of the grid, SL is the measured length of the scale on the printed film and ΣP_x indicates the number of points hitting the X phase and ΣP_y the number of points hitting the reference space Y.

Since the same images are used for the volume fraction estimation of any subject, the number of the points counted (i.e., ΣP) is the only value of the volume fraction formula, which changes. Thus, the formula can be simply changed to:

$$V_V(X,Y) = \frac{\sum P_X}{\sum P_Y} \quad (5)$$

where, ΣP_X indicates the number of points hitting the X phase and ΣP_Y the number of points hitting the reference space, i.e., Y. Usually, the phase within the reference space is smaller in size.

In this case, the use of a simple point-counting grid can provide sufficient sampling opportunity for the section-cut surface area of the reference space, but not for the phase. The combined point-counting grids (CPCG) could be used to give equal sampling opportunity to both of them. A combined point-counting grid is composed of two sets of points of different densities on the same grid. Figure 1 illustrates a CPCG that has four fine points (crosses and encircled crosses) per coarse point (i.e., encircled crosses only). We can describe this grid as a CPCG with 1/4 area fraction. The area per point associated with each coarse point is thus four times larger than that of each fine point; one should consider that encircled points are used as both fine and coarse points. The volume fraction of a component within the organ can be estimated by placing the CPCG over the section series, counting the number of coarse points that hit the reference space including the phase, and counting the number of all points hitting only the phase. As the ratio of fine to coarse points is 1/4, a slightly modified version of the Eq. 3 can be used to estimate the volume fraction of a component within the subject.

$$V_V(X,Y) = \frac{\sum P_X}{4 \times \sum P_Y} \quad (6)$$

In the new formula, none of the parameters in the volume estimation equation is required except the number of points hitting the phase and the reference space. This new

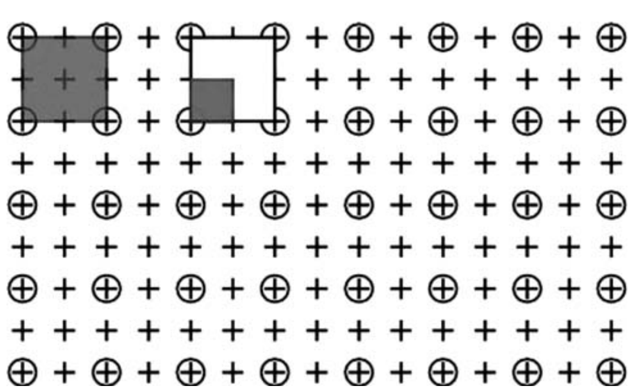

Fig. 1 A combined point-counting grid with 1/4 area fraction. While an *encircled cross* represents a large area, each cross without regarding the encircle represent 1/4 fraction of the large areas

approach is not affected by the reduction/magnification ratio of the images for each group.

Subjects

We carried out the present study on 24 subjects consisting of 12 females and 12 males. The mean (±SD) age of the male group was 20.7 (±2.1) years, while the mean age in the female group was 20.4 (±2.8) years. The male and female groups ages were statistically matching.

The subjects were normal volunteers and written informed consent was taken. Official permissions are also taken from the responsible departments of the university and state hospital administrators. All procedures were fully explained to the subjects. Through history-taking alcohol consumption as well as physical and neurological examinations, the individuals with possible neurological abnormalities were excluded.

We analyzed neurologically intact cranial MR images of the all subjects. We used the protocol which was used for the accumulated MR imaging data. T2-weighted sagittal images using a 0.5 Tesla MR machine (Gyroscan T5 II Vision, Philips, Netherlands) were obtained. The following parameters were used for the imaging process; TR/TE: 3000/120; two excitations, FOV: 250/1.1, 5-mm thickness with a 0.1-mm gap between slices and 250 × 256 matrix.

Estimation of cerebellum and brain stem to brain volume fraction [V_V (cerebellum and brain stem, brain)]

The MR images of a section series with 5-mm thicknesses without interval were used to estimate cerebellum, brain stem and cerebral volumes. These images were printed on films in frames measuring 6 × 8 cm.

The MR images were used to estimate volume fraction of cerebrum, cerebellum and brain stem within the total brain volume (TBV) using a CPCG with 1/4 area fraction, i.e., $d = 0.20$ cm. The films were placed on a light bow and the CPCG was superimposed, randomly covering the entire image frame (Fig. 1). While only the encircled points (i.e., $d = 0.4$ cm) hitting the cerebral hemispheres including the cerebellum and brain stem were counted as an estimate of the reference space (i.e., total brain volume), all points with and without a circle (i.e., $d = 0.20$ cm) hitting the cerebellum and brain stem were counted to estimate volume fraction of cerebellum and brain stem within the cerebral hemisphere [i.e., V_V (cerebellum, brain)] (Fig. 2). The cerebellum to volume fraction value was estimated by means of the following formula.

$$V_V(\text{cerebellum, brain}) = \frac{\sum P_{\text{cerebellum}}}{4 \times \sum P_{\text{totalbrain}}} \quad (7)$$

where $\Sigma P_{\text{cerebellum}}$ is the total number of points hitting the cerebellar surface area and $\Sigma P_{\text{total brain}}$ is the total number

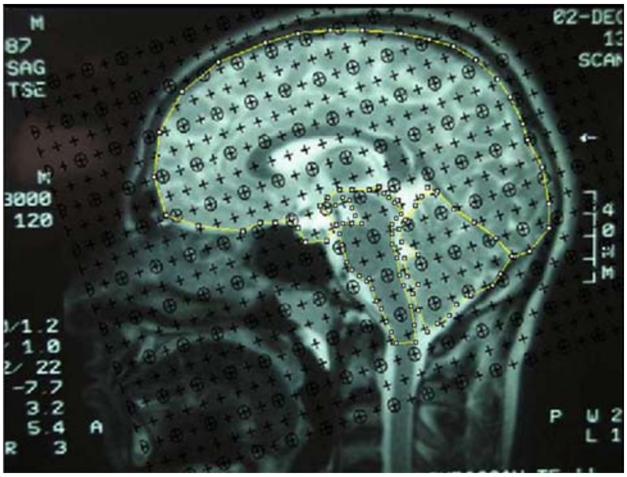

Fig. 2 A sagittal MR scan with a point-counting grid superimposed on it for the estimation of volume and volume fraction of the brain components

of points hitting the total cerebral hemispheres. The value obtained is the volume fraction of the cerebellum to the cerebral hemispheres expressed as a percentage.

The total brain volume (TBV), and the components of other structures, i.e., cerebrum, cerebellum and brain stem volumes were also estimated using the Cavalieri principle of the stereological methods as described in previous studies [22, 31, 32].

Statistics

Values are expressed in terms of the mean and standard deviation (±SD). The volumes of cerebellum, brain and brain stem were compared between the genders using independent *t* test. Pearson correlation test was also applied to see the relation between the results of volume estimates. A P value lower than 0.05 was accepted as being statistically different.

Results

The mean (±SD) total brain volumes (TBV) were 1,202.05 ± 103.51, 1,143.65 ± 106.25 cm^3 in males and females, respectively. The mean (±SD) cerebrum volumes were 1,060.0 ± 94.6, 1,008.9 ± 104.3 cm^3 in males and females, respectively. The mean (±SD) cerebellar volumes were 117.75 ± 10.7, 111.83 ± 8.0 cm^3 in males and females, respectively. Finally, the mean (±SD) brain stem volumes were 24.3 ± 2.89, 22.9 ± 4.49 cm^3 in males and females, respectively (Table 1). Our results revealed that female subjects have less brain, cerebellar and brain stem volumes then males. However, the differences did not rise to a statistically significant level between the values of males and females ($P > 0.05$).

The volume ratio of the cerebrum to total brain volume (TBV), cerebellum to TBV and brain stem to TBV were 88.16 and 88.13% in males and females, 9.8 and 9.8% in males and females, 2.03 and 2.03% in males and females, respectively. The volume ratio of the cerebellum to cerebrum, brain stem to cerebrum and brain stem to cerebellum were 11.12 and 11.16% in males and females, 2.30 and 2.31% in males and females, 20.7 and 20.6% in males and females, respectively. The difference between the genders was not statistically significant ($P > 0.05$), (Table 2). However, there was a correlation between cerebellar and cerebral volumes ($r = 0.612$, $P < 0.001$), between cerebral volume and TBV ($r = 0.996$, $P < 0.001$), between cerebellar volume and TBV ($r = 0.676$, $P < 0.001$). On the contrary, the brain stem volume was not correlated with the volume of TBV, cerebrum and cerebellum.

The mean time (±SD) needed to estimate the cerebellar, cerebral and brain stem volumes and volume fractions using the point-counting technique was 7 ± 3.6 min, with a range of 4–11 min. The mean of CEs (±SEM) for the estimation of cerebral, cerebellar and brain stem volumes were 0.01 ± 0.001, 0.02 ± 0.002 and 0.06 ± 0.009, respectively.

Discussion

The volume of biological structures can be estimated using the sectional radiological imaging techniques and the Cavalieri principle of stereological volume estimation as described in previous studies [23, 25]. The human brain does, however, vary widely in size [14]. Until now, scientists have revealed many of the factors that contribute to this variation. Factors related to brain growth, such as gender and physical size, are thought to influence the maximal size of an individual's brain [24, 33]. Comparing solely the brain volumes or the volumes of other intracranial structures between two groups (i.e., control and experimental groups) will not provide reliable data [14]. In

Table 1 Mean (±SD) volumes of TBV, cerebrum, cerebellum and brain stem for both sexes and the statistical data (independent *t* test)

Genders	TBV (cm^3)	Sig.	Cerebrum (cm^3)	Sig.	Cerebellum (cm^3)	Sig.	Brain stem (cm^3)	Sig.
Male	1,202.05 ± 103.5	0.186	1,060 ± 94.6	0.222	117.75 ± 10.77	0.142	24.3 ± 2.89	0.375
Female	1,143.65 ± 106.2		1,008.91 ± 104.38		111.83. ± 8.04		22.9 ± 4.49	

Table 2 Volume ratios between TBV, cerebrum, cerebellum and brain stem

	Cerebrum/TBV		Cerebellum/TBV		Brain stem/TBV	
Genders	Male	Female	Male	Female	Male	Female
Ratio (%)	88.16 ± 0.7	88.13 ± 1.2	9.8 ± 0.55	9.8 ± 0.88	2.03 ± 0.26	2.03 ± 0.54
Sig.	0.952		0.933		0.997	
	Cerebellum/cerebrum		Brain stem/cerebrum		Brain stem/cerebellum	
Gender	Male	Female	Male	Female	Male	Female
Ratio (%)	11.12 ± 0.72	11.16 ± 1.15	2.30 ± 0.32	2.31 ± 0.64	20.7 ± 2.39	20.6 ± 4.68
Sig.	0.919		0.983		0.947	

this case, another approach, namely, the volume fraction could be used. The volume fraction of a component within a reference volume is a simple and very widely used parameter in biomedical science [8, 25, 26]. It is independent of body size of subjects and examines the volumetric relation between the components of structures.

We presume that there should be a constant volumetric relation between the components of brain, i.e., cerebrum, cerebellum and brain stem. However, we were unable to find a study evaluating volume relation between the components of brain. The given values can be used to evaluate the volume decrease of certain parts of brain. Therefore, the data could be used to evaluate the diseases affecting the certain regions of brain tissue.

Stereological methods provide quantitative data on 3D structures using 2D images. Although several studies have considered estimating the volume fraction of microscopic structures by means of the volume fraction technique [17, 18], we have not seen any study on cerebellum to cerebrum fraction, which applies the unbiased techniques of stereological methods on ordinary MR scans. Sectional imaging modalities have provided an opportunity for volumetric quantification of the intracranial cavity. Both CT and magnetic resonance (MR) imaging may produce reliable measurements of brain and other related structures. MR imaging offers optimal soft tissue contrast resolution and multiplanar capability without the use of ionizing radiation.

The stereological approach gives an opportunity to the researcher making appropriate changes on their sampling or estimating procedures. Therefore, the presented method provides a coefficient of error (CE) of estimation for each volume assessment. Thus, a researcher can see the potential variability in any given volume measurement. When the CE of these measurements is high, it can generate obvious problems in accuracy and hence interpretation. These problems may arise if too few slices or too few points are taken for volume estimation. The observer is eligible to change the spacing of points in the grid or the number of slices available in any CT study to obtain a reasonable CE value. It is also important to note that an appropriate grid size and the number of slices required for volume estimation of an object is crucial at the beginning, obviating the need to calculate the CE value for repeated sessions. A CE value lower than 10% is in acceptable range [22, 32]. The range of CE values changed from 1 to 6%, which are in an acceptable range for the volume estimates and the density of the point-counting grids in the present study could be used safely for the estimation of the hemispheres, brain stem and cerebellum volume on MR images.

Our results regarding cerebellar volume were slightly larger in females, but smaller in males than those reported by Escalona et al. [8], 104 ± 10 cm^3 in female and 122 ± 16 cm^3 in male, and Rhyu et al. [26], 115.4 ± 11.29 cm^3 in female and 126 ± 10.3 cm^3 in male, smaller than those of Luft et al. [16], mean 134.3 ± 14.9 cm^3 in both sexes, and similar to Dupuis [16]. It is not clear that this discrepancy may be due to the racial difference or is due to the variation resulting from different scanning protocols and measuring methods used.

Mayhew [19] reported the mean brain volume of normal subjects was 1,025 cm^3. Cotter [7] stated that the value for the mean total brain volume obtained from the planimetric assessment, 902 cm^3 (SD 133 cm^3) was very similar to that obtained from point counting of hard copy, 927 cm^3 (SD 145 cm^3). Ronan [28] reported the cerebral volume was 1,138 cm^3 in male, 1,091 cm^3 in female.

We found that the mean (SD) cerebral volumes were 1,060.0 ± 94.6 cm^3, 1,008.9 ± 104.3 cm^3 in males and females, respectively. Our result is slightly larger than Mayhew and Cotter results, smaller than Ronan result. We believe that this may be accounted for our mean subject age was much younger than most studies of cerebellar and cerebral volumes in aging.

Our results showed that the volume ratio of the cerebellum to cerebrum, the cerebellum to TBV were 11.12 and 11.16% in males and females, 9.8 and 9.8% in males and females, respectively. Our results revealed that the volumetric composition of the cerebrum and cerebellum does not show sexual dimorphism. The obtained volume fraction values of brain, cerebellum and brain stem may provide an index for volumetric relation of the anatomical structures. Volume fraction method could be a new approach for the evaluation of size changes of the certain brain regions.

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