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Full Length Research Paper

Revolutionizing Schizophrenia Assessment: A Stereological Method Using CT Images to Evaluate Ventricle and Brain Volume Fractions

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There are several studies that have proposed different criteria for evaluating the volumes of the cerebral hemispheres, the lateral and third ventricles in patients with schizophrenia seen on routine computed tomography (CT) images. These approaches use solely the volume of the cerebrum and/or lateral ventricles, length and width measurements of the ventricles, and ventricle to brain ratio (VBR). In the present study, we proposed a new unbiased approach namely ventricle to brain volume fraction (VBF). CT scans of 23 patients with schizophrenia and 23 matched controls were blindly assessed by three independent observers. VBF, total brain volume and ventricle volumes were calculated and compared. The subjects with schizophrenia showed higher VBF than the control subjects (P = 0.000) with mean (±SEM) VBF values of 2.71±0.16 and 1.62±0.10%, respectively. No gender difference was found. Older subjects had a higher VBF than those younger in controls but not patients. Correlation was observed for VBF estimations made by three independent observers (r = 0.979; P = 0.000). The studies measuring VBR on schizophrenia revealed inconsistent findings. Comparing solely the brain volumes or ventricle volumes between two groups, instead of using volume fraction method, will not provide reliable data. VBF described here easily could be used for the analysis of the brain structures of schizophrenia using standard CT scans not requiring any additional expense. In addition; evaluation of the whole section series gives real ventricular and cerebral volumes.

Key words: Cavalieri method, computed tomography (CT), schizophrenia.

INTRODUCTION

Since the 19th Century, there have been many attempts to define a characteristic morphological abnormality in the brains of patients with schizophrenia (Boronow et al., 1985). Of all the methods used to investigate biological abnormalities in psychiatric illnesses, structural neuroimaging studies have provided some of the most consistent evidence of brain abnormalities in schizophrenia. Since the initial report by Johnstone et al. (1976), in which computed tomography (CT) scans showed abnormally large ventricles in patients with chronic schizophrenia, major technological advances in image acquisition and analysis have added significantly to the characterization of normal and abnormal brain structures in schizophrenia *in vivo* (Pearlson and Marsh, 1999). The period of the disease is more than two years in chronic schizophrenia (McKenna, 2001). Enlargement of the cerebral ventricles is one of the most frequently

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replicated neurobiological findings in schizophrenia (Nasrallah et al., 1985). This abnormality in some brain disorders has been demonstrated by *in vivo* brain structure imaging techniques including pneumoencephalography (Haug, 1962), CT and magnetic resonance imaging (Nasrallah et al., 1985, 1986; Sachdev et al., 2006; Chua et al., 2007; Antulov et al., 2009). Also unaffected relatives of patients with schizophrenia had enlarged lateral ventricles but no other volumetric differences (McDonald et al., 2006). Ventricular enlargement is described as a sensitive indicator of central nervous system pathology in schizophrenia as it reflects the volume of the ventricular system (Penn et al., 1978; De Quardo et al., 1994).

Numerous studies report that CT brain scans in some patients with schizophrenia show evidence of cortical or cerebral atrophy (Tanaka et al., 1981; Nasrallah et al., 1985). The enlarged lateral and third ventricles has been reported to be useful data for evaluating patients with schizophrenia using CT images. (Nasrallah et al., 1985; Farmer et al., 1987; Rossi et al., 1989; Jones et al., 1994) Ventricle to brain ratio (VBR) was the most commonly used approach for describing the volume interaction between the ventricle and the brain hemispheres (Ferrari et al., 2006; Ohara et al., 2006; Chua et al., 2007). It was measured on the section showing the maximum ventricular area. The area of the ventricles and the area of the brain or the area of the inner table of skull at the same level were measured, and cerebral ventricular size was expressed as VBR (Nasrallah et al., 1985; Rabins et al., 1987; Rossi et al., 1989; Kemali et al., 1989). Dozens of studies utilizing CT have documented lateral ventricle enlargement, usually by studying the VBR (De Quardo et al., 1996). While certain studies have failed to find lateral ventricle dilatation (Benes et al., 1982; Jernigan et al., 1982), in others, it is only found to be present in a small percentage of the sample (Andreasen et al., 1990). Some studies, using a variety of methods other than VBR, have reported no differences between patients and controls in all or part of their samples (Trimble and Kingsley, 1978; Gluck et al., 1980; Tanaka et al., 1981).

Using a single section to describe the volume fraction changes of the ventricles fails to reflect the real volume fraction of the ventricles, since the whole section series is not taken into account. We have, however, not come across any study that proposes evaluating the whole section series to determine the real ventricular volume to brain volume fraction using CT scans.

In this study, we have for the first time used a new approach to describe the ventricle to brain volume fraction (VBF). This approach is the application of the volume fraction method of stereological techniques, to obtain unbiased and reliable data to evaluate the volume changes of ventricle and brain hemispheres in patients with schizophrenia on routine CT scans. We also evaluated the inter-observer variation and correlation for the estimation of the VBF.

MATERIALS AND METHODS

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 which was described in the previous studies (Odaci et al., 2003; Sahin et al., 2003a; Sahin et al., 2003 b; Canan et al., 2002, 2004; Odaci et al., 2005). The human brain does, however, vary widely in size (Knutson et al., 2001). 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 (Raz et al., 1998; Sgouros et al., 1999). Comparing solely the brain volumes or the volumes of other intracranial structures between two groups (that is, control and experimental groups) will not provide reliable data (Knutson et al., 2001). As the volume of ventricles within the cerebral hemispheres constitutes a certain percentage of total brain volume, however, the volume fraction of the lateral ventricles within the brain can be used to compare reliably certain quantitative data between the groups.

The volume fraction of a component within a reference volume is a simple and very widely used parameter in biomedical science (Howard and Reed, 1998; Mattfeldt et al., 2003, 2004). 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:

$$V_V(X,Y) = \frac{\text{Volume of } X \text{ phase in } Y \text{ reference space}}{\text{Volume of } Y \text{ reference space}} \quad (1)$$

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 (Howard and Reed, 1998).

The volume fraction of a phase can be estimated by means of the Cavalieri principle on radiological images using point-counting approach (Mazonakis et al., 2004; Odacı et al., 2005). The volume fraction formula with the combination of Cavalieri principle can be written as follows:

$$V_V(X,Y) = \frac{V_X = T \cdot \left[((SU)\cdot D)/SL\right]^2 \cdot \sum P_X}{V_Y = T \cdot \left[((SU)\cdot D)/SL\right]^2 \cdot \sum P_Y} \quad (2)$$

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 (that is, ΣP) is the only value of the volume fraction formula, which changes. Thus, the formula can be simply changed to:

$$V_V(X,Y) = \frac{\sum P_X}{\sum P_Y} \quad (3)$$

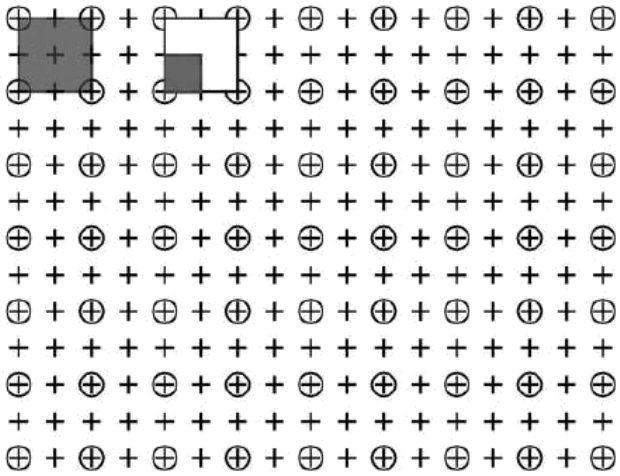

Figure 1. A combined point counting grid with ¼ area fraction. While an encircled cross represents a large area, each crosses without regarding the encircle represent ¼ fraction of the large areas.

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 (that is, encircled crosses only). We can describe this grid as a CPCG with ¼ 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 ¼, a slightly modified version of the equation #3 can be used to estimate the volume fraction of a component within the subject.

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

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

Volume ratio

VBR represents the ratio between brain ventricle and total brain areas. The VBR measurements were performed on slices in which the lateral ventricle body was most prominent. The whole brain, the areas of the left and right bodies of the lateral ventricles was measured. The left and right ventricular body measurements were added together, divided by the total brain area, and multiplied by 100 to give the VBR measurement.

Subjects

Twenty-three patients (10 Male, 13 Female) with DSM-IV diagnosed chronic schizophrenia underwent CT scans as part of their clinical examination at the time of admission in 2006 at Eskisehir Osmangazi University Hospital. This study was approved by the ethical committee of the university and was planned according to the ethical concepts of Helsinki Declaration and universal and international ethical aspects. The mean age of the patients was 39.8±14.9 (±SD) and the average duration of illness was 9.8 ± 5.3 years. All patients had received antipsychotics. Nine patients had been using risperidone, 8 olanzapine, 8 zuclopentixol, 5 quetiapine, 3 haloperidol, 2 clozapine, respectively. But, some of the patients received two antipsychotic medicines. Eighteen of 23 patients were diagnosed as paranoid schizophrenia, 3 undifferentiated, 1 catatonic, and 1 residual schizophrenia.

Twenty-three healthy volunteers (10 Male, 13 Female) were included in the study, and constituted the control group. Control subjects were excluded if there was any history of psychiatric illness. The mean age of the control subjects was 36.3±12.2 (±SD) years. Control subjects were matched with patients on the bases of gender and age. Patients and controls were excluded if they had a lifetime history of serious head trauma, neurological illness, medical or surgical illness or drug/alcohol abuse. All of the subjects were right-handed. Those who attended the study in the patient and control groups were informed of the study and we got their permission. All subjects were scanned in supine position using a high-resolution scanner (Toshiba S Vision XT) without contrast media. Slices at 5 mm thickness were imaged in the axial plane parallel to the orbito-meatal line.

Estimation of ventricle to brain volume fraction (V_V (ventricle, brain)) (VBF)

The CT images of patient and control groups were used to estimate volume fraction of lateral and third ventricles within the cerebrum using a CPCG with ¼ area fraction, that is, d = 0.15 and 0.3 cm. The films were placed on a negatoscope and the CPCG was superimposed, randomly covering the entire image frame (Figure 2). While only the encircled points (that is, d = 0.3 cm) hitting the cerebral hemispheres including the ventricles were counted as an estimate of the reference space (that is, total brain volume), all points with and without a circle (that is, d = 0.15 cm) hitting the third and lateral ventricles were counted to estimate volume fraction of ventricles within the cerebral hemisphere (that is, V_V (*ventricle, brain*)). The VBF values were estimated by means of the following formula.

$$V_V\ (VENTRICLE, BRAIN) = \frac{\sum P_{VENTRICLE}}{4 \cdot \sum P_{BRAIN}} \quad (5)$$

where, $\Sigma P_{ventricle}$ is the total number of points hitting the lateral and third ventricles and ΣP_{brain} is the total number of points hitting the cerebral hemispheres including the ventricles. The value obtained is the volume fraction of the ventricles within the cerebral

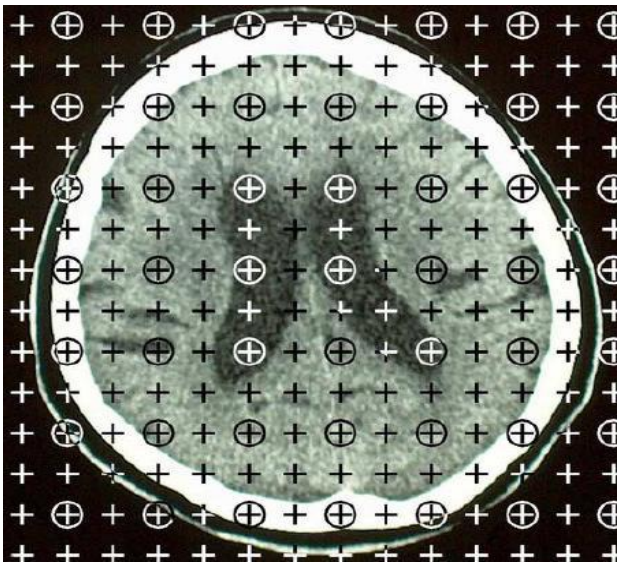

Figure 2. An axial CT scan with a combined point counting grid superimposed on it for the estimation of the VBF.

hemispheres expressed as a percentage.

The total brain and ventricular volume were also estimated using stereological approaches as described in previous studies (Odaci et al., 2003; Sahin et al., 2003a; Sahin et al., 2003b; Canan et al., 2002). The coefficient of error (CE) of volume estimations was done using the formula that is reported by Gundersen and Jensen (1987). The coefficient of variation (CV = Standard deviation/mean) of volume was calculated using the approach that is described in the Gundersen and Osterby (1980) and West et al. (1991). All calculations and other related data were obtained as a spreadsheet using Microsoft ® Excel 2002. 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.

Three observers (experimenters) estimated the VBF, total brain volume and ventricle volume on every image of axial section plane using the same sets of printed sections to check the reproducibility of the estimates according to the observers. The three observers have similar experiences in this study.

In both patient and control groups, Kolmogrov-Smirnov normality test and Levene's test for equality of variances were applied to all measurements. Student-t test was used to compare the VBF, total brain volume and ventricle volume values between the patients with schizophrenia and control groups. One way repeated measures analysis of variance and Friedman repeated measures analysis of variance on ranks tests was applied to compare observers. The Pearson correlation test was performed to define relation between the age and VBF, total brain volume, ventricle volume, and VBR. SPSS 10.0 and SigmaStat 3.1 for Windows were used for statistical analyses.

RESULTS

The mean VBF values (±SEM) of all subjects was 2.16±0.12%. The patients with schizophrenia showed significantly higher VBF than the control subjects (P = 0.000) with mean VBF values of 2.71±0.16 and 1.62±0.10%, respectively. The mean VBFs of the male and female patients with schizophrenia was 2.71±0.29 and 2.71±0.17%, respectively. The mean VBFs of the male and female control group was 1.65±0.18 and 1.59±0.10%, respectively. No significant differences was found in both groups with regard to gender (P = 0.456).

Our results revealed a positive relationship between age and VBF in the control group. Older subjects had higher VBFs than the younger ones in the control group (r = 0.477, P = 0.035). However, no significant age effect was seen among patients with schizophrenia (r = 0.107, P = 0.762).

The mean brain volume (±SEM) of all subjects was 1275.64±20.11 cm^3. The brain volumes of patients with schizophrenia were significantly smaller than the control subjects (P = 0.024) with mean total brain volumes of 1244.48±30.95 and 1306.79±24.68 cm^3, respectively. While, the brain volumes of male and female patients were significantly different (P = 0.032), no significant volume difference were observed between genders in control group (P = 0.688).

There was a negative relationship between age and total brain volume in patients with schizophrenia. Older subjects had smaller brain volume than the younger (r = -0.460, P = 0.035). However, no significant age effect was seen in the control group (r = -0.214, P = 0.576).

The mean ventricle volume (±SEM) of all subjects was 27.26±1.52 cm^3. The schizophrenia subject's ventricular volumes were significantly larger than the control subjects (P = 0.000) with mean ventricular volumes of 33.57±2.11 and 20.95±1.19 cm^3, respectively. No significant difference was found between genders in both groups (P = 0.679).

A positive relationship between age and ventricular volumes was observed in control group. Older subjects had larger ventricular volumes than those younger in the control group (r = 0.446, P = 0.042). However, no significant age effect on ventricular volume was seen in the patients (r = 0.081, P = 0.235).

The detailed information of VBF, total brain volume and ventricle volume is shown in Table 1.

The mean CV of VBF for patients with schizophrenia and control groups were 27 and 28%, respectively. The mean CV of VBF, total brain volume and ventricular volumes were summarized in Table 2.

According to the test results, all variables showed normal distribution. The estimation results of three observers for VBF, total brain volume and ventricular volumes were correlated well (Tables 3 to 5). The mean of CEs (±SEM) for the estimation of total brain volume and ventricular volume were 0.01±0.001 and 0.5±0.002, respectively.

Table 1. The details of VBF total brain volume and ventricle volume estimations.

		Male		Female		Total	
		Patient with schizophrenia	Control	Patient with schizophrenia	Control	Patient with schizophrenia	Control
VBF**	Mean (%±SEM*)	2.71±0.29	1.65±0.18	2.71±0.17	1.59±0.10	2.71±0.16	1.62±0.10
	Min-max	1.16-3.87	1-2.48	1.89-4.01	0.98-2.21	1.16-4.01	0.98-2.48
Brain volume	Mean (cm^3±SEM*)	1370.33±38.46	1341.89±38.63	1147.68±21.40	1279.79±31.21	1244.48±30.95	1306.79±24.68
	Min-max	1204.53-1554.66	1103.4-1504.47	1029.3-1232.91	1112.09-1494.7	1029.3-1554.66	1103.4-1504.47
Ventricle volume	Mean (cm^3±SEM*)	36.75±3.85	21.91±2.34	31.12±2.19	20.22±1.14	33.57±2.11	20.95±1.19
	Min-max	16.93-55.47	13.9-33.69	22.98-46.30	12.17-25.82	16.93-55.47	12.17-33.69

*SEM, Standard error of mean; **VBF, brain volume fraction.

Table 2. The details of CV* (%) calculations for the VBF total brain volume and ventricle volume.

	Male		Female		Total	
	Patient with schizophrenia	Control	Patient with schizophrenia	Control	Patient with schizophrenia	Control
VBF**	32	34	22	22	27	28
Brain volume	8	9	6	8	18	9
Ventricle volume	31	32	24	19	45	27

*CV, Coefficient of variation; **VBF, brain volume fraction.

VBR means (±SEM) was 22.69 (±0.60) and 27.72 (±0.52) for the control and schizophrenia groups, respectively. In both control and schizophrenia groups, there was no significant differences between the three observers for VBR measurements (P = 0.668). For each observer's VBR measurements, significant differences were found between control and schizophrenia groups (P = 0.000).

DISCUSSION

Neuroimagine studies have shown consistent evidence of whole-brain volume deficits, and modern neuropathology studies have uncovered provocative clues pointing to alterations in the neuroanatomy in schizophrenia (Haug, 1962; Nasrallah et al., 1986; Chua et al., 2007; Kreczmanski et al., 2007; Archer, 2010). CT studies documenting significant enlargement of cerebral ventricles and decrease in brain volume in subjects with schizophrenia have provided that schizophrenia is a brain-based disorder (Pearlson and Marsh, 1999, Chua et al., 2007). Recent MRI volumetric studies have confirmed the results of earlier CT studies (Minzenberg et al., 2008).

The ventricle to brain ratio is the most frequently studied anatomic variable. All studies measuring VBR refer to the Synek and Reuben's formula (Synek and Reuben, 1976; Van Horn and McManus, 1992; Shioiri et al., 2000). The results of VBR approach revealed inconsistent findings among the studies on schizophrenia. Most of the researchers' data showed that the patients have larger VBR than the control group (Andreasen et al., 1982; Losonczy et al., 1986; Rossi et al., 1989; Daniel et al., 1991). However, some of these studies reported that there is no statistical difference between patients with schizophrenia and controls in terms of VBR values (Benes et al., 1982; Daradkeh, 1992). Andreason et al. (1990)

Table 3. The estimation results of three independent observers for total brain volume.

Group			Observer 1	Observer 2	Observer 3
Patient with schizophrenia	Mean		1293.52	1373.52	1367.39
	Median		1394	1427	1404
	Minimum		175	499	502
	Maximum		1751	1726	2205
	Std. deviation		369.81	297.08	333.98
	Correlations	Observer 1	1.000	0.995(P = 0.000)	0.95(P = 0.000)
		Observer 2	0.995 (P = 0.000)	1.000	0.94 (P = 0.000)
		Observer 3	0.958 (P = 0.000)	0.947 (P = 0.000)	1.00
Control	Mean		1503.52	1512.26	1494.61
	Median		1527	1526	1540
	Minimum		1146	1136	1150
	Maximum		1692	1749	1702
	Std. deviation		139.90	143.69	136.84
	Correlations	Observer 1	1.000	0.991 (P = 0.000)	0.99 (P = 0.000)
		Observer 2	0.991 (P = 0.000)	1.000	0.98 (P = 0.000)
		Observer 3	0.990 (P = 0.000)	0.988 (P = 0.000)	1.00

Table 4. The estimation results of three independent observers for ventricular volumes.

Group			Observer 1	Observer 2	Observer 3
Patients with schizophrenia	Mean		148.26	150.44	148.26
	Median		136	146	144
	Minimum		59	69	63
	Maximum		239	242	248
	Std. deviation		48.92	50.87	48.81
	Correlations	Observer 1	1.000	0.984(P = 0.000)	0.990(P = 0.000)
		Observer 2	0.984 (P = 0.000)	1.000	0.988 (P = 0.000)
		Observer 3	0.990 (P = 0.000)	0.988 (P = 0.000)	1.00
Control	Mean		97.52	96.57	102.57
	Median		95	95	104
	Minimum		55	52	59
	Maximum		165	152	157
	Std. deviation		29.35	27.09	27.23
	correlations	Observer 1	1.000	0.926 (P = 0.000)	0.920 (P = 0.000)
		Observer 2	0.926 (P = 0.000)	1.000	0.960 (P = 0.000)
		Observer 3	0.920 (P = 0.000)	0.960 (P = 0.000)	1.00

found that the VBR shows a statistically significant gender difference in either the control or the patient group. However, the findings of Kanba et al. (1987) reported that there is no gender difference in either group. Discrepancies were also found among the studies that are investigating the correlation between VBR and age. Farmer et al. (1987) reported a significant correlation between VBR and age while others reported inconsistent findings (Rabins et al. 1987; Rossi et al., 1989).

The VBR value obtained by using a single section to describe the changes in volume fraction of the ventricles is widely used for diagnosis or research purposes. Many investigators reported inconsistent data for the evaluation in patients with schizophrenia due to lack of exact criteria. The problem with VBR measurement lies in the use of two-dimensional images of three-dimensional structures and the evaluation of a single section scan instead of the whole section series. Hence, VBR measurements can only provide limited information on the third dimension. Our new approach VBF gives real volumes for three-

Table 5. The estimation results of three independent observers for VBF.

Group			Observer 1	Observer 2	Observer 3
Patients with schizophrenia	Mean		2.73	2.76	2.74
	Median		2.7	2.8	2.8
	Minimum		1.6	1.6	1.6
	Maximum		3.9	4.2	3.9
	Std. deviation		0.666	0.705	0.708
	Correlations	Observer 1	1.000	0.958(P = 0.000)	0.967(P = 0.000)
		Observer 2	0.958 (P = 0.000)	1.000	0.953 (P = 0.000)
		Observer 3	0.967 (P = 0.000)	0.953 (P = 0.000)	1.00
Control	Mean		0.0163	0.0160	0.0172
	Median		0.0170	0.0160	0.0160
	Minimum		0.010	0.008	0.011
	Maximum		0.026	0.025	0.025
	Std. deviation		0.00498	0.00464	0.00457
	correlations	Observer 1	1.000	0.926 (P = 0.000)	0.920 (P = 0.000)
		Observer 2	0.926 (P = 0.000)	1.000	0.960 (P = 0.000)
		Observer 3	0.920 (P = 0.000)	0.960 (P = 0.000)	1.00

dimensional structures. It may be necessary to make a further study with a larger population.

Stereological methods provide quantitative data on three-dimensional structures using two-dimensional images. As the ventricle volumes within the cerebral hemispheres constitutes a certain percentage of total brain volume, comparing solely the brain volumes or ventricle volumes between two groups, instead of using volume fraction method, will not provide reliable data. Although several studies have considered estimating the volume fraction of microscopic structures by means of the volume fraction technique (Mattfeldt et al., 2003, 2004), we have not seen any study on ventricle to brain fraction, which applies the unbiased techniques of stereological methods on ordinary CT scans.

Our results showed that the mean VBF values of patients with schizophrenia were 2.71%. The mean of the VBF values of control subjects were smaller than patients'. We also examined the total brain volume and ventricular volume in both groups. The schizophrenia subject's brain volumes were significantly smaller than the control subjects. However, the ventricle volumes were significantly larger in patients. The volumetric findings were also similar to those reported in the literature. However, VBF was a more constant value for the comparison between the patients with schizophrenia and control subjects since it is an independent value from the body mass of the examined subjects.

The CVs of patients with schizophrenia and control groups were 27 and 28%, respectively. This means that the number of subjects in both groups were adequate to propose statistical data (Regeur and Pakkenberg, 1989). The CEs of both groups were also lower than 0.05, which means that estimation process of stereological approach is satisfying (Gundersen and Jensen, 1987).

Conclusions

In the light of these findings, we propose a volume fraction estimation approach namely VBF to assess the real volume changes in brain and ventricles using CT scans. This approach provides reliable and unbiased data since all the sections belonging to a person are used to obtain the VBF. The only parameter, which the researcher requires to estimate the VBF, is the number of points hitting the brain and the ventricle. Moreover, the reduction/magnification ratio of the printed sections does not affect the present approach. Furthermore, as the estimation results of three observers correlated well, the suggested approach can be considered to be highly reproducible and reliable. The VBF described here could be used as a sustaining data for the analysis of brain structures in schizophrenia since it has advantages that were mentioned previously.

The present study proposes an easy way of evaluating the ventricle to brain fraction value on CT scans without changing the routine procedure in radiological centers. The results suggest that it is not necessary to further standardize the CT scans in order to estimate the VBF.

VBF values are calculated as three dimensional percent but VBR are obtained by using the ratio between brain ventricle and total brain areas. VBR are measured two dimensionally by using only one slice. However, VBF

measurements include all slices.

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