

The estimation of cerebral asymmetries in schizophrenia by the Cavalieri principle

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ABSTRACT

الأهداف: لإثبات اللاتماثل لنصف الدماغ القياسي في المرضى المصابين بالفصام باستخدام طريقة بسيطة وغير مكلفة، باستخدام الأشعة المقطعية (CT).

الطريقة: لإثبات اللاتماثل لنصف الدماغ القياسي قمنا بمقارنة نتيجة الأشعة المقطعية (CT) لثلاثين مريضاً يعانون من الفصام (14 ذكر - 16 أنثى) مع 39 (13 ذكر - 26 أنثى) مثلوا مجموعة التحكم بجامعة أسكيسيهير عثمان غازي - أسكيسيهير - تركيا، خلال عام 2005م. تم فحص حجم الدماغ بواسطة طريقة بسيطة وغير مكلفة، طريقة كافاليري.

النتائج: في المرضى المصابين بالفصام ومع زيادة العمر، ينخفض حجم نصفي الدماغ الأيمن والأيسر. ولكن، في مجموعة التحكم لم يكن هنالك علاقة بين العمر وحجم نصفي الدماغ. في مجموعة التحكم كان نصف الدماغ الأيسر أكبر بشكل ملحوظ لدى الذكور مقارنة بالإناث. كان هنالك فرقاً ملحوظاً في أحجام كلا النصفين الأيمن والأيسر بين مجموعة التحكم والمجموعة المصابة بالفصام. في المجموعة المصابة بالفصام كان هناك فرقاً ملحوظاً في حجم نصف الدماغ الأيمن بين الجنسين ($p=0.002$) بينما لم يكن هنالك فرقاً لدى مجموعة التحكم. كان هنالك فرقاً في حجم نصف الدماغ الأيسر بين الجنسين في كلتا المجموعتين. كان حجم نصفي الدماغ الأيمن والأيسر لدى المجموعة المصابة بالفصام أصغر من مجموعة التحكم.

خاتمة: اللاتماثل الدماغية موضوع قابل للنقاش لتشخيص الإصابة بالفصام. سوف تكون الطريقة التي استعملناها في هذه الدراسة مفيدة في تقدير حجمي نصفي الدماغ.

Objectives: To demonstrate hemispheric asymmetry in patients with schizophrenia using a cheap, simple stereologic method on the basis of standard CT scans of the brain.

Methods: To demonstrate hemispheric asymmetry, standard CT scans of 30 schizophrenic patients (14 males, 16 females) were compared with 39 (13 male, 26 female) control subjects at Eskisehir

Osmangazi University, Eskisehir, Turkey in 2005. Brain volumes were investigated by using a cheap, simple stereologic method, namely, Cavalieri.

Results: In patients with schizophrenia, we found that as age increases, right and left hemisphere volumes decrease. However, in the control group there was no relationship found between age and hemisphere volumes. In the control group, the left hemisphere was significantly bigger in males compared to females. There was a significant difference in both right and left hemisphere volumes between the control group and the schizophrenic group. In the schizophrenic group, a significant difference was observed in right hemisphere volumes between genders ($p=0.002$), while there was no difference in the control group. There was a difference in left hemisphere volumes between genders in both groups. Right and left hemispheric volumes of the schizophrenic group were smaller than those of control group.

Conclusion: Cerebral asymmetry is an arguable subject for the diagnosis of schizophrenia. The method that we used in this study will be useful in estimating hemispheric volumes.

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Schizophrenia is a serious chronic psychiatric disorder affecting approximately 1% of the population around the world, and is usually characterized by a progressive decline in functioning.¹ Schizophrenia is a disease that is associated with abnormal brain structures. In the human brain, many structures and functions are normally lateralized such as surface areas, volumes, or language.

Many studies have shown that in schizophrenia these normal cerebral asymmetries are absent or reversed. The disruptions in these normal cerebral asymmetries in schizophrenia are thought to reflect abnormalities in the development of the fetal brain. Crow² hypothesized that a human gene, which is essential to evaluate hand dominance and human language also plays a role in contributing to psychosis. Crow³ also hypothesized that the processes related to asymmetries also influence gender differences in schizophrenia. The volume of structures can be estimated using the Cavalieri principle of stereological methods, which requires slices through the object, provided they are parallel, separated by a known distance and begin randomly within the object; criteria that are met by standard CT imaging.^{4,6} The cut surface areas of the sections are estimated using the point counting method. The point-counting method consists of overlying each selected section with a regular grid of test points, which is randomly positioned. After each superimposition, the number of test points hitting the structure of interest on the sections is counted, and the volume of the structure is estimated by multiplying section thickness, total number of points, and the representing area per point in the grid.^{7,8} In this study, we aimed to demonstrate hemispheric asymmetry in patients with schizophrenia with this cheap, simple stereologic method on the basis of standard CT scan of brain.

Methods. Turkish schizophrenic patients and controls with consecutive admissions to the Eskisehir Osmangazi University, Eskisehir, Turkey in 2005 comprised the study population. The study was approved by the ethical committee of Osmangazi University. Patients and controls were excluded if they had a history of substance abuse/dependence, neurological disorders, head trauma, and clinical dementia. Thirty schizophrenic patients (14 males, 16 females) with DSM-IV diagnosed schizophrenia underwent CT scans for clinical examination during their admissions. All patients received neuroleptic medication. The mean age of the patients was 38.9 ± 14.48 years old. The average duration of illness was 10.5 ± 6.2 years. All subjects were scanned in the supine position with axial slices, which were parallel to the orbitomeatal line, without contrast media with a high-resolution scanner (Toshiba X vision XT) in axial plane with 5 mm thick slices at 5 mm intervals. A control group of 39 subjects without any psychiatric disorders were scanned with the same machine under identical conditions. Control subjects were matched with patients on the basis of gender (13 males, 26 females) and age (35.38 ± 11.54 years). The local ethical committee board approved the procedures of our study. Patients or patient's relatives



Figure 1 - The CT image of a schizophrenic patient. Arrows indicate wide right cerebral sulci associated with a decrease in right hemispheric volume.

and controls consented to all procedures. The CT images of schizophrenic and control groups were used to estimate the volume of cerebral hemispheres (Figure 1). These images were printed on films in square frames of side length 6.3 X 6.3 cm. A square grid test system, with $d=0.5$ and 0.3 cm between test points, was used to estimate the sectioned surface area of the slices. For estimation of hemisphere volume, the modified formula used for volume estimations of radiological images was applied.^{6,7,9,10}

$$V = t \times [((SU) \times d) / SL]^2 \times \Sigma P$$

where 't' is the section thickness (including interval) 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 measured length of the scale printed on the film and 'ΣP' is the total number of points hitting the sectioned cut surface areas of brain. The films were placed on a light box, and a transparent square grid test system was superimposed, randomly covering the entire image frame. The points hitting the hemisphere sectioned surface area were counted for each section, and the volume of the entire hemisphere was estimated using the first formula. Three observers estimated the hemispheric volumes on every image of horizontal section plane using the same sets of printed sections to check the accuracy of the estimates and inter-observer variations.

The coefficients of errors (CE) of brain volume estimations were determined as described in previous studies.^{5,7,11} The mean time for the volume estimations was also provided. Calculation of hemispheric volume,

Table 1 - Right and left hemispheric volumes of control and schizophrenic groups shown as mean + SD.

Group	n	Right hemisphere volume (cm ³)	Left hemisphere volume (cm ³)
Control	39	531.59±45.78	532.26±46.23
Schizophrenia	30	496.08±66.72	494.52±68.58
Total	69	516.15±58.18	515.85±59.62

CE of estimates and other related data were obtained as a spreadsheet using Microsoft Excel. After initial setup and preparation of the formula, the point counts and other data mentioned in the first formula were entered for each scan and the final data were obtained automatically. Estimated mean ± SD hemisphere volumes of both groups are demonstrated in Table 1 and compared in point of asymmetry. The relationship between hemisphere volume and age was examined. The statistical program for social sciences SPSS program (version 10) was used for statistical analysis of data. One-way analysis of ANOVA test was used to compare the hemisphere volume values between the schizophrenic and control groups. The Pearson correlation analysis was performed to check the inter-observer variance and relation between the age and hemisphere volume. A "P" value lower than 0.05 was accepted as being statistically different.

Results. There was a significant relationship between age and right hemispheric volume in the group of patients with schizophrenia ($r = -0.48$, $p = 0.007$) while there was no relationship in the control group ($p > 0.05$). There was a significant difference in the right hemispheric volume between males and females in the group of patients with schizophrenia ($p = 0.002$) while there was no difference in the control group ($p > 0.05$). The difference in the right hemispheric volume between the control group and the group of patients was also significant ($p = 0.011$). There was a significant relationship between age and left hemispheric volume in the group of patients with schizophrenia ($r = -0.51$, $p = 0.004$) while there was no relationship in the control group ($p > 0.05$). There was a significant difference in the left hemispheric volume between males and females in both control group ($p = 0.047$) and the group of patients ($p = 0.007$). The difference in the left hemispheric volume between the control group and the group of patients with schizophrenia was also significant ($p = 0.008$). There was no significant difference between right and left hemispheric volume in both control group and the group of patients with schizophrenia ($p > 0.05$). The inter-observer correlation for right and left hemispheric

volumes was also high ($r = 0.99$, $p = 0.000$ for the right, and $r = 0.99$, $p = 0.000$ for the left).

Discussion. In our findings, in patients with schizophrenia, as age increased, right and left hemisphere volume decreased ($p = 0.007$, $p = 0.004$). However, in the control group there was no relationship between the increase of age and right and left hemisphere volume ($p > 0.05$ for both). In the study of Iillowsky et al,¹² it was mentioned that there was no relationship between patients' age and atrophic changes.¹³ In another study using MRI, there was no correlation between cerebral volume and age.¹⁴ In a volumetric MRI study, it was demonstrated that temporal asymmetry was not significant when compared to the control group using the Cavalieri method.¹⁵ In the same study, there was also no relationship between genders. They also mentioned that some of the researchers' findings confirmed their results, while some of the researchers found a significant difference between the groups. In a postmortem study of Highley et al,¹⁶ in the female control group, the left hemisphere was bigger than the right hemisphere, while in males, the right hemisphere was bigger than the left hemisphere. In the schizophrenic group, these were all controversial. In our study, in the control group, the left hemisphere was significantly bigger in males compared to females ($p = 0.047$), while there was no significant difference in right hemisphere between genders.

In a postmortem study using the Cavalieri method, no significant difference was found between control and schizophrenic groups ($p = 0.38$).¹⁷ Sim et al¹⁸ observed that patients had smaller medial temporal lobe volumes compared to controls. In an MRI study, gray matter volumes in the parietal lobe were reduced in schizophrenia.¹⁹ In a study of Leonard,¹⁴ on the basis of MRI, in schizophrenic patients and in the control group, there was no correlation reporting to both age and asymmetry. Niu et al²⁰ showed that female patients had a reduced right amygdala compared with female controls. In a study of Narr et al,²¹ asymmetry indices were not shown between genders. In our study there was a significant difference in both right and left hemisphere volumes between the control group and the schizophrenic group ($p = 0.011$, $p = 0.008$). This was similar to previous studies.²²⁻²⁴ In the schizophrenic group, there was a significant difference in right hemisphere volumes between genders ($p = 0.002$), while there was no difference in the control group ($p > 0.05$). There was a difference in left hemisphere volumes between genders in both groups ($p = 0.007$, $p = 0.047$).

We could not examine all clinical parameters (such as dominant cerebral hemisphere, the duration of illness, and their correlations with brain volumes). The main topic of this study was to emphasize that the Cavalieri

method is a cheap, simple, and reliable method to investigate brain volumes. Many studies have evaluated brain volumes. Although the Cavalieri method has been used frequently to estimate brain volumes, inter-observer correlations were shown in this study. In addition, the experimental groups did not include older patients and controls.

In conclusion, there was no significant difference between right and left hemispheric volumes in both the control group and the schizophrenic group ($p>0.05$). Similar to our findings, it was also shown in other studies that asymmetry was an arguable subject. We suggest that the neutral method that we used in this study will be useful in estimating hemispheric volumes to diagnose schizophrenia. Estimation of cerebral asymmetries may be of added value, although the diagnosis of schizophrenia more heavily relies on clinical judgment than organic brain volume changes or histological findings. We recommend that further studies be carried out using this method on a larger population.

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