Computerised Tomography in Newly Diagnosed Schizophrenia and Schizophreniform Disorder
A Controlled Blind Study

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Patients with newly diagnosed schizophrenia (n = 27) or schizophreniform disorder (n = 22)
and 24 healthy volunteers were investigated by CT scan, the investigators being blind to subject
status. The patients had never received medication or had been treated only briefly with
neuroleptics. The patients had significantly smaller brain volume and brain length than the
controls. The patients had greater sulcal enlargement in the case of both Sylvian and
interhemispheric fissures and surface sulci in the frontal and parietal regions. The sulcal
enlargement was more pronounced in male patients and on the left hemisphere. The study
revealed no enlargement of the lateral ventricles and only a trend towards enlargement of
the third ventricle in the patients. The findings were not explained by substance abuse or
level of education.

In 1976 Johnstone et al first reported that computerised tomography (CT) scans showed larger
ventricular size in chronic schizophrenic in-patients than in normal controls. Since then more than 100
CT studies have been carried out (Shelton & Weinberger, 1987). The focus has been on changes
in size of the lateral and third ventricles, ventricle: brain ratio (VBR), cortical atrophy, brain volume
and brain asymmetries. Most studies have reported significant differences between schizophrenic patients
and controls, with schizophrenic patients having larger VBR or wider third ventricle or sulcal
enlargement and in a few studies smaller brains than the controls.

However, only a few studies have been made on first-admission patients, thus reducing the in
fluence of medication, institutionalisation and long duration of illness on the brain-structure findings.
Four of the CT studies of first-admission patients have reported increased VBR in the patient group
(Nyback et al, 1982; Weinberger et al, 1982; Schulz et al, 1983; Turner et al, 1986), while three studies
(Benes et al, 1982; Owens et al, 1985; Scottish Schizophrenia Research Group, 1989) found no
ventricular enlargement, although one of these (Scottish Schizophrenia Research Group, 1989)
found sulcal enlargement in the schizophrenic group. The sulcal enlargement was more pronounced in male
patients and on the left hemisphere. The study revealed no enlargement of the lateral ventricles and only a
trend towards enlargement of the third ventricle in the patients. The findings were not explained by
substance abuse or level of education.

DeLisi et al (1991) recently made a magnetic resonance imaging (MRI) study incorporating 30
first-episode patients with schizophrenia-like psychoses, 15 patients with chronic schizophrenia and
20 controls. The lateral-ventricle size was increased in first-episode schizophrenics and chronic schizo
phrenic patients, the left side being most impaired. Only chronic schizophrenic patients had reduced
temporal-lobe size, which was also most pronounced on the left side. Follow-up studies including patients
who had been ill for several years at the time of the initial scan (Nasrallah et al, 1986; Illowsky et al,
1988; Vita et al, 1988) and one including first-admission patients (Sponheim et al, 1991) have not
revealed any progression in VBR or cortical atrophy.

At present there is substantial evidence that chronic schizophrenic patients have enlargement of
ventricles and unequivocal enlargement of sulci. The question of whether these structural changes are
present in first-episode schizophrenia and the clinical relevance of the findings have not yet been elucidated.
In the search for further clarification we have performed a prospective study comprising CT scanning
of all psychotic patients in Copenhagen admitted for the first time.

Method

Patients consecutively admitted to psychiatric hospital for the first time who met the DSM-III-R criteria (American
Psychiatric Association, 1987) for schizophrenia or schizophreniform disorder and who were aged 18–45 years were
included in the study. Patients with organic brain disease
Table 1

Distribution of sex, age, height, weight and handedness

<table>
<thead>
<tr>
<th>Sex</th>
<th>Mean age</th>
<th>Mean height</th>
<th>Mean weight</th>
<th>Handedness</th>
<th>Neuroleptic treatment before CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>29</td>
<td>28</td>
<td>175.6</td>
<td>70.0</td>
<td>Right</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>24</td>
<td>177.1</td>
<td>70.5</td>
<td>Left</td>
</tr>
<tr>
<td>(n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None &lt;1 week 1 week to 3 months</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>12</td>
<td>9</td>
<td>24</td>
<td>75.5</td>
<td>Right</td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left</td>
</tr>
</tbody>
</table>

and forensic cases were excluded, as were pregnant women. The catchment area of 500 000 inhabitants covered the entire city of Copenhagen and all four regional psychiatric departments; thus the sample may be considered representative for first-admission cases in the city of Copenhagen. The study included 49 patients (mean age 28, range 19–41 years). The sample was established between 1 December 1988 and 12 December 1990.

There were 24 healthy volunteers recruited as controls (mean age 24, range 18–38 years). Volunteers with significant physical or psychiatric illness, alcohol or drug abuse, or a history of major psychiatric disorder among first-degree relatives were not included. The controls underwent CT scans between 1 January 1990 and 1 November 1990.

The study was approved by the Ethical Committee for Copenhagen and Frederiksberg.

General information concerning the patients and controls is given in Table 1.

Alcohol/cannabis abuse, accidents and duration of illness

The patients were interviewed about abuse of alcohol, cannabis and drugs by psychiatrists at the psychiatric departments in Copenhagen according to SCAN 10 (Schedules for Clinical Assessment in Neuropsychiatry) (World Health Organization, 1992). Abuse, by definition, took place if at any time in life the patient had months-long periods of alcohol consumption of five or more drinks daily or any amount of cannabis use; patients who had tried cannabis a few times in their lives were accepted as non-abusers.

Only six patients had abused drugs; all of these had abused alcohol or cannabis as well and they were thus categorised as abusers.

Three patients years before had experienced accidents and had suffered from central nervous system trauma and unconsciousness lasting from two hours to three days. The CT values for these three patients were compared with those for the other patients, but they did not constitute outliers and thus they were included in the analysis.

For all patients this was the first time that they had been admitted to psychiatric departments. However, previously a few patients had been in very brief contact with the hospital (e.g. some had stayed overnight in a psychiatric emergency room) and some had consulted a psychiatrist outside the hospital.

CT measurements

The CT scans were obtained on a Siemens Somatom DRG scanner depicting 12 slices (0.8 cm thick) through the brain, parallel to and starting 1 cm above the orbitomeatal plane.

The scanner was routinely checked once a month with phantom measurements. In the whole study period the variation in attenuation within the relevant range and across the whole field was within ± 2 Hounsfield units (HU). The variation in linear and area measurements was checked by phantom measurement and throughout the study period for 0.8 cm thick scans was within ± 0.5 mm. The scanner was calibrated before every scanning.

The delineation of the brain and the brain ventricles was computerised (high lighting) according to a present density-discrimination level. All measurements were made blind as to diagnosis (schizophrenia, schizophreniform disorder or healthy volunteer).

The following parameters were estimated.

The lateral ventricle area and brain area were calculated for each hemisphere according to the following procedure. The highest scan incorporating the lateral ventricle was identified. Starting three scans above this and terminating four scans below it, the areas of cerebrospinal fluid (CSF) (absorption range -2 to 20 HU), brain tissue (absorption range 20 to 100 HU) and the lateral ventricle (absorption range -2 to 20 HU within a manually defined circumference close around the ventricle) were determined. The areas of the temporal horns (right and left), third ventricle and cisterna pineal were determined by a similar procedure. The cisterna pineal is the name we have given to the space just below the splenium corpus callosi, behind the corpus pineal and above the vermis of the cerebellum. In reality, this space consists of parts of the cisterna venae magna and cisterna laminae quadrigeminae.

Brain volume, ventricle volume, and volume of CSF spaces were calculated as

\[
\text{volume} = \sum \text{area in all measured slices} \times 0.8 \text{ ml}
\]

Lateral VBR was calculated for each hemisphere and for the whole brain as
Healthy volunteers

In 21 patients with schizophrenia or schizophreniform disorder, all patients were not abusing alcohol or cannabis. GCE level (n=18) (n=29) Brain length: cm

17.09

16.46***

16.24****

16.53**

Width of right fissura Sylvii: cm

0.27

0.31

0.28

0.30

Width of left fissura Sylvii: cm

0.23

0.32****

0.33****

0.32****

Width of fissura interhemispherica: cm

0.22

0.30

0.28

0.30*

Cisterna pineale:brain ratio

0.13

0.19

0.17

0.19*

Right-hemisphere brain volume: ml

549.33

520.52**

514.40*

520.05**

Left-hemisphere brain volume: ml

485.79

460.05**

454.28**

459.25**

Brain volume: ml

1035.11

960.57**

968.67**

979.30**

Right-hemisphere ventricle: brain ratio

1.84

1.79

1.65

1.91

Left-hemisphere ventricle: brain ratio

2.33

2.23

2.06

2.27

Ventricle: brain ratio

2.07

2.00

1.84

2.08

Right-hemisphere CSF volume (spaces): brain ratio

0.93

1.53***

1.45

1.62**

Left-hemisphere CSF volume (spaces): brain ratio

1.18

1.90****

1.75*

1.95**

CSF volume (spaces): brain ratio

1.05

1.71****

1.59

1.78**

Third ventricle: brain ratio

using brain volume in the scans where third ventricle was identified

0.30

0.38

0.37

0.40*

using total brain volume

0.11

0.13

0.13

0.13

Third-ventricle index

2.66

3.02

3.22*

3.02

Right-hemisphere frontal sulcal enlargement

1.57

2.33**

2.44*

2.49***

Left-hemisphere frontal sulcal enlargement

1.76

2.39*

2.61

2.62**

Right-hemisphere general sulcal enlargement

1.43

2.02**

1.89*

2.03*

Left-hemisphere general sulcal enlargement

1.43

2.02*

1.94**

2.06**

The CSF spaces: brain ratio (CSFBR) was calculated for each hemisphere and for the whole brain as

\[ \text{CSFBR} = \frac{\text{CSF (spaces) volume}}{\text{brain volume}} \times 100 \]

The temporal horn: brain ratio, cisterna pineale: brain ratio, and third ventricle: brain ratio were calculated by similar procedures. The third ventricle: brain ratio was calculated twice, once as the volume of third ventricle relative to the brain volume in the slices where the third ventricle was identified, and once as the third-ventricle volume relative to the whole-brain volume.

Computer calculations were made by three raters (one trained neuroradiologist (AK) and two reliable radiographers). For 10% of the participants the measurements were made by all three raters. Pairwise the differences between the raters' measurements were plotted against the means of their measurements. There was no sign of the

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**Table 2**

Mean CT measurements in patients and in healthy volunteers; also in patients without substance abuse and in patients with education to General Certificate of Education (GCE) level

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers (n=21)</th>
<th>Patients with schizophrenia or schizophreniform disorder All patients (n=49)</th>
<th>Patients not abusing alcohol/cannabis (n=18)</th>
<th>Patients with education to GCE level (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain length: cm</td>
<td>17.09</td>
<td>16.46***</td>
<td>16.24****</td>
<td>16.53**</td>
</tr>
<tr>
<td>Width of right fissura Sylvii: cm</td>
<td>0.27</td>
<td>0.31</td>
<td>0.33</td>
<td>0.31</td>
</tr>
<tr>
<td>Width of left fissura Sylvii: cm</td>
<td>0.23</td>
<td>0.32****</td>
<td>0.33****</td>
<td>0.32****</td>
</tr>
<tr>
<td>Width of fissura interhemispherica: cm</td>
<td>0.22</td>
<td>0.30*</td>
<td>0.28</td>
<td>0.30*</td>
</tr>
<tr>
<td>Cisterna pineale:brain ratio</td>
<td>0.13</td>
<td>0.19*</td>
<td>0.17</td>
<td>0.19*</td>
</tr>
<tr>
<td>Right-hemisphere brain volume: ml</td>
<td>549.33</td>
<td>520.52**</td>
<td>514.40*</td>
<td>520.05**</td>
</tr>
<tr>
<td>Left-hemisphere brain volume: ml</td>
<td>485.79</td>
<td>460.05**</td>
<td>454.28**</td>
<td>459.25**</td>
</tr>
<tr>
<td>Brain volume: ml</td>
<td>1035.11</td>
<td>960.57**</td>
<td>968.67**</td>
<td>979.30**</td>
</tr>
<tr>
<td>Right-hemisphere ventricle: brain ratio</td>
<td>1.84</td>
<td>1.79</td>
<td>1.65</td>
<td>1.91</td>
</tr>
<tr>
<td>Left-hemisphere ventricle: brain ratio</td>
<td>2.33</td>
<td>2.23</td>
<td>2.06</td>
<td>2.27</td>
</tr>
<tr>
<td>Ventricle: brain ratio</td>
<td>2.07</td>
<td>2.00</td>
<td>1.84</td>
<td>2.08</td>
</tr>
<tr>
<td>Right-hemisphere CSF volume (spaces): brain ratio</td>
<td>0.93</td>
<td>1.53***</td>
<td>1.45</td>
<td>1.62**</td>
</tr>
<tr>
<td>Left-hemisphere CSF volume (spaces): brain ratio</td>
<td>1.18</td>
<td>1.90****</td>
<td>1.75*</td>
<td>1.95**</td>
</tr>
<tr>
<td>CSF volume (spaces): brain ratio</td>
<td>1.05</td>
<td>1.71****</td>
<td>1.59</td>
<td>1.78**</td>
</tr>
<tr>
<td>Third ventricle: brain ratio using brain volume in the scans where third ventricle was identified</td>
<td>0.30</td>
<td>0.38</td>
<td>0.37</td>
<td>0.40*</td>
</tr>
<tr>
<td>using total brain volume</td>
<td>0.11</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Third-ventricle index</td>
<td>2.66</td>
<td>3.02</td>
<td>3.22*</td>
<td>3.02</td>
</tr>
<tr>
<td>Right-hemisphere frontal sulcal enlargement</td>
<td>1.57</td>
<td>2.33**</td>
<td>2.44*</td>
<td>2.49***</td>
</tr>
<tr>
<td>Left-hemisphere frontal sulcal enlargement</td>
<td>1.76</td>
<td>2.39*</td>
<td>2.61</td>
<td>2.62**</td>
</tr>
<tr>
<td>Right-hemisphere general sulcal enlargement</td>
<td>1.43</td>
<td>2.02**</td>
<td>1.89*</td>
<td>2.03*</td>
</tr>
<tr>
<td>Left-hemisphere general sulcal enlargement</td>
<td>1.43</td>
<td>2.02*</td>
<td>1.94**</td>
<td>2.06**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.005, ****P<0.001.
CT SCAN IN SCHIZOPHRENIA

1200 sulci and fissures visible and continuous but none over 3 mm wide
3 sulci and fissures visible and continuous and one or more over 3 mm wide.

Statistical analysis

The previously-defined hypothesis that the schizophrenia group would have larger lateral- and third-ventricle volumes and a higher degree of sulcal enlargement was tested by a limited number of planned two-sample t-tests. The sulcal enlargement scores measured on the four-point scale were tested by χ² tests. Effects of sex, age, height and handedness were examined by multiple regression analysis.

As none of the healthy volunteers were substance abusers and they all had a high level of education, analyses were done separately with patient subgroups matching the healthy volunteers on each of these two parameters.

Results

Due to a technical failure, three healthy volunteers were scanned with 1.0 cm slices instead of 0.8 cm slices and, consequently, these were excluded from the analysis. Thus the analysis included 49 patients with schizophrenia (n = 27) or schizophreniform disorder (n = 22) and 21 healthy volunteers.

Fig. 2 Brain volume (cm³). Horizontal bar indicates mean (● male, ○ female).

difference increasing as the mean value increased. The standard error of the differences was 1.1 on the brain measurements and 0.1 on the CSF measurements.

The frontal index was calculated as the greatest width of the frontal horns divided by the width of the brain at the same level, × 100; the caudal index was calculated as the greatest width of the frontal horns measured over the nucleus caudatus divided by the width of the brain at the same level, × 100; the third-ventricle index was calculated as the greatest width of the third ventricle divided by the width of the brain at the same level, × 100; the plexus index was calculated as the distance between the centre of the calcified choroid plexus seen in the trigonum areas divided by the width of the brain at the same level, × 100 (Fig. 1).

The length and width of the brain were measured manually at the scan where these were largest. The length and width of the fourth ventricle and the septum caudatum distances were measured manually as well. The widths of the fissura interhemispherica, the fissura Sylvii, the most posterior vermal sulcus and the cisterna ambiens were measured manually.

Sulcal enlargement was estimated on a four-point scale in four cortical regions – frontal, temporal, parietal and occipital – in each hemisphere. The estimate was defined as follows:

0 sulci and fissures not visible
1 sulci and fissures visible but not continuous
2 sulci and fissures visible and continuous but none over 3 mm wide
3 sulci and fissures visible and continuous and one or more over 3 mm wide.

Fig. 3 Brain length (cm). Horizontal bar indicates mean (● male, ○ female).
A technical failure on the floppy disk from one of the healthy volunteers rendered the calculation of brain and ventricle volume impossible, and thus regarding these parameters 20 healthy volunteers were analysed.

**Whole brain**

In the patients and in the healthy volunteers, the right hemisphere was larger (by 7-21%) than the left hemisphere. No difference in the right:left ratio was found between the groups.

The patients had significantly smaller brain volumes bilaterally than the controls ($P<0.01$) (Table 2). In Fig. 2 the distribution of brain volume is shown for each sex separately. Ten of the male patients had smaller brain volume than any of the male controls. Three of the female patients had smaller brain volume than any of the female controls.

The length of the brain was also significantly smaller in the patient group than in the control group ($P<0.002$) (Table 2 and Fig. 3).

These findings remained statistically significant after correction for differences in sex, age, height and handedness.

**Brain surface**

The patient group had significantly wider left fissura Sylvii than the healthy volunteers ($P<0.001$) (Table 2 and Fig. 4). The result remained statistically significant after correction for differences in sex, age, height and handedness. The same tendency was present on the right side, although the difference did not reach significance. We performed analysis of variance considering interaction of side and diagnosis: this did not reach significance.

The patient group also had significantly wider fissura interhemisphera ($P<0.03$) and significantly greater cisterna pineale:brain volume ratio ($P<0.03$) than the control group (Table 2).

The CSFBR was significantly greater in the patient group than in the healthy volunteer group ($P<0.001$): this was found in respect of both the right ($P<0.002$) and the left hemisphere ($P<0.001$) (Table 2).

The findings remained statistically significant after correction for differences in age, sex, height and handedness.

**Sulcal enlargement**

The degree of sulcal enlargement on the four-point scale is shown in Table 3. In the frontal and parietal regions bilaterally and on the general sulcal enlargement scale bilaterally, the patient group had a significantly higher degree of sulcal enlargement than had the controls. In the temporal and occipital regions neither the patients nor the controls were abnormal, but in these regions too the patients had larger sulci than had the healthy volunteers.

There were still significant differences on the sulcal-enlargement scales after correction for differences in age, sex and handedness.

**Lateral ventricles**

No difference was found in the lateral-ventricle volume between the patient and the healthy volunteers, neither when expressed as ventricle volume nor when expressed as VBR for the whole brain or for each hemisphere separately (Table 2). The temporal horn:brain volume was measured separately in each hemisphere; however, no statistical differences between the patients and the healthy volunteers was found on these parameters (Table 2). Surprisingly, the...
<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers (n=21)</th>
<th>Patients with schizophrenia (n=27)</th>
<th>Patients with schizophreniform disorder (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right septum caudatum distance: cm</td>
<td>0.48</td>
<td>0.47</td>
<td>0.54</td>
</tr>
<tr>
<td>Left septum caudatum distance: cm</td>
<td>0.47</td>
<td>0.53</td>
<td>0.58*</td>
</tr>
<tr>
<td>Brain length: cm</td>
<td>17.08</td>
<td>16.47***</td>
<td>16.46**</td>
</tr>
<tr>
<td>Brain width: cm</td>
<td>12.40</td>
<td>12.34</td>
<td>12.41</td>
</tr>
<tr>
<td>Length of fourth ventricle: cm</td>
<td>0.53</td>
<td>0.57</td>
<td>0.60</td>
</tr>
<tr>
<td>Width of fourth ventricle: cm</td>
<td>1.23</td>
<td>1.23</td>
<td>1.20</td>
</tr>
<tr>
<td>Width of right fissura Sylvii: cm</td>
<td>0.27</td>
<td>0.29</td>
<td>0.34</td>
</tr>
<tr>
<td>Width of left fissura Sylvii: cm</td>
<td>0.23</td>
<td>0.30*</td>
<td>0.39****</td>
</tr>
<tr>
<td>Width of fissura interhemispherica: cm</td>
<td>0.22</td>
<td>0.32*</td>
<td>0.27</td>
</tr>
<tr>
<td>Width of last vermis sulcus: cm</td>
<td>0.21</td>
<td>0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of vermis sulci</td>
<td>1.62</td>
<td>1.85</td>
<td>1.45</td>
</tr>
<tr>
<td>Width of cisterna ambiens: cm</td>
<td>0.38</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td>Right-hemisphere brain volume: ml</td>
<td>549.33</td>
<td>522.38*</td>
<td>518.25*</td>
</tr>
<tr>
<td>Left-hemisphere brain volume: ml</td>
<td>485.79</td>
<td>480.04*</td>
<td>480.07*</td>
</tr>
<tr>
<td>Brain volume: ml</td>
<td>1035.11</td>
<td>982.40*</td>
<td>978.32*</td>
</tr>
<tr>
<td>Right lateral ventricle volume: ml</td>
<td>9.96</td>
<td>9.01</td>
<td>9.84</td>
</tr>
<tr>
<td>Left lateral ventricle volume: ml</td>
<td>11.13</td>
<td>9.84</td>
<td>10.70</td>
</tr>
<tr>
<td>Lateral ventricle volume: ml</td>
<td>21.09</td>
<td>18.86</td>
<td>20.35</td>
</tr>
<tr>
<td>Right temporal horn volume: ml</td>
<td>0.25</td>
<td>0.22</td>
<td>0.25</td>
</tr>
<tr>
<td>Left temporal horn volume: ml</td>
<td>0.22</td>
<td>0.18</td>
<td>0.17</td>
</tr>
<tr>
<td>Temporal horn volume: ml</td>
<td>0.47</td>
<td>0.40</td>
<td>0.42</td>
</tr>
<tr>
<td>Right ventricle : brain ratio</td>
<td>1.84</td>
<td>1.73</td>
<td>1.86</td>
</tr>
<tr>
<td>Left ventricle : brain ratio</td>
<td>2.33</td>
<td>2.15</td>
<td>2.32</td>
</tr>
<tr>
<td>Ventricle : brain ratio</td>
<td>2.07</td>
<td>1.93</td>
<td>2.07</td>
</tr>
<tr>
<td>Right temporal horn : brain ratio</td>
<td>0.05</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Left temporal horn : brain ratio</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Temporal horn : brain ratio</td>
<td>0.05</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Right hemisphere CSF (spaces): brain ratio</td>
<td>0.93</td>
<td>1.76***</td>
<td>1.28</td>
</tr>
<tr>
<td>Left-hemisphere CSF (spaces): brain ratio</td>
<td>1.18</td>
<td>2.14***</td>
<td>1.61*</td>
</tr>
<tr>
<td>CSF (spaces): brain ratio</td>
<td>1.05</td>
<td>1.94***</td>
<td>1.43*</td>
</tr>
<tr>
<td>Third ventricle : brain ratio using brain volume in the scans where third ventricle was identified</td>
<td>0.30</td>
<td>0.39</td>
<td>0.37</td>
</tr>
<tr>
<td>using total brain volume</td>
<td>0.11</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>Cisterna pineali : brain ratio</td>
<td>0.13</td>
<td>0.19*</td>
<td>0.18</td>
</tr>
<tr>
<td>Frontal index</td>
<td>30.19</td>
<td>30.17</td>
<td>30.53</td>
</tr>
<tr>
<td>Caudal index</td>
<td>9.24</td>
<td>9.68</td>
<td>14.04</td>
</tr>
<tr>
<td>Third-ventricle index</td>
<td>2.68</td>
<td>3.01</td>
<td>3.03</td>
</tr>
<tr>
<td>Plexus index</td>
<td>36.95</td>
<td>37.01</td>
<td>40.61**</td>
</tr>
<tr>
<td>Right-hemisphere frontal sulcal enlargement</td>
<td>1.57</td>
<td>2.52**</td>
<td>2.09</td>
</tr>
<tr>
<td>Left-hemisphere frontal sulcal enlargement</td>
<td>1.76</td>
<td>2.44*</td>
<td>2.32</td>
</tr>
<tr>
<td>Right-hemisphere parietal sulcal enlargement</td>
<td>1.57</td>
<td>2.15</td>
<td>1.91</td>
</tr>
<tr>
<td>Left-hemisphere parietal sulcal enlargement</td>
<td>1.48</td>
<td>2.19*</td>
<td>2.00</td>
</tr>
<tr>
<td>Right-hemisphere temporal sulcal enlargement</td>
<td>0.90</td>
<td>1.12</td>
<td>1.14</td>
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<tr>
<td>Left-hemisphere temporal sulcal enlargement</td>
<td>0.81</td>
<td>1.59*</td>
<td>1.23</td>
</tr>
<tr>
<td>Right-hemisphere occipital sulcal enlargement</td>
<td>0.24</td>
<td>0.96****</td>
<td>0.68*</td>
</tr>
<tr>
<td>Left-hemisphere occipital sulcal enlargement</td>
<td>0.38</td>
<td>1.04*</td>
<td>0.88</td>
</tr>
<tr>
<td>Right-hemisphere general sulcal enlargement</td>
<td>1.43</td>
<td>2.15*</td>
<td>1.86</td>
</tr>
<tr>
<td>Left-hemisphere general sulcal enlargement</td>
<td>1.43</td>
<td>2.11*</td>
<td>1.91</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.005, ****P<0.001.

Healthy volunteers had larger lateral-ventricle volume than the patients.

**Third ventricle**

There was a non-significant trend (P<0.06) towards larger third-ventricle volume in the patient group when this volume was considered as a proportion of the brain volume in the scans where the third ventricle was identified, but the difference disappeared when third-ventricle volume was analysed relative to the whole brain volume (third ventricle : brain ratio).
Indices

None of the frontal, caudal or plexus indices revealed any differences between the patients and the normal healthy volunteers. For the third-ventricle index a non-significant trend ($P<0.06$) was found towards a larger index in the patient group than in the healthy volunteers.

Results for patient subgroups

None of the healthy volunteers were alcohol/cannabis abusers according to the definition above, while 18 (37%) of the patients were non-abusers. Thus the $t$-tests and the $\chi^2$-tests were repeated with the non-abuser patients and the healthy volunteers. All the above-mentioned statistically significant findings, with the exception of parietal sulcal enlargement, fissura interhemispherica, and cisterna pineale: brain ratio, were found also after analysis of the results for the non-abusing patients and the healthy volunteers. Additionally, the third-ventricle index was significantly higher in the non-abuser patient group than in the control group ($P<0.02$) (Table 2).

All the healthy volunteers had a level of education corresponding to General Certificate of Education level or higher, while this was the case for 29 (59%) of the patients. The analyses with $t$-tests and $\chi^2$-tests were repeated with the educationally matched patient group and healthy-volunteer group. All the above-mentioned statistically significant findings persisted in the analyses with the educationally matched patient group (Table 2).

Table 4 shows the CT measurements in the group of healthy volunteers and in the groups of patients with schizophrenia and schizophreniform psychosis separately. In the sulcal-enlargement scores and the CSF (spaces)/brain ratio, the patients with schizophreniform psychosis took up an intermediate position between the healthy volunteers and the schizophrenic patients. However, on other parameters such as brain length and brain volume, the values for the patients with schizophreniform psychosis were very close to those for the schizophrenic patients.

Discussion

This study of patients admitted for the first time with schizophrenia or schizophreniform disorder is in conformity with previous studies (Benes et al, 1982; Nybach et al, 1982; Schulz et al, 1983; Turner et al, 1986), where structural brain changes were detectable in the early phase of the disease. We found both sulcal enlargement and a trend towards volume enlargement of the third ventricle, but no signs of lateral-ventricle enlargement. Larger VBR has been the most common finding in CT studies and it is thus somewhat surprising that we did not find it in this material.

However, another study of first-episode schizophrenic patients (Scottish Schizophrenia Research Group, 1989) also reported sulcal enlargement without ventriculomegali. This opens up the possibility that while sulcal enlargement may be present already during the first years of disease, the enlargement of lateral and possibly third ventricles may develop later on. The lateral-ventricle enlargement may reach a static state, as follow-up studies of chronic schizophrenic patients have not indicated progression. In a recent MRI study, Delisi et al (1991) found that although first-episode schizophrenic patients as well as chronic schizophrenic patients had enlarged lateral ventricles when compared with controls, the chronic patients had larger lateral ventricles than the first-episode patients, this being significant on the left side. The study, however, was not a follow-up one, but included different cross-sectional samples.

It is uncertain whether sulcal enlargement and lateral and third ventriculomegali are related or pathogenetically independent processes. Pfefferbaum et al (1988) found a significant relationship between the two phenomena. Other studies have indicated that cortical-tissue deficits (Cannon et al, 1989) and small cerebral volume (Schwarzkopf et al, 1991) may be independent of enlargement of the ventricles: the authors suggested that cortical impairment/smaller cerebral volume was related to the genetic load for schizophrenia, whereas ventricular enlargement was related to complications during pregnancy and birth. Recently, however, Done et al (1991), in a large prospective study, found no support for the hypothesis that early brain injury predicts schizophrenia later on.

Suddath et al's study (1990) of monozygotic twins discordant for schizophrenia also indicated that ventricular enlargement may not be exclusively genetically determined. In contrast, Nasrallah et al (1983) found an association between VBR and family history of schizophrenia.

At present, a synthesis of findings in early schizophrenia and in chronic cases seems quite difficult; however, one hypothesis would be that cortical areas (mainly frontotemporal) are structurally involved from the onset of disease, whereas subcortical structures (thalamus, striatum) are initially involved only through functional hyperactivity/malfunction, possibly due to impaired frontostriatal feedback (Weinberger, 1987; Rubin et al, 1991).

Subsequently, subcortical regions may be structurally impaired due to a 'burn-out' effect of continuous hyperactivity (Rubin et al, 1991), this resulting in shrinkage of subcortical structures and clinical deterioration to the level of residual symptoms. Dopaminergic blockade (e.g. with neuroleptics) may alter this process. This theory may explain the present findings as well as the lack of progressive structural change in chronic cases. The hypothesis is to be tested
at reinvestigation of the present cohort of patients and controls.

Our finding of smaller brain volume in the patient group is in agreement with reports made by Andreasen et al (1986), Pearlson et al (1989) and Schwarzkopf et al (1991), who found smaller cerebral and cranial size in CT and MRI studies. But Andreasen et al (1990) were not able to reproduce the findings in a subsequent study where the controls were educationally matched to the patients. However, the schizophrenic patients in Andreasen et al's first study (1986) had smaller cranial area than the educationally matched controls for the second study (1990). Also, post-mortem studies have indicated smaller brains in schizophrenic patients, the weight of the fixed brain being 4.5–8% less for schizophrenics than for controls (Pakkenberg, 1987; Bruton et al, 1990). Two post-mortem studies (Crow et al, 1989; Bruton et al, 1990) also found a reduction in brain length similar to our finding on the CT scans. However, other also well controlled post-mortem studies have not found brain reduction in schizophrenic patients (Heckers et al, 1991). In the present study the findings of greater sulcal enlargement and smaller brain volume were still significant when the educationally matched patients were compared with the healthy volunteers. The same was found concerning the subgroup of patients who were not substance abusers. Our measure of brain volume was based on eight CT scans excluding the uppermost and the lowest CT slices. This naturally leads to a somewhat lower brain volume than that obtained from post-mortem studies. Bruton et al (1990) found mean brain weight to be 1346 g in males and 1188 g in females in their schizophrenic group, and Pakkenberg (1987) found schizophrenic patients to have a mean brain weight (male and female) of 1266 g. Our mean brain volume was 982 ml for the patients. Our method thus reduces brain volume by about one-third. However, as the same method was used in the healthy volunteers, the differences found between the groups seem real.

Some MRI studies reported smaller temporal lobes in chronic schizophrenic patients (Suddath et al, 1989, 1990; DeLisi et al, 1991). The most pronounced difference in these studies was in the left temporal lobe. Crow et al (1989) in a post-mortem study found a highly selective enlargement of the left temporal lobe, and enlargement of the lateral ventricles has been reported to be greatest on the left side (DeLisi et al, 1991). Crow (1990) suggested a relationship between the schizophrenia disease process, asymmetrical brain development, and the gene or genes involved in normal asymmetrical brain development.

In our study the left fissura Sylvii was significantly wider in the patients than in the healthy volunteers, whereas the difference did not reach significance on the right side. Although there was no significant interaction between diagnosis and side, the results suggest an asymmetrical temporal-lobe reduction in the patients. Two other studies (Falkai et al, 1992; Crow et al, 1992) have measured the length of fissura Sylvii and found it reduced, but only on the left side.

The difference in volumes in the two hemispheres, with the right hemisphere being larger, is somewhat surprising, as the post-mortem study by Crichton-Browne (1879) did not find this asymmetry. Most CT, MRI and post-mortem studies do not report brain volume for each hemisphere separately, making knowledge in this area sparse. In our study, brain volume was calculated from eight CT slices, excluding the upper and lower parts of the brain, which leaves the possibility that the whole brain is less asymmetrical. The fact that the left lateral ventricle was greater than the right would predict a larger right-hemisphere brain volume, although the magnitude of difference we found cannot be explained by this fact alone. At present we have no evident explanation of the finding.

The present study indicates quite severe sulcal enlargement as well as smaller brain volume, shorter brain length and possible left temporal lobe reduction in first-episode schizophrenia and schizophreniform disorder. The lateral ventricles were not abnormal, thus suggesting that at least macroscopic impairment was confined mainly to cortical structures at this early stage of disease.

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References


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