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ORIGINAL PAPER

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# Frontal and temporal volume size of grey and white matter in patients with schizophrenia

## An MRI parcellation study

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**Abstract** We previously performed a magnetic resonance imaging (MRI) parcellation study that showed smaller grey and white matter volumes of the temporal lobes and increased CSF volumes in the frontal and temporal lobe in men with schizophrenia. One question that arose from this earlier study was whether similar structural changes in the brain are found in a large group of schizophrenic patients consisting of both men and women. In the present study, MRI scans were acquired from 94 patients of both genders with schizophrenia and 101 healthy subjects. After the automatic segmentation of grey matter, white matter, and cerebrospinal fluid, the frontal, temporal, parietal, and occipital lobes were automatically parcellated according to the Talairach atlas. Compared with healthy subjects, schizophrenic patients showed significantly smaller volumes of grey matter in the temporal lobe and white matter in the frontal lobe. Schizophrenic patients had a greater CSF volume in the frontal and temporal lobes. These results suggest that volume reduction in the cerebrum is prominent in the frontal and temporal lobes in both men and women with schizophrenia.

**Key words** cerebrospinal fluid · frontal lobe · grey matter · magnetic resonance imaging · schizophrenia · parietal lobe · temporal lobe · white matter

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## Introduction

Men with schizophrenia are more likely to exhibit prominent negative symptoms, whereas women with schizophrenia are more likely to present with positive symptoms [17, 15]. Since gender may be a significant factor in the pathophysiology of schizophrenia, it is possible that gender difference may be observed in brain morphology.

We previously reported that 32 men with schizophrenia showed smaller grey and white matter volumes with increased cerebrospinal fluid (CSF) in the temporal lobe compared with the features of 32 healthy men [13]. To investigate the hypothesis that similar structural abnormalities occur in the brains of a larger sample of both women and men with schizophrenia, we performed MRI to compare volumes of grey matter, white matter, and CSF in the temporal lobe, frontal lobe, parietal lobe, occipital lobe, and cerebrum of patients with schizophrenia of both genders and healthy subjects.

## Methods

The protocol was approved by the Institutional Review Board (IRB) at Karolinska Hospital. All subjects gave written informed consent.

### Subjects

Ninety-four men and women with chronic schizophrenia, fulfilling DSM-IV criteria [2], and 101 healthy male and female volunteers,

**Table 1** Number of cases (*n*), age, body mass index (BMI), current neuroleptic dosage converted into haloperidol units, duration of illness and intracranial volumes (ICV) in 94 schizophrenic and 101 healthy subjects of both genders

| | Schizophrenic men | Healthy men | Schizophrenic women | Healthy women | *p*_value (1) | | *p*_value (2) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Men | Women | Schizophrenic subjects | Healthy subjects |
| Number | 72 | 66 | 22 | 35 | | | | |
| Age (years) | 42.1 ± 6.7 | 41.0 ± 9.1 | 39.7 ± 7.7 | 40.8 ± 8.7 | 0.46 | 0.64 | 0.17 | 0.90 |
| Age range [min-max] (years) | 25–54 | 19–54 | 25–50 | 20–56 | | | | |
| BMI | 27.6 ± 5.1 | 26.4 ± 3.9 | 26.4 ± 4.8 | 24.6 ± 4.2 | 0.14 | 0.14 | 0.33 | 0.03 |
| Neuroleptic dosage (mg/day) | 4.2 ± 3.1 | | 3.5 ± 2.8 | | | | 0.39 | |
| Age at onset | 24.5 ± 5.1 | | 24.6 ± 5.7 | | | | 0.94 | |
| Duration of illness (years) | 17.1 ± 7.4 | | 14.2 ± 8.2 | | | | 0.14 | |
| ICV (ml) | 1525 ± 122 | 1535 ± 120 | 1366 ± 96 | 1342 ± 97 | 0.63 | 0.36 | <0.0001 | <0.0001 |

Values are means ± SD in the age, BMI, neuroleptic dosage, duration of illness and ICV.
*p*_value(1): Comparison between diagnosis groups for each of the gender groups using Student's *t*-test.
*p*_value(2): Comparison between gender groups for each of the diagnosis groups using Student's *t*-test.

all Caucasian, were included in this study. The subjects were recruited at the Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden, and investigated between August 1999 and May 2003. Inclusion and exclusion criteria were described in a previous paper [13]. At the time of the investigation, 79 patients were receiving antipsychotic medication. Forty-four patients used typical neuroleptics and 38 atypical neuroleptics. Among these patients, three were prescribed both typical and atypical neuroleptics, while five were given no neuroleptic medication, and the medication of ten patients was unknown. The mean (±SD) dose of neuroleptic medication was 4.0 (±3.1) mg/day when converted into haloperidol units [11]. The patients had an average (±SD) age at onset of illness of 24.5 (±5.2) years and the mean duration of illness was 16.4 (±7.6) years. The mean duration of hospitalization was 10.3 (±11.5) days in schizophrenic patients. Mean scores on the Scale for the Assessment of Positive Symptoms (SAPS) [4] and the Scale for the Assessment of Negative Symptoms (SANS) [3] were 13.2 (±10.7) and 34.5 (±20.1) in schizophrenic patients, respectively.

### MR scan and volume measures

The subjects were examined with a 1.5 Tesla GE Signa (Milwaukee, Wis. USA) system at the MR Center, Karolinska Hospital, Stockholm, Sweden. MR data analysis was performed using the software BRAINS [5]. The procedure was described in a previous report [13]. In brief, contiguous coronal T1- and T2-weighted images with 1.5 mm and 2.0 mm slice thicknesses, respectively, were used. The program provided continuous classification for segmentation of brain tissue based on voxel-based morphometry analysis [10]. We measured the segmented tissue class (grey matter, white matter, and CSF) volumes in the frontal, temporal, parietal, and occipital lobes according to the Talairach atlas [18]; the intracranial volume (ICV) was determined automatically [10, 12]. The measurement volume for the cerebrum was the sum of the frontal, parietal, occipital, and temporal regions, and a subcortical region. The ventricular CSF box included both the lateral ventricles and the third ventricle. External CSF was calculated by subtracting the ventricular CSF from the intracranial CSF. To correct for individual differences in head size, we calculated relative regional volumes (100 × absolute volume/ICV).

The reproducibility and reliability of measuring tissue volumes has been established previously [1, 14]. We measured tissue volumes in regions of interest on 10 scans as intraclass correlation coefficients [16] for grey matter, white matter, and CSF volumes for the frontal box, temporal box, parietal box, occipital box, and intracranium; the interoperator (IA and GO) and intraoperator (GO) reliability for these measurements were both in the range 0.909–0.998.

### Statistical analysis

We used the Student's *t*-test to assess group differences for age, body mass index (BMI), neuroleptic dosage at MRI (here called current medication), age at onset, duration of illness, and intracranial volume (Table 1). Statistical analyses used a 2-tailed $\alpha$ level of 0.05 for significance, unless otherwise stated.

We compared relative volumes in regions of interest between diagnosis groups using analysis of covariance (ANCOVA). The model included diagnosis as a main effect, age and gender as covariates, and the interaction of each covariate and diagnosis. If the interaction terms were not significant ($p < 0.007 = 0.05/7$ (seven regions)) then the terms were dropped from the final model. The analyses were performed on relative grey matter, white matter, and CSF volumes in regions of interest. The main effect and covariates were considered significant if $p < 0.007 = 0.05/7$ (seven regions). The significance level was adjusted using the Bonferroni inequality.

Pearson's correlation was used to test the correlation between relative volumes in regions of interest and BMI, current dose of medication converted to haloperidol units, age at onset, and duration of illness in the patients group.

## Results

### Subject characteristics (Table 1)

There was a significant difference in BMI between men and women among the healthy subjects, but not among the schizophrenic subjects. There were no significant differences in neuroleptic dosage, age at onset, or duration of illness between men and women with schizophrenia. There were significant within-diagnostic differences in ICV between men and women among both schizophrenic and healthy subjects.

### Relative volume measurements by diagnosis and gender and statistical test variables are presented in Table 2

#### Gender-by-diagnosis interaction

Regarding relative tissue volumes, the ANCOVA model included diagnosis as a main effect, and age

**Table 2** Relative MRI volumes of regions of interest, *F*-values and *p*-values of diagnostic and age differences of relative volumes, in 94 schizophrenic patients compared with 101 healthy subjects of both genders

| | Schizophrenic men ($n$ = 72) | Healthy men ($n$ = 66) | Schizophrenic Women ($n$ = 22) | Healthy women ($n$ = 35) | Diagnostic difference | | Covariate of age effect | |
|---|---|---|---|---|---|---|---|---|
| | | | | | *p*-value | *F* value | *p*-value | *F* value |
| Cerebrum | | | | | | | | |
| Grey matter | 44.6 ± 1.2 | 45.4 ± 1.4 | 44.9 ± 1.0 | 45.3 ± 1.3 | 0.004 | 8.75 | <0.001 | 87.8 |
| White matter | 27.6 ± 2.1 | 28.6 ± 1.9 | 28.1 ± 2.2 | 29.0 ± 1.9 | <0.001 | 11.52 | ns | 3.5 |
| CSF | 12.9 ± 2.1 | 11.8 ± 2.1 | 12.3 ± 1.8 | 11.4 ± 1.9 | <0.001 | 15.69 | <0.001 | 37.8 |
| Frontal lobe | | | | | | | | |
| Grey matter | 17.0 ± 0.8 | 17.2 ± 0.7 | 17.0 ± 0.6 | 17.2 ± 0.6 | ns | 5.8 | <0.001 | 38.4 |
| White matter | 10.7 ± 1.0 | 11.1 ± 1.1 | 10.6 ± 1.1 | 11.1 ± 0.7 | 0.002 | 10 | ns | 4.6 |
| CSF | 6.3 ± 1.2 | 5.7 ± 1.2 | 6.2 ± 1.2 | 5.7 ± 1.2 | <0.001 | 11.9 | <0.001 | 27.3 |
| Temporal lobe | | | | | | | | |
| Grey matter | 9.9 ± 0.4 | 10.1 ± 0.4 | 10.1 ± 0.3 | 10.2 ± 0.4 | 0.001 | 11.1 | <0.001 | 27.5 |
| White matter | 4.6 ± 0.4 | 4.8 ± 0.4 | 4.8 ± 0.4 | 4.8 ± 0.3 | ns | 2.4 | ns | 6.4 |
| CSF * | 2.7 ± 0.4 | 2.3 ± 0.3 | 2.5 ± 0.4 | 2.2 ± 0.2 | <0.001 | 53.7 | <0.001 | 18 |
| Parietal lobe | | | | | | | | |
| Grey matter | 9.5 ± 0.4 | 9.5 ± 0.5 | 9.5 ± 0.5 | 9.6 ± 0.4 | ns | 0.6 | <0.001 | 24 |
| White matter | 6.6 ± 0.6 | 6.8 ± 0.5 | 6.8 ± 0.6 | 7.0 ± 0.5 | ns | 4.6 | ns | 2.1 |
| CSF | 2.7 ± 0.7 | 2.7 ± 0.7 | 2.6 ± 0.5 | 2.5 ± 0.6 | ns | 0.01 | <0.001 | 23.3 |
| Occipital lobe | | | | | | | | |
| Grey matter | 4.7 ± 0.4 | 4.7 ± 0.3 | 4.8 ± 0.3 | 4.8 ± 0.3 | ns | 0.06 | ns | 4.4 |
| White matter | 2.8 ± 0.4 | 2.9 ± 0.3 | 2.9 ± 0.3 | 2.9 ± 0.3 | ns | 1.3 | ns | 2.7 |
| CSF | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.05 ± 0.1 | ns | 0.4 | ns | 4.3 |
| Ventricular CSF | 1.8 ± 0.6 | 1.4 ± 0.5 | 1.6 ± 0.7 | 1.2 ± 0.4 | <0.001 | 23.5 | <0.001 | 15.9 |
| External CSF | 14.3 ± 2.1 | 13.3 ± 2.2 | 13.6 ± 1.9 | 12.8 ± 2.1 | 0.002 | 9.6 | <0.001 | 32.5 |

Values are mean volumes ± SD. Diagnostic differences were evaluated by analysis of covariance (ANCOVA) that included diagnosis as a main effect, with age and gender as covariates. The degrees of freedom for the test of Diagnosis difference were $F$(df = 1,df = 191).
*Covariate of gender effect; $F$ = 8.8, df = 1,191, $p$ = 0.004: ANCOVA including diagnosis as a main effect, with age and gender as covariates
ns: Not significant

and gender as covariates. The interaction of each covariate and diagnosis showed that there was no gender-by-diagnosis interaction in any of the studied regions of interest.

### Age-by-diagnosis interaction

In terms of relative volumes, the ANCOVA model included diagnosis as a main effect, and age and gender as covariates. The interaction of each covariate and diagnosis demonstrated that there was no age-by-diagnosis interaction in any region of interest.

### Diagnostic differences

Regarding relative volumes in regions of interest, the ANCOVA model with diagnosis as a main effect and age and gender as covariates demonstrated significant diagnostic differences for cerebral and temporal grey matter, cerebral and frontal white matter, cerebral CSF, frontal CSF, temporal CSF, ventricular CSF and external CSF.

### Covariates of age and gender effects

There was a significant age impact on relative volumes in cerebral grey matter, frontal grey matter, parietal grey matter, temporal grey matter, cerebral CSF, frontal CSF, parietal CSF, temporal CSF, ventricular and external CSF. There was a significant gender impact on relative volumes in temporal CSF.

### Correlation between volumes and clinical measures

Relative volumes of the regions of interest were not significantly correlated with current neuroleptic dosage, age at onset, duration of illness, or BMI among patients.

## Discussion

In this study, patients with schizophrenia demonstrated smaller grey matter volumes in the temporal lobe and cerebrum, smaller white matter volumes in the frontal lobe and cerebrum, and larger CSF volumes in the frontal lobe, temporal lobe and cerebrum, compared with healthy subjects.

There was no significant gender-by-diagnosis effect in the volumes of the frontal lobe, temporal lobe, or cerebrum in this study. The results find support in a study by Flaum et al. [9], who found no gender-by-diagnosis effects in the cerebrum or temporal lobe in patients with schizophrenia compared with healthy subjects.

In the present study, we found smaller white, but not grey matter volumes, in the frontal lobes among patients with schizophrenia. Buchanan et al. [6] reported volume reductions in the prefrontal white matter in patients with schizophrenia as well as volume reduction in the inferior gyri. Chemerinski et al. [8] found that the global measure of grey matter volume in the frontal lobe was not significantly different between schizophrenic patients and healthy subjects, but that subdivided regions of grey matter in the frontal lobe were significantly smaller in schizophrenic patients than in healthy subjects. In the present study, we did not find frontal grey matter to be smaller in schizophrenic patients.

However, our findings do not exclude the possibility that discrete regions within the frontal lobe grey matter might be smaller among our patients than for the corresponding regions in the healthy control subjects. We also cannot exclude that type II errors may have occurred in frontal grey matter volume since a conservative Bonferroni correction was used in the statistical analysis of this study; this could in part explain why we did not find decreased frontal grey matter volume in schizophrenic patients.

We found smaller temporal lobe grey matter volumes in the patients but unchanged temporal white matter volumes. A similar finding in terms of smaller volume size of grey but not white matter has previously been reported for patients with schizophrenia [7]. Our findings of reduced volume in the frontal but not temporal white matter in schizophrenic patients are inconsistent with those of the previous study [13]; this inconsistency may reflect differences in sample sizes.

In the current study, the patients with schizophrenia demonstrated significantly larger CSF volumes of the frontal lobe, temporal lobe, and cerebrum than did the healthy subjects. The present findings of larger CSF spaces are the same as previously reported [13]. The findings were observed in both men and women with schizophrenia.

In conclusion, the findings of the present study support the view that volume reduction of the cerebrum is prominent in the frontal and temporal lobes among both men and women with schizophrenia.

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