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ORIGINAL PAPER

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Reduced grey and white matter volumes in the temporal lobe of male patients with chronic schizophrenia

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Abstract Magnetic resonance imaging (MRI) and tissue segmentation were used to quantify grey matter, white matter and cerebrospinal fluid (CSF) volumes in the brains of 32 males with chronic schizophrenia and 32 healthy males. Tissue volumes in the frontal, temporal, parietal, and occipital regions were measured separately. Males with schizophrenia had significant reductions of grey and white matter volumes in the temporal regions compared with controls. Patients also had significantly smaller white matter volumes in the cerebrum and increased CSF volumes in the frontal and the temporal regions as well as the cerebrum.

The findings of the present study suggest that volumes of grey and white matter are reduced in the temporal region of males with chronic schizophrenia. The volume of white matter in the whole brain also appears to be reduced. Among the different brains regions, grey matter reduction was significant only in the temporal region.

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

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Introduction

In the scientific literature, most authors have reported reduction of grey rather than white matter in the brains of schizophrenic subjects using MRI (see McCarley for review). Recent studies have however demonstrated white matter alterations in schizophrenia as well as alterations of grey matter (e. g., Cannon et al. 1998, Gur et al. 2000, Marsh et al. 1997, Matsumoto et al. 2001, Paillère-Martinot et al. 2001, Sigmundsson et al. 2001, Sowell et al. 2000). This important discrepancy provides a rationale for investigating whether predominantly grey or white matter abnormalities can be demonstrated in the brains of schizophrenic patients and whether there is a regional preference for these abnormalities.

To test the hypothesis that volumes of white as well as of grey matter are reduced in brain regions of schizophrenic subjects, we used MRI and automated tissue segmentation to measure and compare volumes of grey matter, white matter and cerebrospinal fluid (CSF) in male subjects with chronic schizophrenia and healthy male volunteers.

Methods

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

Subjects

Thirty-two males with chronic schizophrenia, fulfilling DSM-IV criteria (American Psychiatric Association, 1994) and 32 healthy male volunteers, all Caucasian, were included in this study (mean age ± SD: 39.3 ± 7.2 and 38.6 ± 7.4 years, respectively). The subjects were recruited at the Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, Sweden, and investigated between August 1999 and April 2001. At the time of the investigation, 29 patients were receiving antipsychotic medication (17 used atypical and 12 used typical antipsychotic drugs). The mean (± SD) dose of neuroleptic medication was 4.5 (± 3.4) mg/day when converted into haloperidol units (Amer-

ican Psychiatric Association, 1997). The patients had an average (± SD) age at onset of illness of 25.4 (± 6.1) years and a mean duration of illness of 14.6 (± 7.7) years. Twenty-eight patients and 30 healthy subjects were right-handed. They were all found to be physically healthy according to physical examination and blood biochemistry. All subjects underwent a psychiatric interview (SCID) (Spitzer et al. 1986) to confirm schizophrenia in the patients and lack of mental disorders in the control subjects. The interview was performed by an experienced psychiatrist who is well trained in the administration of this instrument. Exclusion criteria for the healthy volunteers were current or past treatment for a psychiatric disorder and for all the subjects a history of alcoholism or drug addiction, head trauma with loss of consciousness for more than five minutes, or a history of somatic disorder.

Volumetry

The subjects were examined with a 1.5 Tesla GE Signa (Milwaukee, Wis. USA) system at the MR Center, Karolinska Hospital, Stockholm. MR data analysis was performed using the software BRAINS (Andreasen et al. 1993). For tissue classification, the following MR pulse sequences were used: T1-weighted images, using a spoiled GRASS sequence, were acquired with the following parameters: 1.5 mm coronal slices, no gap, 35° flip angle, TR 24 ms, TE 6.0 ms, 2 NEX, FOV 24 cm, acquisition matrix 256 × 192. T2-weighted images were acquired with the following parameters: 2.0 mm coronal slices, no gap, TE 84 ms, TR 6000 ms, 2 NEX, 24 cm FOV, acquisition matrix 256 × 192. Reproducibility and reliability of this segmentation procedure have been ascertained previously (Harris et al. 1999, Agartz et al. 2002). The quantitative analysis was performed blinded with regard to the two diagnostic categories. Regional measurements were ascertained by transformation of MRI data into Talairach space (Talairach and Tournoux 1988, Collins et al. 1994, Andreasen et al. 1996). The Talairach boxes were assigned to specific regions corresponding to the frontal, temporal, parietal and occipital lobes and to the subcortical region (Nopoulos et al. 1999). We measured the segmented tissue class volumes of each region and the intracranial volume (ICV) automatically and separately (Harris et al. 1999, Magnotta et al. 1999). The CSF tissue class volume contained both internal and external CSF. We analyzed frontal, parietal, occipital and temporal regions and a measure of the cerebrum (frontal, parietal, occipital, temporal regions and the subcortical region added together). Tissue class volumes from both hemispheres were combined in the calculations. To correct for individual differences in head size, we also calculated relative regional volumes (100 ± absolute volume/ICV).

Statistical analysis

Interoperator reliability for the measurement was established for two experienced investigators (I. A. and G. O) who were blind to subject identity and diagnosis on ten of the scans using intraclass correlations (Shrout et al. 1979). Intraclass correlations for inter- and intraoperator reliability for the tissue class (i. e., grey matter, white matter and CSF) volumes of all the regions were excellent ($r^2 > 0.91$).

Group differences were assessed using analysis of variance (ANOVA). Differences were considered to be statistically significant if $p < 0.0033 = 0.05/15$ (five regions, three tissue classes).

Pearson's correlation was used to test the correlation between volume measures and current dose of medication as converted into haloperidol units, age of onset or duration of illness in the patient group.

Results

ICV (ml) was similar in schizophrenic and healthy subjects (1,509.8 ± 127.4, 1,507.1 ± 149.6, respectively). The absolute and relative volumes for the cerebrum and the other regions are shown in Table 1. The absolute CSF volume of the cerebrum and the CSF volume in the temporal region were significantly larger in patients with schizophrenia. With regard to relative volumes, the patients had significantly smaller grey matter and white matter volumes in the temporal lobe and the cerebrum, and larger CSF volumes in the frontal and temporal lobes and the cerebrum.

Table 1 Absolute (ml) and relative volumes of grey matter, white matter and CSF in various brain regions in thirty-two schizophrenic and thirty-two healthy males

Region	Absolute volumes (ml)		Relative volumes	
	Schizophrenic males	Healthy males	Schizophrenic males	Healthy males
Frontal				
grey matter	264.3±26.2	263.7±26.4	17.5±0.8	17.5±0.6
white matter	163.3±20.1	174.0±24.0	10.8±1.2	11.5±1.0
CSF	97.0±23.3	81.6±18.5	6.4±1.3[c]	5.4±1.0
Temporal				
grey matter	152.0±13.9	157.6±14.4	10.1±0.5[d]	10.5±0.5
white matter	67.6±7.6	74.5±10.5	4.5±0.5[e]	4.9±0.5
CSF	39.9±7.1[a]	32.0±8.8	2.6±0.4[f]	2.1±0.5
Parietal				
grey matter	145.1±15.8	143.4±14.5	9.6±0.5	9.5±0.6
white matter	98.3±10.7	103.8±13.8	6.5±0.6	6.9±0.6
CSF	42.1±13.7	37.9±11.0	2.8±0.8	2.5±0.6
Occipital				
grey matter	71.9±9.9	70.3±8.3	4.8±0.4	4.7±0.4
white matter	40.6±6.5	44.4±7.7	2.7±0.4	2.9±0.3
CSF	11.5±4.2	10.0±3.3	0.8±0.3	0.7±0.2
Cerebrum				
grey matter	686.8±62.4	688.3±63.5	45.5±1.5	45.7±1.3
white matter	413.3±43.9	445.5±56.7	27.4±2.3[g]	29.5±2.1
CSF	207.9±45.9[b]	175.3±38.6	13.7±2.4[h]	11.6±1.9

Values are means ± SD. Group difference [a] $F = 16.21$, $p = 0.0002$, [b] $F = 10.07$, $p = 0.0023$, [c] $F = 12.56$, $p = 0.0008$, [d] $F = 10.03$, $p = 0.0024$, [e] $F = 13.96$, $p = 0.0004$, [f] $F = 20.03$, $p < 0.0001$, [g] $F = 14.36$, $p = 0.0004$, [h] $F = 15.33$, $p = 0.0002$, ANOVA

No absolute and relative volumes of any of the regions were significantly correlated with current neuroleptic dosage as converted into haloperidol units. Nor was there any correlation between volume measures and duration of illness nor age of onset.

Discussion

In this study, male patients with schizophrenia had smaller relative volumes of grey and white matter and larger CSF spaces in the temporal region than healthy males. Significantly smaller relative white matter volumes in the cerebrum and larger relative CSF spaces in the frontal and temporal regions and in the cerebrum were also found in the patients.

The present findings are in agreement with those of previous studies reporting temporal white and grey matter alterations (Cannon et al. 1998, Marsh et al. 1997, Sigmundsson et al. 2001). Functionally, various fiber systems are present in the white matter of the temporal lobe: acoustic radiation, optic radiation, temporopontine tract and temporothalamic fasciculus (Sedat and Duvernoy 1990). The volume reduction of the grey and white matter in the temporal lobe of schizophrenic patients may reflect aberrations of some or all of the temporal systems. Methods such as MR diffusion tensor imaging (DTI) may elucidate abnormalities in the white matter tracts particularly in the temporal lobe. However, in a DTI study, our research group found that fractional anisotropy (an indirect measure of the degree of co-linearity of white matter fibers or structural elements) was reduced in the splenium of the corpus callosum and in adjacent occipital white matter in patients with schizophrenia but there were no tissue deficits in the volume of reduced anisotropy (Agartz et al. 2001) so altered anisotropy does not automatically imply that there is tissue loss. The present finding of larger CSF spaces in several regions in schizophrenic patients is consistent with previous MRI studies (Shenton et al. 2001 for review).

In conclusion, the findings of the present study support the view of subtle temporal white as well as grey matter deficits as part of a diversified morphological brain alteration in schizophrenia. Further studies of clinically well-characterized schizophrenic subjects will be necessary to clarify the role of the temporal lobe volume changes in the pathophysiology of schizophrenia.

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