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## Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia

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### Abstract

Thirteen male patients with schizophrenia and thirteen male normal control subjects were compared by magnetic resonance imaging (MRI) on volumes of the straight gyrus (SG), anterior cingulate gyrus, middle frontal gyrus, hippocampus, third ventricle, cavum septi pellucidi, total brain volume and intracranial volume. In addition, neuropsychological tasks were used to measure working memory and executive functions. Healthy volunteers and schizophrenic patients showed no significant differences in mean values for volumes of regions of interests. In the case of the SG, we found a significant difference in laterality: the tendency toward left dominance in healthy volunteers changed to significant right dominance in patients. The schizophrenic patients showed lower performance in working memory tasks, and strongly significant group differences were observed in measures of neurological signs assessed by the Neurological Evaluation Scale (NES). Negative symptoms correlated with the level of spatial working memory and executive functions. Negative symptoms also correlated with the volume of the right hippocampus, while the rate of anhedonia negatively correlated with the relative volume of the left SG.

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**Keywords:** Schizophrenia; Working memory; Executive functions; MRI; Straight gyrus

### 1. Introduction

The brain structural changes correlating with mental disorders are usually subtle ones and are not easily

revealed with macroscopic volumetric analyses. Schizophrenia is in part a neurodevelopmental disorder based on multifocal brain structure changes with a background of defective neuronal migration, myelination and/or cortico–cortico wiring. As a consequence, this disorder is characterised by defective cytoarchitectonic and neurochemical connections within and between certain neuronal networks. Many neocortical areas

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are affected in schizophrenia, principally structures within the prefrontal and medial paralimbic regions. Recent imaging studies revealed changes in the middle frontal gyrus, the anterior cingulate gyrus, the paracingulate gyrus, and the insula as well as in the frontomedial and orbitofrontal cortical areas (Goldstein et al., 1999). An alteration of the superior temporal gyrus (STG) was also found, more specifically of the planum temporale, supramarginal gyrus and Heschl's gyrus (Hirayasu et al., 2000). Among sub-cortical areas, the impairment of the amygdala–hippocampus complex (Wright et al., 2000) and of the thalamus (Konik and Friedman, 2001) was primarily detected. A significant right>left asymmetry was found in certain areas such as the STG, in which left>right difference is typical among healthy subjects, and also in the amygdala–hippocampus complex (Petty, 1999; Sommer et al., 2001). Among developmental anomalies, midline deviations are typical in schizophrenia. The dilatation of the third ventricle and the cavum septi pellucidi (CSP) has also been found to be characteristic (McCarley et al., 1999). In cases with childhood onset, changes are apparent before the onset of psychosis (James et al., 2002).

There has been a continuous development in the methods of topographical mapping of in vivo magnetic resonance imaging (MRI) data in the past decade. A valuable parcellation method has recently been developed by Crespo-Facorro et al. (2000). Crespo-Facorro et al. (2000) realised that landmarks cannot always be identified on each slice as a result of individual variations; therefore they suggested a method by which the continuity of target regions is captured on consecutive slices. They divided the neocortex into 41 regions. Their procedure unites the advantages of the two-dimensional definition of regions in three orthogonal planes (coronal, sagittal and transaxial) and of the simultaneous visualization of the three-dimensional reconstruction of the brain. In the present study, we applied the method of Crespo-Facorro et al. (2000) (see also Kim et al., 2000), and we used the method of a French research group for the volumetric measures of the hippocampus (Duvernoy, 1998).

One of the most influential general models of human cognition is the working memory model, which postulates that short-term memory operates as a working space holding information on-line during comprehension, learning and goal-directed behaviour. The tripartite model of working memory assumes that besides a central executive control system, limited capacity verbal and visuo-spatial subsystems contribute separately to the temporary maintenance and manipulation of

verbal and visuo-spatial information (Baddeley, 1986; Baddeley et al., 1998; Baddeley and Logie, 1999).

Although a wide range of cognitive functions is impaired in schizophrenia, working memory research has been a prominent area of cognitive neuropsychiatric research of the syndrome. A number of recent studies have found that different components of the working memory system are impaired at different levels in schizophrenia, and the severity of impairment correlates with negative and positive symptoms of the illness (for review, see Keefe, 2000). However, the picture is far from clear, partly because of the cognitive heterogeneity of experimental tasks and partly because of the clinical heterogeneity of schizophrenic patient groups (Bressi et al., 1996; Carter et al., 1996; for a review, see Palmer and Heaton, 2000).

The most studied aspect of working memory in schizophrenia is the central executive component. Several lines of research explored the abilities of planning, flexible strategy changing, fluency and inhibition using a wide range of neuropsychological tasks that are usually regarded as screening methods for frontal pathology. A number of studies found significant correlations between clinical symptoms of schizophrenia and working memory functions (see Addington, 2000; Phillips and David, 2000). For instance, Carter et al. (1996) found a strong correlation between spatial working memory capacity and scores on the Scale for the Assessment of Negative Symptoms (Andreasen, 1982). A strong relationship was found between spatial working memory and executive functions and positive symptoms such as thought intrusion, delusion and hallucination (Carter et al., 1996; Bressi et al., 1996). Taking all of these results into consideration, it would be important to clarify the role of working memory subsystems in the development of schizophrenic symptoms and also to identify the brain regions underlying these functional deficits.

In the present study, brain morphology and the clinical and cognitive performances of male schizophrenic patients treated at the psychiatric outpatient clinic of the University of Szeged were investigated. The questions of this preliminary report were whether specific volumetric changes could be observed in schizophrenia in areas thought to be involved in working memory and, in addition, whether the brain size changes would correlate with changes in cognitive functions and with symptomatology.

All patients were in the early phase of the illness, in an interepisodic state and under medical treatment. We measured the intracranial volume, the volume of the whole brain, the external cerebrospinal fluid space, the

third ventricle, both hippocampi, both middle frontal gyri, both anterior cingulate gyri, both straight gyri and the grey matter of the orbitofrontal cortex. With cognitive tests the functioning of verbal and visuo-spatial working memory and the abilities of planning and flexible strategy shifting were assessed.

## 2. Methods

### 2.1. Subjects

Only male subjects participated in the experiment, as we enrolled a relatively low number of subjects in this research and we wanted to exclude the variance of brain size attributable to gender differences. Thirteen patients were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. All patients had a diagnosis of schizophrenia defined by DSM-IV (American Psychiatric Association, 1994) and ICD-10 criteria for research (World Health Organization, 1993). All patients were in a stable interepisodic state, during the early stages of the illness, and under antipsychotic medication. The 13 normal control subjects were recruited from hospital staff and community volunteers. They were evaluated with a modified structured interview (Mini International Neuropsychiatric Interview (MINI) — Hungarian version, Balázs et al., 2001), and we excluded normal control subjects with a family history of psychotic and affective spectrum disorders. All subjects were 25 to 37 years of age, had scores above 85 in full scale IQ (WAIS, Hungarian version, Kun and Szegegi, 1997), had a minimum of 8 years of education (primary school), and were able to give informed consent. Subjects were excluded if they had a lifetime history of neurological illness, any medical illness known to affect brain structure, head injury with loss of consciousness for more than 10 min, psychoactive substance abuse within the last 6 months, or any medical illness that could significantly constrain neurocognitive functions. Patients were excluded if they had previously undergone electroconvulsive therapy.

The demographic and clinical characteristics of the subjects are shown in Table 1. Although there was a significant difference between the groups in education and IQ measured by the WAIS, the average of the schizophrenic group was above 100, and the minimum score was 86. All patients comprehended and carried out all instructions. There was no difference between groups in handedness, every subject enrolled in the study was right-handed judged by the Neurological Evaluation Scale (NES). Because of the low subject

Table 1  
Demographic and clinical characteristics of the subjects

|                             | Control<br>(N=13) | Schizophrenia<br>(N=13) | P <sup>a</sup> |
|-----------------------------|-------------------|-------------------------|----------------|
| Age (years)                 | 29.3 ± 4.7        | 25.9 ± 5.4              | 0.139          |
| Education (years)           | 14.4 ± 2.6        | 11.1 ± 1.9              | 0.004          |
| Full scale IQ               | 124.3 ± 12.7      | 101.1 ± 12.3            | 0.002          |
| Age at onset (years)        |                   | 21.9 ± 4.8              |                |
| Duration of illness (years) |                   | 3.9 ± 3.0               |                |
| Relapses                    |                   | 3.2 ± 2.1               |                |
| PANSS                       |                   |                         |                |
| Positive                    |                   | 9.9 ± 3.8               |                |
| Negative                    |                   | 14.0 ± 5.8              |                |
| Global                      |                   | 27.0 ± 9.0              |                |
| Total                       |                   | 50.9 ± 15.3             |                |
| SANS                        |                   |                         |                |
| Affective                   |                   | 1.2 ± 1.1               |                |
| Alogia                      |                   | 1.2 ± 1.1               |                |
| Avolition                   |                   | 0.9 ± 1.0               |                |
| Anhedonia                   |                   | 1.6 ± 1.2               |                |
| Attention                   |                   | 0.9 ± 1.1               |                |
| SAS                         |                   | 2.5 ± 2.3               |                |
| BAS                         |                   | 0.2 ± 0.6               |                |
| AIMS                        |                   | 0.2 ± 0.4               |                |
| NES                         |                   |                         |                |
| Sensory integration         | 0.1 ± 0.3         | 4.1 ± 2.1               | 0.000          |
| Motor coordination          | 0.1 ± 0.3         | 1.0 ± 1.0               | 0.026          |
| Motor sequencing            | 0.3 ± 0.5         | 4.9 ± 2.6               | 0.000          |
| Global                      | 3.6 ± 2.6         | 19.5 ± 3.9              | 0.000          |
| SDS                         |                   |                         |                |
| Deficit syndrome            |                   | 2 patients              |                |
| Non-deficit                 |                   | 11 patients             |                |

Values represent mean ± S.D.

<sup>a</sup> Mann–Whitney *U*-test.

number we did not consider the effect of antipsychotics. Three of the patients were treated with conventional neuroleptics, six of them with atypical antipsychotics, and four persons with combination of an atypical oral and a conventional depot injectable neuroleptics. All substances were prescribed in medium dose according to their medication protocol. No one of the patients had any known family history of psychotic disorders.

### 2.2. Clinical tests

Clinical symptoms were assessed by psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989), the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989), the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970), the Abnormal Involuntary Movement Scale

(AIMS) (Guy, 1976), and the Barnes Akathisia Rating Scale (BAS) (Barnes, 1989), with assessment of the demographic and epidemiologic data at the time of the MRI study.

### 2.3. Working memory tasks

Widely used neuropsychological tasks were employed to measure working memory and executive functions. The cognitive functions were assessed by psychiatrists, a trained research assistant and a trained undergraduate psychology student. We measured verbal working memory capacity with the Digit Span Forward and Backward tasks (Wechsler, 1981; Kun and Szegedi, 1997), and the Hungarian version of the Nonword Repetition Test (Gathercole et al., 1994; Racsmany et al., 2002). We used the Corsi Blocks (Milner, 1971) and Visual Patterns Test (Della Sala et al., 1997) for measurement of visuo-spatial working memory capacity. We assessed executive functions with the Wisconsin Card Sorting Test (WCST) (Berg, 1948), the Tower of Hanoi (Simon, 1975), Letter Fluency (Benton and Hamsher, 1976), and the Category Fluency task (Spreen and Strauss, 1991).

### 2.4. MRI scans

All the multimodal MRI examinations were performed on a Signa Horizon 1 Tesla MR Unit (General Electric, GE) at the International Medical Center (Szeged, Hungary). Three-dimensional T1 weighted images using the spoiled gradient echo (SPGR) sequence were obtained in the coronal plane with the following parameters: echo time (TE)=3 fr/ms, repetition time (TR)=33 ms, number of excitations (NEX)=1, rotation angle=45°, field of view (FOV)=24 × 18, slice thickness=1.5 mm, and acquisition matrix of 256 × 192. Two-dimensional FSE (fast spin echo) T2 sequences were gained as follows: echo time (TE)=91.1 fr/ms, repetition time (TR)=4300 ms, number of excitations (NEX)=3, field of view (FOV)=25 × 19, acquisition matrix: 384 × 192. The in plane resolution was 1016 × 1016 mm in all three planes. MRI data were postprocessed on an Advantage Windows (Silicon Graphics) workstation with Advantage 3.1 software (developed by GE).

Single manual measurement with intra-rater control and inter-rater supervision was performed on serial coronal or axial slices of all regions of interest. The initial step was the identification of the reference anatomical landmarks that served as boundaries on each plane. The second step was to determine the regions of

interest (ROIs) for tracing, and the third step was to trace by hand in each ROI the surface area or grey matter on the appropriate coronal and axial slices. After manual tracing, the volume of the ROI was calculated by means of the “volume analysis” program.

#### 2.4.1. Guidelines of the tracing

1. *Straight gyrus (SG)*. On each axial slice the SG is defined as the portion of the frontal lobe along the olfactory sulcus (OS) medially. The boundary of the SG on the medial wall is defined by an imaginary line parallel to the line running through the depth of the OS. This represents a medial boundary of the SG. An orthogonal line is traced from the anterior end of the OS to the medial surface of the hemisphere. The posterior margin of the SG is the sub-orbital sulcus (SOS).
2. *Anterior cingulate gyrus (ACG)*. The ACG is traced on serial coronal slices. The most anterior coronal slice is selected as the one in which the cingulate sulcus is clearly visualized. The deepest point of the callosal sulcus and the most medial point of the dorsal bank of the cingulate gyrus constitute the inner and the outer boundaries of the ACG. The posterior margin is determined by the meeting of the inner and outer boundaries.
3. *Orbitofrontal cortex (OFC)*. The OFC is traced in the coronal plane. The deepest point of the lateral orbital sulcus constitutes the lateral boundary of the OFC. The lateral boundary changes to the frontomarginal sulcus (FMS) when the lateral orbital sulcus disappears. At the posterior aspect, the orbitoinsular sulcus (OIS) defines the lateral boundary of the cortex when the lateral orbital sulcus disappears. The deepest point of the olfactory sulcus (OS) constitutes the medial boundary of the OFC on the posterior and intermediate portions of the OFC. On the anterior portion, when the OS disappears, the deepest point of the superior rostral sulcus represents the medial boundary of the OFC.
4. *Middle frontal gyrus (MFG)*. On each coronal slice the deepest points of the superior frontal sulcus (SFS) and the inferior frontal sulcus (IFS) constitute the superior and inferior boundaries of the MFG. The MFG is usually defined after tracing the SFS and the IFS. On transaxial slices an imaginary coronal plane (passing through the most anterior tip of the inner surface of the genu of the corpus callosum) constitutes the anterior border, and the deepest points of the precentral sulcus and the SFS constitute the posterior and the anterior borders.

5. *Third ventricle*. It is traced on coronal and transaxial planes. The third ventricle is formed from its dorsal to basal epithalamus, thalamus, and hypothalamus. The lamina terminalis forms the rostral boundary of the third ventricle. In the area near the hypothalamic sulcus, a groove for the anterior commissure can be found. Near the hypothalamus, two additional diverticula can be seen: the optic recess leading toward the optic chiasm and the infundibular recess directed toward the pituitary stalk. The suprapineal recess is a diverticulum above the pineal gland. A few millimeters below the suprapineal recess is a niche, the pineal recess.
6. *Cavum septi pellucidi*. It is a cavity between the frontal horns of the lateral ventricle. It is traced on the axial plane.
7. *Hippocampus*. It is traced on the coronal and transaxial planes. The hippocampus can be divided into three parts: an anterior part or head (a), a middle part or body (b), and a posterior part or tail (c).
- a. The hippocampus head includes an intraventricular part, the hippocampal digitations and an extraventricular or uncal part. The hippocampal digitations and amygdala are often joined together across the ventricular cavity. Anterior to the hippocampus, the ventricular cavity often extends into the deep part of the uncus, as the uncal process. The uncus, or anterior segment of the parahippocampal gyrus, curls posteriorly to rest on the parahippocampal gyrus itself, separated from the latter by the uncal sulcus.
- b. The body includes the intraventricular or deep part and the extraventricular or superficial part. The

intraventricular part is an element of the floor in the lateral ventricle. The intraventricular part is limited to the dentate gyrus, the fimbria and the hippocampal sulcus. The superficial part of dentate gyrus is the margo denticulatus.

- c. The intraventricular part of the hippocampus tail is flanked medially by the fimbria and laterally by the collateral trigone. The extraventricular part may be divided into initial, middle and terminal segments.

8. *Supratentorial CSF space*. The volume is measured between the internal lamina and the surface of the cerebrum.

### 2.5. Statistical analysis

A Mann–Whitney *U*-test was used to examine group differences on demographic, brain structural, cognitive and clinical variables. Pearson's product-moment correlations tested relationships between variables. The measures of laterality of ROI volumes were subjected to two-way repeated measures analysis of variance (ANOVA). The level of significance was  $P=0.05$  in all cases. In our preliminary report we present the uncorrected *P*-values.

## 3. Results

### 3.1. Differences in brain volume

There were no significant group differences in the total brain volume and in the intracranial volume. There was also no difference in the absolute volume of the target areas or in the relative volume compared with total

Table 2  
Volumes ( $\text{cm}^3$ ) of specific regions of interest, absolute values, and group differences

|                             | Control<br>( $N=13$ ) | Schizophrenia<br>( $N=13$ ) | $P^a$ |
|-----------------------------|-----------------------|-----------------------------|-------|
| Intracranial                | 1343.05 $\pm$ 107.14  | 1361.83 $\pm$ 91.95         | 0.595 |
| Total brain                 | 1228.20 $\pm$ 102.19  | 1231.77 $\pm$ 93.12         | 1.000 |
| External CSF space          | 114.86 $\pm$ 26.63    | 130.06 $\pm$ 30.02          | 0.274 |
| Third ventricle             | 0.94 $\pm$ 0.31       | 1.16 $\pm$ 0.47             | 0.252 |
| Hippocampus, right          | 2.84 $\pm$ 1.14       | 3.00 $\pm$ 0.78             | 0.432 |
| Hippocampus, left           | 2.84 $\pm$ 1.11       | 3.11 $\pm$ 1.00             | 0.274 |
| Anterior cingulate, right   | 3.33 $\pm$ 0.93       | 4.13 $\pm$ 1.13             | 0.067 |
| Anterior cingulate, left    | 3.41 $\pm$ 0.84       | 3.79 $\pm$ 1.05             | 0.403 |
| Straight gyrus, right       | 2.74 $\pm$ 0.62       | 2.82 $\pm$ 0.80             | 0.980 |
| Straight gyrus, left        | 2.85 $\pm$ 0.66       | 2.69 $\pm$ 0.79             | 0.595 |
| Orbitofrontal cortex, right | 9.92 $\pm$ 1.83       | 10.08 $\pm$ 1.55            | 0.738 |
| Orbitofrontal cortex, left  | 10.96 $\pm$ 1.58      | 11.05 $\pm$ 2.51            | 0.784 |
| Middle frontal gyrus, right | 14.27 $\pm$ 2.28      | 14.20 $\pm$ 2.88            | 0.936 |
| Middle frontal gyrus, left  | 14.16 $\pm$ 2.77      | 14.68 $\pm$ 1.98            | 0.503 |

Volumetric values represent mean  $\pm$  S.D.

<sup>a</sup> Mann–Whitney *U*-test.

Table 3

Volumes of specific regions of interest, relative values (%), and the group differences

|                             | Control<br>(N=13) | Schizophrenia<br>(N=13) | $P^a$ |
|-----------------------------|-------------------|-------------------------|-------|
| Hippocampus, right          | 0.23 ± 0.09       | 0.25 ± 0.07             | 0.347 |
| Hippocampus, left           | 0.23 ± 0.09       | 0.26 ± 0.09             | 0.322 |
| Anterior cingulate, right   | 0.27 ± 0.08       | 0.34 ± 0.10             | 0.085 |
| Anterior cingulate, left    | 0.31 ± 0.09       | 0.28 ± 0.07             | 0.347 |
| Straight gyrus, right       | 0.22 ± 0.04       | 0.23 ± 0.06             | 0.742 |
| Straight gyrus, left        | 0.23 ± 0.04       | 0.22 ± 0.06             | 0.231 |
| Orbitofrontal cortex, right | 0.81 ± 0.14       | 0.83 ± 0.10             | 0.738 |
| Orbitofrontal cortex, left  | 0.89 ± 0.11       | 0.90 ± 0.16             | 0.563 |
| Middle frontal gyrus, right | 1.17 ± 0.19       | 1.16 ± 0.25             | 0.979 |
| Middle frontal gyrus, left  | 1.17 ± 0.19       | 1.20 ± 0.20             | 0.611 |

Relative volumetric values represent mean ± S.D.

<sup>a</sup> Mann–Whitney  $U$ -test.

brain volume: the patient and the control groups did not differ significantly in the volume of external CSF space, third ventricle, bilateral hippocampi, SG, and the grey matter of the orbitofrontal cortex, the middle frontal gyri and the anterior cingulate gyri. There was only a tendency toward (absolute volume:  $P=0.067$ , relative volume:  $P=0.085$ ) a difference in the volume of anterior cingulum (increased in patients) on the right side, but no differences were observed on the left side.

We investigated the lateral volume differences with a two-way repeated measurements ANOVA with one between-subjects factor (group: controls vs. patients) and one within-subjects factor (side: left vs. right). We found a significant interaction in the case of the

SG ( $F(1,24)=4.731$ ,  $P=0.04$ ) both for the absolute and the relative volume; however, there was no significant group or side main effects. That means that lateralization of the SG was different in the two groups. In healthy subjects the left SG was significantly larger than the right SG, but in patients with schizophrenia the case was just the reverse. In summary, we found that the asymmetry of the SG was reversed in the patient group with schizophrenia (Tables 2 and 3).

A similar tendency toward a hemispheric asymmetry reversal was found in the volume of the anterior cingulate gyri (Group × Side interaction:  $F(1,24)=1.282$ ,  $P=0.269$ ; group effect:  $F(1,4)=3.057$ ,  $P=0.093$ ) (Tables 2 and 3).

There was a significant main effect of lateralization with left side dominance in the volume of the orbitofrontal cortex for both the absolute ( $F(1,21)=5.033$ ,  $P=0.036$ ) and relative values ( $F(1,21)=5.137$ ,  $P=0.034$ ). However, there was not a significant Group × Side interaction.

### 3.2. Differences in neurocognitive parameters

We conducted Mann–Whitney  $U$ -tests to analyse the performance on each cognitive task. We found significant group differences in verbal working memory performance measured by the Digit Span Forward and Backward and the Nonword Repetition Tests and in controlled association performance measured by Letter (F,A,S) and Category (animals, fruits and vegetables,

Table 4

Neurocognitive parameters

|                                | Control<br>(N=13) | Schizophrenia<br>(N=13) | $P^a$ |
|--------------------------------|-------------------|-------------------------|-------|
| WCST Completed categories      | 4.91 ± 2.07       | 4.00 ± 2.35             | 0.228 |
| WCST Perseverative errors, %   | 15.18 ± 9.17      | 16.23 ± 8.32            | 0.608 |
| WCST Conceptual Level Resp., % | 60.64 ± 24.37     | 52.31 ± 27.21           | 0.531 |
| WCST Failure to Maintain Set   | 0.27 ± 0.47       | 0.54 ± 0.97             | 0.776 |
| Digit Span, forward            | 6.90 ± 0.99       | 5.77 ± 1.17*            | 0.030 |
| Digit Span, backward           | 5.80 ± 1.14       | 4.23 ± 1.01**           | 0.004 |
| Nonword Repetition Test        | 7.90 ± 1.29       | 6.23 ± 1.09**           | 0.004 |
| Corsi Blocks, forward          | 6.10 ± 0.88       | 6.46 ± 0.88             | 0.410 |
| Corsi Blocks, backward         | 6.30 ± 1.25       | 5.85 ± 1.35             | 0.446 |
| Visual Patterns Test           | 9.30 ± 2.63       | 7.54 ± 1.81             | 0.088 |
| Tower of Hanoi (steps)         | 7.90 ± 2.23       | 11.00 ± 5.31            | 0.208 |
| Letter fluency, words          | 12.89 ± 2.24      | 8.56 ± 2.41**           | 0.001 |
| Letter fluency, errors         | 2.04 ± 1.02       | 1.15 ± 0.99             | 0.067 |
| Category fluency, words        | 23.79 ± 3.12      | 14.49 ± 3.26**          | 0.000 |
| Category fluency, errors       | 0.89 ± 0.58       | 0.91 ± 0.82             | 0.656 |

Values represent mean ± S.D.

<sup>a</sup> Mann–Whitney  $U$ -test.

\*  $P$  (uncorrected): <0.05.

\*\*  $P$  (uncorrected): <0.005.

supermarket items) Fluency Tests, with a better performance for the control group in each case (Table 4).

There was no significant group difference in the two visuo-spatial working memory tasks, the Corsi tapping task and the Visual Pattern Task, and similarly, there were no differences in the Tower of Hanoi task and in WCST performance (Table 4).

We found a significant difference between groups in the frequency of neurological signs. The presence of abnormalities in sensory integration ( $P < 0.001$ ), motor coordination ( $P < 0.05$ ), and motor sequencing ( $P < 0.001$ ) was significantly more frequent in the patient group (Table 1). The appearance of neurological signs in the patient group was independent from the extrapyramidal side effects of the pharmacologic treatment.

### 3.3. Correlation between symptom severity and working memory performance

All patients were in an interepisodic, stable state during investigation; there were only a few cases where positive symptoms were present. As a consequence, positive symptoms had almost no impact on the cognitive performance, with one exception: even a small number of positive symptoms correlated negatively with the performance in the Category Fluency task ( $r = -0.56$ ,  $P < 0.05$ ).

There were strong correlations between negative symptoms and spatial working memory performance. The affective scores of the SANS correlated negatively with performance in the Visual Pattern Test ( $r = -0.575$ ,  $P < 0.05$ ). The Corsi Blocks backward task also negatively correlated with the attention ( $r = -0.564$ ,  $P < 0.05$ ) and anhedonia ( $r = -0.560$ ,  $P < 0.05$ ) scores of the SANS.

The strongest correlations were found between planning function and severity of negative symptoms. The performance on the Tower of Hanoi task negatively correlated with almost all the subscales of the SANS: Alogia ( $r = -0.7$ ,  $P < 0.01$ ), Avolition ( $r = -0.84$ ,  $P < 0.01$ ), Anhedonia ( $r = -0.62$ ,  $P < 0.05$ ) and Attention ( $r = -0.83$ ,  $P < 0.01$ ). The performance on this cognitive task also negatively correlated with the Negative subscale of the PANSS ( $r = -0.78$ ,  $P < 0.01$ ), and also with the general ( $r = -0.63$ ,  $P < 0.05$ ) and the total scores ( $r = -0.72$ ,  $P < 0.01$ ) of the PANSS.

### 3.4. Correlation between symptom severity and brain volumes

As we mentioned before, all patients were in an interepisodic, stable state during the investigation, and as only few cases presented positive symptoms, we did

not expect strong correlations between brain volume scores and positive symptoms.

The severity of negative symptoms measured by the negative subscale of the PANSS correlated strongly with the increased volume of the right hippocampus for both the absolute ( $r = 0.69$ ,  $P < 0.05$ ) and the relative volume measures ( $r = 0.58$ ,  $P < 0.05$ ). Within the negative symptom domain, the absolute volume of the right hippocampus also correlated with the severity of affective flattening ( $r = 0.67$ ,  $P < 0.05$ ) measured by the SANS.

The relative volume of the left SG negatively correlated with the anhedonia scores ( $r = 0.60$ ,  $P < 0.05$ ) of the SANS.

### 3.5. Correlation between course features and brain volumes

The age at illness onset negatively correlated with the absolute volume of the right middle frontal gyrus ( $r = -0.6$ ,  $P < 0.05$ ), and positively correlated with the volume of the external CSF space ( $r = 0.8$ ,  $P < 0.01$ ), which also correlated with the chronological age of the patients ( $r = 0.77$ ,  $P < 0.01$ ). The number of relapses significantly correlated with the relative volume of the right AC gyrus ( $r = 0.58$ ,  $P < 0.05$ ).

### 3.6. Correlation between brain volumes and cognitive performance, independently of groups

The pattern we found with cross-correlation of brain volumes and cognitive functions gave no clear picture, so further investigations with larger subject pools are required. There are some results, however, that are worth mentioning: the increase of the volume of the third ventricle negatively correlated with WAIS IQ score ( $r = -0.44$ ,  $P < 0.05$ ), with two subscores of the WCST (Completed Categories:  $r = -0.521$ ,  $P < 0.05$ ; Conceptual Level Responses:  $r = -0.47$ ,  $P < 0.05$ ). The visuo-spatial working memory performance measured by the VPT negatively correlated with absolute ( $r = -0.43$ ,  $P < 0.05$ ) and relative volume of the SG ( $r = -0.45$ ,  $P < 0.05$ ). The volume of the left middle frontal gyrus positively correlated with performance the backward digit span task ( $r = 0.46$ ,  $P < 0.05$ ), which is a combined measurement of verbal working memory and executive function.

### 3.7. Correlation between NES scores and extrapyramidal symptoms

There was no significant correlation between scores of neurological signs (NES) and the extrapyramidal

side effects of pharmacologic treatments (SAS, BAS, AIMS scores).

#### 4. Discussion

Schizophrenia is a multifocal brain disease yielding various correlations between structural and functional brain changes and clinical and cognitive symptoms. There are unitary and heterogeneous theories of schizophrenia. Our research group considers schizophrenia to be a heterogeneous disease, so we use methods and interpret results within a cognitive neuropsychiatric theoretical framework, with the aim of identifying coherent etiological subgroups within schizophrenia. At present our results do not allow us to define relevant subgroups, but they should be considered as a first step in this process.

Our main finding is a change in asymmetry of the SG, a brain area where, according to our current knowledge, no such difference has been detected in schizophrenia. One recent study found decreased volume of the SG in major depression (Bremner et al., 2002), and another one found a strong correlation between decreased volume and surface of the SG and social dysfunction (Chemerinski et al., 2002). These findings underlie the importance of these regions in the appearance of schizophrenic symptoms. The SG (BA 11) is situated medially to the olfactory groove (olfactory sulcus) at the ventromedial edge of the frontal lobe, and is considered to be the frontal extension of the anterior cingulate gyrus. The SG has dense inhibitory connections with the superior temporal gyrus (STG) and the centres of the auditory cortex, and it is part of the emotional–memory network involved in the recall of episodic and autobiographical memories and also in the short-term maintenance of visuo-spatial information (Szatkowska et al., 2001). The change in laterality of the SG may refer to the dysfunctional operation of this region which might play a significant role in the symptoms of self-disorder and hallucinations in schizophrenia. On the basis of this result, further structural and functional analyses of this brain region in schizophrenia seem to be promising.

In the present phase of our research we did not find a significant difference in the volume of intracranial space, total brain volume, and relative volume of specific target regions between male patients with schizophrenia and healthy control subjects. We found significant group differences in verbal working memory and executive function performance, such as the backward digit span and fluency tasks. However, there were no group differences in tasks involving planning and

strategy shifting such as the WCST and the Tower of Hanoi. There was a significant group difference in the frequency of neurological signs; patients with schizophrenia had significantly higher scores on the NES subscales of sensory integration, motor coordination, motor sequencing, and the total score of neurological signs. Negative symptoms showed correlations with spatial working memory and planning functions. Among the assessed cognitive functions, planning was the most sensitive to the presence of negative symptoms. Negative symptoms were restated to the increase of the right hippocampus volume, and the relative volume of left SG correlated negatively with the scores of the anhedonia subscale.

The results of our preliminary report should be interpreted with caution. Here we presented the uncorrected *P*-values, so the strongest correlations are the most acceptable ones. Although some of them are consistent and others are inconsistent with earlier findings, they should be examined in further studies with larger patient samples involving female subjects, and also with larger numbers of control persons matched for education and IQ scores.

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