ELSEVIER

Schizophrenia Research 46 (2000) 45–56

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

# Supporting evidence for the model of cognitive dysmetria in schizophrenia — a structural magnetic resonance imaging study using deformation-based morphometry

Hans-Peter Volz *, Christian Gaser, Heinrich Sauer

*Psychiatric Department, University of Jena, Philosophenweg 3, D-07740 Jena, Germany*

Accepted 7 December 1999

**Abstract**

The aim of the study was to investigate whether there is any structural evidence for the model of 'cognitive dysmetria' in schizophrenia if an automatic whole-brain analysis method is used. High-resolution magnetic resonance scans were obtained for 75 schizophrenic patients and 75 controls. These data were analysed using the recently developed deformation-based morphometry allowing the assessment of volumetric differences without a priori definition of regions of interest. When compared with controls, we found reduced volumes in patients with schizophrenia in the frontal lobe (gyrus frontalis superior, medius and medialis), the temporal lobe (gyrus temporalis superior and inferior), the thalamus, the left cerebellar hemisphere and the right cerebellar vermis. There was an increase in volume in the right putamen. To date, this is the first structural magnetic resonance imaging study to demonstrate that the three key-elements of the model of cognitive dysmetria — frontal lobe, thalamus, and cerebellum — are reduced in volume in schizophrenic patients. This highlights the importance of this concept for future investigations. 

*Keywords:* Brain structure; MRI; Schizophrenia; Whole-brain analysis

## 1. Introduction

Volumetric investigations have presented considerable evidence of cerebral pathology in schizophrenic patients. In their recently published quantitative review of structural MRI studies, Lawrie and Abukmeil (1998) conclude that, besides an overall reduction of the whole brain volume, reductions of both temporal lobes and the amygdala–hippocampus-complex, as well as an increase in the lateral ventricles, are the most robust findings when patients with schizophrenia are compared with controls. Segmentation studies found subtle reductions in grey matter volume. However, the findings are far from being consistent, especially with regard to the sulci and the cortical grey matter regions. Potential reasons for these inconsistencies relate to the heterogeneous patient samples (e.g. age, sex, diagnostic subgroups, state of illness) and to the methodology employed in volumetric analyses. Usually, the respective brain structures are segmented by hand or semi-automatically slice by slice. This approach is very labour-intensive and relies on the definition of anatomical landmarks. Thus, in most studies only a limited, predetermined, number of cerebral structures are segmented along with prespecified

* Corresponding author. Tel.: +49-3641-935284; fax: +49-3641-935280.

*E-mail address:* volz@landgraf.med.uni-jena.de (H.-P. Volz)

0920-9964/00/$ - see front matter 
PII: S0920-9964(99)00236-4

hypotheses. It is probably due to the small number of subjects that can be included in such labour-intensive studies and also to the small differences between patients and controls that only small effect sizes result. These effect sizes can be enhanced by meta-analyses that were published recently (Raz and Raz, 1990; Ward et al., 1996; Lawrie and Abukmeil, 1998; Nelson et al., 1998).

However, such studies have other methodological drawbacks. An attempt to overcome these limitations is to employ techniques not requiring prespecified regions of interest (Andreasen et al., 1994; Davatzikos et al., 1996; De Quardo et al., 1996; Paus et al., 1996; Penhune et al., 1996; Haller et al., 1997; Iosifescu et al., 1997; Thirion and Calmon, 1997; Thompson et al., 1997; Wolkin et al., 1998). For example, Andreasen et al. (1994) used a fully automatic technique for image analysis of magnetic resonance (MR) scans. They generated an 'average brain' of patients and controls. The two averaged brains were used to compare both groups. Using this methodology, the authors observed regional abnormalities in the thalamus and the adjacent white matter, and to a minor extent in the frontal, temporal and parietal regions of the persons with schizophrenia. On the basis of these findings and other results from positron emission tomography (PET) studies, Andreasen and coworkers hypothesized that connectivity is disturbed among nodes located in the prefrontal regions, the thalamic nuclei and the cerebellum. A disruption in this circuitry might produce 'cognitive dysmetria', resulting in difficulties to prioritize, to process and to coordinate, as well as to respond to information (Andreasen et al., 1994, 1996, 1998; Andreasen, 1997). This hypothesis is in accordance with the suggestion that schizophrenia is not caused by a single structural brain defect but by alterations of critical neuronal networks, e.g. a fronto-striatal or fronto-temporal disturbance (e.g. Buchsbaum et al., 1992; Frith et al., 1995). This is inconsistent with 'monotopical' approaches of some structural MR imaging (MRI) studies, which attributed an isolated defect in a certain brain region to a single subsyndrome. Thus, hallucinations were thought to be linked to disturbances in temporal lobe structures, thought disorders to hippocampal abnormalities and negative symptoms to altered frontal structures.

The purpose of the present study was to explore whether a novel whole-brain approach, which compared high numbers of schizophrenic and control brains without predefined specific regions of interest, would result in similar findings. This might provide further evidence to support the model of 'cognitive dysmetria'.

## 2. Methods and materials

### 2.1. The sample

A total of 75 schizophrenic in- and out-patients and 75 normal controls matched for sex and age (within a range of 5 years) participated in the study. This population is part of a more extensive investigation exploring the methodology of deformation-field-based volumetry (Gaser et al., 1999). Diagnoses were made according to DSM-III-R criteria after an unstructured interview (American Psychiatric Association, 1987) by experienced research psychiatrists unaware of brain imaging data. They were confirmed by a careful review of the patient charts. Psychopathology was determined using the following scales: the brief psychiatric rating scale (BPRS; Overall and Gorham, 1962), the scale for the assessment of positive symptoms (SAPS; Andreasen, 1984), and the scale for the assessment of negative symptoms (SANS; Andreasen, 1983). All subjects were screened thoroughly for internal and neurological symptoms, and excluded if such symptoms existed. Participants were also excluded if they had a concurrent history of alcohol and/or substance abuse, of severe head trauma, a neurological disorder, or first-degree relatives with severe neurological disorders. A psychiatric examination was also performed in controls. Subjects who showed any symptoms and those with a history of psychiatric disturbances were excluded. This was also the case if first-degree relatives suffered from a major psychiatric disorder. The study was approved by the ethical review board of the University of Jena. After a complete description of the study, written informed consent was obtained. The demographic and clinical characteristics of the patients and controls are given in Table 1.

Table 1
Demographic characteristics of schizophrenic patients and controls (abbreviations: BPRS, brief psychiatric rating scale; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms)

| Variable | Patient | Controls |
|---|---|---|
| Subjects *n* (males/females) | 75 (52/23) | 75 (53/22) |
| Age (mean ± SD, years) | 34.71 ± 10.45 | 31.2 ± 9.0 |
| Illness duration (mean ± SD, years) | 8.07 ± 7.85 | – |
| Number of hospitalizations | 3.76 ± 3.62 | – |
| BPRS (mean ± SD) | 47.77 ± 11.11 | – |
| SAPS (mean ± SD) | 20.67 ± 17.87 | – |
| SANS (mean ± SD) | 45.29 ± 22.10 | – |

### 2.2. MRI scanning procedures

All MRI scans were performed on a 1.5 T Philips Gyroscan ACSII clinical scanner. The heads of the participants were positioned in a head coil fixation device and were stabilized during the scanning procedure by head supports. Spin–lattice relaxation time (T1)-weighted sagittal slices at 90° to the anterior commissure–posterior commissure line were obtained with a repetition time (TR) pulse sequence of 13.1 ms, an echo time (TE) pulse sequence of 4.6 ms, a $256 \times 256$ matrix size, and a 256 mm field of view. The slices were 1 mm thick and contiguous with no gaps.

### 2.3. Data analysis

Data were analysed with a newly developed deformation-based morphometric approach (Gaser et al., 1999). Images were normalized using the spatial normalization routines of SPM99b (Ashburner and Friston, 1999). First, images were smoothed with an isotropic Gaussian kernel [full width at half maximum (FWHM) of 8 mm] and an affine transformation with 12 parameters was applied to all images to normalize them to Talairach space (Talairach and Tournoux, 1988). Since this transformation step is intensity based, no predefined surface points or landmarks are necessary (Friston et al., 1995). The transformed images were resized to a voxel size of 2 mm and scalp-edited by masking with a probability image of cerebral tissue. Thus, extracerebral parts of the brain were excluded to eliminate the confounding effects of scalp differences. The nonlinear registration used afterwards is based on a regularized minimization process of the residual squared signal intensity difference between an image and a template of the same modality, assumed to be in Talairach-space. A linear combination of $11 \times 13 \times 10$ three-dimensional discrete cosine transform basis functions was estimated to perform this registration (Ashburner and Friston, 1999).

As a result of this registration, we obtained a deformation field of each subject that defines a three-dimensional displacement vector in each voxel. This vector describes the transformations required to map a voxel of one brain onto its corresponding position in the template. The statistical analysis of the deformation fields is based on a multivariate general linear model. We used a subtractive design with one confounding variable (a constant vector for modelling the effect of equal means) to compare the groups of patients with schizophrenia and controls. The resulting Hotelling's $T^2$-map was thresholded at a height of $T^2 = 17.38$ ($P = 0.001$) and a spatial extent of $k = 72$ voxels. To specify whether the change in each voxel was due to volume reduction or enlargement, we calculated the Jacobian determinant of the displacement vector (Gurtin, 1987).

## 3. Results

Significant volume differences in schizophrenic patients compared with the control sample were detected in the following regions: frontal lobe, temporal lobe, basal ganglia, thalamus and cerebellar hemispheres. The following detailed description provides anatomical localizations. The respective Talairach-coordinates are presented in Table 2.

In the *frontal lobe* (Figs. 1 and 3) both hemispheres were affected in schizophrenic patients. The gyrus frontalis medius (GFm) and the gyrus frontalis medialis (GFmed) were reduced on the right side, whereas it was the gyrus frontalis superior (GFs) on the left side.

In the *temporal lobe* (Figs. 1–3) the gyrus temporalis superior (GTs) was found to be bilaterally reduced in the patient sample. On the left side, the insula was also altered, and on the right side the gyrus temporalis inferior (GTi).

Table 2
Resulting $T^2$-values of the comparison between 75 schizophrenic patients and 75 controls. Tabular data characterize regions exceeding a height of $T^2=17.38$ ($P=0.001$) and spatial extent of 72 voxels. The location of the maximal $T^2$-value in each region is given with the size of the region and maximal height. Coordinates conform to the Talairach and Tournoux (1988) atlas. The global maxima in each region are in normal type, whereas the local maxima are in bold type. The footnote[a] specifies the thresholds and parameters used relating to this analysis (abbreviations: GFm, gyrus frontalis medius; GFmed, gyrus frontalis medialis; GFs, gyrus frontalis superior; GTi, gyrus temporalis inferior; GTs, gyrus temporalis superior)

| Cluster size $k$ | Voxel height[b] $T^2$ | $x$ (mm) | $y$ (mm) | $z$ (mm) | Anatomical regions |
|---|---|---|---|---|---|
| 1247 | 33.73 | −22 | −4 | 8 | left thalamus, perithalamic white matter |
| | **21.41** | **−46** | **−6** | **6** | **left insula/GTs** |
| 330 | 32.25 | −48 | −48 | −44 | left cerebellum |
| 86 | 29.58 | 50 | −6 | −48 | right Gti |
| 164 | 27.79 | 6 | 56 | −10 | right GFmed |
| 387 | 27.44 | −26 | 36 | 52 | left GFs |
| 159 | 26.73 | 2 | 50 | 54 | right GFmed |
| | **25.82** | **2** | **38** | **62** | **right GFmed** |
| 246 | 25.85 | 24 | 4 | 44 | right GFm |
| 134 | 25.80 | 44 | −8 | −10 | right GTs |
| 227 | 25.23 | 30 | 10 | 2 | right putamen |
| 363 | 22.02 | 16 | −12 | 6 | right thalamus |
| | **19.44** | **6** | **−14** | **6** | **right thalamus** |
| 80 | 19.97 | 4 | −62 | −50 | right cerebellum (vermis) |

[a] Height threshold $T^2=17.38$, $P=0.001$. Volume $S=240\,679$ voxels. Extent threshold $k=72$ voxels. Degrees of freedom due to error: 3.0, 146.0. Smoothness FWHM (mm): 19.7, 20.0, 19.4; (voxels) 9.8, 10.0, 9.7.

[b] Owing to the application of a multivariate analysis we have listed the voxel height as a $T^2$-value, which is the multivariate equivalent to the $T$-value.

The *thalamus* (Figs. 1 and 2) was the region exhibiting the greatest differences between controls and patients with schizophrenia. In patients, a volume reduction was present bilaterally, but it was more pronounced on the left side. Interestingly, in the white matter dorsally adjacent to the thalamus, a volume increase in patients became evident on both sides, but was more pronounced on the left side.

Regarding the *basal ganglia* (Figs. 1 and 2), the putamen was affected. In patients there was an increase in volume on the right side.

In the *cerebellum* (Figs. 1 and 3), a volume reduction in the left hemisphere, to a smaller degree also in the right vermis, was apparent in the group with schizophrenia.

## 4. Discussion

The main findings of the present investigation are as follows. There were structural brain alterations in 75 schizophrenic patients compared with 75 controls. Volume reductions were found in the frontal/prefrontal cortex, the GTs, the thalamus and the cerebellum, and there was an increase of volume in the putamen. These findings were obtained by a novel whole-brain analysis method with no prespecified regions of interest. Before discussing the potential functional impact of these results, we would like to make some methodological remarks and to compare our results with prior findings.

So far, the 'gold standard' for volumetric analysis has been manual ROI segmentation. However, our new approach offers some methodological advantages. It describes subtle changes within a given structure, e.g. parts of the gyrus frontalis medius or parts of the gyrus temporalis superior. These subtle changes are detectable because of the increased sensitivity and resolution of the deformation-field-based method compared with manual segmentation procedures. Using manual segmentation procedures volume changes can only be detected in rather big brain regions, like the frontal lobe of the dorso-lateral prefrontal cortex (with

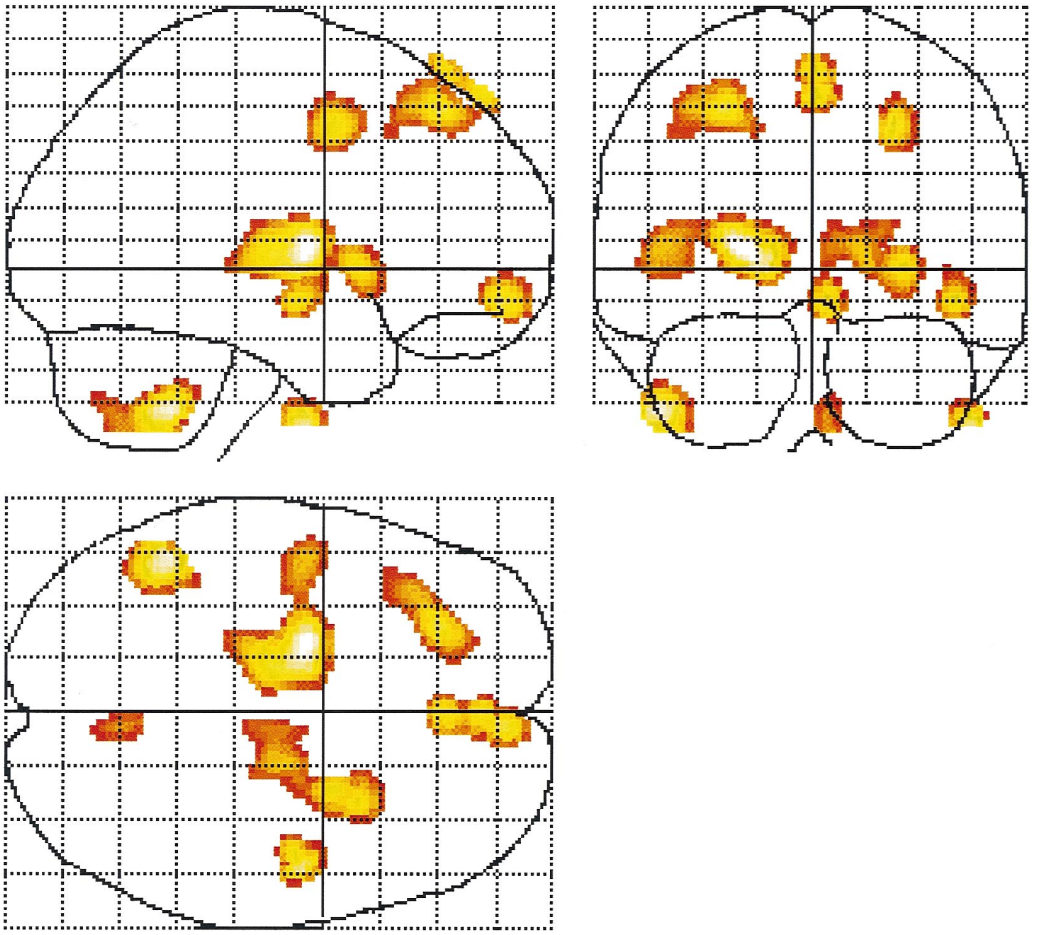

Fig. 1. Result of the comparison between 75 schizophrenic patients and 75 controls. The $T^2$-map is displayed as maximum intensity projections in sagittal, coronal and transverse planes. The structural differences were obtained by statistical analysis of deformations required to match the template brain onto each object brain. The map thresholds at a height of $T^2=17.38$ ($P=0.001$) and spatial extent of $k=72$ voxels. Red/yellow colour was used for voxels found to be volume-reduced in schizophrenic patients. The space conforms to Talairach and Tournoux (1988).

more or less arbitrarily defined boundaries). Moreover, such volume changes will only be apparent if either the whole brain region concerned is diffusely volume-reduced or if the volume reduction of the critical substructure is pronounced enough so as to reduce the whole brain region concerned.

Since our method is more sensitive and able to measure alterations in parts of the structures, its results cannot adequately be compared with those of manual ROI segmentation. Thus, the problem of validation can only be solved by using the face validity. In this respect, the alterations described are both meaningful and understandable in the light of predescribed results and well-known theories concerning the etiopathogenesis of schizophrenia.

The increased sensitivity of the transformation procedures used is directly dependent on the variance of the deformation. This variance is homogeneously distributed within each type of tissue. Among the different tissues, variance is smallest in the white matter, followed by the grey matter. The highest variance, and thus the smallest sensitivity,

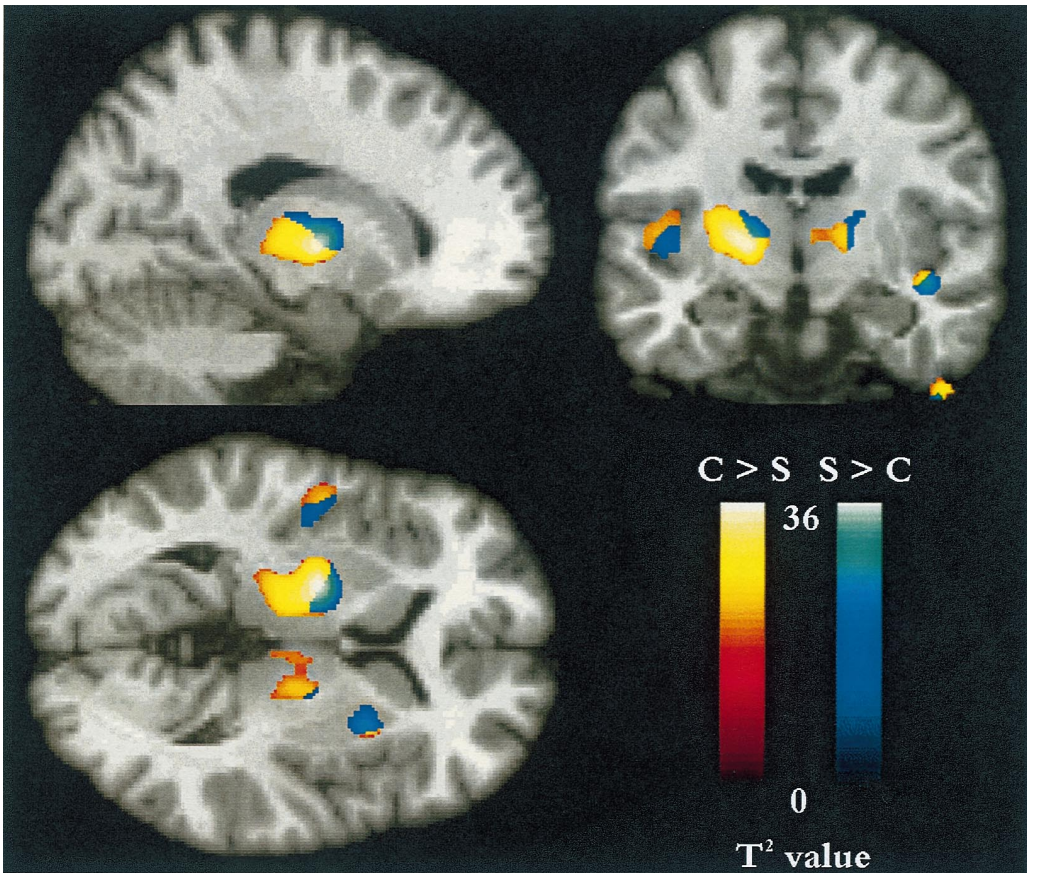


Fig. 2. The $T^2$-map presented in Fig. 1 is sectioned in three orthogonal planes and is overlaid on the template of the same anatomical space. The coordinates of the sections conform to the atlas of Talairach and Tournoux (1988): $x = -16$ mm, $y = -10$ mm, and $z = 4$ mm. The colour scale is arbitrary (red/yellow colour was used for voxels found to be volume-reduced in schizophrenic patients compared with controls, whereas voxels with volume enlargement are shown in blue).

is present in the cerebro-spinal fluid. This might be the reason why we have not been able to detect the most robust finding in previous studies exploring brain volume differences between schizophrenic patients and controls, i.e. enlarged third (and lateral) ventricle volumes.

After these methodological comments, the results presented will be compared with published morphometric findings. Various MRI studies have found a reduced volume of the frontal lobe (Andreasen et al., 1986; Stratta et al., 1989; Jernigan et al., 1991; Williamson et al., 1991; Raine et al., 1992; Zipursky et al., 1992). Negative findings were also obtained (Smith et al., 1987; Kelsoe et al., 1988; Suddath et al., 1989; Andreasen et al., 1990). In a meta-analytical study, Lawrie and Abukmeil (1998) state that the overall median volume reduction of the frontal lobe is only slightly greater than that for the whole brain. Our results favour the findings of this meta-analysis as we also found volume reductions in the frontal lobes. However, the question of whether the substructures *within* the frontal lobe are similarly affected is of even greater importance. Our data demonstrate that on the left side the GFs was affected, whereas on the right side the GFm and GFmed were volume reduced. In most of the MRI studies so far (with some exceptions, e.g. Schlaepfer et al., 1994; Wible et al., 1997; Buchanan et al., 1998), only the volume of the whole frontal lobe or the

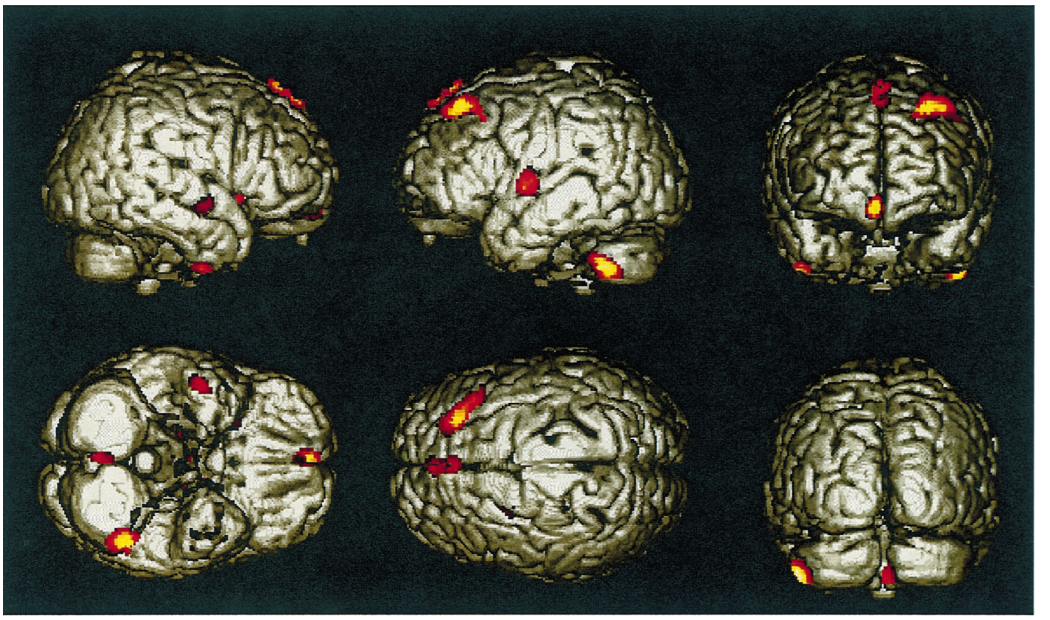

Fig. 3. The resulting $T^2$-map of Figs. 1 and 2 is superimposed on the rendered surface of the template brain. Only the $T^2$-values that are less than 30 mm deep are shown.

volumes of the grey and white matter were measured, not the volumes of different subregions or even a single gyrus. Therefore, such subtle differences in volume reduction between the left and right sides could not be detected.

Volume decreases of the temporal lobe are among the most robust MRI structural findings when patients with schizophrenia are compared with controls. However, even for this brain region, some studies could not find a difference between schizophrenic patients and controls (Lawrie and Abukmeil, 1998). Results concerning the GTs are more clear-cut. Ten MRI studies have investigated the GTs. Eight of these studies reported GTs volume reductions (Barta et al., 1992; Shenton et al., 1992; DeLisi et al., 1994; Schlaepfer et al., 1994; Zipursky et al., 1994; Flaum et al., 1995; Menon et al., 1995; Hajek et al., 1997), whereas two studies did not (Vita et al., 1995; Kulynich et al., 1996). Barta et al. (1992) and Shenton et al. (1992) described left GTs volume reductions and suggested a connection with occurrences of auditory hallucinations and thought disorders. Both negative studies did not segment grey and white matter of the GTs separately and, therefore, may have inadvertently obscured possible differences between groups. Our results, therefore, are well in line with the majority of reports showing volume decreases in the GTs.

With respect to the thalamus, current results are as inconsistent as those for the frontal lobe. Some MRI studies have reported significant reductions of thalamic volume (Andreasen et al., 1990, 1993, 1994; Flaum et al., 1995; Buchsbaum et al., 1996), although these findings could not be replicated in another study (Portas et al., 1998). Portas et al. (1998) suggested that significant differences between persons with schizophrenia and controls only emerge when single specific thalamic nuclei are considered. The study of Buchsbaum et al. (1996) supported this suggestion. They did not find a total thalamic volume reduction in schizophrenic patients compared with controls; they only found a significant reduction of the right posterior and left anterior regions. Andreasen et al. (1994) also described a similar pattern of the thalamic volume reduction. We found abnormalities of the right and left posterior and anterior regions. These anterior thalamic areas comprise mainly the dorsomedial and anterior thalamic nuclei, which are

primary thalamic subregions that connect with the prefrontal cortex. Interestingly, Andreasen et al. (1994) found differences in the white matter adjacent to the thalamus. Here we detected a left-sided pronounced volume increase, which may suggest a compensatory process due to a reduced thalamic volume. Thus, in schizophrenic patients the white matter projections from the thalamus to the prefrontal cortex seem to be changed.

Changes in the basal ganglia could be detected in several studies [Kelsoe et al., 1988; Mion et al., 1991; Young et al., 1991; for a review see Chua and McKenna (1995)]. However, Jernigan et al. (1991) presented MRI data of enlarged lenticular nuclei (putamen and globus pallidus), Swayze et al. (1992) found increased putamen volumes in male schizophrenic patients compared with controls. Elkashef et al. (1994) reported on volume increases of putamen and globus pallidus. Interestingly, the putamen was, as in our study, only increased on the right side in patients. Hokama et al. (1995) were the first to use thin adjacent slices with no gaps and separate segmentation of globus pallidus, putamen and caudate. In this investigation, all segmented basal ganglia structures were found to be increased, ranging from 9.5% volume increase for the caudate and 15.9% for the putamen to 27.4% for the globus pallidus. This result was confirmed by Iosifescu et al. (1997), who compared an automated registration algorithm for measuring subcortical brain structures with conventional segmentation.

As for the reasons for volume increase, two explanations have to be taken into consideration: (i) the effect of chronic neuroleptic medication, and (ii) disturbed pruning processes. Animal studies (Benes et al., 1985) have demonstrated that increase in neuronal size and synaptic proliferation can be caused by chronic neuroleptic treatment. Our patients, and those of Elkashef et al. (1994), Hokama et al. (1995) and Iosifescu et al. (1997), and also probably those of Jernigan et al. (1991) and of Swayze et al. (1992), were on continuous neuroleptic medication. Regarding the caudate, Chakos et al. (1994) were able to show that enlargement occurs early in the course of treatment, but this could not be demonstrated in drug naive schizophrenic patients. Frazier et al. (1996) were able to demonstrate that the caudate of patients with childhood-onset schizophrenia who had been treated with typical neuroleptics was increased compared with controls. After 2 years of treatment with the atypical neuroleptic clozapine there were no more differences compared with controls. This shows that the previous increase had been caused by the treatment with typical neuroleptics and was reversible when patients received atypicals for a certain time period. Unfortunately, in this study, other basal ganglia structures were not analysed. Our findings regarding the putamen might also be explained by a developmental deficit in pruning of subcortical brain regions (Feinberg, 1982), by a delayed or failed neuronal reinervation (Stevens, 1992) or by a compensatory increase in synaptic density secondary to a decreased input from other brain regions like the sensorimotor, cingulate, prefrontal, and insular cortices and from the amygdala (Graybiel, 1990). An altered structure of the putamen might, therefore, account for many of the schizophrenic symptoms.

For many years the cerebellum was regarded as solely involved in motor functions. Recently, a major role regarding cognition has also been discussed (e.g. Leiner et al., 1995). Only a few structural MRI studies on the cerebellum have been published, most of them describing no difference in vermal size between schizophrenic patients and controls (Mathew and Partain, 1985; Coffman et al., 1989; Courchesne et al., 1989; Nasrallah et al., 1991; Aylward et al., 1994). Rossi et al. (1993) described a smaller area in male rather than in female persons with schizophrenia. MRI studies of the whole cerebellar volume have found a lower volume in male compared with female schizophrenic patients (Flaum et al., 1995), a significantly lower white matter volume of both cerebellar hemispheres and lower volumes of lobules IX and X of the vermis in male schizophrenic patients compared with sex-matched controls (Deshmukh et al., 1996) and even a larger volume of a combined cerebellum/brainstem measure in male patients (Lewitt et al., 1996). Recently, it could be demonstrated that adolescent schizophrenic patients with childhood-onset exhibited decreased volumes in total cerebellum and of the

inferior posterior lobe along with volume reduction of the vermis (Jacobsen et al., 1997a). In the right cerebellum DeLisi et al. (1997) described a statistically significantly enhanced volume decrease over time in persons with schizophrenia compared with controls. In our study, a quite pronounced volume reduction on the left cerebellar hemisphere became evident. This structural finding fits in with the $^{15}O$ $H_2O$-PET results of Andreasen et al. (1996). During 'practised recall' a significantly decreased activation of the left superior cerebellum became evident in schizophrenic patients compared with controls. A similar effect was found with carbon-11-2-desoxyglucose-PET at rest by Volkow et al. (1992), whereas Jacobsen et al. (1997b) described a bilaterally increased cerebellar metabolic rate of $^{18}F$-fluordesoxyglucose in childhood-onset patients with schizophrenia performing the continuous performance test.

Our main findings, i.e. the volume reduction in prefrontal areas, thalamic nuclei, and the cerebellum, are well in line with the results of Andreasen et al. (1994) and corroborate their hypothesis of a disturbed feedback loop that involves the frontal regions, the cerebellum and the thalamus (Andreasen, 1997). This hypothesis has also been supported by PET studies (Andreasen et al., 1996), which demonstrated not only decreased thalamic and prefrontal, but also decreased left-sided cerebellar activity. As Andreasen et al. (1996) summarized, the cerebellum shares the feature of an enormous phylogenetic increase in size with the prefrontal cortex and possesses substantial anatomic connections to the prefrontal cortex. This suggests that the cerebellum could perform not only motor, but also cognitive functions. In this model, the prefrontal node is responsible for the classic executive functions, e.g. decision making, strategy development and response initiation. The thalamus acts as a filter forwarding only relevant information and the cerebellum might serve as a matching module adjusting data in a timely precise fashion (Andreasen, 1997). This concept of 'cognitive dysmetria' as the basic disturbance in schizophrenia is in line with our results. The thalamus, as the central filter, might play a major role in this context, but only together with the other altered cerebral areas, like the prefrontal cortex and the cerebellum, is the whole disturbed information pathway evident. Cognitive dysmetria results in difficulties in coordination, processing, prioritization, retrieval, and expression of information. This fundamental deficit might explain, according to Andreasen (1997), the entire spectrum of schizophrenic symptoms such as delusions, hallucinations, disorganized speech and behaviour, alogia, affective blunting or avolition and anhedonia (Andreasen et al., 1998).

In addition to the concept of Andreasen, we also found volume reductions of the GTs, which might, as already mentioned, be of critical importance for the generation of (auditory) hallucinations (e.g. Silbersweig and Stern, 1996).

To our knowledge, our study is the first structural investigation demonstrating simultaneously that the three key elements of the responsible network — prefrontal cortex, thalamus and cerebellum — are volume reduced in schizophrenic patients compared with controls.

## References

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders. third ed., American Psychiatric Press, Washington, DC.

Andreasen, N.C., 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa.

Andreasen, N.C., 1984. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa.

Andreasen, N.C., 1997. The role of the thalamus in schizophrenia. Can. J. Psychiatry 42, 27–33.

Andreasen, N.C., Nasrallah, H.A., Dunn, V., Olson, S.C., Grove, W.M., Ehrhardt, J.C., Coffman, J.A., Crossett, J.H., 1986. Structural abnormalities in the frontal system in schizophrenia. Arch. Gen. Psychiatry 43, 136–144.

Andreasen, N.C., Ehrhardt, J.C., Swayze 2nd, V.W., Alliger, R.J., Yuh, W.T., Cohen, G., Ziebell, S., 1990. Magnetic resonance imaging of the brain in schizophrenia: the pathophysiological significance of structural abnormalities. Arch. Gen. Psychiatry 47, 35–44.

Andreasen, N.C., Cizadlo, T., Harris, G., Swayze 2nd, V., O'Leary, D.S., Cohen, G., Ehrhardt, J., Yuh, W.T., 1993. Voxel processing techniques for the antemortem study of neuroanatomy and neuropathology using magnetic resonance imaging. J. Neuropsychiatry Clin. Neurosci. 5, 121–130.

Andreasen, N.C., Arndt, S., Swayze 2nd, V., Cizadlo, T., Flaum, M., O'Leary, D., Ehrhardt, J.C., Yuh, W.T., 1994.

Thalamic abnormalities in schizophrenia visualized through magnetic resonance image avaraging. Science 266, 294–298.

Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Ponto, L.L., Watkins, G.L., Hichwa, R.D., 1996. Schizophrenia and cognitive dysmetria: A positron-emission tomography study of dysfunctional prefrontal–thalamic–cerebellar circuitry. Proc. Natl. Acad. Sci. USA 93, 9985–9990.

Andreasen, N.C., Paradiso, S., O'Leary, D.S., 1998. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical–subcortical–cerebellar circuitry? Schiz. Bull. 24, 203–218.

Ashburner, J., Friston, K., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7, 254–266.

Aylward, E.H., Reiss, A., Barta, P.E., Tien, A., Han, W., Lee, J., Pearlson, G.D., 1994. Magnetic resonance imaging measurement of posterior fossa structures in schizophrenics. Am. J. Psychiatry 151, 1448–1452.

Barta, P.E., Pearlson, G.D., Powers, R.E., Menon, R., Richards, S., Tune, L.E., 1992. Temporal lobe in schizophrenia (abstract). APA New Res. Abstr. 1992, 146

Benes, F.M., Paskevich, P., Davidson, J., Domesick, V.B., 1985. The effects of haloperidol on synaptic patterns in rat striatum. Brain Res. 329, 265–274.

Buchanan, R.W., Vlader, K., Barta, P.E., Pearlson, G.D., 1998. Structural evaluation of the prefrontal cortex in schizophrenia. Am. J. Psychiatry 155, 1049–1055.

Buchsbaum, M.S., Haier, R.J., Potkin, S.G., Nuechterlein, K., Bracha, H.S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P.A., Trenary, M., Traffala, R., Reynolds, C., Bunney, W.E., 1992. Frontostriatal disorder of cerebral metabolism in never medicated schizophrenics. Arch. Gen. Psychiatry 49, 935–942.

Buchsbaum, M.S., Someya, T., Teng, C.Y., Abel, L., Chin, S., Najafi, A., Haier, R.J, Wu, J., Bunney Jr, W.E., 1996. PET and MRI of the thalamus in never-medicated patients with schizophrenia. Am. J. Psychiatry 153, 191–199.

Chakos, M.H., Lieberman, J.A., Bilder, R.M., Borenstein, M., Lerner, G., Bogerts, B., Wu, H., Kinon, B., Ashtari, M., 1994. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. Am. J. Psychiatry 151, 1430–1436.

Chua, S.E., McKenna, P.J., 1995. Schizophrenia — a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. Br. J. Psychiatry 166, 563–582.

Coffman, J.A., Schwarzkopf, S.B., Olson, S.C., Nasrallah, H.A., 1989. Midsagittal cerebral anatomy by magnetic resonance imaging. The importance of slice position and thickness. Schizophr. Res. 2, 287–294.

Courchesne, E., Press, G.A., Murakami, J.A., Berthoty, D., Grafe, M., Wiley, C.A., Hesselink, J.R., 1989. The cerebellum in sagittal plane — anatomic-MR correlation: 1. The vermis. AJR Am. J. Roentgenol. 10, 829–835.

Davatzikos, C., Vaillant, M., Resnick, S.M., Prince, J.L., Letovsky, S., Bryan, R.N., 1996. A computerized approach for morphological analysis of the corpus callosum. J. Comput. Assist. Tomogr. 20, 88–97.

DeLisi, L.E., Hoff, A.L., Neale, C., Kushner, M., 1994. Asymmetries in the superior temporal lobe in male and female first-episode schizophrenic patients: measures of the planum temporale and superior temporal gyrus by MRI. Schizophr. Res. 12, 19–28.

DeLisi, L.E., Sakuma, M., Tew, W., Kushner, M., Hoff, A.L., Grimson, R., 1997. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res. Neuroimaging 74, 129–140.

De Quardo, J.R., Bookstein, F.C., Green, W.D.K., Brunberg, J.A., Tandon, R., 1996. Spatial relationship of neuroanatomic landmarks in schizophrenia. Psychiatry Res. Neuroimaging 67, 81–95.

Deshmukh, A., Sullivan, E.V., Mathalon, D.H., Desmond, J.E., Matsumoto, B., Lim, K.O., Pfefferbaum, A., 1996. Cerebellar volume deficits in schizophrenia (abstract). Biol. Psychiatry 39, 600.

Elkashef, A.M., Buchanan, R.W., Gellad, F., Munson, R.C., Breier, A., 1994. Basal ganglia pathology in schizophrenia and tardive dyskenisia: an MRI quantitative study. Am. J. Psychiatry 151, 752–755.

Feinberg, I., 1982. Schizophrenia and late maturational brain changes in man. Psychopharmacol. Bull. 18, 29–31.

Flaum, M., Swayze 2nd, V.W., O'Leary, D.S., Yuh, W.T., Ehrhardt, J.C., Arndt, S.V., Andreasen, N.C., 1995. Effects of diagnosis, laterality and gender on brain morphology in schizophrenia. Am. J. Psychiatry 152, 704–714.

Frazier, J.A., Giedd, J.N., Kaysen, D., Albus, K., Hamburger, S., Alaghband-Rad, J., Lenane, M.C., McKenna, K., Breier, A., Rapoport, J.L., 1996. Childhood-onset schizophrenia: brain MRI rescan after 2 years of clozapine maintenance treatment. Am. J. Psychiatry 153, 564–566.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.B., Heather, J.D., Frackowiak, R.S.J., 1995. Spatial registration and normalization of images. Hum. Brain Mapp. 2, 165–189.

Frith, C.D., Friston, K.J., Herold, S., Silbersweig, D., Fletcher, P., Cahill, C., Dolan, R.J., Frackowiak, R.S.J., Liddle, P.F., 1995. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. Br. J. Psychiatry 167, 343–349.

Gaser, C., Volz, H.P., Kiebel, S., Riehemann, S., Sauer, H., 1999. Detecting structural changes in whole brain based on nonlinear deformation — application to schizophrenia research. Neuroimage 10, 107–113.

Graybiel, A.M., 1990. Neurotansmitters and neuromodulators in the basal ganglia. Trends Neurosci. 13, 244–254.

Gurtin, M.E., 1987. An Introduction to Continuum Mechanics. Academic Press, New York.

Hajek, M., Huonker, R., Boehle, C., Volz, H.P., Nowak, H., Sauer, H., 1997. Abnormalities of auditory evoked magnetic fields and structural changes in the left hemisphere of male schizophrenics — a magnetoencephalographic–magnetic resonance imaging study. Biol. Psychiatry 42, 609–616.

Haller, J.W., Banerjee, A., Christensen, G.E., Gado, M., Joshi,

S., Miller, M.I., Sheline, Y., Vannier, M.W., Csernansky, J.G., 1997. Three-dimensional hippocampal MR morphometry with high-dimensional transformation of a neuroanatomic atlas. Radiology 202, 504–510.

Hokama, H., Shenton, M.E., Nestor, P.G., Kikinis, R., Levitt, J.J., Metcalf, D., Wible, C.G., O'Donnell, B.F., Jolesz, F.A., McCarley, R.W., 1995. Caudate, putamen and globus pallidus volume in schizophrenia: a quantitative MRI study. Psychiatry Res. Neuroimaging 61, 209–229.

Iosifescu, D.V., Shenton, M.E., Warfield, S.K., Kikinis, R., Dengler, J., Jolesz, F.A., McCarley, R.W., 1997. An automated registration algorithm for measuring MRI subcortical brain structures. Neuroimage 6, 13–15.

Jacobsen, L.K., Giedd, J.N., Berquin, P.C., Krain, A.L., Hamburger, S.D., Kumra, S., Rapoport, J.L., 1997a. Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. Am. J. Psychiatry 154, 1663–1669.

Jacobsen, L.K., Hamburger, S.D., van Horn, J.D., Vaituzis, A.C., McKenna, K., Frazier, J.A., Gordon, C.T., Lenane, M.C., Rapoport, J.L., Zametkin, A.J., 1997b. Cerebral glucose metabolism in childhood onset schizophrenia. Psychiatry Res. 75, 131–144.

Jernigan, T.L., Zisook, S., Heaton, R.K., Moranville, J.T., Hesselink, J.R., Braff, D.L., 1991. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Arch. Gen. Psychiatry 48, 881–890.

Kelsoe Jr, J.R., Cadet, J.L., Picar, J.L., Weinberger, D.R., 1988. Quantitative neuroanatomy in schizophrenia: a controlled magnetic resonance imaging study. Arch. Gen. Psychiatry 45, 533–541.

Kulynich, J.J., Vladar, K., Jones, D.W., Weinberger, D.R., 1996. Superior temporal gyrus volume in schizophrenia: a study using MRI morphometry assisted by surface rendering. Am. J. Psychiatry 153, 50–56.

Lawrie, S.M., Abukmeil, S.S., 1998. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br. J. Psychiatry 172, 110–120.

Leiner, H.C., Leiner, A.L., Dow, R.S., 1995. The underestimated cerebellum. Hum. Brain Mapp. 2, 244–254.

Lewitt, J.J., Donnino, R., Shenton, M.E., Kikinis, R., Jolesz, F.A., McCarley, R.W., 1996. A quantitative volumetric MRI study of the brainstem and cerebellum in schizophrenia (abstract). Biol. Psychiatry 39, 639.

Mathew, R.J., Partain, L., 1985. Midsagittal sections of the cerebellar vermis and fourth ventricle obtained with magnetic resonance imaging of schizophrenic patients. Am. J. Psychiatry 142, 970–971.

Menon, R.R., Barta, P.E., Aylward, E.H., Richards, S.S., Vaughn, D.D., Tien, A.Y., 1995. Posterior superior temporal gyrus in schizophrenia: grey matter changes and clinical correlates. Schizophr. Res. 16, 127–135.

Mion, C.C., Andreasen, N.C., Arndt, S., Swayze 2nd, V.W., Cohen, G.A., 1991. MRI abnormalities in tardive dyskinesia. Psychiatry Res. 40, 157–166.

Nasrallah, H.A., Schwarzkopf, S.B., Olson, S.C., Coffman, J.A., 1991. Perinatal brain injury and cerebral vermal lobules I–X in schizophrenia. Biol. Psychiatry 29, 567–574.

Nelson, M.D., Saykin, A.J., Flashman, L.A., Riordan, H.J., 1998. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging. A meta-analytic study. Arch. Gen. Psychiatry 55, 433–440.

Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R., Evans, A.C., 1996. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cereb. Cortex 6, 207–214.

Penhune, V.B., Zatorre, R.J., MacDonald, J.D., Evans, A.C., 1996. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb. Cortex 6, 661–672.

Portas, C.M., Goldstein, J.M., Shenton, M.E., Hokama, H.H., Wible, C.G., Fischer, I., 1998. Volumetric evaluation of the thalamus in schizophrenic male patients using magnetic resonance imaging. Biol. Psychiatry 43, 649–659.

Raine, A., Lencz, T., Reynolds, G.P., Harrison, G., Sheard, C., Medley, I., Reynolds, L.M., Cooper, J.E., 1992. An evaluation of structural and functional prefrontal deficits in schizophrenia. MRI and neuropsychological measures. Psychiatry Res. 45, 123–137.

Raz, S., Raz, N., 1990. Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerized imaging. Psychol. Bull. 108, 93–108.

Rossi, A., Stratta, P., Mancini, F., de Cataldo, S., Casacchia, M., 1993. Cerebellar vermal size in schizophrenia: a male effect. Biol. Psychiatry 33, 354–357.

Schlaepfer, T.E., Harris, G.J., Tien, A.Y., Peng, L.W., Lee, S., Federman, E.B., 1994. Decreased regional cortical gray matter volume in schizophrenia. Am. J. Psychiatry 151, 842–848.

Shenton, M.E., Kikinis, R., Jolesz, F.A., Pollak, S.D., LeMay, M., Wible, C.G., Hokama, H., Martin, J., Metcalf, D., Coleman, M., McCarley, R.W., 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N. Engl. J. Med. 327, 604–612.

Silbersweig, D.A., Stern, E., 1996. Functional neuroimaging of hallucinations in schizophrenia: toward an integration of bottom-up and top-down approaches. Mol. Psychiatry 1, 367–375.

Smith, R.C., Baumgartner, R., Calderon, M., 1987. Magnetic resonance imaging of brains of schizophrenic patients. Psychiatry Res. 20, 33–46.

Stevens, J.R., 1992. Abnormal reinervation as a basis for schizophrenia: a hypothesis. Arch. Gen. Psychiatry 49, 238–243. correction: 1992. Arch. Gen. Psychiatry 49, 708.

Stratta, P., Rossi, A., Gallucci, M., Amicarelli, I., Passariello, R., Casacchia, M., 1989. Hemispheric asymmetries and schizophrenia: a preliminary magnetic resonance imaging study. Biol. Psychiatry 25, 275–284.

Suddath, R.L., Cassanova, M.F., Goldberg, T.E., Daniel, D.G.,

Kelsoe, J.R., Weinberger, D.R., 1989. Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am. J. Psychiatry 146, 464–472.

Swayze 2nd, V.W., Andreasen, N.C., Alliger, R.J., Yuh, W.T.C., Ehrhardt, J.C., 1992. Subcortical and temporal structures in affective disorders and schizophrenia: a magnetic resonance imaging study. Biol. Psychiatry 31, 221–240.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme, Stuttgart.

Thirion, J.P., Calmon, G., 1997. Deformation analysis to detect and quantify active lesions in 3D. Medical Image Sequences. Inria, Technical Report 3101.

Thompson, P.M., MacDonald, D., Mega, M.S., Holmes, C.J., Evans, A.C., Toga, A.W., 1997. Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. J. Comput. Assist. Tomogr. 21, 67–81.

Vita, A., Dieci, M., Giobbio, G.M., Caputo, A., Ghiringhelli, L., Comazzi, M., Garbarini, M., Mendini, A.P., Morganti, C., Tenconi, F., Cesana, B., Invernizzi, G., 1995. Language and thought disorder in schizophrenia: brain morphological correlates. Schizophr. Res. 15, 243–251.

Volkow, N.D., Levy, A., Brodie, J.D., Wolf, A.P., Cancro, R., van Gelder, P., Henn, F., 1992. Low cerebellar metabolism in medicated patients with schizophrenia. Am. J. Psychiatry 149, 686–688.

Ward, K.E., Friedman, L., Wise, A., Schulz, S.C., 1996. Meta-analysis of brain and cranial size in schizophrenia. Schizophr. Res. 22, 197–213.

Wible, C.G., Shenton, M.E., Fischer, I.A., Allard, J.E., Kikinis, R., Jolesz, F.A., Iosifescu, D.V., McCarley, R.W., 1997. Parcellation of the human prefrontal cortex using MRI. Psychiatry Res. 28, 29–40.

Williamson, P., Pelz, D., Merskey, H., Morrison, C., Conlon, P., 1991. Correlation of negative symptoms in schizophrenia with frontal lobe parameters on magnetic resonance imaging. Br. J. Psychiatry 159, 130–134.

Wolkin, A., Rusinek, H., Vaid, G., Arena, L., Lafargue, T., Sanfilipo, M., 1998. Structural magnetic resonance image averaging in schizophrenia. Am. J. Psychiatry 8, 1064–1073.

Young, A.H., Blackwood, D.H.R., Roxborough, H., 1991. A magnetic resonance imaging study of schizophrenia: brain structure and clinical symptoms. Br. J. Psychiatry 158, 158–164.

Zipursky, R.B., Lim, D.O., Sullivan, E.V., Brown, B.W., Pfefferbaum, A., 1992. Widespread cerebral gray matter volume deficits in schizophrenia. Arch. Gen. Psychiatry 49, 195–205.

Zipursky, R.M., Marsh, L., Lim, K.O., DeMent, S., Shear, P.K., Sullivan, E.V., 1994. Volumetric MRI assessment of the temporal lobe structures in schizophrenia. Biol. Psychiatry 35, 501–506.