Reduced Cerebellar Volume and Neurological Soft Signs in First-Episode Schizophrenia

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Abstract

Recent studies indicate that the cerebellum is involved in schizophrenia. Since the cerebellum is crucial for motor coordination one may ask whether the respective changes are associated with motor dysfunction in the disease. To test these hypotheses in a clinical study, we investigated cerebellar volumes derived from volumetric magnetic resonance imaging of 37 first episode patients with schizophrenia, schizophreniform or schizoaffective disorder and 18 healthy controls matched for age, gender and handedness. To control for potential interindividual differences in head size, intracranial volume was entered as a covariate. Neurological soft signs (NSS) were examined after remission of acute symptoms.

When compared with the controls, patients had significantly smaller cerebellar volumes ($p < 0.0001$) for both hemispheres. Furthermore, NSS in patients were inversely correlated with tissue volume of the right cerebellar hemisphere ($r = -.41$, $p < 0.05$) partialling for intracranial volume. No associations were detected between cerebellar volumes and psychopathological measures obtained on admission in the acute psychotic state nor after remission, treatment duration until remission, treatment response or prognostic factors, respectively. These findings support the hypothesis of cerebellar involvement in schizophrenia and indicate that the respective changes are associated with NSS.

Keywords: Magnetic resonance imaging; Cerebellum; Neurological soft signs;

1. Introduction

Recently, an elaborate model of cortical-subcortical-cerebellar circuitry has been proposed (Andreasen, 1998), encompassing frontal, cerebellar as well as thalamic regions. The concept of “cognitive dysmetria" hypothesizes a disruption in this cortico-cerebellar-thalamic-cortical circuit (CCTCC) leading to impaired sequencing and coordination of mental processes, manifested in symptoms associated with schizophrenia (Andreasen et al., 1996).

This model is supported by functional neuroimaging studies demonstrating an involvement of the cerebellum in higher cognitive functions such as recalling complex narrative material (Andreasen et al., 1996), episodic memory retrieval (Andreasen et al., 1999), verbal fluency (Schlösser et al., 1998) and reasoning (Osherson et al., 1998) and their related deficits in patients with schizophrenia. The important role of the cerebellum in motor coordination is well established. These functions are known to be deficient not only in patients with manifest schizophrenia, but also in probands with an increased genetic liability (Niethammer et al., 2000). Clinically these deficits present as neurological soft signs (NSS). However, the association between cerebellar changes and NSS has to date not been sufficiently addressed.

Morphological changes of the cerebellum were reported in a number of computed tomography (CT) and magnetic resonance imaging (MRI) studies (Tables 1 and 2). While these studies yielded conflicting results, only one CT-study and one MRI-Study concentrated on first episode patients. An association between cerebellar changes and NSS in first episode patients would facilitate the hypothesis that cerebellar changes, like NSS, may precede clinical manifestation of the disease.

Insert Tables 1 and 2 about here

The purpose of the present study was to examine possible cerebellar volume differences between subjects with schizophrenia, schizophreniform disorder or schizoaffective disorder and healthy control subjects. In order to rule out potential medication effects and to address the question of whether changes accompany or may even precede the initial episode we enrolled first-episode patients only. Moreover, potential cerebellar volume changes were investigated with respect to neurological soft signs and other important clinical characteristics of the disease.

2. Methods

2.1 Subjects

Data of 37 patients and 18 healthy controls (see table 3) entered statistical analyses. All subjects were dominantly right handed (Oldfield, 1971). The patients‘ group consisted of first-episode patients with diagnoses of schizophrenia, schizophreniform disorder or schizoaffective disorder who had been consecutively admitted to the inpatient unit of the University of Heidelberg Psychiatric Hospital. Subjects were excluded if they had a life-time history of major head trauma with loss of consciousness, neurological disease, severe substance abuse, or serious medical disease. This was true for 2 patients, namely suffering from epilepsy and polycythemia vera (Pantel et al., 1999), respectively**,** and a third case of suspected infectious disease of the central nervous system**.** A fourth patient refused further treatment on day five and was discharged against medical advice. His data were subsequently excluded, as well. For the remaining 37 patients being subject to this study DSM-IV

diagnoses at discharge as assessed by SCID were schizophrenia (n = 20), schizophreniform disorder (n = 14), schizoaffective disorder (n = 2), and psychosis not otherwise specified (n = 1). All patients experienced their first hospitalization for a psychotic episode and none had a life-time history of any significant neuroleptic treatment. Clinical and sociodemographic variables of patients are depicted in Table 3.

For neuroleptic treatment, butyrophenones in combination with biperiden were initially administered in all but 6 patients. In the course of treatment, the medication was changed to atypical neuroleptics if clinically warranted (i.e. persisting symptoms, extrapyramidal side effects); this was the case in 26 of the 37 patients included. Further psychopharmacological substances such as benzodiazepines or antidepressants were given as needed.

2.2 Clinical Assessment

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was administered on three occasions throughout the period of hospitalization, namely on admission, at the end of the first week of treatment, and after remission of acute symptoms before discharge. Treatment response was defined as the percentage decrease in total PANSS score between admission and remission. Neurological soft signs (NSS) were examined on the Heidelberg Scale (Schröder et al., 1992b) after remission of florid symptoms, scoring from 0 (no prevalence) to 3 (marked prevalence) for right and left hand, respectively, their total number present being determined. The scale consists of 5 items assessing motor coordination (Ozeretzki's Test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), 3 items assessing integrative functions (station and gait, tandem walking, two-point discrimination), 2 items assessing complex motor tasks (finger-to-nose test, fist-edge-

palm test), 4 items assessing right/left and spatial orientation (right/left orientation, graphesthesia, face-hand test, stereognosis), and 2 items assessing hard signs (arm holding test, mirror movements). Potential extrapyramidal side effects were protocolled on the scales by Simpson & Angus (1979), Barnes (1989), and on the Abnormal Involuntary Movement Scale (AIMS) (NIMH, 1976). The Strauss-Carpenter Scale (Strauss & Carpenter, 1974) was administered at study intake, and handedness was ascertained by means of the Edinburgh Inventory (Oldfield, 1971). All ratings were preformed by two raters who had undergone formal training.

Insert Table 3 about here

2.3 MRI Acquisition and Analysis

MR imaging was undertaken a median of 14 (range 0-81) days after treatment initiation. Scanning was performed using a 1.5-T clinical MR scanner (Magnetom Vision, Siemens, Erlangen, Germany). Two 3D image sets of the whole brain were acquired with the standard head-coil for all subjects: a set of T1-weighted images providing a good differentiation between the gray and white matter, and additionally a set of T2-weighted images providing differentiation between tissue and cerebrospinal fluid. A three-dimensional MPRAGE sequence (TE/TR/TI/α = 10 ms/4 ms/300 ms/12°) (Mugler and Brookeman, 1990) was used for the T1 and a 3D DESS sequence (TE/TR/α = 9 ms/25 ms/35°) (Hardy et al., 1996) or a 3D PSIF sequence (TE/TR/α = 7 ms/17 ms/50°) (Hawkes et al., 1997) for the T2-weighted images. Of the 55 subjects included in this study, 16 individuals (13 patients, 3 controls) were scanned using the original sequence and 39 individuals (24 patients, 15 controls) using the following sequence. The T2 sequence was changed for technical reasons, i.e. in order to

obtain a better gray-white differentiation and to minimize motion artifact the original sequence was rather susceptible to. In detail, motion artifact had resulted in the inability of the analysis software to process 16 further data sets originally acquired. Both 3D coronal image sets had an in-plane resolution of 1.1x1.1 mm^2 and consisted of 128 3D-partitions of 1.8 mm thickness. The total measurement time was approximately 15 minutes per patient.

Scans were analysed using the BRAINS software (Andreasen et al., 1992, 1993, 1994). In brief, this software family enables automatic measurement of specific brain regions. The brain is first resampled into a standard orientation along the interhemispheric fissure in the axial and coronal views and along the AC-PC line in the sagittal view. The bounding box for the brain is defined along with the AC and PC points to define how the Talairach grid system is mapped onto the brain of interest. All stereotactically defined boxes in the Talairach atlas are assigned to a certain brain region and its respective hemisphere (Andreasen et al., 1996b). The original Talairach grid has been extended in the Talairach box definition method developed by Andreasen et al. to include two rows of boxes that are inferior to those proposed by Talairach and Tournoux (1988). This Talairach box coordinate system was used to measure the size of the cerebellum. The definition for right and left was generated by dividing the cerebellum based on the midline of the brain. The definition of right and left include the vermis and consider the cerebellar structure as a whole. A detailed description of the segmentation technique is given in Harris et al. (1999) or on the WEB site (http://www.psychiatry.uiowa.edu/ipl). For volumetric measurement contents of the boxes defined as belonging to one specific brain region are summed up for gray matter, white matter cerebrospinal fluid (CSF) and venous blood, separately. In the case of the cerebellum, the partition into various tissue types has not yet been validated. Therefore, the below analyses

are constrained to the more conservative variable of total tissue volume comprising gray matter and white matter. All volumetric data refer to discrete classification.

Insert Figures 1 and 2 about here

2.4 Statistical Analysis

Statistical analyses were performed using statistical analyses system (SAS). Chi-Square Tests and T-Tests were run in order to allow the detection of a possible group effect on age or gender and a possible type of sequence effect on cerebellar volumes, respectively. Analyses of covariance (ANCOVAs) were calculated for cerebellar total tissue volume for each hemisphere, separately, with group as independent variable. Intracranial volume (ICV), computed as the volume of tissue and CSF contained under the pia matter, was used as a covariate to control for variance associated with overall brain size.

For correlational analyses, Pearson correlations between cerebellar volumes and clinical variables were run, intracranial volume being partialled out. Finally, we determined the correlations between cerebellar volume measurements and sociodemographic data such as age and educational level.

3. Results

In a first step, demographic variables were tested for significant group differences. Patients and controls did not significantly differ regarding gender, age or handedness.

Insert Table 4 about here

In a second step it was ruled out that type of sequence caused a systematic effect. Then, volumetric data was investigated. Table 4 gives cerebellar volumes for the two hemispheres separately in patients and normal controls. The ANCOVA revealed a significant group effect for both hemispheres, with schizophrenic patients having reduced volumes as compared to controls (right: $F = 18.71$, $df = 1$, $p < 0.0001$; left: $F = 17.2$, $df = 1$, $p < 0.0001$). ICV, however, did not differ between groups ($F = 0.95$, $df = 1$, $p < 0.33$), neither did whole brain volume ($F = 2.48$, $df = 1$, $p < 0.12$). Furthermore, NSS scores in patients were inversely correlated with total tissue volume of the right ($r = -0.41$, $p < 0.05$) but not left ($r = -0.21$, $p = 0.22$) cerebellar hemisphere partialling for ICV. In detail, this significant association with the right cerebellar hemisphere referred to the items " pronation/supination" ($r = -0.34$, $p < 0.05$ for the right hand, and $r = -0.36$, $p < 0.05$ for the left hand), "diadochokinesia" ($r = -0.34$, $p < 0.05$ for the left hand), "finger-to-thumb opposition" trendwise ($r = -0.31$, $p = 0.07$), and "stereognosis" ($r = -0.36$, $p < 0.05$ for the right hand, and $r = -0.31$, $p = 0.07$ for the left hand). Furthermore, no significant correlation arose between cerebellar volumes and PANSS scores on any of the three occasions throughout the study. There was also no significant correlation between volumetric measurements and treatment duration until remission, treatment response, age, educational level, or the SCS.

Insert Figure 3 about here

4. Discussion

Our study yielded two major findings: 1) first-episode patients with schizophrenia have reduced cerebellar volumes bilaterally compared to healthy controls, and 2) decreased volumes of the right cerebellar hemisphere in patients are associated with increased NSS scores.

The present investigation provides evidence of cerebellar volume reduction in first-episode schizophrenia. This significant difference was demonstrated independent of intracranial volume and did not refer to potential confounding factors, in particular age, gender, or educational level. Patients had received neuroleptic treatment for a median of 14 days, implying that medication is unlikely to contribute to the morphologic differences between groups. Further potential confounding variables such as severe substance abuse known to cause cerebellar atrophy served as exclusion criteria in order to reduce variance and minimize the possibility of external influences.

Although potential cerebellar changes in schizophrenia were addressed in a considerable number of CT and MRI studies, the results appear to be rather inconclusive. While 8 of 13 CT studies (see table 1) found indications of significant cerebellar atrophy by visual inspection or planimetric measurements in schizophrenia, corresponding changes were only reported in 5 of 24 MRI studies (see table 2). However, the latter also comprised 4 planimetric MRI studies which uniformly showed no cerebellar changes. A number of methodological aspects have to be taken into account, however, when discussing results. Differences in head size were addressed in 19 of the 20 volumetric MRI studies by analyzing relative data (1 study) or covarying for a variety of measures: for intracranial volume (3 studies), height (2 studies), age

(1 study), total cerebral volume (2 studies), whole brain volume (1 study), or combinations of some of the above (10 studies). Analogously, a considerable diversity exists with regard to MRI acquisition techniques, in particular sequence applied, slice thickness or plane in which images were obtained. The comparability of studies is further impeded by differences between patients' samples, namely with respect to age, stage and course of the disease. The single study investigating patients with childhood-onset schizophrenia (Jacobsen et al., 1997) found significantly smaller vermal volumes in the patients compared to the controls, indicating that the differences in the vermis may occur before age-related volumetric changes. In addition, one of the two existing studies comprising exclusively first-episode patients was able to show vermian atrophy in patients but not in controls (Weinberger et al., 1982). This finding is compatible with our result of reduced cerebellar volume, giving rise to the question whether the initial episode of acute psychosis constitutes a period of unique structural vulnerability and malleability. However, the most recent study by Cahn and co-workers (2002) on 20 first-episode antipsychotic-naive patients with a comparably high educational level, a late age at onset and a relatively low PANSS score did not find volumetric differences of the cerebellum compared to controls. Since the group reported similar volumes in the controls but larger volumes in the patients than the present study one may argue in accordance with the authors that their patient sample might have been less severely ill than those investigated by others. In patients with a chronic illness course, however, confounding variables such as prolonged neuroleptic treatment, in combination with the heterogeneity of the disease itself may conceal disease-inherent processes.

The increasing body of research indicating a possible involvement of the cerebellum in structural as well as functional changes in schizophrenia (Andreasen et al., 1996; Rapoport et al., 2000) is compatible with a disruption in the cortico-cerebellar-thalamic-cortical circuit

proposed by Andreasen et al. (1996; 1998). This elaborate model is thought to lead to impaired sequencing and coordination of mental processes termed ”cognitive dysmetria” and manifested in symptoms present in schizophrenia. In part, it overcomes the restrictions of distinct loci being associated with different symptom-complexes and syndromes of the schizophrenias, offering a theoretical framework to connect primarily independent findings. Our results of reduced bilateral cerebellar volume are in line with the assumption of a disrupted cortical-subcortical-cerebellar circuitry and may thus provide support to the concept.

Neurological soft signs were significantly inversely correlated with the volume of the right cerebellar hemisphere in patients indicating that with reduced cerebellar tissue volume the frequency and degree of neurological soft signs increased. Findings of increased prevalence of neurological soft signs in patients with schizophrenia have been consistently reported, comparisons included healthy family members (Woods et al., 1986; Kinney et al., 1986; Ismail et al., 1998), monozygotic co-twins discordant for schizophrenia (Cantor-Graae et al., 1994; Niethammer et al., 2000), other psychiatric disorders (Cox & Ludwig, 1979; Youssef et al., 1988), and normal volunteers (Gupta et al., 1995; Rubin et al., 1994; Schröder et al., 1992a; Schröder et al., 1996, Schröder et al., 1998).

To our knowledge, only one study to date has published data investigating an association between cerebellar volume and neurological soft signs (Keshavan et al., 2003). Neuroleptic-naive patients with first-episode schizophrenia (n = 90) were examined with the Neurological Evaluation Scale (Buchanan et al., 1989) and a sub-sample (n = 12) additionally received MRI. After principal-components analysis a significant inverse correlation emerged between cerebellar volume and the two factors with the highest Eigenvalue, namely repetitive motor

tasks and cognitively demanding and perceptual tasks. Further research into neurological abnormalities in combination with volumetric measures revealed the former to be correlated with sulcal enlargement, but not enlargement of the lateral ventricles, as well as with reduced brain length in the CT study by Rubin et al. (1994). The authors assessed 45 first-hospitalized patients with schizophrenia or schizophreniform disorder and 24 healthy volunteers with a standardized neurological examination, finding significant differences between groups solely with regard to neurological functions located in the cerebellum. Two further CT studies were unable to detect an effect relating neurological soft signs to cerebral ventricular size in chronic schizophrenic patients (King et al., 1991; Kolakowska et al., 1985). Previous reports by our own group demonstrated width of the third ventricle and changes of the basal ganglia to be significantly correlated with neurological soft signs in a sample of 50 patients with schizophrenia (Schröder et al., 1992b). These findings were confirmed by Mohr et al. (1996) who reported neurological soft signs to be significantly correlated with relative width of the third ventricle, the interhemispheric fissure and with the lateral sulci. A study on first episode, drug naïve patients with schizophrenia found extrapyramidal side effects but not NSS to be associated with dopamine D2 receptor upregulation as indicated by an increased IBZM uptake following standardized neuroleptic treatment with a conventional neuroleptic (Schröder et al., 1998). Further studies with functional magnetic resonance imaging revealed an association between NSS and a decreased activation of the sensorimotor cortices – partly also the supplementary motor area – in schizophrenia (Schröder et al., 1995 and 1999).

Our finding of increased number and degree of neurological soft signs with decreased volume of the right cerebellar hemisphere reflects the functional role of the cerebellum for the development of neurological abnormalities such as disturbances of coordination and diadochokinesia. Neuroleptic or other drugs are rather unlikely to have influenced the

presence or markedness of NSS as has been consistently shown. While extrapyramidal side effects have been demonstrated to increase significantly during the clinical course, NSS are known to show a decline with remission of the acute symptomatology (Jahn et al., in press; Schröder et al, 1992b; Schröder et al., 1998; for review, see: Schröder, 2003). Additionally, extrapyramidal side effects, but not NSS corresponded with D2 dopamine receptor upregulation in the basal ganglia under neuroleptic therapy (Schröder et al., 1998).

In conclusion, the results of our study indicate that there is a cerebellar involvement in schizophrenia. They are compatible with the assumption of a cortico-thalamic-cerebellar circuit being disrupted in patients with this disease (Andreasen et al., 1996; 1998). Future research will overcome the limitations of the present study in delineating cerebellar subdivisions and determining whether these are selectively affected in schizophrenia or whether there is a general deficit to the cerebellum. Neurological soft signs, symptoms frequently observed in patients with schizophrenia, are associated with cerebellar changes. While for this study we can only state this association for the patients' group, an investigation into the relation of NSS and cerebellar volumes in healthy controls is currently underway. There has been considerable scientific debate as to whether structural pathology in schizophrenia is associated with developmental factors or degenerative processes. Longitudinal data are called for to answer the question of whether cerebellar volume reduction in schizophrenia is progressive or not. Yet, the above results give notion that structural changes are present at the time of the initial episode, indicating that altered cerebellar morphology occurs early in the disease process and is not restricted to chronicity.

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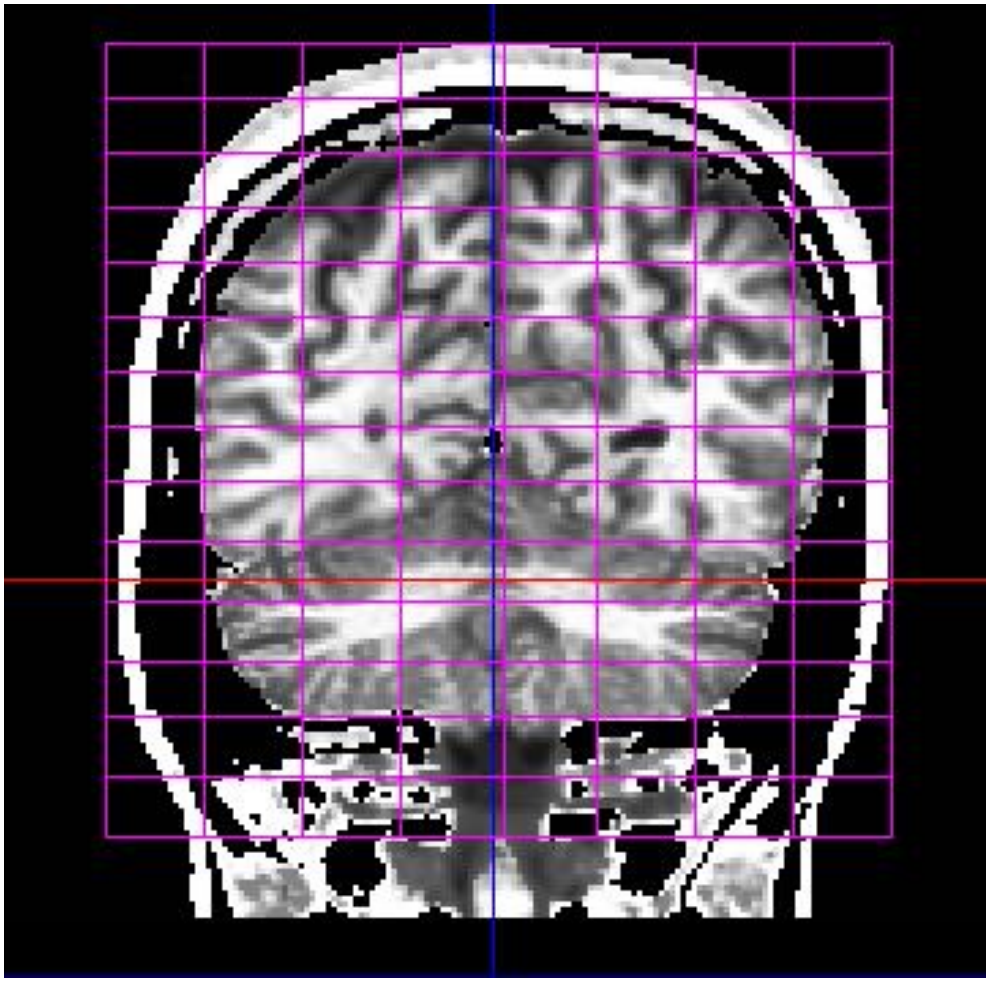

Figure 1.:
Coronal view of an image processed with BRAINS software

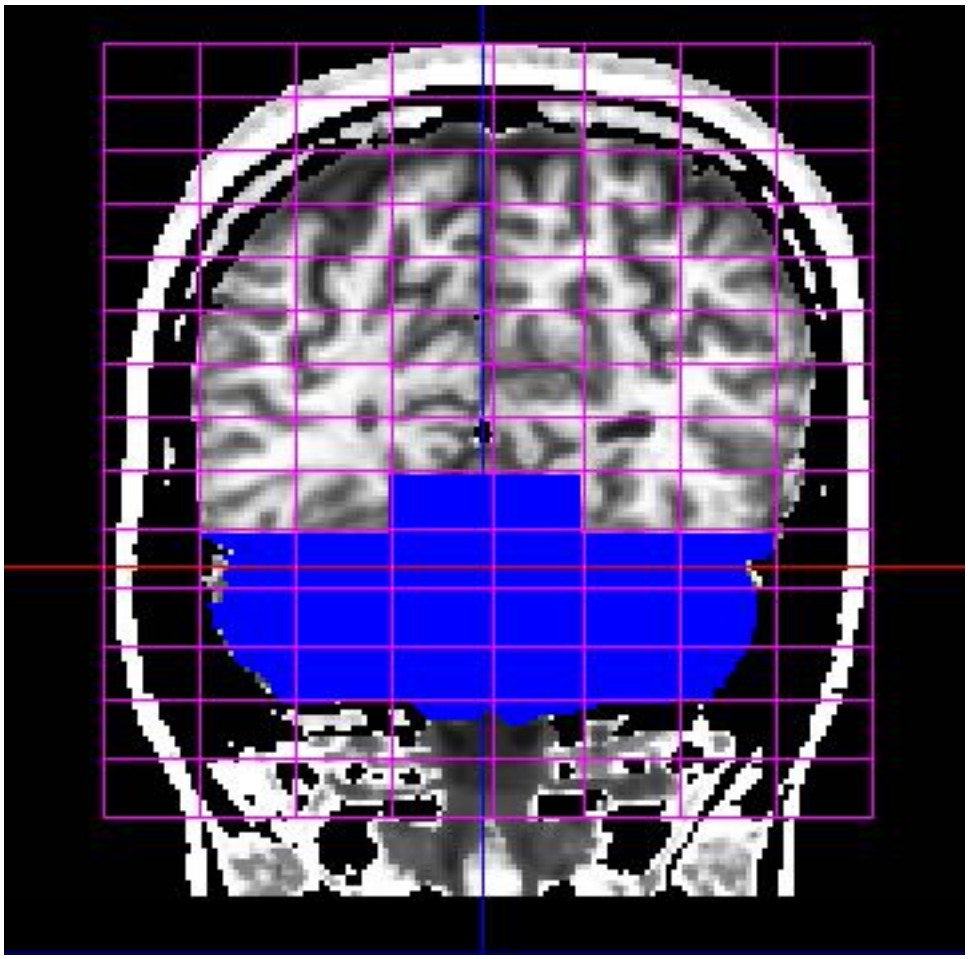

Figure 2.:
Extended Talairach box coordinate system for the measurement of the cerebellum.

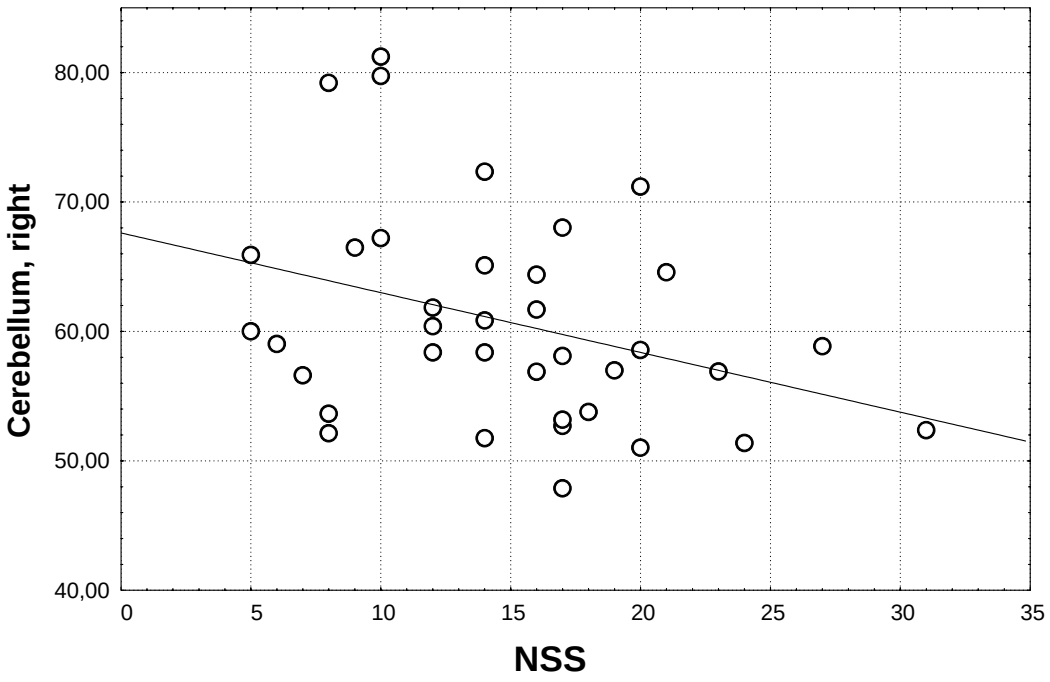

Figure 3:

Negative correlation between volume of the right cerebellar hemisphere and Neurological Soft Signs (NSS), ($r = -0.41$, $p < 0.05$).

Table 1: CT studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Weinberger et al., 1979	Visual assessment	Cerebellar vermis	60 sz	Chronic	9 of 60 (15%) sz pat showed vermal atrophy
Heath et al., 1979	Visual assessment	Cerebellar vermis	85 sz	Not specified	34 of 85 (40%) pat showed pathology of the vermis
Coffman et al., 1981	Planimetry, ratio of vermis to brain area	Cerebellar vermis	14 sz 21 cont	Chronic	n.s.
Nasrallah et al., 1981; 1982	Visual assessment	Cerebellum	43 (55) sz, male 36 (27) cont, male	Chronic	n.s.

Table 1 cont.: CT studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Heath et al., 1982	Visual assessment	Cerebellar vermis	50 sz	Not specified	25 of 50 (50%) pat showed vermal atrophy
Lippmann et al., 1982	Visual assessment	Cerebellar vermis	54 sz 79 cont	Not specified	Significantly more vermal abnormalities in pat compared to cont
Weinberger et al., 1982	Visual assessment	Cerebellar vermis	35 sf 17 sz/sa 26 cont	First episode Chronic	Significantly more chronic sz/sa pat (12%) showed vermian atrophy compared to first-episode sf pat (0%) and cont (0%).
Dewan et al., 1983	Width and density	Cerebellar vermis	23 sz 23 cont	Chronic	Significantly decreased vermian width in pat compared to cont. N.s. findings with regard to density measurements.
Rieder et al., 1983	Visual assessment	Cerebellum	28 sz 15 sa	Chronic	2 of 18 (11%) sz pat showed cerebellar atrophy 1 of 15 (7%) sa pat showed cerebellar atrophy

Table 1 cont.: CT studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Boronow et al., 1985	Visual assessment	Cerebellum	30 sz/sa 26 cont	Chronic	n.s. 1 of 30 (3%) pat and 2 of 26 (8%) cont showed cerebellar atrophy
DeLisi et al., 1986	Visual assessment	Cerebellum	26 sz/sa 20 cont	Mixed	n.s.
Sandyk et al., 1991	Visual assessment	Cerebellar vermis	23 sz	Chronic	10 of 23 (43,5%) pat showed vermian atrophy
Wilcox, 1991	Visual assessment	Cerebellum	17 catatonic sz 30 noncatatonic sz 15 cont	Chronic	Significantly more catatonic pat (29%) showed cerebellar atrophy compared to noncatatonic sz (8%) and cont (0%)

[a] sz = schizophrenia, sa = schizoaffective disorder, sf = schizophreniform disorder, cont = normal controls

[b] stating presence/absence of main effect Group (pat vs. cont) unless specified differently

[c] giving solely those control groups comprising healthy subjects, although some studies included multiple control groups

Table 2: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Mathew & Partain, 1985	Planimetry	Cerebellar vermis	12 sz 12 cont	Not specified	n.s.
Uematsu & Kaiya, 1988	Planimetry	Cerebellar vermis	40 sz, male 17 cont, male	Not specified	n.s.
Nasrallah et al., 1991	Planimetry	Cerebellar vermis	30 sz/sa, male 11 cont, male	Not specified	n.s.
Rossi et al., 1993	Planimetry	Cerebellar vermis	23 sz 16 cont	Relapsing	n.s.
Andreasen et al., 1994	Volumetry	Cerebellum	52 sz 90 cont	Chronic	n.s.

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Aylward et al., 1994	Planimetry	Cerebellar vermis	36 sz 51 cont	Not specified	n.s.
Flaum et al., 1995	Volumetry	Cerebellum	102 sz 87 cont	Mixed	n.s.
Jacobsen et al., 1997	Planimetry Volumetry	Vermal area Vermal volume Cerebellum	24 sz, adolescents 52 cont, “	Childhood onset	Significantly smaller inf. post. lobe area and volume and vermal volume in pat compared to cont. N.s. finding with regard to total cerebellar volume.
Nopoulos et al., 1997	Volumetry	Cerebellum	80 sz 80 cont	Not specified	n.s.

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Gaser et al., 1999; Volz et al., 1999	Volumetry	Cerebellum Cerebellar vermis	75 (85) sz 75 cont	Not specified	Significantly smaller volume of the left cerebellar hemisphere in pat compared to cont. N.s. finding with regard to vermis volume.
Levitt et al., 1999	Volumetry	Cerebellum Cerebellar vermis	15 sz, male 15 cont, male	Chronic	N.s. findings with regard to total cerebellar and cerebellar hemispheric white and gray matter volumes Significantly larger vermian white matter volume in pat compared to cont
Sachdev et al., 1999	Volumetry	Cerebellum	23 sz (Onset before age 35) 24 sz (Onset after age 50) 34 cont		n.s.

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Wassink et al., 1999	Volumetry	Cerebellum	63 sz	50% first episode	Smaller cerebellar volume was significantly correlated with greater psychosocial impairment, duration of negative and psychotic syndrome
Staal et al., 2000	Volumetry	Cerebellum	32 sz 32 unaffected siblings 32 cont	Not specified	n.s.
Sullivan et al., 2000	Volumetry	Cerebellum Cerebellar vermis	27 sz 61 cont	Not specified	n.s.

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Ichimiya et al., 2001	Volumetry	Cerebellum Cerebellar vermis	20 sz, male 20 cont, male	Not specified	Significantly smaller vermal volume in pat compared to cont. N.s. finding with regard to total cerebellar or hemispheric volumes.
Loeber et al., 2001	Volumetry	Cerebellar lobules	19 sz 19 cont	Not specified	Significantly smaller inferior vermal volume and total vermal volume in pat compared to cont
Staal et al., 2001	Volumetry	Cerebellum	45 sz 23 cont	Chronic	n.s.
Wilke et al., 2001	Volumetry	Cerebellum	48 sz 48 cont	Not specified	Significantly larger gray matter volume in pat compared to cont

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
McDonald et al., 2002	Volumetry	Cerebellum	66 sz 99 unaffected relatives 68 cont	Not specified	n.s.
Saeed & Puri, 2002	Volumetry	Cerebellum	10 sz 10 cont	Not specified	n.s.
Hulshoff Pol et al., 2002	Volumetry	Cerebellum	159 sz 158 cont	Chronic	n.s.
Cahn et al., 2002	Volumetry	Cerebellum	20 sz 20 cont	First-episode	n.s.

Table 2 cont.: MRI studies investigating cerebellar pathology in schizophrenia

Study	**Method**	**ROI**	**Subjects**[a,c]	**Course**	**Results**[b]
Okugawa et al., 2002	Volumetry	Cerebellar vermis	30 sz, male 18 cont, male	Chronic	Significantly smaller posterior superior vermis volume in pat compared to cont

[a] sz = schizophrenia, sa = schizoaffective disorder, cont = normal controls

[b] stating presence/absence of main effect Group (pat vs. cont) unless specified differently

[c] giving solely those control groups comprising healthy subjects, although some studies included multiple control groups

Table 3. Demographic and clinical data of the patients and healthy controls (mean ± standard deviation)

	Patients	Controls
Age (yrs)	25.65 ± 6.4	25.50 ± 2.4
Gender (m : f)	20 : 17	9 : 9
Education (yrs)	12.11 ± 1.5	12.94 ± 0.2
Handedness (r : l)	37 : 0	18 : 0
Neurological soft signs	14.81 ± 6.1	
PANSS score on admission	107.97 ± 20.6	
PANSS score on remission	52.49 ± 14.6	
Strauss-Carpenter-Prognostic Scale	57.38 ± 9.5	
Treatment duration until remission (days)	38.16 ± 14.5	
Treatment response (%)	50.34 ± 14.2	
AIMS	0.75 ± 2.0	
Barnes	0.86 ± 1.7	
Simpson & Angus	12.19 ± 1.8	

Table 4. Cerebellar volumes and intracranial volume in first-episode patients with schizophrenia and healthy controls

ROI	First-episode patients	Controls	p-value
Left cerebellar hemisphere	60.74 ± 8.3	69.74 ± 9.5	$p < 0.0001$
Right cerebellar hemisphere	60.78 ± 8.3	69.63 ± 8.6	$p < 0.0001$
Intracranial volume	1414.71 ± 119.5	1453.49 ± 171.7	n.s.

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