Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia

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Abstract

Recent studies indicate that morphological and functional abnormalities of the cerebellum are associated with 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. Compared with the controls, patients had significantly smaller cerebellar volumes for both hemispheres. Furthermore, NSS in patients were inversely correlated with tissue volume of the right cerebellar hemisphere partialling for intracranial volume. No associations were detected between cerebellar volumes and psychopathological measures obtained at hospital admission when patients were in the acute psychotic state or 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 et al., 1998), encompassing frontal, cerebellar and thalamic regions. The concept of “cognitive dys-
metria” 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., 1996a). 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., 1996a), 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 not to date been sufficiently addressed.

Morphological changes of the cerebellum were reported in a number of computed tomography (CT) and magnetic resonance imaging (MRI) studies.

Table 1
CT studies investigating cerebellar pathology in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>ROI</th>
<th>Subjectsa,b</th>
<th>Course</th>
<th>Resultsc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberger et al., 1979</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>60 sz</td>
<td>Chronic</td>
<td>9 of 60 (15%) sz pat showed vermian atrophy</td>
</tr>
<tr>
<td>Heath et al., 1979</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>85 sz</td>
<td>Not specified</td>
<td>34 of 85 (40%) pat showed pathology of the vermis</td>
</tr>
<tr>
<td>Coffman et al., 1981</td>
<td>Planimetry, ratio of vermis to brain area</td>
<td>Cerebellar vermis</td>
<td>14 sz (21 cont)</td>
<td>Chronic</td>
<td>N.S.</td>
</tr>
<tr>
<td>Nasrallah et al., 1981, 1982</td>
<td>Visual assessment</td>
<td>Cerebellum</td>
<td>43 (55) sz, male (36 (27) cont, male)</td>
<td>Chronic</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heath et al., 1982</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>50 sz</td>
<td>Not specified</td>
<td>25 of 50 (50%) pat showed vermian atrophy</td>
</tr>
<tr>
<td>Lippmann et al., 1982</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>54 sz (79 cont)</td>
<td>Not specified</td>
<td>Significantly more vermian abnormalities in pat than in cont</td>
</tr>
<tr>
<td>Weinberger et al., 1982</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>35 sf (17 sz/sa (26 cont)</td>
<td>First episode Chronic</td>
<td>Significantly more chronic sz/sa pat (12%) showed vermian atrophy than first-episode sf pat (0%) and cont (0%)</td>
</tr>
<tr>
<td>Dewan et al., 1983</td>
<td>Width and density</td>
<td>Cerebellar vermis</td>
<td>23 sz (23 cont)</td>
<td>Chronic</td>
<td>Significantly decreased vermian width in pat compared with cont. N.S. findings with regard to density measurements</td>
</tr>
<tr>
<td>Rieder et al., 1983</td>
<td>Visual assessment</td>
<td>Cerebellum</td>
<td>28 sz (15 sa)</td>
<td>Chronic</td>
<td>2 of 18 (11%) sz pat showed cerebellar atrophy, 1 of 15 (7%) sa pat showed cerebellar atrophy N.S. 1 of 30 (3%) pat and 2 of 26 (8%) cont showed cerebellar atrophy N.S.</td>
</tr>
<tr>
<td>Boronow et al., 1985</td>
<td>Visual assessment</td>
<td>Cerebellum</td>
<td>30 sz/sa (26 cont)</td>
<td>Chronic</td>
<td>N.S. 1 of 30 (3%) pat and 2 of 26 (8%) cont showed cerebellar atrophy</td>
</tr>
<tr>
<td>DeLisi et al., 1986</td>
<td>Visual assessment</td>
<td>Cerebellum</td>
<td>26 sz/sa (20 cont)</td>
<td>Mixed</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sandik et al., 1991</td>
<td>Visual assessment</td>
<td>Cerebellar vermis</td>
<td>23 sz (20 cont)</td>
<td>Chronic</td>
<td>10 of 23 (43,5%) pat showed vermian atrophy</td>
</tr>
<tr>
<td>Wilcox, 1991</td>
<td>Visual assessment</td>
<td>Cerebellum</td>
<td>17 catatonic sz (30 noncatatonic sz (15 cont)</td>
<td>Chronic</td>
<td>Significantly more catatonic pat (29%) showed cerebellar atrophy compared with noncatatonic sz (8%) and cont (0%)</td>
</tr>
</tbody>
</table>

a sz=schizophrenia, sa=schizoaffective disorder, sf=schizophreniform disorder, cont=normal controls.
b Giving solely those control groups comprising healthy subjects, although some studies included multiple control groups.
c Stating presence/absence of main effect Group (pat vs. cont) unless specified differently.
(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.

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. To rule out potential medication effects and to address the question of whether changes accompany or even precede the initial episode, we enrolled first-episode patients only. Moreover, potential cerebellar volume changes were investigated with respect to NSS 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 patient 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 lifetime history of major head trauma with loss of consciousness, neurological disease, severe substance abuse, or serious medical disease. This was true for two 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 5 and was discharged against medical advice. His data were subsequently excluded as well. For the remaining 37 patients, DSM-IV diagnoses at discharge as assessed by the 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 lifetime history of any significant neuroleptic treatment. Table 3 presents clinical and sociodemographic variables of the patients.

For neuroleptic treatment, butyrophenones in combination with biperiden were initially administered in all but six 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. After remission of the patients’ florid symptoms, NSS were examined on the Heidelberg Scale (Schröder et al., 1992b), with scores from 0 (no prevalence) to 3 (marked prevalence) for the right and left hand, respectively, the total number present being determined. The scale consists of five items assessing motor coordination (Ozeretzki’s Test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), three items assessing integrative functions (station and gait, tandem walking, two-point discrimination), two items assessing complex motor tasks (finger-to-nose test, fist-edge-palm test), four items assessing right/left and spatial orientation (right/left orientation, graphesthesia, face–hand test, stereognosis), and two items assessing hard signs (arm holding test, mirror movements). Potential extrapyramidal side effects were assessed with the scales of Simpson and Angus (1979) and Barnes (1989), as well as the Abnormal Involuntary Movement Scale (AIMS) (National Institute of Mental Health, 1976). The Strauss–Carpenter Scale (Strauss and Carpenter, 1974) was administered at study intake, and handedness was ascertained by means of the Edinburgh Inventory (Oldfield, 1971). All ratings were performed by two raters who had undergone formal training.
Table 2
MRI studies investigating cerebellar pathology in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>ROI</th>
<th>Subjects&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Course</th>
<th>Results&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathew and Partain, 1985</td>
<td>Planimetry</td>
<td>Cerebellar vermis</td>
<td>12 sz, 12 cont</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Uematsu and Kaiya, 1988</td>
<td>Planimetry</td>
<td>Cerebellar vermis</td>
<td>40 sz, male, 17 cont, male</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Nasrallah et al., 1991</td>
<td>Planimetry</td>
<td>Cerebellar vermis</td>
<td>30 sz/sa, male, 11 cont, male</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rossi et al., 1993</td>
<td>Planimetry</td>
<td>Cerebellar vermis</td>
<td>23 sz, 16 cont</td>
<td>Relapsing</td>
<td>N.S.</td>
</tr>
<tr>
<td>Andreasen et al., 1994</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>52 sz, 90 cont</td>
<td>Chronic</td>
<td>N.S.</td>
</tr>
<tr>
<td>Aylward et al., 1994</td>
<td>Planimetry</td>
<td>Cerebellar vermis</td>
<td>36 sz, 51 cont</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Flaum et al., 1995</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>102 sz, 87 cont</td>
<td>Mixed</td>
<td>N.S.</td>
</tr>
<tr>
<td>Jacobsen et al., 1997</td>
<td>Planimetry</td>
<td>Vermal area</td>
<td>24 sz, adolescents</td>
<td>Childhood onset</td>
<td>Significantly smaller inferior post lobe area and volume and vermal volume in pat compared with cont. N.S. finding with regard to total cerebellar volume</td>
</tr>
<tr>
<td>Nopoulos et al., 1997</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>80 sz, 80 cont</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gaser et al., 1999; Volz et al., 1999</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>75 (85) sz, 75 cont</td>
<td>Not specified</td>
<td>Significantly smaller volume of the left cerebellar hemisphere in pat compared with cont. N.S. finding with regard to vermis volume</td>
</tr>
<tr>
<td>Levitt et al., 1999</td>
<td>Volumetry</td>
<td>Cerebellum, Cerebellar vermis</td>
<td>15 sz, male, 15 cont, male</td>
<td>Chronic</td>
<td>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 with cont N.S.</td>
</tr>
<tr>
<td>Sachdev et al., 1999</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>23 sz (onset before age 35), 24 sz (onset after age 50), 34 cont</td>
<td>Not specified</td>
<td>Smaller cerebellar volume was significantly correlated with greater psychosocial impairment, duration of negative and psychotic syndrome N.S.</td>
</tr>
<tr>
<td>Wassink et al., 1999</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>63 sz</td>
<td>50% first episode</td>
<td>Smaller cerebellar volume was significantly correlated with greater psychosocial impairment, duration of negative and psychotic syndrome N.S.</td>
</tr>
<tr>
<td>Staal et al., 2000</td>
<td>Volumetry</td>
<td>Cerebellum</td>
<td>32 sz, 32 unaffected siblings, 32 cont</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sullivan et al., 2000</td>
<td>Volumetry</td>
<td>Cerebellum, Cerebellar vermis</td>
<td>27 sz, 61 cont</td>
<td>Not specified</td>
<td>N.S.</td>
</tr>
<tr>
<td>Ichimiya et al., 2001</td>
<td>Volumetry</td>
<td>Cerebellum, Cerebellar vermis</td>
<td>20 sz, male, 20 cont, male</td>
<td>Not specified</td>
<td>Significantly smaller vermal volume in pat compared with cont. N.S. finding with regard to total cerebellar or hemispheric volumes</td>
</tr>
<tr>
<td>Loeber et al., 2001</td>
<td>Volumetry</td>
<td>Cerebellar lobules</td>
<td>19 sz, 19 cont</td>
<td>Not specified</td>
<td>Significantly smaller inferior vermal volume and total vermal volume in pat compared with cont</td>
</tr>
</tbody>
</table>
2.3. MRI acquisition and analysis

MR imaging was undertaken a median of 14 (range 0–81) days after treatment began. 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 3D MPRAGE sequence (TE/TR/TI/a = 10 ms/4 ms/300 ms/120°) (Mugler and Brookeman, 1990) was used for the T1 and a 3D DESS sequence (TE/TR/a = 9 ms/25 ms/35°) (Hardy et al., 1996) or a 3D PSIF sequence (TE/TR/a = 7 ms/17 ms/50°) (Hawkes and Patz, 1987) 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. to obtain a better gray–white differentiation and to minimize motion artifact to which the original sequence was rather susceptible. 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 1.1 mm² and consisted of 128 3D partitions of 1.8-mm thickness. The total measurement time was approximately 15 min 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 anterior commissure (AC)–posterior commissure (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 definitions 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, the 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. In the case of the cerebellum, the partition into various tissue types has not yet been validated. Therefore, the 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 (see Figs. 1 and 2).

2.4. Statistical analysis

Statistical analyses were performed using the Statistical Analysis System (SAS). Chi-square tests and t-tests were run 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 the 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, with 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.
In a second step it was ruled out that type of sequence caused a systematic effect. Then, volumetric data were investigated. Table 4 gives cerebellar volumes for the two hemispheres separately in patients and normal controls. The ANCOV A revealed a significant group effect for both hemispheres, with schizophrenic patients having reduced volumes compared with controls (right: $F = 18.71, df = 1, P < 0.0001$; left: $F = 17.2, df = 1, P < 0.0001$). However, neither ICV ($F = 0.95, df = 1, P < 0.33$) nor whole brain volume ($F = 2.48, df = 1, P < 0.12$) differed between groups. Furthermore, NSS scores in patients were inversely correlated with total tissue volume of the right ($r = -0.41, P < 0.05$) but not the left ($r = -0.21, P = 0.22$) cerebellar hemisphere partialling for ICV (see Fig. 3). 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 emerged 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 SCS.

4. Discussion

Our study yielded two major findings: (1) first-episode patients with schizophrenia have reduced cerebellar volumes bilaterally compared with 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 ICV and did not refer to potential confounding factors, in particular age, gender, or

<table>
<thead>
<tr>
<th>ROI</th>
<th>First-episode patients</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left cerebellar hemisphere</td>
<td>60.74 ± 8.3</td>
<td>69.74 ± 9.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right cerebellar hemisphere</td>
<td>60.78 ± 8.3</td>
<td>69.63 ± 8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intracranial volume</td>
<td>1414.71 ± 119.5</td>
<td>1453.49 ± 171.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 3. Negative correlation between volume of the right cerebellar hemisphere and neurological soft signs (NSS) ($r = -0.41, P < 0.05$).
educational level. Patients had received neuroleptic treatment for a median of 14 days, implying that medication is unlikely to contribute to the morphological 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 four planimetric MRI studies that 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 with the controls, indicating that the differences in the vermis may occur before age-related volumetric changes. In addition, one of the two existing studies that exclusively comprised first-episode patients was able to show vermic 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 coworkers (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 with control values. Since Cahn et al. (2002) reported similar volumes in the controls but larger volumes in the patients than found in 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., 1996a; Rapoport et al., 2000) is compatible with a disruption in the cortico–cerebellar–thalamic–cortical circuit proposed by Andreasen et al. (1996a,b, 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 cortico–subcortical–cerebellar circuitry and may thus provide support to the concept.

The significant inverse correlation of NSS with the volume of the right cerebellar hemisphere in patients indicates that with reduced cerebellar tissue volume the frequency and degree of NSS increased. Findings of increased prevalence of NSS in patients with schizophrenia have been consistently reported; comparisons included healthy family members (Woods et al., 1986; Kinney et al., 1999; Ismail et al., 1998), monozygotic co-twins discordant for schizophrenia (Cantor-Graae et al., 1994; Niethammer et al., 2000), other psychiatric disorders (Cox and Ludwig, 1979; Youssef and Waddington, 1988), and normal volunteers (Gupta et al., 1995; Rubin et al., 1994; Schröder et al., 1992a, 1996, 1998; Bachmann et al., 2005).

To date, only one study has published data investigating an association between cerebellar volume and NSS (Keshavan et al., 2003). Neuroleptic-naive patients with first-episode schizophrenia (n = 90)
were examined with the Neurological Evaluation Scale (Buchanan and Heinrichs, 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 Eigenvalues, 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 NSS in a sample of 50 patients with schizophrenia (Schröder et al., 1992b). These findings were confirmed by Mohr et al. (1996), who reported NSS to be significantly correlated with relative width of the third ventricle, the interhemispheric fissure, and 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 up-regulation as indicated by an increased uptake of 123I-iodobenzamide 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, 1999).

Our finding of an increased number and degree of NSS 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 marked-ness 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, 1998; for review, see: Schröder, 2003). Additionally, extrapyramidal side effects, but not NSS, corresponded with D2 dopamine receptor up-regulation 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., 1996a, 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. In the present study, NSS, 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 about 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. Yet, the above results suggest 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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