Reduced Volume of the Cerebellar Vermis in Neuroleptic-Naive Schizophrenia

Tetsuya Ichimiya, Yoshiro Okubo, Tetsuya Suhara, and Yasuhiko Sudo

Background: Neuroimaging studies have suggested the possible role of the cerebellum in the pathophysiology of schizophrenia. However, no study has investigated the detailed structures of the cerebellum in patients without a history of neuroleptic medication. The objective of this study is to examine the volume of detailed structures of the cerebellum in neuroleptic-naive schizophrenic patients and to examine the relationship between cerebellar morphology and clinical symptoms.

Methods: Magnetic resonance imaging scans were acquired from 20 male neuroleptic-naive schizophrenic patients and 20 healthy control subjects. We measured the volumes of the cerebrum, cerebellar hemisphere, cerebellar gray and white matter, and vermis. Symptoms were assessed with the Brief Psychiatric Rating Scale. Total Brief Psychiatric Rating Scale scores and subscale scores were used for analysis.

Results: The volume of the vermis was significantly reduced in the schizophrenic group relative to the control group, whereas no significant differences were found in the volumes of other cerebellar structures and the cerebrum. Reduction in the vermal volume correlated with the total Brief Psychiatric Rating Scale Depression subscore and Paranoia subscore.

Conclusions: This study indicates that the volume of the vermis is reduced in patients with schizophrenia, and reduction in vermal volume is suggested to be related to the pathophysiology of the disease. Biol Psychiatry 2001;49:20–27 © 2001 Society of Biological Psychiatry

Key Words: Vermis, cerebellum, schizophrenia, MRI, volumetry, BPRS

Introduction

A growing body of data from functional neuroimaging studies has demonstrated that the cerebellum contributes not only to motor function but also to nonmotor function such as cognition and emotion (Gao et al 1996; Kim et al 1994; Leaton and Supple 1986; Middleton and Strick 1994; Sanes et al 1990). Schizophrenic patients show cognitive abnormalities in processing input from outside and in expressing their responses fluently. Recent evidence has suggested that the cerebellum may have functional abnormalities that are related to cognitive abnormalities in schizophrenia (Andreasen et al 1996; Crespo-Facorro et al 1999; Volkow et al 1992; Wiser et al 1998). In addition to the cognitive abnormalities, neurologic abnormalities have also been demonstrated in schizophrenia. Careful observation indicated that patients have subtle neurologic abnormalities of posture, gait, and coordination (Gupta et al 1995; Kinney et al 1999). A variety of visual motor disturbances (i.e., saccadic eye movements, smooth pursuit eye movements) have been reported in schizophrenia. Visual motor disturbances may also, to a certain extent, be attributable to the cerebellum (Buttner and Fuhray 1995).

Postmortem and neuroimaging studies have demonstrated morphological abnormalities of the cerebellum in schizophrenia. A postmortem brain study of schizophrenia has revealed a smaller anterior vermis relative to normal or psychiatric control subjects (Weinberger et al 1980). Reduced linear density and size of Purkinje cells have been reported in the vermis (Reyes and Gordon 1981; Tran et al 1998). Computed tomography (CT) studies have also reported the smaller vermal size in patients with schizophrenia (Heath et al 1979; Nasrallah et al 1981; Weinberger et al 1979). However, limitations of early cross-sectional CT studies using only one slice have been pointed out. As for magnetic resonance imaging (MRI) studies, most of them have focused on only the midsagittal area of the vermis or total cerebellar volume, producing inconsistent results (Table 1) (Aylward et al 1994; Flaum et al 1995; Mathew and Partain 1985; Nasrallah et al 1991; Nopoulos et al 1999; Rossi et al 1993). Thus, volumetric MRI studies of the detailed cerebellar structures have been
awaited. Recently there were two studies that have measured the volume of cerebellar regions in detail. One (Jacobsen et al 1997) reported a significantly smaller volume of the vermis, whereas the other (Levitt et al 1999) reported it to be significantly larger. In the latter, a possible effect of neuroleptic medication on the enlargement of vermal volume was suggested. Such inconsistent results emphasized the need for MRI studies to investigate the regional volume of the cerebellum in patients without a history of neuroleptic medication. In this study, therefore, we examined the cerebellar structures in neuroleptic-naive patients with schizophrenia, and we compared the patients to age-, gender-, and handedness-matched healthy control subjects.

**Methods and Materials**

**Subjects**

We examined 20 neuroleptic-naive patients. Patients were aged 28.3 ± 6.9 years (mean ± SD). All patients were male and right-handed. The duration of illness was 5.1 ± 5.2 years (mean ± SD). The length of formal education of the patients was 13.4 ± 2.1 years (mean ± SD). The patients all met the DSM-IV criteria for schizophrenia or schizophreniform disorder. One patient diagnosed with schizophreniform disorder at the time of the scan was followed up and then fulfilled the DSM-IV criteria for schizophrenia. The subtypes were paranoid (15 subjects), disorganized (three), and undifferentiated (two). The control subjects were recruited from the surrounding community and entered this study as volunteers. Twenty male control subjects were aged 26.3 ± 4.5 years (mean ± SD) and were right-handed. They did not have any psychiatric problems or any history of psychiatric disorder. The length of formal education of the controls was 16.2 ± 1.8 years (mean ± SD).

From direct interview and medical history, we excluded subjects who were taking any medication or had a history of major physical illness, neurologic disorder, substance abuse, alcohol abuse, or electroconvulsive therapy.

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiologic Sciences. After providing a complete explanation of the study, written informed consent was obtained from all subjects.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjecta</th>
<th>Duration/</th>
<th>Method</th>
<th>Regions</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathew and Partain 1985</td>
<td>12/12</td>
<td>9.58 ± 5.00</td>
<td>Area</td>
<td>Vermis (total)</td>
<td>No difference</td>
</tr>
<tr>
<td>Nasrallah et al 1991</td>
<td>30/11</td>
<td>Not described</td>
<td>Area</td>
<td>Vermis (lobules I-V/VI-VII/VIII-X)</td>
<td>No difference (larger trend in lobules I-V/VIII-X for patients)</td>
</tr>
<tr>
<td>Rossi et al 1993</td>
<td>23/16</td>
<td>6.17 ± 5.14</td>
<td>Area</td>
<td>Vermis (lobules I-V/VI-VII/VIII-X)</td>
<td>No difference, smaller lobules I-V in male patients than in female patients</td>
</tr>
<tr>
<td>Aylward et al 1994</td>
<td>36/51</td>
<td>Not described</td>
<td>Area</td>
<td>Vermis (lobules I-V/VI-VII/VIII-X)</td>
<td>No difference</td>
</tr>
<tr>
<td>Flaum et al 1995</td>
<td>102/87</td>
<td>9.7 ± 8.1</td>
<td>Volume</td>
<td>Total cerebellum</td>
<td>No difference</td>
</tr>
<tr>
<td>Jacobsen et al 1997</td>
<td>24'/52</td>
<td>Not described</td>
<td>Area and volume</td>
<td>Vermis (total, lobules VIII–X)</td>
<td>Smaller area/volume of total vermis and lobules VIII–X in patients, no difference in cerebellar hemispheres</td>
</tr>
<tr>
<td>Levitt et al 1999</td>
<td>15/15</td>
<td>Not described</td>
<td>Volume</td>
<td>Vermal gray/white matter</td>
<td>Larger vermal white matter in patients, no difference in cerebellar hemispheres</td>
</tr>
<tr>
<td>Nopoulos et al 1999</td>
<td>65/65</td>
<td>Not described</td>
<td>Area or volume</td>
<td>Vermal (area, lobules I–V/VI–VII/VIII–X)</td>
<td>Smaller lobules I–V in patients, no difference in total cerebellum</td>
</tr>
</tbody>
</table>

*aSchizophrenic/control.  
bDuration of illness, mean ± SD years.  
cChildhood-onset schizophrenia, mean age = 14.1 years.  
dMean age at onset = 10.0 years.
MRI Image Acquisition

All subjects were scanned with a Philips Medical Systems (Best, The Netherlands) Gyroscan 1.5-T magnetic resonance scanner at the National Institute of Radiologic Sciences. A scout midline sagittal image was used to determine the anterior and posterior commissures and to define the anterior and posterior limits of the scan. We then acquired 2 mm–thick contiguous slices in the coronal plane by an inversion recovery sequence (repetition time $= 2500$ msec, echo time $= 20$ msec, inversion time $= 300$ msec, flip angle $= 90^\circ$, acquisition matrix $= 256 \times 205$, number of excitations $= 1$, field of view $= 23$ cm). The acquisition protocol consisted of 92 slices including the entire cranial cavity. No gross pathologic lesions were observed in any of the subjects.

Image Analysis

Image analysis on all scans was performed using a software package for image analysis (NIHImage, National Institutes of Health, Research Service Branch, Bethesda, MD). Brain measurements were derived by manually outlining regions of interest (ROIs) on each slice. The size of the ROIs was computed automatically as an area measurement within the NIHImage software program. Then the areas of ROIs were summed across slices and multiplied by slice thickness, yielding an approximate volume. All of the areas of the ROIs were measured in the coronal view, since cerebellar structures were all visible in the coronal slices (Duvernoy 1995). Figure 1 provides an example of the outlines of the vermis and cerebellar gray and white matters on coronal slices from the brain MRI of a healthy control subject. We separated the cerebrospinal fluid (CSF) from each ROI and separated the cerebellar gray and white matters from each other by using the thresholding technique available in the NIHImage software. The thresholding function makes it possible to separate each structure by assigning nonoverlapping signal intensity ranges to gray matter, white matter, and CSF. The volumes of the following structures were measured: 1) intracranium, 2) cerebrum, 3) left and right cerebellar hemispheres, 4) left and right cerebellar gray matter, 5) left and right cerebellar white matter, and 6) vermis.

**INTRACRANIUM.** The cerebral regions, brain stem, cerebellum, and CSF were all included.
CEREBRUM. The cerebrum was discriminated from the brain stem by a line drawn between the two peaks of the left and right edges of the tentorium cerebella. The structures above this line were all included as part of the cerebrum. Then we separated CSF from the cerebrum by using the threshold technique.

LEFT AND RIGHT CEREBELLAR HEMISPHERES AND LEFT AND RIGHT CEREBELLAR GRAY/WHITE MATTER. Cerebellar hemispheres were measured in every slice in which they were visible. Cerebellar hemispheres consisted of lobules I–X, and therefore tonsils and flocculonodular lobes were included in this study. Making reference to the atlas of anatomy (Duvernoy 1995), we outlined the boundary between cerebellar hemispheres and the vermis manually and discriminated cerebellar hemispheres and the vermis. Since the anterior lobe of the vermis has cortex buried beneath the overlying midline cortex, some boundaries of these structures were difficult to identify. We separated the cerebellar hemisphere from the vermis by the lateral aspect of the paramedian white matter laminae. The measurement of cerebellar hemispheric structures was divided into two steps: 1) after CSF in cerebellar fissures was removed from cerebellar hemispheres by the thresholding technique and 2) after separating the left and right cerebellar gray/white matter.

VERMIS. The vermis was measured in every slice in which it was visible. It was measured from the slice where the lingula (lobules I and II) appeared, and until the slice where the superior posterior vermis decline, folium of vermis, or tuber of vermis (lobules VI–VII) disappeared. Therefore, lobules I–X were all included in this study. The areas of the vermis were measured after CSF in vermal fissures was removed from the vermis. The vermis was not divided into gray and white matter.

All ROIs were measured by a single investigator (TI). Information that identified the subject and data of scanning were removed and replaced with a randomly generated code number. Therefore, scans were analyzed blind to the subject’s diagnosis and age.

Ten subjects were examined twice by the same investigator (TI). Intraclass correlation coefficients were as follows: intracranium, .99; cerebrum, .98; left and right cerebellar hemispheres, .94; left cerebellar gray matter, .91; right cerebellar gray matter, .90; left and right cerebellar white matters, .89; and vermis, .91.

Psychiatric Rating Scale
The clinical conditions at the time of MRI were assessed using the Brief Psychiatric Rating Scale (BPRS). Three raters (YO, TS, YS) reviewed the ratings after the interview and resolved any disagreements by consensus. The consensus ratings were used in this study. In addition to the total scores, BPRS scores were divided into subscale scores and then used for analysis: Psychosis (conceptual disorganization, hallucination, and unusual thought content), Retardation (emotional withdrawal, motor retardation, and blunted affect), Depression (anxiety, guilt feeling, and depressive mood), and Paranoia (hostility, suspiciousness, and uncooperativeness) (Hedlund and Viewweg 1980).

Statistical Analysis
The t test was used to assess group differences in the length of formal education. Although there was a difference in the duration of education \( t(1,32) = 4.02, p = .0004 \), the final educational level of the patients may be related to some extent to the disruptive effect that their illness may have had on their education potential. We did not adjust for this value in our analysis.

We observed the interaction between intracranial volume and all ROI volumes. Then group differences were assessed using the analysis of covariance (ANCOVA) with intracranial volume as a covariate. Differences were considered to be statistically significant if \( p < .0056 = .05/9 \) (brain regions).

To assess the relationship between brain morphology and clinical variables (age, duration, onset age, and total BPRS score), we used partial correlation analysis, controlling for the effect of intracranial volume. Correlation was considered to be significant if \( p < .05 \). Additionally, we examined the correlation

Table 2. Volumes of Cerebellar Structures and the Cerebrum in Schizophrenic Patients and Control Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (N = 20)</th>
<th>Patients (N = 20)</th>
<th>ANCOVA (diagnosis)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Intracranium</td>
<td>1,535</td>
<td>114</td>
<td>1,487</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>1,208</td>
<td>91</td>
<td>1,174</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>136.6</td>
<td>10.7</td>
<td>129.6</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>65.9</td>
<td>5.2</td>
<td>60.9</td>
</tr>
<tr>
<td>Gray matter</td>
<td>43.1</td>
<td>5.1</td>
<td>41.8</td>
</tr>
<tr>
<td>White matter</td>
<td>20.3</td>
<td>2.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>62.8</td>
<td>4.9</td>
<td>60.0</td>
</tr>
<tr>
<td>Gray matter</td>
<td>44.9</td>
<td>4.3</td>
<td>43.2</td>
</tr>
<tr>
<td>White matter</td>
<td>17.8</td>
<td>2.6</td>
<td>16.8</td>
</tr>
<tr>
<td>Vermis</td>
<td>9.63</td>
<td>0.88</td>
<td>8.60</td>
</tr>
</tbody>
</table>

ANCOVA, analysis of covariance.
*Intracranial volume was used as a covariate.
with BPRS subscale scores (significant if $p < .0125 = .05/4$ scores).

Results

The mean and SD of absolute volumes of the measured regions and the results of ANCOVA for all regions are shown in Table 2. The volume of the vermis was significantly smaller in schizophrenic patients than in control subjects ($F(1,37) = 9.74, p = .003$). Figure 2 shows the distribution of vermal volume in both groups. There were no significant differences between the schizophrenic and healthy control groups in the volume of the cerebrum, left and right cerebellar hemispheres, left and right cerebellar gray matter, and left and right cerebellar white matter.

We observed no significant correlation between vermal volume and age in either the schizophrenic or the control group.

In the schizophrenic group, neither duration of illness nor onset age correlated with vermal volume, whereas a significant correlation was found between the volume of the vermis and total BPRS score ($r = -.65, p = .003$) (adjusted for intracranial volume). Furthermore, we assessed the relationship between the vermis and four BPRS subscores and found a significant correlation in Depression ($r = -0.74, p < .001$) and Paranoia ($r = -0.58, p = .012$) (adjusted for intracranial volume).

Discussion

In this study we found a significantly reduced volume of the vermis in patients with schizophrenia. This finding is consistent with the previous area measurement studies using CT (Dewan et al 1983; Heath et al 1979; Sandyk et al 1991; Weinberger et al 1979) and some MRI studies (Jacobsen et al 1997; Nopoulos et al 1999) that have reported a small vermal size in schizophrenia. There has been controversy regarding the methods of the previous studies, since early cross-sectional CT studies used only one slice (Coffman et al 1981; Dewan et al 1983; Heath et al 1979; Nasrallah et al 1981; Weinberger et al 1979; Yates et al 1987), and most of the MRI studies focused on only the midsagittal area of the vermis (Aylward et al 1994; Mathew and Partain 1985; Nasrallah et al 1991; Nopoulos et al 1999; Rossi et al 1993). Nevertheless, our result obtained from more precise volumetry also showed small size of the vermis in schizophrenia, clearly confirming that there are schizophrenic patients with a smaller vermis.

There have been two volumetric MRI studies of detailed cerebellar structures. One study reported a significant reduction of vermal volume in childhood-onset schizophrenic patients and no group difference in volumes of the left and right cerebellar hemispheres (Jacobsen et al 1997), in agreement with our present results. The other investigated chronic schizophrenia (Levitt et al 1999) and found that the volume of the vermis was significantly larger. One possible explanation for this discrepancy is the different methods used for image analysis. In the latter study, the vermis was discriminated from cerebellar hemispheres by drawing a straight line, and we consider that the border of the anterior lobe and inferior posterior lobes of the vermis is inaccurate. On the other hand, we distinguished the vermis from cerebellar hemispheres by tracing along the contour of the vermis. Although the boundaries between these structures were obscure at some points in the middle body of the vermis, we separated the cerebellar hemispheres from the vermis by the lateral aspect of the paramedian white matter laminae and obtained an approximate volume. Depending on the definition of the lateral boundary, vermal volume varies considerably (Schmahmann et al 1999). Another possible explanation for the discrepancy may be that neuroleptic medication causes enlargement of vermal volume. From the report that neuroleptics caused axonal sprouting in animals (Benes et al 1983), it has been speculated that neuroleptic medications have an enlarging effect on vermal volume (Levitt et al 1999). A recent neuropathologic study has reported a

![Figure 2. Volume of the vermis in schizophrenic patients and control subjects. Horizontal lines represent means. **Significantly reduced volume in the schizophrenic patients relative to the control group ($p < .01$).](image-url)
significant positive correlation between neuroleptics and Purkinje cell size in the vermis (Tran et al 1998). It might also be speculated that neuroleptic medications might promote enlargement of Purkinje cells in the vermis in schizophrenia.

We found no significant differences in cerebellar hemispheres or total cerebella between groups, which were in agreement with most previous MRI studies measuring cerebellar hemispheres or total cerebella (Flaum et al 1995; Jacobsen et al 1997; Levitt et al 1999; Nopoulos et al 1999). These findings indicate that the gross morphological abnormality of the cerebellum in schizophrenia may be confined to the vermis. Since there was no correlation between vermal volume and duration of illness, this volume reduction could be caused by disturbance of the early developmental process of the vermis. The timing of neurogenesis and the migrations of Purkinje and granule cells differ in the vermis and cerebellar hemispheres (Altman and Bayer 1985). The distinctive developmental timetables of the vermis and cerebellar hemispheres may be one of the underlying factors accounting for their differential vulnerability/susceptibility to environmental insults or genetically determined cellular events. And the complex functional derangements at the cellular level, such as altered expression and processing of neuroprotective/excitoprotective calcium binding proteins and/or altered synaptology, may account for the volume reduction in the vermis (Katsetos et al 1997).

We found a significant negative correlation between total BPRS score and vermal volume. This correlation was derived mainly from positive symptoms and abnormalities in emotion or affect.

It is suggested that the cerebellum serves to prevent, detect, and correct errors of thought in the same way as it does for errors of movement (Ito 1993), and it is also suggested that the cerebellar contribution to cognition is one of modulation rather than generation (Schmahmann 1991) through various direct or indirect connections as anatomic substrates. Although these may better apply to the cerebellar hemisphere than to the vermis, considering that the vermis has a connection with the thalamus, limbic systems, and frontal lobe regions via fastigial nucleus (Harper and Heath 1973), abnormality in the vermis can cause this circuit to be disrupted and the cognitive function to be out of tune, which could result in positive symptoms.

It is noteworthy that the reduction in vermal volume correlated with the Depression subscore. Several studies have suggested strong involvement of the pathology of the vermis in emotional abnormalities. Highly aggressive monkeys became quite docile by artificial vermal lesion and showed no aggression in confrontational situations (Berman et al 1978). Additionally, in clinical investigations patients who underwent resection of the vermis showed abnormalities of emotion or affect such as unstable emotion and impulsiveness (Levisohn et al 1997; Schmahmann and Sherman 1998). From these findings, the vermis has been hypothesized to be a modulator of emotion (Schmahmann 1991; Schmahmann and Sherman 1998). There have been reports that neurodevelopmental disorders such as autism (Courchesne et al 1988), attention-deficit/hyperactivity disorder (Berquin et al 1998), and fragile X syndrome (Mostofsky et al 1998) exhibit reduction of vermal volume. These disorders also show emotional abnormalities. Therefore, although these emotional abnormalities appear nonspecific to schizophrenia and their expression may differ in each patient and time, the modulation of emotion could become disrupted and emotional instability could be caused due to the pathology of the vermis in schizophrenia. As a consequence of the emotional unstableness, anxiety or depressive mood could emerge.

In this study we found a significant reduction of vermal volume in schizophrenia relative to control subjects and also demonstrated a correlation between vermal morphology and clinical symptoms. However, our study is not without limitations. First, the number of subjects was not large, which may be the reason for the failure of detection of a relationship between the vermis and demographic variables. Second, this study examined only male subjects. It has been demonstrated that gender difference exists only in schizophrenic and not in healthy control subjects, with male patients having a smaller area of the vermis than female patients (Rossi et al 1993). However, we are unable to comment on this aspect. Third, since we assessed the clinical symptoms on only one point using the BPRS, our result may only reflect the cross-sectional feature of the disease.

Although this study has limitations, our results provide further evidence that the volume of the vermis is reduced in patients with schizophrenia and suggest that the vermal abnormality may be associated with the pathophysiology of schizophrenia.

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