Reprinted from the German Journal of Psychiatry · http://www.gjpsy.uni-goettingen.de · ISSN 1433-1055

Striato-Cerebellar Abnormalities in Never-Treated Schizophrenia: Evidence for Neurodevelopmental Etiopathogenesis

G. Venkatasubramanian[1], B.N. Gangadhar[1], P.N. Jayakumar[2], N Janakiramaiah[1], M. S. Keshavan[3]

[1]Department Of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India.
[2]Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neurosciences, Bangalore, India.
[3]Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593

Corresponding author: Dr. B. N. Gangadhar, Professor of Psychiatry, Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore –560029. E-Mail: bng@nimhans.kar.nic.in

Abstract

Background: Preliminary evidence suggests abnormal basal ganglia and cerebellar loops in schizophrenia. Few studies have examined the striatocerebellar system in never-treated schizophrenia. Objective: The study objective was to examine the striato-cerebellar system using Magnetic Resonance Imaging (MRI) in never-treated schizophrenia. Methods: MRI was done in never treated, right-handed, schizophrenia (DSM-IV) patients (n=15) and age-, sex-, education- and handedness-matched healthy controls (n=15). Right and left caudate volumes as well as cerebellar vermis area were measured using Scion Image software. Psychopathology was assessed using Positive and Negative Syndrome Scale. Results: Patients had significantly smaller right (df=2, 27; F =4.5; p=0.042) and left (df=2, 27; F=4.3; p=0.048) caudate volumes as well as smaller cerebellar vermis area (df=2, 27; F=6.5; p=0.017) were significantly smaller in patients than controls after controlling for intracranial area. Cerebellar vermis area correlated significantly with right caudate volume (r=0.6; p=0.04) in patients but not in controls. Conclusions: Smaller caudate nuclei and cerebellar vermis in never-treated schizophrenia supports neurodevelopmental etiopathogenesis. Significant correlation between right caudate and cerebellar vermis in patients suggests related striato-cerebellar abnormality in schizophrenia (German J Psychiatry 2003; 6: 1-7).

Keywords: Magnetic resonance imaging, caudate, cerebellar vermis, schizophrenia

Received: 13.12.2002
Published: 20.02.2003

Acknowledgements: This work was supported by Indo-US project 1 R43 04370-01A1 1997-2001.

Introduction

Several lines of evidence implicate the basal ganglia (Busatto and Kerwin, 1997; Ring and Serra-Mestres, 2002) and cerebellar vermis (Andreasen et al., 1999; Loeber et al., 2001) in the pathophysiology of schizophrenia.

Magnetic Resonance Imaging (MRI) studies of the basal ganglia have appeared in the literature with conflicting results (see for review, Shenton et al., 1997). These inconsistencies may be related to methodological issues, e.g., use of thick slices with interslice gaps, making it difficult to avoid partial volume effects. Evidence suggests that treatment with antipsychotic can alter the size of caudate (Keshavan et al., 1994; Gur et al., 1998; Westermoreland et al., 1999). Most of the studies on caudate nucleus in schizophrenia involved previously treated schizophrenic patients and hence neuroleptic exposure could be a confounding factor. Of the few studies comparing caudate volumes in neuroleptic-naïve schizophrenia patients and controls subjects, three studies have reported the caudate nucleus to be

significantly smaller in patients (Shihabuddin et al., 1998; Keshavan et al., 1998; Corson et al., 1999). Similarly, MRI studies have shown conflicting results with regard to cerebellar vermis measurements in patients with schizophrenia (see for review, Loeber et al., 2001). The only study involving neuroleptic-naïve patients has shown smaller cerebellar vermis in schizophrenia (Ichimiya et al., 2001).

The traditional view that the basal ganglia and cerebellum are simply involved in the control of movement has been challenged in recent years. Neural networks reciprocally interconnect cerebral cortical areas with the basal ganglia and cerebellum. Recently, alterations in basal ganglia and cerebellar loops have been suggested in schizophrenia (Middleton and Strick, 2000).

Few studies have examined the striato-cerebellar abnormalities in never-treated schizophrenia. In this study, we have examined the relationship between caudate nucleus and cerebellar vermis using MRI in never-treated schizophrenia.

Methods

Subjects

The subjects for the study consisted of fifteen patients and fifteen age, sex, education, and handedness matched healthy controls. The patients were recruited from National Institute of Mental Health and Neurosciences (NIMHANS) outpatient department if they met DSM-IV criteria for schizophrenia and had never received antipsychotic medication or electro convulsive therapy. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Version 2.1) (World Health Organization, 1998) was administered (GVS) for the diagnosis of patients. (The first author (GVS) underwent training program for administering SCAN before starting the study). This diagnosis was re-confirmed by consensus following independent clinical interview by two experienced psychiatrists (BNG & NJR). The diagnosis was found to be stable at one-year follow-up as re-assessed by one of these two experienced psychiatrists (BNG or NJR). Psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al., 1987).

Hospital staff members, their relatives and friends formed the control group. The controls were selected after screening using GHQ (12 items version) (Goldberg et al., 1997). A detailed history was taken to rule out psychosis in any of the family members. None of the normal controls had any family history of psychotic illness. Normal controls, as a group, were matched with the schizophrenia patients for age, sex, handedness, and number of years of education.

The demographic and clinical information regarding the subjects were collected with the help of a structured proforma. A detailed history is obtained and a comprehensive mental state and physical examination was conducted. All subjects were right-handed as assessed by Annett's questionnaire (Annett, 1967). No subject had any contraindications to MRI (cardiac pacemaker, aneurysm clip, cochlear implants, pregnancy, IUD, history of metal fragment in eyes, neurostimulators, weight of 250 lbs. or more, claustrophobia). None of the subjects had any medical illness that may significantly influence CNS function or structure, significant neurologic disorder such as seizure disorder, cerebral palsy, or history suggestive of delayed developmental milestones (suggestive of mental retardation), family history of hereditary neurologic disorder that may complicate diagnosis, co-morbidity for DSM-IV psychoactive substance dependence, or lifetime history of head injury associated with any of the following: loss of consciousness longer than 10 minutes, seizures, neurological deficit, depressed skull fracture, surgical intervention, or central nervous system infection. Female subjects were neither pregnant nor were within the postpartum period. None of the subjects had dyskinesia (as assessed using the Abnormal Involuntary Movements Scale (Guy, 1976)) or parkinsonism (as assessed using the Simpson and Angus Scale (Simpson and Angus, 1970). All participants provided written informed consent. The Institute's ethics committee approved the study protocol.

Magnetic Resonance Imaging (MRI) Methodology

MRI acquisition

Magnetic Resonance Imaging (MRI) was done with Siemens 1.5 Tesla Magnetom vision system (Erlangen, Germany) at the Department of Neuroimaging and Interventional Radiology, NIMHANS.

The list of MR protocols used in the study was: Proton Density (PD) & T_2 weighted transverse images; T_2 weighted coronal images; and T_1 Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence.

A set of sagittal scout images (2D fast spin echo, TR=15 msec, echo time (TE) = 6 msec, FOV = 300 mm, approximately 3 slices, slice thickness = 8 mm, slice gap = 0.2 mm, NEX = 1, matrix = 256 x 256, scan time = 10 sec) was collected.

This was followed by a set of proton density and T_2 weighted axial images covering the whole brain (2D fast echo, TR = 3800 msec, TE = 22 msec and 90 msec, FOV = 250 mm approximately 21 slices, slice thickness = 5 mm, slice gap = 0.3 mm, NEX = 1, matrix = 200 x 256, scan time 2 min 5 sec).

This was followed by a set of proton density and T_2 weighted coronal images covering the whole brain (2D fast echo, TR = 3710 msec, TE = 22 msec and 90 msec, FOV = 230 mm approximately 21 slices, slice thickness = 5 mm,

slice gap = 0.3 mm, NEX = 1, matrix = 190 x 256, scan time 2 min 24 sec).

Then, T_1 weighted three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) imaging was performed in the sagittal plane. (TR = 9.7 msec, TE = 4 msec, nutation angle = 12°, FOV = 250 mm, slice thickness 1 mm, NEX = 1, matrix = 200 x 256, scan time 6 min 12 sec). A set of 160 images (approximately) covering the entire brain was obtained.

MR images were examined by a neuroradiologist (PNJ) for morphological abnormalities blind to the status of subjects. The images were transferred on to a personal computer (PC) platform. They were stored with coded identification.

Volumetric analysis

Software for MRI image analysis

Volumetric measurements were conducted blind to clinical data using Scion Image software (Scion corporation, 2000). It runs on PC and Macintosh platforms. Measurements can be stored separately from images. This software provides valid and reliable measurements of specific structures using a semi automated segmentation approach (Keshavan et al., 1995). This semi automated segmentation method to measure volume of brain structures correlated highly with the point-counting stereological approach (Keshavan et al., 1995). This software has been used reliably to measure different brain structures and volumes in children, adolescents, and adults. The functions of this software include segmentation, magnification and contrast adjustment, data smoothening and orientation & location recall.

Volumetric method

All measurements were automatically calculated by the computer using the Scion Image software. The desired structure was outlined and measured by the rater using the computer mouse controlled pointer. The raters were blind to the subjects' clinical details at the time of the brain measurements on coded MRI sections.

Measurement of the caudate nucleus

The caudate nucleus was measured in coronal sections of MRI scan (Figures 1 & 2). The first step in measuring the caudate was to define the inferior border. The inferior border of the caudate was demarcated by drawing a line along the length of the anterior commissure. The anterior commissure is a thin, reasonably straight line of white matter that will appear inferior to the lateral ventricles at about the point at which the fornix is first seen. The line was extended to be placed directly underneath the lateral ventricles to eliminate the tail of the caudate from the measurement. The first slice was the most anterior slice where a small patch of gray matter appears laterally to either the left or right lateral ventricle. The rater continued to trace around the caudate in successive slices posteriorly through the brain, being careful not to extend the outline beyond the line used as the inferior border. The posterior limit of the caudate was defined as the first slice at which the pons is seen.

The first author (GVS) who was initially trained by the neuroradiologist (PNJ) to measure the caudate performed inter-rater reliability exercise with another rater in 10 subjects on coded images. The Inter-rater reliability as measured by Intra-Class Correlation Coefficient was 0.94 for the left caudate nucleus and 0.95 for the right caudate nucleus.

Measurement of cerebellar vermis intracranial areas using midsagittal MRI section

Midsagittal MRI section

The intracranial area was measured in the mid-sagittal section. From the set of T_1 weighted three-dimensional MP-RAGE sagittal images, the midsagittal section was chosen manually (Figure 3). Criteria (Woodruff et al., 1993) for the inclusion of midsagittal slices include the following:

1. A distinct outline of the CC
2. An easily identified cerebral aqueduct
3. Clear visibility of cortical gyral crests both anteriorly and posteriorly to the CC and
4. Absence of visible intrusion into gray and white matter.

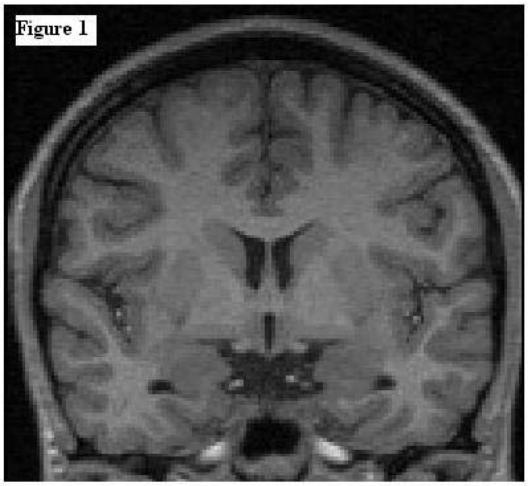
All the selected images were inspected and approved by the neuroradiologist (PNJ). Since the slice thickness was 1 mm and uniform image acquisition software protocol was used, midsagittal images of all the subjects satisfied the inclusion criteria. Intracranial area was measured by tracing along inner table of the skull, above the sphenoid sinus, along the basisphenoid, and across the foramen magnum (Keshavan et al., 2002). The cerebellar vermis area was measured as defined by Rossi et al (1993) (Figure 4).

To assess inter-rater reliability, two raters (GVS & PNJ (neuroradiologist)) independently rated sixteen coded midsagittal sections. The rater (GVS) was trained initially by the neuroradiologist (PNJ). Both the raters were blind to the clinical details of the subjects. The inter-rater reliability was calculated by intraclass correlation coefficient (ICC). The intraclass correlation coefficient for the intracranial area was 0.95 and that for cerebellar vermis area was 0.93.

Statistics

Statistical Package for Social Sciences (version 10.0.1) was used for Pearson's correlation, Independent samples t-test, chi-square test, Analysis of Covariance (ANCOVA), Repeated Measures Analysis of Variance (RMANOVA). The alpha was set at 0.05 for statistical significance.

Figure 1 & 2: Caudate Volume Measurement by Segmentation Technique using Scion Image Software



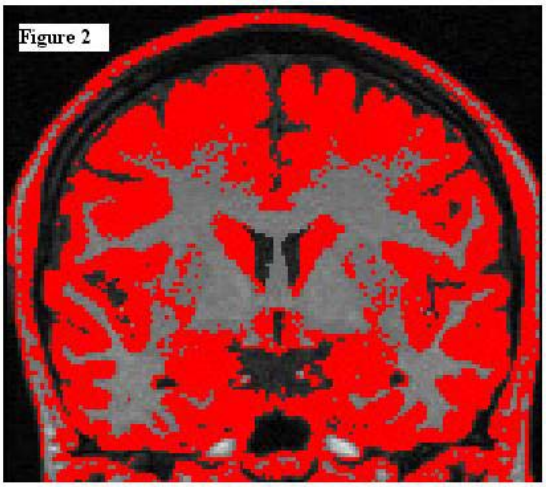


Figure 3: Midsagittal MRI Image

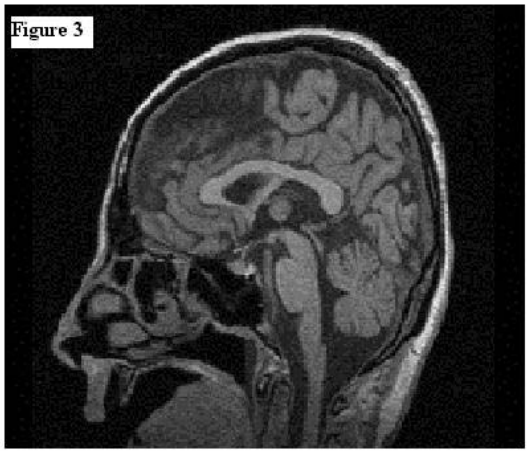
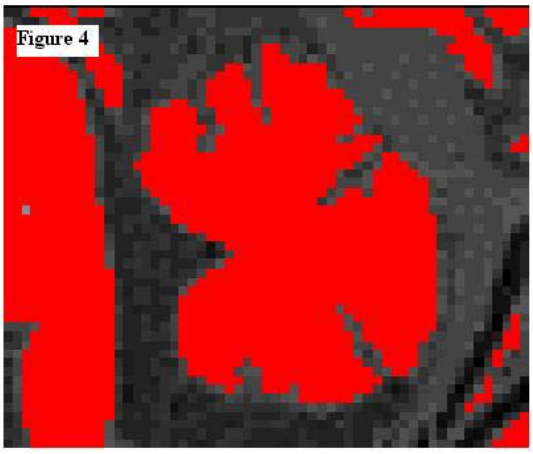


Figure 4: Cerebellar vermis segmentation



Results

Demographic and clinical profile

The sociodemographic profile of the patients and controls is given in Table 1. The average illness duration of the patients was 52 months (range: 6 – 144 months). The Positive And Negative Syndrome Scale (PANSS) Scores (Mean ± SD) were as follows: Positive syndrome = 25±9; Negative syndrome = 25±8; General psychopathology = 43±9; Total PANSS score = 93±15.

Table 1. Demographic Profile

Variable*	Patients (n=15)	Controls (n=15)
Age (years)**	33 ± 10	30 ± 9
Sex (M: F)	8:7	8:7
Education (Years)**	11 ± 4	13 ± 2

* - No significant difference between patient and control groups (independent samples t-test)

** - Mean ± standard deviation

Brain measurements

Intracranial area (Mean ± SD) did not differ significantly between patients (127±11 cm^2) and controls (127±13 cm^2) (t = 0.1; p = 0.9). The mean (± SD) of the caudate volumes and cerebellar vermis area are given in Table 2. Repeated Measures Analysis of Variance (RMANOVA) using the right and left caudate nuclei volumes as the repeated measures and the intracranial area as covariate showed significant effect of the diagnosis with the patients having smaller caudate volume than the controls (df = 2,27; F = 4.5; p = 0.044). To analyze the effect of diagnosis on individual caudate volumes as well as cerebellar vermis area, univariate analysis of variance with intracranial area as covariate (ANCOVA) was performed separately for the cerebellar vermis area and right as well as the left caudate volumes. Caudate volumes (right as well as left) and cerebellar vermis area were significantly smaller in the patients than the controls (Table 2; Figures 5 & 6).

Relationship between brain structures and clinical variables

Illness duration did not correlate significantly with either right caudate volume (r = - 0.13; p = 0.65) or left caudate volume (r = - 0.10; p = 0.7) or cerebellar vermis area (r = - 0.2; p = 0.5). Similarly, no significant correlation was found between brain measures and psychopathology (PANSS scores). The correlation between cerebellar vermis and caudate was examined after controlling for the effect of intracranial area. Significant correlation was found in the patients after controlling for the effect of intracranial area between cerebellar vermis and right caudate volume (r = 0.6; p = 0.04) but not the left caudate (r = 0.5; p = 0.07). However, no significant correlation was found in the controls between cerebellar vermis and the right (r = 0.4; p = 0.1) or left (r = 0.3; p = 0.2) caudate volumes.

Table 2: Brain measure (Mean ± SD) comparison

Brain Structure	Patient (n=15)	Controls (n=15)	df	F*	p*
Right Caudate (mL)	2.4 ± 0.6	2.8 ± 0.6	2,27	4.5	0.042**
Left Caudate (mL)	2.4 ± 0.6	2.8 ± 0.6	2,27	4.3	0.048**
Cerebellar Vermis (cm^2)	12 ± 2	14 ± 2	2,27	6.5	0.017**

* - Analysis of covariance with intracranial area as covariate

** - p < 0.05, significant.

SD – Standard deviation

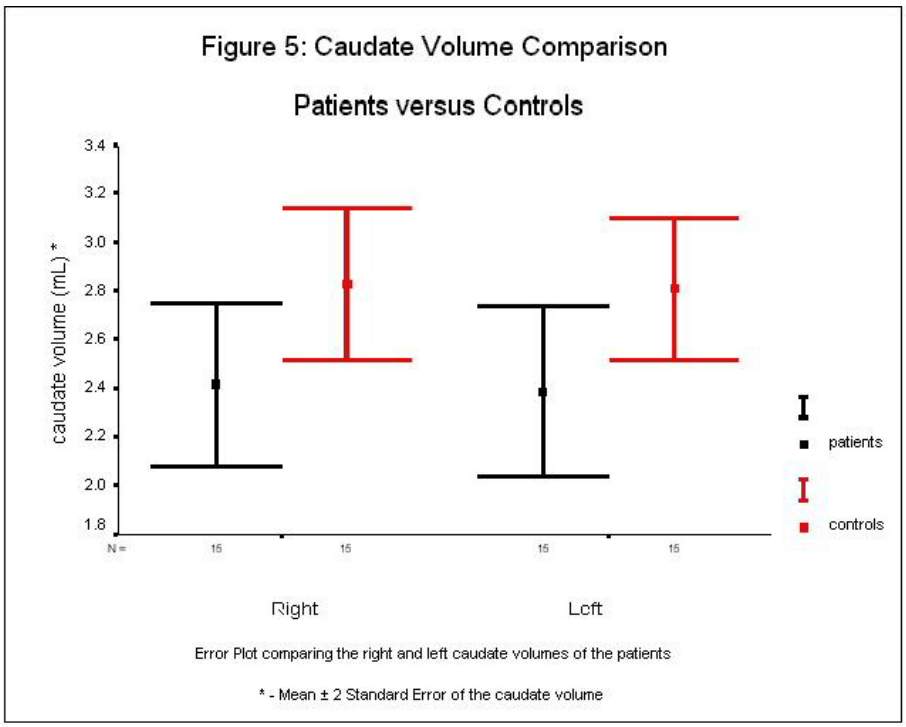
Discussion

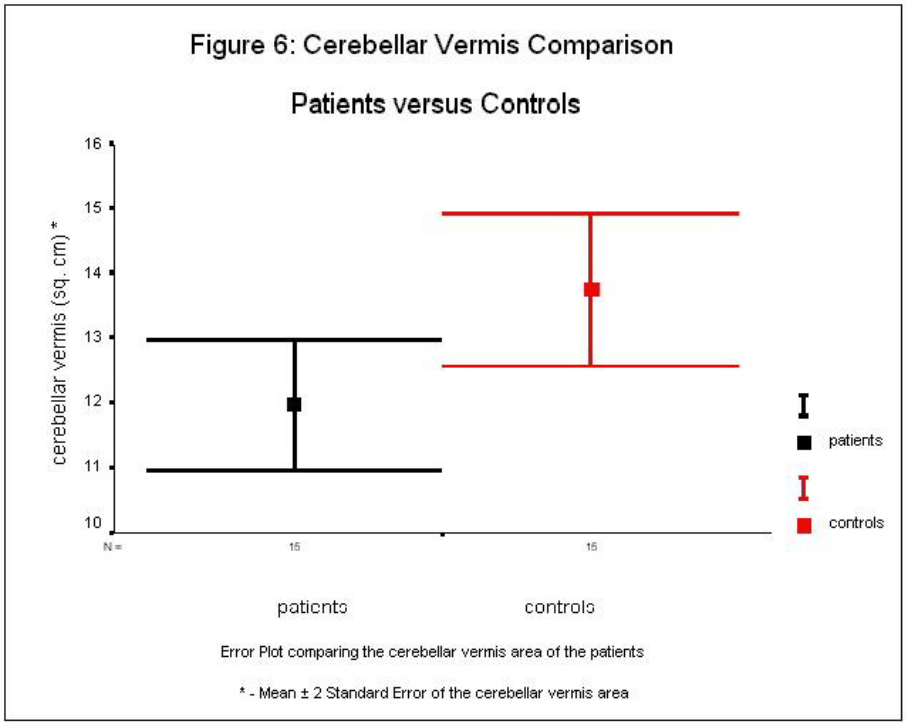
This is one of the first studies examining the striato-cerebellar system in never-treated schizophrenia. This study has demonstrated significantly smaller caudate nucleus volume and cerebellar vermis area in patients with never-treated schizophrenia in comparison to age, sex, education and handedness matched controls. Cerebellar vermis correlated significantly with right caudate in the patients but not in the controls. No significant correlation was found between illness duration and brain measurements (caudate and cerebellar vermis) or psychopathology.

The Schedules for Clinical Assessment in Neuropsychiatry (Version 2.1) was used (GVS) for arriving at DSM-IV diagnosis. This diagnosis was also confirmed by consensus following independent clinical interview by two experienced psychiatrists (BNG & NJR). The diagnosis was found to be stable at follow-up after one year. None of the patients had a change in the diagnosis. Only few of the previous neuroimaging studies in schizophrenia have reported about the stability of diagnosis. Subjects were excluded if they had substance dependence, confounding medical illness and lifetime history of significant head injury. Pregnancy or postpartum period also was one of the exclusion criteria. Thus the effect of confounding factors was minimized.

All patients were treatment-naïve. Medications were started only after completion of all assessments and investigations. This was done with informed consent. Evidence suggests that treatment with antipsychotic can alter the size of caudate (Keshavan et al., 1994; Gur et al., 1998; Westermoreland et al., 1999). Assessing never-treated schizophrenia patients avoided the confounding effect of neuroleptics.

Since caudate nuclei exhibit hemispheric lateralization handedness may be a factor influencing the structure of caudate (Watkins et al., 2001). In this study, handedness was assessed using Annett's Handedness Questionnaire (Annett, 1967) and all subjects were right handed. This helped in avoiding the confounding effect of handedness.





Magnetic Resonance Imaging (MRI) was done using state-of-the-art Siemens 1.5 Tesla scanner. The stronger the magnet used for imaging the better will be the image resolution (Filipek et al., 1989). The slice thickness used in this study was one mm and the slices were contiguous. Very few studies have used such a thin MRI slice. The resolution of the image is affected by section thickness. The thinner the slice better will be the image resolution. The thicker the slice, the more likely that voxels will manifest partial volume effects, rather than be fully volumed (Lim et al., 1995). Use of thin sections minimizes the error of estimating volume over multiple sections (Filipek et al., 1989). Thus the importance of using thin sections cannot be overemphasized for accurate volume measurement (Free et al., 1995).

The image analysis was done using coded MRI sections. The rater was blind to the clinical status of the subject. Measurements were done using computerized semi-automated software. These ensured elimination of rater bias.

The brain area measurements were done under the supervision of a senior neuroradiologist (PNJ). The semi-automated Scion Image software provides valid and reliable measurements of specific structures using a semi automated segmentation approach (Keshavan et al., 1995). Good inter-rater reliability was established with a senior neuroradiologist (PNJ) for morphometric ratings. This ensured reliable brain measurements.

There is inter-individual variation in the size of the brain. To control for this variation several methods have been described. Use of intracranial area instead of intracranial volume may be seen as a limiting factor. But, it has been shown that corrections for inter-individual brain size variations by covariate correction using either intracranial volume or intracranial area are comparable (Free et al., 1995). Few of the previous studies have used brain ratio measurements to correct for the brain size variations. However, Harvey et al (1990) have recommended a statistical correction using brain size as a covariate being superior to a ratio measure while controlling for brain size variations. In this study, Analysis of Covariance (ANCOVA) statistic was done using intra-cranial area as a covariate. This statistical correction avoided the confounding effect of inter-individual brain size variations.

Striato-Cerebellar Abnormalities in Schizophrenia

Recently, alterations in basal ganglia and cerebellar loops have been suggested in schizophrenia (Middleton and Strick, 2000). The findings of this study, together with those of Keshavan et al (1998), Shihabuddin et al (1998) and Corson et al (1999) support the notion that schizophrenia is associated with basal ganglia abnormality. The average volume reduction of caudate demonstrated in this study is almost similar to one of the earlier studies (which demonstrated 14% volume reduction) by Keshavan et al (1998). Also, the study finding of smaller cerebellar vermis is similar to prior studies (Loeber et al., 2001; Ichimiya et al., 2001). In this study, cerebellar vermis correlated significantly with right caudate in the patients but not in the controls. This finding is in consonance with the findings of a recent functional magnetic resonance imaging study, which has demonstrated abnormalities in right caudate nucleus and cerebellar vermis in schizophrenia patients (Kircher et al., 2001). These findings suggest related striato-cerebellar abnormalities in never-treated schizophrenia. However, the right caudate volume alone correlating with the cerebellar vermis area requires further exploration in future studies.

Neurodevelopmental etiopathogenesis in schizophrenia

Neurodevelopmental abnormality has been suggested to explain the etiopathogenesis of schizophrenia (Weinberger, 1987; Keshavan, 1997). An exaggeration of periadolescent synaptic pruning, perhaps in glutamatergic corticosubcortical neurons, may be involved (Keshavan et al., 1994). Reduced activity in these corticostriatal neurons, by diminishing trophic effects on the striatum, could conceivably lead to reduced synaptic neurophil, and thereby reduced size of basal ganglia; this view is consistent with a recent observation of reduced striatal dendritic spine size in postmortem brains of schizophrenia patients (Roberts et al., 1996). Studies have suggested that the maldeveloped neural circuitry producing schizophrenic symptoms may include the cerebellum (Jacobsen et al., 1997). Hence, the finding of smaller caudate as well as cerebellar vermis in never-treated schizophrenia supports neurodevelopmental etiopathogenesis in schizophrenia.

In this study, despite wide range of illness duration, there was no significant correlation between brain structures and illness duration. This lack of correlation may be due to the absence of neurodegeneration in the evaluated brain structures. This suggests neurodevelopmentally-mediated pathogenesis in schizophrenia.

In conclusion, we have found significantly smaller cerebellar vermis and caudate nuclei in never-treated schizophrenia. There was significant positive correlation between cerebellar vermis and right caudate in the patients but not in the controls. There was no significant correlation between illness duration and brain structures. These findings suggest neurodevelopmental striato-cerebellar abnormalities in schizophrenia.

References

Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassnik T, Flaum M. Defining the phenotype of schizophrenia: Cognitive Dysmetria and its neural mechanisms. Biological Psychiatry 1999;46:908-920.

Annett, M. The binomial distribution of right, mixed and left-handedness. Quarterly Journal of Experimental Psychology 1967;19:327-333.

Busatto GF, Kerwin RW. Schizophrenia, psychosis, and the basal ganglia. Psychiatry Clinics of North America 1997;20:897-910.

Corson PW, Nopoulos P, Andreasen NC, Heckel D, Arndt S. Caudate size in first-episode Neuroleptic-naïve schizophrenic patients measured using an artificial neural network. Biol Psychiatry 1999:46:712 – 720.

Filipek PA, Kennedy DN, Caviness VS, Rossnick SL, Spraggins TA, Starewicz PM. Magnetic resonance imaging-based brain morphometry: Development and application to normal subjects. Annals of Neurology 1989;25:61- 67.

Free SL, Bergin PS, Fish DR, Cook MJ, Shorvon SD, Stevens JM. Methods for normalization of hippocampal volumes measured with MR. Am J Neuroradiology 1995;16:637-643.

Goldberg DP, Gater R, Sartorius N. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychological Medicine, 1997;27(1):191-7.

Gur RE, Maany V, Mozley PD, Swanson C, Bilker W, Gur RC. Subcortical MRI volumes in neuroleptic naïve and treated patients with schizophrenia. American Journal of Psychiatry 1998;155:1711 - 1717.

Guy W. Abnormal Involuntary Movements Scale (AIMS). ECDEU Assessment Manual for Pharmacology. Rockville, Md: US Dept of Health, Education, and Welfare. 1976

Harvey I, Williams M, Toone BK, Lewis SW, Turner S, McGuffin P. The ventricular-brain ratio in functional psychosis: the relationship of lateral ventricular and total intracranial area. Psychological Medicine 1990;20:55 – 62.

Ichimiya T, Okubo Y, Suhara T, Sudo Y. Reduced volume of the cerebellar vermis in neuroleptic-naive schizophrenia. Biol Psychiatry 2001;49(1):20-7

Jacobsen LK, Geidd JN, Berquin PC, Krain AL, Hamburger SD, Kumara S, Rapoport JL. Quantitative morphology of the cerebellum and fourth ventricle in child-

hood-onset schizophrenia. Am J Psychiatry 1997;154:1663 – 1669.

Kay SR., Fizbein A, Opler A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophrenia Bulletin 1987;2:261-276.

Keshavan MS, Anderson S, Beckwith C, Nash K, Pettergrew J, Krishnan KRR. A comparison of stereology and segmentation techniques for volumetric measurements of brain ventricles. Psychiatric Research Neuroimaging 1995;61: 53-60.

Keshavan MS, Anderson S, Pettergrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? the Feinberg hypothesis revisited. Journal of Psychiatric Research 1994;28:239-245.

Keshavan MS, Bagwell WW, Hass GL, Sweeney JA, Schooler NR, Pettergrew JW. Changes in caudate volume with neuroleptic treatment. Lancet 1994; 344:1434.

Keshavan MS, Diwadkar VA, Bagwell WW, Harenski K, Rosenberg DR, Sweeney JA, Pettergrew JW. Abnormalities of Corpus Callosum in first episode treatment naïve schizophrenia. Journal of Neurology, Neurosurgery, Psychiatry 2002;72(6):757-60.

Keshavan MS, Rosenberg D, Sweeney JA, Petergrew JW. Decreased caudate volume in neuroleptic-naïve psychotic patients. Am J Psychiatry 1998;155:774 - 778.

Keshavan MS. Neurodevelopment and schizophrenia: quo vadis? In: Keshavan MS, Murray RM, editors. Neurodevelopment & Adult Psychopathology. 1st ed. London: Cambridge University Press; 1997. p. 267 – 277.

Kircher TTJ, Liddle PF, Brammer MJ, Williams SCR, Murray RM, McGuire PK. Neural correlates of formal thought disorder in schizophrenia. Preliminary findings from a functional magnetic resonance imaging study. Arch Gen Psychiatry. 2001;58:769-774.

Loeber RT, Cintron CMB, Yurgelun-Todd DA. Morphometry of individual cerebellar lobules in schizophrenia. American Journal of Psychiatry 2001;158:952-954.

Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Research Reviews 2000;31:236 – 250.

Ring HA, Serra-Mestres J. Neuropsychiatry of the basal ganglia. J Neurol Neurosurg Psychiatry 2002;72:12 - 21.

Roberts RC, Conley R, Kung L, Peretti FJ, Chut J. Reduced striatal spine size in schizophrenia: a postmortem ultrastructural study. Neuroreport 1996;7:1214-1218.

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

Scion Corporation. Scion Image for Windows. www.scioncorp.com 2000.

Shenton ME, Wible CG, McCarley RW. A review of magnetic resonance imaging studies of brain abnormalities in schizophrenia, in brain imaging in child psychiatry. Edited by Krishnana KRR, Doraiswamy PM, New York, Marcel Dekker, 297-380. 1997.

Shihabuddin L, Buchsbaum M, Hazlett EA, Haznedar MM, Harvey PD, Newman A. Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. Archives of General Psychiatry 1998;55:235-243.

Simpson GM, Angus JWS. (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl., 1970;212:11-19.

Watkins KE, Paus T, Lerch JP, Zijdenbos A, Collins DL, Neelin P, Taylor J, Worsley KJ, Evans AC. Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Cerebral Cortex 2001;11(9):868-77.

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987:44:660-669.

Westermoreland Corson, P, Nopoulos P, Arndt SV, Miller D, Andreasen NC. Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. American Journal of Psychiatry 1999;156(8):1200-4.

Woodruff P, Pearson G, Geer M, Barta P, Childoat H. A computerized magnetic resonance imagning study of corpus callosum morphology in schizophrenia. Psychological Medicine 1993;23:45–56.

World Health Organization. Schedules for Clinical Assessment in Neuropsychiatry (version 2.1). World Health Organization, Geneva. 1998