INDIAN JOURNAL OF PSYCHIATRY, 2003, 45(1), 20-24

AWARD PAPER

Reduced Caudate Volume in Never-Treated Schizophrenia : Evidence for Neuro developmental Etiopathogenesis

Received Bombay Psychiatric Society Silver Jubilee Award in the Annual National Conference of Indian Psychiatric Society (Hyderabad, January 2003).

GANESAN VENKATASUBRAMANIAN, B.N. GANGADHAR, P.N. JAYAKUMAR, N JANAKIRAMAIAH, M. S. KESHAVAN

ABSTRACT

Background: Evidence suggests that caudate nucleus abnormalities have a role in schizophrenia. Structural brain imaging studies on caudate size in schizophrenia are inconclusive due to confounding factors.

Methods: In this study, caudate volume was measured on coronal Magnetic Resonance Images (1-mm) in consenting 15 never-treated schizophrenia (DSM-IV) patients and 15 age, sex, handedness, education and socioeconomic status matched controls using semi-automated Scion image software.

Results: Multivariate analysis revealed significantly smaller caudate volume in patients than controls after controlling for intracranial area ($df = 2,27$; $F = 5.4$; $p = 0.028$). Separate univariate analysis showed that right ($df = 2,27$; $F = 5.4$; $p = 0.028$) and left ($df = 2,27$; $F = 5.2$; $p = 0.031$) caudate were significantly smaller in patients than controls after controlling for intracranial area. Illness duration did not correlate significantly with either right ($r = -0.13$; $p = 0.65$) or left ($r = -0.10$; $p = 0.7$) caudate volume.

Discussion: Significantly smaller caudate nucleus in patients with never-treated schizophrenia suggests that some aspect of the disease process of schizophrenia influences the caudate nucleus. In conclusion, smaller caudate volume in never-treated schizophrenia with lack of correlation between illness duration and caudate size supports neurodevelopmental etiopathogenesis in schizophrenia.

Key words: Schizophrenia, caudate, neurodevelopment, Magnetic Resonance Imaging

INTRODUCTION

Several lines of evidence implicate the basal ganglia in the pathophysiology of schizophrenia (Busatto and Kerwin, 1997; Ring and Serra-Mestres, 2002). Basal ganglia play a critical role in higher cognitive functions such as attention, working memory, and goal-directed behavior (Middleton and Strick 1994; Levy et al 1997; Graybiel 1997). Abnormalities of basal ganglia in disorders such as Huntington's chorea may result in disturbances in thinking and behavior reminiscent of schizophrenia (Heckers 1997). Involuntary movements were described in schizophrenia long before the era of neuroleptics (Kraepelin 1919); unusual movements are also seen in preschizophrenic children long before illness onset (Walker and Lewin 1990).

Magnetic Resonance Imaging (MRI) allows noninvasive in vivo examination of the structural abnormalities of the basal ganglia. Several MRI studies of the basal ganglia have appeared in the literature with conflicting results (Shenton et al 1997). Studies have reported either increased volume of one or other basal ganglia structures (Breier et al 1992; DeLisi et al 1991; Hokama et al 1995; Frazier et al 1996) or no differences in basal ganglia size (Corey-Bloom et al 1995; Kelsoe et al 1988; Flaum et al 1995). Studies have also shown a reduction in caudate size in schizophrenia patients (Mion et al 1991; Dalgalarrondo et al 1994; Young et al 1991; Brown et al 1996). 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. Further, most of these studies involved previously treated schizophrenic patients, which suggests that the observed changes may be related to neuroleptic treatment.

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) and two studies have found no differences (Chakos et al 1994; Gur et al 1998). In the only Indian study, caudate nucleus volume did not differ significantly between patients and controls (McCreadie et al 2002).

Our study attempted to examine whether there is an independent underlying structural abnormality of caudate nucleus in never-treated schizophrenia.

MATERIALS AND METHODS

Subjects

The subjects for the study consisted of fifteen patients and fifteen age, sex, education, handedness and socioeconomic status 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, number of years of education and parental socioeconomic status.

The demographic and clinical information regarding the subjects were collected with the help of a structured proforma. A detailed history was 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, lifetime 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.

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. 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 as tested by 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. 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 grey 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 INTRACRANIAL AREA

Midsagittal 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. 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).

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.

STATISTICAL TECHNIQUES

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 Multivariate Analysis of Variance (RM – MANOVA). The alpha was set at 0.05 for statistical significance.

RESULTS

Demographic and clinical:

The sociodemographic profile and caudate volume of the patients and controls is given in table 1. The average illness duration of the patients was 48 months (range: 6 – 144 months). The Positive And Negative Syndrome Scale (PANSS) Scores (Mean ± SD) were as follows: Positive syndrome = 24±9; Negative syndrome = 27±8; General psychopathology = 44±7; Total PANSS score = 95±13.

TABLE 1 : Demographic Profile

No	Variable*	Patients (n=15)	Controls (n=15)
1	Age (years)**	31 ± 11	30 ± 9
2	Sex (M: F)	7: 8	8: 7
3	Education (Years)**	11 ± 4	13 ± 2

* No significant difference between patient and control groups
** $p<0.05$, significant

BRAIN MORPHOMETRY

Intracranial area (Mean ± SD) did not differ significantly between patients (127±11 cm^2) and controls (127±13 cm^2) as tested by independent samples t-test ($t = -0.06$; $p = 0.95$). The mean (± SD) of the caudate volumes 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 right and left caudate volumes than the controls ($df = 2,27$; $F = 5.4$; $p = 0.028$). To analyze the effect of diagnosis on individual caudate volumes, univariate analysis of variance with intracranial area as covariate (ANCOVA) was performed separately for the right and left caudate volumes. Mean right and left caudate volumes were significantly smaller in the patients than the controls (table 2 & figure).

Correlation of Caudate Volume with Illness duration and psychopathology

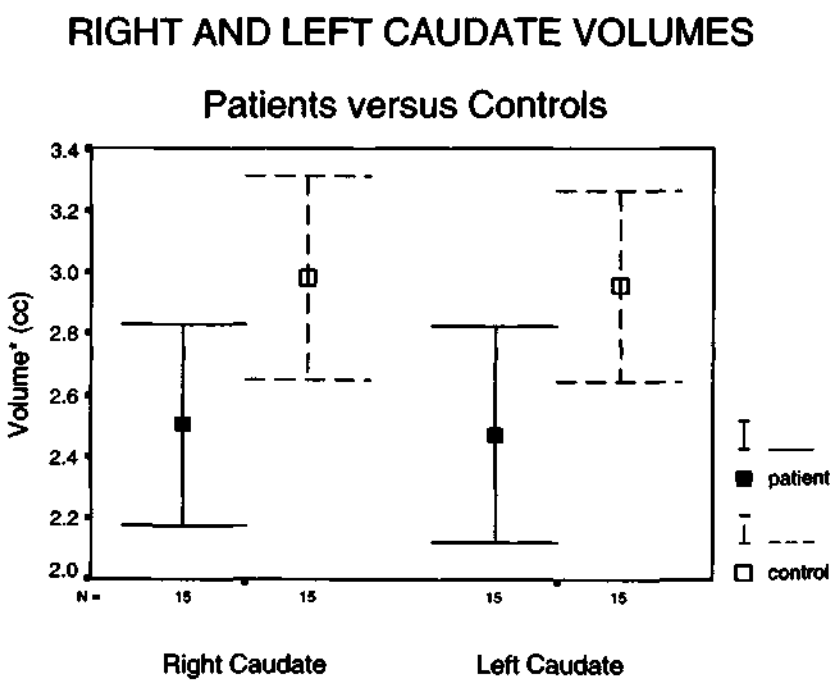
Illness duration did not correlate significantly with either right caudate volume ($r = -0.13$; $p = 0.65$) or left caudate volume ($r = -0.10$; $p = 0.7$). No significant correlation was found between caudate volume and PANSS scores (positive syndrome, negative syndrome, general psychopathology and total scores).

TABLE 2 : Brain measure comparison

Brain Structure	Patient (n=15)	Controls (n=15)	df	F*	p*
Right Caudate (mL)	2.3 ± 0.6	2.7 ± 0.6	2,27	7.6	0.01**
Left Caudate (mL)	2.3 ± 0.6	2.8 ± 0.6	2,27	6.0	0.02**
Intracranial Area (sq.cm)	12.2 ± 1.7	13.7 ± 2.3	2,27	5.9	0.02**

* - Analysis of Covariance with Intracranial Area as covariate

** - $p < 0.05$, significant.



Error Plot comparing the right and left caudate volumes of the patients and controls.
* - Mean ± 2 Standard Error of the caudate volume

DISCUSSION

This study has demonstrated significantly smaller caudate nucleus volume in patients with never-treated schizophrenia in comparison to age, sex, education and handedness matched controls. Our findings, together with those of Keshavan et al (1998), Shihabuddin et al (1998) and Corson et al (1999) support the notion that some aspect of the disease process of schizophrenia influences the caudate nucleus. The average volume reduction (16%) in our study is almost similar to one of the earlier studies (which demonstrated 14% volume reduction) by Keshavan et al (1998). To our knowledge, this is the first Indian study to demonstrate a reduction in caudate nucleus volume in never-treated schizophrenia. The only other Indian study by McCreadie et al (2002) did not show any difference in caudate volume between patients and controls.

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 had a change in the diagnosis. Only few of the previous studies 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. Many volumetric studies of the striatum in schizophrenia have found enlargement of the striatal regions (Breier et al 1992; Buchanan et al 1993; Heckers et al 1991; Hokama et al 1995; Jernigan et al 1991; Swayze et al 1992). Evidence suggests that this enlargement is a consequence of neuroleptic treatment. Studies by Chakos et al (1994), Keshavan et al (1994), Elkashef et al (1994), Rodriguez et al (1997) and Gur et al (1998) noted that the increase in caudate volume in schizophrenia patients followed treatment with typical neuroleptics. Following the introduction of atypical neuroleptics, several follow-up studies noted a decrease in volume when patients were switched from typical to atypical neuroleptics (Chakos et al 1995; Frazier et al 1996; Westermoreland et al 1999). Assessing never-treated schizophrenia patients avoided the confounding effect of neuroleptics.

The caudate nuclei exhibit hemispheric lateralization with the right caudate being larger than the left caudate (Watkins et al 2001). Thus handedness may be a factor influencing the structure and function of caudate. In this study, handedness was assessed using Annett's Handedness Questionnaire (Annett, 1967) and all subjects were right handed in this study. 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). Two of the earlier studies have used lower than 1.5 Tesla scanner for MRI scan of the brain (0.5 Tesla in the study by McCreadie et al 2002 and 1.0 Tesla in the study by Chakos et al 1994). Interestingly, these two studies

did not find any difference in caudate volume.

The slice thickness used in this study was one mm. 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 overestimated 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 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 the correction process using intracranial volume as well as intracranial area in the midsagittal section helps in the reduction of variance of volumetric measures of brain structures (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.

Compared to the prior studies, our study has smaller sample size. However, even with this smaller sample size difference in caudate volume was detected by our study. Our observation of caudate volume reduction in never-treated schizophrenia may reflect primary pathophysiology of schizophrenia. Recent studies have shown that the caudate nucleus is activated during working memory-related tasks (Monchi et al 2001). Thus, caudate may be a part of a distributed neuronal network subserving functions associated with the dorsolateral prefrontal cortex (Keshavan et al 1998). Significantly reduced basal ganglia metabolism has been observed in unmedicated schizophrenia patients through use of positron emission tomography (Weisel et al 1987; Buchsbaum et al 1992; Siegel et al 1993) and single photon emission tomography (Vita et al 1995). Thus, this study finding is also consistent with functional neuroimaging research in schizophrenia.

Despite the wide range of illness duration in the patient sample, no significant correlation was found between caudate volumes and illness duration. This finding of lack of association between caudate volume and illness duration & the observation of caudate volume reduction in never-treated schizophrenia provide some indirect support for neurodevelopmentally-mediated pathology in schizophrenia (Weinberger, 1987). 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).

In summary, this study aimed to examine whether there is an independent underlying structural abnormality of caudate nucleus in never-treated schizophrenia. Though the small sample size and use of intracranial area instead of intracranial volume as covariate may make one derive cautious interpretations, the study is methodologically rigorous owing to the following reasons:

1. Patients were never-treated,
2. All subjects were right handed,
3. SCAN interview for establishing the diagnosis,
4. Confirmation of diagnosis by two experienced psychiatrists,
5. Stability of diagnosis in all patients at 1-year follow-up as re-assessed by one of the two experienced psychiatrists,
6. MRI slices were of 1 mm thickness,
7. Ratings of brain measurements were done in coded MRI sections making the rater blind to clinical data,
8. Good inter-rater reliability for brain measurements,
9. Use of covariate rather than a ratio measure to correct for brain size variations.

Thus, this research rigor matches with contemporary caudate imaging studies in schizophrenia.

In conclusion, we have found significantly smaller caudate volume in never-treated schizophrenia. In addition there was no significant correlation between caudate volume and illness duration. These findings suggest neurodevelopmental etiopathogenesis in schizophrenia.

REFERENCES

American Psychiatric Association (1994). DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. 4th ed., American Psychiatric Association, Washington, DC.

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

Breier, A., Buchanan, R.W., Elkashef, A., Munson, R.C., Kirkpatrick, B., Gellad, F. (1992) Brain morphology in schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex and caudate structures. Arch Gen Psychiatry, 49, 291-926.

Brown, K.W., Wardlaw, J.M., White, T., Walker, N.C. (1996) Caudate nucleus area in drug-induced parkinsonism. Acta Psychiatr Scand, 94, 348 - 351.

Buchanan, R.W., Breier, A., Kirkpatrick, B., Elkashef, A., Munson, R.C., Gellad, F., Carpenter, W.T. (1993) Structural abnormalities in deficit and nondeficit schizophrenia. Am J Psychiatry, 150, 59-65.

Buchsbaum, M.S., Porkin, S.G., Siegel, B.V. Jr., Lohr, J., Katz, M., Gottschalk, L.A., Gulasekaram, B., Marshall, J.F., Lottenberg, S., Teng, C.Y. (1992) Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. Archives of General Psychiatry, 49, 966 - 974.

Busatto, G.F., Kerwin, R.W. (1997) Schizophrenia, psychosis, and the basal ganglia. Psychiatry Clinics of North America, 20, 897-910.

Chakos, M.H., Lieberman, J.A., Alvir, J., Bilder, R., Ashtari, M. (1995). Caudate nuclei volumes in patients treated with typical antipsychotics or clozapine (letter). Lancet, 345, 456-457.

Chakos, M.H., Lieberman, J.A., Bilder, R.M., Borenstein, M., Lerner, G. (1994) Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. American Journal of Psychiatry, 151, 1430 - 1436.

Corey-Bloom, J., Jernigan, T., Archibald, S., Harris, M.J., Jeste, D.V. (1995) Quantitative magnetic resonance imaging of the brain in late-life schizophrenia. American Journal of Psychiatry, 152, 447 - 449.

Corson, P.W., Nopoulos, P., Andreasen, N.C., Heckel, D., Arndt, S. (1999) Caudate size in first-episode Neuroleptic-naive schizophrenic patients measured using an artificial neural network. Biol Psychiatry, 46, 712 - 720.

Dalgalarrondo, P., Gattaz, W.F. (1994) Basal ganglia abnormalities in tardive dyskinesia: possible relationship with duration of neuroleptic treatment. Eur Arch Psychiatry Clin Neuroscience, 244, 272 - 277.

DeLisi, L.E., Hoff, A.L., Schwartz, J.E., Shields, G.W., Halthore, S.N., Gupta, S.M., Henn, F.A., Anand, A.K. (1991) Brain morphology in first-episode schizophrenia-like psychotic patients: a quantitative magnetic resonance imaging study. Biological Psychiatry, 29, 159 - 175.

Elkashef, A.M., Buchanan, R.W., Gellad, F., Munson, R.C., Breier, A. (1994) Basal ganglia in schizophrenia and tardive dyskinesia: An MRI quantitative study. Am J Psychiatry, 151(5), 752 - 755.

Filipek, P.A., Kennedy, D.N., Caviness, V.S., Rossnick, S.L., Spraggins, T.A., Starewicz, P.M. (1989) Magnetic resonance imaging-based brain morphometry: Development and application to normal subjects. Annals of Neurology, 25, 61- 67.

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

Frazier, J.A., Gied, J.N., Kaysen, D., Albus, K., Hamburger, S., Alaghband-Rad, J. (1996) Childhood onset schizophrenia: Brain MRI rescan after 2 years of clozapine maintenance therapy. American Journal of Psychiatry, 153, 564 - 566.

Free, S.L., Bergin, P.S., Fish, D.R., Cook, M.J., Shorvon, S.D., Stevens, J.M. (1995) Methods for normalization of hippocampal volumes measured with MR. Am J Neuroradiology, 16, 637-643.

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

Graybiel, A.M. (1997) The basal ganglia and cognitive pattern generators: Schizophr Bulletin, 23(3), 459-469.

Gur, R.E., Maany, V., Mozley, P.D., Swanson, C., Bilker, W., Gur, R.C. (1998) Subcortical MRI volumes in neuroleptic naïve and treated patients with schizophrenia. American Journal of Psychiatry, 155, 1711 - 1717.

Guy, W. (1976) Abnormal Involuntary Movements Scale (AIMS). ECDEU Assessment Manual for Pharmacology. Rockville, Md: US Dept of Health, Education, and Welfare, 534-537.

Harvey, I., Williams, M., Toone, B.K., Lewis, S.W., Turner, S., McGuffin, P. (1990) The ventricular-brain ratio in functional psychosis: the relationship of lateral ventricular and total intracranial area. Psychological Medicine, 20, 55 - 62.

Heckers, S., Heinsen, H., Heinsen, Y., Beckmann, H. (1991) Cortex, white matter and basal ganglia in schizophrenia: A volumetric postmortem study. Biological Psychiatry, 29, 556-566.

Heckers, S. (1997). Neuropathology of schizophrenia: cortex, Thalamus, Basal ganglia and neurotransmitter-specific projection systems. Schizophrenia Bulletin, 23, 403-421.

Hokama, H., Shenton, M.E., Nestor, P.G., Kikinis, R., Levitt, J.J., Metcalf, D. (1995) Caudate, Putamen and globus pallidus volume in schizophrenia: A quantitative MRI study. Psychiatry Research Neuroimaging, 61, 209-229.

Jernigan, T.L., Zisook, S., Heaton, R.K., Moranville, J.K., Hesselink, J.R., Braff, D.L. (1991) Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Archives General Psychiatry, 48, 881-890.

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

Kelsoe, J.R. Jr, Cadet, J.L., Pickar, D., Weinberger, D.R. (1988) Quantitative neuroanatomy in schizophrenia: a controlled magnetic resonance imaging study. Archives of General Psychiatry, 45, 533 - 541.

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

Keshavan, M.S., Anderson, S., Pettergrew, J.W. (1994) Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? the Feinberg hypothesis revisited. Journal of Psychiatric Research, 28, 239-245.

Keshavan, M.S., Diwadkar, V.A., Bagwell, W.W., Harenski, K., Rosenberg, D.R., Sweeney, J.A., Pettergrew, J.W. (2002) Abnormalities of Corpus Callosum in first episode treatment naïve schizophrenia. Journal of Neurology, Neurosurgery, Psychiatry, 72(6):757-60.

Keshavan, M.S., Rosenberg, D., Sweeney, J.A., Petergrew, J.W. (1998) Decreased caudate volume in neuroleptic-naïve psychotic patients. Am J Psychiatry, 155, 774 - 778.

Kraepelin E. Dementia Praecox and Paraphrenia (1919). Translated by ed. Barclay RM, Robertson GM. New York: Robert E Kreiger, 1971:77 - 83.

Levy, R., Friedman, H.R., Davachi, L., Goldman-Rakic, P.S. (1997) Differential activation of the caudate nucleus in primates performing spatial and non spatial working memory tasks. Journal of Neuroscience 17, 3870-3882.

Lim, K.O., Rosenbloom, M., Pfefferbaum, A. (1995) In vitro structural brain assessment. In Psychopharmacology - The Fourth Generation of Progress, Eds. Bloom, F.E., Kupfer, D.J. Raven Press, Ltd., New York , 881 - 894.

McCreadie, R.G., Thara, R., Padmavathi, R., Srinivasan, T.N., Jaipurkar, S.D. (2002) Structural brain differences between never-treated patients with schizophrenia, with and without dyskinesia, and normal control subjects. A magnetic resonance imaging study. Arch Gen Psychiatry, 59, 332-336.

Middleton, F.A., Strick, P.L. (1994) Anatomical

evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science. 266, 458-461.

Mion, C.C., Andreasen, N.C., Arndt, S., Swayze, V.W.I.I., Cohen, G.A. (1991) MRI abnormalities in tardive dyskinesia. Psychiatry Research, 40, 157 - 166.

Monchi, O., Petrides, M., Petre, V., Worsley, K., Dagher, A. (2001) Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. Journal of Neurosciences, 21(19), 7733-41.

Ring, H.A., Serra-Mestres, J. (2002) Neuropsychiatry of the basal ganglia. J Neurol Neurosurg Psychiatry, 72, 12 - 21.

Roberts, R.C., Conley, R., Kung, L., Peretti, F.J., Chute, D.J. (1996) Reduced striatal spine size in schizophrenia: a postmortem ultrastructural study. Neuroreport, 7, 1214-1218.

Rodriguez, R., Flaum, M., Nopoulos, P. (1997) The effect of cumulative Neuroleptic exposure on caudate and putamen volume (abstract). Schizophrenia Research 24, 154 - 155.

Shenton, M.E., Wible, C.G., McCarley, R.W. (1997) 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. pp 297-380.

Shihabuddin, L., Buchsbaum, M., Hazlett, E.A., Haznedar, M.M., Harvey, P.D., Newman, A. (1998). Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. Archives of General Psychiatry, 55, 235 - 243.

Siegel, B.V., Buchsbaum, M.S., Bunney, W.F., Gottschalk, L.A., Haier, R.J., Lohr, J.B., Lottenberg, S., Najafi, A. (1993) Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. American Journal of Psychiatry, 150, 1325-1336.

Simpson, G.M., Angus, J.W.S. (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl., 212, 11-19.

Swayze, V.W.I.I., Andreasen, N.C., Alliger, R.J., Yuh, W.T., Ehrhardt, J.C. (1992) Subcortical and temporal structures in affective disorder and schizophrenia: A magnetic resonance imaging study. Biological Psychiatry, 3, 221- 240.

Vita, A., Bressi, S., Perani, D., Invernizzi, G., Giobbio, G.M., Dieci, M., Garbarini, M., Del Sole, A., Fazio, F. (1995) High-resolution SPECT study of regional cerebral blood flow in drug-free and drug-naive schizophrenic patients. American Journal of Psychiaty, 152, 876-882.

Walker, E., Lewin, R.J. (1990) Predictions of adult-onset schizophrenia from childhood home movies of the patients. Am J Psychiatry, 147, 1052-1056.

Watkins, K.E., Paus, T., Lerch, J.P., Zijdenbos, A., Collins, D.L., Neelin, P., Taylor, J., Worsley, K.J., Evans, A.C. (2001) Structural asymmetries in the human brain: a voxel-based statistical analysis of 142 MRI scans. Cerebral Cortex, 11(9), 868-77.

Weinberger, D.R. (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry, 44, 660-669.

Weisel, F.A., Wilk, G., Sjogren, J., Blomquist, G., Greitz, T. (1987) Altered relationships between metabolic rates of glucose in brain regions of schizophrenic patients. Acta Psychiatrica Scandinavica, 76, 642-647.

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

Woodruff, P., Pearson, G., Geer, M., Barta, P., Childoat, H. (1993) A computerized magnetic resonance imaging study of corpus callosum morphology in schizophrenia. Psychological Medicine, 23, 45 - 56.

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

Young, A.H., Blackwood, D.H., Roxborough, H., McQueen, J.K., Martin, M.J., Kean, D. (1991) A magnetic resonance imaging study of schizophrenia: brain structure and clinical symptoms. British Journal of Psychiatry, 158, 158 - 164.

---

*GANESAN 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

*Correspondence

E-Mail: maniangvs@yahoo.com

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