AWARD PAPER

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

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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 (I-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; Flum et al 1995). Studies have also shown a reduction in caudate size in schizoaffective patients (Miom 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
MCNAGNETIC 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) & T1 weighted transverse images; T2 weighted coronal images; and T1 Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence.

This was followed by a set of proton density and T1 weighted axial images covering the whole brain (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 T1 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 T1 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, T1 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 smoothing 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 T1 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 (RMANOVA). 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.

BRAIN MORPHOMETRY

Intracranial area (Mean ± SD) did not differ significantly between patients (127±11 cm²) and controls (127±13 cm²) 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 I : 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
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  | 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.

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 was also one of the exclusion criteria. Thus the effect of confounding factors was minimized.

All patients were treatment-naive. 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 perinatal synaptic pruning, perhaps in glutamatergic corticosubcortical neurons, may be involved (Keshavan et al. 1994). Reduced activity in these cortico-striatal neurons, by diminishing trophic effects on the striatum, could conceivably lead to reduced synaptic neuropil, 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 (Robert 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.

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

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: manijangw@yahoo.com

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