Journal of Child Neurology
http://jcn.sagepub.com/

Attention Deficit- Hyperactivity Disorder and Asymmetry of the Caudate Nucleus

George W. Hynd, Kelly L. Hern, Edward S. Novey, Deborah Eliopulos, Richard Marshall, Jose J. Gonzalez and Kytja K. Voeller

J Child Neurol 1993 8: 339
DOI: 10.1177/088307389300800409

Attention Deficit–Hyperactivity Disorder and Asymmetry of the Caudate Nucleus

George W. Hynd, EdD; Kelly L. Hern, PhD; Edward S. Novey, MD; Deborah Eliopulos, RT; Richard Marshall, PhD; Jose J. Gonzalez, MA; Kytja K. Voeller, MD

Abstract

The neurologic basis of attention deficit–hyperactivity disorder (ADHD) is poorly understood. Based on previous studies that have implicated metabolic deficiencies in the caudate-striatal region in ADHD, we employed magnetic resonance imaging to investigate patterns of morphology of the head of the caudate nucleus in normal and ADHD children. In normal children, 72.7% evidenced a left-larger-than-right (L > R) pattern of asymmetry, whereas 63.6% of the ADHD children had the reverse (L < R) pattern of asymmetry of the head of the caudate nucleus. This reversal of normal asymmetry in ADHD children was due to a significantly smaller left caudate nucleus. The reversal in asymmetry of the head of the caudate was most notable in ADHD males. These results suggest that normal (L > R) morphologic asymmetry in the region of the caudate nucleus may be related to asymmetries observed in neurotransmitter systems implicated in ADHD. The behavioral symptoms of ADHD may reflect disinhibition from normal levels of dominant hemispheric control, possibly correlated with deviations in asymmetric caudate-striatal morphology and deficiencies in associated neurotransmitter systems. (*J Child Neurol* 1993;8:339–347).

Attention deficit–hyperactivity disorder (ADHD) is a behaviorally diagnosed syndrome characterized by problems in attention, impulse control, and motor regulation.[1,2] Although there is considerable controversy as to the empirical validation of current diagnostic criteria,[3,4] it is generally agreed that approximately 3% to 6% of all school-age children suffer from ADHD.[5,6]

The recognition that ADHD may cooccur with developmental learning disorders[4,7] and that it is frequently associated with other psychiatric disturbance in the child and his or her parents[8] has led to studies that suggest a familial-genetic etiology.[9,10] The notion that ADHD is of constitutional origin has been supported by a long history of research that indicates that many of these children respond favorably to stimulant medication.[11,12] Nonetheless, the neurobiologic basis of ADHD remains poorly understood.[6,11,12]

The symptoms of inattention, impulsivity, and hyperactivity that characterize ADHD have led many to conclude that children with ADHD suffer from dysfunction of the arousal-motor regulatory systems associated with the frontal-striatal regions.[11,12] Support for this view can be derived from behavioral studies in humans[13–16] and animals[11,17,18] with known lesions of this system. Clinical-psychometric studies of children with ADHD document deficits in attention, response inhibition, and motor regulation as well.[19,20]

Studies by Lou et al[21,22] using computed tomography/regional cerebral blood flow with children diagnosed as having ADHD indicate hypoperfusion in the caudate-striatal region. Children with pure ADHD evidence significant hypoperfusion in the

Received March 13, 1992. Received revised July 29, 1992. Accepted for publication Sept 3, 1992.

From the Departments of Special Education (Drs Hynd and Marshall and Mr Gonzalez) and Psychology (Dr Hynd), University of Georgia, Athens, GA; Department of Neurology (Dr Hynd), Medical College of Georgia, Augusta, GA; Center for the Study of Development and Learning (Dr Hern), University of North Carolina, Chapel Hill, NC; Athens Magnetic Imaging (Dr Novey and Ms Eliopulos); Athens, GA; Department of Psychiatry (Dr Voeller), University of Florida School of Medicine, Gainesville, FL.

Address correspondence to Dr Hynd, Department of Special Education, EXC-Aderhold Hall, University of Georgia, Athens, GA 30602.

right striatum, whereas those with cooccurring neurologic disorders (eg, mild mental retardation or dysphasia) showed bilateral hypoperfusion in the caudate-striatal region.[22] Methylphenidate, known to potentiate dopaminergic neurons by decreasing dopamine reuptake, increased perfusion in both striatal regions but significantly so only in the left striatum.

Thus, there appears to be converging evidence that dysfunction in the striatal-frontal regulatory system may be implicated in ADHD. In this context, we sought to determine if morphologic differences existed in the region of the caudate nucleus in ADHD. The caudate nucleus, putamen, and globus pallidus compose the basal ganglia. Of these three structures, the head of the caudate nucleus is most easily visualized in magnetic resonance imaging (MRI) because it bulges into the anterior horn of the lateral ventricle. Based on previous MRI studies that have suggested that the frontal region is symmetrical in ADHD children, in contrast to normal left-less-than-right (L < R) asymmetry,[23] and that the genu of the corpus callosum is smaller in ADHD children,[24] we hypothesized that the head of the caudate nucleus would be smaller or show unusual asymmetry in children with ADHD.

Subjects and Methods

Subjects

Children who participated in this study were either outpatients of the Center for Clinical and Developmental Neuropsychology at the University of Georgia, Athens, or were recruited as normal control subjects from the community. The Center provides diagnostic and referral services for northeast Georgia. Referrals came primarily from area physicians, other university clinics, or school districts.

The 11 ADHD children were consecutive referrals, excluding patients who received other primary *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, revised *(DSM-III-R)* diagnoses or those children diagnosed as having mild mental retardation (Full Scale IQ < 70), epilepsy, closed head trauma, or other neurologic conditions. All subjects, both ADHD and normal controls, were white, native English-speaking, and were from lower-middle to middle socioeconomic environments. All children were reported by their parents to be right-handed.

Because there is considerable controversy as to the diagnostic nomenclature most appropriate for this disorder,[3] it should be noted that all ADHD children also qualified for a diagnosis of attention deficit disorder with hyperactivity in accordance with the criteria of the unrevised *DSM-III*.[1] There were eight boys and three girls in the ADHD group, and six boys and five girls in the control group. Subject and psychometric data are presented in Table 1.

Diagnostic Procedures

All ADHD and control children participated in a day-long comprehensive diagnostic examination. Each child was accompanied by one of her or his biologic parents (usually the mother) from whom permission to participate in the clinical examination and MRI scan was obtained.

The neuropsychological examination included intellectual assessment using the Wechsler Intelligence Scale for Children–Revised(WISC-R),[25] achievement measures, and both more traditional and experimental neuropsychological procedures. Handedness was assessed by observing performance on 10 items from the Edinburgh Inventory.[26] This inventory yields a laterality quotient such that a score of −100 indicates consistent left-handedness, and a score of +100 indicates pure right-handedness. These data were collected so that we would have comparable data to our previous MRI study involving ADHD children and to verify parental report of right-handedness.[23]

Behavioral information was collected through parent and, in some cases, teacher interviews employing a revision of the Schedule for Affective Disorders and Schizophrenia for School-Age Children.[27] This interview schedule was updated to include questions about all symptoms found in the *DSM-III* and *DSM-III-R* for the diagnosis of conduct disorder, attention deficit disorder with and without hyperactivity, ADHD, overanxious disorder, separation anxiety disorder, major depressive episode, dysthymic disorder, and oppositional defiant disorder. Additional behavioral assessment employed parent- and teacher-completed SNAP Checklists[28] and the parent-completed Achenbach Child Behavior Checklist.[29]

The diagnosis of ADHD required average or better intellectual ability (Full Scale IQ ≥ 85); no reported family history of significant neurologic problems, documented behavioral problems in attention, impulse control, and motor activity (hyperactivity) consistent with the listing of symptoms in the *DSM-III-R*. All ADHD children were considered to be favorable responders by their physician and family to stimulant medication. Control children were administered the same battery of behavioral and neuropsychological measures and were required to have average or better intellectual ability (Full Scale IQ ≥ 85); no reported family history of learning or psychiatric problems; no significant deficit in academic achievement; and no reported or observed medical, educational, social, or psychiatric difficulties.

Clinical diagnosis was based on procedures reported previously.[23,30] Diagnostic decisions were reached separately by two psychologists after considering all relevant historical, behavioral, and psychometric data. Diagnosis was required to reflect the above noted criteria as well as the specific diagnostic criteria noted in the *DSM-III-R*. Cooccurring diagnoses were also reached using *DSM-III-R* criteria. Disagreement in clinical diagnosis by the two psychologists was resolved through mutual discussion. These clinical procedures have resulted in reliable diagnosis[8,23,30] and meet accepted criteria for reliability in psychiatric diagnosis.[31]

Magnetic Resonance Imaging Protocol

Sequential T_1 sagittal and axial MRI planes were obtained using a 0.6-T Health Images scanner (Atlanta, GA) for each child entered into the study protocol. The protocol selected involved fifteen 7.5-mm sagittal planes (T_R = 690 ms; T_E = 32 ms) and eleven 5-mm axial planes (T_R = 500 ms; T_E = 32 ms). Head position was carefully monitored using scout scans. This was done to insure that proper alignment was obtained because slight rotations of the head could potentially affect morphometric results.

Region of interest measurements were obtained on a midaxial scan that best visualized the region of the anterior horn of the lateral ventricles and the head of the caudate nucleus. Care was taken to insure that each axial scan selected for the measurements visualized the same midaxial structures. Measurements were made by one of the authors who had received training in obtaining reliable morphometric measurements[23] but who was blind to the purpose of the study and group membership of the subjects.

Figure 1 shows how the head of the caudate nucleus was measured using the Health Images measurement software system. A previous study indicated that these and other morphometric measurements can be made reliably.[23] All MRI scans for the ADHD and control children were read as normal.

Results

There was no significant ($P > .05$) difference in chronologic age between groups. However, there was a significant difference in general intellectual ability ($t[20] = 2.39$; $P < .01$); the control children had a significantly higher WISC-R Full Scale IQ (mean = 118.45) than the ADHD children (mean = 102.18). There was no significant ($P > .05$) difference in handedness between the normals (mean = 90.91) and the ADHD (mean = 86.36) children as assessed on the Edinburgh Inventory.[26] Consistent with parental reports, all children, both control and ADHD, were determined to be right-handed.

The two groups did differ significantly in the number of codiagnoses ($\chi^2[1] = 10.27$; $P < .001$) in that the control children had no other diagnoses, whereas the ADHD children had a total of seven codiagnoses. Among the ADHD children, one was diagnosed as conduct disordered, one as dysthymic, two as oppositional defiant disordered, and three as having a developmental arithmetic disorder.

As suggested by the behavioral data presented in Table 1 and consistent with the diagnosis of ADHD, the two groups did not differ significantly ($P > .05$) on the Internalizing Scale of the Achenbach Child Behavior Checklist.[29] The control and ADHD children did differ significantly ($t[16] = -3.97$; $P < .001$) on the Externalizing Scale, with ADHD children scoring one and a half standard deviations above the mean. Consistent with this finding were the significantly higher *t*-scores for the ADHD children on the Hyperactivity Scale ($t[16] = -5.30$; $P < .001$), Delinquent Scale ($t[16] = -2.54$; $P < .01$), and Aggression Scale ($t[16] = -2.40$; $P < .01$) of the Achenbach checklist.[29]

Before examining possible differences in the area of the head of the caudate nucleus in the control and ADHD children, potential differences in overall brain size were examined in these two groups of children. The supratentorial area was measured on a midsagittal MRI scan, and the ADHD (mean = 116.53 cm^2; SD = 7.70 cm^2) and control (mean =

TABLE 1
Subject and Psychometric Data by Group

Variable	Controls (n = 11)	ADHD (n = 11)
Chronologic age, mo	132.36(33.23)*	132.91 (30.26)
No. of codiagnoses	0	7†
Handedness, % right	90.91(14.46)	86.36 (23.78)
Achenbach CBCL (selected scales)		
Internalizing	51.11 (6.27)	58.33 (12.79)
Externalizing	52.00 (5.68)	66.78† (9.60)
Hyperactivity	55.56 (1.13)	72.00† (9.23)
Delinquent	57.75 (3.15)	66.88† (9.65)
Aggressive	56.78 (2.73)	65.66† (10.75)
WISC-R IQs		
Verbal	115.82(16.10)	102.30† (11.23)
Performance	117.55(12.81)	97.10† (19.16)
Full Scale	118.45(14.72)	102.18† (17.17)

CBCL = Child Behavior Checklist; WISC-R = Wechsler Intelligence Scale for Children–Revised.
*Mean (SD).
†$P < .01$.

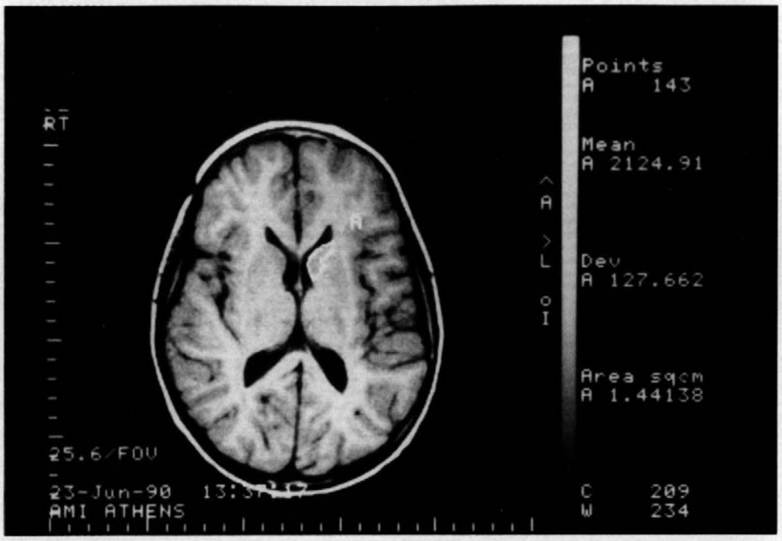

FIGURE 1
MRI scan of the brain of a child with ADHD showing how the area (in cm^2) of the head of the caudate nucleus was obtained.

119.89 cm^2; SD = 7.42 cm^2) children did not differ significantly ($P > .05$). As there were significant differences in general intellectual ability between the control and ADHD children, the correlations between all three WISC-R (Verbal, Performance, and Full Scale) IQ measures and the area of the supratentorial and left and right caudate were examined. None of these correlations was significant ($P > .05$), and they were therefore not employed as covariates. Furthermore, no significant ($P > .05$) differences in brain morphology existed according to sex.

A 2 (group) × 2 (left, right caudate) analysis of variance indicated no significant ($P > .05$) group or laterality effect. However, a significant ($F[1,43] = 5.79$; $P < .03$) interaction effect between group and the measurements for the left and right head of the caudate nucleus was found. Posthoc tests revealed that there was no significant ($P > .05$) difference between the area measurements of the right caudate, but that the effect was due to the significantly ($P < .03$) smaller left caudate in the ADHD children. Table 2 presents subject as well as group data, and Figure 2 illustrates the relative magnitude of the group differences.

In order to understand how the patterns of asymmetry of the head of the caudate may characterize children in the control and ADHD groups, each child was classified as having a L > R, L < R, or L = R pattern if the measurement of the left and right caudate differed by 0.1 cm^2. As can be seen in Table 3, 72.7% (8 of 11) of the control children had a L > R pattern while 63.6% (7 of 11) of the ADHD children had a L < R pattern. There was a significant ($\chi^2[2] = 7.11$; $P < .03$) difference between the two groups in their pattern of asymmetry of the head of the caudate nucleus.

Exploratory Analyses

Considering that this study employed a relatively small number of subjects per group, and despite the fact that sex did not seem to be a significant variable with the total sample, it was deemed appropriate to qualitatively examine the potential relationship of sex, handedness, and patterns of caudate asymmetry, because sex and handedness have been identified as important in other studies of ADHD children.[6] To accomplish this, we charted the Edinburgh Handedness Inventory[26] laterality quotient by the caudate laterality quotient (L/R × 100) for each male and female subject in the control and ADHD groups. Figure 3 illustrates these relationships derived from data presented in Table 2.

As can be seen, all subjects were indeed right-handed, although three subjects (two ADHD and one control) had handedness laterality quotients <90. Importantly, however, seven of the nine subjects who had caudate laterality quotients < 100 (symmetry) were ADHD children. Of those children who had caudate laterality quotients < 90 (L < R), all six were ADHD boys. This encouraged a further examination of the boys despite the small number of subjects.

TABLE 2
Subject and Group Data for the Left and Right Caudate Nucleus in the Control and ADHD Children

Subject	Sex	% Right-Handedness	Head of Caudate Left (cm^2)	Head of Caudate Right (cm^2)	Caudate LQ (L/R × 100)
Control					
1	M	90	1.44	1.46	99
2	M	90	1.28	.69	185
3	M	50	1.28	1.17	109
4	F	90	1.78	1.16	153
5	F	100	2.01	1.70	118
6	F	90	1.65	1.48	112
7	M	90	1.40	1.08	129
8	F	100	1.14	1.27	90
9	M	100	1.89	1.85	102
10	F	90	1.11	1.01	110
11	M	100	1.13	1.08	105
Mean (SD)	—	—	1.47 (0.32)	1.27 (0.33)	119.27 (27.51)
ADHD					
1	M	100	1.25	1.64	76
2	M	90	1.53	1.84	83
3	M	100	1.59	1.44	110
4	M	20	1.25	1.77	71
5	F	90	.57	.61	93
6	M	90	.80	1.37	58
7	M	100	1.20	1.39	86
8	M	100	1.18	1.56	76
9	F	100	1.11	1.10	101
10	M	90	1.57	1.21	130
11	F	70	1.08	.74	146
Mean (SD)	—	—	1.19 (.31)	1.33 (.39)	93.64 (26.39)

ADHD = attention deficit–hyperactivity disorder; LQ = laterality quotient.

If one eliminates girls from consideration, there are six control boys and eight ADHD boys. Again, handedness was not significant ($P > .05$). However, the mean caudate laterality quotient for the boys in the two groups (control, 121.50 ± 32.87; ADHD, 86.25 ± 23.08) was statistically significant ($t[12] = 2.37$; $P < .02$). Consequently, although handedness does not seem to be a relevant variable with these right-handed boys, the head of the caudate laterality quotient was clearly different. Recognizing the possibility that the small number of boys examined could have resulted in significant differences between groups, it does seem that these results highlight the potential importance of sex.

TABLE 3
Patterns of Asymmetry of the Caudate Nucleus in Control and ADHD Children

Group	L > R, no. (%)	L < R, no. (%)	L = R, no. (%)
Control (n = 11)	8 (72.7)	1 (9.1)	2 (18.2)
ADHD (n = 11)	3 (27.3)	7 (63.6)	1 (9.1)

ADHD = attention deficit–hyperactivity disorder.

Comment

The carefully diagnosed ADHD subjects in our study seem representative of other descriptions of these children in the literature. Consistent with previous studies,[4–6,23,24] our ADHD children were rated as significantly deviant from the controls on behaviors associated with hyperactivity, aggression, and delinquency. This is consistent with the high number of *DSM-III-R* codiagnoses most typically reflecting externalizing psychopathology (Table 1).[4–6]

Our results provide support for the notion that the caudate-striatal region may be implicated in ADHD. In contrast to the control children who evidenced L > R asymmetry of the head of the caudate nucleus, the ADHD children were characterized as a group by L < R asymmetry. Most importantly, however, the significant group by asymmetry interaction

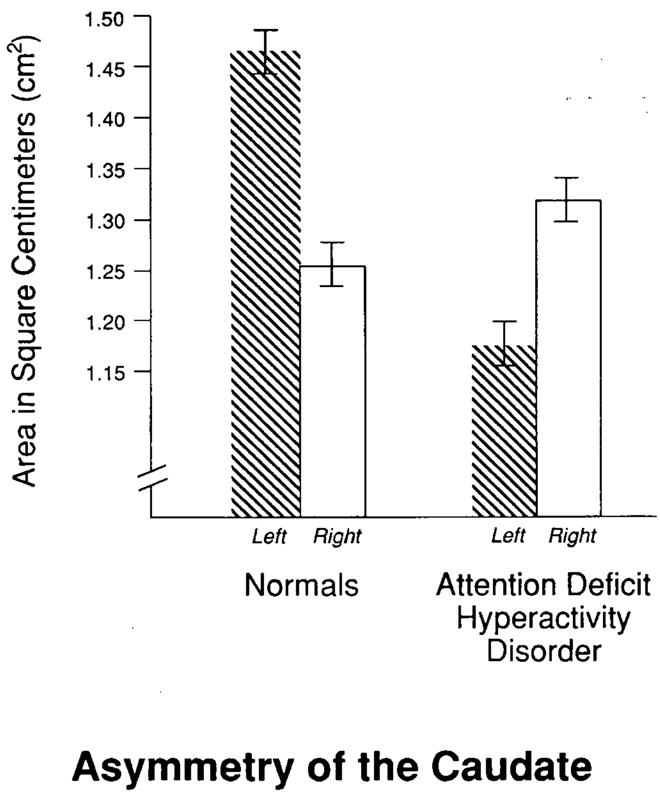

FIGURE 2
Group and caudate differences (cm^2).

was due to the relatively smaller left caudate nucleus in the ADHD children.

While modal differences clearly exist, it is notable that 72.7% (eight of 11) of the control children had a L > R pattern of caudate asymmetry, whereas only 27.3% (three of 11) of the ADHD children showed this pattern of asymmetry. Conversely, only 9.1% (one of 11) of the normal control children had reversed L < R caudate nucleus asymmetry, whereas 63.6% (seven of 11) of the ADHD children evidenced this pattern. The fact that no significant differences existed in overall brain size suggests that this regional variation may be due to a more specific deviation in brain ontogeny.

Patterns of asymmetry, reversed asymmetry, and symmetry clearly differ between ADHD and control children in this study. However, exploratory analyses revealed that the reversed pattern of caudate asymmetry (L < R) was predominately found in the eight ADHD boys, who differed significantly from the six control boys, who evidenced the pattern of L > R caudate asymmetry. Overall, sex effects were not significant, but an examination of Figure 3 highlighted the fact that the male ADHD children contributed most to the pattern of reversed asymmetry of the head of the caudate nucleus. When only boys were considered, caudate laterality quotients were statistically significantly different between the control and ADHD children. This finding, despite the low number of boys in each group, underscores the importance for future studies to examine or control for sex and suggests that male ADHD children may be at additional risk for deviations in normal patterns of asymmetry during brain ontogeny compared to girls. This latter point may be important because male dyslexics also seem more often characterized by deviations from normal patterns of brain asymmetry.[23]

Overall, the reversal in the direction of the asymmetry of the head of the caudate nucleus in the ADHD group may relate to previous findings with these children. This finding is particularly interesting in light of the computed tomography/regional cerebral blood flow results reported by Lou et al,[22] who found that methylphenidate-mediated activation occurred in their ADHD subjects in the left striatum, significantly more so than in the right. Although the possible relationship between morphologic asymmetries and correlated metabolic activity in the striatal-caudate region is not known, especially in ADHD children, the implication of the left caudate-striatum in the study by Lou et al[22] and the left caudate in our study warrants consideration.

It has been demonstrated repeatedly for most right-handed individuals that reliable cerebral asymmetries exist.[32] For example, the planum temporale is typically larger on the left than the right,[33] the right frontal volume typically exceeds that of the left,[34] and the left posterior region is often wider than the right.[35] Further, these patterns of asymmetry appear to be related to functional correlates.[32] For example, deviations from these normal patterns of asymmetry appear to be related to cognitive-behavioral deficits in developmental disorders such as dyslexia.[23,35]

ADHD, unlike dyslexia, is believed to result from a disruption of subcortical pathways related to the regulation of arousal and motor inhibition that manifest as deficits in attention, impulse control, and motor activity.[11] It is not unreasonable to suspect that the caudate-striatal region may be implicated, because lesions to this region may produce behavioral deficits similar to those seen in ADHD children.[36,37]

Animal studies have demonstrated asymmetries in some neurotransmitter systems.[38] In particular, choline acetyltransferase and dopamine seem signif-

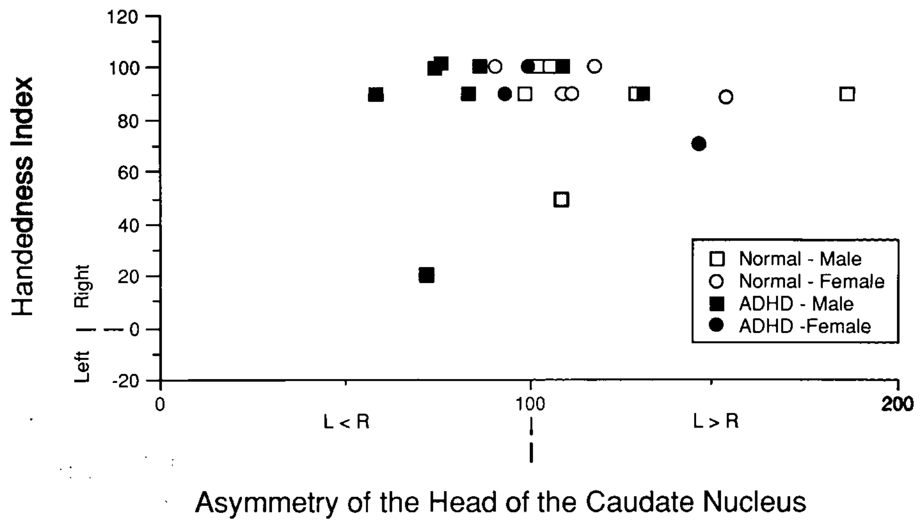

FIGURE 3
The relationship between the handedness, laterality index, and asymmetry of the head of the caudate nucleus in male and female control and ADHD children.

icantly left-biased in the region of the globus pallidus, caudate nucleus, and putamen. Furthermore, there seems to be a relationship between asymmetry of choline acetyltransferase and dopamine and activity level in that when there is a right-sided bias in activity (using labeled deoxyglucose as an index), it is associated with higher levels of motor activity.[39]

Based on our results, it may be hypothesized that L > R asymmetry of the head of the caudate nucleus is associated with the natural L > R asymmetry of the choline acetyltransferase and dopamine systems and normal levels of motor activity.[38,39] Conversely, the significantly smaller left caudate found in the ADHD children may correlate with a right-sided bias in choline acetyltransferase and dopamine, which in turn may be related to the increased levels of motor activity characteristic of our ADHD children.

Consistent with this line of reasoning that asymmetries in neurotransmitter systems (and perhaps morphologic asymmetries) are related to the behavioral manifestations of ADHD, Heilman et al[13] have proposed that methylphenidate may redress asymmetric imbalances in neurotransmitter systems in favor of processes mediated by the dominant (left) hemisphere. Animal studies have led to the same conclusion.[38] Thus, the right hemispheric deficits some authors have observed in ADHD children[13,40] may reflect disinhibition from normal levels of dominant hemispheric control, possibly correlated with deficiencies in asymmetric caudate-striatal neurotransmitter functioning. A recent single photon emission computed tomography study using *N*-isopropyl-[^{123}I]-*p*-iodoamphetamine in ADHD children supports this notion because reduced iodoamphetamine activity was observed in the left frontal region (Sieg et al, submitted).

It remains to be determined how asymmetry of the head of the caudate nucleus may relate to asymmetries of neurotransmitter systems, especially in regard to possible deficiencies in dopamine in ADHD. Further, the caudate nucleus is known to have extensive connections to the frontal lobes and thalamus. In particular, the dorsolateral prefrontal and lateral orbitofrontal circuits may be deficient in terms of normal activation due to deviations in normal functioning in the caudate-striatal region.

A related and equally important issue is, what effect does maturation of the caudate-striatal region have on the asymmetries observed in this study? In vivo stereologic assessment using MRI with adults (24 to 79 years of age) indicates symmetry of the left and right caudate, with significant age-related decreases in volume.[41] Although the age of complete maturation of subcortical structures such as the caudate is unknown, there is some evidence to suggest that synaptic density in the frontal cortex reaches adult levels by age 16 years.[42] This raises the possibility that there may be correlated ontogenetic changes in associated subcortical structures, such as the caudate nuclei, which have extensive connections to the frontal cortex. Clearly, there is a need for research that addresses developmental-morphologic changes in the patterns of asymmetry and symmetry of the caudate nucleus.

Behavioral studies that examine performance on tasks sensitive to disruptions in these regions in ADHD children and that seek possible interactions with asymmetry, symmetry, or reversed asymmetry of the head of the caudate nucleus may be especially revealing. Most relevant in this regard may be behavioral tasks that differentiate anterior attentional processes that may be deficient in ADHD children.[43] MRI procedures that allow for whole-brain reconstructions, such that the volume of the entire body of the caudate may be visualized and morphometrically analyzed, may significantly advance our understanding of the developmental relationship between asymmetry of the caudate-striatal region and the pathophysiology of ADHD.[44,45]

At present, the exact pathogenesis of ADHD remains unknown. Lou et al[22] have proposed that the right striatum may be selectively more dysfunctional due to early cerebral hypoxic-ischemic insult. His own results, however, suggest that it is the left striatum that is implicated in ADHD. These results are consistent with our morphometric findings regarding asymmetry of the head of the caudate nucleus. Postmortem studies may articulate more clearly whether cytoarchitectonic anomalies differentially impact on the left and right caudate-striatal systems or whether differences in patterns of caudate-striatal asymmetry are indeed associated with ADHD.

Acknowledgment

The research reported in this article was supported by grants from the Donald D. Hammill and RGK Foundations. Their support is gratefully acknowledged.

References

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed. Washington, DC, American Psychiatric Association, 1980.
2. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed, revised. Washington, DC, American Psychiatric Association, 1987.
3. Cantwell D, Baker L: Issues in the classification of child and adolescent psychopathology. *J Am Acad Child Psychiatry* 1988;27:521–533.
4. Lahey BB, Carlson CL: Validity of the diagnostic category of attention deficit disorder without hyperactivity: A review of the literature. *J Learn Disabil* 1991;24:110–120.
5. Shaywitz S, Shaywitz BA: Introduction to the special series on attention deficit disorder. *J Learn Disabil* 1991;24:68–71.
6. Barkley RA (ed): *Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment.* New York, Guilford Press, 1990.
7. Dykman RA, Ackerman PT: Attention deficit disorder and specific reading disability: Separate but often overlapping disorders. *J Learn Disabil* 1991;24:96–103.
8. Lahey BB, Piacentini JC, McBurnett K, et al: Psychopathology in the parents of children with conduct disorder and hyperactivity. *J Am Acad Child Psychiatry* 1988;27:163–170.
9. Biederman J, Munir K, Knee D, et al: A family study of patients with attention deficit disorder and normal controls. *J Psychiatr Res* 1986;20:263–274.
10. Biederman J, Faraone SV, Keenan K, et al: Family-genetic and psychosocial risk factors in DSM III attention deficit disorder. *J Am Acad Child Psychiatry* 1990;29:526–533.
11. Zametkin A, Rapoport J: The pathophysiology of attention deficit disorder with hyperactivity: A review, in Lahey BB, Kazdin A (eds): *Advances in Clinical Child Psychology.* New York, Plenum Press, 1986, pp 177–216.
12. Shaywitz SE, Shaywitz BA: Attention deficit disorder: Current perspectives, in Kavanagh TJ, Truss TJ (eds): *Learning Disabilities.* Parkton, MD, York Press, 1988, pp 369–523.
13. Heilman KM, Voeller KKS, Nadeau SE: A possible pathophysiological substrate of attention deficit hyperactivity disorder. *J Child Neurol* 1991;6(Suppl):S74–S79.
14. Drewe EA: Go–no go learning after frontal lobe lesions in humans. *Cortex* 1975;11:8–16.
15. VerFaellie M, Heilman KM: Response preparation and response inhibition after lesions of the medial frontal lobe. *Arch Neurol* 1987;44:1265–1271.
16. Luria AR: Frontal lobe syndrome, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology,* Vol 2. Amsterdam, Elsevier, 1969, pp 725–757.
17. Shaywitz SE, Hunt RD, Jatlow P, et al: Psychopharmacology of attention deficit disorder: Pharmacokinetic, neuroendocrine, and behavioral measures following acute and chronic treatment with methylphenidate. *Pediatrics* 1982;669:688–694.
18. Olmstead CE, Villablanca JR: Effects of caudate or frontal cortex ablations in cats and kittens: Passive avoidance. *Exp Neurol* 1980;68:335–345.
19. Chelune GJ, Ferguson W, Koon R, et al: Frontal lobe disinhibition in attention deficit disorder. *Child Psychiatry Hum Dev* 1986;16:221–234.
20. Trommer BL, Hoeppner J-AB, Zecker SG: The go–no go test in attention deficit disorder is sensitive to methylphenidate. *J Child Neurol* 1991;6(Suppl):S126–S129.
21. Lou HC, Henriksen L, Bruhn P: Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Arch Neurol* 1984;41:825–829.
22. Lou HC, Henriksen L, Bruhn P, et al: Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch Neurol* 1989;46:48–52.
23. Hynd GW, Semrud-Clikeman M, Lorys AR, et al: Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. *Arch Neurol* 1990;47:919–926.
24. Hynd GW, Semrud-Clikeman M, Lorys AR, et al: Corpus callosum morphology in attention deficit hyperactivity disorder. *J Learn Disabil* 1991;24:141–146.
25. Wechsler D: *Wechsler Intelligence Scale for Children–Revised.* New York, Psychological Corporation, 1974.
26. Oldfield RC: The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* 1971;9:97–113.
27. Puig-Antich J, Chambers W: *The Schedule for Affective Disorders and Schizophrenia.* New York, New York State Psychiatric Institute, 1978.
28. Pelham WE, Atkins MS, Murphy HA: Attention deficit disorder with and without hyperactivity, in Pelham WE (ed): *DSM*

III Category of Attention Deficit Disorders. Los Angeles, American Psychological Association, 1981.
29. Achenbach T: *Manual for the Child Behavior Checklist and Revised Behavior Profile.* Burlington, VT, Department of Psychiatry, University of Vermont, 1983.
30. Hynd GW, Lorys AR, Semrud-Clikeman M, et al: Attention deficit disorder without hyperactivity (ADD/WO): A distinct behavioral and neurocognitive syndrome. *J Child Neurol* 1991;6(Suppl):S35–S41.
31. Spitzer RJ, Cohen J, Fleiss JL, Endicott J: Quantification of agreement in psychiatric diagnosis. *Arch Gen Psychiatry* 1967;17:83–87.
32. Witelsen SF: Structural correlates of cognition in the human brain, in Scheibel AB, Wechsler AF (eds): *Neurobiology of Higher Cognitive Function.* New York, Guilford Press, 1990, pp 167–183.
33. Witelsen SF, Kigar DL: Asymmetry in brain follows asymmetry in anatomical form: Gross, microscopic, postmortem, and imaging studies, in Boller F, Grafman J (eds): *Handbook of Neuropsychology,* Vol 1. Amsterdam, Elsevier, 1988, pp 111–142.
34. Weinberger DR, Luchins DJ, Morihisa J, Wyatt RJ: Asymmetrical volumes of the right and left frontal and occipital regions in the human brain. *Neurology* 1982;11:97–100.
35. Hynd GW, Semrud-Clikeman M: Dyslexia and brain morphology. *Psychol Bull* 1989;106:447–482.
36. Mendez MF, Adams NL, Lewandowski KS: Neurobehavioral changes associated with caudate lesions. *Neurology* 1989;39: 349–354.
37. Richfield EK, Twyman R, Berent S: Neurological syndrome following bilateral damage to the head of the caudate nuclei. *Ann Neurol* 1987;22:768–771.
38. Glick SD: Cerebral lateralization in the rat and tentative extrapolutions to man, in Myslobodsky MS (ed): *Hemisyndromes: Psychobiology, Neurology, Psychiatry.* New York, Academic Press, 1983, pp 7–26.
39. Ross DA, Glick SD, Meibach RC: Sexually dimorphic cerebral asymmetries in 2-deoxy-D-glucose uptake during postnatal development in the rat: Correlations with age and relative brain activity. *Dev Brain Res* 1982;3:341–347.
40. Voeller KKS: The neurological basis of attention deficit hyperactivity disorder. *J Child Neurol* 1991;6(Suppl):S49–S65.
41. Ranga Krishnan K, Husain MM, McDonald WM, et al: In vivo stereological assessment of caudate volume in man: Effect of normal aging. *Life Sci* 1990;47:1325–1329.
42. Huttenlocher PR: Morphometric study of the human cerebral cortex development. *Neuropsychologia* 1990;28:517–529.
43. Swanson JM, Posner M, Potkin S, et al: Activating tasks for the study of visual-spatial attention in ADHD children: A cognitive anatomic approach. *J Child Neurol* 1991;61(Suppl): 117–125.
44. Filipek P, Kennedy DN, Caviness VS, et al: Magnetic resonance imaging-based brain morphometry: Development and application to normal subjects. *Ann Neurol* 1989;25:61–67.
45. Steinmetz H, Volkmann J, Jancke L, Freund H-J: Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers. *Ann Neurol* 1991;29: 315–319.