Putamen Lesions and the Development of Attention-Deficit/Hyperactivity Symptomatology

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ABSTRACT

Objective: To investigate the association between focal stroke lesions of the putamen and either attention-deficit/hyperactivity disorder or traits of the disorder (ADHD/Traits). **Method:** Twenty-five children with focal stroke lesions were studied with standardized psychiatric assessments and anatomic brain magnetic resonance imaging. The pattern of lesion overlap in subjects with ADHD/Traits was determined. **Results:** Fifteen of 25 subjects had ADHD/Traits. The densest area of overlapping lesions ($n = 7$) in subjects with ADHD/Traits included the posterior ventral putamen. The median lesion volume was 9.7 cm^3, and the distribution was highly skewed. Lesion volume was not associated with ADHD/Traits. Therefore the following analyses focused on the 13 subjects with lesions < 10 cm^3: ADHD/Traits were exhibited in 6/7 subjects with putamen lesions versus 2/6 with no putamen lesions (Fisher exact test $p = .1$). Half (4/8) of the subjects with ADHD/Traits had overlapping lesions encompassing the posterior ventral putamen. None of the 5 subjects without ADHD/Traits had lesions in this empirically derived region of interest (Fisher exact test $p = .1$). **Conclusions:** Lesions within the dopamine-rich ventral putamen, which is part of the ventral or limbic striatum, tended to increase the risk of ADHD/Traits. ADHD/Traits may therefore be a disinhibition syndrome associated with dysfunction in this cortical-striato-thalamocortical loop. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(5):563–571. **Key Words:** attention-deficit/hyperactivity disorder, childhood stroke, putamen.

Focal brain lesions caused by cerebrovascular accidents in prenatal and postnatal child development may provide an elegant and previously untried vehicle in the study of brain–behavior relationships. This methodology may be particularly fruitful in the study of attention-deficit/hyperactivity disorder (ADHD), which has long been recognized as evidence of brain disease when it occurs in patients with brain insults such as encephalitis lethargica (Ebaugh, 1923) and epilepsy (Ounsted, 1955). ADHD affects 6% of school-age children (Szatmari et al., 1989), but its neurobiological basis is as yet undetermined. Structural and functional imaging studies have implicated dysfunction of prefrontal cortical-striatal-pallidal pathways and the cerebellar vermis (Castellanos et al., 2001; Ernst et al., 1997; Teicher et al., 2000; Vaidya et al., 1998), with the basal ganglia primarily involved and the frontal lobe variably involved (Hendren et al., 2000). The basal ganglia region is by far the most common site of cerebral infarction in children (Roach and Riela, 1995a), and the resulting lesions frequently involve the putamen, which, together with the caudate, constitutes the striatum (Afifi and Uc, 1998). Thus, we hypothesized that focal lesions of the putamen would be related to ADHD and traits of the disorder (this combined group is referred to hereafter as ADHD/Traits).

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METHOD

The study design was cross-sectional in nature and included 25 children with a history of a single stroke. There were 16 males, 23 white and 2 biracial children. Age means (SD) of subjects were 11.5 (4.0) years. Assent from the child and written consent from parents/guardians was obtained in accordance with the institutional review board approved protocol. Inclusion criteria were: (1) neuroimaging documentation of the presence of a focal, nonrecurrent and nonprogressive supratentorial brain parenchymal lesion caused by stroke before age 14; (2) aged 5–19 years at the assessment; (3) ≥1 year since stroke; and (4) English as first language. The following exclusions were applied: (1) neonatal bleeds (e.g., intraventricular hemorrhages, germinal matrix hemorrhages) potentially associated with prematurity; (2) neonatal watershed infarcts associated with hypoxia (3) hemoglobinopathies; (4) progressive neurometabolic disorders; (5) Down syndrome and other chromosomal abnormalities; (6) malignancy; (7) congenital hydrocephalus; (8) shunts; (9) congenital and acquired central nervous system infections; (10) clotting factor deficiency; (11) stroke in a pregnant minor; (12) transplant status; (13) cerebral cysts; (14) trauma; (15) transient ischemic attack; (16) moya moya; (17) severe and profound mental retardation; (18) quadriplegia, triplegia, or diplegia diagnoses; (19) syndromatic vascular malformations (excluding arteriovenous aneurysm ruptures); (20) systemic lupus erythematosis; and (21) multiple lesions (unless in close proximity).

A pediatric neurologist (K.M.) supervised a record review guided by *ICD-9* codes (US Department of Health and Human Services, 1994) for stroke and congenital cerebral palsy. Thirty stroke subjects and 30 individually matched orthopedic controls were originally studied in a larger study (Max et al., 2002); however, this lesion-behavior correlates manuscript included only 25 of the stroke subjects. The 5 stroke subjects who were dropped from the analyses included 1 subject who was found to have subtle bilateral lesions only on the research MRI, 3 subjects who did not undergo a research MRI, and 1 subject who had prestroke ADHD. Thus 25 subjects with single stroke lesions (confirmed by the research MRI) and no prestroke ADHD (confirmed by the research psychiatric assessment) were included the present study. They included 16 subjects who acquired their lesions prenatally or up to age 12 months and 9 who acquired their lesions after 1 year of age. Mechanisms of stroke were occlusive in 19 cases and hemorrhagic in 6 cases. Etiology included 13 idiopathic occlusive cases, 4 cases related to congenital heart disease (3 after cardiac surgery or catheterization and 1 after varicella infection), 1 case possibly linked to comorbid ulcerative colitis, 1 case following a varicella infection, 5 cases of arteriovenous malformation rupture, and 1 idiopathic hemorrhagic case. Both cases associated with varicella infections were presumed to be due to vasculitis, and there was no evidence for encephalitis (Roach and Riela, 1995b). The distribution of lesions included 7 cases of predominantly putamen lesions, 7 large middle cerebral artery (MCA) distribution infarcts including deep gray structures, 8 cases of smaller MCA distribution frontotemporal or temporoparietal lesions sparing the deep gray (including 2 focal anterior lateral temporal lobe lesions), and 3 cases of parietal or parieto-occipital strokes (Fig. 1).

Psychiatric Assessment

DSM-IV psychiatric diagnoses (American Psychiatric Association, 1994) were derived by using a semistructured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL is an integrated parent-child interview that generates diagnoses based on a clinician synthesizing data collected from parent and child separately, querying present and lifetime symptoms as well as providing data regarding the timing of symptom onset in relation to the stroke. If subjects have significant symptoms on questions for a particular syndrome in a K-SADS-PL screen interview, a corresponding K-SADS-PL supplementary interview module is completed to clarify the diagnosis.

The outcome measures were the diagnoses of ADHD and ADHD traits. This approach recognized the dimensional nature of ADHD symptomatology (Levy et al., 1997). The diagnosis of ADHD was made when the symptom complex resulted in clinically significant impairment, even after considering overall developmental level of the child, and was not based simply on symptom counts. The ADHD subtypes (combined, predominantly inattentive, predominantly hyperactive/impulsive, and not otherwise specified) were applied only to subjects with a clinically significant ADHD syndrome. The designation of ADHD traits was given to subjects with a subsyndromal condition. ADHD traits were defined a priori as at least three of four symptoms in the screening interview for ADHD rated as positive but "subthreshold," or at least one screener question rated as "threshold" and at least 5 additional symptoms on the supplementary ADHD interview rated as "subthreshold" or "threshold." The one stroke subject with resolved ADHD (see below) was considered a "case" because brain plasticity can lead to compensatory processes or recovery.

A board-certified child and adolescent psychiatrist (J.E.M), who was blind to the imaging data, administered all interviews. All interviews were videotaped. Six interviews (from the original 30 stroke subject interviews) were selected randomly and rated by a child psy-

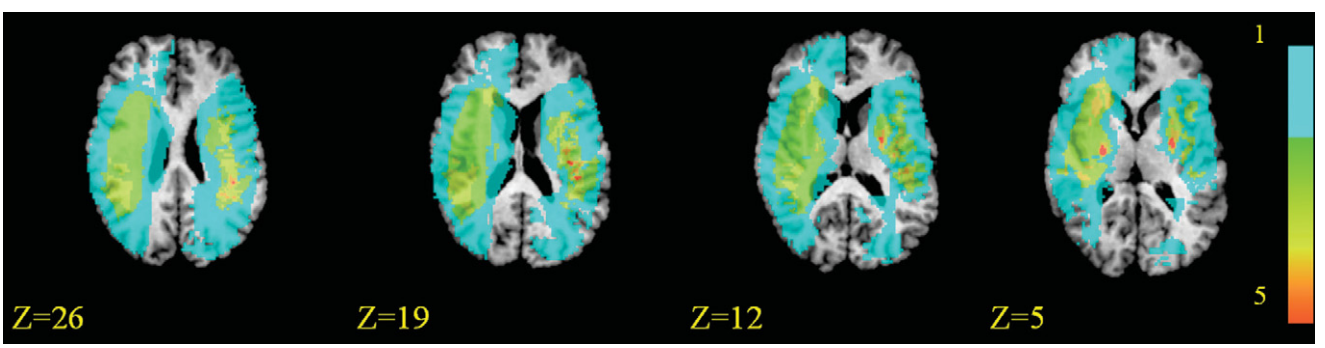

Fig. 1 Cumulative distribution of lesions in all subjects (n = 25). Increasing density of lesion overlap (number of subjects) is demonstrated by color coding from blue, green, yellow, to red. Lesions are superimposed on axial slices of a representative brain in Talairach space (Kochunov et al., 2001). The value of Z is an indication of the location of the axial slice: Z at the level of the anterior commissure/posterior commissure line is zero, and +74 and –74 are at the most superior and most inferior axial sections of the brain, respectively.

chiatrist (B.A.M.R.) to assess interrater reliability. Agreement regarding the presence of ADHD, ADHD subtype, ADHD traits, or no ADHD/Traits was 6/6 (100%) or 5/5 (100%) for those 25 subjects who were the focus of this manuscript.

Image Acquisition and Analysis

MRI scans were obtained (T1-weighted volumetric mode, SPGR/40°, TR/TE = 2600/7 msec, NEX = 2, X/Y/Z = 1 × 1 × 1.5-mm thickness with no skip; T2-weighted dual-echo, FSE/V, TR = 2350, TE = 17/102, NEX = 1, X/Y/Z = 1 × 1 × 1.5-mm thickness with 1 mm skip). All images were globally spatially normalized through transformation to the Talairach coordinate system by using SN software (Lancaster et al., 1995) (available at *http://ric.uthscsa.edu/projects/*).

A neurologist (F.F.M.) marked the lesions on hard copy films. Guided by these lesion markings, an experienced neuroanatomist "painted" each lesion using a three-dimensional brain morphometrics package (Paus et al., 1996) under supervision of P.T.F. and J.L.L. Lesion volume was computed in native and Talairach coordinate systems for intersubject differences in brain size (Lancaster et al., 1997). The computerized Talairach atlas (Lancaster et al., 2000) (available at *http://ric.uthscsa.edu/projects/*) was used to obtain anatomical labels for painted lesions. The Talairach Region Extraction (TREX) software was used to calculate volumes of anatomical structures that were covered by painted lesions. A representative brain in Talairach space that was developed from 20 normal subjects was used to demonstrate anatomical locations of painted lesions (Kochunov et al., 2001).

WISC-III

Prorated Full Scale IQ was derived from a prorated Performance IQ (Picture Arrangement, Block Design, and Coding subtests) and a prorated Verbal IQ (Information and Similarities subtests) (Wechsler, 1991). We applied the upper age-limit norms for this test to the few subjects who were above the age range for published norms.

Family Psychiatric History

The Family History Research Diagnostic Criteria interview (Andreasen et al., 1977) was conducted in most cases by a trained research assistant and in other cases by J.E.M. Criteria were modified to conform with *DSM-III-R* criteria (American Psychiatric Association, 1987). At least one parent per family acted as the informant.

Medical History

Medical history data were systematically collected (e.g., history of seizures and surgeries, childhood illnesses, developmental milestones).

Statistical Analysis

The groups of subjects with or without ADHD/Traits were compared with independent sample *t* tests for continuous variables and with the Fisher exact test for categorical variables.

RESULTS

Twenty-five subjects without evidence of prestroke ADHD who underwent research MRI scans that confirmed single focal lesions were the focus of this study. Fifteen of these 25 subjects had either ADHD or traits of the disorder (ADHD/Traits). Eleven subjects were diagnosed with current ADHD (5 inattentive, 4 not otherwise specified, 1 hyperactive/impulsive, and 1 combined subtype). Three subjects had current ADHD traits at the time of the assessment. One additional subject had a resolved ADHD not-otherwise-specified diagnosis. Subjects with the not-otherwise-specified subtype had predominantly inattentive symptoms. However, all but 1 subject with ADHD/Traits had at least some hyperactivity/impulsivity symptomatology. Of all subjects with ADHD/Traits, only 2 had ever received specific treatment for this problem. Among subjects with ADHD/Traits there were no distinctive patterns across gross lesion categories (predominantly putamen, large MCA distribution infarcts including deep gray structures, smaller MCA distribution frontotemporal or temporoparietal infarcts sparing the deep gray, and parietal or parieto-occipital infarcts) in terms of ADHD subtype and severity or comorbid psychiatric disorders.

We have illustrated the cumulative distribution of cerebrovascular accident lesions in the 25 subjects (Fig. 1). The distribution is extremely widespread because of large lesions in several subjects. We have also illustrated the distribution of lesions according to whether or not the subjects were diagnosed with ADHD/Traits (Fig. 2, A and B). The densest area of overlapping lesions (n = 7) in subjects with ADHD/Traits includes the posterior ventral putamen. For subjects without ADHD/Traits, the densest area of overlapping lesions (n = 6) was in the insula area.

The presence of ADHD/Traits in subjects was not associated with lesion volume (mean [SD]: ADHD/Traits 35.5 [50.7] cm^3 versus no ADHD/Traits 48.3 [82.2] cm^3, t = .48, df = 23, $p > .6$). A nonparametric analysis yielded a similar nonsignificant result. The median lesion volume was 9.7cm^3. This suggested that the syndrome was not simply a function of nonspecific neuronal damage.

Table 1 displays medical characteristics including lesion, etiology, complications, treatment, and intellectual outcome. Table 2 outlines personal and family psychiatric characteristics. Both tables are arranged in ascending order regarding lesion volume. Because ADHD/Traits was not merely a function of nonspecific neuronal damage, we elected to focus on subjects (n = 13) with small lesions (<10 cm^3) to decrease the "noise" that is inherent in lesion-behavior correlates of large lesions. This noise may be related to lesions in complex neuronal pathways that can change the behavioral manifestation of (functional or structural) smaller structure lesions within the networks. Examples of this phenomenon include capsulotomy for obsessive-compulsive disorder (Lippitz et al., 1999) and

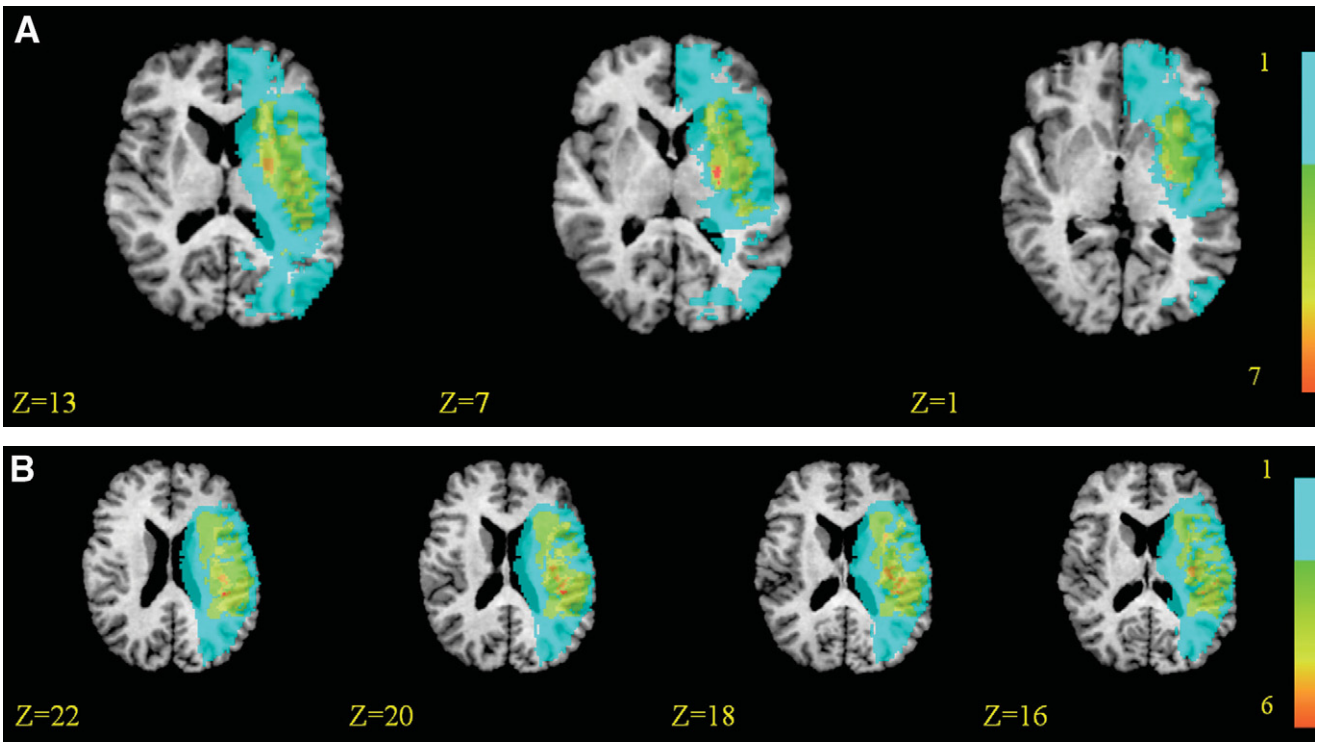

Fig. 2 Distribution of lesions according to classification of attention-deficit/hyperactivity disorder or traits of the disorder (ADHD/Traits) (all subjects; n = 25). Figure 2 (A and B) illustrates the increasing density of lesion overlap (similar to Fig. 1) in subjects with ADHD/Traits (n = 15) and subjects without ADHD/Traits (n = 10), respectively. All lesions are represented on the right to maximize lesion overlap in this relatively small sample.

pallidotomy for Parkinson's disease (Obeso et al., 2000). We have shown (Fig. 3) the distribution of these smaller lesions in areas in which there was overlap of at least two subjects with or without ADHD/Traits respectively, superimposed on a three-dimensional rendering of an average brain (Kochunov et al., 2001). The area of greatest lesion overlap (n = 4) for ADHD/Traits is again seen to include the posterior ventral putamen.

We analyzed the sample of subjects with smaller lesions to test our hypothesis that focal lesions of the putamen would be significantly associated with ADHD/Traits. Among the 13 subjects with smaller lesions, 7 had putamen lesions and 6 had other lesions that did not involve the putamen (Table 1). Eight of these 13 youths met the defined criteria for ADHD/Traits. Six of 7 subjects with putamen lesions versus 2/6 with no putamen lesions had ADHD/Traits (Fisher exact test p = .1). We then conducted an additional analysis to investigate whether the empirically derived region of densest overlap (n = 4) of ADHD/Traits subjects was significantly associated with ADHD/Traits. This analysis revealed that 4/8 subjects with ADHD/Traits had their lesions in this region of interest, versus 0/5 subjects without ADHD/Traits (Fisher exact test p = .1). Thus the subject with a putamen lesion who did not have ADHD/Traits did not overlap this region of densest overlap. Another subject with ADHD/Traits failed to overlap this region of interest by only 1 mm. Thus, despite the small sample and weak statistical power in these analyses, we found a statistical trend in support of our hypothesis that lesions of the putamen were related to ADHD/Traits.

Exceptional Cases

Closer scrutiny of exceptional subjects from the entire cohort (n = 25) can be informative.

ADHD/Traits and Involvement of Areas Other Than Putamen. Among the subjects with smaller lesions, the two ADHD/Traits subjects without putamen lesions had nonoverlapping lesions in the inferior temporal gyrus. The latter area corresponds roughly to area TEO, which, when lesioned in primates, has specifically disrupted attentional mechanisms (De Weerd et al., 1999). Primates lesioned in a related portion of inferior temporal cortex (area TE) have behavioral disturbances resembling ADHD

TABLE 1
Pediatric Stroke: Demographics, Neurological Status, and Cognitive Status

ID	Age (yr)	Sex	Age at Stroke	Lesion Volume (cm^3)	Lesion Location	Laterality	Mechanism	Etiology	Seizures History	Seizure Control	AED	% Right-Handed	FSIQ
Lesion volume $<10^3$													
1	17	M	5	0.21	Putamen	R	Occ	Varicella zoster	Yes	No Seiz	None	100	84
2	14	M	Pre	0.27	Putamen	L	Occ	Idiopathic	No	NA	NA	0	89
3	8	F	4	0.45	Putamen	R	Occ	Idiopathic	No	NA	NA	100	95
4	7	M	Pre	0.56	Fr-T/Temp-P	R	Occ	Idiopathic	No	NA	NA	90	111
5	15	M	10	0.58	Temporal	L	Occ	Ulcerative colitis	No	NA	NA	30	97
6	6	M	3:05	0.70	Putamen	R	Occ	Idiopathic	No	NA	NA	40	88
7	13	F	Pre	1.03	Putamen	L	Occ	Idiopathic	Yes	No Seiz	None	0	98
8	14	F	Pre	1.35	Putamen	L	Occ	Idiopathic	No	NA	NA	0	63
9	5	F	1 day	1.75	Temporal	L	Hem	Idiopathic	Yes	No Seiz	Carbamazepine	90	77
10	14	M	2.5 mo	3.00	Fr-T/Temp-P	R	Occ	Cardiac: surgery	Yes	No Seiz	None	100	87
11	13	F	5	3.84	Fr-T/Temp-P	R	Hem	AVM	No	NA	NA	100	105
12	9	M	8	6.40	Putamen	R	Occ	Cardiac: varicella zoster	No	NA	NA	100	90
13	10	M	1 day	9.66	Parieto-Occip	R	Occ	Cardiac: surgery	No	NA	NA	100	88
Lesion volume $>10^3$													
14	6	M	Pre	18.32	Parietal	L	Occ	Idiopathic	No	NA	NA	0	75
15	12	F	9	21.79	Fr-T/Temp-P	R	Hem	AVM	No	NA	NA	100	130
16	8	M	Pre	22.86	Fr-T/Temp-P	R	Occ	Idiopathic	No	NA	NA	100	102
17	8	M	5	39.26	MCA	L	Hem	AVM	No	NA	NA	0	75
18	19	M	11	42.24	MCA	L	Hem	AVM	Yes	No Seiz	None	100	108
19	11	M	Pre	43.17	MCA	R	Occ	Idiopathic	No	NA	NA	100	64
20	12	F	1 day	54.47	Fr-T/Temp-P	L	Hem	Idiopathic	No	NA	NA	0	82
21	11	M	Pre	66.93	Parieto-Occip	R	Occ	Idiopathic	Yes	Controlled	Phenytoin	90	83
22	19	F	Pre	124.61	MCA	L	Occ	Idiopathic	Yes	Controlled	Carbamazepine; primidone	10	59
23	16	M	9 mo	143.78	MCA	R	Occ	Cardiac: catheterization	Yes	Controlled	Carbamazepine	100	44
24	8	M	Pre	150.73	MCA	L	Occ	Idiopathic	No	NA	NA	0	64
25	13	F	Pre	256.82	MCA	L	Occ	Idiopathic	No	NA	NA	0	95

Note: AED = antiepileptic drug; AVM = arteriovenous malformation; Fr-T/Temp-P = frontotemporal/temporoparietal; Hem = hemorrhagic; L = left hemisphere; M = male; F = female; MCA = middle cerebral artery; NA = not applicable; Occ = occlusive; Parieto-Occip = parieto-occipital; Pre = prenatal; R = right hemisphere; Seiz = seizure; FSIQ = Full Scale IQ.

TABLE 2
Pediatric Stroke: Child and Family ADHD Characteristics

ID	First-Degree Relative With ADHD	Presence or History of ADHD or ADHD Traits	ADHD Threshold Symptoms (Inattentive, Hyperactive)	ADHD Subthreshold Symptoms (Inattentive, Hyperactive)
Lesion volume $<10^3$				
1[a]	No	Present[b]	2, 0	0, 3
2[a]	No	—	0, 0	1, 0
3[a]	No	Present	9, 0	0, 5
4	No	—	0, 0	0, 0
5	Unknown	Present	9, 0	0, 1
6[a]	No	Present	4, 4	2, 3
7[a]	No	Present[c]	4, 0	2, 1
8[a]	Unknown	Present	9, 7	0, 1
9	No	Present	5, 8	3, 1
10	No	—	0, 0	0, 0
11	No	—	0, 0	0, 0
12[a]	Yes	Present	5, 1	3, 0
13	No	—	0, 0	0, 0
Lesion volume $>10^3$				
14	Unknown	Present[b]	0, 0	2, 1
15	No	—	0, 0	0, 0
16	No	—	0, 0	0, 0
17	No	—	0, 0	1, 0
18	No	Present	7, 0	0, 1
19	No	Present	4, 0	0, 0
20	No	Present	7, 0	1, 2
21	No	Present	9, 0	0, 2
22	No	—	0, 0	0, 0
23	Yes	Present[b]	3, 0	0, 1
24	No	Present	3, 2	1, 0
25	No	—	0, 0	0, 0

Note: ADHD = attention-deficit/hyperactivity disorder.
[a] Youths with predominantly putamen lesion.
[b] Traits of ADHD only.
[c] ADHD, resolved.

(Merjanian et al., 1989). Furthermore, there is evidence that neonatal temporal limbic damage can affect striatal dopamine receptors (Heinz et al., 1999); thus, these lesions and putamen lesions may result in a common pathophysiology for ADHD/Traits.

Predominantly Putamen Lesions Without ADHD/Traits. There was only one of seven subjects with a lesion predominantly involving the putamen who did not exhibit ADHD/Traits. This subject's lesion was the second smallest in the cohort (0.27 cm^3) and overlapped that of one subject with ADHD/Traits who had one of the larger lesions (>10 cm^3). The former subject was one of only two subjects in the entire cohort who had ADHD symptomatology but did not meet criteria for ADHD traits. The other subject with this minimal but measurable ADHD symptomatology also had the putamen component of his much larger lesion (39.26 cm^3) overlapping those of six other subjects with ADHD/Traits.

Characteristics of ADHD/Traits Subtypes. The only ADHD/Traits subject with no hyperactivity/impulsivity symptoms at all had the putamen component of his large lesion (43.17 cm^3) overlap those of five other ADHD/Traits subjects. The only subject with the combined type of ADHD had her 1.35 cm^3 lesion in the superior anterior portion of the putamen overlapping those of five other subjects with ADHD/Traits. Finally, the only subject with the hyperactive/impulsive type had a small lesion limited to the inferior temporal gyrus.

Other Correlates of ADHD/Traits

Although they were unrelated to our hypothesis, we examined other variables of general interest that could potentially influence the presentation of ADHD/Traits in the whole cohort ($n = 25$). Respectively, the ADHD/Traits and no ADHD/Traits groups did not differ in terms of: age at assessment (mean [SD]: 11.3 [4.3] versus 11.8 [3.7];

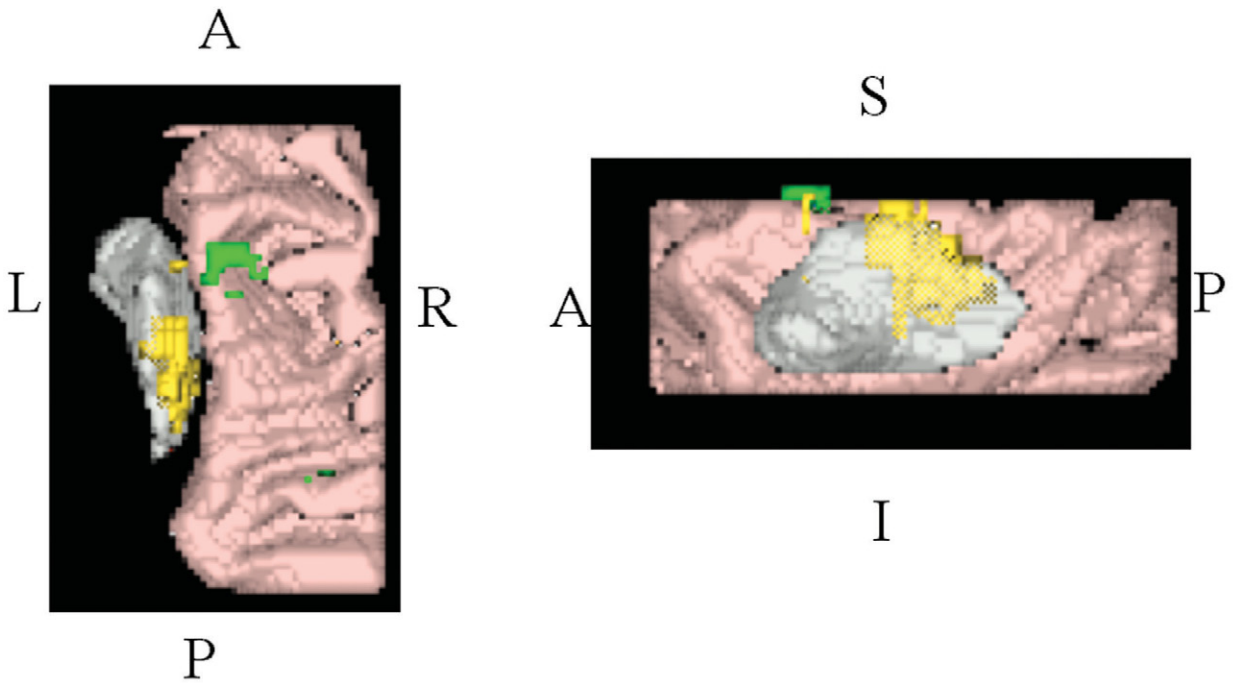

Fig. 3 Three-dimensional representation of lesion distribution according to classification of attention-deficit/hyperactivity disorder or traits of the disorder (ADHD/Traits) (only lesions < 10cm^3; n = 13). Subjects' overlapping lesions are superimposed on a three-dimensional rendering of the right putamen and insula cortex generated from a representative brain (Kochunov et al., 2001). Intervening white matter and other structures have been removed graphically for clarity. The image on the left illustrates an axial view from inferior. The image on the right illustrates a sagittal view of the right hemisphere. Green and yellow are the keys for an overlap of at least two subjects with no ADHD/Traits or ADHD/Traits, respectively. A = anterior; I = inferior; L = left; P = posterior; R = right; S = superior.

t = .28, df = 23, p > .78), age of lesion onset (ADHD/Traits occurred in 9/16 subjects with lesions occurring prenatally and before 1 year of age versus 6/9 subjects with lesions occurring thereafter; Fisher exact test > .69), gender (10/16 males versus 5/9 females had ADHD/Traits; Fisher exact test = 1.00), lesion laterality (7/13 right versus 8/12 left had ADHD/Traits; Fisher exact test > .68), seizure activity history (9/17 subjects with no seizure activity versus 6/8 with seizure activity had ADHD/Traits; Fisher exact test > .40), family history of ADHD in first-degree relatives (2/2 subjects with a family history versus 10/20 without a family history had ADHD/Traits; Fisher exact test > .48), and family history of ADHD/ADHD symptoms in first- or second-degree relatives (3/6 subjects with a family history versus 9/16 without a family history had ADHD/Traits; Fisher exact test = 1.00).

Subjects with ADHD/Traits had a significantly lower Verbal IQ (Wechsler, 1991) compared with those without ADHD/Traits (mean [SD]: 84.6 [16.9] versus 100.2 [15.1]; t = 2.36, df = 23, p < .03). There was no significant difference in Performance IQ (Wechsler, 1991) (mean [SD]: 79.9 [18.1] versus 88.7 [23.4]; t = 1.06, df = 23, p > .3) nor in Full Scale IQ (Wechsler, 1991) (mean [SD]: 80.8 [16.8] versus 94.1 [19.6]; t = 1.82, df = 23, p > .08).

DISCUSSION

This correlational study demonstrated that a striatal lesion involving the posterior ventral putamen may lead to the manifestation of ADHD/Traits in the absence of caudate damage. This is interesting because striatal findings emanating from structural imaging studies of ADHD have emphasized the caudate nucleus, usually (but not always) reporting decreased volume, and often with contradictory results regarding laterality (Castellanos et al., 1996, 2001; Filipek et al., 1997; Hynd et al., 1993; for a review see Hendren et al., 2000). However, functional MRI (fMRI) and positron emission tomography (PET) studies have identified putamen differences in subjects with ADHD. One study found decreased activation in the caudate and putamen in subjects with ADHD during response inhibition tasks (Vaidya et al., 1998). Another fMRI study of ADHD reported significantly higher T2 relaxation time measures in the putamen bilaterally, but

not in the thalamus or caudate (Teicher et al., 2000). A PET study found that the lower regional cerebral glucose metabolic rate in the left subcortical regions of girls with ADHD was contributed to mainly by the anterior putamen (Ernst et al., 1997). Furthermore a study of childhood traumatic brain injury, complicated by characteristic diffuse axonal injury, reported a higher risk for ADHD associated with deep brain lesions specifically in the right putamen (Herskovits et al., 1999), as well as the thalamus and basal ganglia (Gerring et al., 2000).

The specific posterior ventral putamen region that tended toward a statistical association with ADHD in our study is not surprising. The dopamine-rich ventral putamen is part of the ventral (limbic) striatum that receives fibers from a number of sources, including the medial orbitofrontal cortex. ADHD may be an example of a disinhibition syndrome associated with a lesion in this cortical-striato-thalamocortical loop (Afifi and Uc, 1998). It is important to note that the ventral putamen is just one component of this loop and that ADHD may just as likely be related to lesions in other parts of this circuit. Furthermore, it is unlikely that dopamine dysfunction alone (related to putamen lesions and temporal limbic lesions) results in ADHD because there may be a role for other neurotransmitters in the pathophysiology of ADHD (Castellanos, 1997).

The study further showed that although hyperactivity/impulsivity was almost always present in subjects with ADHD/Traits, the syndrome was overshadowed by inattention symptoms. Our data suggest that inattention is closer to the core of the syndrome of ADHD, at least when it is preceded by a putamen lesion. This is consistent with adult case series that indicated that in addition to characteristic motor signs, short-term memory deficits were common after isolated putamen lesions (Giroud et al., 1997).

It will be important to expand upon this lesion study of childhood stroke in multiple sites to have enough statistical power to confirm the trend of association between putamen lesions and ADHD/Traits. Furthermore, it will be interesting to determine whether there are lesions typically not associated with ADHD/Traits, or other lesions such as cerebellar vermis, caudate, or inferior temporal gyrus lesions that may be associated with ADHD/Traits. As with many psychiatric syndromes, it is likely that the expression of ADHD/Traits is a final common behavioral expression of varied neuropathologies. Our findings, together with recent evidence of functional differences in the putamen of children with ADHD in the absence of brain lesions (Ernst et al., 1997; Teicher et al., 2000; Vaidya et al., 1998), strengthen the case that neural pathways involving this part of the striatum are important in the phenomenology of ADHD. In this sense. these findings are relevant to the broader problem of ADHD in the community because studying pathways that involve the putamen could be a fruitful avenue in clarifying pathophysiology and possible future definitive treatments.

Limitations

First, our main finding is a statistical trend. This is likely related to the sample size. Small sample size is characteristic of studies on childhood stroke, and this study represents one of the largest reports on this subject group. The likelihood that ADHD/Traits may be a final common behavioral expression of varied neuropathologies results in statistical challenges. For example, in our sample, we have assumed that the two subjects with ADHD/Traits and inferior temporal gyrus lesions did not support our hypothesized behavior-lesion correlate and therefore reduced its statistical association. A follow-up study could incorporate inferior temporal gyrus lesions in the hypothesized relationship with ADHD/Traits. Second, the stroke sample is heterogeneous in etiology, and the developmental level of the children was broadly distributed at time of insult and assessment. This could affect the children's pattern of psychiatric symptomatology. Third, it is impossible to say with certainty which children, especially those with strokes before age 7 and those with a family history of ADHD, would have developed ADHD/Traits regardless of their stroke. However, in the larger controlled study (Max et al., 2002), the stroke group had significantly more children with lifetime ADHD/Traits than an individually matched control group with non-CNS prenatal or postnatal onset medical conditions (15/25 versus 6/25; Fisher exact test < .03; unpublished data) despite a similar rate of positive family history of ADHD or ADHD symptoms in first- and second-degree relatives (6/22 versus 9/25; Fisher exact test > .50; unpublished data). Fourth, the stroke sample is not an epidemiological sample but rather represents the results of a case finding strategy of children diagnosed with stroke at a university teaching hospital. However, the children were not referred for their psychopathology but rather for neurological diagnosis, treatment for cardiac problems, or orthopedic procedures for residual neurologically based musculoskeletal problems. Fifth, the psychiatrist

did not have the benefit of a teacher's report in reaching diagnostic decisions.

Clinical Implications

Children with a history of stroke should be screened for ADHD, especially because clinically significant inattentive symptoms are common and may be frequently overlooked. Consideration of the range of treatments should be made in collaboration with a pediatric neurologist and/or a pediatric cardiologist because of the potential risk of vascular or cardiac side effects.

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