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When does Huntington's disease begin?

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Abstract

Recent studies have detected basal ganglia atrophy in clinically asymptomatic persons with the genetic mutation that causes Huntington's disease (HD). Whether reductions in caudate and putamen volume on MRI scans are associated with changes in cognitive and neurologic functioning was examined in 13 healthy adults with the IT-15 mutation. Reduced striatal volume was found to correlate with greater neurologic (largely motor) impairment, slower mental processing speed, and poorer verbal learning, although none of the participants met even liberal criteria for clinical diagnosis of HD. These correlations are strikingly similar to those observed in symptomatic HD patients, possibly reflecting the earliest manifestations of disease. (*JINS*, 1998, *4*, 467–473.)

Keywords: Huntington's disease, Genetics, Presymptomatic testing, MRI scans, Cognitive tests

INTRODUCTION

Huntington's disease (HD) is a degenerative brain disorder characterized primarily by death of neurons in the caudate nucleus and putamen (VonSattel et al., 1985). Patients with this genetically transmitted disease invariably develop a dementia syndrome, typically considered "subcortical" dementia (Brandt & Butters, 1986, 1996). Even early in the course of HD, deficits in memory retrieval, executive functioning, and psychomotor speed are prominent (Brandt, 1994; Brandt & Bylsma, 1993). Several independent studies of HD patients have revealed an association between atrophy of the striatum and impairments in learning and memory, mental processing speed, and cognitive flexibility (Bamford et al., 1995; Berent et al., 1988; Hasselbalch et al., 1992; Starkstein et al., 1992). Furthermore, size of the neostriatum, as revealed by brain imaging, has been shown to correlate positively with functional capacity (Shoulson et al., 1982) and negatively with neurologic impairment (Harris et al., 1996; Starkstein et al., 1988). In spite of a large and growing literature on neuropsychological and brain anatomic correlations in symptomatic HD patients, no study to date has attempted to examine these characteristics in clinically healthy persons who carry the genetic mutation for HD.

Since the discovery of the first polymorphic DNA marker linked to the HD gene locus (Gusella et al., 1983) and the more recent identification of the trinucleotide repeat mutation at IT-15 (Huntington's Disease Collaborative Research Group, 1993), it has become possible to study clinically unaffected persons who carry the HD mutation and who will eventually become ill. Consistent with previous studies (Grafton et al., 1990, 1992; Hayden et al., 1987), Aylward et al. (1994) demonstrated that MRI volumes of the caudate head, putamen, and globus pallidus are significantly smaller in healthy mutation carriers than noncarriers, even after controlling for age, total brain volume, and presence of minor neurologic signs. Preliminary data from our HD Center also suggest that the striatum continues to shrink as persons approach the likely time of symptom onset (i.e., diagnosable illness) (Aylward et al., 1996).

Although most well-controlled studies of asymptomatic HD mutation carriers have detected no abnormalities in cognitive test performance (Blackmore et al., 1995; Campodonico et al., 1996; Giordani et al., 1995; Rothlind et al., 1993; Strauss & Brandt, 1990), some studies do report impairments in mutation carriers (Diamond et al., 1992; Foroud et al., 1995; Jason et al., 1988). However, no study to date has examined the relationship between basal ganglia volumes and neuropsychological functioning. It may be rea-

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sonable to hypothesize that early atrophic changes in the striatum are associated with minor, subclinical alterations in cognitive and motor functioning. Recently, Campodonico et al. (1996) found that healthy mutation carriers who were nearing the likely age of onset of movement disorder showed minor declines in sustained attention and mental speed over a 2-year period, although their scores remained in the normal range. However, it is unclear whether these declines reflected early neuronal loss of the basal ganglia.

In the present study, we obtained brain MRI scans, standardized neurological examinations, and neuropsychological testing from healthy adults with and without the HD mutation. Our major aim was to determine whether volume reductions in the neostriatum are associated with minor alterations in neurologic and neuropsychological functioning in these individuals. If striatal atrophy is predictive of slower mental processing speed and deficits in learning and memory in symptomatic HD patients, a similar, albeit weaker, relationship might be expected among mutation carriers who are not yet overtly symptomatic.

METHOD

Research Participants

A total of 26 clinically healthy adults in the Presymptomatic Testing Program of the Baltimore Huntington's Disease Project at the Johns Hopkins University School of Medicine participated in this study. They were all at risk for HD (by virtue of having an affected parent) and had testing for the expanded triplicate repeat in the "huntingtin" gene at IT-15. Participants testing positive for the mutation had more than 36 *CAG* repeats ("mutation-positive"), whereas those testing negative had fewer than 31 repeats ("mutation-negative"). All participants knew their genetic test results at entry to this study and were included only if they did not meet clinical criteria for HD (as judged by an experienced neuropsychiatrist or neuropsychiatric research nurse) on the basis of a standardized, quantified neurological examination (QNE; Folstein et al., 1983) and psychiatric interview (SADS-L; Endicott & Spitzer, 1978). The research protocol is described in detail elsewhere (Brandt et al., 1989, 1996).

Twenty-two of the original 27 participants (9 mutation-positive, 13 mutation-negative) who participated in Aylward et al. (1994) were included in this study by virtue of having clinical examinations and neuropsychological testing at the time of their scans. Four additional participants were added. Thus, our sample consisted of 13 mutation-positive participants and 13 mutation-negative participants, group-matched on age and education.

Neuropsychological Tests

Neuropsychological tests were completed by participants at the time of MRI scanning. The tests were selected because of their demonstrated sensitivity to the dementia of HD (Brandt, 1991). They included the Symbol Digit Modalities Test (Smith, 1973), which assesses rapid mental coding; the Hopkins Verbal Learning Test (HVLT; Brandt, 1991; Brandt et al., 1992), which assesses verbal learning and memory; the Standardized Road Map Test of Directional Sense (Money, 1976) and Extrapersonal Orientation Test (Bylsma et al., 1992; Semmes et al., 1963), which assess left/right spatial orientation; the Stroop Color and Word Test (Stroop, 1935; Golden, 1978), which assesses response inhibition; and the Wisconsin Card Sorting Test (Berg, 1948; Heaton, 1981), which assesses hypothesis testing and conceptual reasoning.

Imaging Methods

MR images were obtained on a General Electric 1.5 Tesla Signa scanner, using a protocol identical to that described in previous articles (Aylward et al., 1994, 1996). A sagittal series was first obtained. A line connecting the anterior and posterior commissure (AC–PC line) was used for orientation of the remaining series. Proton-density (3,000/30/1) and T_2 (3,000/100/1) axial sections were simultaneously obtained through the region of the basal ganglia, parallel to the AC–PC line, with 3-mm-thick interleaved slices and 256×192 spatial resolution. A spoiled gradient acquisition in the steady state (SPGR) coronal series (TR = 35, TE = 5) was obtained throughout the entire brain, with 1.5-mm-thick slices, 0 gap, flip angle of 45° and 256×128 spatial resolution. All images were acquired using a field of view of 24 cm, archived on nine-track magnetic tape and then transferred to read/write optical disks. Analysis of images was performed on a Gateway 2000 workstation.

Measures were obtained for head of caudate, putamen, and globus pallidus. Proton-density images were added to the T_2-weighted images to enhance CSF spaces. Structures were measured using MEASURE, a custom graphics software program developed locally (Barta et al., 1997). Structure boundaries were outlined in each slice using a mouse-controlled cursor. For each structure, measurement began in the most inferior slice in which the caudate and putamen were clearly separated by the internal capsule. Measurement continued in a superior direction until the head of the caudate merged with the body of the caudate. The borders of the caudate were defined laterally by the anterior limb of the internal capsule and medially by the frontal horn or body of the lateral ventricle. The most superior slice in which the head of caudate was measured was the one below that in which the caudate head and body fused. The borders of the putamen were defined laterally by the external capsule. At more inferior levels, the medial borders of the putamen were defined by the globus pallidus; at more superior levels, the medial borders were defined by the internal capsule. The globus pallidus was defined laterally by the putamen and medially by the posterior limb of the internal capsule.

For each structure, areas within slices were calculated, summed across slices, and multiplied by slice thickness, resulting in an approximate structure volume. Striatal volume was calculated by adding the volumes of the caudate and putamen. Because of movement artifact, caudate and glo-

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bus pallidus volumes could not be calculated for two participants (1 mutation-positive, 1 mutation-negative). All measurements were made by one experienced technician, who was blind to genetic status and neuropsychological test performance. Interrater reliability and validity of the volumetric measurements have been demonstrated previously (Aylward et al., 1994).

Because the axial series did not include the entire brain, brain volumes were obtained from the SPGR coronal series. A semiautomated thresholding program was used to measure total brain area (brain + ventricular space) in every third image of the series. Areas were multiplied by slice thickness (1.5 mm) and then multiplied by 3 (to adjust for unmeasured slices), yielding approximate brain volumes. Eight participants (5 mutation-positive, 3 mutation-negative) did not have the SPGR coronal series throughout the entire brain; therefore total brain volumes could not be calculated for these individuals.

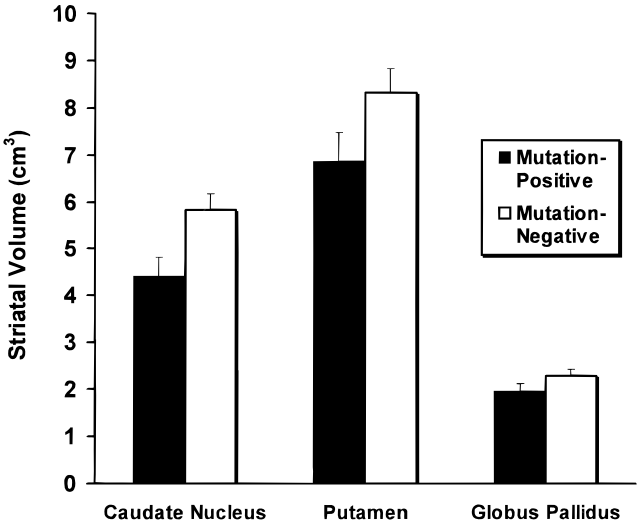

Fig. 1. Mean basal ganglia volumes (cm^3) of mutation-positive and mutation-negative presymptomatic groups.

RESULTS

Between-Group Comparisons

Mutation-positive and mutation-negative groups did not differ in sex distribution nor in mean age, years of education, estimated IQ, or total brain volume (see Table 1). Although mean QNE score for the mutation-positive group was significantly higher (i.e., showed greater neurologic abnormality) than that for the mutation-negative group, scores were well within the normal range for all participants. (In our clinic, new-onset HD patients typically obtain QNE scores above 20 when first diagnosed.) After careful examination, even the participant with a QNE score of 16 was judged not to meet clinical criteria for HD (Folstein et al., 1986). The next highest QNE score was 10. Nonetheless, to guard against the possibility that participants who may be already mildly symptomatic with HD are contributing to any group differences in basal ganglia volume, QNE score was used as a covariate in all analyses.

Mutation-positive and mutation-negative groups were compared on brain morphometric and cognitive characteristics using analysis of covariance and independent *t* tests (one-tailed). Because of the large number of statistical comparisons, α was set at .01 to minimize Type I statistical errors.

The raw basal ganglia volumes for the mutation-positive and mutation-negative groups are shown in Figure 1. After covarying for age and QNE score, significant group differences were found for both caudate [$F(1,21) = 9.2$, $p = .006$] and putamen [$F(1,22) = 9.4$, $p = .006$], but not globus pallidus [$F(1,21) = 0.1$, $p = .73$]. The findings were unaffected by covarying for total brain volume. After controlling for age and QNE, the two groups did not differ on any of the cognitive tests.

Correlates of Striatal Volume

To test the hypothesis that striatal atrophy is associated with poorer cognitive test performance and higher QNE scores, Pearson product–moment correlations were computed ($\alpha = .01$, one-tailed). QNE scores were subjected to a $\log_{10}$-transformation to reduce the skewness in their distribution. Volumes of the caudate head and putamen were added to

Table 1. Demographic and clinical characteristics of participant groups

Characteristic	Mutation-positive	Mutation-negative	*p*
N	13	13	—
Male/Female	5/8	4/9	.69
Age at study	35.5 (6.4)	40.0 (10.0)	.19
Education (yrs.)	14.3 (1.9)	14.1 (2.3)	.78
Estimated IQ[1]	109.5 (11.0)	108.4 (11.3)	.81
CAG repeat length	44.6 (2.7) range = 41–51	22.5 (1.3) range = 20–25	<.0001
Total brain volume (cm^3)	410.9 (26.5)	421.3 (37.5)	.26
Quantified Neurological Exam[2]	4.8 (4.4) range = 1–16	1.7 (2.6) range = 0–8	.03

[1]IQ estimate based on WAIS–R Vocabulary and Block Design subtests.
[2]Maximum score = 123.

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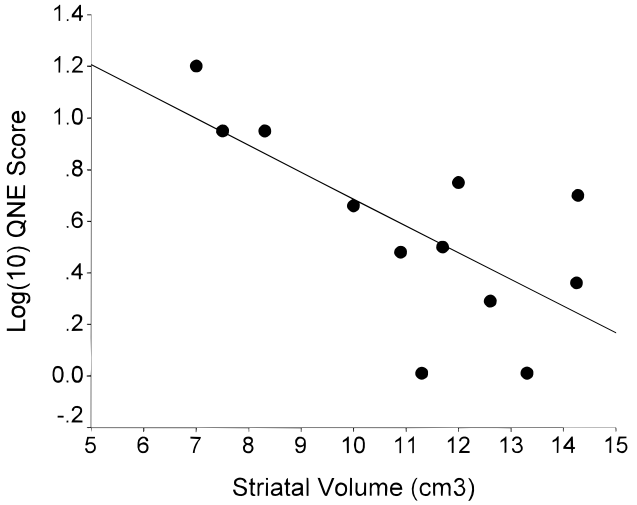

Fig. 2. Regression of $\log_{10}$ Quantified Neurological Exam score on striatal volume.

Table 2. Partial correlations (controlling for age) between striatal volume and neuropsychological test scores in 12 healthy adults with the HD mutation

Test	*Striatal volume* (partial *r*)	*p*
Quantified Neurological Exam ($\log_{10}$ score)	−.70	.01
Symbol Digit Modalities Test		
Written Trial	.39	.11
Oral Trial	.64	.02
Hopkins Verbal Learning Test (sum of recall on Trials 1–3)	.62	.02
Road Map Test of Directional Sense (s)	−.13	.35
Extrapersonal Orientation Test (total errors)	−.03	.47
Stroop Color and Word Test (interference T score)	.50	.11
Wisconsin Card Sorting Test (cards per sort)	−.53	.04

form a composite striatal volume. The globus pallidus was excluded from the analysis since it did not differ in volume between the groups. For each neuropsychological test, a representative variable was selected, based on how well it reflected overall test performance. The analysis was adjusted for age, since age was inversely associated with striatal volume in participants with the gene mutation [$r(11) = -.53$, $p = .04$].

The partial (age-adjusted) correlations between striatal volume and test scores for mutation-positive participants are presented in Table 2.[1] There was a significant correlation between striatum volume and $\log_{10}$ QNE score, such that minor neurologic abnormality was associated with smaller size (see Figure 2). Correlations between striatal volume and performance on the Symbol Digit Modalities Test (Oral Trial) and Hopkins Verbal Learning Test (sum of recall on Trials 1–3) were marginally significant (see Figures 3 and 4). A closer inspection of the striatal constituents revealed that only putamen volume correlated with QNE score [partial $r(10) = -.73$, $p < .003$] and performance on the Symbol Digit Modalities Test [partial $r(10) = .67$, $p < .01$], whereas only caudate size was associated with recall on the Hopkins Verbal Learning Test [partial $r(9) = .71$, $p < .01$]. To guard against the possibility that these significant partial correlations are attributable to the inclusion of individuals mildly affected with HD, QNE score was then added to age as a covariate. None of the associations was altered.

DISCUSSION

Consistent with several earlier studies from our center and others, clinically healthy individuals with the HD gene mutation did not, as a group, differ from those with the normal gene on neuropsychological tests sensitive to early-stage disease. However, they did have smaller caudate nuclei and putamens. Furthermore, reduced size of basal ganglia was associated with greater neurologic abnormality, slower mental processing speed, and poorer verbal learning for individuals who inherited the mutation. These findings suggest that subclinical brain anatomic and cognitive changes begin to occur before persons with the expanded triplicate repeat at IT-15 become overtly symptomatic with HD.

The neuropsychological and neurologic correlates of striatal size in our healthy mutation carriers parallel those reported in symptomatic HD patients. Starkstein et al. (1988)

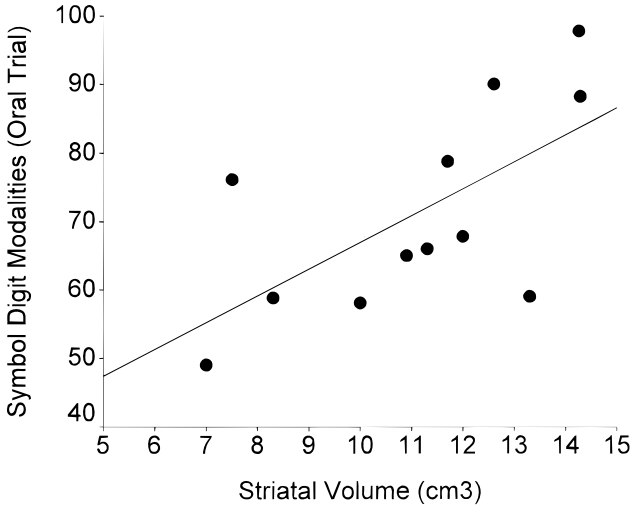

Fig. 3. Regression of score on Oral Trial of Symbol Digit Modalities Test on striatal volume.

[1] None of these correlations was significant among mutation-negative participants.

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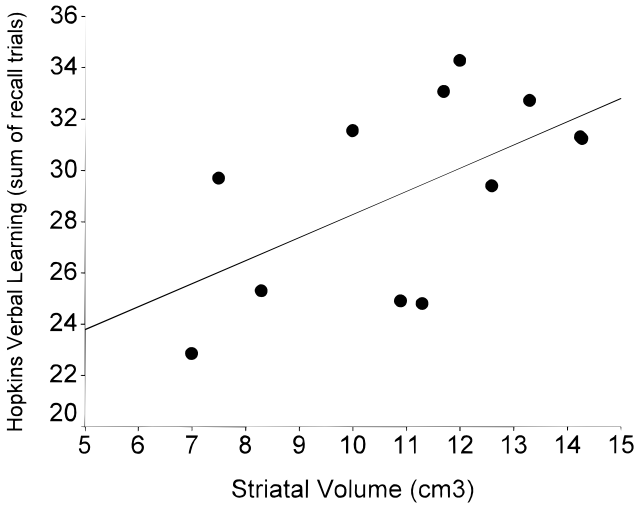

Fig. 4. Regression of sum words recalled on Trials 1–3 of Hopkins Verbal Learning Test on striatal volume.

found an association between an index of caudate atrophy on CT scans and performance on the Symbol Digit Modalities Test (Oral Trial), Trail Making Test (Parts A and B), and a measure of eye movement abnormalities in their HD patients. These researchers suggested that caudate pathology produces abnormal saccades, thereby impairing rapid visual search and tracking. In a subsequent study, Starkstein et al. (1992) reported significant correlations between memory and psychomotor speed and measures of striatal atrophy, frontal cortical atrophy, and width of the Sylvian fissure. Bamford et al. (1995) found that CT measures of striatal atrophy in HD patients correlated with declines in psychomotor speed and memory functioning over a 3-year period. Therefore, it appears that atrophy of the striatum is associated with a characteristic pattern of cognitive and movement-related abnormalities.

In our sample, verbal learning varied as a function of caudate size, while degree of motor abnormality was dependent on putamen size. Among clinically symptomatic patients, Harris et al. (1996) found that both morphologic and cerebral blood flow measures of the putamen, but not caudate, were related to QNE scores, while MMSE scores correlated specifically with extent of caudate atrophy. The caudate nucleus has strong reciprocal connections with dorsolateral prefrontal neocortex and few connections with movement-related cortical regions (DeLong et al., 1990). The putamen has anatomical and functional connections to supplemental motor cortex (Alexander et al., 1986) and appears to be critically involved in movement (Berent et al., 1988; Starkstein et al., 1992).

One could argue that some of our participants may already have been clinically ill with HD. However, it is unlikely that such persons were included in the study, since (1) we did not detect any outliers that might have accounted for the positive findings; (2) we excluded individuals at the outset of the study who met even liberal clinical criteria suggestive of early HD; (3) 18 months have now passed since the most recent scans, and none of the participants has yet been diagnosed; and (4) we controlled statistically for the possible influence of minor neurologic abnormalities on cognitive performance. Thus, it appears that our findings apply to participants who are free of overt signs of HD.

It might be argued that the observed neuropsychological correlates of striatal volume have nothing to do with HD, but rather reflect relationships present in the normal brain. However, we consider this unlikely since we did not find a single significant correlation between brain morphometry and test performance in our mutation-negative participants.

Although we may have identified very early changes associated with HD, it would be premature to use this information for clinical diagnosis without replication. But if cognitive and neuroanatomic changes reliably occur before symptoms of HD are evident on clinical examination, a set of criteria might be developed for earlier detection of disease onset. This improved diagnostic sensitivity would allow the testing of new pharmacologic interventions earlier in disease development, where they are most likely to be effective in forestalling the onset of HD or slowing its progression.

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