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Neuropsychological correlates of brain atrophy in Huntington's disease: a magnetic resonance imaging study

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Summary. Magnetic resonance imaging and a comprehensive cognitive evaluation were carried out in a series of 29 patients with mild to moderate Huntington's disease (HD). A factor analysis of the neuropsychological test scores provided three factors: a memory/speed-of-processing factor, a "frontal" factor, and a response inhibition factor. The memory/speed factor correlated significantly with measures of caudate atrophy, frontal atrophy, and atrophy of the left (but not the right) sylvian cistern. There were no significant correlations between the "frontal" or response inhibition factors and measures of cortical or subcortical brain atrophy. Our findings confirm that subcortical atrophy is significantly correlated with specific cognitive deficits in HD, and demonstrate that cortical atrophy also has important association with the cognitive deficits of patients with HD.

Key words: Huntington's disease – Magnetic resonance imaging – Brain atrophy

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by disordered movement, progressive dementia, and disturbances of emotion and behavior [1]. The most conspicuous neuropathological finding is marked atrophy of the basal ganglia, although cortical atrophy and atrophy of other structures, such as the cerebellum and brain stem, may also be present [1].

Several neuroradiological studies have examined anatomical correlates of cognitive dysfunction in patients with HD [2–4]. Most demonstrated a significant correlation between striatal atrophy and neuropsychological scores [2, 4]. In contrast, no studies reported significant correlations between cortical atrophy and neuropsychological scores [2]. One important limitation of these studies is that they used X-ray CT, which affords limited resolution. As a result, direct measures of small subcortical structures, such as the head of the caudate, putamen, and thalamus could not be carried out. Moreover, since CT does not routinely provide coronal or sagittal brain slices, atrophy of relevant cortical structures such as as the cingulate gyrus could not be assessed. We herefore examined a series of patients with HD using MRI. Our major aim was to determine whether we could replicate our previous findings [2] using MRI and a larger population of patients. In addition, we sought to determine whether the putamen, caudate nucleus and thalamus had different relationships with cognitive deficits, and whether MRI would reveal significant correlations between atrophy and cognitive deficits.

Patients and methods

The 29 patients with HD in the study were part of a consecutive series participating in a drug trial of D-α-tocopherol. The diagnosis of HD was based on a positive family history, and the presence of characteristic chorea or voluntary motor disorder characteristic [5]. To be included in the study, patients had to be ambulatory and have a Mini-Mental State Examination (MMSE) [5] score of at least 15 points. Thus, only patients with mild to moderate disease who could undergo MRI and complete the neuropsychological evaluation were included. All neuropsychological and neuroradiological studies were carried out before patients began the drug trial.

Neuropsychological examination

The neuropsycholoical battery consisted of tests shown to be sensitive to dementia in HD: Digit Span (forward and backward) [6], Controlled Word Association Test [7], Design Fluency Test [8], Trail Making Test [9], CERAD Verbal Learning Test [10], Luria Sequential Hand Positions Test [11], a modified Wisconsin Card Sorting Test [12], Benton Visual Retention Test (multiple-choice version) [13], Motor Go/No-Go Test [11], and Stroop Color-Word Test [14]. Tests were administered and scored according to standard procedures, and the examiners were blind to the neuroradiological data.

Magnetic resonance imaging

Images were obtained using TR 800 ms, TE 20 ms and FOV 20 cm, two excitations, and a 256 × 256 matrix. Patients with anxiety or who could not remain still were sedated with chloral hydrate. Axial slices were parallel to the anterior posterior commisure line, and coronal slices were perpendicular to this line. Axial, coronal, and sagittal slices were 3 mm thick, with 1.5 mm interslice gap.

Table 1. Correlation between neuropsychological factors and MRI measures ($n = 29$)

	Factor 1	Factor 2	Factor 3
Subcortical measures			
Bicaudate ratio	0.70*	0.12	0.11
Caudate nucleus area	0.64*	0.02	0.15
Putamen area	0.37	0.19	0.12
Thalamic area	0.17	0.13	0.07
Ventricle-brain ratio	0.36	0.33	0.09
Cortical measures			
Frontal interhemispheric area	0.57*	0.17	0.07
Left sylvian cistern area	0.59*	0.04	0.02
Right sylvian cistern area	0.34	0.14	0.38
Cingluate gyrus area	0.27	0.18	0.12

* $P < 0.0001$

Linear and area measurements were taken with a digitizing tablet connected to a microcomputer. All measurements were carried out blind to the neuropsychological data. We found interrater reliability for all the measurements to range from $r = 0.95$ to 0.99 ($n = 10$). More detailed information on these measurements may be found elsewhere [15, 16].

Subcortical measures

Bicaudate ratio (BCR) is the distance between the maximal indentations of the head of the caudate nucleus on the frontal horns, divided by the inner table diameter at the same level.

Caudate area (CAU) is half the area of the head of the left and right caudate nuclei in the slice immediately above the foramen of Monro, divided by the area of the brain at the same level.

Putamen area is half the area of the left and right putamina traced on the slice passing through the foramen of Monro, divided by the area of the brain at the same level.

Thalamic area is half area of the left and right thalami traced in the slice passing through the foramen of Monro divided by the area of the brain at the same level.

Ventricular-brain ratio is the area of the lateral ventricles at their waist, divided by the area of the brain at the same level.

Cortical measures

Cingulate area is the area of the anterior cingulate gyrus on the midsagittal slice, divided by the area of the brain at the level of the CAU. Since the anterior cingulate gyrus could be clearly seen in only one slice, measures represent either the left or right gyrus.

Frontal interhemispheric area (FIA) is the average area of the interhemispheric fissure at the level of the frontal lobes on the first coronal slice in which the septum pellucidum could be observed, and the next two posterior slices, divided by the area of the brain at the CAU level.

Sylvian cistern area (SYL) is the area of the sylvian cistern on the same slices as the FIA. Since the left sylvian area plays an important role in language functions and may have specific correlations with verbally related tasks, left and right SYL were examined separately and not averaged.

Statistical analysis

Statistical analysis was carried out using a factor analysis for the neuropsychological data, and Pearson correlations between neuropsychological factors and MRI measurements, with a Bonferroni correction for multiple comparisons.

Results

Demographic findings

The patients had a mean age of 46 years (range 27–68), with a mean duration of illness of 6 years (range 1–16), 14 years of education (range 3–22), and a mean MMSE of 26 points (range 18–30).

Neuropsychological findings

In order to reduce the number of dependent variables in the neuropsychological battery, the test scores of all patients included in the larger drug trial ($n = 63$) were subjected to a principal components factor analysis. Three orthogonal factors with eigenvalues greater then 1.0 were retained, which together accounted for 63% of the variance in the intercorrelation matrix ($P < 0.05$). The first factor, which accounted for 44% of the total variance, was characterized by high loadings for tests requiring memory, graphomotor speed, and alternating sets (i.e., the Stroop test, CERAD Verbal Learning test, Benton Visual Retention Test, and parts A and B Trail Making Test). The second accounting for 10% of the total variance had high loadings on "frontal lobe" tests, such as the Wisconsin Card Sorting Test, and both verbal and design fluency tests, while the third, which accounted for 8% of the variance, had high loadings on tests related to responce inhibition and attention (i.e., Motor Go/No-Go and Digit Span Backward).

Correlation between neuroradiological and neuropsychological variables

Pearson product moment correlations were performed between the nine MRI variables and the three neuropsychological factors (Table 1). Factor 1 (memory/speed) significantly correlated with the BCR, CAU, lateral ventricle area, FIA, and the left sylvian cistern.

While there were trends for factor 2 ("frontal") to correlate with the lateral ventricle area, and factor 3 (response inhibition and attention) to correlate with the right sylvian cistern, they did not reach significance after Bonferroni correction. The fact that factors 2 and 3 accounted for a smaller part of the variance as compared to factor 1 may have also contributed to the presence of weaker correlations between these factors and MRI measures. There were thus three main findings. First, we found a significant correlation between subcortical atrophy (mainly in the head of the caudate nucleus), and cognitive dysfunction. Second, there also was a significant correlation between cortical atrophy and cognitive deficits. Third, there was some specificity for both cortical and subcortical correlations, since caudate but not putaminal or thalamic measures and atrophy in the left, but not right, sylvian area correlated with cognitive deficits.

Discussion

Several studies have examined the presence of correlations between brain atrophy on CT and cognitive deficits in patients with HD [2–4]. Across studies, results are very consistent, with most reporting significant correlations between

the BCR and tasks that involve visuospatial planning and rapid mental processing. The present study is the first to use MRI to examine correlations between brain atrophy and cognitive deficits in HD. There are many advantages of MRI over CT. First, due to greatly improved definition of anatomical structures [17] on MRI, we could reliably measure the area of specific subcortical structures, such as the head of the caudate nucleus, putamen, and thalamus. Moreover, we could measure the area of several cortical regions, such as the anterior cingulate gyrus, and cisternal spaces, using imaging planes not available with CT.

We examined HD patients with mild to moderate disease, and reduced the number of neuropsychological variables by factor analysis. A Bonferroni correction for multiple comparisons was applied to minimize the chance of spurious correlations (type 1 error).

Factor 1 loaded significantly on tests of verbal and visuospatial memory, graphomotor speed, switching sets, and response inhibition. Among the subcortical measures, only the BCR and the area of the caudate nucleus correlated significantly with this factor; we previously found a significant correlation between the Trail Making Test and the BCR [2]. Thus, these findings support the speculation that the head of the caudate nucleus, not the putamen, is the critical basal ganglion structure involved in cognitive functions [18]. Moreover, they do not support an important role for the thalamus in the production of cognitive deficits in HD.

A new finding is that several measures of cortical atrophy also correlated significantly with performance of factor 1, in contrast to our previously finding no significant correlation between cortical atrophy and cognitive deficits in HD. These positive findings may be a result of the better imaging technique or of the use of area instead of linear measures. One interesting finding was that the left but not the right sylvian cistern correlated significantly with factor 1, suggesting that atrophy of the left opercular area is more important than right in the production of specific cognitive impairments in HD.

The second cognitive factor included test classically associated with frontal lobe functions, and there only was a trend towards a correlation with the area of the lateral ventricles (a measure of diffuse subcortical atrophy). Since the head of the caudate nucleus has strong connenctions with the frontal lobes, we expected to find significant correlations between its area and factor 2. The fact that we did not find such a correlation may indicate that atrophy of the head of the caudate nucleus may be necessary but not sufficient to produce "frontal lobe" deficits. Atrophy of other subcortical brain areas (as suggested by the nearly significant correlation between factor 2 and the area of the lateral ventricle) may also be required.

The third factor included a task of motor inhibition response and a task of attention. There was only a trend towards correlation with the right (but not left) sylvian cistern, which may reflect the dominant role of the right hemisphere in some aspects of attention.

The present study thus confirms the importance of subcortical atrophy (invotring mainly the head of the caudate nucleus) in the production of cognitive deficits in HD. Moreover, we report the first demonstration that cortical atrophy, mainly in the left hemisphere, is related to the cognitive dysfunction.

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