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Premanifest Huntington's disease : a study of early biomarkers

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Chapter 2



Basal ganglia volume and clinical correlates in preclinical Huntington's disease

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Abstract

Objective: To establish differences in basal ganglia and thalamic volume between preclinical carriers and non-carriers of the Huntington's disease (HD) gene and to link the volume to motor, cognitive and behavioural characteristics in carriers.

Methods: Sixteen HD gene carriers without overt clinical motor signs and 14 non-gene carriers underwent clinical evaluation and a MRI scan. Volumes of the caudate nucleus, putamen, globus pallidus and thalamus were measured using T1-weighted MR images. Motor, cognitive and behavioural functioning was assessed using the Unified Huntington's Disease Rating Scale (UHDRS), cognitive testing and the Beck Depression Inventory (BDI-II).

Results: Volumes of the caudate nucleus, putamen and globus pallidus were significantly smaller in carriers than in non-carriers while no differences between groups were found on clinical evaluation. In gene carriers smaller globus pallidus volume was associated with more motor abnormalities. A smaller putamen volume correlated significantly with worse psychomotor function on the Symbol Digit Modalities Task and the Trail Making Test B.

Conclusions: In line with previous research we demonstrated that basal ganglia abnormalities precede overt disease manifestation of HD. Besides we showed that smaller basal ganglia volumes are related to subtle motor abnormalities and worse psychomotor performance in gene carriers without clinical diagnosis. Motor and psychomotor measures may be suitable clinical markers in future neuroprotective trials when combined with volumetric imaging.

Introduction

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by progressive motor, cognitive and behavioural deficits. The most striking neuropathological changes are found in the caudate nucleus and the putamen, but other subcortical and cortical regions of the brain also exhibit neuronal loss.^{1,2} As the age at onset, progression rate and severity in HD are very variable, insight in these aspects by studying the disease development in gene carriers without overt clinical signs should help in selecting suitable clinical and biological markers for future neuroprotective trials.

Up to now subtle motor, cognitive and behavioural abnormalities have been reported in preclinical carriers, but with inconsistent results.³⁻⁷ Volumetric imaging studies focusing on the basal ganglia in this group showed evidence of preclinical abnormalities and reported smaller volumes of caudate nucleus and putamen many years before the clinical diagnosis could be made.⁸⁻¹² Approaching disease onset globus pallidus volume and thalamus volume was found to be reduced as well.^{8,9,12} Interestingly, alterations in these structures have been associated with specific clinical characteristics in the symptomatic phase of HD. Striatal changes have been linked to motor impairment and cognitive deficits, including attention problems, memory impairment, executive and psychomotor dysfunction.¹³⁻¹⁷ In one study smaller thalamus volume was found to be associated with impairment in psychomotor tasks.¹⁸ Relatively few studies investigated such associations in the preclinical phase of HD. Smaller striatal volume has been linked to worse motor functioning in some preclinical studies.^{9,19,20} Furthermore smaller striatal volume was associated with worse psychomotor performance in one study¹⁹ and with lower scores on a verbal episodic memory task.^{19,21} The associations between striatal volumes and specific clinical characteristics in the preclinical phase of HD needs further investigation to find a combination of biological and clinical markers suitable to predict and monitor the earliest changes in HD. Furthermore, to our knowledge globus pallidus and thalamic volumes have not yet been studied in relation to motor, cognitive and behavioural functioning in preclinical HD. Therefore, this study aimed firstly to establish differences in the volume of the caudate nucleus, putamen, globus pallidus and thalamus between HD gene carriers and non-carriers and secondly to relate these volumes to motor, cognitive, and behavioural characteristics in gene carriers.

Patients and Methods

Seventeen preclinical Huntington's disease gene carriers and 15 non-gene carriers were invited to participate in this study. All participants had undergone gene testing at an earlier time. According to the international guidelines gene carriers were defined by more than 35 CAG repeats, while those with fewer than 27 repeats were considered non-gene carriers.²² The gene carriers in this study had a CAG-repeat ranging from 40 to 49 (*table 1*). Gene carriers were considered 'preclinical' in the absence of unequivocal motor signs on the Unified Huntington's Disease Rating Scale (UHDRS), as assessed during their last visit to our outpatient clinic. Reassessment of motor functioning during study enrolment resulted in the exclusion of one gene carrier who was rated as 'unequivocal' HD. One non-gene carrier who showed evidence of neurological disease on MRI was also excluded from analysis.



The clinical data are summarized in *table 1*. The estimated probabilities of neurologic symptom onset within 5 years were determined according to the formulas described by Langbehn et al. (2004) based on current age and CAG repeat length.²³

The study had been approved by the LUMC Medical Ethical Committee. All subjects gave informed consent.

Assessment

All participants underwent motor, cognitive, behavioural and MRI investigations, with no more than four months between clinical assessment and MRI-scan (mean: 30 days, SD: 44 days).

Motor functioning

The motor part of the Unified Huntington's Disease Rating Scale (UHDRS)²⁴ was scored by a neurologist (RACR/YAMG) who was blind to genetic status. A Total motor score was calculated by summing up all separate motor items (range 0-124), with higher scores representing more motor abnormalities.

Cognition

Neuropsychological tests included the Mini Mental State Examination (MMSE),²⁵ Wechsler Memory Scale (WMS),²⁶ Hopkins Verbal Learning Test (HVLT),²⁷ the Trail Making Test, consisting of a simple (TMT A) and a more complex (TMT B) version,²⁸ the Stroop colour-word test,²⁹ the Controlled Oral Word Association Test (FAS),³⁰ the Symbol Digit Modalities Test (SDMT),³¹ the Boston naming task,³² reaction time measurements,³³ and VMI perception.³⁴ Tests were administered by a trained psychological assistant under supervision of a psychologist (CKJ).

Behaviour

The behavioural part of the UHDRS was administered by a psychologist (CKJ). The Total behavioural score was retained for analysis, obtained by adding the products of frequency and severity for each item. Additionally, the Beck Depression Inventory (BDI-II) was administered.³⁵ Higher scores correspond with more depressive feelings.

MRI

MRI was performed using a 3.0 Tesla device (Philips Medical Systems, Best, The Netherlands). MRI consisted of 3D-T1-weighted images (acquisition parameters were as follows: TR = 9.8 msec; TE = 4.6 msec; flip angle = 8°; section thickness = 1.2 mm; number of sections = 120; no section gap; whole brain coverage; FOV = 224 mm; matrix = 192, reconstruction matrix = 256). Whole brain volume was measured, using an automated method, the cross-sectional version of the Structural Image Evaluation of Normalized Atrophy (SIENAX, part of FMRIB Software Library).³⁶ Manual segmentation of the caudate nucleus, putamen, globus pallidus and thalamus was performed using Software for Neuro-Imaging Processing in Experimental Research (SNIPER), designed by the Laboratory for Clinical and Experimental Image Processing (LUMC, Radiology). Two raters (CKJ/LvdW) who were blinded to subject identity and genetic status performed volumetric measurements on axial images.

For each structure volume in cc was calculated by multiplying voxel size and the number of segmented (colored) voxels. Boundaries of the basal ganglia were comparable to Aylward et al. (1994).⁹ Segmentation began in the most superior slice in which the caudate nucleus was first visible. Measurement continued in an inferior direction until the last slice in which the caudate and putamen were still clearly separated by the internal capsule. The borders of the caudate were defined laterally by the anterior limb of the capsula interna and medially by the lateral ventricle. The borders of the putamen were defined laterally by the external capsule. At more superior levels, the medial borders are defined by the internal capsule and at more inferior levels by the globus pallidus. Whole thalamus segmentation started when the top of the thalamus appeared as a dark round and ended when the thalamus outlines were not visible anymore. The thalamus is defined medially by the third ventricle and laterally by the capsula interna. Structure outlines were rechecked in the coronal and the sagittal plane. Ten randomly selected brains were segmented twice to assess interrater reliability of the volumes (intraclass correlation coefficients (ICC) for caudate= 0.95, for putamen= 0.91, for globus pallidus= 0.94, for thalamus= 0.82).

Statistical analysis

SPSS for Windows (release 12.0.1) was used for data analysis. Group differences were analyzed with parametric or non-parametric tests when appropriate. Analysis of covariance was used to control group differences for possible confounding variables. Pearson correlation analysis was used to investigate associations between MRI volumes and clinical measures. Partial correlations were used to control for age and brain size. The level of statistical significance was set at $p < 0.01$.

Results

Demographic and clinical characteristics

There were no significant differences between groups for gender, age or years of education and for motor, cognitive or behavioural functioning (*table 1*). In gene carriers the estimated probabilities of neurological symptom onset within 5 years ranged from 0% to 73% (median 17%).

MRI

Gene carriers had significantly smaller volumes of the caudate nucleus, putamen and globus pallidus compared to non-carriers (*table 2*). These results did not alter significantly when corrected for age and whole brain volume. No significant left right differences were found. No differences between groups emerged for whole brain volume and thalamus volume.

Associations between measures in gene carriers

The results of the correlation analyses in gene carriers are given in *table 3*. A strong association between globus pallidus volume and UHDRS Total motor score ($r = -.78, p < .001$) was found. Putamen volume was associated with TMT B ($r = -.69, p = .003$) and SDMT ($r = .67, p = .005$). Smaller volumes corresponded with more motor abnormalities and worse psychomotor performance (*figure 1*).

No associations were found with behavioural measures. Thalamus volume was not associated with any of the clinical characteristics. Results did not change when partial correlation analyses controlling for age and whole brain volume were performed. A greater probability of developing the disease within 5 years was only significantly associated with more motor abnormalities on the UHDRS ($r = .65$, $p = .008$) whereas a trend significance was found with a smaller globus pallidus ($r = -.59$, $p = .02$). There was no correlation between CAG repeat and any of the structural volumes.

Table 1. Demographic and clinical characteristics

	Gene carriers (n = 16)	Non gene carriers (n = 14)
Male/ female ^a	6/10	6/8
Age (years)	41.9 (10.0)	47.2 (9.2)
CAG repeat length ^b	42 (40-49)	19 (16-24)
Probability of onset within 5 years ^{bc}	17 (0-73)	
Education (years)	12.9 (2.7)	12.6 (2.8)
UHDRS Total motor score ^d	3.5 (3.5)	2.4 (2.3)
Neuropsychological tests		
Global		
MMSE	28.4 (1.2)	29.1 (1.0)
Memory		
WMS MQ	114.0 (19.3)	124.2 (14.1)
HVLTL	25.8 (4.5)	26.9 (5.0)
Psychomotor		
TMT A ^e	29.3 (10.2)	25.1 (7.0)
TMT B ^e	54.1 (20.5)	41.9 (14.1)
Stroop color	72.3 (13.0)	80.9 (16.2)
Stroop word	96.6 (10.6)	100.1 (19.6)
Stroop interference	42.3 (7.7)	45.6 (6.8)
FAS	38.5 (13.6)	39.0 (10.4)
SDMT	52.5 (11.8)	60.6 (11.7)
Language		
Boston	27.2 (2.5)	28.5 (1.5)
Reaction time		
RT simple ^e	478.6 (73.8)	465.7 (97.9)
RT complex ^e	634.7 (84.0)	624.8 (131.4)
Perception		
VMI	23.6 (2.0)	24.0 (2.3)
UHDRS Total behavioural score ^d	12.4 (11.4)	15.8 (17.6)
Beck depression inventory ^d	10.4 (8.6)	8.3 (7.3)

Values in the table are means with SD in parentheses. No significant motor, cognitive or behavioural differences were found between carriers and non-carriers. Student's t-test analysis, ^aPearson's χ^2 -test, ^bMedian (range), ^cEstimated probabilities of neurologic symptom onset within 5 years in %.

^dHigher scores correspond with more abnormalities. ^eHigher scores correspond with worse performance. UHDRS= Unified Huntington's Disease Rating Scale. MMSE= Mini Mental State Examination, WMS MQ= Wechsler Memory Scale Memory Quotient, HVLTL= Hopkin's Verbal Learning Task (number correct immediate recall), TMT= Trail Making Test (sec), Stroop (number correct), FAS= Verbal fluency (number correct), SDMT= Symbol Digit Modalities Test (number correct), Boston= Boston naming task (number correct), RT simple= Reaction time single stimulus conditions (milliseconds), RT complex= Reaction time complex conditions (milliseconds), VMI= Visual Motor Integration, subtest visual perception (number correct).

Table 2. Structural brain volumes

	Gene carriers (n = 16)	Non gene carriers (n = 14)	P value
Whole brain volume	1150.1 (86.2)	1205.2 (108.8)	.133
Caudate nucleus	6.4 (1.1)	7.6 (0.9)	.002*
Putamen	6.0 (1.1)	7.2 (1.1)	.004*
Globus pallidus	1.2 (0.5)	1.8 (0.5)	.004*
Thalamus	10.6 (1.3)	11.3 (1.1)	.109

Values in the table are means with SD in parentheses. Student's t-test analysis, * $p < 0.01$. Volumes in cc.

Table 3. Associations between structural brain volumes and motor, cognitive and behavioural assessment in gene carriers (n= 16)

		Caudate nucleus	Putamen	Globus pallidus	Thalamus
UHDRS Total motor score		-.56	-.52	-.78**	.13
Neuropsychological tests					
Global	MMSE	.48	.53	.58	-.01
Memory	WMS MQ	.25	.33	.05	-.25
	HVLTL	.43	.14	.30	-.25
Psychomotor	TMT A	-.30	-.58	-.11	-.37
	TMT B	-.50	-.69*	-.56	-.10
	Stroop color	.44	.33	.29	-.18
	Stroop word	.15	.23	.28	-.30
	Stroop interference	-.32	.27	.24	-.11
	FAS	.15	-.02	.04	-.41
	SDMT	-.59	.67*	.53	-.02
Language	Boston	.27	.57	.44	-.11
Reaction time	RT simple	-.17	-.45	-.54	-.35
	RT complex	.08	-.20	-.22	-.18
Perception	VMI	.14	.08	.33	-.29
UHDRS Total behavioural score		.18	-.04	.31	-.10
Beck depression inventory		-.07	-.22	-.34	-.06

Values are Pearson's correlation coefficients. Significant associations are printed bold. *Correlation with $p < .01$. **Correlation with $p < .001$. UHDRS= Unified Huntington's Disease Rating Scale. MMSE= Mini Mental State Examination, WMS MQ= Wechsler Memory Scale Memory Quotient, HVLTL= Hopkin's Verbal Learning Task, TMT= Trail Making Test, FAS= Verbal fluency, SDMT= Symbol Digit Modalities Test, Boston= Boston naming task, RT simple= Reaction time single stimulus conditions, RT complex= Reaction time complex conditions, VMI= Visual Motor Integration, subtest visual perception.

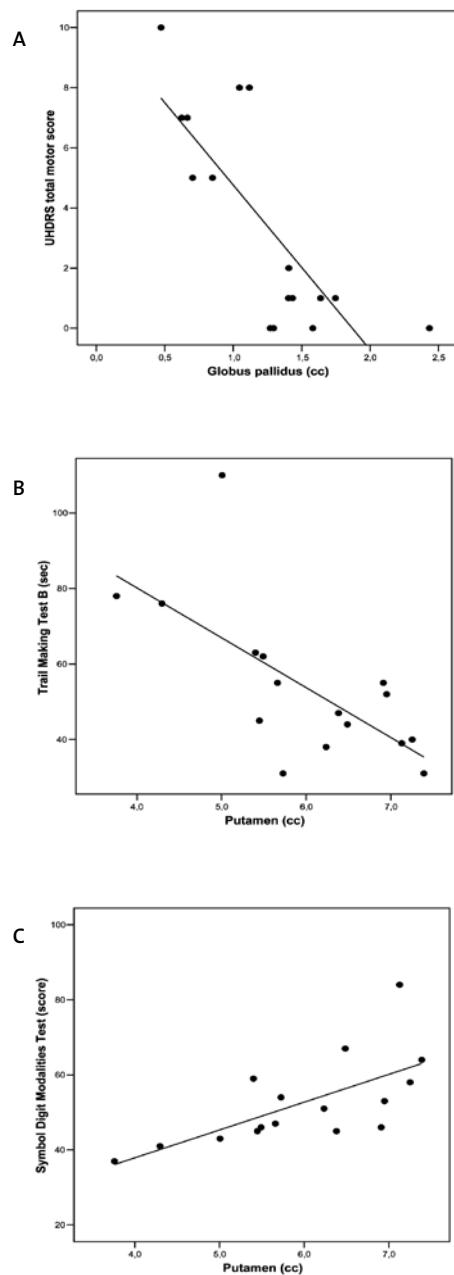


Figure 1. Scatter plots of significant associations between globus pallidus volume and UHDRS total motor score (A), putamen volume and TMT B (B) and putamen volume and SDMT (C) in gene carriers.

Discussion

In line with previous studies we demonstrated that structural brain abnormalities precede overt clinical signs of HD. The main new finding is that smaller basal ganglia volumes in gene carriers were associated with subtle motor abnormalities and worse performances on psychomotor tasks.

The results confirm previous MRI studies showing that gene carriers in the preclinical stage of HD have a smaller caudate nucleus, putamen and globus pallidus compared to non-gene carriers.^{9,10,12,20,37} However, we could not confirm the finding that thalamus volume was reduced in gene carriers.¹² An explanation may be the heterogeneity in closeness to disease onset in this group, with the majority of the participants being more than 5 years away from estimated disease onset. Being closer to onset was slightly associated with a smaller globus pallidus. Only the presence of more motor abnormalities was significantly related to approaching onset. This confirms that the currently existing models for estimating age of onset are mainly suitable in predicting HD motor symptom onset.

Only one previous study focused on associations between the volumes of basal ganglia and motor as well as cognitive functioning in preclinical HD.¹⁹ In the present study we extended volume measurements to include the globus pallidus and thalamus and added behavioural measurements. We showed that smaller globus pallidus volume corresponds with more motor abnormalities on the UHDRS, especially subtle eye movement abnormalities and slight involuntary movements. These are among the minor motor changes described previously in preclinical HD.^{2,3} Smaller putamen volume was strongly associated with worse performance on the psychomotor tasks Trail Making Test B and Symbol Digit Modalities Test, confirming the results of Campodonico et al (1998).¹⁹ These associations cannot be explained exclusively on the basis of motor phenomena as after controlling for the TMT A, that highly depends on motor skills, results did not change significantly. We could not confirm two previous studies that smaller striatal volumes were related to worse performance on a verbal memory task in carriers of the HD gene without clinical diagnosis.^{19,21} Harris et al (1996) suggested that putamen volume was generally superior to caudate nucleus volume for correlation with motor as well as cognitive tasks.¹³ However, studies in symptomatic HD subjects most often linked putamen volume to the motor deficits and stated that caudate atrophy parallels with cognitive decline.³⁸ An extensive meta-analysis of studies on basal ganglia lesions also demonstrated a substantial role of the globus pallidus and the putamen in motor functioning and of the caudate nucleus in cognitive functioning.³⁹ Interestingly, we could confirm the association with motor functioning, even in the preclinical phase of disease. Degenerative diseases however have a more widespread pathology than focal lesions therefore resulting in a more complex influence on the equilibrium of facilitating and inhibiting pathways in the cortico-basal ganglia-thalamo-cortical circuits.

Joel et al (2001) state that a disruption at any level of these circuits may result in altered motor, cognitive and behavioural functions.⁴⁰ They propose an open interconnected model where restricted damage to only one of the basal ganglia circuits can result in coexisting symptoms. Therefore, future studies should at least include caudate nucleus, putamen as well as globus

pallidus to monitor disease onset and progression. Furthermore, alterations in these structures may be seen as a predictor of specific motor and psychomotor abnormalities. Cognitive studies already pointed out the sensitivity of psychomotor tasks^{5,41} and we expect TMT B and SDMT to be sensitive for the transition into manifest HD in our group. Longitudinal evaluation, including also individuals further from estimated disease onset than in the current sample, and individuals with early clinical HD, should give more insight in the time course of these structural changes and the clinical consequences. Besides, more brain regions in a larger sample could be included since recent preclinical research provided evidence of more widespread brain abnormalities including decreased white matter volume and cortical changes and linked these to clinical functioning in the preclinical phase as well.^{12,42,43} Behavioural changes and even clinical heterogeneity may be related to this type of degeneration.¹

In conclusion, our findings indicate that structural brain changes in 'preclinical' HD already result in subtle motor and psychomotor alterations, beneath the clinical diagnostic threshold. The current study included quantitative and reliable segmentation methods, striatal as well as extrastriatal structures and evaluated all phenotypical characteristics of HD. Combining volumetric and clinical evaluation is helpful in determining suitable endpoints for future therapeutic trials in HD and in developing predictive models that are based not only on the first motor signs but focus on other clinical and biological markers as well.

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