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Structure and function of the cerebral cortex in Huntington's disease

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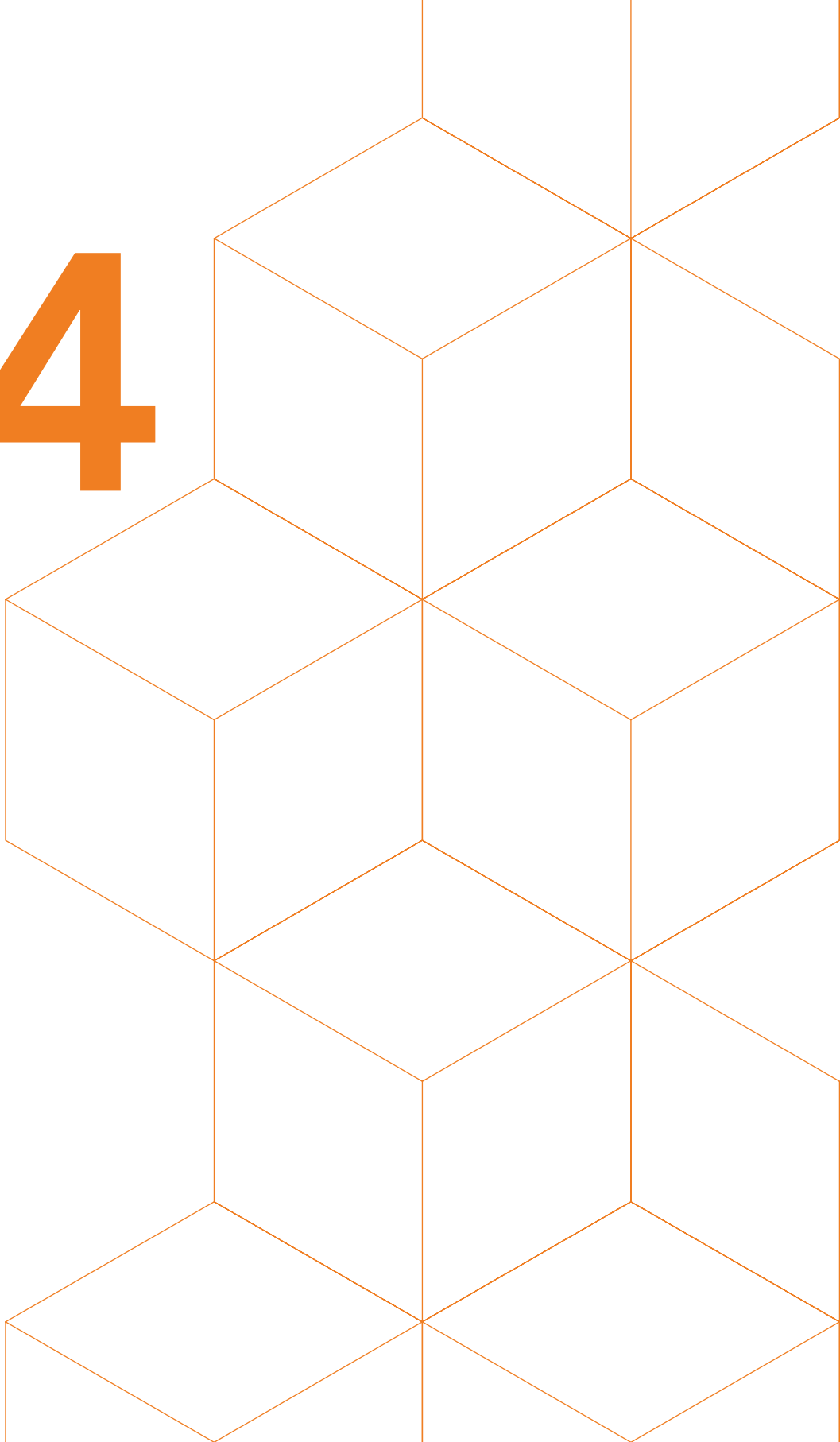
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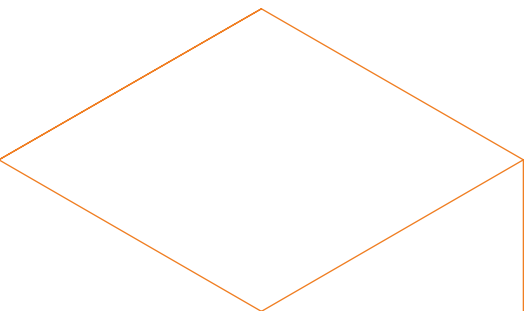
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Patterns of corticostriatal degeneration in early Huntington's disease patients

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Submitted



ABSTRACT

Background: Progressive striatal atrophy is the neuropathological hallmark of Huntington's disease (HD), a hereditary neurodegenerative disorder. Cortical atrophy is additionally present in HD, but it is unknown if striatal degeneration is related with cortical atrophy or if these are independent neurodegenerative processes.

Objective: To investigate the extent of corticostriatal degeneration in early manifest disease stages and examine the relationship between cortical thinning and striatal volume loss.

Methods: Ninety-two participants (18 healthy controls, 31 HD stage 1, and 43 HD stage 2) underwent structural MRI scanning. Thickness and surface area of cortical brain regions and striatal volumes were calculated using FreeSurfer. Based on independent corticostriatal circuits (motor, oculomotor, prefrontal, limbic, and visual loops), associations between cortical thickness and striatal volumes (caudate nucleus, putamen, and accumbens nucleus) in HD gene carriers were assessed using multiple linear regression analyses adjusted for age and gender, and corrected for multiple comparisons ($p < 0.003$).

Results: Atrophy of the striatum, especially the caudate nucleus, was more extensive than thinning of the cerebral cortex in HD gene carriers. In HD stage 2, cortical thinning was mainly located in parietal and occipital cortices. Although both striatal volume loss and cortical thinning was observed, no significant associations were found between cortical thickness and striatal volumes.

Conclusion: In early stage HD, cortical atrophy is mainly located in parietal and occipital brain regions. Since no relationship was observed in the degree of atrophy within corticostriatal circuits, our findings imply that cortical degeneration might be independent from striatal atrophy.

1. INTRODUCTION

Progressive striatal degeneration is the neuropathological hallmark of Huntington's disease (HD), an autosomal dominant inherited neurodegenerative disorder caused by an elongated cytosine-adenosine-guanine (CAG) repeat length on chromosome four.^{1,2} The gradual loss of medium spiny projection neurons in the striatum are thought to explain the clinical signs of HD, such as choreiform movements, oculomotor dysfunction, and even cognitive and psychiatric symptoms.³⁻⁵ Early microscopic changes in the striatum usually begins in the body and tail of the caudate nucleus, and further deterioration occurs in a dorsal to ventral direction.⁴ In addition to striatal atrophy, widespread neuronal cell loss in different regions of the cerebral cortex have been found in advanced HD patients, resulting in an overall brain weight loss of more than 40%.⁶⁻⁸ Regional cortical atrophy can also be detected in early disease stages, although to a lesser extent than striatal atrophy.⁹⁻¹⁴

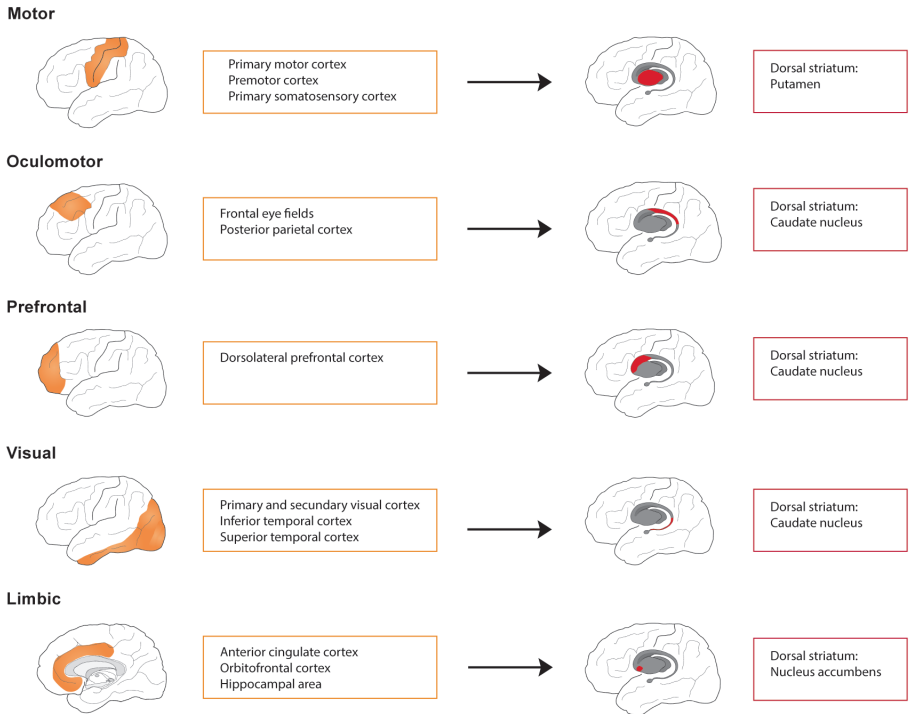
Currently, it is suggested that cortical atrophy in HD originates in posterior brain regions and progresses to the anterior cerebral cortex,¹⁵ but it is unknown if the degree of regional cortical degeneration is related to striatal volume loss. It is hypothesized that either the striatum is the primary site of degeneration in HD and other subcortical and cortical brain regions are subsequently affected, or that striatal atrophy is secondary to degeneration in the cerebral cortex.¹ However, it is also possible that striatal and cortical degeneration occur relatively independent of each other.¹⁶

In general, different cortical regions have projections to different striatal regions (i.e., the putamen, caudate nucleus, or accumbens nucleus) that subsequently project to the pallidum, thalamus, and finally back to the cortex. Five major independent corticostriatal circuits have been identified: the motor, oculomotor, prefrontal, limbic, and visual loops (Figure 1).^{5,17-19} Dysfunction of the corticostriatal pathways may lead to neurodegeneration of both cortical and striatal neurons.⁶

Identifying the pathways of corticostriatal neurodegeneration in HD is important because this can provide more insight into the debate to which extent the striatum plays a causal or modulatory role in the onset of clinical signs. To date, striatal atrophy is often used as a marker to track disease progression or to measure the effect of a pharmacological treatment in clinical trials. When cortical degeneration indeed occurs independent from striatal atrophy, this could have consequences for future clinical trial designs and therapeutic interventions, especially since cognitive, affective and behavioral disturbances in HD patients have been linked to cortical atrophy.^{9,13}

Therefore, with this study, we aimed to identify the degree of corticostriatal degeneration in early manifest HD disease stages and examine the relationship between cortical thinning and striatal volume loss.

FIGURE 1 Corticostriatal circuits



Schematic overview of the main corticostriatal circuits in the human brain, adapted from Alexander et al.¹⁷ and Lawrence et al.¹⁸ Each circuit is a closed loop projecting from the cerebral cortex to specific regions of the striatum, pallidum, and thalamus, which project back to the cerebral cortex. The sensorimotor cortex mainly connects to the putamen, the orbitofrontal, parietal, and occipital cortices with the caudate nucleus, whereas the limbic structures and prefrontal cortex are involved with the nucleus accumbens. Note that the connections between striatal regions (i.e., the indirect and direct pathways), and to the pallidum and thalamus are not displayed in this figure.

2. METHODS

2.1. Participants

A total of 92 individuals (18 healthy controls and 31 manifest HD gene carriers stage 1 (HD1) and 43 manifest HD gene carriers stage 2 (HD2)) were included in this study. Participants were recruited from the outpatient clinic of our Neurology department. Spouses and gene-negative relatives without neurological or psychiatric disorders were included as healthy controls. All HD gene carriers had a genetically confirmed CAG repeat length of ≥ 36 and scored above 5 points on the Total Motor Score of

the Unified Huntington's Disease Rating Scale (UHDRS), a scale to evaluate motor functioning in HD, ranging from 0 to 124.²⁰ Usually, a score above 5 points on the UHDRS-TMS refers to clinical presence of typical HD-related motor signs.¹⁰ Based on the UHDRS Total Functional Capacity (TFC) score, which assesses global daily functioning, manifest HD gene carriers were divided into diseases stages²¹ The TFC score ranges from 0 to 13, with lower scores indicating more impaired function. This resulted in 31 patients in the earliest disease stage (HD1) with TFC score between 11 and 13, and 43 patients in the second disease stage (HD2), with TFC score between 7 and 10. The disease burden score was calculated as indicator of disease pathology, based on the following formula: $\text{age} \times (\text{CAG} - 25.5)$.²²

The local medical ethical committee approved this study and written informed consent was obtained from all participants.

2.2. MRI acquisition

All participants underwent structural Magnetic Resonance Imaging (MRI) scanning between January 2016 and December 2017 on a 3 Tesla MRI scanner (Philips Achieva, Best, the Netherlands). Anatomical T1-weighted images were acquired using a standard 32-channel whole head coil. The following image parameters were used: TE = 3.3, TR = 7.2 ms, flip angle = 9°, FOV = 256 x 240 x 176 mm and 176 slices with a slice thickness of 1 mm and no gap between slices, resulting in a voxel size of 1.00 x 1.00 x 1.00 mm, and scan duration of approximately 9 minutes.

2.3. Image processing

FreeSurfer (version 5.3.0) was used to calculate the cortical thickness and surface area of the cortical brain regions.²³ Automated parcellation and segmentation was performed by the FreeSurfer algorithm, which assigns a neuroanatomical label to each location on a cortical surface model, based on probabilistic information. Frontal, medial and lateral temporal, parietal, occipital and cingulate regions in each hemisphere were identified based on the Desikan-Killiany atlas, resulting in 34 cortical regions.²⁴ Thickness and surface area measures were averaged across the two hemispheres. Then, average thickness values per region (comprising of the frontal, parietal, temporal, and occipital lobes and the cingulate cortex) were calculated based on a weighted sum of mean thickness which accounted for surface area that has been described previously.^{13,25}

In addition, volumetric measures of striatal structures, i.e., caudate nucleus, putamen, and nucleus accumbens were obtained automatically using FreeSurfer's subcortical segmentation pipeline.²⁶

2.4. Statistical analysis

Group differences in demographic variables were analyzed using analysis of variance (ANOVA) or χ^2 for continuous and categorical data respectively. Differences between HD1 and HD2 for clinical outcome measures (CAG, disease burden score, disease duration and UHDRS-TMS) were analyzed using independent samples t-tests.

Differences between HD1, HD2, and controls in striatal volumes and average cortical thickness for each lobe were analyzed using ANOVA, with Bonferroni correction.

Based on the corticostriatal circuits presented in Figure 1, we used multiple linear regression analyses in all HD gene carriers (i.e., HD1 and HD2 combined) to assess associations between cortical thickness of specific brain regions within each circuit and the corresponding striatal volumes (i.e., caudate nucleus, putamen, and accumbens nucleus). Each specific cortical region's thickness was entered as dependent variable with the corresponding striatal volume as independent variable, adjusted for age and gender. All independent variables were entered in one block.

An alpha-level of $p < 0.05$ was used as significant threshold and, if applicable, an adjusted p -value was set to account for multiple comparisons. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Mac, version 23, SPSS Inc.).

3. RESULTS

3.1. Demographic characteristics

Demographic data are presented in Table 1. There were no significant group differences in age and gender. CAG repeat length and disease burden score were not different between the HD disease stages. The HD2 group had a significant longer disease duration and higher score on the UHDRS-TMS compared to HD1.

3.2. Striatal volume and cortical thickness

Significant reduced volumes of all striatal structures were found for both HD1 and HD2 compared to controls (Table 2 and Figure 2).

The caudate nucleus showed the largest volume loss in HD gene carriers compared to controls with 31.1% and 31.4% volume loss in HD1 and HD2 respectively. There were no significant differences in striatal volumes between HD1 and HD2. After correction for multiple comparisons, each lobe showed reduced average cortical thickness in HD2 compared to controls, with largest volume reductions in the parietal and occipital brain regions, while no significant reductions in HD1 compared to controls were found.

TABLE 1 Demographic characteristics of study population

	Controls	HD1	HD2	<i>p</i> -value
N	18	31	43	
Age (years)	46.2 ± 10.7 (24.1 – 61.3)	50.1 ± 9.1 (30.5 – 64.8)	51.2 ± 10.1 (28.4 – 65.7)	0.198
Gender (M/F)	7/11	17/14	22/21	0.548
Disease burden score	NA	375 ± 86 (246 – 562)	382 ± 87 (185 – 544)	0.741
Disease duration (years)	NA	3.5 ± 2.6	5.3 ± 2.9	0.005
CAG	NA	43.3 ± 2.4 (40-49)	43.2 ± 1.9 (40-48)	0.973
UHDRS – Total motor score	NA	17.1 ± 8.1 (6 – 40)	24.4 ± 12.3 (8 – 52)	0.007

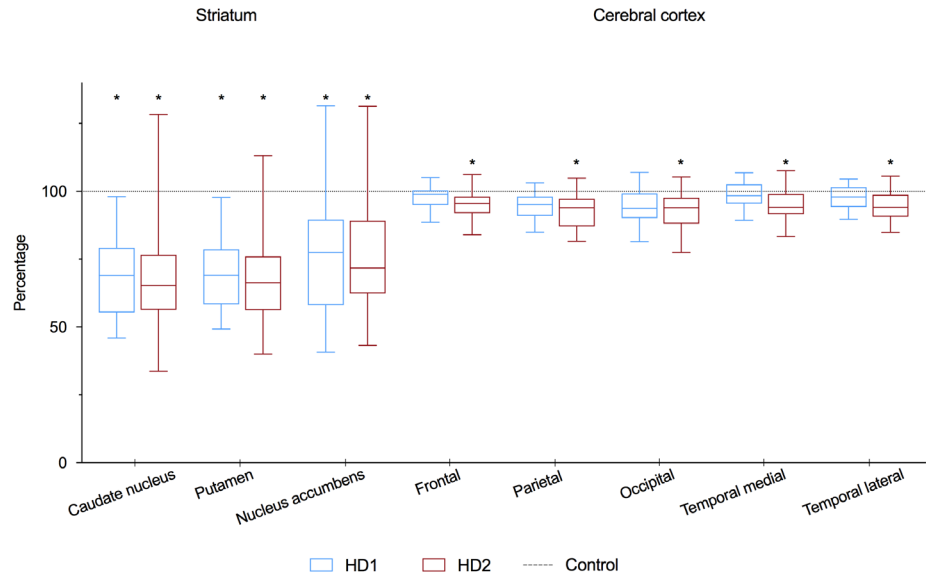
Data are presented with mean ± SD (range), except for gender (male/female) in numbers. UHDRS: Unified Huntington's Disease Rating Scale – Total Motor score. NA: not applicable. Significant group differences are displayed in bold.

TABLE 2 Structural brain data

	Controls	HD1	HD2	Controls vs. HD1 <i>p</i> -value	Controls vs. HD2 <i>p</i> -value
Average subcortical volumes (mm³)					
Caudate	3580 ± 426	2467 ± 584	2449 ± 662	< 0.001	< 0.001
Putamen	4863 ± 586	3392 ± 644	3333 ± 643	< 0.001	< 0.001
Accumbens	472 ± 112	378 ± 115	362 ± 102	0.014	0.002
Average cortical thickness per brain region (mm)					
Frontal cortex	2.55 ± 0.11	2.49 ± 0.09	2.43 ± 0.12	0.227	< 0.001
Medial temporal cortex	2.86 ± 0.17	2.81 ± 0.14	2.71 ± 0.16	0.997	0.003
Lateral temporal cortex	2.75 ± 0.12	2.68 ± 0.12	2.60 ± 0.14	0.262	< 0.001
Parietal cortex	2.34 ± 0.11	2.22 ± 0.11	2.17 ± 0.14	0.006	< 0.001
Occipital cortex	2.03 ± 0.12	1.92 ± 0.13	1.88 ± 0.14	0.016	< 0.001
Cingulate cortex	2.56 ± 0.14	2.50 ± 0.09	2.43 ± 0.11	0.209	< 0.001

Mean ± SD of subcortical volumes (mm³) and cortical thickness per brain region (mm) are presented. The average cortical thickness for each brain region was calculated using a weighted sum of thickness values accounted for surface area using the following formula described previously by Johnson et al., 2015¹³, and Segura et al., 2014²⁵: Average thickness of region A and B = ((Thickness region A * Surface area region A) + (Thickness region B * Surface area region B)) / (Surface area region A + Surface area region B). One-way ANOVA was used to analyze group differences, with post-hoc comparisons using Bonferroni correction. Significant differences compared to controls after correction for multiple comparisons (*p* < 0.006) are displayed in bold.

FIGURE 2 Striatal volume and cortical thickness in HD gene carriers



Boxplots of striatal volumes and cortical thickness per region in HD gene carriers compared to controls (100%). Using analysis of variance (ANVOA), significant reductions in caudate nucleus and putamen volumes were observed for both HD1 and HD2 patients compared to controls. Furthermore, significant cortical thinning for all brain regions was present in HD2 patients compared to controls.

* Significant different compared to controls, $p < 0.006$ (corrected for multiple comparisons, 0.05/8)

3.3. Relationship between cortical and striatal atrophy

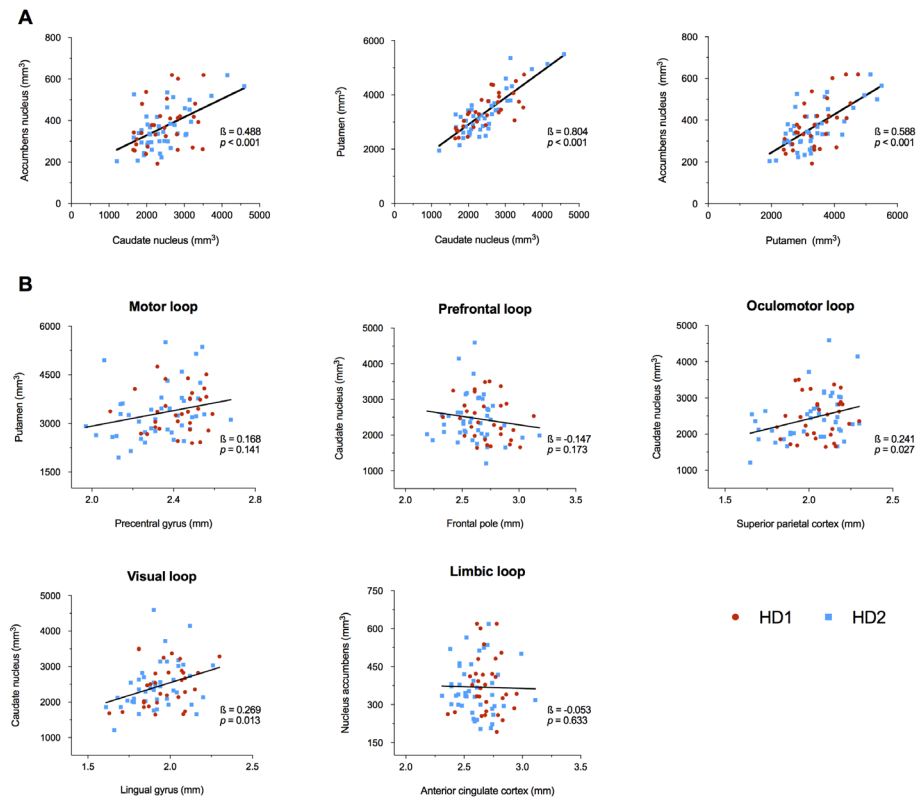
In the whole HD gene carriers group (HD1 and HD2 combined), the relationship between striatal volume and cortical thickness was examined adjusted for age and gender for each corticostriatal loop described in Figure 1. Multiple linear regression analyses after correction for multiple comparisons showed no significant associations between any cortical region and corresponding striatal volume within a corticostriatal loop (Table 3 and Figure 3).

TABLE 3 Associations between regional cortical thickness and striatal volumes

	Cortical region	Lobe	Caudate nucleus		Putamen		Nucleus accumbens	
			Standardized β	<i>p</i> -value	Standardized β	<i>p</i> -value	Standardized β	<i>p</i> -value
Motor loop	Precentral gyrus (BA4)	Frontal			0.168	0.141		
	Paracentral lobule (BA6)	Frontal			0.020	0.410		
	Postcentral gyrus (BA1, 2,3)	Parietal			0.151	0.170		
Prefrontal loop	Middle frontal gyrus (BA9, 46)	Frontal	0.074	0.513				
	Frontal pole (BA10)	Frontal	-0.147	0.173				
Oculomotor loop	Superior frontal gyrus (BA8)	Frontal	0.077	0.504				
	Precuneus (BA7)	Parietal	0.237	0.022				
	Superior parietal cortex (BA5, 7)	Parietal	0.241	0.027				
Visual loop	Inferior frontal gyrus (BA44, 45)	Frontal	-0.033	0.776				
	Inferior temporal cortex (BA20)	Lateral temporal	0.019	0.863				
	Superior temporal (BA22)	Lateral temporal	-0.008	0.945				
	Pericalcarine cortex (BA17)	Occipital	0.091	0.408				
	Cuneus (BA18)	Occipital	0.239	0.028				
	Lingual gyrus (BA18)	Occipital	0.269	0.013				
	Lateral occipital cortex (BA19)	Occipital	0.265	0.014				
	Fusiform (BA19, 37)	Medial temporal	0.191	0.084				
	Orbitofrontal cortex (BA47)	Frontal					0.022	0.836
	Entorhinal cortex (BA28, 34)	Medial temporal					-0.010	0.925
Limbic loop	Parahippocampal gyrus (BA27, 28)	Medial temporal					0.077	0.471
	Anterior cingulate cortex (BA24)	Cingulate					-0.053	0.633

Data are standardized Beta coefficients using linear regression corrected for age and gender. Unadjusted significant *p*-values ($p < 0.05$) are displayed in bold. After correction for multiple comparisons ($p < 0.003$), no significant associations were observed between regional cortical thickness and striatal regions.

FIGURE 3 Relationship within striatum and in corticostriatal circuits



A: Scatter plots of relationships between striatal structures (i.e., caudate nucleus, putamen, and accumbens nucleus). The most pronounced association was present between the putamen and caudate nucleus.
B: Scatter plots of relationships between cortical thickness and striatal volume in HD gene carriers. For each corticostriatal circuit, an example is presented. However, after correction for multiple comparisons, there were no significant associations between cortical thickness and striatal volumes for all corticostriatal loops.

4. DISCUSSION

This study showed striatal atrophy and cortical thinning, primarily in parietal and occipital regions in the earliest manifest HD disease stage, but we found no association between cortical thinning and striatal volume loss. This suggests that striatal degeneration in early HD gene carriers might be independent of cortical degeneration and can therefore be seen as two separate neurodegenerative processes that occur simultaneously.

Furthermore, it is surprising that the frontal lobe is relatively unaffected in early disease stages, since the striatum predominantly projects to frontal cortical regions, such as the primary motor cortex and dorsolateral prefrontal cortex.^{17,18} Still, the parietal and occipital cortices, brain regions that seem to be mainly affected in HD, are also connected to the striatum.¹⁹ More specifically, orbitofrontal, parietal, and occipital brain regions are connected to the caudate nucleus, whereas the sensorimotor cortex in the fronto-parietal cortices are mainly connected with the putamen.^{17–19} The limbic structures and the prefrontal cortex have projections to the nucleus accumbens, the ventral part of the striatum.^{17–19} Our findings showed a trend towards a possible association between the volume of the caudate nucleus and the thickness of cortical regions of the oculomotor loop and visual loop. However, these associations were not significant after correction for multiple comparisons.

Early manifest HD gene carriers can be divided in disease stage 1 (HD1) and stage 2 (HD2) based on the patients' capacity of daily functioning.²¹ In our study, extensive atrophy of the caudate nucleus, putamen, and nucleus accumbens was present in similar degrees in both disease stages. Cortical thinning, however, was found throughout the entire brain in HD2 patients. In HD1 patients, our data showed a trend towards thinning of parietal and occipital cortices compared to controls, however, this was not significant due to correction for multiple comparisons. These results suggest that the degree of striatal atrophy seems to stabilize after disease onset whereas the degree of cortical atrophy increases, beginning in the posterior brain regions with relative sparing of the frontal, parietal, and cingulate cortices. Our findings are consistent with previous studies in manifest HD that showed thinning of the superior and posterior cortical brain regions with minimal involvement of the anterior frontal and lateral temporal lobes.^{9,10} Other studies additionally showed that cortical involvement contributes to behavioral, cognitive and motor symptoms in HD patients.^{6,9,13,14} For instance, worse performance on attentional and executive tasks was correlated with thinning in the primary motor cortex, and parietal and occipital regions.^{9,13} In addition, cell loss in the

anterior cingulate cortex was found in HD patients with prominent mood symptoms,⁶ whereas oculomotor abnormalities have been related with volume reductions in occipital regions.¹⁴

Our findings support the hypothesis that cortical and striatal degeneration might be independent neurodegenerative processes in HD. This could explain the fact that affective, behavioral and cognitive symptoms of HD have been linked to cortical atrophy instead of striatal atrophy.^{6,9,13}

Only few studies have previously assessed cortical thinning in early manifest HD gene carriers and most studies consisted of small sample sizes without subdividing manifest HD gene carriers in different disease stages.^{9,27–30} The strength of our study lies in the fact that we can confirm a distinct pattern of cortical thinning in a relatively large sample of early manifest HD gene carriers, considering HD is a rare neurodegenerative disorder.

A limitation of this study is that we used automated global volumetric segmentations of striatal structures using relatively large structural models. In the early disease stages of HD, striatal atrophy mainly involves the body and tail of the caudate nucleus.⁴ However, our structural models did not allow us to subdivide the caudate nucleus. Furthermore, although we assessed patterns of neurodegeneration in different disease stages to better understand the structural changes during disease progression, longitudinal studies are still necessary to validate our findings.

Many longitudinal studies have previously focused on evaluating the rate of decline in striatal volume in different disease stages, even in HD gene carriers close to disease onset but without motor symptoms.^{10,31,32} Striatal atrophy has also been linked to clinical signs in HD, such as motor symptoms,^{11,14} and executive dysfunction,^{33,34} thus making striatal volume an interesting outcome measure in clinical intervention trials.

Nevertheless, given the relationship of cortical atrophy with other specific HD related signs and our suggestion that cortical degeneration occurs independent from striatal atrophy, cortical thickness measurements might also be valuable for future clinical trial designs.

In conclusion, cortical degeneration in the earliest manifest HD disease stage primarily begins in parietal and occipital brain regions, while the frontal lobe remains less affected in this stage. This is interesting, since the striatum mainly projects to the frontal lobe. Still, thinning of parietal and occipital cortices is not related with striatal atrophy, suggesting that cortical and striatal degeneration are independent neurodegenerative processes in HD. This is important for future clinical trial designs that target cognitive, affective or behavioral symptoms in HD patients, as these symptoms have been linked to cortical atrophy.

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