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Regional cortical thinning in preclinical Huntington disease and its relationship to cognition

Abstract—The authors studied presymptomatic individuals with the Huntington disease (HD) mutation to determine whether cortical thinning was present. They found thinning that was regionally selective, semi-independent of striatal volume loss, and correlated with cognitive performance. Early, extensive cortical involvement occurs during the preclinical stages of HD.

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The earliest and most striking neuropathologic changes in Huntington disease (HD) are thought to occur in the neostriatum,¹ but significant cortical pathology has also been shown to occur early.² The cortex provides important glutamatergic input to the striatum and recent studies have suggested that alterations in the cortex can lead to reduced corticostriatal trophic support³ and altered physiology,⁴ both of which may contribute to striatal degeneration. We hypothesized that frontal and sensorimotor regions were thinned before motor symptoms. Therefore, we sought to investigate whether cortical thinning was present in presymptomatic individuals carrying the genetic mutation (PHD) and to determine whether a relationship between regional cortical pathology and cognitive performance was present.

Methods. *Study procedures.* Fifteen PHD individuals who were without equivocal motor symptoms of HD and 27 age-matched controls were recruited. Participants were evaluated on cognitive portions of the Unified Huntington's Disease Rating Scale (UHDRS); higher scores reflect better performance. Scanning was performed on a 1.5-T Siemens Sonata MR scanner (Siemens, Germany). Two whole-brain high-resolution T1-weighted MPRAGE scans (TE = 3.0 msec, TR = 7.25 msec, flip angle 7 degrees, field of view 256 mm, matrix 256 × 192, 1.33 mm sagittal acquisition, NEX = 1) were motion corrected, averaged to enhance the gray-to-white contrast to noise, and smoothed using an iterative nearest neighbor averaging procedure (250 iterations, equivalent to a gaussian smoothing kernel, full width half maximum of 29 mm). Cortical thickness estimates were made as previously

described,² using a spherical coordinate system that achieves vertex-to-vertex correspondence. Striatal and whole brain volumes were also determined.⁵

Statistical analyses. Statistical thickness difference maps were constructed using a *t* statistic. We used a general linear model in which the main effects of group (thickness difference) are shown, covarying for age. Thickness across participants was modeled as [(offset + (slope * age)] + an error term. Statistical differences between groups at each vertex were calculated by comparing their offsets. Putamen and caudate volumes, adjusted for total intracranial volume, were also added as covariates in the model to determine their effect on the surface model.

Correlations between thinning and cognitive score were modeled using a model of the thickness for each subtest: [offset + (slope * cognitive score)]. The offset and slope are subject-independent regression coefficients estimated separately for each vertex using a general linear model. Pearson correlation coefficients were calculated from the slope and mapped on the surface. *t* Statistics at each vertex were used to test the hypothesis that the slope coefficient was equal to zero.

Results. *Sample characteristics.* Characteristics of the study groups are given in the table. The groups did not differ significantly with respect to age, gender, or education. There was no difference in performance on the UHDRS cognitive tests between groups.

Cortical thickness measures. Statistical maps of regional cortical thinning and regional relationships with striatal volumes are shown in figure 1. Cortical thinning appeared to be regionally selective; even within gyri, thinning was heterogeneous. Significant thinning was present bilaterally in precentral, superior, and middle frontal (approximating Brodmann areas [BA] 4, 6, and 8), superior parietal (approximating BA 7), superior temporal (approximating BA 22, 41, 42), middle and inferior temporal, occipital (approximating BA 17, 18, 19), and L precuneus (approximating BA 31). There was no statistical difference in whole brain volumes between groups ($p = -0.46$).

To determine the contribution of striatal volume loss to cortical degeneration, the surface model was reexamined, introducing into the model volumes of caudate or putamen, or both, as independent variables. Introducing putamen volume into the model resulted in the reduction of apparent cortical thinning over posterior frontal areas; in contrast, introducing the caudate volume resulted in an apparent reduction of thinning over portions of superior temporal cortex. There was no effect on some areas of cortical thinning, when controlling for both caudate and putamen volumes.

Correlation with cognitive scores. A significant correlation between each cognitive measure and selective cortical thinning was present in the PHD group (figure 2) but not in the control group. Poorer performance on the Symbol

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Table Subject demographics

	Controls	PHD
Demographics		
Age	43.3 ± 9.8 (28–56)	43.4 ± 7.7 (32–56)
Gender	11 M, 16 F	7 M, 8 F
CAG repeat length	NA	42 ± 1.3 (40–45)
Education	17.2 ± 2.6	15.9 ± 2.5
UHDRS Cognitive scores		
UHDRS Verbal Fluency	42.2 ± 25.5	49.3 ± 10.7
UHDRS Symbol Digit	51.2 ± 13.4	53.3 ± 6.7
UHDRS Stroop Color Word	40.6 ± 11.6	44.6 ± 10.1
Motor confidence rating	NA	0.67 (0–2)*
UHDRS motor scores	NA	6.9 ± 3.2

There was no significant difference between groups with respect to age, gender, or education. There was no difference on cognitive test scores between PHD subjects and controls.

* One subject had a confidence rating of 2. The confidence rating is a measure of the rater's confidence that the subject has motor symptoms of Huntington disease (HD) (1 = nonspecific motor abnormalities <50% confidence, 2 = motor signs that may be signs of HD, 50–89% confidence). CAG repeats available for 13 of the subjects. Higher cognitive scores reflect better performance. Total motor score includes all motor components of the Unified Huntington's Disease Rating Scale; lower scores reflect fewer motor abnormalities.

UHDRS = Unified Huntington's Disease Rating Scale; NA = not available.

Digit correlated with more thinning within: right frontal opercula, right anterior insula, inferior portions of the right pre- and postcentral gyri, right superior and middle temporal, right superior and inferior parietal, right gyrus rectus, left superior frontal gyrus, middle portions of the left superior temporal lobe, posterior middle and inferior temporal, left anterior cingulate, left precuneus and left occipitotemporal. Poorer performance on the Stroop Color Word corresponded with more significant thinning within the left dorsolateral prefrontal, left precentral, left pari-

etal, left precuneus, left occipital temporal, right precentral, right superior temporal, planum temporale, right inferior temporal, and right precuneus regions. Poorer performance on the Verbal Fluency corresponded with more significant thinning in portions of: L superior temporal, L middle occipital, L temporal pole, R superior planum temporale, and R inferior temporal regions.

Discussion. Our results provide evidence of early and selective cortical degeneration during the motor preclinical stages of HD, earlier than previously reported. They extend our previous work in symptomatic HD and support an important role of the cortex early, before motor symptoms, in the pathophysiology and clinical expression of disease. The selective vulnerability of the cortex very early in disease is not surprising given that huntingtin aggregates can be readily detected in the cortex of individuals at risk of HD who died before exhibiting any symptoms.⁶ Additionally, previous studies have demonstrated that throughout the course of disease, aggregates are far more concentrated in the cortex rather than the striatum⁷ and their distribution throughout the cortex is heterogeneous.^{7,8}

A causative role for the cortex in striatal degeneration has been proposed from studies demonstrating that alterations in the cerebral cortex in HD led to reduced corticostriatal trophic support³ and altered physiology.⁴ Furthermore, the cortex provides important glutamatergic input to the striatum and thus may play an excitotoxic role in striatal degeneration. Several studies in transgenic mouse models have also demonstrated that clinical symptoms are present in the absence of striatal pathology,⁹ suggesting that alterations in excitatory corticostriatal inputs may be primary rather than secondary to striatal alterations in HD. However, the complex interconnectedness of the cortex and striatum makes it difficult to determine whether cortical degeneration precedes, results from, or is independent of striatal

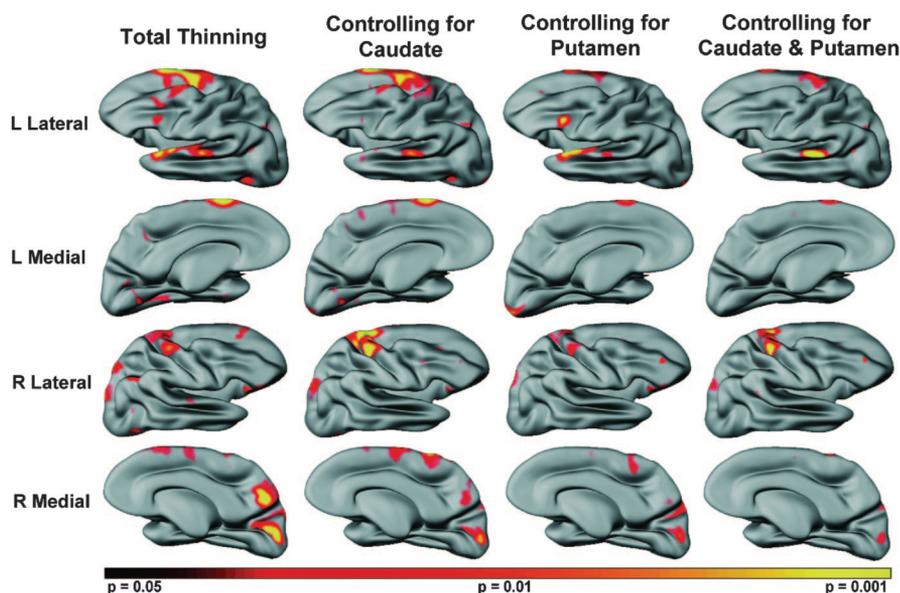


Figure 1. Evidence of regional cortical thinning in PHD and its relationship to striatal volume. Cortical surface reconstruction maps. Significant cortical thinning was present in the PHD group as compared to controls. When adjusting for caudate volumes, the intergroup variance in thinning was less prominent over portions of superior temporal gyrus; when adjusting for putamen volumes, variance was less prominent over posterior frontal regions. Some areas of thinning appeared to be independent of caudate or putamen volumes. Maps are displayed on an average composite brain, with areas of more thinning transitioning from red ($p < 0.05$) to yellow ($p < 0.001$), unadjusted for multiple comparisons.

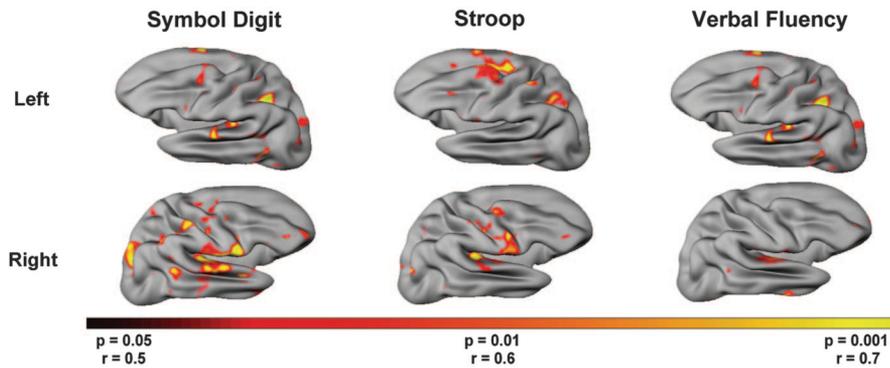


Figure 2. Correlations of regional thinning and performance on neuropsychological tests. Pearson correlation coefficients demonstrating a correlation between regional thickness, calculated by vertex, and performance on the cognitive components of the UHDRS. Correlations range from r value of 0.5 to 0.7, ranging in value from $p < 0.05$ to < 0.005 , as the gradient transitions from red to yellow.

degeneration. In our study, several distinct areas of cortical thinning correlated with either caudate or putamen volumes, but some areas appeared to be independent of striatal volumes. Putamen volumes correlated most strongly with cortical areas generally associated with the motor corticostriatal loop and caudate correlated most with temporal thinning, more generally associated with the cognitive corticostriatal loop.

Our results also support a role of the cortex in the expression of clinical symptoms. Worse performance on UHDRS cognitive subtests correlated with more thinning in specific cortical areas previously shown to be important in the execution of the specific task. The relative contributions of striatal and cortical dysfunction and degeneration to the symptoms of HD, nevertheless, remain unclear, and the complex relationship of the cortex and striatum makes understanding these relationships exceedingly difficult. Nevertheless, our study suggests that HD has an early, multifocal pathology whose distribution, temporal course, and relationship to clinical symptoms remain to be fully characterized.

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