Regional and progressive thinning of the cortical ribbon in Huntington’s disease

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Abstract—Background: Huntington’s disease (HD) is a fatal and progressive neurodegenerative disease that is accompanied by involuntary movements, cognitive dysfunction, and psychiatric symptoms. Although progressive striatal degeneration is known to occur, little is known about how the disease affects the cortex, including which cortical regions are affected, how degeneration proceeds, and the relationship of the cortical degeneration to clinical symptoms. The cortex has been difficult to study in neurodegenerative diseases primarily because of its complex folding patterns and regional variability; however, an understanding of how the cortex is affected by the disease may provide important new insights into it. Methods: Novel automated surface reconstruction and high-resolution MR images of 11 patients with HD and 13 age-matched subjects were used to obtain cortical thickness measurements. The same analyses were performed on two postmortem brains to validate these methods. Results: Regionally specific heterogeneous thinning of the cortical ribbon was found in subjects with HD. Thinning occurred early, differed among patients in different clinical stages of disease, and appeared to proceed from posterior to anterior cortical regions with disease progression. The sensorimotor region was statistically most affected. Measurements performed on MR images of autopsy brains analyzed similarly were within 0.25 mm of those obtained using traditional neuropathologic methods and were statistically indistinguishable. Conclusions: The authors propose that the cortex degenerates early in disease and that regionally selective cortical degeneration may explain the heterogeneity of clinical expression in HD. These measures might provide a sensitive prospective surrogate marker for clinical trials of neuroprotective medications.

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Huntington’s disease (HD) is a progressive, fatal, autosomal dominant neurodegenerative disease, characterized neuropathologically by the progressive degeneration of the basal ganglia and clinically by abnormalities of movement, cognition, and behavior. Because of the severe pathologic changes that the striatum undergoes, it has often been presumed to be the direct or indirect site of most of the clinical symptoms of HD. It is likely that some of the clinical symptoms of the disease are also related to cortical dysfunction and degeneration. The anatomic interconnectedness between the striatum and cortex makes it difficult to understand how dysfunction or degeneration of the striatum, the cerebral cortex, or both contributes to symptoms of HD. The striatum receives reciprocal topographically organized projections from many cortical regions. Projections from the temporal, parietal, and occipital association areas have been shown to terminate as irregular patches in all divisions of the caudate nucleus, while projections from the premotor, primary motor, and somatosensory regions have been shown to terminate almost exclusively in the putamen. Pathologic changes in cortical regions of the brain

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have long been known to occur in HD, including occipital, parietal, temporal, primary motor, cingulate, and prefrontal cortices, which have been reported to show neuronal loss in postmortem studies. However, the precise patterns of cortical degeneration in HD have not been well characterized primarily because accurately measuring the degree of cortical atrophy is technically difficult; it is more difficult to quantify changes in an extensively folded sheet (cortex) than the compact basal ganglia structures.

Little is actually known about the regional specificity and relationship of the cortical degeneration to the clinical symptoms. Several neuropathologic studies have demonstrated generalized cortical atrophy, but these studies were generally performed on postmortem tissue of individuals who died in advanced stages of disease. Only few patients have been examined in early stages of disease. It is not known how the cortex degenerates; that is, if it occurs uniformly or nonuniformly, some areas degenerating earlier or more rapidly than other areas.

Morphometric studies done in vivo, including those of presymptomatic gene-positive individuals, have been generally limited to the determination of brain volumes, suggesting early loss of frontal lobe volumes. Pathologic measurements of cortical thickness, however, have been particularly difficult to obtain because the highly folded nature of the cortex can result in measurement errors in regions in which the cortical surface is not perpendicular to any of the cardinal axes. Not only are these types of analyses prone to overestimates, but they may provide only limited information as there is considerable natural heterogeneity in thickness from region to region or even within brain regions. Additionally, it is not technically possible to sample more than a small number of cortical regions from a single brain. What little is known comes from studies on autopsy material that sampled regions of cortex and extrapolated volumes or estimated cortical thickness.

We present results from automated surface reconstruction, transformation, and high-resolution intersubject alignment procedures for accurately measuring the thickness of the cerebral cortex across the entire brain as well as for generating cross-subject statistics in a coordinate system based on cortical anatomy in a cohort of patients with HD. We performed the same analyses on two postmortem brains and compared the measurements obtained using these techniques with the measurements obtained using classic neuropathologic techniques. We found that the two measurements were statistically indistinguishable. Our results suggest that cortical degeneration is present in early stages of disease and may explain at least some of the clinical symptoms.

Subjects and methods. Subjects. Subjects with HD were recruited from the Massachusetts General Hospital (MGH) Huntington’s Disease Unit. Each subject had definite clinical signs of HD as well as either a positive family history or a known trinucleotide repeat expansion. Procedures were fully explained to all subjects, and written informed consent was obtained before scanning. Scanning was performed in compliance with the relevant laws and institutional guidelines of the Internal Review Board of the MGH. Eleven subjects with HD were scanned: six men and five women. The mean age of HD subjects was 43.8 ± 10.3 years. All subjects, except for one with advanced disease, were living independently at the time of scanning. HD subjects were in various stages of disease, ranging from recent onset of motor symptoms (one; 1 year from onset of motor symptoms) to advanced (one; 10 years from onset of motor symptoms). Thirteen normal age-matched control subjects were scanned: eight men and five women. The mean age of normal subjects was 44.5 ± 9 years. All HD subjects were right-handed; 12 of the normal control subjects were right-handed.

Imaging. We utilized a Siemens 1.5 T Signa scanner (Milwaukee, WI) to obtain our scans. T1-weighted images were obtained from subjects; image acquisition included echo time (TE) = 3.0 ms, repetition time (TR) = 7.25 ms, flip angle = 7°, field of view = 256 mm, matrix = 256 × 192, 1.33-mm sagittally acquired slices, number of excitations = 1. High-resolution proton density images of postmortem brains were obtained; image acquisition included TE = 14 ms, TR = 10,000 ms, flip angle = 180°, and slice thickness = 1 mm. Ten proton density scans were acquired for each postmortem brain. Two acquisitions were obtained for each living subject. Scans were motion corrected and averaged.

Surface reconstructions and estimation of cortical thickness. In vivo data. MRI data were analyzed and the surfaces reconstructed as described previously. In brief, an estimate of the gray/white boundary was constructed by classifying all white matter voxels in an MRI volume. The surface of the connected white matter voxels was refined to obtain subvoxel accuracy in the representation of the gray/white boundary and then subsequently deformed outward to find the pial surface as described previously. The surface deformation involves the local adaptive estimation of the MRI values at the gray/white and pial surfaces. The deformation is accomplished by minimizing a constrained energy functional, with the constraint that the surface be smooth at the spatial scale of a few millimeters. In addition, an absolute constraint is placed on the surface during the deformation, which maintains the natural topology of the brain. Figure 1A demonstrates the cortical models that are generated with our surface reconstruction techniques. The left panel demonstrates a sample brain used to generate the analyses. The right panel demonstrates the inflated surface. Light gray areas correspond to gyri and dark gray areas correspond to sulci. The inflated brain allows for better visualization of sulcal regions while maintaining topology.

Cortical thickness estimates were obtained as follows. For each point on the white matter surface, the shortest distance to the pial surface was first computed. Next, for each point on the pial surface, the shortest distance to the white matter was found, and the cortical thickness at that location was set to the average of these two values. All subjects were aligned to a common surface template using a high-resolution surface-based averaging technique that...
aligns cortical folding patterns. To test whether alignment to the common surface could be performed accurately in brains that might be spatially distorted because of atrophy, as may be seen in HD, the central sulcus was painted onto the common surface and the transformation was reversed, transferring the label onto the original surfaces. Figure 1B demonstrates that the central sulcus registers perfectly from the backward registration. A small surface-based Gaussian blurring kernel with an SD of 7 mm was applied to the thickness estimates to remove noise-induced variations in the measurements. Each spatial location was then treated as a random variable, with one observation per subject.

Statistical analysis. The statistical maps were generated using a random effects model with 1 degree of freedom for each subject to generate a t-test for each cortical location. Thickness maps from the 11 subjects with HD were averaged using our high-resolution surface-based averaging techniques and compared with thickness measurements from the thickness maps of the normal control subjects averaged equivalently. Mean cortical thickness and variance of the mean were calculated at each location.

Autopsy data. To validate our measurements, we performed the same analyses on two postmortem brains: one from an individual with HD and one from an age-matched normal control subject. Ten high-resolution three-dimensional proton density scans were obtained from each postmortem brain and averaged off-line. The surface models of the cortex were then constructed (figure 2), and the thickness of the cortex was estimated as described. One-centimeter blocks were then removed from the fixed brains in regions of relatively low curvature near the crowns of gyri, so that accurate manual thickness measurements could be made. Photographs were taken of the exposed surfaces (see figure 2); these were scanned, and the images were used to estimate the thickness of the cortex with NIH Image (Bethesda, MD). Ten measurements were made in each region and then averaged to obtain the mean thickness for each block. The fixed brains were then rescanned, and these MR images were used to locate the precise region of the removed block in the reconstructed cortical model. The automated thickness measures were then sampled and averaged in the corresponding regions.

Results. Cortical thickness measures. Figure 3A demonstrates absolute cortical thinning measurement using the average folding pattern of the surface reconstructions.
of three separate HD subjects in early, mid, and late clinical stages of disease compared with normal age-appropriate control subjects. The color scale shows the dynamic range of thinning from red to yellow, demonstrating lesser to greater areas of thinning across the Gaussian kernel. Full yellow corresponds to at least 0.4 mm of thinning. The thickness maps demonstrate that cortical thinning occurs in all stages of disease. The greatest differences between the HD and normal control subjects were on the order of 1 mm. Patchy cortical thinning was more prominent in the left hemisphere. In the early case, cortical thinning was most prominent over the middle occipital region, the middle temporal region, and the angular and supramarginal gyri. These areas correspond roughly to Brodmann areas 18, 19, 39, and 44. With increasing duration of illness, thinning extended to more extensively involve the aforementioned areas and to more anterior regions, corresponding roughly to Brodmann areas 18, 19, 44, 3, 2, and 1. In the more advanced case, cortical thinning was more generalized and extended further anteriorly to include most of the frontal lobe; more specifically, this included Brodmann areas 45, 46, 6, 9, and 10. In each case, cortical thinning was more prominent in the left hemisphere.

Figure 3B demonstrates statistical maps comparing the average thickness of all 11 HD subjects in different clinical stages of disease compared with the 13 normal control subjects. Regions of statistically thinner (p < 0.001) cortex in HD subjects are color coded, with red to yellow indicating a lesser to greater significance (yellow corresponding to p < 0.005). HD subjects had significantly thinner cortical ribbons bilaterally, most prominently in pre- and postcentral regions (Brodmann areas 4, 3, 2, and 1), inferior temporal region (Brodmann 37), and dorsal occipital cortex (Brodmann 17, 18, and 19). Once again, cortical thinning was more prominent in the left hemisphere.

Validation: Surface reconstruction of brain pathology.
Ten cortical thickness measurements were taken at each location. The average of the 10 measurements obtained using these two methods agreed in all locations to within 0.20 mm (figure 4), with a mean difference of 0.077 mm, confirming the accuracy of the automated technique.

Discussion. We report thinning of the cortical gray ribbon in subjects with HD using novel automated surface reconstruction and high-resolution intersubject registration procedures of MR images.10-12 Thinning was more prominent over more posterior cortical regions earlier in the disease; with increasing duration of symptoms, more anterior cortical regions were affected. Cortical thinning was heterogeneous, even within gyral regions. Some areas were as much as 1 mm thinner. The thickness of the cerebral cortex varies between 1 and 4.5 mm, with an overall thickness of approximately 2.5 mm across the entire brain15,16; hence, 0.4 mm of thinning corresponds to approximately a 20% loss of thickness. In some areas, thinning was as much as 1 mm, corresponding to >30% loss of thickness. Our data suggest that the cortex undergoes a gradual, regionally specific, and progressive degeneration, much of which occurs in the striatum.

Our findings, which suggest that more posterior cortical regions degenerate earlier, are provocative. Previous neuropathologic studies have reported early posterior cortical degeneration.17 In addition, several in vivo reports have also suggested early dysfunction of posterior cortical regions. For example, several neuropsychologic studies have reported early profound impairments in visual recognition, including impaired face and facial expression and facial recognition even relatively early in the disease18 and recognition of disgust.19 These are functions thought to be subserved by the temporal lobes; TE, a higher visual area in the temporal lobe, is known to be an output target of the striatum.20 In another study,21 patients with HD also showed greater impairment than patients with AD on a test of pattern recogni-
tion memory, sensitive to temporal lobe lesions and amygdalohippocampectomy but not to frontal lobe lesions. Patients with HD have been shown to demonstrate deficits in spatial working memory, demonstrating a high degree of perseverative responses and difficulties with attentional set shifting, referable to lateral and eventually ventral prefrontal cortical dysfunction. Later involvement of the frontal lobes is supported by work done using MR morphometry, which demonstrated evidence of volume loss of the frontal lobes only in individuals who were moderately affected by disease but not in individuals in early stages of disease. Additionally, frontal lobe volumes did not correlate with symptom severity or general cognitive dysfunction. These observations suggest that cognitive dysfunction may be related to...
disruption or alterations of not only known frontostriatal circuits but also of other less well-characterized circuits involving more posterior cortical regions. A larger study may more fully address the temporospatial patterns of cortical degeneration that occur in HD.

Across all subjects in different stages of disease, we found statistically significant cortical thinning in the sensorimotor region. Thinning of the sensorimotor region has also been reported in previous neuropathologic studies and might be expected based on the known topology of striatal pathology and known corticostriatal connections. In both the mean thickness and the statistical maps, the left hemisphere was more affected. Interestingly, this laterality is consistent with a similar laterality we have previously observed both in striatal atrophy and in lactate elevation in HD, suggesting that the left corticostriatal system may be affected in concert by the disease process.

We performed the same analysis on two postmortem brains to validate our methods. Measurements were taken from crown regions as these regions provided the greatest likelihood of sampling perpendicular to the plane of section. Measurements obtained using these advanced methods on MR images acquired from the postmortem brains and with traditional neuropathologic techniques were within 0.2 mm of each other. This suggests that our novel surface reconstruction methods accurately measure cortical changes that are occurring in the disease.

Thinning of the cortical ribbon has been reported previously in HD in a number of neuropathologic studies. Layers III, V, and VI have demonstrated significant loss of pyramidal cells in a study of dorsolateral prefrontal cortex and in another study of dorsal frontal cortex. Morphologic changes occur in striatal medium spiny neurons and in cortical pyramidal cells prior to degeneration, including dendritic remodeling and altered size and number of dendritic spines. This suggests they undergo a period of stress and injury before succumbing, which could be related to the presence of huntingtin aggregates. The dysmorphology and loss of dendrites and axons that occur in this predegenerative period likely cause thinning of the cortical ribbon as well as neuronal loss. Therefore, the site of predilection for neuronal loss in layers III, V, and VI, lamina of origin of corticocortical and corticosubcortical projections, could provide a substrate for the clinical deficits in HD.

The application of these types of analyses to more and better-characterized subjects could provide a better understanding about structure–function relationships between the striatum and the cerebral cortex and how they are altered in HD. This is of special importance as individuals transition from health to illness. This basic understanding not only will provide powerful insight into the disease but may also be a sensitive measure of disease severity and hence a much needed surrogate marker of disease for use in therapeutic clinical trials.

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References


