RESEARCH ARTICLE

A Tale of Two Factors: What Determines the Rate of Progression in Huntington's Disease? A Longitudinal MRI Study

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ABSTRACT: Over the past several years, increased attention has been devoted to understanding regionally selective brain changes that occur in Huntington's disease and their relationships to phenotypic variability. Clinical progression is also heterogeneous, and although CAG repeat length influences age of onset, its role, if any, in progression has been less clear. We evaluated progression in Huntington's disease using a novel longitudinal magnetic resonance imaging analysis. Our hypothesis was that the rate of brain atrophy is influenced by the age of onset of Huntington's disease. We scanned 22 patients with Huntington's disease at approximately 1-year intervals; individuals were divided into 1 of 3 groups, determined by the relative age of onset. We found significant differences in the rates of atrophy of cortex, white matter, and subcortical structures; patients who developed symptoms earlier demonstrated the most rapid rates of atrophy compared with those who developed symptoms during middle age or more advanced age. Rates of cortical atrophy were topologically variable, with the most rapid changes occurring in sensorimotor, posterior frontal, and portions of the parietal cortex. There were no significant differences in the rates of atrophy in basal ganglia structures. Although both CAG repeat length and age influenced the rate of change in some regions, there was no significant correlation in many regions. Rates of regional brain atrophy seem to be influenced by the age of onset of Huntington's disease symptoms and are only partially explained by CAG repeat length. These findings suggest that other genetic, epigenetic, and environmental factors play important roles in neurodegeneration in Huntington's disease.

Key Words: magnetic resonance imaging longitudinal atrophy; neurodegeneration; phenotypic variability; Huntington's disease

Ages of onset, clinical manifestations, and rates of progression in Huntington's disease (HD) vary dramatically between patients. Although the CAG repeat length (CAG_n) is an important influence, it accounts for less than 50% of the variability in the age of onset and may have only a modest relationship to the rate

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Funding agencies: Support for this research was provided in part by the National Institutes of Health, National Institute for Neurological Disorders and Stroke (R01 NS042861, NS058793, NS05792, NS052585, R21NS072652), National Institute of Nursing Research (NR010827), and the National Center for Research Resources (P41-RR14075, and the NCRR BIRN Morphometric Project BIRN002, U24-01). Additional support came from RR021382, the National Institute for Biomedical Imaging and Bioengineering (R01EB006758), and the National Institute on Aging (AG022381). Additional support was provided by CHDI and the Autism & Dyslexia Project, funded by the Ellison Medical Foundation.
Relevant conflicts of interest/financial disclosures: Nothing to report.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 22 October 2010; **Revised:** 22 February 2011; **Accepted:** 28 March 2011
Published online 24 May 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23762

of progression.[1–3] Clinical heterogeneity poses many challenges for designing clinical trials aimed at slowing the progression of HD. The primary instrument currently used to measure progression in clinical trials is the Total Functional Capacity (TFC) scale, part of the United Huntington's Disease Rating Scale (UHDRS).[4] The TFC measures progressive functional losses that accumulate in HD; however, because of clinical and measurement variability, hundreds of patients must be followed for several years to provide sufficient power for phase III interventional studies. The TFC is also not useful in typical phase II studies for providing preliminary evidence of disease modification. More efficient and objective measures of clinical progression are greatly needed. Novel longitudinal neuroimaging approaches provide sensitive, reliable, and objective measures that could enhance the efficiency of clinical trials in HD; they also provide a unique opportunity to more fully characterize the neurobiology of clinical heterogeneity and to understand whether there may be definable subtypes that progress and respond to therapies differently.

A major source of clinical heterogeneity and of variability in the TFC is the marked difference in the rate of progression between patients. Our hypothesis, based on clinical experience, was that more rapid progression, irrespective of CAG_n, was associated with earlier age of onset, and, by extension, slower progression was associated with later age of onset. We used serial MRI to study rates of atrophy in individuals who were at approximately the same stage of disease but who had developed symptoms at different ages. We took advantage of a novel within-subject analytical algorithm to evaluate the rates of change in cortical thickness and the volumes of gray and white matter and subcortical structures. We limited our study to those individuals with CAG_n ranging from 40 to 55 to avoid the extremes often encountered in juvenile HD and to subjects in the early stages. We found that individuals who had developed motor symptoms younger than age 40 had more rapid rates of atrophy compared with individuals who developed HD in midlife; those who developed symptoms after age 55 progressed even more slowly. Both the rate and topological distribution of changes were distinct across groups. Although CAG_n was independently associated with the rate of change in a small number of regions, it did not entirely explain observed differences. Clinical progression was also more rapid in younger subjects, paralleling rates measured by MRI. Our study supports an important role of the cortex in explaining clinical variability and demonstrates the potential utility of neuroimaging biomarkers to monitor progression in the setting of marked phenotypic variability. This is the first study to systematically evaluate the relationship between age of onset and the rates of regional progressive changes in the brain in early HD and to demonstrate variable progression related to age.

Patients and Methods

Subjects

Twenty-two individuals with early symptomatic HD (stage I or II, as defined by the UHDRS TFC) were recruited. We used the median age of onset of 45 in our cohort to define groups. Individuals were classified as "Young" if they developed symptoms when younger than age 40 (n = 5; 2 women/3 men; mean age, 31.4 ± 3.4 years; CAG_n, 52.2 ± 2.4), as "Mid" if they developed motor symptoms between the ages of 40 and 55 (n = 9; 6 women/3 men; mean age, 49.3 ± 4.2 years; CAG_n, 43.8 ± 1.6), and as "Old" if they developed symptoms older than age 55 (n = 8; 4 women/4 men; mean age, 62.2 ± 6.3 years; CAG_n, 42.1 ± 1.5). Subjects had comparable TFCs at the time of the first scan (no significant difference between groups, $P = .13$). Although CAG_n was larger in Young, there was no significant difference between Mid and Old ($P = .3$). All subjects were recruited through the HD Center at Massachusetts General Hospital (MGH) and assessed by a neurologist with HD expertise. Subjects returned approximately 1 year later for follow-up. Procedures were explained and consent obtained according to the Declaration of Helsinki. Protocols were approved by the MGH Internal Review Board. Baseline group characteristics are provided in Table 1.

Image Acquisition and Processing

Scan Acquisition

Two T1-weighted images (TE, 3.31 ms; TR, 2730 ms; flip angle, 7°; FOV, 256 mm; matrix, 256 × 171; 1.33 mm sagittal acquisition; Siemens 1.5T Avanto System, Erlangen, Germany) with 1.3 × 1 × 1.3 mm resolution were acquired. The image-processing methods, using FreeSurfer 4.5, have been previously described in detail.[5,6] Thickness values were calculated in the native MRI scanner space of an individual subject's brain and computed as the shortest distance between the pial and the gray/white surfaces. These methods have been previously shown to be reliable[7] and comparable to manual measurements.[8]

We developed a novel, improved, inverse consistent rigid registration, allowing for more accurate within-subject registrations, to determine the rate of within-subject change.[9] Briefly, an unbiased template image was created from 2 time points for each subject, used as an initiation point for anatomical segmentations and surface reconstructions, and then submitted to nonlinear iterative optimizations including topology correction, nonlinear atlas registration, and nonlinear spherical surface registrations. Within-subject measurements have been shown to reduce variability.[9–11]

TABLE 1. Group demographics

	HD Young (n = 6)	HD Mid (n = 9)	HD Old (n = 8)
Age	33.1 ± 3.4	49.3 ± 3.6	62.2 ± 6.3
Sex	3 F/3 M	7 F/3 M	4 F/4 M
CAG repeat	52.2 ± 2.1	43.8 ± 1.6	42.1 ± 1.5
TFC	9.3 ± 1.2	10.6 ± 1.4	10.0 ± 2
Verbal fluency	9 ± 2	14 ± 7	11 ± 3
Stroop	25 ± 6	31 ± 10	22 ± 8
Symbol digit	21 ± 6	34 ± 13	23 ± 10

Cortical regions of interested were obtained as previously described.[12]

To compute the rate of change per year, we normalized the average thickness or volume across the 2 time points. If M1 and M2 represent the cortical thickness measures and T1 and T2 represent the respective time points, we obtain the "symmetrized" percent change (SPC) as: SPC $= 2(M2 - M1)/([M1 + M2][T2 - T1])$.[13]

An automated segmentation scheme was used to obtain whole-brain subcortical volumes, adjusted for intracranial volume.

Statistical Analysis

We evaluated differences in the slopes of change from T1 to T2 among groups in regional thickness and volume measures using 1-way analysis of variance models, as well as *t* tests. Statistical analyses were performed using R.[14] To more precisely determine the relationship, if any, between CAG_n and regional rates of cortical thinning, CAG_n was regressed on a vertex-by-vertex basis. *T* statistics at each vertex were used to test the hypothesis that the slope coefficient was equal to zero. Results are presented uncorrected.

Results

Group Comparisons: Rate of Cortical Atrophy/Thinning

Whole-brain volumes were reduced at a rate of 3.6% per year in Young ($P < .05$, compared with Mid and Old); in Mid, the rate of whole-brain atrophy was 1.55% per year; and in Old, 1.77% per year (not significantly different, $P = .7$). Rates of gray and white matter loss over 1 year, however, were significantly different among the groups. In Young, white matter volume was lost at a rate of approximately 4.6% per year and at approximately 1.8% per year in both Mid and Old ($P = .02$ for the groups combined; $P = .02$ Young vs Mid and Young vs Old). Similarly, total gray matter volume was lost at approximately 5% per year in Young, approximately 2.1% in Mid, and 1.7% in Old ($P = .02$ across groups; $P = .01$ Young vs Old; $P = .04$ Young vs Mid).

We evaluated rates of thinning across the cortical parcellations and found significant differences between Young versus Old in the right precentral ($P = .053$), right posterior frontal (pars opercularis; $P = .026$), right inferior parietal ($P = .052$), left cuneus ($P = .053$), and a trend in the right caudal middle frontal ($P = .059$). There were significant differences between Young and Mid in the left posterior cingulate ($P = .031$) and a trend toward significance in portions of the left anterior cingulate ($P = .057$). Table 2 outlines the rates for several

TABLE 2. Rates of thinning: select cortical parcellation

Parcellation	Overall rate	Young	Mid	Old
L/R superior frontal	1.6%/2.6%	1.4%/0.6%	2.3%/3.8%	1.0%/2.5%
L/R anterior middle frontal	2.0%/5.2%	0.4%/4.2%	3.9%/7.0%	0.9%/3.7%
L/R posterior middle frontal	3.1%/5.5%	2.9%/8.9%	4.7%/6.1%	1.4%/2.8%
L/R posterior inferior frontal[a]	4.5%/3.4%	6.3%/5.7%	5.0%/4.7%	2.9%/4.6%
L/R anterior cingulate	1.1%/3.7%	1.9%/3.6%	1.6%/7.5%	0.3%/0.5%
L/R precentral[a]	4.0%/5.0%	5.5%/9.0%	4.2%/3.0%	3.1%/4%
L/R postcentral	1.7%/3.7%	0.4%/7.2%	1.5%/1.5%	2.8%/4.0%
L/R supramarginal	3.0%/4.9%	2.3%/8.1%	2.7%/4.7%	3.6%/3.1%
L/R superior parietal	1.7%/3.7%	3.5%/7.5%	1.4%/2.8%	0.9%/2.3%
L/R paracentral	1.2%/2.2%	0.5%/0.2%	2.3%/3.4%	0.5%/2.2%
L/R inferior parietal[a]	2.8%/5.3%	6.8%/1.1%	2.3%/4.2%	0.9%/3.3%
L/R precuneus[a]	2.5%/4.0%	5.7%/5.4%	2.5%/5.0%	0.7%/2.0%
L/R isthmus cingulate	3.5%/5.7%	8.6%/1.0%	1.1%/5.4%	3.0%/4.7%
L/R superior temporal	2.6%/4.0%	1.8%/5.2%	3.6%/2.8%	1.9%/4.7%
L/R middle temporal	3.0%/4.0%	2.7%/6.8%	3.3%/3.5%	2.7%/3.0%
L/R inferior temporal	3.1%/5.4%	5.0%/6.0%	4.0%/7.2%	1.2%/3.0%
L/R parahippocampal	2.6%/4.6%	2.7%/5.3%	4.3%/7.0%	0.4%/1.4%
L/R cuneus[a]	1.4%/1.9%	3.2%1.0%	0.7%/3.5%	1.0%/1.8%
L/R pericalcarine	1.6%/0.4%	0.3%/0.6%	1.7%/0.1%	2.5%/0.1%
L/R lingual	2.2%/2.4%	0.3%/0.9%	2.7%/3.2%	3.2%/2.3%
L/R fusiform	3.2%/4.8%	4.3%/5.0%	4.0%/5.3%	2.0%/4.2%
L/R lateral occipital	2.1%/2.6%	2.8%/3.0%	1.8%/2.2%	1.8%/2.7%

[a]Cortical parcellations in which the rate of thinning was significantly faster in the younger patients, $P < .05$, uncorrected.

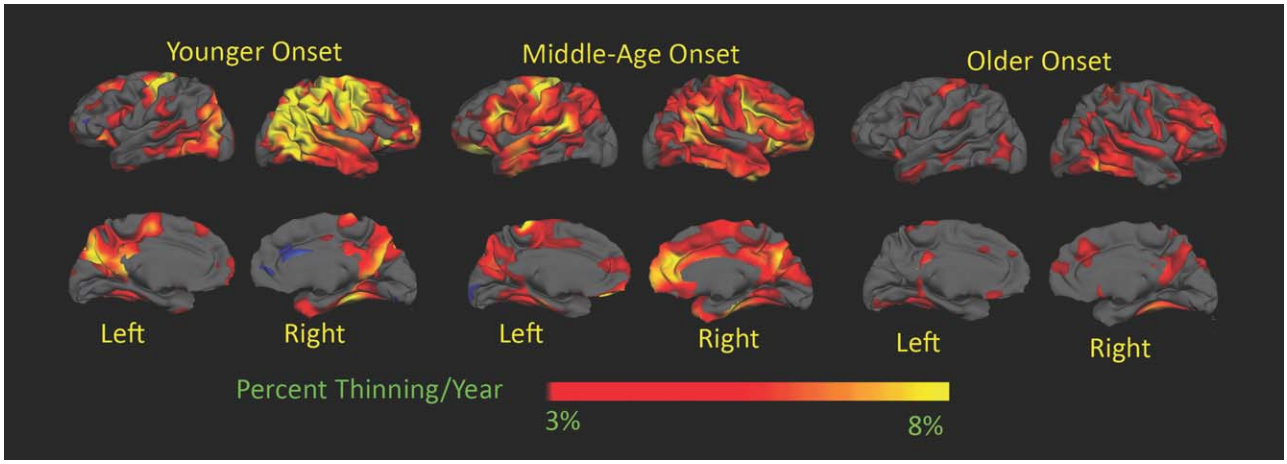

FIG. 1. Surface-based maps of the rate of cortical thinning: young (**A**), middle aged (**B**), old (**C**). Younger patients had a much more rapid rate of thinning, especially in the sensorimotor and parietal cortical regions. The general distribution of thinning was similar, however, in the young and middle-aged groups. In older patients, the rate of thinning was much slower than either of the other groups. Maps are presented on a semi-inflated cortical surface of an average brain. The color scale at the bottom represents the yearly rate of thinning, transitioning from red (3% or greater) to yellow (8% or greater).

cortical parcellations for the entire sample as well as for the distinct groups. In most instances, the rates of thinning were faster in the Young group.

We also evaluated more generated surface-based maps on a voxel-by-voxel basis, shown in Figure 1. In the Young group, the rate of thinning approximated 8% per year in sensorimotor (pre- and postcentral, corresponding with BA 4, -3, -2, -1; $P < .05$), inferior parietal (corresponding with BA 5), and precuneus bilaterally, superior and middle frontal, superior parietal and middle frontal on the right hemisphere, and approximated 5% per year over the right superior, middle, and inferior temporal right hemisphere regions. The rate of thinning in the Mid group followed the same general distribution as the Young group but was less, between 3% and 5% yearly, over those regions. In contrast, the rate of thinning in the Old group approached 3% only in the superior temporal, lingual gyrus, portions of the superior and inferior frontal right hemisphere, and over the right precuneus. When thresholds were reduced, rates of cortical thinning in Mid were generally greater than 1.5% per year throughout most cortical regions restricted to sensorimotor, portions of the superior, middle, and inferior temporal regions, superior and inferior frontal, portions of the inferior parietal, and parahippocampal gyrus in Old. In comparison, rates of thinning in healthy older adults have been reported as approximately 0.5% per year.[15]

The rate of decline in the TFC in Young was on the average 1.7% per year; in contrast, the change in TFC was closer to 0.8% per year in the other 2 groups. Although the differences were not significant ($P = .13$), a test for linear trend approached significance ($P = .06$).

Corpus Callosum

We evaluated rates of thinning of the corpus callosum (CC). With the exception of the midportion of the CC, the rate of thinning was in general faster in Young across all other regions of the CC, with differences reaching significance in the most posterior

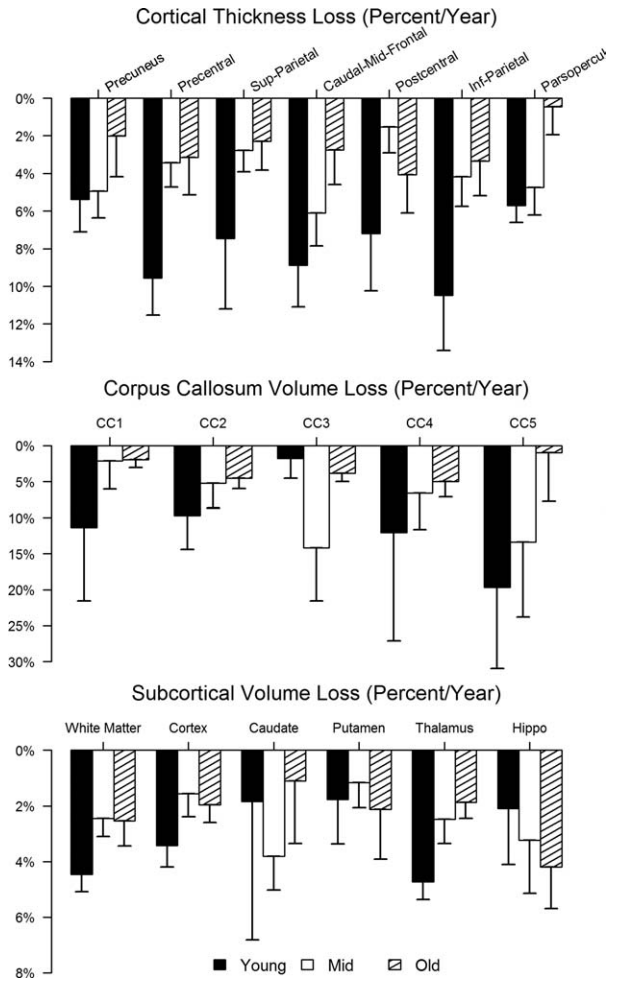

FIG. 2. Rate of change of thickness of select parcellations. Results from the cortical parcellations recapitulate the heterogeneity in the rate and topological distribution of progressive cortical thinning in the 3 groups.

TABLE 3. Baseline subcortical volumes: proportion of ICV

	LCaud	RCau	L Put	R Put	L Pall	R Pall	L Hipp	R Hipp	L Amyd	R Amyd
Young	0.09[a]	0.10[a]	0.19[a]	0.18[a]	0.061[a]	0.060[a]	0.21	0.21	0.06	0.078
Middle	0.14	0.15	0.26	0.24	0.077	0.066	0.25	0.25	0.08	0.09
Old	0.15	0.16	0.24	0.22	0.077	0.070	0.21	0.21	0.07	0.08

ICV adjusted volumes for the caudate, putamen, and pallidum were significantly smaller in the younger-onset group, compared with the Middle and Old groups; [a]$P < .05$, uncorrected.

segment (CC5; $P = .037$) and a trend in the most anterior segment (CC1; $P = .063$). Results are shown in Figure 2.

Subcortical Structures

Also shown in Figure 2 are rates of volume change of subcortical structures in the 3 groups. There was no significant difference in the rate of atrophy in any basal ganglia structure. In contrast to what was expected, the rate of caudate atrophy was slower in the Young compared with the Old, suggesting a possible floor effect. Consistent with this, baseline volumes for the Young were significantly smaller (Table 3), adjusted caudate volumes in the Young were, on the average, 40% smaller than those of either the Mid or the Old; putamen and pallidum volumes were approximately 25% and 20% smaller, respectively.

The Effect of Expanded CAG Repeat Length and Rate of Progression

Surface-based maps suggested a correlation between CAG_n and regional thinning in restricted cortical regions. In the cortical parcellations, we found significant correlations with CAG_n and the right precentral ($P = .009$), right caudal middle frontal ($P = .017$), right inferior parietal ($P = .018$), left precuneus ($P = .028$), left pars triangularis ($P = .043$), and right postcentral ($P = .043$). On average, for those areas that were correlated, each unit increase in CAG_n was associated with a 0.3% faster rate of thinning. The surface-based correlations are displayed in Figure 3. We

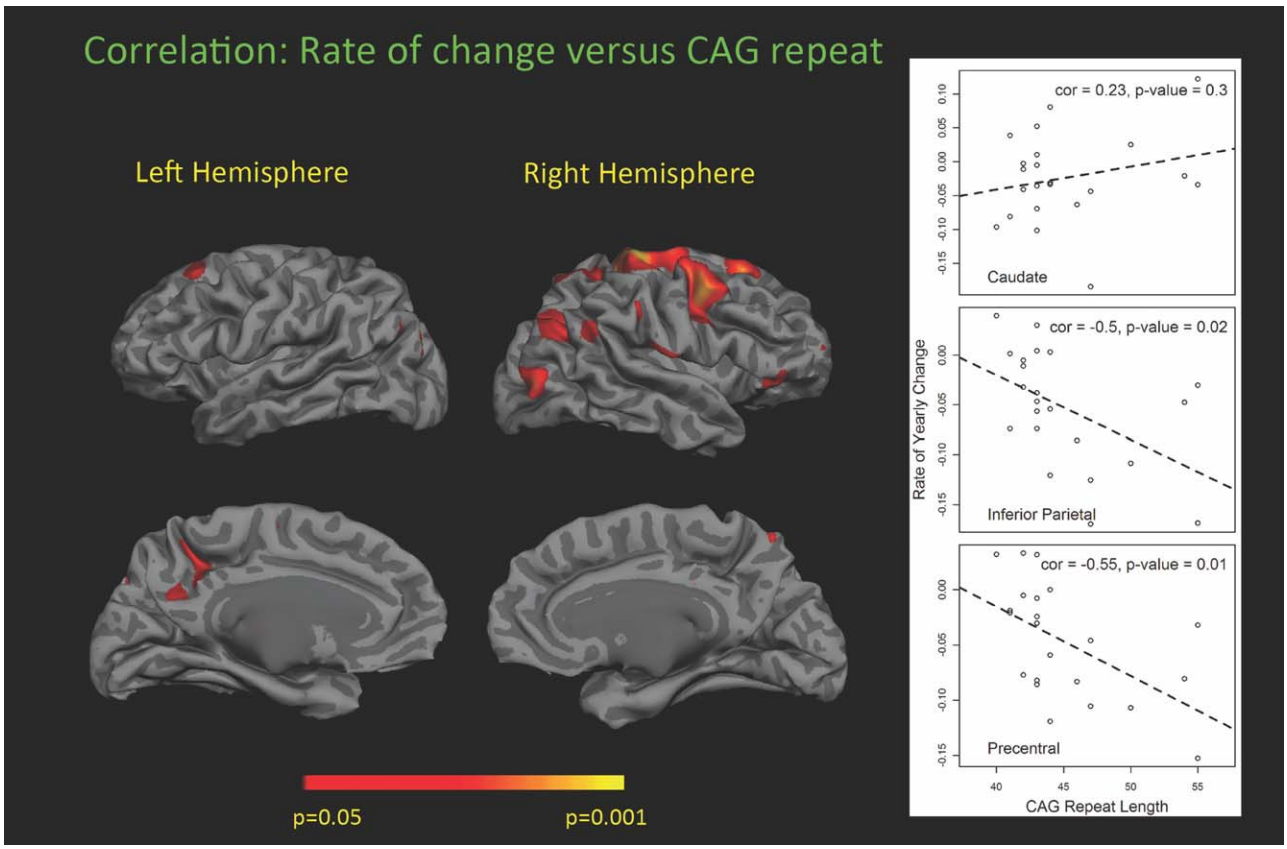

FIG. 3. Relationship between cortical thinning and CAG repeat. **A:** Surface-based maps. **B:** Scatter plots showing the relationship of the caudate and examples of the cortex. Higher CAG repeats were associated with faster rates in distinct cortical regions, but not globally. This suggests that factors other than the CAG repeat length may be important in the variable rate of progression.

found no significant relationship between the expanded CAG_n and *rate* of volume loss for any subcortical structure, including caudate, putamen, and thalamus. In contrast, we found a very significant relationship between cross-sectional caudate volumes at baseline and CAG_n ($P = .0002$).

Discussion

This is the first study to systematically evaluate variable rates of progression in HD using structural neuroimaging. The most striking finding was that both the rate of progression and the topological distribution of cortical thinning were highly influenced by the age of onset as defined clinically, rather than by the length of the CAG repeat. The rates of change for more than two thirds of cortical regions demonstrated more rapid thinning in Young than in either Mid or Old.

In Young, we found regional rates of cortical thinning greater than twice those of either Mid or Old in several regions. This was true for sensorimotor cortex, portions of the interior frontal, superior parietal, inferior parietal, and the cuneus, where the rates of thinning were greater than 8%. However, even within the Young group, the rate of cortical thinning was highly heterogenous, with much slower rates of thinning in the superior temporal, pericalcarine, and lingual regions. In contrast, the rates of cortical thinning were considerably slower in the Old group, where the most rapid changes were on the order of, at most, 3% per year, primarily in portions of the precentral, superior, middle, and inferior temporal and the precuneus; thinning of most other brain regions was much slower. The Mid group, in general, demonstrated rates of thinning intermediate between the Young and Old. It is noteworthy that this pattern was recapitulated in the corpus callosum, the major conduit for information transfer between the cortical hemispheres.[11] Total white matter and gray matter volume reductions were also significantly more rapid in the Young. Reductions in whole-brain volumes, although not significant, were also more rapid in Young subjects than in either Mid or Old subjects. The general implication is that phenotypic variability in Huntington's disease is, indeed, complex[16] and extends to include highly variable rates of progression.

Although the number of subjects studied was relatively small, the findings in the cortex were recapitulated in the more rapid volume loss in whole-brain volumes and in the corpus callosum in Young; rates in Old were significantly slower.

In contrast with the cortex and perhaps surprisingly, the rates of change in subcortical structures were not significantly different among the groups. Atrophy rates for the basal ganglia structures were consistent with what has been published previously.[17] Of note, the initial volumes measured in the Young group were significantly smaller than those of the other 2 groups, suggesting a potential "floor" effect. These findings also independently support an important role of the cortex in clinical progression.

Relationship to CAG Repeat Length

CAG repeat length appeared to have some influence on the rates of progressive thinning, but in only fewer than 11% of cortical regions was the correlation significant. In these regions, each increase in repeat length was associated with a 0.1% faster rate of change; a similar association has been reported with the TFC.[2,18] CAG repeats were, as expected, larger in the Young than in the Old, but there was considerable overlap with the Mid. There was no significant difference in CAG_n between Mid and Old; despite this, there was still a difference in the rates of thinning for many cortical regions, suggesting that cortical thinning is not strongly dependent on the CAG_n. It is also important to note that patients with repeat lengths in the ranges that have been associated with juvenile onset, typically larger than 55, were not included in these analyses, as juvenile HD is difficult to equate clinically with adult HD. We suspect that rates of progression in juvenile HD are even faster than our Young group.

We did not find any relationship between CAG_n and the rate of volume loss in any subcortical structure, but did find a relationship between the cross-sectional volume at the baseline scan and CAG_n, as has been reported previously.[19] Other studies have put into question the role of CAG_n in clinical heterogeneity.[16] Our findings suggest that CAG_n does not appear to play a significant role in the *rate* of atrophy for any structure or region, but rather, that once the genetic influence sets off the pathogenic cascade, subsequent factors dominate the pathology and influence disease progression much more than CAG_n. Our findings also illustrate the importance of carefully evaluating models developed from cross-sectional data in longitudinal studies.

Relationship to Clinical Progression

It is important to note that the groups were in similar stages of disease at the time of the first assessment, thereby reducing potential confounding because of disease severity; clinical rates of progression may vary according to stage.[20] Nevertheless, the change in the TFC in the Young group was more than double the change in either the Mid or the Old group. Typically, the TFC has been reported to change by approximately 0.72 units yearly. In our study, the Young had a mean reduction of approximately 2 points over 1 year, suggesting that the Young were also clinically progressing more quickly than expected; change scores in the Mid and Old, were closer to expected values.

Age, which has been shown to affect cortical changes independently, did not significantly influence regional rates of progression.

Conclusions

Selective vulnerability in the brain in Huntington's disease remains poorly understood. This selectivity appears to extend to regional cortical rates of progression. One possible explanation is differential transcriptional dysregulation, which is believed to be heterogeneous throughout the brain and may render certain regions more vulnerable.[21] Oxidative stress may independently contribute to vulnerability.[22–24] Differentially altered metabolism and cerebral perfusion may also be important; these, too, have been demonstrated to differ regionally.[25] If neither CAG_n nor age can fully account for the variability in progression, there must be additional environmental, genetic, or epigenetic factors that modulate progression.[26] Much remains to be understood about clinical heterogeneity in a disorder defined by a single genetic mutation.

Our findings also have important implications for clinical trials. At present, the high clinical variability in HD necessitates enrolling hundreds of patients who must be followed for years in neuroprotective phase III studies in which the TFC is the primary outcome measure. The TFC also has little power to provide preliminary evidence of efficacy in early-phase studies, so it is difficult to either systematically build preliminary data for promising therapies or to terminate them. Our study demonstrates that progression defined structurally by MRI is indeed highly variable. However, it also demonstrates that neuroimaging approaches can objectively and sensitively measure variability and thus help to contain it. Thus, there is great potential for neuroimaging to enhance our understanding of important phenotypic variability and to provide biomarkers to enhance the efficiency of clinical trials.

Caveats

The total number of subjects included in this study was small; findings need to be replicated. The Young group tended to have a longer CAG_n; although not unexpected, one cannot entirely rule out the potential influence of CAG_n on progression. Although adjustment for multiple comparisons was not done, the consistency of trends (higher rates in Young vs Mid and in Mid vs Old) observed in a majority of regions and the similarity of results using different analytical algorithms give us confidence that our conclusions would be replicated and supported in larger studies.

Acknowledgments: We are very grateful to the New England Center HDSA Center of Excellence and its patients who so generously contributed to this work. A special tribute to Jason.

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