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Basal ganglia atrophy in prodromal Huntington's disease is detectable over one year using automated segmentation

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Abstract

Background—Future clinical trials of neuroprotection in prodromal Huntington's (known as *preHD*) require sensitive *in vivo* imaging biomarkers to track disease progression over the shortest period. Since basal ganglia atrophy is the most prominent structural characteristic of Huntington's pathology, systematic assessment of longitudinal subcortical atrophy holds great potential for future biomarker development.

Methods—We studied 36 *preHD* and 22 age-matched controls using a novel method to quantify regional change from T₁-weighted structural images acquired one year apart. We assessed cross-sectional volume differences and longitudinal volumetric change in seven subcortical structures – the accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus.

Results—At baseline, accumbens, caudate, pallidum, and putamen volumes were reduced in *preHD* vs. controls (all $p < .01$). Longitudinally, atrophy was greater in *preHD* than controls in the caudate, pallidum, and putamen (all $p < .01$). Each structure showed a large between-group effect size, especially the pallidum where Cohen's d was 1.21. Using pallidal atrophy as a biomarker, we estimate that a hypothetical one-year neuroprotection study would require only 35 *preHD* per arm to detect a 50% slowing in atrophy and only 138 *preHD* per arm to detect a 25% slowing in atrophy.

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Conclusions—The effect sizes calculated for preHD basal ganglia atrophy over one year are some of the largest reported to date. Consequently, this translates to strikingly small sample size estimates that will greatly facilitate any future neuroprotection study. This underscores the utility of this automatic image segmentation and longitudinal nonlinear registration method for upcoming studies of preHD and other neurodegenerative disorders.

Keywords

Huntington's disease; prodromal HD; longitudinal atrophy; volumetric MRI; MRI biomarkers

INTRODUCTION

Intense efforts are underway to develop therapeutic agents that modify the course of Huntington's disease (HD)¹. For example, methods such as RNA interference have shown potential in mouse models of HD by reducing the expression of the mutant gene². However, before such strategies can be translated towards human benefit, the validation of disease-sensitive biomarkers is crucial. This is especially important for the prodromal stage of HD (also known as premanifest HD³, preclinical HD^{4, 5}, or abbreviated preHD³⁻⁵), i.e. before the onset of major neuronal cell death^{4, 5}. Additionally, the most useful biomarkers are those that are automated (which will facilitate multi-center deployment) and that can identify longitudinal change over a short period of time (e.g. one year).

Structural magnetic resonance imaging (MRI) has emerged as a strong potential source of preHD biomarkers. When comparing preHD with controls, cross-sectional structural differences are evident in cortical gray matter⁶⁻¹⁰, white matter⁸⁻¹¹, and subcortical structures, especially the striatum^{10, 12-15}. However, longitudinal studies that assess the magnitude of neurodegeneration across time can provide better insights for preHD biomarker development. While early longitudinal studies of volumetric change used manual tracing to delineate structures such as the caudate^{16, 17} – something both time consuming and prone to error due to inter-rater variability – recent studies have employed automated analysis methods¹⁸⁻²⁵. However, the available automated methods differ in sensitivity (to change across time) and specificity (in terms of the precision of affected structures). Several methods focus on whole-brain volumetric change, which can be detected in a period as short as one year with moderate between-group effect sizes^{24, 25}. One of these analyses, by Majid and colleagues²⁵, also estimated the number of individuals needed to detect a 50% slowing of atrophy in a hypothetical neuroprotection study, with the result that both treatment and placebo arms would require 74 preHD individuals, assuming they are within 6 years of clinical onset (i.e. near-onset).

An alternative to the whole-brain approach is to use regional volumetric measures, e.g. biomarkers focused on individual basal ganglia structures. These may be more sensitive to preHD change and thus require smaller sample sizes for future studies. In a two-year follow-up of the PREDICT-HD study, Aylward and colleagues²² showed greater preHD longitudinal change compared to controls in the caudate, putamen, pallidum, and thalamus. The effect sizes of these changes were moderate, ranging between 0.50 and 0.75, and the

authors calculated that approximately 150 to 400 near-onset preHD individuals would be needed to detect a 50% slowing in atrophy.

In the above study, Aylward and colleagues²² determined longitudinal change by taking the difference of volumetric measures obtained separately from the T₁ image at each timepoint. However, an alternative method of longitudinal analysis is to determine change by registering the two T₁ images together. This reduces variability and leads to larger between-group effect sizes. One such tool is the Caudate-specific Boundary Shift Integral (C-BSI)^{21, 24}. Whereas Aylward and colleagues²² report a moderate two-year caudate atrophy effect size of 0.6, this effect size increased to 0.9 when using C-BSI for the same two-year period²¹. Furthermore, C-BSI is also sensitive enough to detect preHD caudate atrophy in a shorter one-year period, increasing the feasibility of any future study²⁴.

A limitation of the C-BSI method is that it is constrained to the caudate, yet change in other subcortical structures could be even greater. Indeed, cross-sectional volume differences between preHD and controls suggest that atrophy in the accumbens, pallidum, and putamen is more predictive of HD motor disturbances than atrophy in the caudate¹⁵. In addition, Aylward and colleagues²² report that two-year putamen and pallidum longitudinal atrophy exceeds that of the caudate.

Here, we acquired T₁-weighted images at two timepoints one year apart. We used the Quarc (Quantitative anatomical regional change) analysis method, recently developed and validated in the Alzheimer's Disease Neuroimaging Initiative (ADNI)^{26, 27}. This measured longitudinal change in seven subcortical structures (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus). Here we show that this produces a very precise assessment of longitudinal change capable of detecting preHD atrophy with large effect sizes within just one year.

METHODS

Participants

There were 38 preHD (38 CAG repeats) and 22 healthy age- and sex-matched control participants. Consent was provided in accordance with an Institutional Review Board at the University of California, San Diego. Participants were studied longitudinally, on two visits, with a one-year interval between visits (Table 1).

Global cognitive ability was measured using the Mini-Mental State Exam (MMSE)²⁸ at both timepoints. A movement disorder specialist (JCB) evaluated the preHD participants with the Unified Huntington's Disease Rating Scale (UHDRS)²⁹. Based on this scale, participants were assigned a 'motor score' (range: 0 to 124) and were rated as to the level of confidence that the presenting motor abnormalities represent symptoms of HD (range: 0 to 4). A confidence rating of 0 represents a normal evaluation and no motor abnormalities, a rating of 1 represents < 50% confidence of an HD diagnosis, and a rating of 4 represents a definitive HD diagnosis. UHDRS scores were obtained from all participants at baseline and only from preHD participants at follow-up. All participants were rated below 2 at baseline, confirming preHD status. At follow-up, two initially preHD participants were rated 4, indicating

conversion to manifest HD. These were removed from the analysis, leaving a preHD group of 36. The length of the CAG repeat expansion was used to calculate estimated years-to-onset (YTO) using both the Aylward and Langbehn methods^{13, 30}.

MR Image acquisition

Data were acquired with a General Electric (Milwaukee, WI, USA) 1.5 T EXCITE HDx scanner (Software Version 14x) with an 8-channel phased-array head coil. Image acquisition included a General Electric “PURE” calibration sequence and a high-resolution three-dimensional T₁-weighted IRSPGR sequence (echo time = 2.798 msec, repetition time = 6.496 msec, inversion time = 600 msec, flip angle = 12°, bandwidth = 244.141 Hz/pixel, field of view = 24 cm, matrix = 256×192, slice thickness = 1.2 mm).

Baseline cross-sectional analysis of regional volume

Baseline images were corrected for spatial distortion due to gradient non-linearity³¹ and B₁ field inhomogeneity³². Volumetric segmentation^{33, 34} – using a probabilistic atlas and applying a Bayesian classification to assign a neuroanatomic label to each voxel – was performed using a data analysis pipeline based on the FreeSurfer software package (<http://surfer.nmr.mgh.harvard.edu/>) and customized Matlab code. The method is fully automated except for qualitative review by a trained operator in the case of occasional technical failures in segmentation.

The left and right volumes for each structure were summed and normalized based on a participant's total intracranial volume, e.g. (left caudate volume + right caudate volume)/intracranial volume.

Longitudinal analysis of regional volume change

The longitudinal analysis was performed on a subject-specific basis, using a recently developed method, Quarc (Quantitative anatomical regional change)^{26, 27}. Follow-up MRIs for each subject were fully affine-registered to the baseline image, and intensities were brought to local agreement (i.e. corrected for relative B₁-induced intensity distortion) using an iterative procedure. A deformation field was then calculated from the nonlinear registration and used to align scans at the sub-voxel level. From the deformation field a volume-change field is calculated, which, when integrated over the baseline segmentation for each subcortical structure, gives that structure's percentage volume change from baseline. The percentage change of the left and right hemisphere structures was then averaged and compared between groups.

Sample size calculations and power analysis

Based on our longitudinal results we estimated the sample sizes needed for a hypothetical two-arm study of neuroprotection in preHD. For each arm of the study (treatment vs. placebo), the minimum sample size required to detect slowing in the yearly atrophy rate can be computed using the following formula³⁵:

$$n = 2\sigma^2(z_{(1-\alpha/2)} + z_{\text{power}})^2 / (\Delta\beta)^2$$

Here, σ^2 is the variance of the longitudinal change for a particular structure in the preHD group, and z_x is the x th quantile of the standard normal distribution. Sample sizes were calculated for a study powered at either 90% or 80% and with a 5% two-sided significance level (α). δ denotes the desired detectable slowing in atrophy, calculated for both a 50% and 25% estimate. β denotes the magnitude of the yearly atrophy relative to controls³⁶, calculated by taking the difference between the mean change of the preHD group versus an age- and sex-based pair-matched subset of control subjects. Sample size 95% confidence intervals (CIs) were computed using the Matlab bootstrapping function *bootci* with 100,000 iterations.

RESULTS

Participant characteristics

At study entry, control and preHD groups had similar age and MMSE scores ($p=.941$ and $.132$, respectively) (Table 1). For MMSE, ANOVA [group $\times$ timepoint] revealed no between-group difference ($F(1,56)=1.347$, $p=.25$), but did show a main effect of time ($F(1,56)=7.658$, $p=.008$), with scores decreasing in both groups as time progressed. There was no interaction ($F<1$). Therefore, the groups were well-matched longitudinally. UHDRS motor scores were significantly elevated in preHD compared to controls at baseline ($t[56]=3.809$, $p<.001$), consistent with subtle motor signs, albeit insufficient to meet diagnostic criteria for manifest HD. Follow-up UHDRS motor scores were significantly elevated in the preHD group after the one-year duration, indicating a slightly worsening condition ($t[35]=3.292$, $p=.002$).

Baseline cross-sectional analysis

At baseline, volume was reduced in the accumbens, amygdala, caudate, pallidum, and putamen in preHD compared to controls (Table 2, Figure 1A). After Bonferroni correction, group differences were significant only for the accumbens, caudate, pallidum, and putamen. Within the preHD group, those patients with greater atrophy of the amygdala and pallidum had greater subclinical motor signs on the UHDRS (both $p<.05$) (see supplemental table 1). Furthermore, atrophy correlated with greater proximity to disease onset – caudate, pallidum, and putamen atrophy correlated with both the Langbehn and Aylward years-to-onset estimates, while accumbens atrophy correlated with the Langbehn estimate alone (all $p<.05$) (see supplemental table 1).

Longitudinal analysis using Quarc

Using the Quarc algorithm to assess longitudinal change, preHD showed greater change in the amygdala, caudate, pallidum, and putamen (Table 3, Figure 1B). After Bonferroni correction for multiple comparisons, the atrophy was significant only in the caudate, pallidum, and putamen. One-year preHD atrophy in each of these three structures correlated weakly with one or both years-to-onset estimates. Caudate change correlated with the Aylward estimate ($r[36]=.379$, $p=.022$) but not with the Langbehn estimate ($r[36]=.313$, $p=.063$). Putamen change correlated with the Langbehn estimate ($r[36]=.334$, $p=.046$) but not with the Aylward estimate ($p=.34$). Pallidal change correlated with both the Aylward estimate ($r[36]=.371$, $p=.026$) and the Langbehn estimate ($r[36]=.341$, $p=.042$). Longitudinal

change did not correlate with change in UHDRS motor score in any brain structure (all $p > .1$).

Sample size estimates

We estimated the sample sizes needed to power a two-arm neuroprotective treatment study (treatment vs. placebo) designed to detect either a 50% or 25% slowing of atrophy in each of the subcortical structures for which group differences were identified (Table 4).

Relative to controls, detecting a 50% slowing in atrophy with 90% power requires sample sizes of 103 for the caudate (95% CI: 91–2038), 58 for the putamen (95% CI: 53–829), and 35 for the pallidum (95% CI: 26–213) (Figure 1D). Detecting a more moderate 25% slowing with the same power requires sample sizes of 412 for the caudate (95% CI: 360–8038), 230 for the putamen (95% CI: 213–3221), and 138 for the pallidum (95% CI: 104–822).

Stratifying based on proximity to disease onset has been shown to further reduce the sample sizes needed^{22, 24, 25}. Using a subset of individuals in our preHD sample closest to disease onset (18 preHD out of total 36; 11.7 years to onset, Langbehn method), we find that sample sizes reduce only modestly. For instance, to detect a 25% slowing in pallidal atrophy, 115 individuals (95% CI: 57–597) would be required in each study arm with such stratification vs. 138 without (see above).

DISCUSSION

We used Freesurfer-based automatic segmentation to examine cross-sectional volume differences and Quarc to examine longitudinal volume change in preHD vs. controls. Seven subcortical structures were investigated at baseline and over a one-year period. At baseline, the accumbens, caudate, pallidum, and putamen were significantly smaller in preHD vs. controls. Moreover, the longitudinal analysis after follow-up showed that neurodegeneration in preHD can be identified within merely one year with large effect sizes for caudate, putamen and pallidum. For the pallidum, which showed the largest effect size, we estimate that only 35 preHD individuals would be required in both the treatment and placebo arms of a hypothetical study to detect a 50% slowing in atrophy with 90% power.

One-year subcortical atrophy did not correlate with change in UHDRS motor score. This, however, is expected in this preHD population, in whom, by definition, overt motor symptoms are too low to warrant diagnosis of manifest HD. Indeed, one of the strongest motivations for developing MRI biomarkers is to detect brain changes *before* symptoms emerge.

Striatal medium spiny neurons are disproportionally affected in HD³⁷. Consistent with this, cross-sectional preHD volume reductions were found in those structures populated by medium spiny cell bodies (i.e. the accumbens, caudate, and putamen, which collectively make up the striatum). Changes were also found in the pallidum, which receives axonal input from the striatum. Many cross-sectional studies have corroborated this pallidal involvement^{9, 12, 13, 15, 38, 39}. It should be noted that the pallidal changes we see are unlikely due to the death of cells whose bodies are within the pallidum. In histopathological studies

of late stage HD, for instance, volume loss in the pallidum is accompanied by a relative sparing of neuronal cell count and an increase in cell density⁴⁰. This suggests that pallidal volume loss may be due to the loss of striatopallidal fibers projecting from striatal medium spiny neurons (see Douaud et al.⁴¹ for in vivo imaging evidence). Both striatal and pallidal atrophy in preHD thus may result from the same pathological process of striatal medium spiny neuron loss.

Effect sizes for cross-sectional comparisons were large for each of these structures, ranging from 0.81 for the caudate to 1.50 for the putamen. Furthermore, volumes in all these structures correlated with years-to-onset estimates, suggesting a progressive course of the disease that our subsequent longitudinal findings confirm.

Within the one-year period, Quarc successfully detected volumetric change in the caudate, pallidum, and putamen with large effect sizes for all three structures (0.88, 1.21, and 1.12, respectively, Figure 1C). By contrast, the corresponding effect sizes reported in the two-year follow-up of the PREDICT-HD study were moderate (0.60, 0.67, and 0.63, respectively)²². This suggests that Quarc may provide a definitive improvement in identifying change in shorter amounts of time. Furthermore, Quarc extends the benefit of tools that have been specialized for longitudinal analysis, such as the Caudate Boundary Shift Integral (C-BSI) method^{21, 24}, to a greater number of subcortical structures. Indeed, as we have shown, yearly preHD atrophy in both the pallidum and putamen shows considerably larger effect sizes compared to caudate atrophy in this and other studies^{15, 22} and may thus serve as a stronger biomarker.

Confirming the benefits of Quarc over other analysis tools will require a comparison of each method applied to the same subject data, which we have not done here. We cannot therefore conclude that Quarc is superior to all other methods previously used to assess longitudinal change in preHD. However, head-to-head comparison of similar methods in the ADNI dataset has revealed benefits of Quarc (in terms of larger identifiable effect sizes in detecting Alzheimer's disease-related changes) when compared to the standard FreeSurfer-cross-sectional and FreeSurfer-longitudinal methods²⁶. These are related to the method previously used by Aylward and colleagues²². Additionally, Quarc also showed some slight benefit in whole-brain quantification of change compared to the standard BSI method (KN-BSI), though this was not found to be significant²⁶. Thus, while the other longitudinal analysis methods applied to preHD may also yield results as strong as what we have shown here, our findings do flag the use of Quarc as having great potential in future studies of preHD neuroprotection.

These findings – effect sizes larger than any previously reported in preHD research to date – have clinical relevance in translating into smaller sample sizes required for such future therapeutic trials. Here, we calculated that approximately 103 preHD individuals would be required in each therapeutic study arm (treatment vs. placebo) to detect a 50% slowing in caudate atrophy with 90% power. This dropped to 58 preHD individuals in each study arm for the putamen and to only 35 for the pallidum (Figure 1D).

Focusing on a subgroup of preHD participants who are closer to disease onset has been shown to reduce sample sizes^{22, 24, 25}. Here we find only moderate sample size reductions with this approach. Although subject stratification does provide some benefit, Quarc's ability to yield small, feasible sample sizes in a non-stratified preHD population further argues for the strength of the Quarc longitudinal methodology.

By contrast, the two-year follow-up of the PREDICT-HD study estimated sample sizes of 235 near-onset preHD individuals (10 years to onset, Langbehn method) to detect a 50% slowing of caudate atrophy and 188 for pallidal atrophy²². The most useful biomarker reported by the PREDICT-HD study, however, was change in cerebral white matter volume, which we did not study. Even with this measure, an estimated 61 near-onset preHD individuals are needed to detect a 50% slowing in atrophy over two years²². Thus, Quarc may offer the ability to detect a similar therapeutic improvement with fewer preHD individuals, within a time period that is half the length, and without constraints on participant inclusion based on proximity to estimated disease onset.

Future HD therapies are likely to have a moderate protective effect, and the expectation of a 50% slowing in atrophy may be difficult to achieve. A moderate expectation of a 25% slowing is more likely but will also require larger sample sizes (see Table 4). Nonetheless, the Quarc-based estimates still remain well within feasibility, requiring only 138 individuals in each study arm when using pallidal atrophy as a biomarker.

In summary, our results complement and extend recent results, showing that automated subcortical segmentation combined with longitudinal nonlinear registration can detect disease-related volumetric change within a short one-year time period. We used Quarc, which evidently shows improvements over available methods, be they whole brain^{24, 25} or regionally specific^{21, 22, 24}. Quarc can simultaneously evaluate longitudinal change in several subcortical structures, yielding large effect sizes for the caudate, pallidum, and putamen between preHD and controls. In the case of the pallidum, effect sizes were larger than any yet reported. This sets the stage for large-scale clinical trials of neuroprotective agents, which will be highly feasible given the relatively small sample size and study length requirements demonstrated here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Elan Corporation, the University of Rochester, the Alzheimer's Disease Cooperative Study, and the Huntington's Study Group. Dr. Dale is a founder and holds equity in CorTechs Labs and also serves on its Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. A patent application for Quarc has been filed by Dr. Dale through the UCSD Technology Transfer Office.

REFERENCE LIST

1. Fecke W, Gianfriddo M, Gaviraghi G, Terstappen GC, Heitz F. Small molecule drug discovery for Huntington's Disease. *Drug Discov Today*. 2009; 14(9–10):453–464. [PubMed: 19429504]
2. Boudreau RL, McBride JL, Martins I, et al. Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice. *Mol Ther*. 2009; 17(6):1053–1063. [PubMed: 19240687]
3. Tabrizi SJ, Scahill RI, Durr A, et al. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol*. 2011; 10(1):31–42. [PubMed: 21130037]
4. Aylward EH. Change in MRI striatal volumes as a biomarker in preclinical Huntington's disease. *Brain research bulletin*. 2007; 72(2–3):152–158. [PubMed: 17352939]
5. Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. *Brain research reviews*. 2008; 58(1):209–225. [PubMed: 18486229]
6. Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology*. 2005; 65(5):745–747. [PubMed: 16157910]
7. Nopoulos P, Magnotta V, Mikos A, Paulson H, Andreasen N, Paulsen J. Morphology of the cerebral cortex in preclinical Huntington's disease. *The American journal of psychiatry*. 2007; 164(9):1428–1434. [PubMed: 17728429]
8. Stoffers D, Sheldon S, Kuperman JM, Goldstein J, Corey-Bloom J, Aron AR. Contrasting gray and white matter changes in preclinical Huntington disease: an MRI study. *Neurology*. 2010; 74(15):1208–1216. [PubMed: 20385893]
9. Paulsen JS, Nopoulos PC, Aylward E, et al. Striatal and white matter predictors of estimated diagnosis for Huntington disease. *Brain research bulletin*. 2010
10. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol*. 2009; 8(9):791–801. [PubMed: 19646924]
11. Squitieri F, Cannella M, Simonelli M, et al. Distinct brain volume changes correlating with clinical stage, disease progression rate, mutation size, and age at onset prediction as early biomarkers of brain atrophy in Huntington's disease. *CNS neuroscience & therapeutics*. 2009; 15(1):1–11. [PubMed: 19228174]
12. Aylward E, Brandt J, Codori A, Mangus R, Barta P, Harris G. Reduced basal ganglia volume associated with the gene for Huntington's disease in asymptomatic at-risk persons. *Neurology*. 1994; 44(5):823–828. [PubMed: 8190282]
13. Aylward EH, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt J. Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. *Arch Neurol*. 1996; 53(12):1293–1296. [PubMed: 8970459]
14. Paulsen JS, Magnotta VA, Mikos AE, et al. Brain structure in preclinical Huntington's disease. *Biol Psychiatry*. 2006; 59(1):57–63. [PubMed: 16112655]
15. van den Bogaard SJ, Dumas EM, Acharya TP, et al. Early atrophy of pallidum and accumbens nucleus in Huntington's disease. *J Neurol*. 2010
16. Aylward E, Li Q, Stine O, et al. Longitudinal change in basal ganglia volume in patients with Huntington's disease. *Neurology*. 1997; 48(2):394–399. [PubMed: 9040728]
17. Aylward EH, Sparks BF, Field KM, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. *Neurology*. 2004; 63(1):66–72. [PubMed: 15249612]

18. Kipps CM, Duggins AJ, Mahant N, Gomes L, Ashburner J, McCusker EA. Progression of structural neuropathology in preclinical Huntington's disease: a tensor based morphometry study. *J Neurol Neurosurg Psychiatr*. 2005; 76(5):650–655. [PubMed: 15834021]
19. Hobbs NZ, Henley SMD, Ridgway G, et al. The Progression of Regional Atrophy in Premanifest and Early Huntington's Disease: A Longitudinal Voxel-Based Morphometry Study. *J Neurol Neurosurg Psychiatr*. 2009
20. Henley SMD, Wild EJ, Hobbs NZ, et al. Whole-brain atrophy as a measure of progression in premanifest and early Huntington's disease. *Mov Disord*. 2009; 24(6):932–936. [PubMed: 19243073]
21. Hobbs NZ, Henley SMD, Wild EJ, et al. Automated quantification of caudate atrophy by local registration of serial MRI: evaluation and application in Huntington's disease. *Neuroimage*. 2009; 47(4):1659–1665. [PubMed: 19523522]
22. Aylward EH, Nopoulos PC, Ross CA, et al. Longitudinal change in regional brain volumes in prodromal Huntington disease. *J Neurol Neurosurg Psychiatr*. 2010
23. Wild EJ, Henley SMD, Hobbs NZ, et al. Rate and acceleration of whole-brain atrophy in premanifest and early Huntington's disease. *Mov Disord*. 2010; 25(7):888–895. [PubMed: 20461806]
24. Tabrizi SJ, Scahill RI, Durr A, et al. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol*. 2011; 10(1):31–42. [PubMed: 21130037]
25. Majid DS, Stoffers D, Sheldon S, et al. Automated structural imaging analysis detects premanifest Huntington's disease neurodegeneration within 1 year. *Mov Disord*. 2011
26. Holland D, Dale AM. Nonlinear registration of longitudinal images and measurement of change in regions of interest. *Med Image Anal*. 2011
27. Holland D, Brewer JB, Hagler DJ, et al. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2009; 106(49):20954–20959. [PubMed: 19996185]
28. Folstein M, Folstein S, McHugh P. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–198. [PubMed: 1202204]
29. Group HsS. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord*. 1996; 11(2):136–142. [PubMed: 8684382]
30. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR, Group IHsDC. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet*. 2004; 65(4):267–277. [PubMed: 15025718]
31. Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *Neuroimage*. 2006; 30(2):436–443. [PubMed: 16300968]
32. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998; 17(1):87–97. [PubMed: 9617910]
33. Fischl B, Salat D, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33(3):341–355. [PubMed: 11832223]
34. Fischl B, Salat DH, van der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004; 23(Suppl 1):S69–84. [PubMed: 15501102]
35. Fitzmaurice, GM., Laird, NM., Ware, JH. *Applied Longitudinal Analysis*. Boston: John Wiley & Sons; 2004.
36. Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. *Arch Neurol*. 2000; 57(3):339–344. [PubMed: 10714659]
37. Graveland GA, Williams RS, DiFiglia M. Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. *Science*. 1985; 227(4688):770–773. [PubMed: 3155875]
38. Campodonico J, Aylward E, Codori A, et al. When does Huntington's disease begin? *J Int Neuropsychol Soc*. 1998; 4(5):467–473. [PubMed: 9745236]

39. Jurgens CK, van de Wiel L, van Es ACGM, et al. Basal ganglia volume and clinical correlates in 'preclinical' Huntington's disease. *J Neurol*. 2008; 255(11):1785–1791. [PubMed: 19156490]
40. Wakai M, Takahashi A, Hashizume Y. A histometrical study on the globus pallidus in Huntington's disease. *J Neurol Sci*. 1993; 119(1):18–27. [PubMed: 8246007]
41. Douaud G, Behrens TE, Poupon C, et al. In vivo evidence for the selective subcortical degeneration in Huntington's disease. *Neuroimage*. 2009; 46(4):958–966. [PubMed: 19332141]

Figure 1.

Subcortical atrophy over one year can provide powerful biomarkers in preHD A) Cross-sectional differences at baseline. PreHD volume reductions in the accumbens, caudate, pallidum, and putamen were significant after Bonferroni correction. B) Longitudinal volume change. One-year percent volume change in the caudate, pallidum, and putamen was significantly greater in preHD after Bonferroni correction. C) Longitudinal between-group effect sizes for structures with significant preHD change. D) Estimated sample sizes needed for both arms (treatment vs. placebo) of a hypothetical neuroprotection study to detect a 50% slowing in atrophy of a particular structure. The study is powered at 90% with a 5% two-sided significance level.

Abbreviations: Ac. – Accumbens; Am. – Amygdala; Cau. – Caudate; Hip. – Hippocampus; Pal. – Pallidum; Put. – Putamen; Thal. – Thalamus.

Table 1

Participant characterization by group

	Controls (N=22)		PreHD (N=36)	
	Baseline	Follow-up	Baseline	Follow-up
Age at start (yrs, mean± SD)	40.1±12.2		40.4±10.3	
Sex (F/M)	15/7		20/16	
Between-scan interval (yrs, mean ± SD)	1.0±.1		1.0±.1	
MMSE (mean ± SD) *	28.8±1.4	28.4±1.7	29.2±1.0	28.4±1.5
Number of CAG repeats (mean ± SD) [range]	N/A		42.4±2.4 [38–48]	
Estimated years-to-onset, Aylward method (yrs, mean ± SD)	N/A		6.3±7.3	
Estimated years-to-onset, Langbehn method (yrs, mean ± SD)	N/A		14.4±7.2	
UHDRS motor score (mean ± SD) **	0.1±0.3	N/A	1.5±1.7	3.8±4.5
UHDRS confidence score (<i>score</i> : # of participants)	0: 22	N/A	0: 24 1: 12	0: 16 1: 10 2: 9 3: 1

SD = standard deviation, MMSE = Mini-mental state exam, CAG = cytosine-adenine-guanine, UHDRS = Unified Huntington's Disease Rating Scale, PreHD = prodromal/premanifest Huntington's disease, N/A = not applicable

* ANOVA revealed main effect of time ($p=.008$) but no effect of group.

** Significantly different between groups at baseline ($p<.001$) and between timepoints in preHD group ($p=.002$). UHDRS was not obtained for controls at follow-up.

Table 2

Baseline volume differences

	Control (N=22)	PreHD (N=36)	t-statistic (56 d.f.)	p-value	Effect size (Cohen's <i>d</i>)
Accumbens *	0.08 ± 0.01	0.07 ± 0.01	3.100	.003	0.84
Amygdala	0.21 ± 0.02	0.20 ± 0.02	2.107	.040	0.58
Caudate *	0.46 ± 0.05	0.42 ± 0.06	2.949	.005	0.81
Hippocampus	0.54 ± 0.04	0.51 ± 0.05	1.809	.076	0.49
Pallidum *	0.23 ± 0.02	0.21 ± 0.03	3.166	.002	0.88
Putamen *	0.67 ± 0.06	0.57 ± 0.08	5.379	<.001	1.50
Thalamus	0.89 ± 0.07	0.88 ± 0.08	0.609	.545	0.17

Values indicate percent total intracranial volume summed bilaterally ± standard deviation

* Significantly different after Bonferroni correction ($p < .05/7 = .007$)

Table 3

Percent volume change from baseline over one year

	Control (N=22)	PreHD (N=36)	t-statistic (56 d.f.)	p-value	Effect size (Cohen's <i>d</i>)
Accumbens	-0.86 ± 1.10	-1.23 ± 1.66	0.924	.36	0.26
Amygdala	-0.25 ± 0.78	0.44 ± 1.33	-2.200	.032	0.63
Caudate *	-0.37 ± 1.31	-1.58 ± 1.42	3.234	.002	0.88
Hippocampus	-0.02 ± 0.72	0.22 ± 0.84	-1.087	.282	0.30
Pallidum *	0.09 ± 0.67	-0.68 ± 0.59	4.541	<.001	1.21
Putamen *	-0.19 ± 0.69	-0.95 ± 0.68	4.132	<.001	1.12
Thalamus	-0.33 ± 0.73	-0.42 ± 0.68	0.461	.646	0.12

Values indicate percent volume change averaged bilaterally ± standard deviation

* Significantly different after Bonferroni correction ($p < .05/7 = .007$)

Table 4**Power analysis**

Sample sizes needed to detect a given slowing in yearly atrophy in a two-arm neuroprotection study using a 5% two-sided significance level compared to controls. Parentheses indicated 95% confidence interval.

<i>Study Power</i>	90%		80%	
<i>Atrophy Slowing</i>	50%	25%	50%	25%
Caudate	103 (91–2038)	412 (360–8038)	77 (68–1521)	308 (269–5999)
Pallidum	35 (26–213)	138 (104–822)	26 (20–159)	103 (78–614)
Putamen	58 (53–829)	230 (213–3221)	43 (40–619)	172 (159–2404)