Mapping Regional Brain Aging in Huntington's Disease Using Structural MRI and Machine Learning

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ABSTRACT

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder. Models of brain biological age have shown evidence of accelerated aging relative to chronological age, but they typically rely on a single whole-brain measure. While studies in other neurodegenerative diseases suggest region-specific brain age models can provide deeper insights, this approach remains underexplored in HD. Such regional models could benefit clinical trials, which depend on sensitive biomarkers to monitor therapeutic effects.

Objectives: This study aimed to characterise region-specific patterns of brain aging across HD-ISS stages and evaluate their associations with cognitive, motor, and functional scores.

Methods: We employed machine learning to train brain age models on structural MRI data from 1,936 controls. These models were applied to 531 persons with HD. Associations between regional brain age gap, HD-ISS stages, and clinical scores were assessed.

Results: Whole-brain aging increased progressively at HD-ISS stages 2 and 3. Region-specific analyses revealed the dominance of subcortical, temporal, and parietal aging trajectories, which exhibited significant stage-wise increases in brain age gap. A higher brain age gap in these regions was associated with declines in cognitive, motor, and functional performance. In contrast, insular and frontal regions showed flatter patterns and no significant associations with clinical measures.

Conclusion: This study highlights distinct region-specific components of brain aging in HD. Regional analysis provides deeper insights into HD progression and could be employed as a sensitive biomarker for monitoring therapeutic effects in clinical trials. Future work should explore these findings in younger cohorts and investigate network-specific aging with multimodal imaging.

Key Words: Huntington's Disease; Neuroimaging; Regional Brain Aging; Biomarkers; Clinical Trials; Machine Learning

1. Introduction

Disease-modifying clinical trials in Huntington's Disease (HD) rely on sensitive monitoring biomarkers[1] to screen for intervention effects, especially in the early stages when detectable clinical symptoms are absent.[2] This is crucial as a shift has emerged toward conducting preventive interventions even before the onset of clinical symptoms.[3] To date, various imaging biomarkers have been proposed that characterise the underlying mechanisms of HD progression.[4] For example, volume loss in the caudate and putamen, as early indicators of pathogenesis caused by the mutant huntingtin protein (mHTT), are incorporated into the Huntington's Disease Integrated Staging System (HD-ISS). This paves the way for early-stage trials by providing a comprehensive framework for classifying the entire HD course, including all persons with HD (PwHD).[5]

However, neurodegeneration in HD is not limited to the striatum; it spreads through the brain's connectome to other subcortical and cortical regions.[6] Therefore, enhanced metrics that encompass the brain in its entirety may be more effective in tracking disease progression.[7] In recent years, the concept of biological age has gained attention, offering a way to quantify how an organ's health deviates from the norm for individuals of the same chronological age. In this context, machine learning models leverage structural or functional brain features to estimate an individual's age.[8,9] The gap between the estimated age and the actual chronological age reflects deviations from normal brain aging patterns, seen in various neurological conditions.[10–13]

A study on participants in the GENERATION-HD1 tominersen trial (NCT03761849) revealed that their brain age was, on average, more than a decade older than their chronological age. Moreover, brain age significantly predicted clinical status, showing a strong correlation with disease severity, as measured by the composite Unified Huntington's Disease Rating Scale (cUHDRS), and outperformed chronological age, CAG repeats, and the CAG-age product (CAP) score.[14] Using brain age gap, as a measure of HD progression, five distinct states were identified,[15] as compared to the three common CAP score groups used for stratification (far, medium, and near to motor diagnosis).[16]

Brain age serves as a 'reverse' normative model that captures complex interactions between imaging-derived phenotypes. However, summarising these measurements into a single metric may oversimplify brain aging complexity.[17] A study highlighted this limitation, reporting that brain aging may involve up to 62 distinct aspects.[18] To address this limitation, localised brain age have emerged, where input features are segregated based on anatomical regions or functional networks.[19–21] This approach avoids oversimplifying brain aging dynamics by training multiple models, each capturing a specific feature of normal or neuropathologic brain aging.[22] Nonetheless, region-specific decomposition of brain age modelling remains unexplored in HD. Moreover, given the growing importance of HD-ISS as a standard framework in clinical trials, its integration with brain age modelling is critical.

Therefore, the present study: 1) investigates how brain age gap changes across HD-ISS stages; 2) provides a mapping of its regional trajectories; and 3) shows how they are associated with common HD motor, cognitive, and functional biomarkers. Findings from this research could potentially aid future HD trials by offering insights into expected neurodegeneration at each stage, enabling more efficient targeting of intervention endpoints and monitoring strategies.

2. Materials and methods

2.1. Datasets and participants

We used 3 Tesla T1-weighted MRI scans from non-huntingtin gene expansion carriers (non-HGEC) to train brain age models and applied them to data from PwHD. The datasets consisted of longitudinal observational studies including TRACK-HD,[7,23] TrackON-HD,[24] PREDICT-HD,[25,26] and IMAGE-HD[27,28] as well as cross-sectional studies including IXI, AOMIC,[29] SALD,[30] and NARPS.[31] The pooled datasets comprised 3,562 images from a total of 1,936 non-HGECs (1,087 females, age range: 18-82 years, mean age: 33.1) and 2,429 images from 531 PwHD (317 females, age range: 18.6-73.5 years, mean age: 43.1). Detailed demographic information is summarised in Table 1. Supplementary Figures S1 and S2 show the distribution of the number of scans per individual, where a single stage is presumed for PwHD who progress to a more advanced stage. For cross-sectional datasets, each participant contributed a single scan, so the number of scans equalled the number of individuals. For a description of the clinical measures in Table 1, see Supplementary Materials.

2.2. Brain imaging-derived phenotypes

All the images in the datasets (Section 2.1) were processed using FreeSurfer v6.0 to extract a total of 354 morphological features related to both grey matter and white matter. From segmented subcortical structures, bilateral volumes (mm^3) were measured. Features derived from parcellated cortical regions included bilateral volumes (mm^3), thicknesses (mm), surface area (mm^2), mean curvature (mm^{-1}), and white matter volumes (mm^3). Supplementary Table S1 details specific scanner and acquisition protocol for each cohort. Although scanner parameters varied slightly across sites, all T1-weighted images were pre-processed using the same pipeline and quality-controlled to ensure comparable measures. The quality control

procedure is detailed in our previous work.[32] We applied neuroCombat harmonization[33] to the derived morphometric measures in the non-HGECs. Sex was included as a covariate to preserve biological variability, and harmonization was performed using empirical Bayes estimates with cohort as the batch variable. This approach removes scanner-related additive effects while retaining variance related to biological covariates.

2.3. Brain age models: training, validation, and utilisation

To train brain age models for the whole brain as well as the six segregated regions of interest (ROIs), we used Light Gradient-Boosting Machines (LightGBM).[34,35] The chronological age of non-HGECs at the time of the scan was used as the target output and imaging-derived features as inputs. To correct for the inherent bias toward the mean age of the aggregated training datasets, chronological age was regressed out from the predicted age gaps.[36] To evaluate the performance of the models, we used 10-fold cross-validation, with accuracy being assessed using Pearson's correlation coefficient (r) and mean absolute error (ε) between estimated and chronological age in non-HGECs,

For regional brain age models, we restricted the focus to the subcortex and to individual lobes defined by the Desikan-Killiany atlas: frontal, parietal, occipital, insular, or temporal.[37] Supplementary Table S2 enlists the sub-regional features for each segregated ROI. Sex was included as a covariate in all the models.

The whole-brain and region-specific models were applied to cross-sectional data in PwHD to compute brain age gap. For each HD-ISS stage, an age- and sex-matched non-HGEC group from TRACK, PREDICT, or IMAGE, unseen during training, was used for within-stage comparison. Spearman's correlation between age gaps and HD-ISS was calculated.

Additionally, Pearson's correlations between age gaps and cognitive, motor, and functional biomarkers were computed.

Using longitudinal scans from PwHD, regional brain age gaps were computed for all time points. Linear mixed-effect models (LMMs) were then fit to these gaps, adjusting for CAG repeat length and chronological age and assuming random intercepts for subjects.

3. Results

3.1. Whole-brain age model

Figure 1(A) illustrates predicted age versus chronological for non-HGECs. Utilising the trained model, age gaps for PwHD at baseline are estimated and shown in Figure 1(B), with stages stratified. The average age gap was positive at all HD-ISS stages, with between-stage differences significantly observed at stages 2 and 3. Within-stage comparison against matched non-HGECs revealed significant differences at all stages.

3.2. Associations between regional age gap and HD-ISS: cross-sectional analysis

Figure 2 shows how the distributions of region-specific age gaps differ from the whole-brain model. The strength of accelerated brain aging was quantified by measuring the Spearman's correlation (ρ) between age gaps and HD-ISS stages.

For the subcortex, temporal and parietal lobes, a progressive stage-wise increase in age gap was observed. Conversely, the occipital, insula, and frontal age gaps did not strongly associate with disease stages (non-significant or negative ρ). It is noteworthy that breaking down the set of input features when training the regional brain age models led to a loss of accuracy (compare

r and ε for the whole-brain and regional models in Figure 2). Supplementary Tables S3 and S4 compare the accuracy metrics of regression models other than LightGBM.

3.3. Cognitive, motor, and functional correlates of brain aging components

Using baseline data, associations between regional components of brain aging and cognitive, motor, and functional scores were measured. Significant results are shown in Table 2. All p-values were adjusted for multiple testing using the False Discovery Rate (FDR) method. The occipital region was not included in this analysis, since its model reliability was notably limited (see Figure 2: r = 0.64, ε = 9.6).

3.4. Trajectories of regional components of brain aging: longitudinal analysis

Figure 3 shows the LMM-predicted age gaps through HD-ISS stages at the median age (44.4 years) and median CAG (43), revealing region-specific trajectories of accelerated brain aging. The subcortical component exhibited the most pronounced stage-related increases, suggesting it was the primary driver of whole-brain aging effects. Significant stage effects were also observed in the temporal and parietal regions.

4. Discussion

In the present study, we employed the concept of brain biological aging to investigate how its trajectory, throughout HD-ISS stages, deviates from healthy cohorts. Most importantly, we focused on region-specific brain aging, predicted by anatomically segregated imaging-derived input features to gain a deeper understanding of how accelerated aging in HD can be disentangled into spatial components.

Our results revealed that, on average, all regions had older-appearing structure across all stages. While the whole-brain age gap progressively increased at HD-ISS stages 2 and 3, its trajectory was largely driven by the subcortical component, followed by temporal, and parietal. In contrast, the frontal and insular lobes exhibited relatively flatter trajectories. With respect to insular cortex volumetry, the measurements in the present study align with the findings of Douaud et al.[38] and Peinemann et al.,[39] where the insula showed atrophy compared with matched controls (see Supplementary Figures S9–S12). However, unlike the subcortical volumes, the insular cortex does not exhibit a consistent trajectory of decreasing volume across HD-ISS stages 0 to 3. Specifically, while significant differences from matched non-HGECs are evident in HD-ISS stages 2 and 3 for PwHD, the trajectory of insular cortical volume across all stages does not appear to reflect the same pattern of "accelerated aging" observed in the subcortex (compare $\rho = 0.54$ for the subcortical and $\rho = 0.01$ for the insular age gaps in Figure 2).

Evidence from molecular, cellular, animal, and system-level studies suggest abnormal cortical development in HD.[40–44] According to this hypothesis, the mHTT protein influences neurodevelopment long before striatal neurodegeneration becomes evident.[45] Kubera et al. found that cortical folding complexity for motor and visual areas of the cortex differed in pre-HD, compared to controls. However, the difference did not associate with putamen atrophy, suggesting that the cortical irregularity originated from a neurodevelopmental factor independent of the striatal neurodegeneration process.[46] Kids-HD[47] is an observational study focusing on participants aged 6–20 years, significantly younger than HD individuals in our study.[48] In this younger group, PwHD far from motor onset displayed larger brain volumes and distinct cortical morphometric patterns compared to non-HGECs. These differences were accompanied by better cognitive and behavioural performance.[49,50] Based on these findings, Kids-HD investigators suggested that mHTT may cause brain development in HD to involve

an atypical phase of advantageous brain growth and maturation that precedes the accelerated aging.[51] Similarly, among Enroll-HD participants in the neurodevelopmental phase of HD and far from their predicted motor onset, higher number of CAG repeats were associated with better cognitive scores.[52] Similarly, our analyses showed that brain aging in the frontal and insular lobes followed trajectories distinct from subcortical accelerated aging; however, we did not observe superior cognitive patterns. Nonetheless, it is crucial to apply brain age modelling to cohorts at HD-ISS stage 0 who are younger than those included in this study. Notably, as opposed to Kids-HD, the HD-YAS study did not report a cognitive advantage in pre-HD individuals far from motor onset.[53]

One of the limitations of the present study is the size of the normative population (non-HGECs) used for model training, especially when compared to the brain age literature.[54] This limitation is more critical for regional models, as their applicability becomes restricted due to reduced accuracy. For instance, despite substantial evidence that the occipital lobe is severely affected in HD,[55–57] and is associated with poorer cognitive and motor performance,[58] a flat trajectory was observed for this region in the current study, which should be interpreted with caution. Future studies should integrate finer features such as cortical gyrification[59] and explore advanced modelling approaches such as ensembled ML techniques or deep learning[13] that account for disease-specific brain changes during training,[60] not solely during deployment.

In summary, this study for the first time investigated region-specific and stage-wise brain biological aging in HD. We observed stage-related accelerated aging in the subcortical, temporal, and parietal regions. These findings underscore the importance of utilising region-specific brain age models, which provide greater insight into HD progression compared to whole-brain models. This could potentially inform future HD trials by enabling improved monitoring strategies for therapeutic effects. To translate the findings of this study, further

research with larger, more diverse cohorts is essential, along with the integration of advanced ML techniques to refine normative models and enhance prediction accuracy.

Ethics Statement

PREDICT-HD procedures were approved by the institutional review boards at each site (32 sites across the United States, Canada, Australia, and Europe). TRACK-HD and TrackON-HD were approved by the local ethics committees at each study site in the Netherlands, United Kingdom, France, and Canada. IMAGE-HD was approved by the Monash University and Melbourne Health Human Research Ethics Committees as a single site study in Melbourne, Australia. For all studies, each participant provided written informed consent. We also used publicly available datasets that were collected and shared under institutional ethical approval with informed consent for secondary data use: the Amsterdam Open MRI Collection, the Southwest University Adult Lifespan Dataset the Neuroimaging Analysis Replication and Prediction Study, and the IXI dataset.

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et al., 2021), the Southwest University Adult Lifespan Dataset (SALD) (Wei et al., 2018), the Neuroimaging Analysis Replication and Prediction Study (NARPS) (Botvinik-Nezer et al., 2019), and the IXI dataset (available at brain-development.org). We gratefully acknowledge the investigators and participants who contributed to these projects and made the data publicly available.

Data Availability Statement

AOMIC, SALD, and NARPS are open-access datasets that can be obtained from the OpenNeuro platform. IXI is publicly available from brain-development.org. TRACK-HD, TrackON-HD, IMAGE-HD, and PREDICT-HD datasets can be accessed upon request and subject to agreement with the CHDI Foundation through enroll-hd.org.

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(2) Statistical analysis: A. Design, B. Execution, C. Review and critique;

(3) Manuscript preparation: A. Writing of the first draft, B. Review and critique;

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Figure Captions

Figure 1. Brain age model training and utilisation: (**A**) 10-fold cross validation was used to measure accuracy metrics for a model fed with 'whole brain' features. r = Pearson's correlation coefficient and ε = mean absolute error between brain-predicted and actual chronological age. The identity line after bias correction is shown in green. (**B**) Brain age gap in PwHD compared against non-HGECs across HD-ISS stages.

Figure 2. Top: Stage-wise comparison of brain age gap distributions in PwHD for the whole-brain and regional models. **Middle**: ρ = Spearman's correlation between age gap and HD-ISS stage with corresponding p-values. significance: $p < 0.05$ (*), < 0.01 (**), < 0.001 (***); ns = not significant. **Bottom**: Metrics of model reliability, including r = Pearson's correlation coefficient and ε = mean absolute error between brain-predicted and actual chronological age in non-HGECs.

Figure 3. Linear mixed-effect models (LMMs) for mapping whole-brain and region-specific aging trajectories across HD-ISS stages. Accelerated aging was most prominent in the subcortical region.

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