Differential tractography as a dynamic imaging biomarker: A methodological pilot study for Huntington’s disease

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ABSTRACT

Huntington’s disease (HD) is a neurodegenerative disorder characterized by motor, psychiatric, and cognitive symptoms. Due to its diverse manifestations, the scientific community has long recognized the need for sensitive, objective, individualized, and dynamic disease assessment tools. We examined the feasibility of Differential Tractography as a biomarker to evaluate correlation of symptom severity and of HD progression at the individual level. Differential tractography is a novel tractography modality that maps pathways with axonal injury characterized by a decrease of anisotropic diffusion pattern. We recruited sixteen patients scanned at 0-, 6-, and 12-month intervals by diffusion MRI scans for differential tractography assessment and correlated its volumetric findings with the Unified Huntington’s Disease Rating Scale (UHDRS). Deterministic fiber tracking algorithm was applied. Longitudinal data was modeled using the generalized estimating equation (GEE) model and correlated with UHDRS scores, in addition to Spearman correlation for cross-sectional data. Our results show that volumes of affected pathways revealed by differential tractography significantly correlated with UHDRS scores in longitudinal data (p-value < 0.001), and chronological changes in differential tractography also correlated with the changes in UHDRS (p-value < 0.001). This technique opens new clinical avenues as a clinical translational tool to evaluate presymptomatic and symptomatic gene positive individuals. Our results provide support that differential tractography has the potential to be used as a dynamic imaging biomarker to assess at the individual level in a non-invasive manner, disease progression in HD. Critically important, differential tractography proves to be a quantitative tool for following degeneration in presymptomatic patients, with potential applications in clinical trials.

1. Introduction

Huntington’s disease (HD) is a progressive chronic neurodegenerative disorder, resulting from a mutation in the huntingtin gene consisting of a CAG repeat expansion. The resulting protein has an expanded glutamine repeat near the N-terminus, resulting in a toxic gain of function. No effective treatment is available for HD, and the disease is universally fatal. Hallmarks of HD include choreic movements, extrapyramidal motor abnormalities, and cognitive impairment. HD patients may also present with behavioral abnormalities including anxiety, depression and compulsive behaviors (Craufurd et al., 2001). A reliable approach to evaluate disease severity and progression has been challenging in HD. The assessment of the severity of clinical symptoms relies mostly on the Unified Huntington’s Disease Rating Scale (UHDRS) for disease stage stratification (Kieburtz et al., 2001). UHDRS evaluates the motor, cognitive, behavioral, and functional capacity allowing for a quantitative assessment based on clinical presentation. Despite the usefulness of UHDRS, there is still an ongoing need for an objective

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imaging biomarker to assess disease onset, progression, and severity. Studies such as PREDICT-HD (Biglan et al., 2009) and TRACK-HD (Tabrizi et al., 2009) have used standard MRI to quantify gross structural findings and investigate the correlation between neuroimaging findings with cognitive and biological imaging and motor outcome measures. TRACK-HD correlated volumetric MRI with UHDRS in premanifest and manifest patients. Both PREDICT-HD and TRACK-HD confirmed previous reports supporting the value of imaging markers, especially of striatal and whole-brain atrophy during the premanifest stage (Biglan et al., 2009; Tabrizi et al., 2009). A recent study (Zeun et al., 2022) that applied fixel-based analysis in a large sample of premanifest individuals suggests that white matter structures such as the cortico-basal ganglia display signs of degeneration or “vulnerability” at around 11–25 years after diagnosis, with preserved integrity as early as 25 years before diagnosis has been established. In addition, the aforementioned study observed that the sensory and motor components of the thalamus and the limbic and motor striatum have demonstrated to be at risk in this population, suggesting that clear observable white matter changes at the voxel level can be demonstrated years after diagnosis and not during the premanifest phase. These interesting findings allow the opportunity for the emergence of biomarkers capable of detecting onset of neurodegeneration before clinical manifestations, which in turn, with early initiation of disease modifying therapies, can potentially represent a better quality of life for these patients. Other studies have shown that white matter atrophy is evident in T1-weighted MRI with posterior-frontal white matter degeneration evident in at-risk individuals far from disease onset (Tabrizi et al., 2009). Structural MRI allows for the examination of gradual changes that occur in premanifest HD with MRI studies showing that these subjects have brain atrophy years before disease manifestation in pyramidal projection neurons in the motor and prefrontal cortices, and cingulate and angular gyri (Macdonald and Halliday, 2002; Thu et al., 2010). However, volumetric findings in the above-mentioned studies applied a group-based approach and individual difference are of the utmost importance for clinical applications. Although it is recognized that structural MRI has been sensitive to measure for neuronal loss and total volume measurement in grey and white matter cortical areas (Tan et al., 2021), there is still ongoing efforts to increase the search for specific markers for localization of volume loss and atrophy (Adanyeguh et al., 2021).

White matter changes have been studied by implementing diffusion MRI to explore its clinical value in neurodegeneration. Techniques such as Diffusion Tensor Imaging (DTI) (Basser et al., 1994) are capable of detecting structural changes in axonal pathways in HD patients (Dumas et al., 2012; Georgiou-Karistianis et al., 2011; Gregory et al., 2015; Kloppe et al., 2008; Phillips et al., 2013; Poudel et al., 2014; Rosas et al., 2010; Ross et al., 2014; Weaver et al., 2009). Disruption of several white matter pathways including cortico-striatal motor projections, cingulum, uncinate fasciculus, thalamocortical projections, corpus callosum, and corticospinal tract, have been found in HD (Dumas et al., 2012; Georgiou-Karistianis et al., 2011; Müller et al., 2013; Nopoulos et al., 2010; Phillips et al., 2013; Rosas et al., 2010; Weaver et al., 2009). Furthermore, cognitive and motor parameters correlated with white matter DTI alterations in several studies (Dumas et al., 2012; Georgiou-Karistianis et al., 2011; Gregory et al., 2015; Phillips et al., 2013; Poudel et al., 2014; Rosas et al., 2010; Ross et al., 2014; Weaver et al., 2009). DTI remains a commonly used technique to study structural white matter changes in neurodegeneration, however, its clinical applications are limited due to its inability to resolve complex fiber orientations in the presence of free water (i.e., CSF volume acting as an artifact) (Berlot et al., 2014; Jeurissen et al., 2013; Metzler-Baddeley et al., 2012), while still only demonstrating a difference in HD patients at a group level when compared to a control population. Recent studies have applied beyond-DTI methods such as fixel-based analyses using constraint spherical deconvolution (CSD) in early HD (Adanyeguh et al., 2021; Oh et al., 2021) and in premanifest HD (Zeun et al., 2022) to identify neurodegeneration in HD. However, although the fixel-based approach provides a high angular resolution advantage (Tournier et al., 2004), several technical considerations need to be taken to avoid a critical flaw in tractography clinical studies (Parker et al., 2013). Furthermore, the acceptance that DTI-based metrics are non-specific for neurodegeneration and disease progression assessment, warrants the opportunity to move beyond DTI-based approaches (Farquharson et al., 2013; Fernandez-Miranda, 2013; Tournier et al., 2004).

Recently advanced diffusion MRI has acquired a more sophisticated diffusion model by resolving multiple diffusion sensitization and hundreds of diffusion sampling directions (Sotirios et al., 2013). This significant improvement has allowed to resolve complex fiber orientation by using or resorting to a nonparametric approach (Tuch et al., 2003). This has led to the development of beyond-DTI tractography that can handle crossing-fibers (Tournier et al., 2011) and cope with the partial volume of free water (Zhang et al., 2013). Beyond-DTI tractography has been used in patients with aphasia to demonstrate a clear functional correlation of tractography white matter fiber bundles such as the arcuate fasciculus (AF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), and middle longitudinal fasciculus (MLF) with semantic and phonological abilities involved in language production (Hula et al., 2020). Conventional tractography is not sensitive during early neuronal degeneration as tractography differences can only be demonstrated if anisotropy drops substantially below the tracking threshold, and although diffusion MRI has been explored as a potential biomarker for early onset neurodegeneration, anisotropy as a measurement at the voxel level is susceptible to local variability including but not limited to partial volume effect (Henf et al., 2018; Wang et al., 2011; Yeh et al., 2019) restricting its potential in the clinical setting (Melonakos et al., 2011; Yeh et al., 2019). Our recent study demonstrated that differential tractography (Yeh et al., 2019) addressed these limitations by focusing on differences in anisotropy to track only the segment of the pathway with neuronal degeneration. In the aforementioned study, the analysis required two longitudinal scans of the same subjects to derive differences, but in the present study we implemented an advanced protocol that compared one patient’s scan with a cohort of control subjects. Differential tractography accomplishes a substantial improvement when compared to conventional tractography. The method performs a comparison of voxel-wise differences of diffusion properties, such as quantitative anisotropy (QA), allowing to only track changes resulting in highlighted tractograms with segments of degeneration. Volumes extracted from obtained tractograms result in a simple measurement of the amount of neurodegeneration. The volume of specific pathways with a decrease in anisotropy was used as a quantitative biomarker to correlate with clinical UHDRS scores. This novel modification allowed us to derive a numeric value of altered pathways for individual patients, hence enabling the opportunity to study the advantages of a true diffusion-based analysis technique as a clinical translational biomarker for early neuronal injury, in contrast to other techniques such as Tractwise Fractional Anisotropy Statistics (TFAS) which applies fiber tracks as a skeleton to obtain underlying voxel Fractional Anisotropy (FA) for statistical analysis (Müller et al., 2016). Furthermore, since differential tractography tracks neuronal injury along a fiber pathway, this provides the ability to differentiate true findings from errors occurring at the local voxel level, as errors generated locally stay within the local limits, versus true neuronal injury that disseminates along axons (Yeh et al., 2019).

In the present study we applied differential tractography in premanifest and manifest HD to localize differences in anisotropy between base and repeat scans, along with statistical correlation of anisotropic differences with UHDRS clinical scores, including total motor score (UHDRS TMS), dystonia total, chorea total, rapid alternating movements (RAM), strop color word, behavior, and total functional capacity (UHDRS TFC). In addition, compromised fiber pathways in HD patients were identified by comparing them with healthy controls and quantifying the volume of each affected pathways as a biomarker. Although we have not taken in consideration any hypothesis to specific
2. Materials and methods

2.1. Patient characteristics and demographics

We recruited sixteen patients, including twelve manifest HD patients and four pre-manifest patients (Table 1). All patients gave their informed consent prior to their inclusion in the study. Manifest were symptomatic and pre-manifest were asymptomatic (all confirmed gene positive). Patients had three scans over a period of two years. Twelve patients had three scans, one patient had two scans, and three patients had one scan. The average scan interval from the first to the second scan was 6 ± 0.4 months (range 5 to 10 months) and the average scan interval from the first to the third scan was 12 ± 1 months (range 11 to 24 months). Patients underwent a comprehensive clinical evaluation on the day of the scan conducted by a neurologist specializing in movement disorders. Previous to each MRI, subjects were evaluated to assess their Unified Huntington Disease Rating Scale (UHDRS) (Kieburtz et al., 2001) scores, including motor, behavior, cognitive and functional assessments. A reconstructed averaged template was included from the CMU-60 database, a compiled diffusion MRI dataset of 60 healthy individuals acquired with a 257-diffusion sampling direction that served as control for our study.

2.2. MRI acquisition

Diffusion spectrum imaging data were acquired on a 3 T Tim Trio System (Siemens, Erlangen, Germany) using a 32-channel coil. A head stabilizer was utilized to prevent head motion. A 25 min, 257-direction DSI scan with a twice-refocused spin-echo planar imaging sequence and System (Siemens, Erlangen, Germany) using a 32-channel coil. A head

2.2.1. Differential tractography for individuals

The flowchart of our revised differential tractography (Yeh et al., 2013a) analysis is demonstrated in Fig. 1. Diffusion imaging data of each patient (Fig. 1A) was reconstructed to a common stereotaxic space using a high-resolution anatomical image using a 9-min T1-weighted axial MP RAGE sequence (repetition time = 9116 ms, echo time = 157 ms, voxel size = 2.4 mm × 2.4 mm × 2.4 mm, field of view = 231 mm × 231 mm, maximum b-value = 7000 s/mm²) was performed. For anatomical comparison, we included a developed and open-source software DSI Studio (http://dsi-studio.labsolver.org). Deterministic tractography applies quantitative anisotropy (QA) which relies on generalized q-sampling imaging (GQI) to estimate the orientation of individual fibers (Yeh et al., 2010), and spin distribution function (SDF) to provide the amount or density of diffusing water in any direction within a single voxel (Yeh et al., 2016), therefore posing a great advantage over widely used diffusivity-based estimations such as FA. The tracking begins from each local fiber orientation as seeds and propagates until no orientation is found in the propagation direction. A maximum turning angle of 60° was used with a step size of 1 mm. The determined trajectories, termed the affected tracts, are used to identify pathways with decreased connectivity.

2.3. Statistical methods

We conducted a statistical analysis to determine the correlation of the UHDRS scores with quantitative data of each region of interest obtained by differential tractography. Data was evaluated using a one-sided t-test and was then organized by longitudinal and cross-sectional analyses to determine the efficacy of the dynamic biomarker tested and have more control over brain regions tested and their correlation with clinical scores.

Longitudinal measures of subjects were modeled using the generalized estimating equation (GEE) model, a linear model similar to the mixed effect model that can investigate the correlation between tract volume and the clinical scores that evaluated the cognitive levels and severity of the disease. Sandwich estimate of the variance was used to avoid violations of normality.

Using the GEE model, we correlated differential tractography findings and UHDRS total scores for motor, cognitive, behavior, and functional capacity. Since the motor scores include assessments to evaluate the motor dysfunction in detail, we further correlated differential tractography with subscores under the motor assessment, including Total Motor Score (TMS), Dystonia Total, Chorea Total and RapidAlternating Movements (RAM), to see whether there are meaningful findings specific to these subscore s. The same setting was applied to the cognitive component represented by the subscore Stroop Color-Word. Lastly, the UHDRS Behavioral Total, and TFC (Total Functional Capacity) scores were correlated. Using our novel method, we obtained several tract bundles with decreased anisotropy. All bundles obtained by differential tractography were further segmented into five different white matter regions, which included cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and the whole brain. This allowed us to study region-specific correlation.

Targeted fiber tracking analysis was performed for each scan using their corresponding differential tractography results. Quantitative data such as tract volume for each segmented region was registered as a reference for tract involvement, higher volumes indicate greater magnitude of affected tracts.

Table 1

| Patient demographics. | average (minimum — maximum) |
|-----------------------|-----------------------------|
| Age                   | 50.8 (36 — 62) |
| Age of onset          | 47 (37 — 56) |
| CAG Repeats           | 43 (41 — 46) |
| UHDRS TMS             | 27 (0 — 67) |
| UHDRS Behavior        | 11 (0 — 36) |
| UHDRS TFC             | 10 (2 — 14) |
| Stroop Color-Word     | 34 (0 — 63) |
Overall, a total of 35 comparisons were performed to determine statistical correlation, which translate to 35 hypotheses, one for each longitudinal and cross-sectional analyses. For cross-sectional analysis, we correlated the volume extracted from each fiber bundle with each clinical score. Furthermore, we correlated the change in tract volume with the change in clinical scores which yielded 35 hypotheses. Each hypothesis was tested in repeat scans of pre-manifest and manifest subjects using the GEE model. We also studied these 35 correlation hypotheses for each scan time point (scans 1, 2, and 3) as three independent cross-sectional studies using the Spearman correlation model, a nonparametric method to investigate the correlation using the rank of the tract values.

The longitudinal change in tract volume and the clinical scores of the above-mentioned 35 correlation hypotheses, were also studied using the GEE model for the manifest patients. Three separate Spearman correlation analyses were conducted to study the change between scan one and scan two, scan one and scan three, and scan two and scan three. The hypothesis was tested using a one-sided tail t-test. A p-value of 0.05 was corrected using Bonferroni correction to obtain familywise significance and eliminate false positive results, yielding a p-value of 0.001 or less to be considered statistically significant. All analyses were conducted in SAS 9.3.

The statistics of this study and its interpretation were supervised by a statistician (YF. C.).

3. Results

3.1. Individual differential tractography results

Table 2 shows differential tractography volume measurements of cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and whole brain in all manifest and premanifest subjects, which were mapped automatically by differential tractography. As noted in Table 2, increased tract volumes (mm$^3$) denote reduced tract integrity compared to normal population. The color red in Table 2 helps to differentiate tracts with higher volume (dark red color) from tracts with lower volumes (light red color). The UHDRS Total Motor Score (TMS) and differential tractography results were assessed independently. Differential tractography progression was demonstrated in nine out of twelve manifest subjects (75%), and in one out of four premanifest subject (25%) with a time-dependent increased volume of affected tracts. Subjects A, B, and C were selected to demonstrate a correlation based on their UHDRS TMS, in which higher deteriorating motor function was evident (Fig. 2). Higher UHDRS TMS indicates worse performance, and all three subjects demonstrated an increased volume of affected tracts, likely correlating with decreased connectivity (Fig. 2). This progression corresponded with UHDRS TMS higher scores at each measurement, with the exception of subject C, in which an increase in the volume of degenerating tracts did not correspond with UHDRS TMS, remaining unchanged at 6-months compared to the baseline scan. To visualize inter-individual variability, please refer to Table S1.

3.2. Manifest versus premanifest patients

Significant differences were observed in the manifest and premanifest group. Initial scans in symptomatic patients demonstrated a significant number of affected bundles. In contrast none or a small number of affected tracts in the premanifest group (Table S1). These results provide further validation of this technique in identifying affected pathways and distinguishing presymptomatic from symptomatic patients.

3.3. Longitudinal versus cross-sectional analyses

Longitudinal data was evaluated to determine the correlation between affected tract volumes and UHDRS clinical scores. We performed two longitudinal analyses and the time frame was 6–12 months. First, we studied the correlation between UHDRS clinical scores and tract volumes in each brain region (cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and whole brain). In addition, a second longitudinal analysis was performed to examine the correlation between change in clinical scores and the change in volumes of tracts, including cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and whole brain.

Out of 35 correlations in our initial longitudinal analysis, twelve (34.3%) showed statistical significance between tract volume and clinical scores, which included 2 correlations (5.7%) with statistical significance (p-value < 0.0001) and ten correlations (28.6%) statistically significant (p-value < 0.0001). In addition, all brain bundles (cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and whole brain) significantly correlated with clinical scores as follows. UHDRS TMS was statistically significant (p-value < 0.0001) in cingulum.
| Subject | Scan | Manifest/Premanifest | Cingulum Volume (mm$^3$) | Corpus Callosum Volume (mm$^3$) | Corticostratal Pathway Volume (mm$^3$) | Corticospinal Pathway Volume (mm$^3$) | Whole Brain Volume (mm$^3$) |
|---------|------|----------------------|-------------------------|-------------------------------|--------------------------------------|--------------------------------------|--------------------------|
| A       | 1    | Manifest             | 760                     | 6032                          | 4736                                 | 2224                                 | 15103                    |
|         | 2    |                      | 824                     | 5360                          | 5432                                 | 2040                                 | 17878                    |
|         | 3    |                      | 1176                    | 21152                         | 8176                                 | 17112                                | 39588                    |
| B       | 1    | Manifest             | 1872                    | 13336                         | 0                                    | 19816                                | 33236                    |
|         | 2    |                      | 4120                    | 35296                         | 6352                                 | 21992                                | 61214                    |
|         | 3    |                      | 2656                    | 26688                         | 3096                                 | 26096                                | 51240                    |
| C       | 1    | Manifest             | 952                     | 5248                          | 968                                  | 15944                                | 16502                    |
|         | 2    |                      | 1312                    | 21168                         | 3624                                 | 37496                                | 56512                    |
|         | 3    |                      | 2096                    | 23304                         | 6440                                 | 39296                                | 64686                    |
| D       | 1    | Manifest             | 0                       | 0                             | 0                                    | 0                                    | 5917                     |
|         | 2    |                      | 0                       | 0                             | 520                                  | 0                                    | 6323                     |
|         | 3    |                      | 0                       | 3184                          | 752                                  | 0                                    | 10370                    |
| E       | 1    | Manifest             | 3080                    | 40032                         | 4832                                 | 36200                                | 77794                    |
|         | 2    |                      | 5768                    | 41640                         | 608                                  | 31272                                | 80894                    |
| F       | 1    | Manifest             | 408                     | 5872                          | 688                                  | 1512                                 | 11690                    |
|         | 2    |                      | 0                       | 0                             | 1048                                 | 1176                                 | 6413                     |
|         | 3    |                      | 0                       | 0                             | 1352                                 | 0                                    | 5664                     |
| G       | 1    | Manifest             | 1608                    | 41504                         | 1896                                 | 43168                                | 87789                    |
|         | 2    |                      | 37064                   | 37064                         | 13280                                | 44872                                | 119938                   |
| H       | 1    | Premanifest          | 280                     | 9144                          | 7336                                 | 36184                                | 55752                    |
|         | 2    |                      | 0                       | 1216                          | 0                                    | 0                                    | 3769                     |
|         | 3    |                      | 0                       | 1984                          | 664                                  | 2680                                 | 6223                     |
| J       | 1    | Manifest             | 0                       | 19352                         | 4176                                 | 1736                                 | 23829                    |
|         | 2    |                      | 1232                    | 52248                         | 9672                                 | 42800                                | 97512                    |
|         | 3    |                      | 1856                    | 35184                         | 8168                                 | 16608                                | 60167                    |
| K       | 1    | Manifest             | 592                     | 9904                          | 1776                                 | 14976                                | 27213                    |
|         | 2    |                      | 2808                    | 48720                         | 3480                                 | 43592                                | 91088                    |
|         | 3    |                      | 2104                    | 28136                         | 7944                                 | 28216                                | 58704                    |
| L       | 1    | Premanifest          | 0                       | 0                             | 0                                    | 280                                  | 130                      |
| M       | 1    | Premanifest          | 0                       | 272                           | 840                                  | 5480                                 | 9763                     |
|         | 2    |                      | 0                       | 0                             | 0                                    | 0                                    | 0                        |
|         | 3    |                      | 0                       | 0                             | 0                                    | 0                                    | 0                        |
| N       | 1    | Premanifest          | 0                       | 0                             | 224                                  | 3328                                 | 5059                     |
|         | 2    |                      | 0                       | 0                             | 0                                    | 1192                                 | 2961                     |
|         | 3    |                      | 816                     | 4864                          | 3464                                 | 17336                                | 22114                    |
| O       | 1    | Manifest             | 496                     | 32096                         | 8696                                 | 26536                                | 60015                    |
|         | 2    |                      | 560                     | 41472                         | 12128                                | 32992                                | 67966                    |
|         | 3    |                      | 2608                    | 66248                         | 22800                                | 56328                                | 137436                   |
| P       | 1    | Manifest             | 592                     | 712                            | 1816                                 | 656                                  | 7210                     |
|         | 2    |                      | 0                       | 3976                          | 3664                                 | 1464                                 | 10892                    |
|         | 3    |                      | 2344                    | 34240                         | 7416                                 | 10920                                | 51041                    |

* Higher tract volumes (mm$^3$) denotes reduced tract integrity compared to normal populations (dark red).
Fig. 2. Fiber pathways affected in three manifest subjects mapped by differential tractography. The red–green–blue colors represents the orientation of diffusion (red: left–right; green: anterior–posterior; blue: superior–inferior). Tract volumes are represented in mm$^3$. The greater the volume of affected fibers, the higher the UHDRS Total Motor Score (UHDRS TMS) that subjects will display, showing a deteriorating performance in motor functions. Subject A displays a significant correlation between fiber pathways affected and UHDRS TMS (35, 41, and 58) with increasing tract volumes (13,752 mm$^3$, 13,656 mm$^3$, and 46,728 mm$^3$) in three different scanning time points respectively (0 month, 6 months, 1 year). Subject B shows a UHDRS TMS of 45, 49, and 52 with tract volumes of 34,840 mm$^3$, 53,288 mm$^3$, and 57,560 mm$^3$ at 0 month, 6 months, and 1 year, respectively. Subject C is the subject with the most change among the three, with a UHDRS TMS of 35, 35, and 64 and tract volumes of 22,168 mm$^3$, 61,384 mm$^3$, and 68,488 mm$^3$ at 0 month, 6 months, and 1 year, respectively. Interestingly, subject C shows no change in the UHDRS TMS between 0 and 6 months, nevertheless, a significant increase in tract volume was observed in this time period (22,168 mm$^3$ and 61,384 mm$^3$ respectively), providing evidence that differential tractography can be used as a dynamic biomarker to predict pre-clinical manifestations.

Table 4 show results for cross-sectional and longitudinal data in manifest patients. Correlation analysis was applied to evaluate the relationship between clinical scores and tract volumes in cross-sectional data from the first, second, and third scans, yielding a total of 105 correlations that were corrected using Bonferroni correction to consider familywise significance. In addition, Table 5 shows results of correlation analysis which was applied to evaluate the relationship between the changes in all clinical scores and the changes in tract volumes in three separate groups: (1) changes observed from first to second scan, (2) changes observed from the first to the third scan, and (3) changes observed from the second to the third scan. No statistical significance was observed when tract volumes were compared to clinical scores in cross-sectional data, or when tract volumes were compared to the changes in clinical scores in longitudinal data (Tables 4 and 5). However, it is unlikely to achieve significance when familywise p-value is considered (Bonferroni correction) due to the small number of subjects included in the analysis, and this does not diminish the important findings obtained in the longitudinal analysis (Table 3). For better visualization, supplementary Table S4 and S5 represent visual components of Table 3 for better visualization.

In the second longitudinal analysis, seven correlations (20%) were statistically significant (p-value < 0.0001) as follows. A statistical significance was observed in dystonia total with cingulum and corpus callosum (p-value < 0.0001); and UHDRS TFC was significant with cingulum and corticostriatal pathway (p-value < 0.0001), and with corticospinal pathway (p-value < 0.001) (Table 3). Supplementary Tables S2 and S3 represent visual components of Table 3 for better visualization.

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4. Discussion

In this study we evaluated differential tractography as a clinical translational tool by conducting correlation analyses between white matter volumes measurements and clinical scores in manifest and premanifest HD patients. Overall results indicate that differential tractography appears to be a robust dynamic biomarker with high statistical significance in longitudinal data to determine changes in tract volumes of white matter tracts with the potential to supplement the UHDRS in manifest and premanifest HD. Differential tractography appears to be a highly reliable monitoring biomarker to delimit changes exhibited in cingulum, corpus callosum, corticostriatal pathway, corticospinal pathway, and whole brain when correlated with UHDRS. Moreover, an increase of volume of damaged tracts was observed before symptom onset in one particular subject (Subject C, Fig. 2). This prediction power can be taken in consideration to anticipate onset at the premanifest stage.
Table 3
Correlation analysis between tract volume and clinical scores in longitudinal data.

| Clinical scores | Correlation between clinical scores and tract volume | Correlation between the change in clinical scores and change in tract volumes |
|-----------------|-----------------------------------------------|-----------------------------------------------|
|                 | coefficient | standard error | p-value | coefficient | standard error | p-value |
|                 |             |               |         |             |               |         |
| Unified Huntington Disease Rating Scale (UHDRS) TMS | 0.088 | 0.018 | \(<0.001^*\) | 0.380 | 0.403 | 0.173 |
| Dystonia total | 0.187 | 0.093 | 0.022 | 0.870 | 0.158 | \(<0.001^*\) |
| Chorea total | -0.032 | 0.118 | 0.608 | -0.325 | 0.379 | 0.804 |
| RAM | 0.522 | 0.075 | \(<0.001^*\) | 0.602 | 0.148 | \(<0.001^*\) |
| Stroop Color/Word | -0.115 | 0.029 | \(<0.001^*\) | 0.032 | 0.216 | 0.559 |
| UHDRS Behavior | 0.081 | 0.055 | 0.067 | 0.317 | 0.132 | 0.008 |
| UHDRS TFC | 0.046 | 0.007 | \(<0.001^*\) | -0.258 | 0.144 | 0.964 |
| Corticospinal Pathway | 0.070 | 0.013 | \(<0.001^*\) | 0.185 | 0.358 | 0.303 |
| Dystonia total | 0.305 | 0.132 | 0.011 | 0.337 | 0.228 | 0.070 |
| Chorea total | 0.058 | 0.097 | 0.276 | -0.663 | 0.369 | 0.964 |
| RAM | 0.420 | 0.073 | \(<0.001^*\) | 2.587 | 0.279 | \(<0.001^*\) |
| Stroop Color/Word | -0.080 | 0.028 | 0.003 | 0.569 | 0.982 | 0.719 |
| UHDRS Behavior | -0.014 | 0.065 | 0.587 | -0.121 | 0.181 | 0.748 |
| UHDRS TFC | 0.030 | 0.007 | \(<0.001^*\) | -0.071 | 0.074 | 0.831 |
| Corticospinal Pathway | 0.054 | 0.025 | 0.015 | 0.288 | 0.396 | 0.234 |
| Dystonia total | 0.169 | 0.161 | 0.147 | 0.458 | 0.278 | 0.050 |
| Chorea total | -0.069 | 0.143 | 0.685 | -0.517 | 0.425 | 0.888 |
| RAM | 0.408 | 0.097 | \(<0.001^*\) | 3.009 | 0.310 | \(<0.001^*\) |
| Stroop Color/Word | -0.105 | 0.044 | 0.009 | 0.814 | 1.130 | 0.764 |
| UHDRS Behavior | 0.028 | 0.069 | 0.344 | -0.131 | 0.217 | 0.728 |
| UHDRS TFC | 0.030 | 0.010 | \(<0.001^*\) | -0.171 | 0.087 | 0.976 |
| Whole Brain | 0.053 | 0.020 | 0.003 | 0.385 | 0.446 | 0.194 |
| Dystonia total | 0.145 | 0.058 | 0.006 | 0.560 | 0.301 | 0.031 |
| Chorea total | 0.083 | 0.072 | 0.123 | -0.548 | 0.441 | 0.893 |
| RAM | 0.293 | 0.097 | \(<0.001^*\) | 3.249 | 0.309 | \(<0.001^*\) |
| Stroop Color/Word | -0.067 | 0.026 | 0.005 | 0.854 | 1.200 | 0.762 |
| UHDRS Behavior | -0.011 | 0.039 | 0.611 | -0.094 | 0.225 | 0.661 |
| UHDRS TFC | 0.021 | 0.007 | 0.002 | -0.206 | 0.101 | 0.980 |

- Significant (p-value < 0.001).
- Family-wise significant (p-value < 0.05/35 = 0.001).

UHDRS: Unified Huntington Disease Rating Scale. TMS: Total motor score. RAM: Rapid alternating movements. TFC: Total functional capacity.
### Table 4
Cross-sectional correlation between clinical scores and tract volume.

|                      | Clinical scores | First Scan |  | Second Scan |  | Third Scan |  |
|----------------------|-----------------|------------|---|-------------|---|------------|---|
|                      |                 | corr       | p-value | corr | p-value | corr | p-value |
| Claustrum            |                 |            |         |     |         |     |         |
| UHDRS TMS            | -0.223          | 0.757      | 0.240   | 0.267 | 0.417   | 0.868 |
| Dystonia total       | -0.253          | 0.786      | 0.160   | 0.340 | -0.698  | 0.982 |
| Chorea total         | -0.246          | 0.780      | 0.101   | 0.398 | -0.343  | 0.817 |
| RAM                  | -0.495          | 0.949      | -0.034  | 0.534 | -0.119  | 0.620 |
| Stroop C W           | -0.347          | 0.135      | 0.315   | 0.796 | -0.150  | 0.350 |
| UHDRS Behavior       | 0.239           | 0.227      | 0.228   | 0.278 | 0.285   | 0.229 |
| UHDRS TFC            | -0.012          | 0.515      | 0.042   | 0.457 | -0.433  | 0.878 |
| Corpus Callosum      |                 |            |         |     |         |     |         |
| UHDRS TMS            | -0.050          | 0.561      | -0.184  | 0.682 | -0.033  | 0.534 |
| Dystonia total       | 0.027           | 0.467      | -0.023  | 0.523 | -0.213  | 0.709 |
| Chorea total         | -0.042          | 0.552      | -0.563  | 0.943 | -0.251  | 0.743 |
| RAM                  | -0.412          | 0.909      | 0.042   | 0.457 | 0.111   | 0.388 |
| Stroop C W           | 0.028           | 0.535      | -0.268  | 0.243 | -0.133  | 0.366 |
| UHDRS Behavior       | 0.177           | 0.291      | 0.277   | 0.235 | 0.720   | 0.014 |
| UHDRS TFC            | -0.071          | 0.586      | -0.150  | 0.650 | -0.100  | 0.601 |
| Corticostriatal Pathway|             |            |         |     |         |     |         |
| UHDRS TMS            | 0.110           | 0.367      | 0.251   | 0.257 | 0.460   | 0.106 |
| Dystonia total       | -0.312          | 0.839      | 0.274   | 0.238 | 0.098   | 0.401 |
| Chorea total         | 0.032           | 0.461      | 0.345   | 0.182 | 0.046   | 0.453 |
| RAM                  | -0.279          | 0.810      | -0.193  | 0.691 | 0.303   | 0.214 |
| Stroop C W           | -0.305          | 0.168      | 0.351   | 0.823 | -0.243  | 0.265 |
| UHDRS Behavior       | 0.165           | 0.304      | -0.101  | 0.602 | 0.193   | 0.309 |
| UHDRS TFC            | 0.090           | 0.391      | -0.133  | 0.634 | 0.243   | 0.265 |
| Corticopontine Pathway|             |            |         |     |         |     |         |
| UHDRS TMS            | 0.046           | 0.444      | 0.251   | 0.257 | 0.067   | 0.432 |
| Dystonia total       | -0.382          | 0.890      | 0.160   | 0.341 | -0.289  | 0.775 |
| Chorea total         | 0.011           | 0.487      | 0.109   | 0.390 | 0.075   | 0.424 |
| RAM                  | -0.348          | 0.867      | -0.025  | 0.526 | -0.017  | 0.517 |
| Stroop C W           | -0.273          | 0.196      | 0.268   | 0.757 | -0.150  | 0.350 |
| UHDRS Behavior       | 0.147           | 0.324      | 0.252   | 0.256 | 0.167   | 0.333 |
| UHDRS TFC            | 0.067           | 0.418      | 0.067   | 0.432 | -0.200  | 0.697 |

- **Positive Correlation.**
- **Negative Correlation.**

Familywise significant ($p\text{-value}<0.05/35=0.001$).

† Higher Stroop Color Word Score indicate better cognitive performance. Negative value does not indicate negative correlation.

UHDRS: Unified Huntington Disease Rating Scale. TMS: Total motor score. RAM: Rapid alternating movements. TFC: Total functional capacity.
Table 5
Cross-sectional correlation between change in clinical scores and the change in tract volumes.

| Clinical scores | Change 1st scan to 2nd scan | Change: 1st to 3rd scan | Change: 2nd to 3rd scan |
|-----------------|-----------------------------|-------------------------|-------------------------|
|                 | corr | p-value | corr | p-value | corr | p-value |
| Cingulum        |      |         |      |         |      |         |
| UHDRS TMS       | 0.477 | 0.097 | -0.214 | 0.695 | 0.548 | 0.080 |
| Dystonia total  | 0.602 | 0.043 | -0.400 | 0.837 | 0.115 | 0.393 |
| Chorea total    | 0.128 | 0.371 | -0.539 | 0.916 | 0.445 | 0.135 |
| RAM             | 0.375 | 0.160 | 0.528 | 0.089 | 0.358 | 0.192 |
| Stroop C W      | 0.513 | 0.921 | -0.707 | 0.025 | 0.283 | 0.752 |
| UHDRS Behavior  | 0.351 | 0.177 | 0.313 | 0.225 | 0.602 | 0.057 |
| UHDRS TFC       | 0.427 | 0.126 | -0.238 | 0.715 | 0.645 | 0.042 |
| Corpus Callosum |      |         |      |         |      |         |
| UHDRS TMS       | -0.067 | 0.568 | 0.071 | 0.433 | 0.335 | 0.208 |
| Dystonia total  | 0.842 | 0.002 | -0.170 | 0.656 | 0.374 | 0.181 |
| Chorea total    | -0.213 | 0.709 | -0.455 | 0.871 | 0.417 | 0.152 |
| RAM             | -0.220 | 0.716 | 0.712 | 0.024 | -0.410 | 0.843 |
| Stroop C W      | 0.234 | 0.728 | -0.503 | 0.102 | 0.755 | 0.985 |
| UHDRS Behavior  | 0.367 | 0.166 | 0.386 | 0.173 | 0.096 | 0.411 |
| UHDRS TFC       | -0.233 | 0.727 | -0.190 | 0.674 | 0.084 | 0.422 |
| Corticostriatal Pathway |      |         |      |         |      |         |
| UHDRS TMS       | -0.400 | 0.857 | 0.071 | 0.433 | 0.036 | 0.466 |
| Dystonia total  | 0.337 | 0.188 | -0.170 | 0.656 | -0.181 | 0.666 |
| Chorea total    | -0.741 | 0.989 | -0.455 | 0.871 | -0.012 | 0.512 |
| RAM             | -0.254 | 0.745 | 0.712 | 0.024 | 0.133 | 0.377 |
| Stroop C W      | 0.025 | 0.526 | -0.503 | 0.102 | 0.419 | 0.849 |
| UHDRS Behavior  | 0.183 | 0.318 | 0.386 | 0.173 | 0.431 | 0.143 |
| UHDRS TFC       | -0.083 | 0.584 | -0.190 | 0.674 | 0.503 | 0.102 |
| Corticospinal Pathway |      |         |      |         |      |         |
| UHDRS TMS       | -0.483 | 0.906 | 0.238 | 0.285 | 0.048 | 0.455 |
| Dystonia total  | 0.614 | 0.039 | 0.012 | 0.489 | 0.410 | 0.157 |
| Chorea total    | -0.383 | 0.846 | -0.491 | 0.892 | -0.147 | 0.636 |
| RAM             | -0.576 | 0.948 | 0.589 | 0.062 | -0.711 | 0.976 |
| Stroop C W      | -0.008 | 0.492 | -0.132 | 0.378 | 0.539 | 0.916 |
| UHDRS Behavior  | 0.333 | 0.190 | 0.506 | 0.100 | -0.156 | 0.644 |
| UHDRS TFC       | -0.467 | 0.897 | 0.262 | 0.265 | -0.156 | 0.644 |
| Whole Brain     |      |         |      |         |      |         |
| UHDRS TMS       | -0.150 | 0.650 | 0.071 | 0.433 | 0.347 | 0.200 |
| Dystonia total  | 0.703 | 0.017 | 0.158 | 0.645 | 0.434 | 0.141 |
| Chorea total    | -0.179 | 0.677 | -0.419 | 0.849 | 0.209 | 0.310 |
| RAM             | -0.297 | 0.781 | 0.565 | 0.072 | -0.374 | 0.819 |
| Stroop C W      | 0.310 | 0.791 | -0.395 | 0.166 | 0.790 | 0.990 |
| UHDRS Behavior  | 0.483 | 0.094 | 0.422 | 0.149 | 0.096 | 0.411 |
| UHDRS TFC       | -0.083 | 0.584 | 0.071 | 0.433 | 0.192 | 0.325 |

- Positive Correlation.
- Negative Correlation.

Familywise significant (p-value < 0.05/35 = 0.001).

† Higher Stroop Color Word Score indicate better cognitive performance. Negative value does not indicate negative correlation.

UHDRS: Unified Huntington Disease Rating Scale. TMS: Total motor score. RAM: Rapid alternating movements. TFC: Total functional capacity.
to characterize disease progression, adding great value and high reli-
ability to differential tractography as a predictive monitoring biomarker. The use of different scanners will have introduced a fixed
bias in our correlation analysis, bringing the same intercept for our
variable. Thus, the correlation coefficient will not have been affected,
since the scanner difference is the same for all subjects, and our hy-
thesis would have remained the same.

It is also noteworthy the distinction that differential tractography
provides when comparing manifest vs premanifest individuals, as
affected tracts in manifest subjects displayed higher tract volumes as
expected, in opposition to gene-positive individuals who yielded few or
no tracts at all (as seen in Supplementary Table S1), supporting the
accuracy of the technique. Since differential tractography findings are
associated with damage appearing in pathway trajectories, the tech-
nique provides the amount of degeneration (in volume measurements)
in addition to providing a better localization of disease. In this sense, we
have been able to map segments of disconnectivity in white matter areas
to find the link between lesions and grey matter to better understand
functional changes due to neuronal degeneration. Therefore, our
diffusion-based analysis technique exhibits a significant novelty over
conventional tractography by differentiating errors in local voxels
versus true findings that spread along a fiber trajectory. This in turn,
provides a biological advantage for not only localizing neuro-
degeneration with precision, but also for tracking the evolution of dis-
ease and treatment response, as suggested by a previous study (Yeh
et al., 2019). By applying deterministic tractography, we have an
advantage by the novelty of the technique which is capable of resolving
crossing fibers. Deterministic tractography makes use of quantitative
anisotropy (QA) which relies on generalized q-sampling imaging (GQI)
to estimate the orientation of individual fibers (Yeh et al., 2010), and
spin distribution function (SDF) to provide the amount or density of
diffusing water in any direction within a single voxel (Yeh et al., 2016),
therefore posing a great value over widely used diffusivity-based esti-
mations such as FA. The use of differential tractography paired with a
robust clinical evaluation at the pre-clinical stage in gene positive
asymptomatic populations, can be of utmost clinical significance in
routine clinical follow-up, and although our study provides a small
number of subjects, we acknowledge that future studies are granted to
obtain robust measures for when assessment of new treatment and
therapies are required in clinical trials.

4.1. Implications of the clinical data

Longitudinal analysis demonstrated the highest statistical correla-
tion with progression of clinical UHDRS scores in all brain regions
(cingulum, corpus callosum, corticostriatal pathway, and corticospinal
pathway), in relation to UHDRS TMS, Stroop Color-Word, UHDRS Total
Functional Capacity (TFC), and especially in relation to Rapid Alter-
nating Movements (RAM), which was statistically significant (p-value <
0.0001) in all brain regions. Since Bonferroni correction was applied
to consider familywise significance in multiple comparison analyses, re-
results from the cross-sectional analysis did not yield significant findings.
However, this does not hinder the potential of differential tractography
as a tool to further understand the biological mechanism of white matter
loss, and further studies with larger samples are required to determine a
true significant value in cross-sectional data and larger group studies.
Despite this limitation, results further confirm the role of white matter
pathways involved in HD progression (Poudel et al., 2014; Rosas et al.,
2010). Demonstrated changes on differential tractography in both pre-
manifest and manifest HD, and particularly in the earlier stages, may be
of value in future longitudinal and cross-sectional studies (Poudel et al.,
2015). In premanifest HD where clinical markers of disease progression
do not exist, differential tractography can be used as a non-invasive tool
to dynamically monitor clinically asymptomatic disease progression. In
manifest HD, the observed disease progression made by differential
tractography can be used to supplement existing clinical markers of
progression.

4.2. Speculative mechanisms

Degeneration in the association, commissural and projection fibers are
implicated in the course of the disease and its clinical manifestations.
Degeneration of corticospinal and corticostriatal pathways white matter
tracts are linked to changes in motor functions behavior, executive
function, movement, and the lack of integration of motor and cognitive
function resulting in progression of UHDRS TMS, RAM, Stroop Color
Word, UHDRS TFC. Thus, statistical correlation of Corticospinal and
corticostriatal pathways with UHDRS TMS, RAM, and UHDRS TFC
supports the relationship with motor dysfunction, and studies have
supported these findings in manifest HD, and several important behav-
ioral changes such as global apathy have been recently associated with
degeneration of corticostriatal pathway (De Paepe et al., 2019; Phillips
et al., 2015). Statistical correlation exhibited by the corticospinal tract in
relation to UHDRS TMS, Stroop Color Word, TFC, and especially with
RAM corroborates the critical relationship between corticospinal tract
demyelination and motor symptoms at the premanifest and manifest
stages which is associated with progression of UHDRS motor scores
(Phillips et al., 2015). The highest correlation found with respect to RAM
in longitudinal data studied by differential tractography, is validated by
the motor involvement of the disease. Therefore, differential tractog-
raphy represents a novel monitoring biomarker allowing detection of the
exact anatomical location of degeneration and its subsequent cor-
relation with loss of clinical function as measured by existing markers of
progression.

4.3. Differential tractography in relation to premanifest and manifest
disease and UHDRS scores

Despite the small number of patients, significant differences were
observed between the premanifest and manifest HD. Relatively few
areas were affected in premanifest patients in relation to patients in the
manifest group (as in Supplementary Table S1), thereby lending further
credibility to this imaging method. As expected, significant progression
was observed at 6 and 12 months in manifest patients in relation to the
baseline scan. The observed increase in volume of affected tracts cor-
responded with an increase in the UHDRS clinical scores. Despite being a
reliable gold-standard to determine clinical progression in HD for many
years (Kieburtz et al., 2001), the UHDRS assessment can be prone to
variability. Differential tractography as an automated method is less
prone to variability, and can supplement the use of the UHDRS in
manifest HD. In premanifest patients, differential tractography can
demonstrate changes in white matter preceding disease onset.

4.4. Future directions and limitations

We demonstrate the feasibility of differential tractography as a po-
tential biomarker to anticipate disease onset in premanifest and manifest
HD. Our main limitation was the small number of subjects which pre-
vented obtaining statistical significance in cross-sectional data, and this
limitation prevented us to obtain a more homogeneous clinical and
longitudinal data. Additional research with larger samples is required to
obtain a clear validation. We acknowledge that we cannot estimate ef-
fact size, as the method is for individual diagnosis which places more
emphasis on sensitivity and specificity. Therefore, although differential
tractography has potential for group diagnosis, future studies with a
greater number of subjects will be necessary to evaluate the effect size at
the group level. We did not account for time between scans in the sta-
tistical model, and this will certainly be a variable which must be con-
considered in future larger studies. In addition, premanifest HD diag-
nosis was made based of genetic profile and we did not acquire clinical
markers such as CAP score (CAG - Age Product Scaled score) or DBS
(Disease Burden Score), for which we will consider obtaining in future
studies. There is a mismatch between differential tractography and the UHDRS TMS in few cases as shown by one patient (subject F, Table S1) with decreasing volumes and progression of the UHDRS TMS. In manifest HD, differential tractography demonstrated changes or progression at an anatomical level that may not be readily discernible with UHDRS scores. At this stage we do not have a clear understanding of the nature of the mismatch and thus differential tractography will require further validation in a larger study. Lastly, although differential tractography provides encouraging results to carry future larger studies, we recognize the limitation that differences between manifest and premnain patients cannot be generalizable due to the small number of subjects in each group. Nevertheless, the overall findings confirmed the applicability of differential tractography as a dynamic non-invasive biomarker. Differential tractography can be considered in future studies with larger cohorts with more homogenous clinical and longitudinal data to assess the efficacy of therapeutic trials particularly in premnain HD, where future drug trials will be aimed to prevent symptomatic conversion.

Data availability statement

Data supporting the findings of this study are not publicly available as it contains sensitive information that may compromise the privacy of the participants of this study.

CRediT authorship contribution statement

Jessica V. Barrios-Martinez: Investigation, Writing – original draft, Writing – review & editing, Visualization. David T. Fernandes-Cabral: Formal analysis, Investigation, Writing – original draft. Kumar Abhijnav: Writing – review & editing. Juan C. Fernandez-Miranda: Funding acquisition, Conceptualization, Supervision. Yue-Fang Chang: Formal analysis, Validation, Supervision. Valerie Suski: Data curation, Investigation, Supervision, Validation, Writing – review & editing. Fang-Cheng Yeh: Data curation, Funding acquisition, Methodology, Project administration, Software, Supervision, Writing – review & editing, Visualization. Robert M. Friedlander: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Robert M. Friedlander is on the Board of Neubase Therapeutics and Diffusion Technologies. All other authors report no conflict of interest.

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Appendix A. Supplementary data

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