The relationship between fronto-striatal tractography and cortical morphometry changes in Huntington's Disease: Image-HD

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Abstract

This paper aimed to investigate the relationship between cortical folding and white matter integrity changes in Huntington's disease. Cortical morphometry and tractography changes in three gyral based regions of interest (i.e., precentral, rostral middle frontal and superior frontal gyri) were examined. Neuroimaging data from the IMAGE-HD database comprised of 25 pre-symptomatic, 27 symptomatic and 25 healthy control individuals at three separate time points (baseline, 18-months, 30-months). Cortical morphometry measures of local gyrification index and cortical thickness were derived using Freesurfer 6.0's longitudinal pipeline. Tractography integrity measures of fractional anisotropy, axial diffusivity and radial diffusivity were obtained using MRTrix3. Gyral-based regions of interest were identified using the Desikan-Killiany Atlas. A hierarchical regression analysis was conducted to investigate whether baseline white matter tractography could predict cortical morphometry changes. We found baseline white matter integrity measures did not predict tractography changes in any of the regions of interest. A hierarchical regression analysis was conducted to investigate whether tractography or cortical morphometry changes could predict change in clinical measures (i.e., disease burden score and the Unified Huntington's Disease Rating Scale – total motor score) over and above group (i.e., clinical diagnosis) in the pre-symptomatic and symptomatic groups. Tractography and cortical morphometry changes did not significantly predict change in clinical measures over and above group. These findings suggest cortical morphometry changes in these brain regions may occur independently to the health of the cortico-striatal tracts leading to them. Furthermore, these changes appear to have no significant relationship to motor symptoms in HD or life-time disease exposure.

Full Text

Huntington's Disease (HD) is a rare neurodegenerative disease caused by cytosine-adenine guanine (CAG) repeat expansion on the Huntingtin (HTT) gene (Bates et al., 2015). Whilst the striatum remains the principal site of disease-related damage in HD (Domínguez et al., 2016; Georgiou-Karistianis, Scahill, et al., 2013), there is evidence that as the disease advances, alterations to the morphology of the cortical surface occur (Kubera et al., 2019; Nopoulos et al., 2007; H D Rosas et al., 2005; Shishegar et al., 2019; Tabrizi et al., 2011). These changes have been reported to differentially occur in specific regions of the brain at varying stages of disease (H D Rosas et al., 2005; Tan et al., 2022). Specifically, the visual and primary motor cortices have been identified as the two regions that experience the most pronounced cortical morphometry alterations in HD (Kubera et al., 2019; Tabrizi et al., 2009; Tan et al., 2022), with anterior frontal and parietal regions becoming involved as the disease progresses (H D Rosas et al., 2005). One recent study found that pre-symptomatic HD (pre-HD, i.e. individuals who have tested positive for the HD gene but not developed clinical diagnosis) and symptomatic HD (symp-HD, i.e. those who have tested positive for the HD gene and received a clinical diagnosis) demonstrated significant differences in local gyrification index (LGI), a measure of the foldedness of the brain, compared to controls (Tan et al., 2022). Furthermore, there is evidence that whilst pre-HD (and symp-HD individuals experience LGI abnormalities at baseline in the lateral occipital region, only the symp-HD group demonstrated

longitudinal change in this area (Tan et al., 2022). Such a finding highlights the possibility that there may be an unidentified process that occurs throughout the symptomatic stage of the disease, that causes these cortical changes. However, the biological mechanisms underpinning changes to cortical morphometry in these regions is not adequately understood.

One proposed hypothesis for changes to cortical morphometry in HD is that a flattened gyrus is a result of reduced white matter tension to these regions (Tan et al., 2022; Van Essen, 1997) resulting in reduced LGI. Another, theory posits that disease related toxic agents (i.e. mutant huntingtin protein) proliferates along axonal pathways, propagating from the striatum to the cortical surface (Babcock & Ganetzky, 2015). This hypothesis is supported by studies that have found white matter tracts degenerate throughout HD (Tabrizi et al., 2013) along specific white matter networks (Govinda R Poudel et al., 2014, 2015). Mapping of white matter networks has shown that white matter degeneration is not uniform (Govinda R Poudel et al., 2015). Tractography analyses in HD have focused on the frontal and parietal (Aylward et al., 2011; Bourbon-Teles et al., 2019; Tabrizi et al., 2013) lobes with particular vulnerability identified in the posterior frontal region (Govinda R Poudel et al., 2015; H Diana Rosas et al., 2006). A longitudinal analysis of white matter connectivity in HD found longitudinal degeneration of white matter connectivity was not uniform, and symp-HD individuals were more vulnerable to white matter microstructure change, compared to pre-HD. It was also reported that clinical and motor symptoms predicted longitudinal white matter microstructure change in symp-HD (Govinda R Poudel et al., 2015).

At present there have been no other studies examining the longitudinal relationship between white matter degeneration and cortical morphometry changes in both pre-HD and symp-HD individuals. Thus, the time course of various regions considered most vulnerable throughout the disease is inadequately understood. Prevailing questions remain, such as: i) which stage of disease do these changes occur in relation to one another; ii) whether white matter degeneration predicts cortical morphometry changes; and iii) whether these processes occur independently of one another. The present study aimed to answer these questions by investigating whether baseline white matter integrity predicted cortical morphometry changes over time in specific gyral based regions of interest in both pre-HD and symp-HD individuals. We also aimed to investigate whether these changes could predict change in clinical outcome measures using the Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS) and disease burden score (DBS). We selected the pre-central, post-central, superior, inferior parietal and lateral occipital regions from the well-validated Desikan-Killiany brain atlas (Desikan et al., 2006) as the five specific regions of interest for our analysis. These regions were specifically chosen based on previous findings that the visual, primary motor and parietal cortices are those that experience the most pronounced cortical morphometry and white matter alterations in HD (Kubera et al., 2019; Govinda R Poudel et al., 2015; H Diana Rosas et al., 2006; Tan et al., 2022).

Methods And Materials

Participants

IMAGE-HD provides a longitudinal data base of clinical, cognitive, as well as multimodal neuroimaging measures acquired at three time-points: baseline, 18-month and 30-month. A total of 108 participants were originally recruited (Georgiou-Karistianis, Gray, et al., 2013), comprising 36 healthy controls, 36 pre-HD and 36 symp-HD. Healthy controls were matched to pre-HD participants by age and gender. For this study, 12 controls, 10 pre-HD and 10 symp-HD were excluded from the original set due to incomplete longitudinal data, a requirement for the FreeSurfer longitudinal pipeline (outlined below), or image analysis fails. The final sample was thus comprised of 24 healthy controls (7 males, 17 females; mean age: 42.9), 25 pre-HD (9 males, 16 females; mean age: 41.1), 26 symp-HD (17 males, 9 females; mean age: 53.61). The age-range of participants was 28–45 years for the pre-HD group and 45–60 years of age for the symp-HD group. To account for differences in age between groups, age and gender were used as a covariate in all analyses. Pre-HD and symp-HD participants underwent gene testing prior to enrolment to the study. CAG repeat length ranged from 39–46 for pre-HD and 40–49 for symp-HD.

The Unified Huntington's Disease Rating Scale (UHDRS) motor assessment (Tabrizi et al., 2009) was administered by a qualified clinician to assess pre-HD and symp-HD participants prior to enrolment and at each additional time point. A UHDRS total motor score (UHDRS-TMS) was derived and as per Tabrizi et al. (2009), HD participants who scored ≤ 5 on the UHDRS-TMS were included in the pre-HD group and those who scored ≥ 5 were included in the symp-HD group. All symp-HD participants also had a clinical diagnosis of HD. Lifetime exposure to the mutant huntingtin protein was measured by the Disease Burden Score (DBS). The DBS is a widely used in HD clinical research as its formula is expressed as: Age x (CAG − 35.5). The mean DBS for pre-HD participants was 269.21 ± 59.44 and for symp-HD participants was 374.16 ± 66.99. Inclusion criteria for the study required participants to be right-handed, have normal visuospatial abilities, no history of head injury, stroke or seizure. Table 1. (below) for a summarises demographic and clinical data for each group at each time point.

Table 1
Demographic and Clinical Data for each group, at each time point.

		Controls (*n* = 24)	Pre-HD (*n* = 25)	Symp-HD (*n* = 26)
		Mean ± SD	Mean ± SD	Mean ± SD
Gender (M:F)	Baseline	7:17	9:16	17:9
Age (Years)	Baseline	42.99 ± 12.98	41.13 ± 9.71	53.61 ± 9.29
CAG	Baseline	-	42.36 ± 2.04	42.77 ± 2.21
UHDRS-TMS	Baseline	-	0.92 ± 1.19	19.12 ± 9.71
	18-month	-	2.84 ± 4.04[a]	21.92 ± 11.03[a]
	30-month	-	2.80 ± 4.43	23.92 ± 13.19[b]
DBS	Baseline	-	269.21 ± 59.44	374.16 ± 66.99
	18-month	-	279.69 ± 61.39	385.34 ± 70.03
	30-month	-	287.02 ± 63.01	393.00 ± 71.80

Note: SD = Standard Deviation; UHDRS-TMS = Unified Huntington's Disease Rating Scale-Total Motor Score; DBS = Disease Burden Score; [a] = Significant from Baseline ($p = 0.05$); [b] = Significant from 18-month ($p = 0.05$).

MRI acquisition

MRI scanning was conducted at the Murdoch Children's Research Institute (Royal Children's Hospital, Vic, Australia), using a Siemens 3 Tesla scanner. T1-weighted images were acquired for each participant (192 slices, 0.9mm slice thickness, 0.8mm x 0.8mm in-plane resolution, 320 x 320 field of view, TR = 1900ms, TE = 2.6ms, flip angle = 9°). (Refer to Dominguez et al., 2013 and Georgiou-Karistianis et al., 2014 for further details.)

Diffusion weighted brain images were acquired using double spin echo diffusion weighted EPI sequence (TR = 5800msec, TE = 82.3msec, acquisition matrix = 128x128, FOV = 24cm^2, slice thickness 2.5mm, 50 contiguous axial slices). The diffusion-sensitizing gradient encoding (B1) was applied in 60 directions (b = 1200s/mm^2) and 5 images acquired without diffusion weighting (b = 0s/mm^2).

MRI processing

Grey Matter – Cortical Thickness and LGI

T1 images were processed to reconstruct cortical surfaces and quantify measures of brain surface anatomy using FreeSurfer (version 6.0 [https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki] (Dale et al., 1999; Fischl et al., 1999)). This process included removal of non-brain tissue using

watershed/surface deformation procedure, tessellation of the grey/white-matter boundary, and automated topology correction. Processing was then completed following the Freesurfer longitudinal processing pipeline (Reuter & Fischl, 2011), see also https://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing. This pipeline involved the creation of an un-biased within-subject base template using robust, inverse, consistent registration. Cortical surfaces underwent skull stripping, Talairach transforms and atlas registration using common information from the within-subjects base template. The bases were manually edited by improving skull-stripping and using control points to improve the grey-white segmented junction. Longitudinal time points were constructed using base templates (Reuter, Rosas, et al., 2012; Reuter, Schmansky, et al., 2012). Cortical brain regions were provided by the Desikan-Killiany Brain Atlas (68 gyral based regions, two hemispheres X 34 maps) an automated labelling system (Desikan et al., 2006). Note, this atlas automatically generates maps for each hemisphere separately. As such, all analyses were performed accordingly on each hemisphere (Right and Left).

White Matter – Tractography

Probabilistic tractography streamlines were generated using MRtrix3. MRtrix3 provides a suite of tools for image processing, analysis and visualisation of white matter using diffusion-weighted MRI (Tournier et al., 2019). Images were pre-processed using the DWI pre-processing pipeline outlined in [https://mrtrix.readthedocs.io/en/latest/dwi_preprocessing/denoising.html]. This included DWI distortion correction, image registration, atlas registration, DWI pre-processing and tissue segmentation.

Atlas registration was completed to provide cortical and subcortical (i.e. caudate) brain regions. This was completed using the well-validated Desikan-Killiany brain atlas, an automated labelling system (Desikan et al., 2006). Note, that this atlas automatically generates maps for each hemisphere separately. As such, all analyses were performed calculating mean values for both hemispheres of each brain region in order to minimise the number of multiple comparisons.

Once pre-processing was complete, images were processed to quantify measures of white matter integrity and generate a visual map of white matter tracts.

Whole-brain tractography streamline reconstruction included brain mask generation, response function generation and streamline generation using “Second-order Integration Over Fiber Orientation Distributions” (iFOD2). “Spherical-deconvolution Informed Filtering of Tractograms” (SIFT) was used to improve the quality of tract reconstruction outlined in https://mrtrix.readthedocs.io/en/latest/quantitative_structural_connectivity/sift.html. White matter tractography measures were generated for the tracts of interest using subcortical and cortical parcellations from the Desikan-Killiany brain atlas as noted in the section above.

Measures

Cortical Measures

Mean cortical thickness and LGI were calculated as the mean value of all vertices within each of the ROIs.

Cortical Thickness

Cortical thickness was measured by calculating the distance between the inside (white/grey) boundary of the cortex and the outside (grey/pial) boundary of the cortex using the FreeSurfer pipeline (Fischl & Dale, 2000; Spalletta et al., 2018).

Local Gyrification Index

Local Gyrification Index (LGI) quantifies the foldedness of the cortex by measuring the amount of cortex buried beneath the sulcal folds (Schaer et al., 2008; Spalletta et al., 2018). Following standard pipelines for longitudinal processing (Reuter & Fischl, 2011), a validated LGI add-on metric was calculated using FreeSurfer (Schaer et al., 2012). In short, this involved: (1) creating an outer surface using a morphological closing algorithm then; (2) overlapping circular regions of interest over the outer surface; and (3) defining the corresponding regions of interest on the pial surface.

White matter tractography measures

The mean fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) were calculated as the mean value of all fixels (fibre bundles within each voxel), within each of the four regions of interest. The directionality of diffusivity (as measured by AD and RD) can provide more granular information into the nature of axonal damage or demyelination occurring in HD.

Fractional Anisotropy (FA)

FA is a metric that provides a simple and robust measure of the degree of anisotropic diffusion of water occurring within a region (Smith et al., 2012). Because FA reflects the degree of anisotropic diffusion, it will be high (i.e., approaching unity) in regions of high organization (e.g., corpus callosum), intermediate in regions with some degree of organization (e.g., white matter regions that have no strong predominant axon fibre axis orientation), and low in tissues where the predominant cell shape, and therefore diffusion, is not specifically oriented (e.g., grey matter) and approaching zero in free fluids (e.g., CSF) (Pfefferbaum et al., 2000). Reductions in FA are associated with axonal damage.

Axial Diffusivity (AD)

AD is a metric which quantifies the diffusion of water parallel to white matter fibres. Whilst a decrease in AD is indicative of axonal damage (Song et al., 2003), an increase in AD may represent axonal degeneration and loss due to neuronal trimming (Beaulieu, 2002).

Radial Diffusivity (RD)

RD is a metric which quantifies the diffusion of water perpendicular to white matter fibres. An increase in RD is indicative of axonal damage (Song et al., 2005) and reflective of demyelination (Beaulieu, 2002).

Statistical Analysis

Hierarchical Regression Analysis

To determine whether white matter connectivity predicted cortical morphometry changes in specific regions of interest, we first calculated change scores (30-month minus baseline) for morphometry measures (LGI and cortical thickness). We chose to conduct the analysis on baseline white matter tractography rather than change in white matter tractography as there was no significant longitudinal change in white matter connectivity in any of the chosen regions of interest. However, there were group differences at baseline in white matter connectivity, thus raising the question of whether these differences might predict changes to the cortical surface.

We conducted a series of hierarchical regression analyses using LGI and cortical thickness as dependent variables (DVs) and baseline tractography measures, and group as independent variables (IVs) for each region of interest. Age and gender were used as covariates for all analyses. Bonferroni corrections were made for multiple comparisons between the four regions of interest.

Relationship between Cortical Morphometry, Tractography and Clinical Measures

To determine whether white matter degeneration was more predictive of clinical severity than cortical morphometry changes (LGI/cortical thickness), we conducted a hierarchical multiple regression analysis with clinical score as the DV. The first block of IVs included WM change and morphometry change scores. The second block included group (control, pre-HD, symp-HD). The analysis thus asked whether group classification could predict clinical changes above and beyond the WM and cortical morphometry changes separately.

Results

Simple Regression Analysis

Hierarchical regression analyses were performed to predict LGI and thickness based upon baseline tractography measures in each of the regions of interest. Preliminary analyses were performed to ensure there was no violation of the assumption of normality and linearity.

Precentral Region

Change in Precentral LGI was not significantly predicted by change in any baseline tractography measures, ($F(5, 74)$, $p = 0.78$, with an R^2 of 0.04). Change in Precentral thickness was not significantly predicted by any baseline tractography measures ($F(5, 74)$, $p = 0.20$, with an R^2 of 0.10).

Rostral Middle Frontal Region

Change in Rostral Middle Frontal LGI was not significantly predicted by any baseline tractography measures ($F(5, 74)$, $p = 0.24$, with an R^2 of 0.09). Change in Rostral Middle Frontal thickness was not

significantly predicted by any baseline tractography measures (F (5, 74), $p = 0.25$, with an R^2 of 0.09).

Superior Frontal Region

Change in Superior Frontal LGI was not predicted by any baseline tractography measures (F (5, 74), $p = 0.27$, with an R^2 of 0.09). Change in Superior Frontal Thickness was not predicted by any baseline tractography measures (F (5, 74), $p = 0.11$, with an R^2 of 0.12).

Hierarchical Linear Regression Analysis

Relationship between UHDRS Total Motor Score and Tractography and Cortical Morphometry changes

Change in UHDRS-TMS was not significantly predicted by baseline tractography or cortical morphometry changes in any regions of interest.

Group significantly predicted change in UHDRS-TMS over and above baseline tractography and cortical morphometry changes.

Relationship between Disease Burden Score and Tractography and Cortical Morphometry changes

Change in DBS was not significantly predicted by baseline tractography and cortical morphometry changes in any regions of interest.

Group significantly predicted DBS over and above baseline tractography and cortical morphometry changes.

Discussion

For the first time, we investigated the relationship between white matter integrity and changes in cortical morphometry in pre- and symp-HD individuals. We found that baseline tractography measures (FA, RD, AD) did not significantly predict change in cortical morphometry (LGI and cortical thickness) in any of the chosen regions of interest. This finding was somewhat surprising given previous theories posit that reduced gyrification of the cortical surface could be the result of reduced white matter tension (Ronan & Fletcher, 2015; Van Essen, 1997) or that disease agents travel along white matter tracts from the striatum to the cortical surface through a prion-like process (Babcock & Ganetzky, 2015). Indeed one previous study found that trans-neuronal propagation of the mutant Huntington protein contributed to the spread of cortico-striatal degeneration (G R Poudel et al., 2019). Furthermore, our previous study found a network diffusion model across the human brain connectome was adequately able to explain the spread of pathology across the brain (G R Poudel et al., 2019). On the contrary, our current results indicate that neural dysfunction and cortical morphometry changes in HD may be unrelated, occurring independently

of one another. However, when these changes occur and over what period, could not be determined by the current study.

We also reported that baseline tractography and changes in cortical morphometry did not together significantly predict changes in measures of clinical severity. As many theories of neurological and cognitive deficit are predicated upon damage to white and grey matter structures (GET SOURCES), this was not an expected finding. However, it has been well established that the striatum is the key site of pathology in HD (Georgiou-Karistianis, Scahill, et al., 2013; Tabrizi et al., 2012), and motor symptoms seen in HD could be due primarily to changes in this region. A simplified biological explanation for this is that mutant huntingtin proteins cause the striatum to produce weaker chemical signals, leading to fewer inhibitory transmitters, less inhibition of the motor cortex and ultimately, chorea (Labbadia & Morimoto, 2013)). Thus, the involvement of cortico-striatal tracts and cortical morphometry changes may be independent to the development of motor deficits in HD, or merely secondary to this process. The present study did not include cognitive measures of clinical severity, and further research would be required to determine whether abnormal white matter integrity and cortical morphometry could account for some of these deficits.

Group classification was the most significant predictor of change in these clinical measures over and above tractography and morphometry changes. This finding mimics those from previous studies (Tan et al., 2022), both of which found no significant associations between tractography or cortical morphometry measures and changes in clinical measures (despite UHDRS-TMS and DBS being significantly different between time points). Thus, the findings of the present study provide evidence that baseline tractography and changes in cortical morphometry in these regions are unrelated to the severity of motor symptoms seen in symp-HD (UHDRS-TMS) or severity of disease exposure (DBS). As previously mentioned above, and as noted in other studies (Tan et al., 2022), changes occurring in other regions of the brain (both subcortical and cortical) could be responsible for some of the clinical outcomes observed in HD. For example, the superior parietal lobe (responsible for visuomotor control and motor planning) may be one region of interest in further studies.

It is possible that methodological limitations prevented the detection of a relationship between tractography and cortical morphometry measures. For example, the time-period between baseline and 30-month follow-up could be inadequate to detect subtle longitudinal changes impacting white matter tracts and cortical morphometry. Previous studies have been similarly unable to find longitudinal change to white matter tracts or cortical morphometry (Tan et al., 2022), and have suggested that methodological limitations (i.e. inadequate time period between testing, and relatively small sample sizes)could be responsible for these non-findings.

Conclusion

To date, our longitudinal study remains the only one to investigate the relationship between tractography and cortical morphometry changes in certain regions of interest in HD. We found that baseline

tractography was not able to predict change in cortical morphometry in the precentral, superior frontal, or rostral middle frontal regions of the brain. Additionally, baseline tractography and cortical morphometry changes were not predictive of worsening motor symptoms or related to disease exposure. Put together, these findings suggest that cortical morphometry changes in these brain regions may occur independently to the health of the cortico-striatal tracts leading to them. Furthermore, these changes appear to have no significant relationship to the motor symptoms in HD or life-time disease exposure.

Declarations

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Ethical Approval:

Ethical Approval was provided by the Monash University Human Research Ethics Review Committee (Project ID: 14105).

Consent to Participate:

This study used data collected for the IMAGE-HD study, as such informed consent had previously been obtained.

Consent to Publish:

As above.

Author Contributions:

Author contributions included conception and study design (BT, RS, AF and NGK) statistical analysis (BT, SO), interpretation of results (BT, RS, AF and NGK), drafting the manuscript work or revising it critically for important intellectual content (BT, RS, AF and NGK) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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Competing Interests:

The authors declare no conflicts of interest.

Conflict of Interest Disclosure:

None of the authors have a conflict of interest to declare.

Availability of Data and Materials:

All data and materials were collected as part of the IMAGE-HD study and are available upon request

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