UCL Centre for Medical Image Computing

UNCOVERING THE TEMPORAL SEQUENCE OF REGIONAL BRAIN VOLUME AND NEURAL CONNECTIVITY CHANGES IN HUNTINGTON'S DISEASE

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1. Huntington's Disease

Huntington's Disease (HD) is a progressive neurodegenerative disorder, caused by a cytosine-adenine-guanine trinucleotide repeat expansion in the huntingtin gene which results in the production of mutant huntingtin protein, triggering neurodegeneration and cell death. HD can be characterised by measurements of brain volume loss and neural connectivity changes using magnetic resonance imaging (MRI).

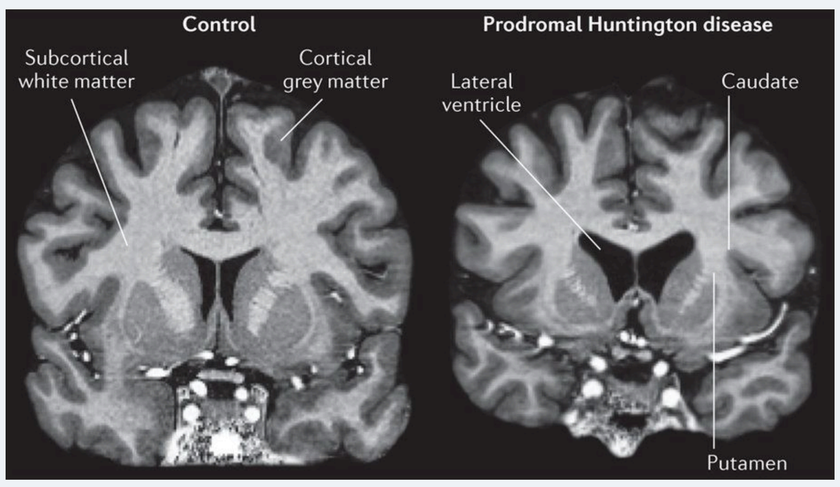


Figure 1: Brain atrophy in prodromal Huntington's Disease shown using 7T MRI – Bates et al (2015)

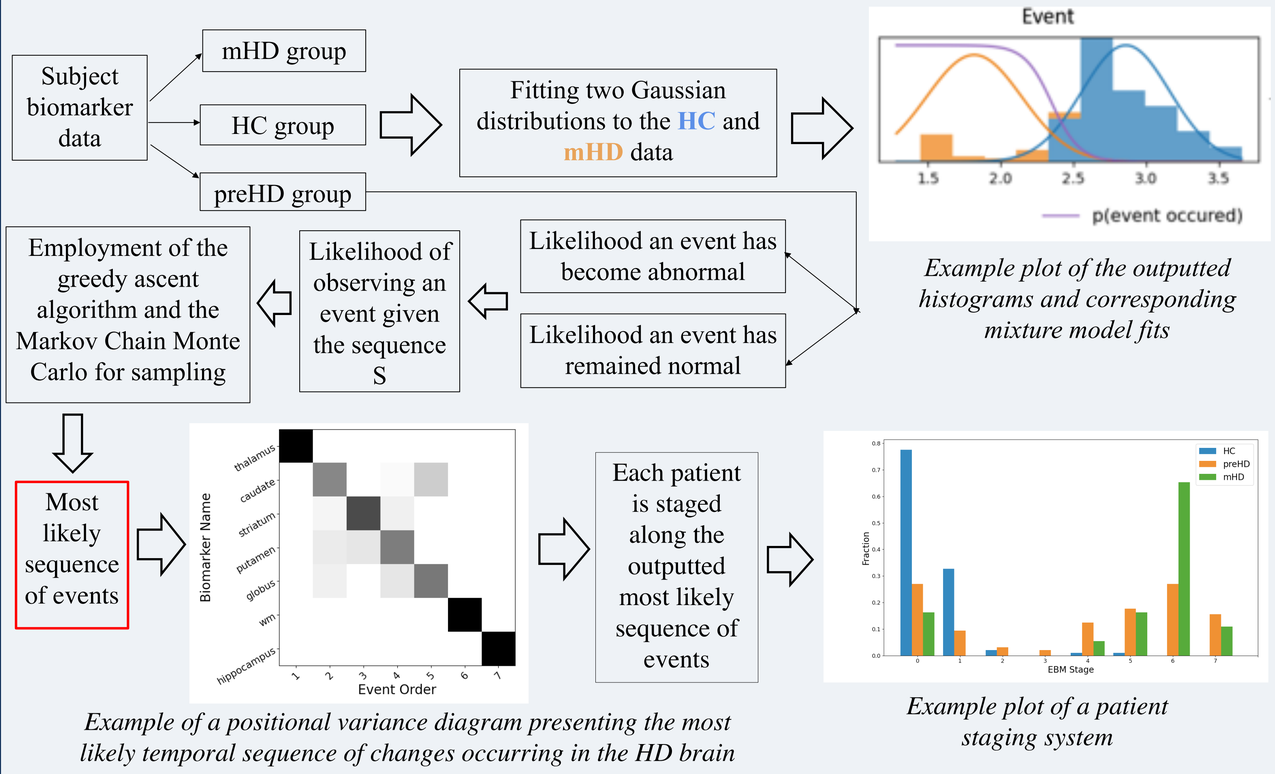
2. Motivation

We recently developed a probabilistic disease progression model to gain insight into the most likely temporal sequence of MRI-derived regional brain volume changes occurring during HD progression (Wijeratne et al. 2018). However, there is currently significantly less information regarding the sequence of neural connectivity changes in HD progression, and whether these changes precede or follow brain volume loss.

→Here we aim to expand our previous model of structural MRI changes by including neural connectivity markers to uncover a new temporal sequence of events occurring in the HD brain.

3. The Event-Based Model

We apply the event-based model (EBM), a probabilistic disease progression model, to cross-sectional structural MRI and functional connectivity data from both healthy controls (HC) and genotype-confirmed HD patients, including pre-manifest HD (preHD) patients and early manifest HD (mHD) patients. The model uses biomarker values as inputs and outputs the most likely ordering of events occurring in the HD brain to determine the sequence in which HD biomarkers become abnormal and stage individuals along this sequence.



Example plot of the outputted histograms and corresponding mixture model fits

Example of a positional variance diagram presenting the most likely temporal sequence of changes occurring in the HD brain

Example plot of a patient staging system

Figure 2: Summary flowchart showing the different steps in the EBM – Summarised from Wijeratne et al. (2018) and Fonteijn et al. (2012)

4. Patient data

Track HD Study (Tabrizi et al. 2009)
- Conducted between 2009 and 2013
- Across 4 research sites (Leiden, Paris, London and Vancouver)
- Includes preHD patients, mHD patients and HC

Track-On HD Study (Klöppel et al. 2015)
- Two year follow up study from the Track-HD cohort i.e. six years from baseline
- Includes 106 preHD patients, 22 mHD patients and 111 HC from which most of the preHD (91) and HC were from the Track-HD cohort

→ We used neuroimaging data from the Track-On HD study which included MRI-derived volumetric measures of the caudate, globus pallidus, striatum, putamen, thalamus, hippocampus and white matter as well as 36 different functional connectivity measures.

5. Biomarker selection

The entire dataset was first controlled for covariates including age, sex, intracranial volume and study site. We then performed a two-tailed t-test between the HC and mHD groups for each biomarker to select a set of statistically significant structural and connectivity biomarkers (estimated by the p-value) with high effect sizes (estimated by the t-score). The chosen t-test threshold ($t > 2$ **and** $p < 0.05$) identified a set of nine structural and connectivity biomarkers (Table 1) which were then inputted into the EBM to estimate the final sequence of events.

r: right; l: left; DLPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex; MFG: medial frontal gyrus; SMG: supramarginal gyrus

Biomarker	T-score	P-value
Putamen	9.762382	1.762851e-07
Striatum	9.714705	2.387076e-07
Globus	8.509688	1.103561e-06
Caudate	8.019484	1.545191e-06
White matter	3.135994	6.674776e-03
Vwm_lPPC_rPPC	3.111306	6.984971e-03
Vwm_rPPC_lPPC	2.900702	1.096008e-02
L_DLPFC_l_MFG	2.475718	2.612431e-02
L_DLPFC_r_SMG	2.065294	4.854488e-02

Table 1: Top 9 most significant biomarkers ranked by descending t-score

6. Final temporal sequence of events

The EBM revealed a sequence of events beginning with the atrophy of structural subcortical markers (putamen, striatum, globus and caudate) followed by the atrophy of white matter and finally the degeneration of four neural connections: left posterior parietal cortex (PPC) to right PPC, right PPC to left PPC, left dorsolateral prefrontal cortex (DLPFC) to left medial frontal gyrus (MFG) and left DLPFC to right supramarginal gyrus (SMG).

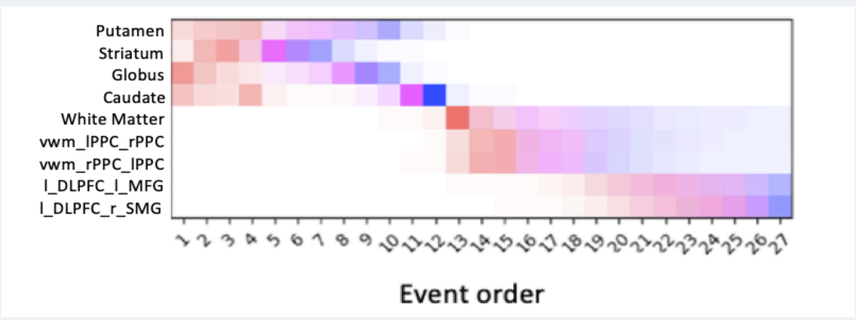


Figure 3: Positional variance diagram presenting the final temporal sequence of structural and connectivity changes in the HD brain.

→These findings are in accordance with clinical knowledge of HD progression, and provide the first data-driven evidence that brain volume loss precedes connectivity changes in HD.

7. Limitations

The EBM follows two key assumptions:

HOMOGENEITY: all patients follow the same pattern of disease progression

MONOTONICITY: all biomarkers decrease monotonically during disease progression

HOWEVER

There may not be a single way in which the brain is deteriorating during the progression of HD. As shown below (Figure 4), the majority of patients increase in EBM stage over time but there are a few outliers that either remain in the same stage or even decrease in stage over time.

Each biomarker was plotted over time (Figure 5) and the connectivity markers were shown to have non-monotonic effects, decreasing during the first year of disease progression and increasing during the second year or vice versa.

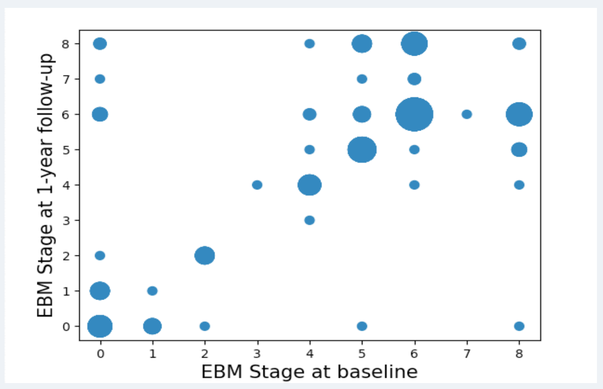


Figure 4: Scatter plots showing patient staging at baseline vs 1-year follow-up

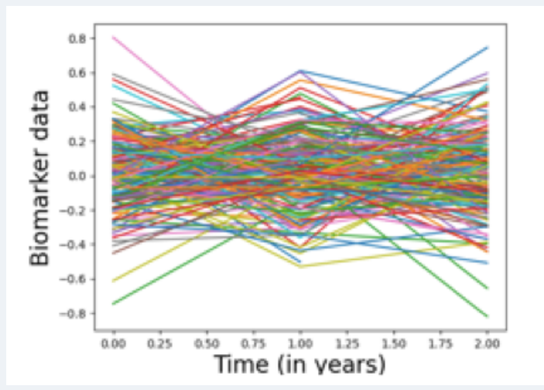


Figure 5: Longitudinal analysis of the l_DLPFC_MFG connectivity marker during disease progression

8. Future work

1. Include patients with late stage mHD to have a representation of the complete time course of HD brain changes.

2. Include microstructural changes as biomarkers to further understand the genetic and molecular processes which prompt brain atrophy during the progression of HD.

3.Employ a subject-specific event ordering model instead of assuming that HD is a homogeneous disease.

Scan for references

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