Gaussian Process Progression Modelling of structural MRI changes in Huntington's disease

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Declaration of Financial Interests or Relationships

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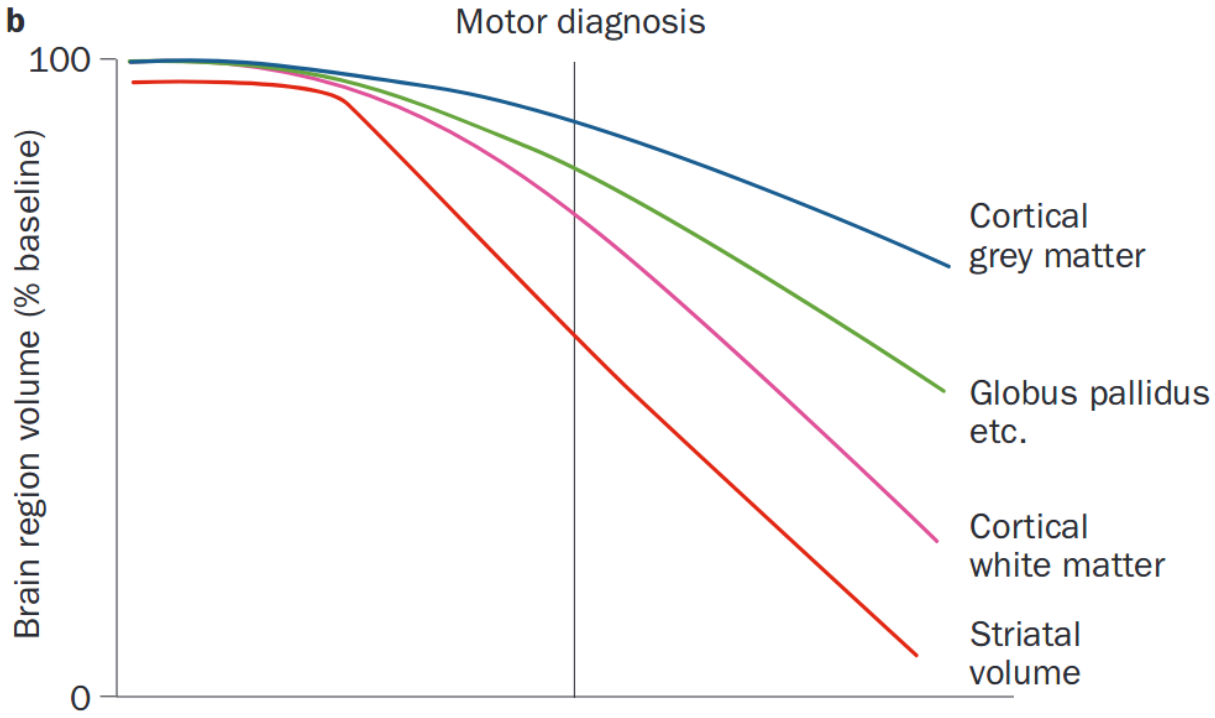
I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Background: Huntington's disease

Ross et al. Nature Reviews 2014



- Neurodegenerative disease that causes progressive deterioration and death ~ 55 years old
- Caused by an expansion in the number of cytosine-adenine-guanine (CAG) repeats in the huntingtin gene
- Characterised by a long (~10 years) pre-manifest period before clinical symptoms develop
- Clinical progression is mirrored by monotonic change in regional brain volumes

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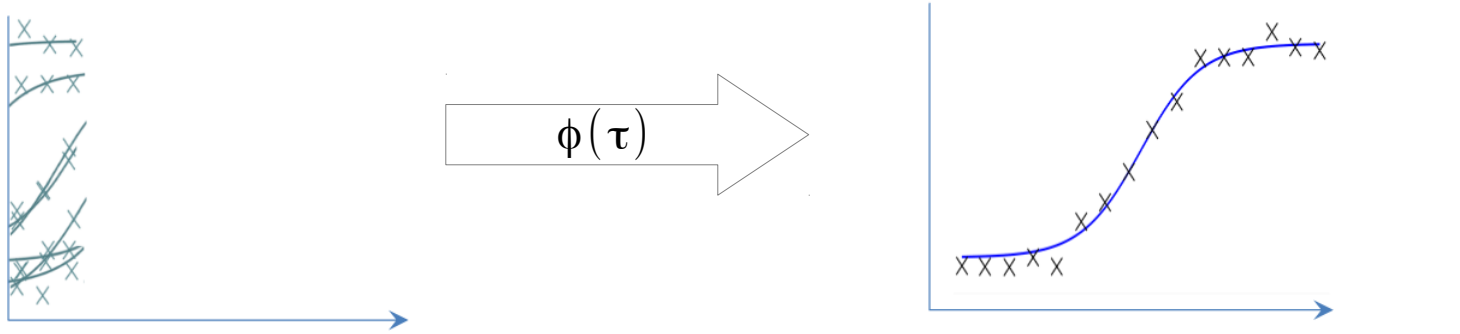
Objectives

1. Infer biomarker dynamics from longitudinal individual-level data

2. Estimate where a patient is along the disease trajectory

• **Problem** – patients are observed at unknown disease time which doesn't necessarily correspond to observation time; this confounds time-series regression

• **Solution** – learn both temporal covariance (regression) and latent disease stage (time-shift) using a generative, time-reparameterised Gaussian Process Progression Model (GPPM)*



$$y^j(t) = f(t) + \nu^j(t) + \epsilon$$

$$y^j(\phi^j(\tau)) = f(\phi^j(\tau)) + \nu^j(\phi^j(\tau)) + \epsilon$$

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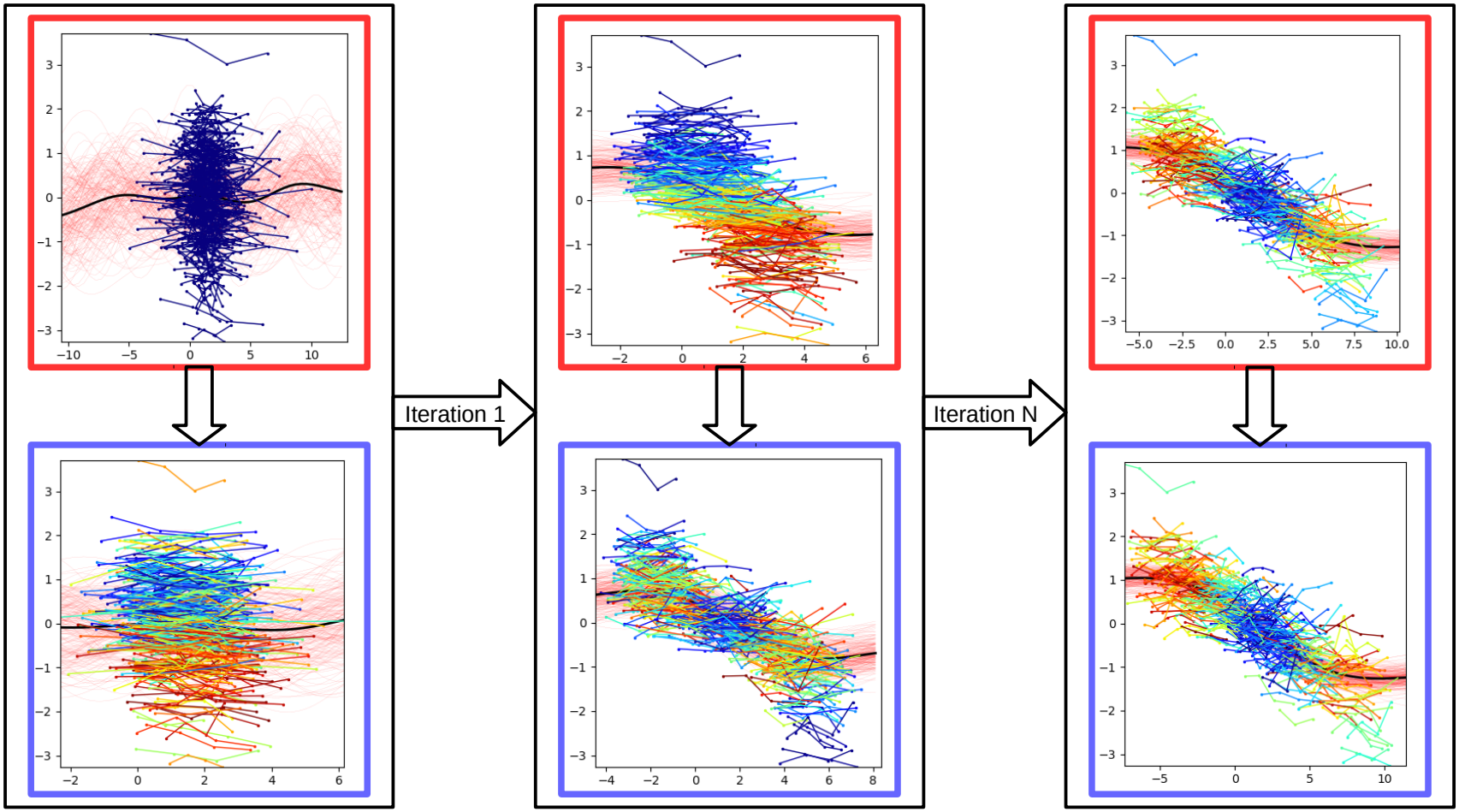
* Lorenzi et al. NeuroImage. 2018; 190:56-58

Methods: Gaussian Process Progression Model



- We define a cost function: sum of model likelihood + regularisation term
- Monotonicity constraint* – enforced by constraining first derivative of fixed-effects
- Sequentially fit regression parameters and individual time shift

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* Lorenzi & Filippone. 2018. arXiv:1802.05680

Methods: Datasets

Demographic Characteristic	HC (TRACK-HD)	PreHD (TRACK-HD)	HD (TRACK-HD)	HC (PREDICT-HD)	PreHD (PREDICT-HD)
N	100	104	80	36	128
Sex (F:M)	58:42	55:49	43:37	25:11	82:46
Age (mean ± std)	46.3 ± 10.4	41.2 ± 8.8	48.5 ± 9.3	45.1 ± 10.9	41.5 ± 10.9
CAG (mean ± std)	-	43 ± 2.3	43.8 ± 3	-	42.5 ± 2.7

- TRACK-HD and PREDICT-HD are longitudinal multi-centre cohort studies of Huntington's disease
- T1-weighted 3T sMRI scans from 3 time-points were longitudinally registered using SPM12
- Regional volumes were segmented and parcelleted using the GIF segmentation tool*
- Regional volumes were adjusted for covariates (age, sex, site, total intracranial volume)
- CAG data used for evaluation, not training

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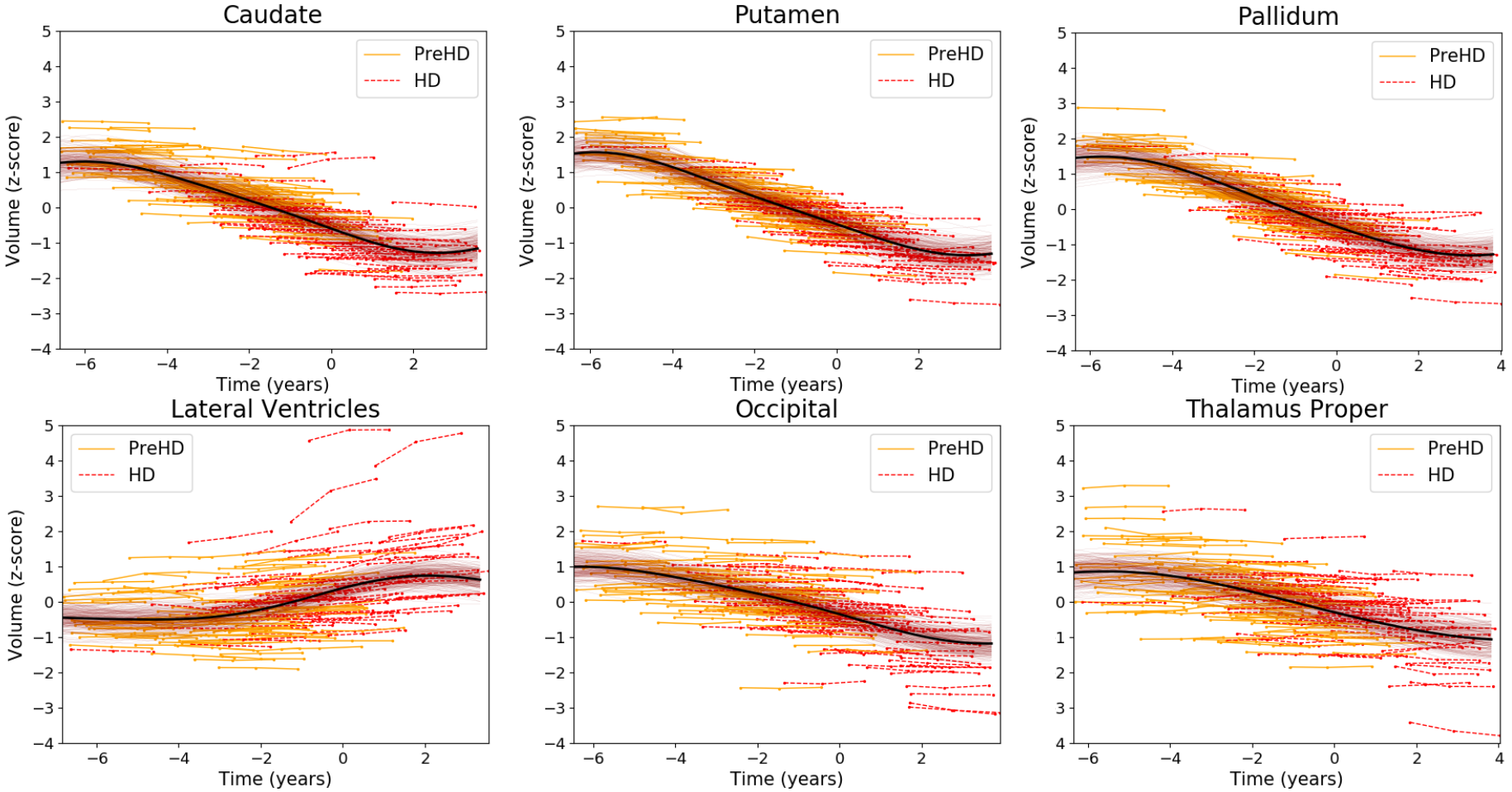
* MJ Cardoso et al. IEEE TMI. 2015; 34:1976-88

Results: Trajectories



- Predicted volumetric changes in 6 key anatomical regions
- Mostly sigmoidal, but pronounced non-linearity in lateral ventricles
- Absolute magnitude ranging from 7-22% over ~11 years

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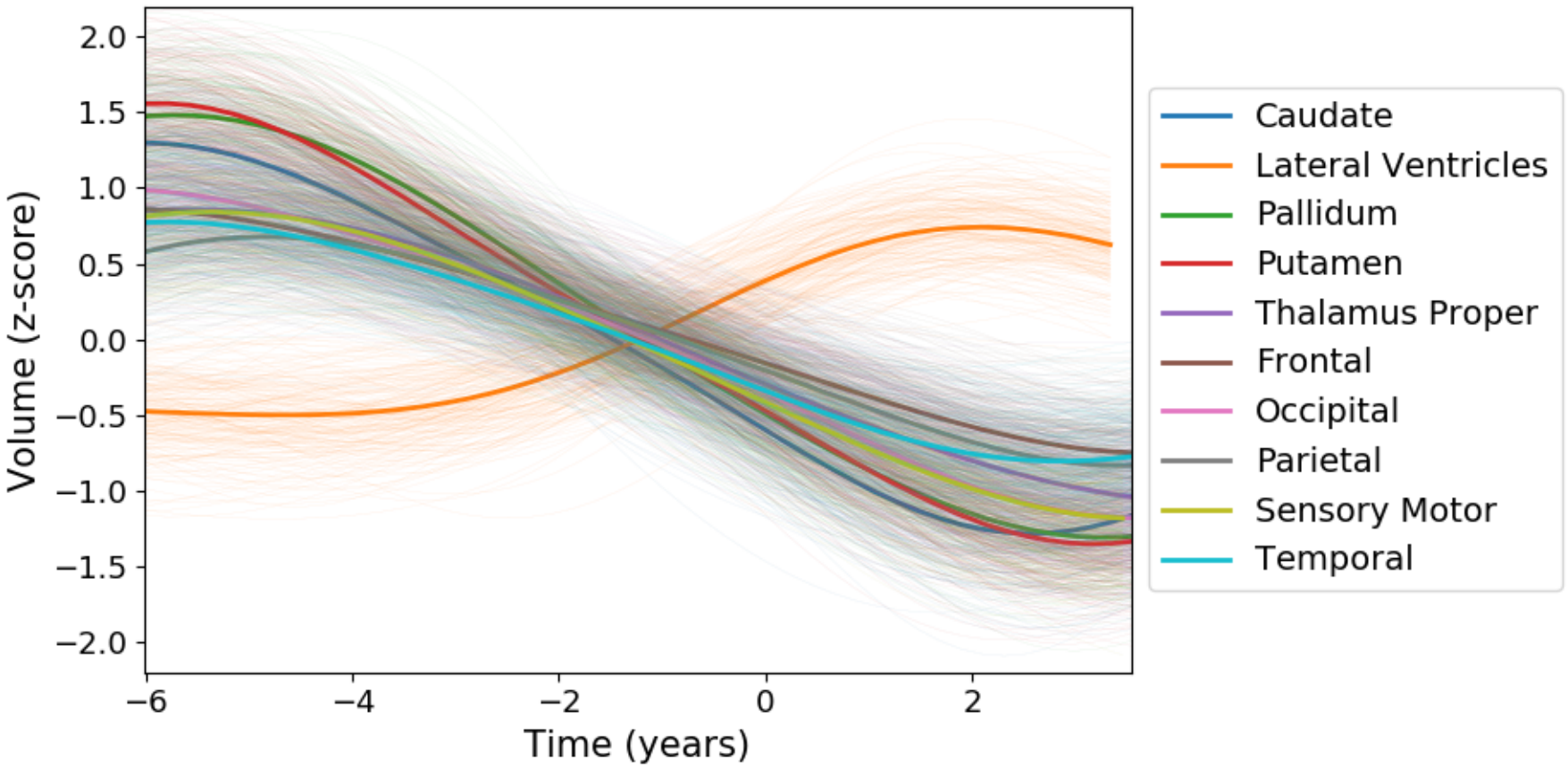
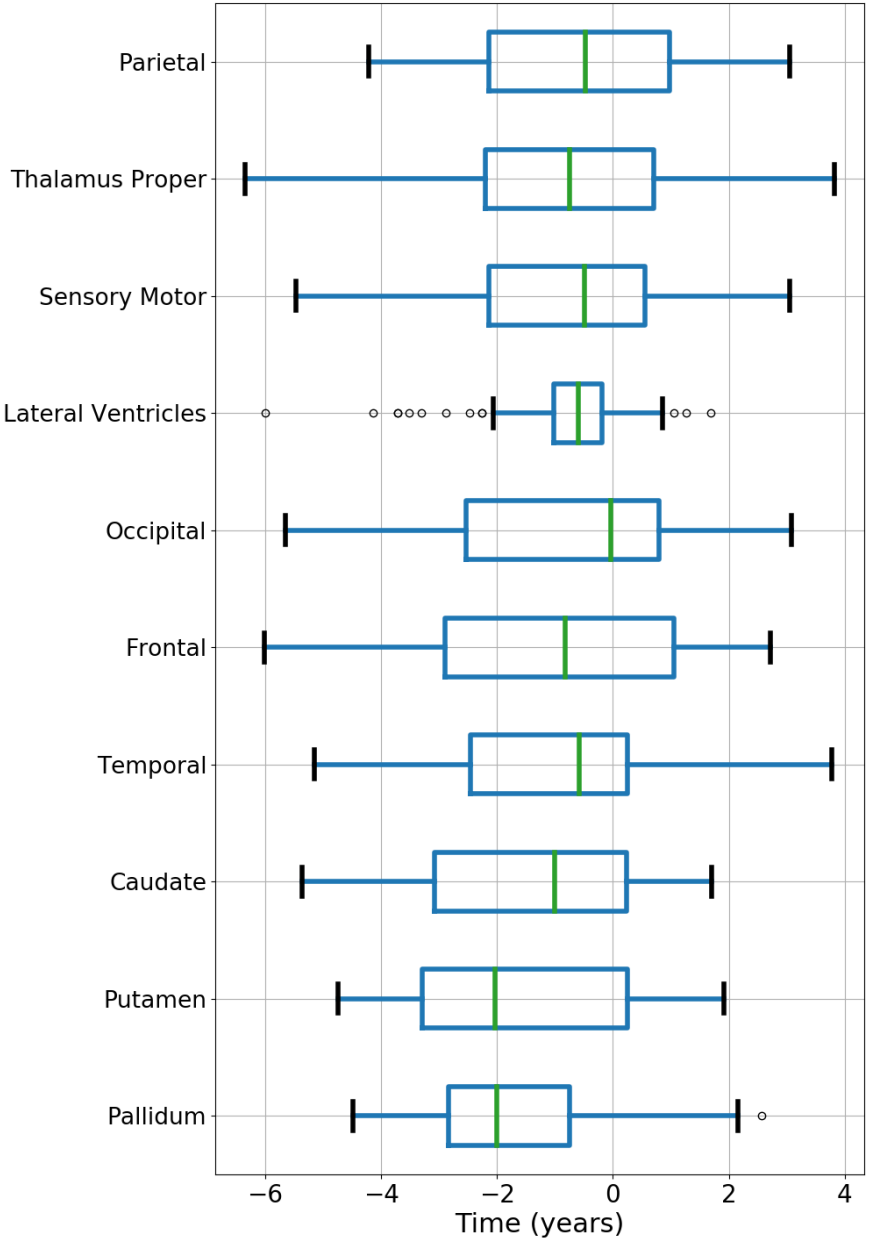
Results: Trajectories (group-level)



- Predicted volumetric changes in 10 key sub-cortical and cortical regions
- Larger and mostly non-linear change in sub-cortex (except thalamus)
- Smaller and mostly linear change in cortex (except sensory motor)

Results: Change point ordering



- Time at maximum gradient → time at transition from pre-manifest to manifest HD
- Estimate maximum change time from 1000 samples from posterior for each region
- Model predicts earliest changes in basal ganglia (pallidum, putamen, caudate)
- Also predicted by completely separate methodology using cross-sectional data*
- Followed by changes across the cortex over period of ~2 years

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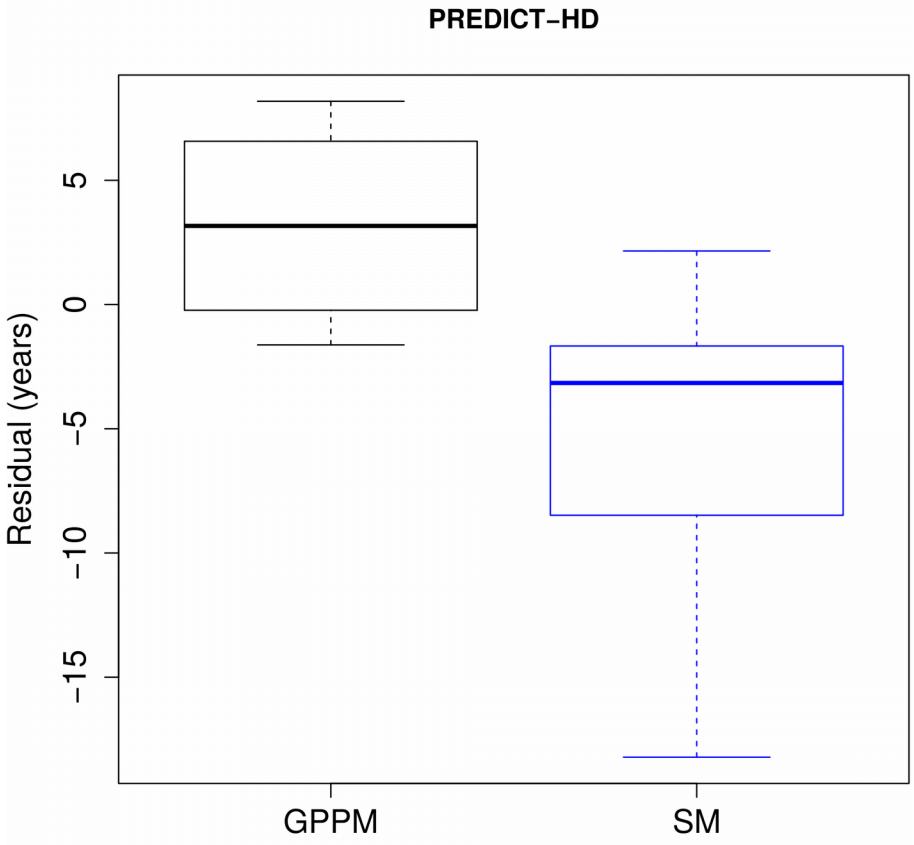
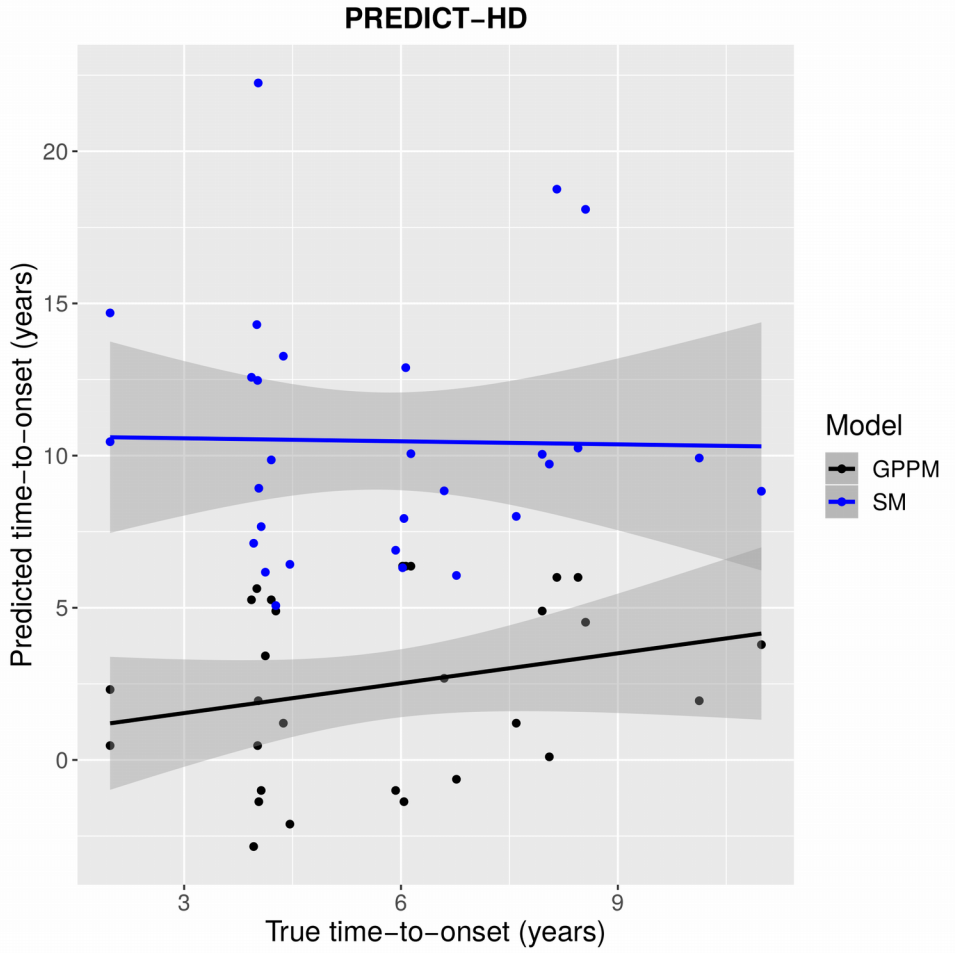
* Wijeratne et al. Ann. Clin. Trans. Neurol. 2018; doi: 10.1002/acn3.558

Results: Prediction of onset





- Compare accuracy of predicted time-to-onset with benchmark survival model (SM) based on age and CAG*

- GPPM provides a smaller uncertainty and tracks disease progression better than the SM

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* Langbehn et al. Am J Med Neuropsychiatr Genet. 2011; 153:397-408

Conclusions

- The Gaussian Process Progression Model (GPPM) can be used to infer longitudinal changes in regional imaging volumes

- Provides clinically meaningful information:

    - Biomarker temporal progression (group-level)
    - Staging (individual-level)
    - Biomarker temporal ordering

- GPPM predictions also outperforms the benchmark survival model in HD

→ **Disease progression modelling can improve sMRI as a biomarker**

- Can easily used to model to include any types of dynamic marker – different imaging modalities (e.g. DWI, PET), biofluids, clinical markers…

- Online GPPM interface available here: https://epione-demo.inria.fr/

Thanks for listening – get in touch!

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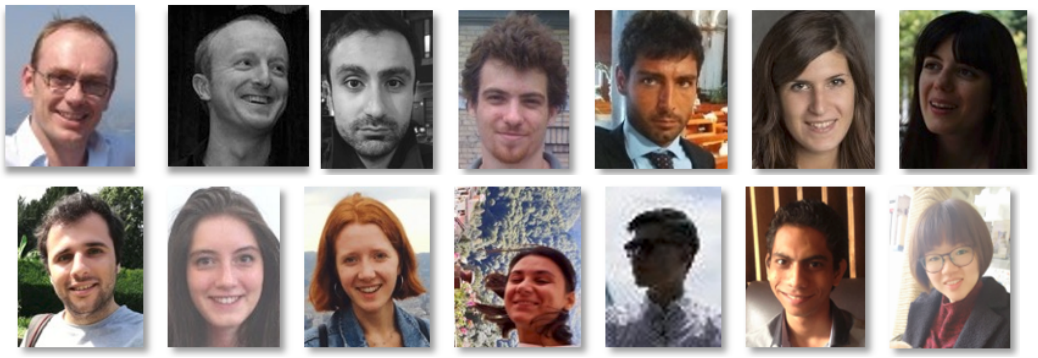
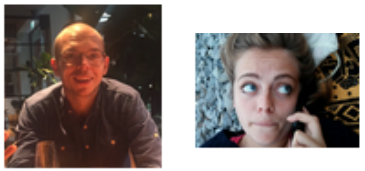
Acknowledgements





And all the participants of the Huntington's disease studies used here.

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