Parsing neurodegenerative heterogeneity with biological trans-diagnostic normative modelling

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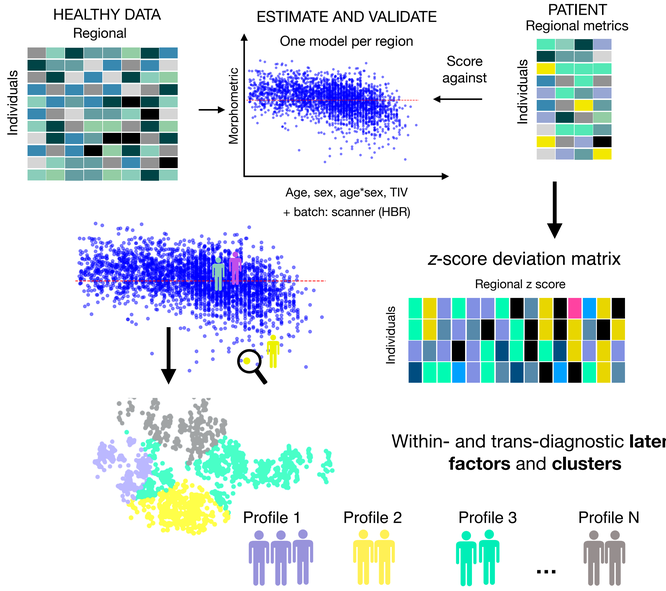
Introduction

Background. Neurodegenerative diseases present a great degree of heterogeneity, both clinically and biologically. Different neurodegenerative pathologies and genetic commonalities are frequently observed across disease and no one disorder is captured by one type of pathology. One diagnosis does not correspond to only one pathology in the brain. This heterogeneity is a challenge to link specific symptoms to underlying mechanisms and to target such mechanisms for treatment.

Aim and Rationale. The overarching aim of the project is to understand and characterise the variability of presentation and progression of dementia by parsing its heterogeneity with normative modelling, to ***uncover which neuroimaging features are linked to specific impairments, and if these features operate across disorders.***



We designed a normative model of the ageing brain across multiple morphometrics allowing to score individual patients against the model, providing a ***probabilistic and multivariate interpretation of deviation from the normative range across all brain regions capable of capturing spatially distributed differences.***

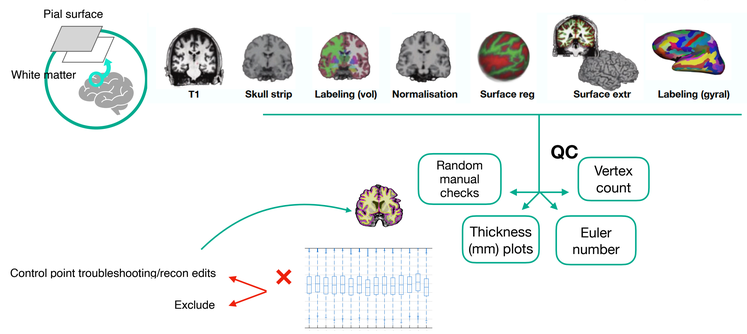
Data and Participants.

Participants. We include from open access and private datasets T1-weighted MRI scans of 1) N=3000 healthy participants (35-95 years) and patients (N=800) with different disorders (Alzheimer's, Parkinson's, Lewy body and Frontotemporal disease). This is vital for the accurate demonstration of specificity, which cannot be assessed using only one diagnostic group.

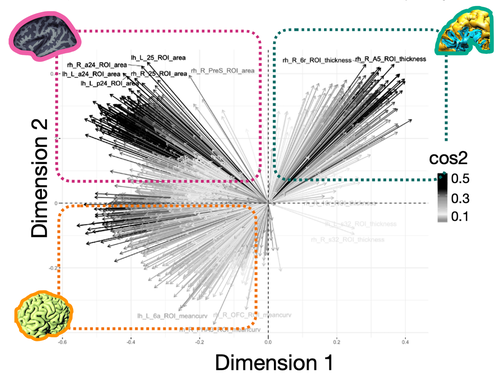
This will allow to determine transdiagnostic profiles shared across individuals, and how these profiles relate to canonical neurochemical anatomy maps.

Materials and Methods

Data pre-processing.



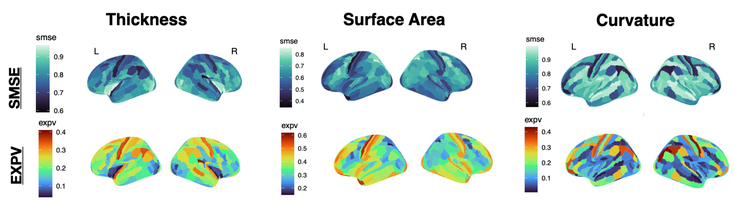
Inspection of different morphometrics. We ran a PCA to examine which morphometrics explained most of the variance. Thickness, surface area and curvature explain different types of variance and were all entered in the model together with subcortical volumes. We carried out separate models for cortical thickness, surface area, curvature and subcortical subfields (not presented here).



We used PCNtoolkit for normative modelling. All models used hierarchical Bayesian regression, modelled site effects using scanner as a batch variable, allowed for heteroscedasticity, and included the same set of covariates:

The model is first estimated for each region using healthy control data. Patients are then scored against the model using a transfer step, yielding a z-score matrix (participants × brain features) indicating the features on which they deviate from the norm.

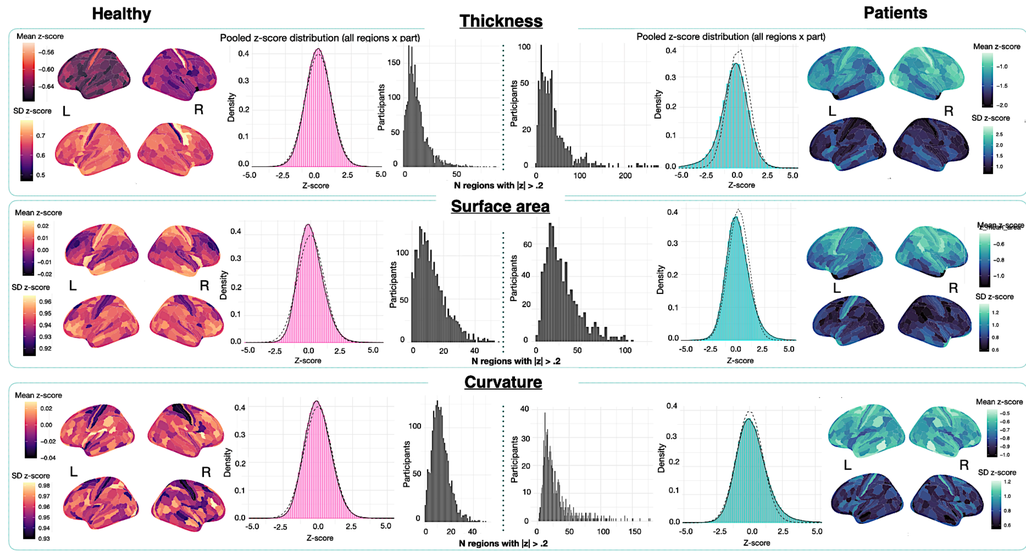
Initial Results: HC model fits



Thickness and surface area perform particularly well (.6 < smse < .85, .4 < rho <.8, .2< expv <.6), curvature performs worse overall .8 < smse < .98, .3 < rho <.65, .1< expv <.4) but some of the regions (e.g. inferior temporal) where curvature explains some variance are not as well explained by the others, suggesting it adds relevant information about ageing-related processes.

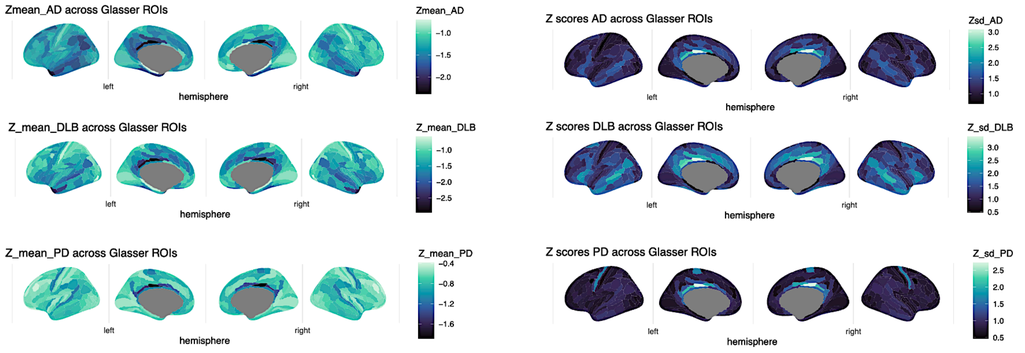
Initial results: Patient Dataset

Z-score distribution: HC vs. Patients per Morphometric



The amount of heterogeneity in the HC sample is low across the brain (see SD z-scores on the left), whereas in patients (on the right) SD of z-scores spans across a wider range. Patients show with more extreme z-scores (distribution plotted in green) if compared to controls (plotted in pink). The patient sample includes more individuals with a higher N of regions with high deviation (plotted in grey).

Patients Z-scores only: cortical thickness. The patient scores in the plot above however include different diagnoses. When braking down patients by diagnostic group heterogeneity remains very high (example for thickness shown here for AD, PD and DLB). Each patient group not only has more extreme mean z-scores per region as expected, but also a much broader standard deviation.



Conclusions and Next Steps

Multiple morphometrics explain different components of ageing as shown by the pre-modelling PCA.

Surface area and cortical thickness capture a large portion of the ageing-related variance in the HC sample.

When examining patient scores, **even within the same diagnostic group patients are much more dissimilar from one another than controls are**. To leverage this high heterogeneity, understanding and characterise individuals we are:

- performing trans-diagnostic spectral clustering and factor analysis to identify biologically pleasing groupings
- validating these clusters with cognitive measures
- Validating the clusters using receptor density maps