Model-based subtypes of disease progression in Parkinson's

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A data-driven take on understanding heterogeneity in Parkinson's disease.

Subtype and Stage Inference (SuStaIn):

Computational model of disease progression + Clustering

Parkinson's disease (PD)

➢ 2nd most common neurodegenerative disease

➢ Highly heterogeneous

∃ **no validated biomarkers of progression for PD**

➢ Needed for clinical trials

We estimate a data-driven signature of PD progression subtypes as sequences of measurable abnormality

in the Parkinson's Progression Markers Initiative (PPMI)

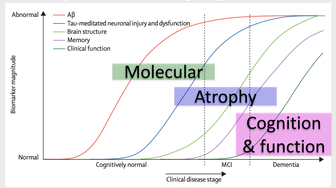
Study overview: SuStaIn + KDE-EBM

- Event-based model (EBM) [1,2] estimates a probabilistic sequence of cumulative abnormality in a set of N features using mixture modelling to quantify abnormality
- KDE-EBM [3], Kernel Density Estimation mixture model
- ***Methodological novelty here****: variable bandwidth KDE*
- SuStaIn [4]: split-and-fit KDE-EBM clusters
- Patient subtype and stage inferred from best fitting (max. likelihood) combination of abnormal features
  - "Stage M" ≅ M out of N markers are abnormal

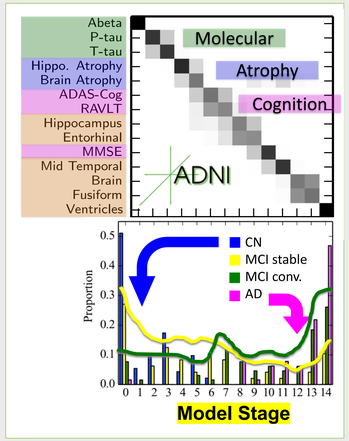
Methods and Data

Event Based Model (EBM) [1,2] estimates a probabilistic sequence of biomarker abnormality => fine-grained staging tool

inspired by hypothetical model: (Alzheimer's) [5]



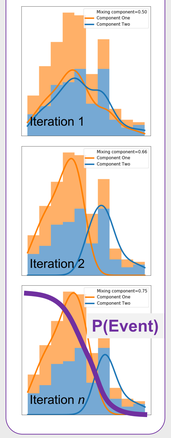
developed a data-driven model: [1,2]



Key:
Grayscale intensity (per row) represents the likelihood of the biomarker event occurring in that sequence position

which provides a staging tool: [2]

KDE Mixture Modelling [3]



Data

- 9 "Imaging plus X" [6] features: clinical, cognitive, DaTscan SPECT striatal binding ratio
- Inclusion criteria: complete data

Group	N	Disease duration	Age (years)
HC	175	n/a	61 ± 11
de novo PD	405	0.6 ± 0.5 years	62 ± 10
SWEDD	56	0.6 ± 0.7 years	62 ± 10

PARKINSON'S PROGRESSION MARKERS INITIATIVE

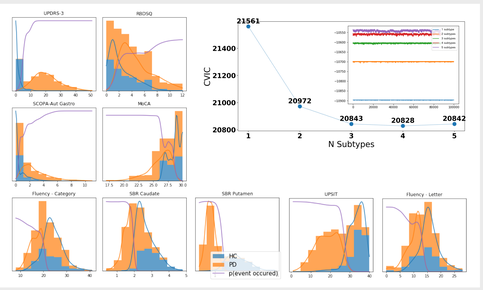
ppmi-info.org

Results: subtypes of Parkinson's

Figure 1.
KDE Mixture Models for p(Event)

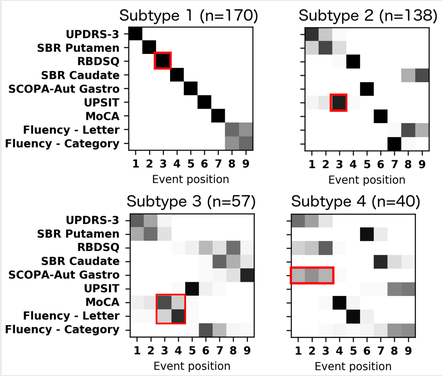
and

Cross-Validation



UPDRS-3 = motor symptoms
RBDSQ = sleep problems
SCOPA Gastro = gastrointestinal
MoCA = cognition
SBR = dopamine deficiency
UPSIT = olfactory problems
HC = healthy controls

Figure 2.
PD progression subtypes:
1. Sleep
2. Smell
3. Cognition
4. Gastrointestinal (SWEDD?)



Key observations:
a) dopamine deficiency always putamen before caudate, and is usually early;
b) when cognition is involved early, letter fluency is consistently before category fluency;
c) sleep problems early in 3 subtypes.

d) CVIC: is it 3/4/5 subtypes?
=> motivates methods-development work on improving model parsimony, e.g., explicitly hierarchical subtypes that split and merge as appropriate.

Contributions

- Parkinson's disease understanding: fine-grained sequences of subtypes
- New, flexible KDE mixture modelling

Considerations and future work

Method:
- Improve model parsimony

Application:
- Validate in prodromal cohorts
- Other markers:
  - MRI
  - Vision

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