AI FOR SUPPORT OF DECISION MAKING IN PERSONALIZED HEALTHCARE

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AI & Data Science Group @Fraunhofer SCAI
Mission: Bringing Better Treatments to the Right Patients

- Omics
- Longitudinal clinical
- Real World Evidence
- Digital biomarkers
- Unstructured text

>130 publications

Methodologies, e.g.

Hybrid AI: combining human knowledge with AI

(Generative) time series models

Multi-modal, multi-scale data fusion

AI & Data Science

Application focus

Precision medicine

Early Drug Discovery

- Pharma
- Biotech
- Insurances
- Hospitals

Our value chain:

Biological system reconstruction & modeling → Drug target identification → The right drug for the right patients → Clinical trial design: simulation of synthetic cohorts

https://www.scai.fraunhofer.de/de/geschaeftsfelder/bioinformatik/forschungsfelder/AI-DAS.html

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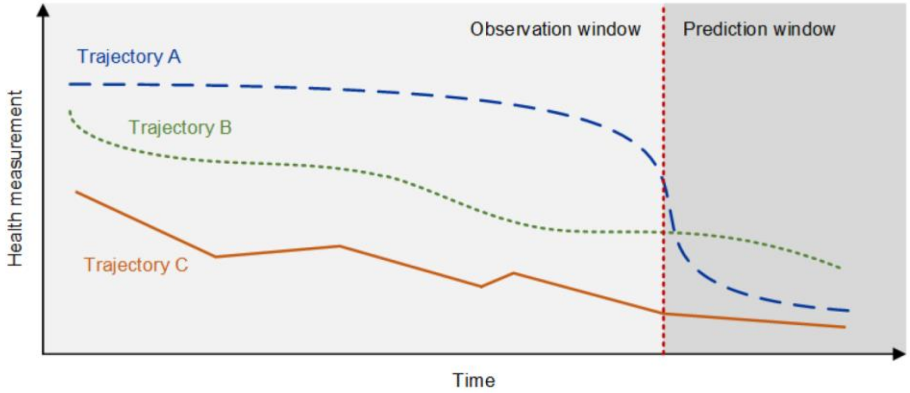
Motivation: AI for Analyzing Patient Trajectories

- Highly heterogenous disease trajectories in many disease areas
  - Example: neurogenerative diseases
- Patient trajectories provide rich information about
  - Disease dynamics
  - Disease state
  - Future disease outcomes
- Possible use of patient trajectories
  - Clustering
  - Patient pathways
  - Risk models



Allam et al., Journal of Medical Internet Research, 2021

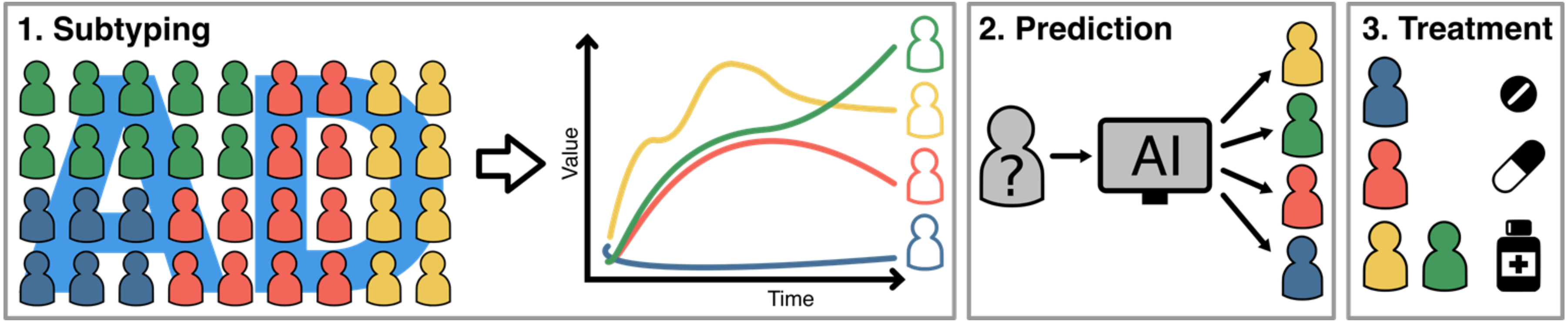
De Jong, …, Fröhlich, Giga Science, 2019

Birkenbihl, Salimi, Fröhlich, Alzheimer's & Dementia, 2022

e.g.: Linden, …, Fröhlich, Frontiers in Artificial Intelligence, 2021

Motivation: Clustering of Patient Trajectories

- Identify patients with similar patient journeys
- Personalized prediction of type of progression
- Treatment tailored to type of progression



Challenges

Clinical time series data is short: typically < 10 time points

- Existing time series clustering methods designed for more time points

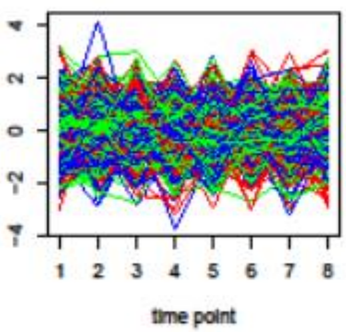
Data are limited: few hundred patients

Missing values, e.g. due to patient drop-out ➔ missing data <u>not</u> at random (MNAR)

- Correlation between missingness and observed data possible
- Multiple imputation methods exist, but errors will propagate further into clustering

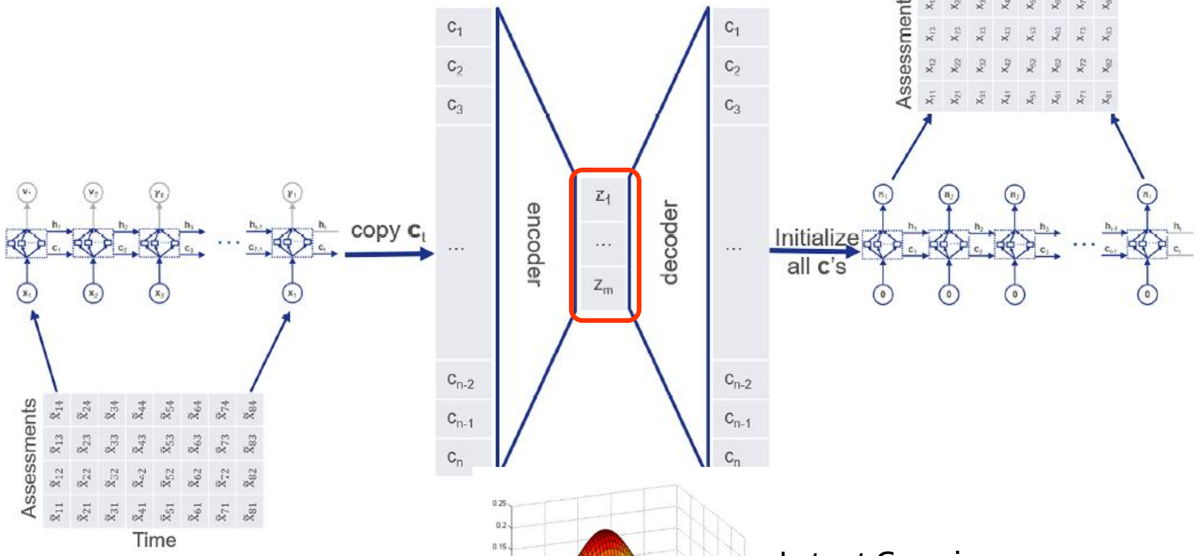
Variational Deep Embedding with Recurrence (VADER)

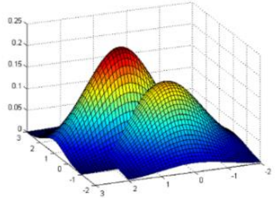
$$\mathcal{L}_{\mathrm{ELBO}}(\mathbf{x}) = E_{q(\mathbf{z},c|\mathbf{x})}[\log p(\mathbf{x}|\mathbf{z})] - D_{KL}(q(\mathbf{z},c|\mathbf{x})||p(\mathbf{z},c))$$



Multivariate short time series data

Embedding (peephole LSTM)





Latent Gaussian Mixture Model

Handling of missing data as <u>part of model training</u>

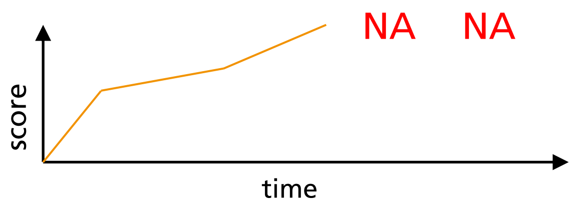
- Data augmentation + modification of VAE loss function

De Jong, …, Fröhlich, Giga Science, 2019

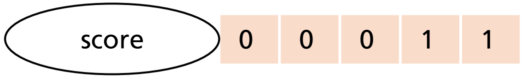
Implicit Imputation via „Imputation“ Layer

Model should only learn to reconstruct *observed* data

- Indicator variables encode missingness pattern
- Consider only observed data in reconstruction loss term in ELBO criterion



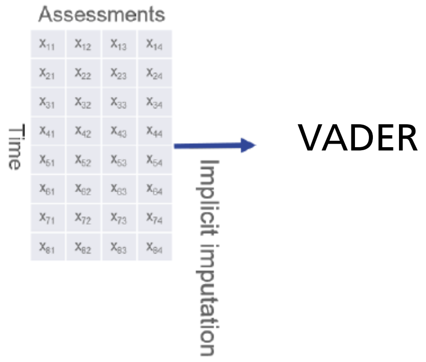
$$\frac{NM}{|A|}\sum_{l=1}^{L}\sum_{i=1}^{N}\sum_{j=1}^{M}(1-\mathbf{1}_A(x_{ij}^l))(x_{ij}^l-\widehat{x_{ij}^l})^2$$



„Implicit“ imputation („Imputation“ layer)

$$\tilde{x}_{ij}^l = x_{ij}^l \times (1-\mathbf{1}_A(x_{ij}^l)) + b_{ij} \times \mathbf{1}_A(x_{ij}^l)$$

trainable



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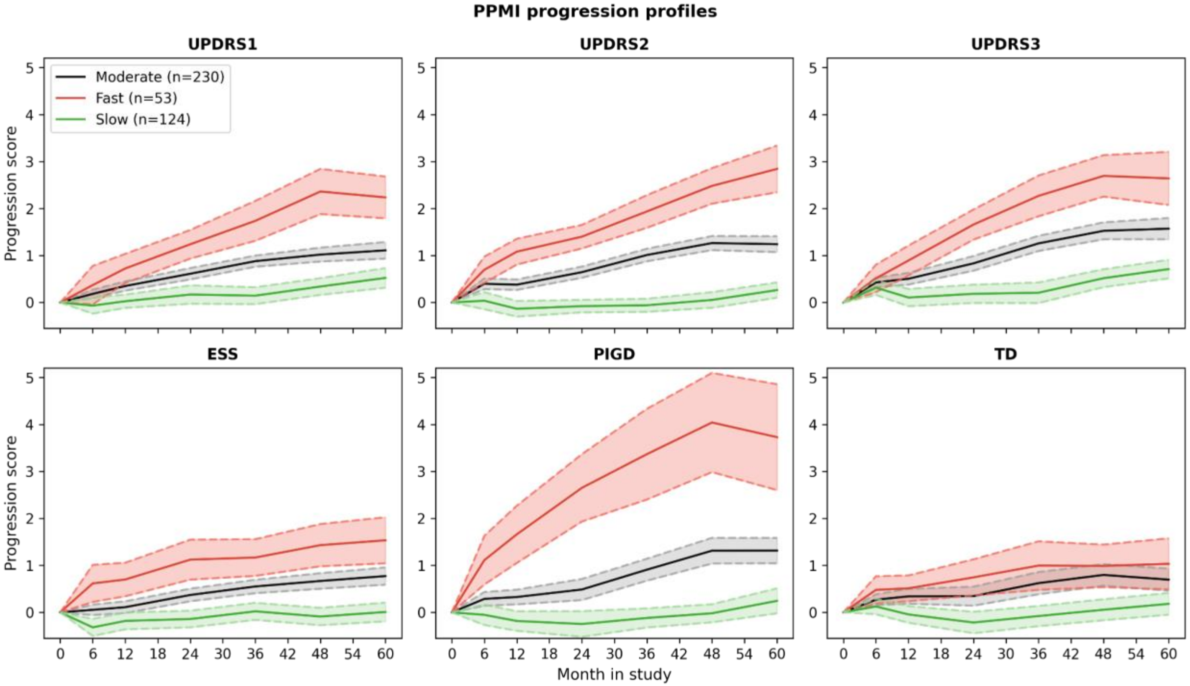
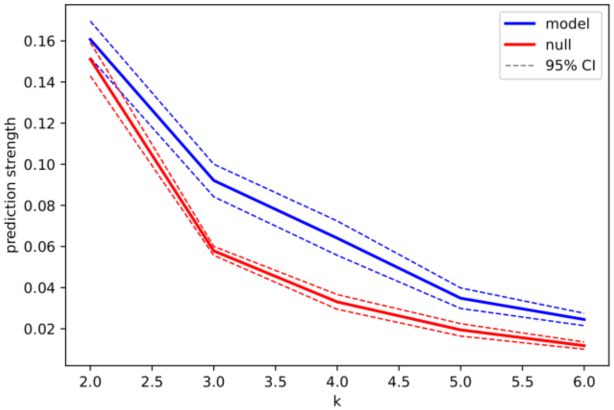
Application to Parkinson's Disease





Tibshirani & Walters, Journal of Computational and Graphical Statistics, 2005

~1/3 of patients do not demonstrate significant disease progression

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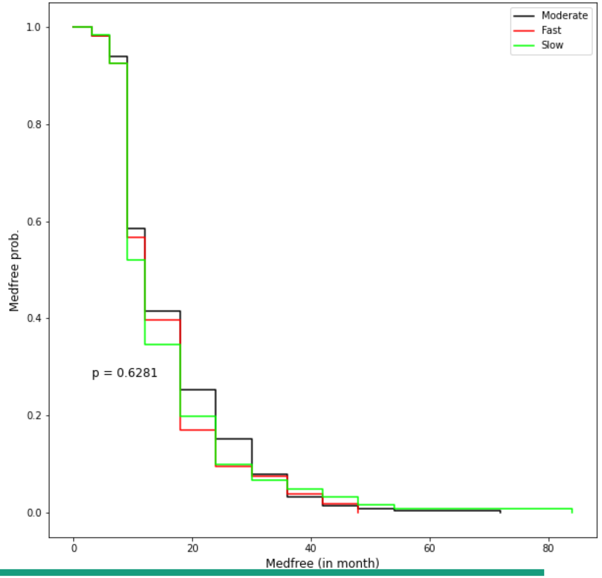
Are Clusters a Result of Confounding Effects?

- No significant differences in
  - Time since initial diagnosis
  - Time till start of therapy
  - Gender
- Slow progressors are younger
  - Later disease onset ➔ faster progression

Cluster	N	Age (Years)	Number of Females	Months since diagnosis	MDS-UPDRS I	MDS-UPDRS II	MDS-UPDRS III
Slow	124	60.2 ± 9.3	49 (39.5 %)	0.5 ± 0.5	5.4 ± 4.2	5.9 ± 4.2	21.0 ± 9.1
Moderate	230	62.7 ± 9.7	78 (33.9 %)	0.6 ± 0.5	5.1 ± 3.5	5.4 ± 3.9	20.6 ± 8.7
Fast	53	64.2 ± 10.8	13 (25.5 %)	0.7 ± 0.8	7.3 ± 4.7	7.2 ± 4.9	21.0 ± 8.8



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Association with Distinct Symptoms, Genetic Loci and Biological Mechanisms

Slow	Moderate	Fast
• Hand movement, rigidity of ipsilateral extremities • Daytime sleepiness • Anxiety, depression, fatigue • Reduced semantic fluency • Polygenic risk score + several PD associated SNPs • vitamin and disaccharide metabolism (includes GBA) • Interleukin receptors	• eating • reduced agility in the ipsilateral leg • Several SNPs • Cholesterol metabolism • Vascular endothelial growth factor	• Hallucinations • Postural instability • Gait impairment • REM sleep behavior disorder (RBD) • Several PD associated SNPs • SNARE vesicle transport • Rap1 signaling / nigrostriatal dopaminergic pathway in medium spiny neurons • Low CSF amyloid beta

Method: bootstrapped sparse group lasso

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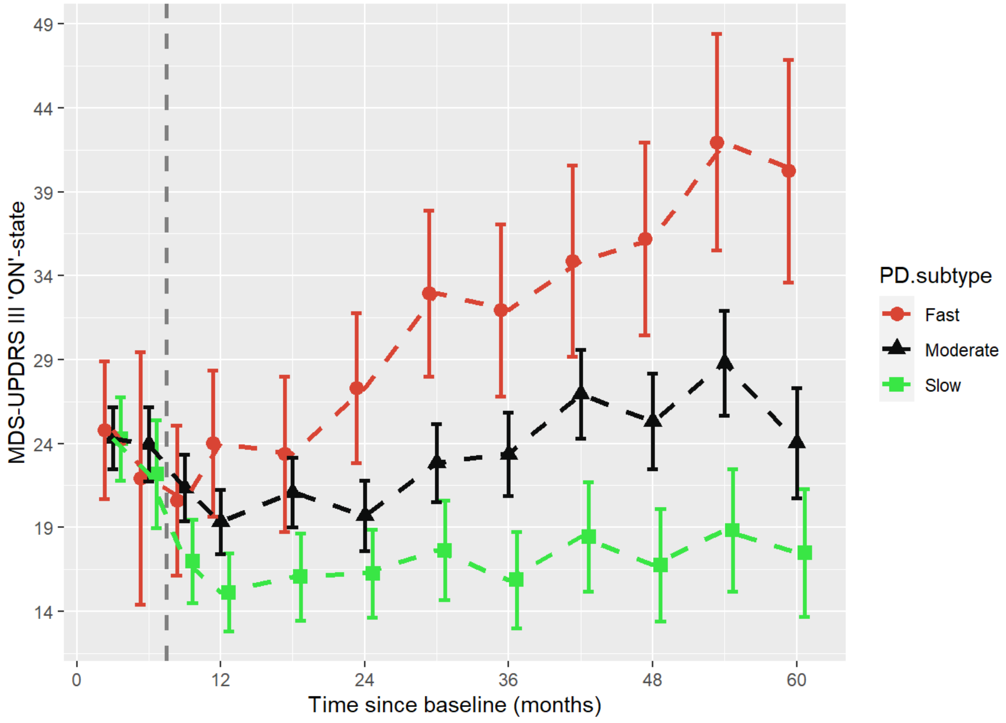
Differential Response to Motor Symptom Therapy

- No differences in
  - treatment regime
  - LDOPA equivalent daily dose



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Summary and Impact of this Project

Many diseases demonstrate highly heterogenous trajectories

Disease trajectories have to be understood as multivariate, short time series with missing data

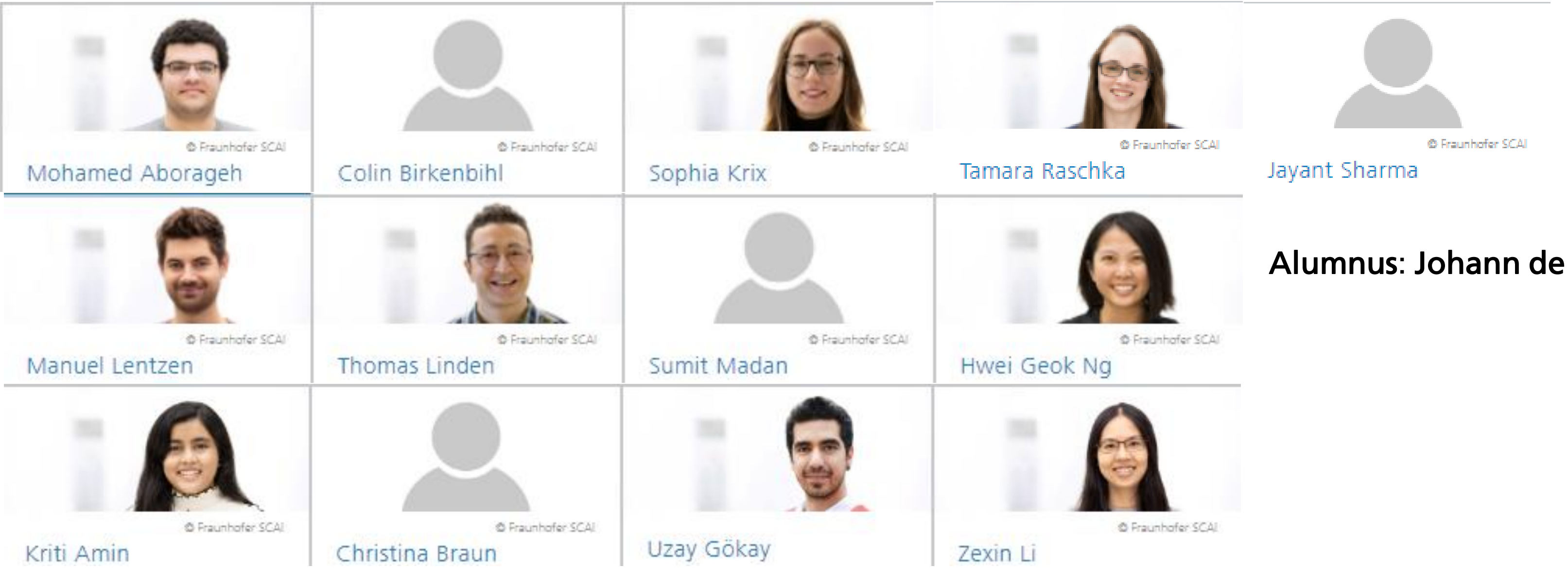
- VADER is a novel approach to cluster such data

Impact:

- Exclude patients that are likely slow progressors
- Use of stratification in statistical analysis at EOS

- Association with molecular mechanisms opens the door to develop subgroup specific treatments

Acknowledgements



Alumnus: Johann de Jong

AETIONOMY

The Virtual Brain Cloud

RADAR-AD

DIGIPD

nfdi4health

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Backup

ELBO-Criterion for VADER

$$
\begin{aligned}
p(c) &= \mathrm{Cat}(c|\boldsymbol{\pi}) \\
p(\mathbf{z}|c) &= \mathcal{N}\left(\mathbf{z}|\boldsymbol{\mu}_c, \boldsymbol{\sigma}_c^2\mathbf{I}\right) \\
p(\mathbf{x}|\mathbf{z}) &= \mathrm{Ber}(\mathbf{x}|\boldsymbol{\mu}_x) \quad or \quad \mathcal{N}(\mathbf{x}|\boldsymbol{\mu}_x, \boldsymbol{\sigma}_x^2\mathbf{I})
\end{aligned}
$$

$$
\begin{aligned}
\mathcal{L}_{\mathrm{ELBO}}(\mathbf{x}) &= E_{q(\mathbf{z},c|\mathbf{x})}\left[\log \frac{p(\mathbf{x},\mathbf{z},c)}{q(\mathbf{z},c|\mathbf{x})}\right] \\
&= E_{q(\mathbf{z},c|\mathbf{x})}\left[\log p(\mathbf{x},\mathbf{z},c) - \log q(\mathbf{z},c|\mathbf{x})\right] \\
&= E_{q(\mathbf{z},c|\mathbf{x})}[\log p(\mathbf{x}|\mathbf{z}) + \log p(\mathbf{z}|c) \\
&\quad + \log p(c) - \log q(\mathbf{z}|\mathbf{x}) - \log q(c|\mathbf{x})]
\end{aligned}
$$

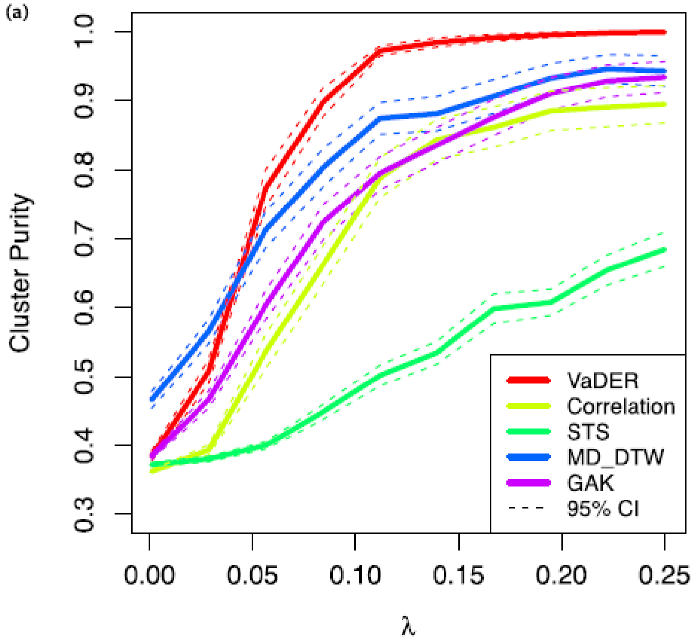
Probabilistic cluster assignment:

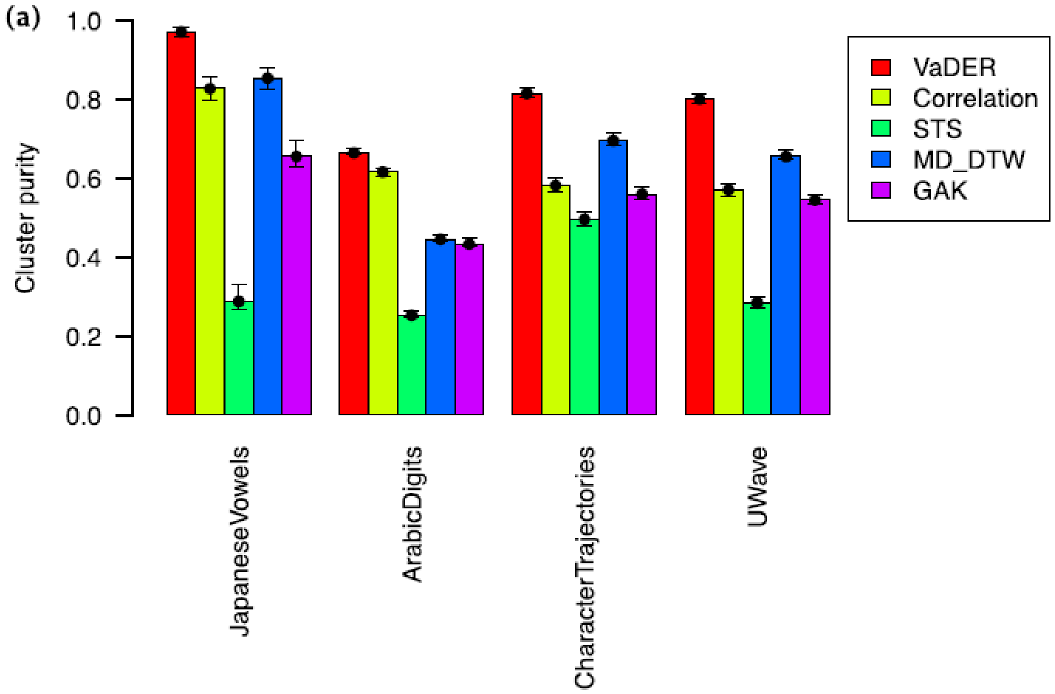
$$
q(c|\mathbf{x}) = p(c|\mathbf{z}) \equiv \frac{p(c)p(\mathbf{z}|c)}{\sum_{c'=1}^{K} p(c')p(\mathbf{z}|c')}
$$

$$
\mathcal{L}_{\mathrm{ELBO}}(\mathbf{x}) = \underbrace{E_{q(\mathbf{z},c|\mathbf{x})}[\log p(\mathbf{x}|\mathbf{z})]}_{\text{(Modified) reconstruction error}} - \underbrace{D_{KL}(q(\mathbf{z},c|\mathbf{x})||p(\mathbf{z},c))}_{\text{Deviance from Gaussian mixture prior = regularization}}
$$

Jiang Z, Zheng Y, Tan H, et al. Variational deep embedding: an unsupervised and generative approach to clustering. In: Proceedings of the Twenty-Sixth International Joint Conference on Artificial Intelligence (IJCAI-17). 2017:1965–72.

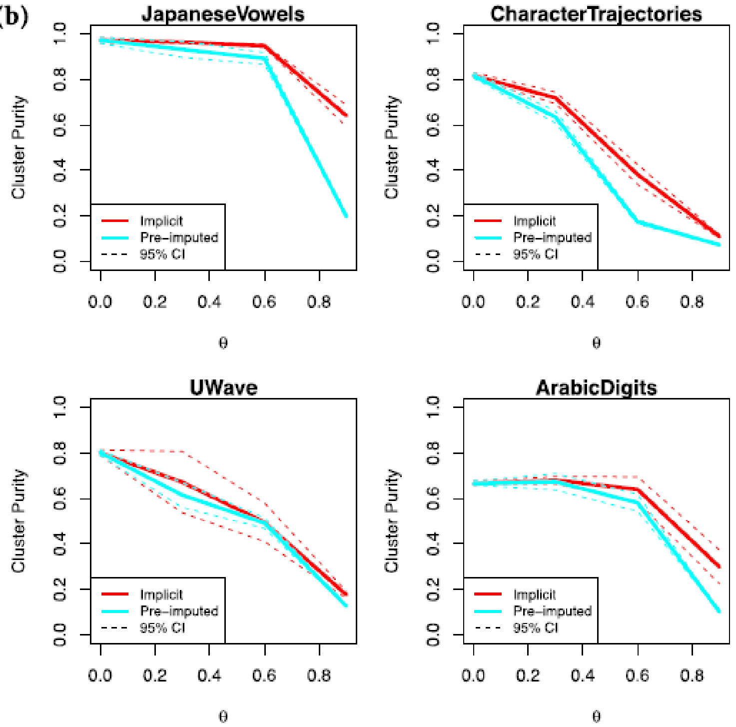
Validation of VADER



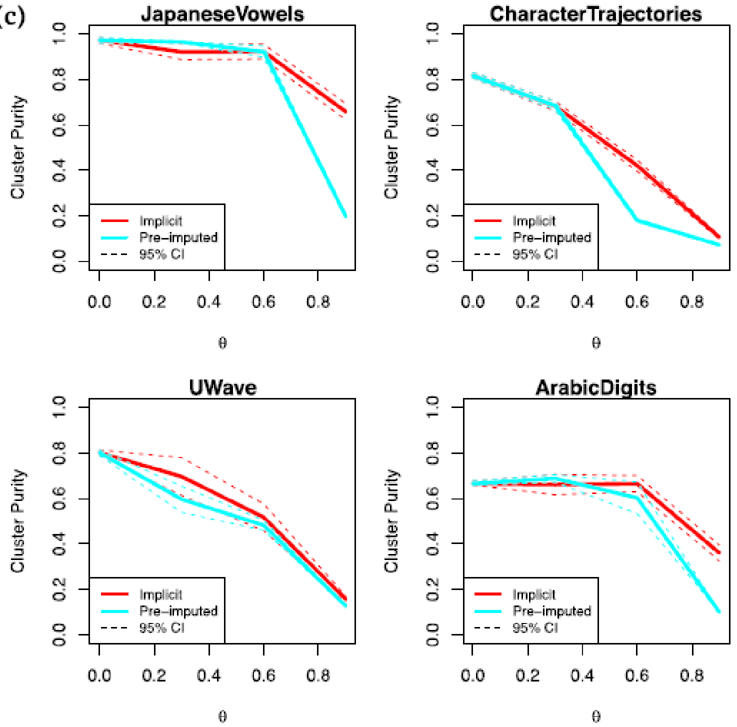


VADER Dependency on Missingness

(b)



(c)



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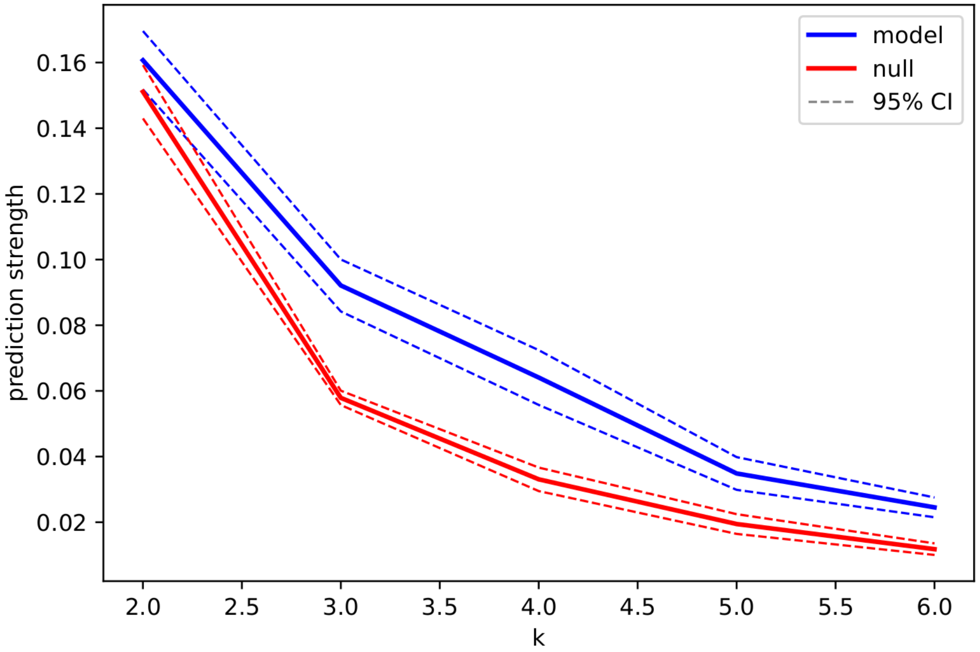
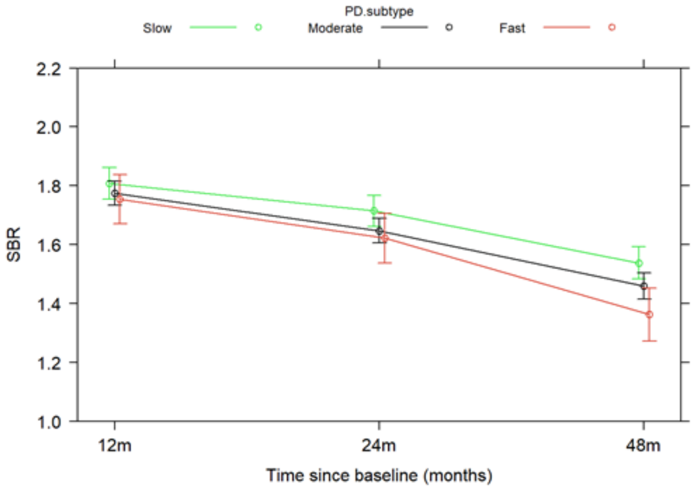
Choice of number of clusters

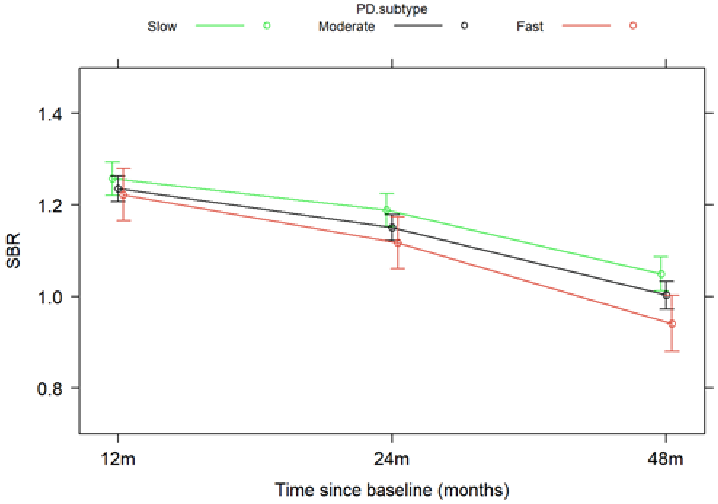


Differences in Dopaminergic Dificiency after 48 months

Caudate



Striatum



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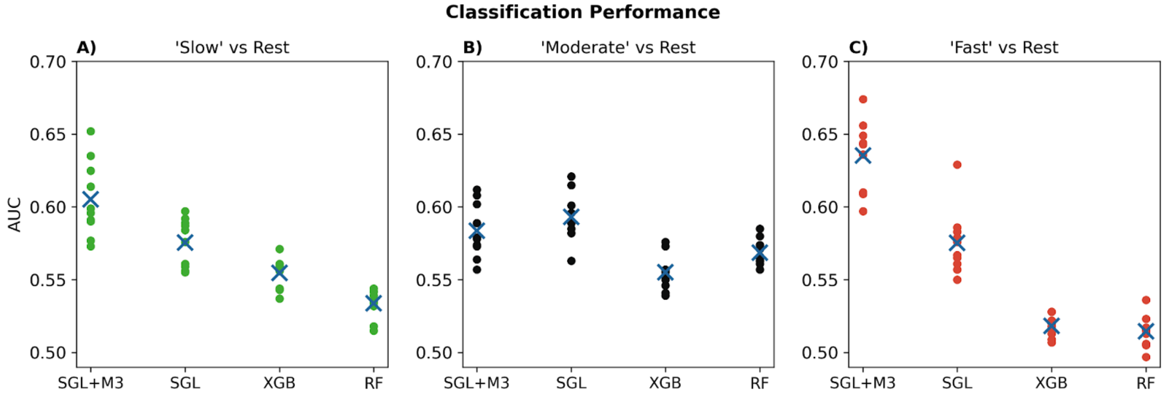
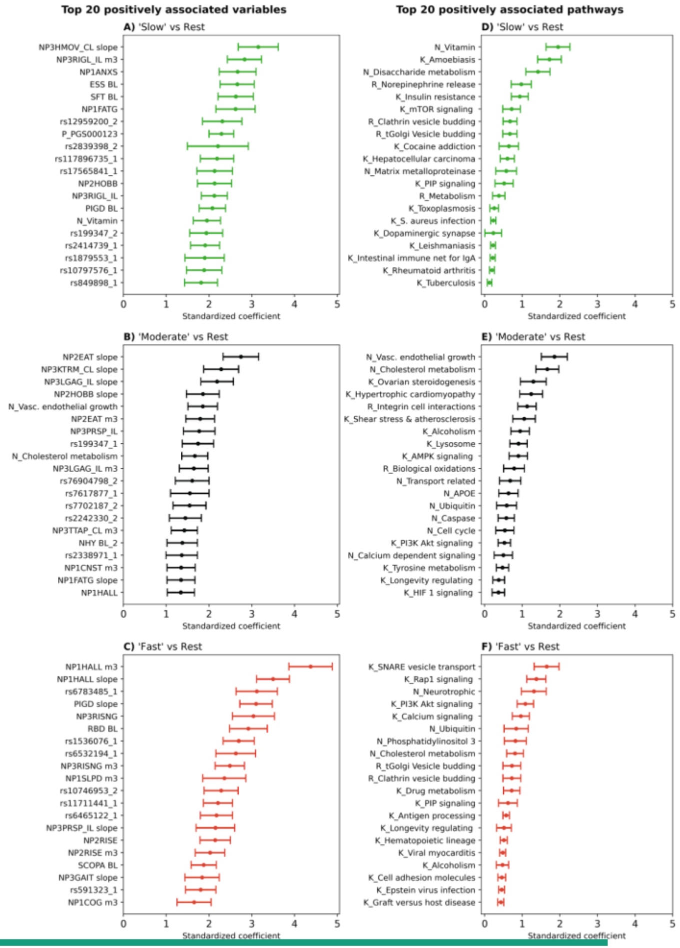
Association with Distinct Symptoms and Genetic Loci





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