Reconceptualising psychopathology using machine learning and big data neuroscience

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Acknowledgments



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Thomas Wolfers



Pierre Berthet



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Pieter Barkema



Charlotte Fraza



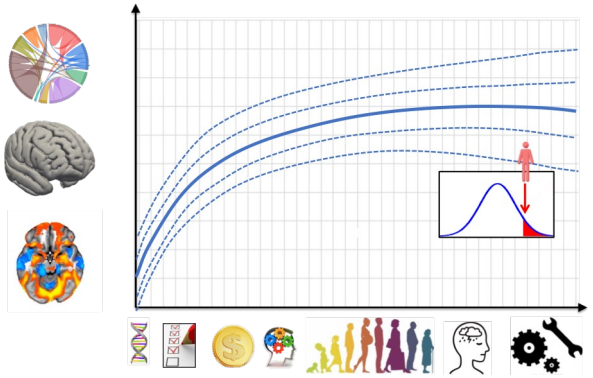
Nathalie Holz



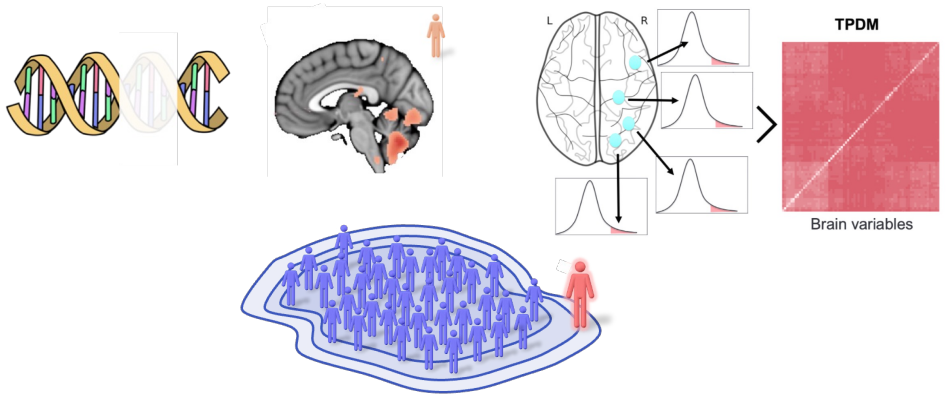
Barbora Rehák Bučková

- Christian Beckmann
- Ole Andreasson
- Lars Westlye
- Paola Dazzan
- Gunter Schumann

Overview



Parsing structured variation using normative models

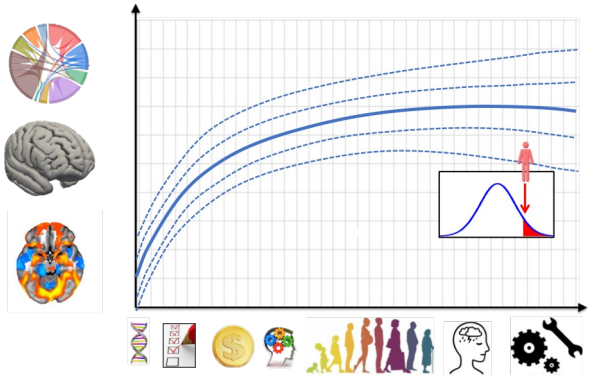


From group effects to individual predictions

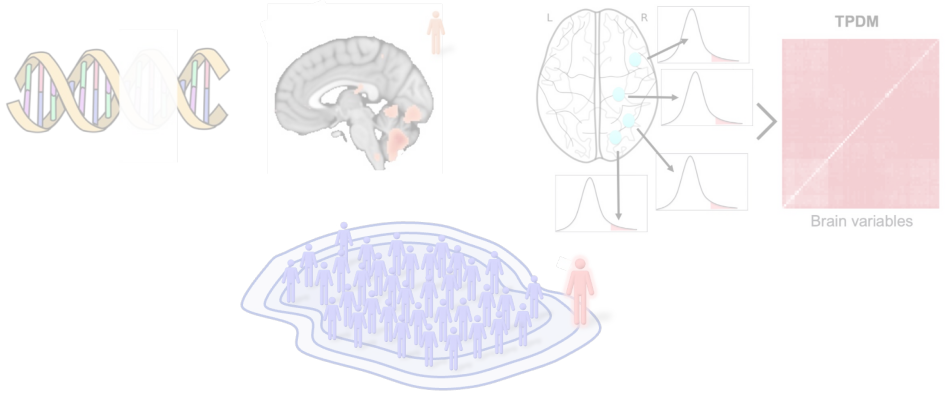


Combining multimodal data for an integrated perspective

Overview



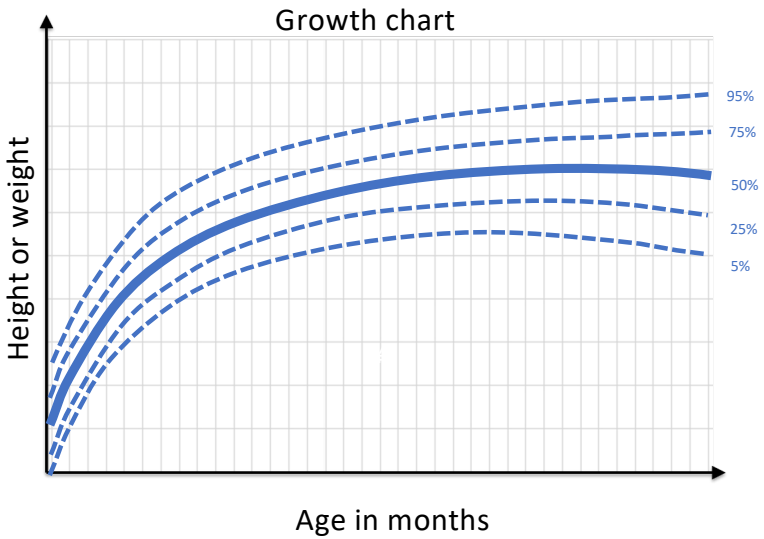
Parsing structured variation using normative models



From group effects to individual predictions

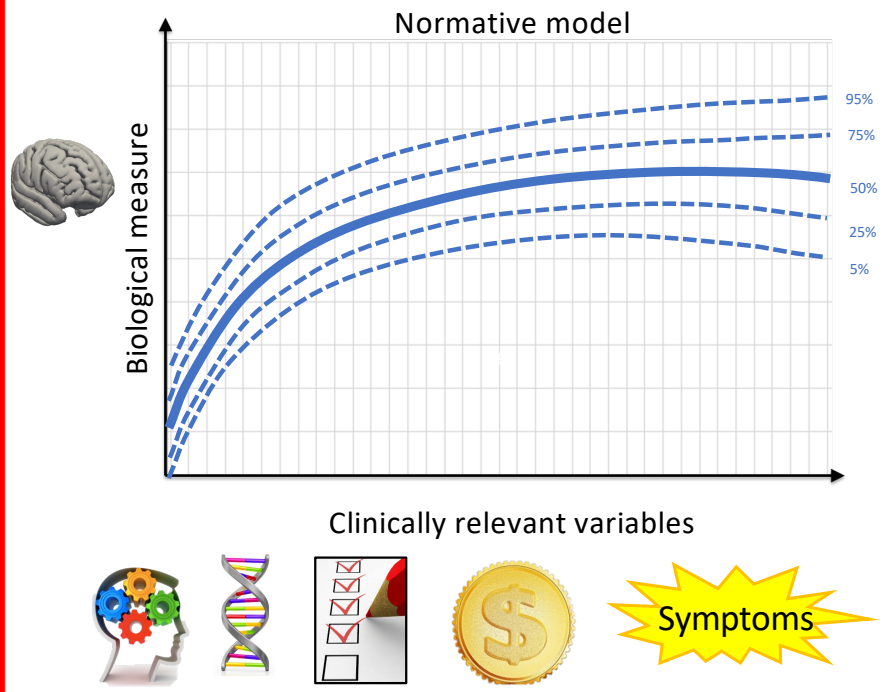


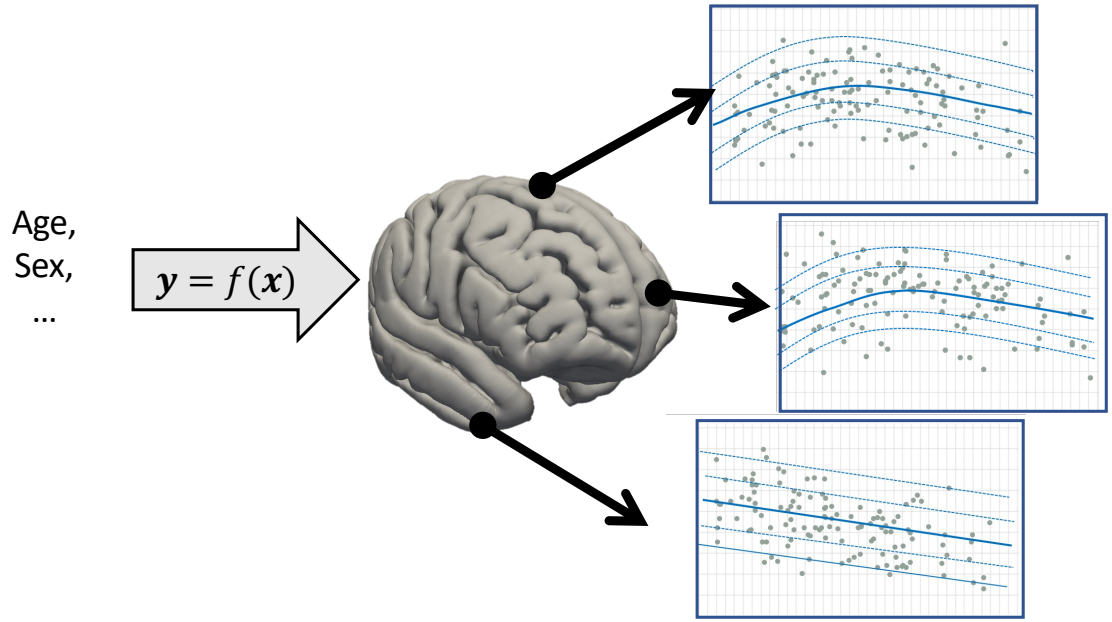
Combining multimodal data for an integrated perspective



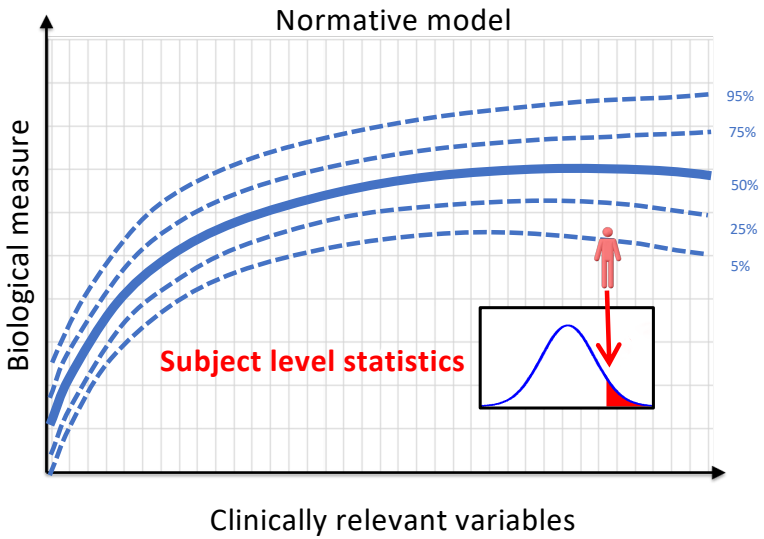


Marquand et al 2016b, 2019



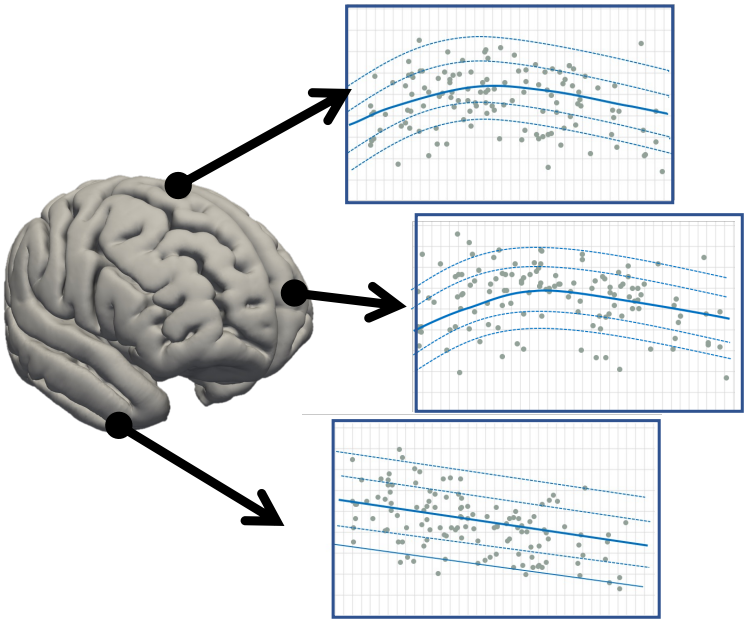


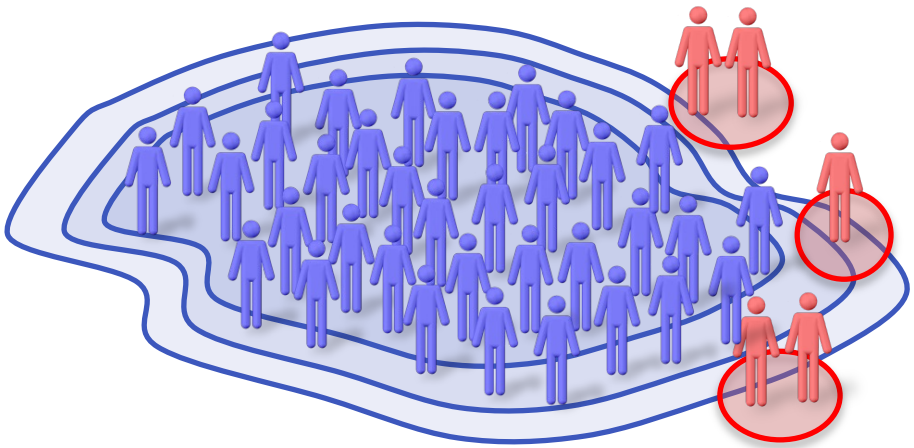
Marquand et al 2016b, 2019



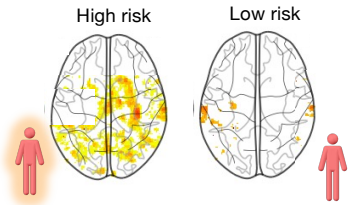
Age,
Sex,
...

$y = f(x)$

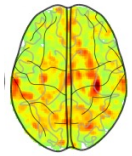


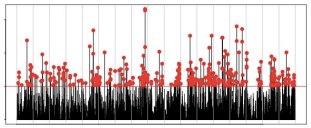


Marquand et al 2016b, 2019



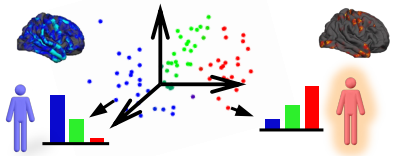
Individualised risk scores





Extreme value statistics

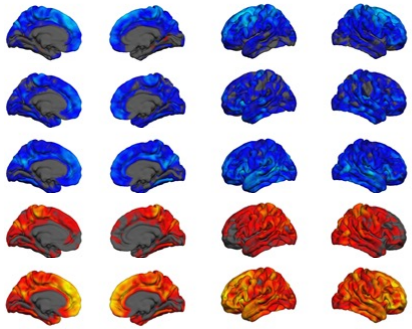
Participant-level expression profiles



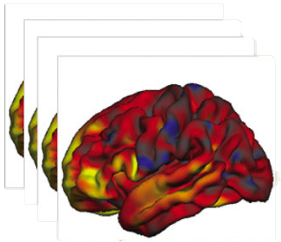


Matrix Factorization

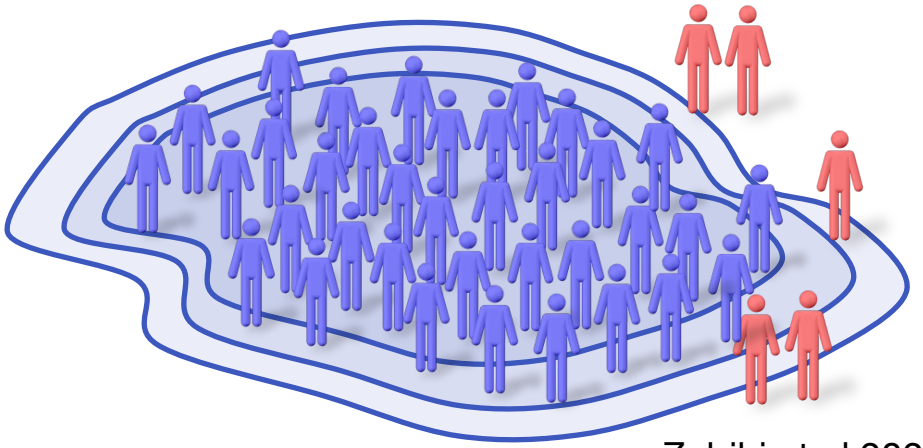
Autism ‘biotypes’



Clustering



Individual deviations

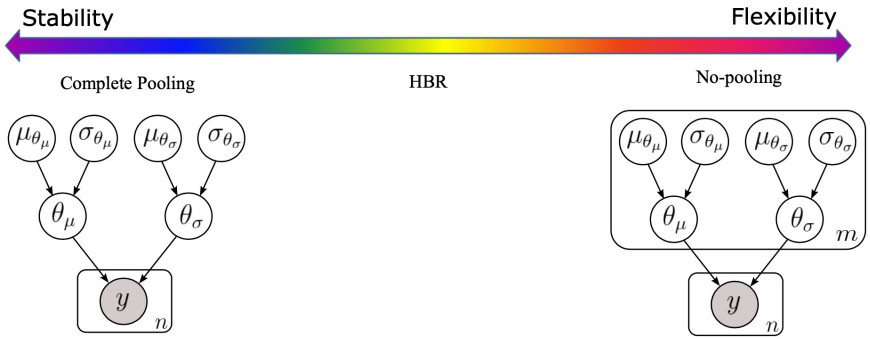


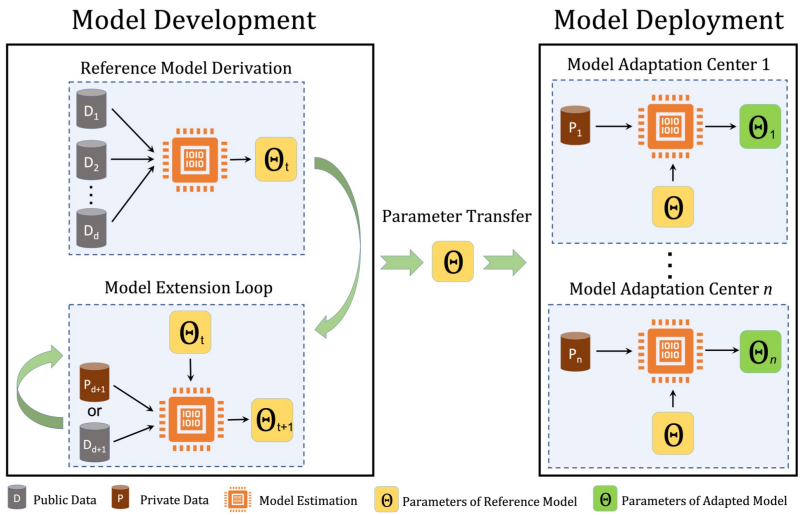


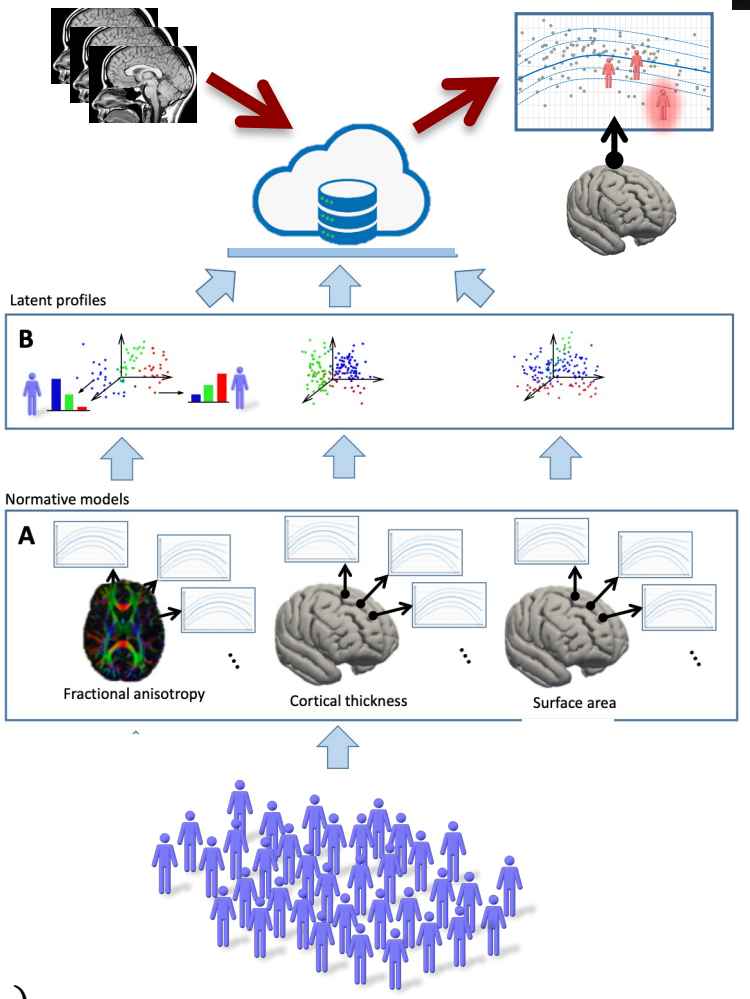




Zabihi et al 2020; Holz et al 2022; Fraza et al (2022)









Vague prior

$$p(\Theta|\mathbf{y},\Theta_0) \propto p(\mathbf{y}|\Theta)p(\Theta_0)$$

Θ

Informative prior

$$p(\Theta|\mathbf{y}) \propto p(\mathbf{y}|\Theta)p(\Theta|\mathbf{y},\Theta_0)$$

Kia et al 2020,2022

Modelling non-Gaussianity



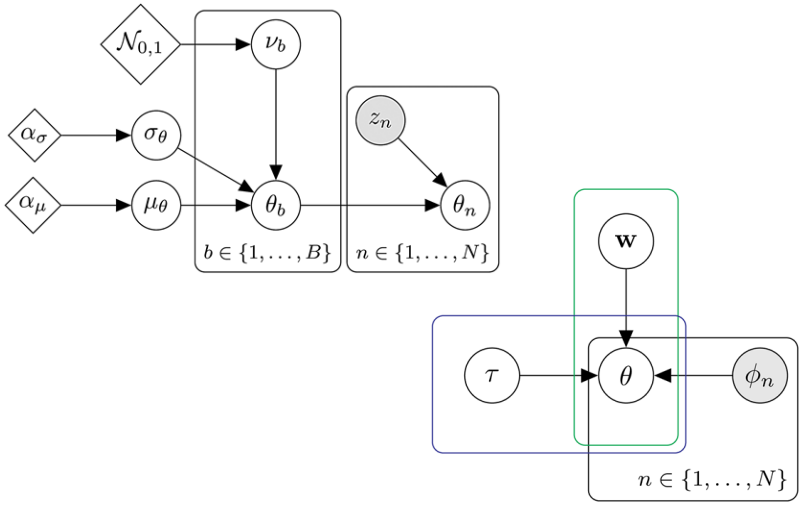
$$\theta_i \sim p_{\theta_i}$$

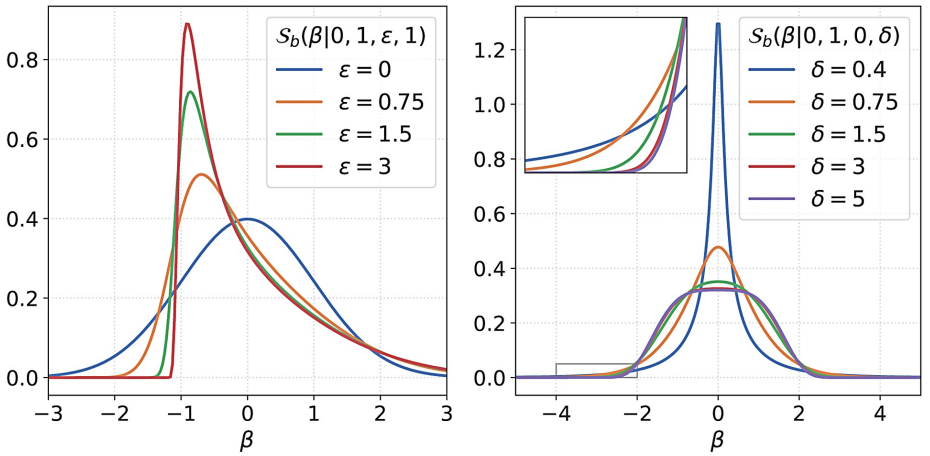
$$Y \sim \mathcal{L}(Y \mid \{\theta_i\})$$

"SHASH" distribution

$$S_{\epsilon,\delta}(x) = \sinh(\delta \sinh^{-1}(x) - \epsilon)$$

$$S^{-1}_{\epsilon,\delta}(x) = \sinh((\sinh^{-1}(x) + \epsilon)/\delta)$$

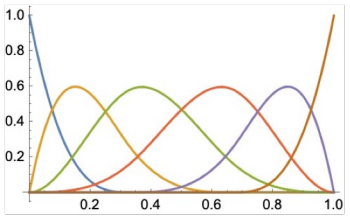




Linear basis function model

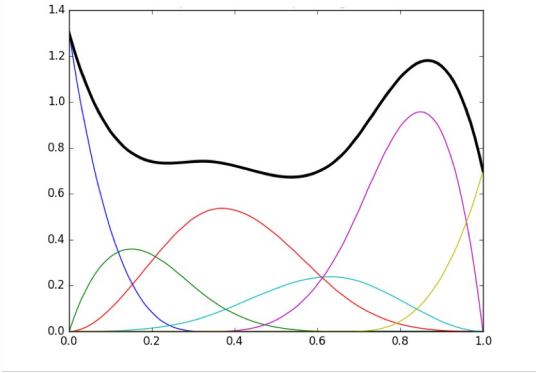
B-spline basis set

$\phi(\mathbf{x})$



Non-linear functions of the input

$\phi(\mathbf{x})^T\mathbf{w}$



Weighted combination of functions

De Boer et al 2024

Modelling non-Gaussianity



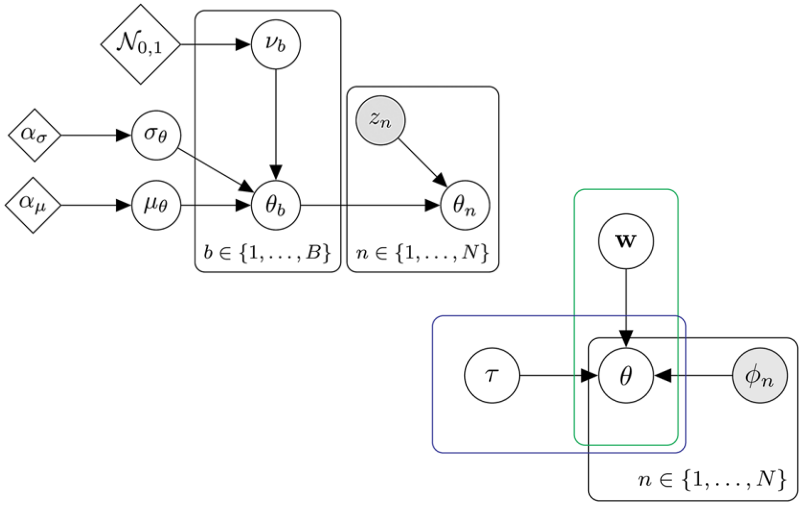
$$\theta_i \sim p_{\theta_i}$$

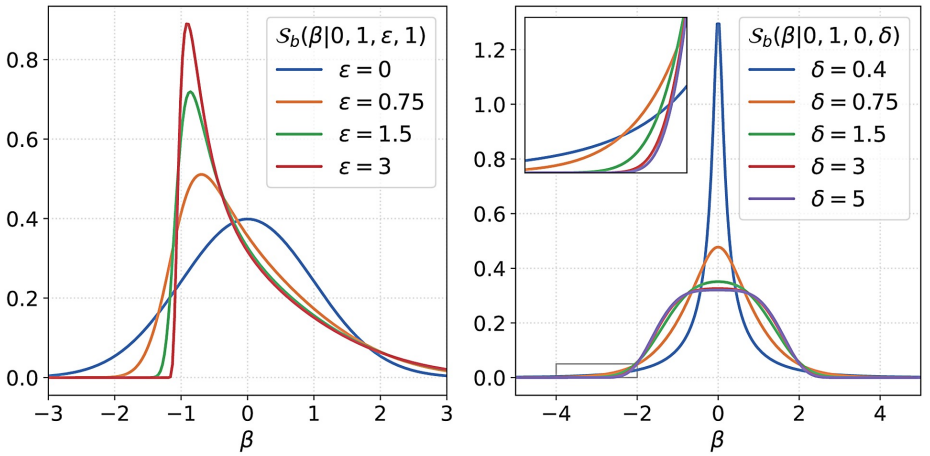
$$Y \sim \mathcal{L}(Y \mid \{\theta_i\})$$

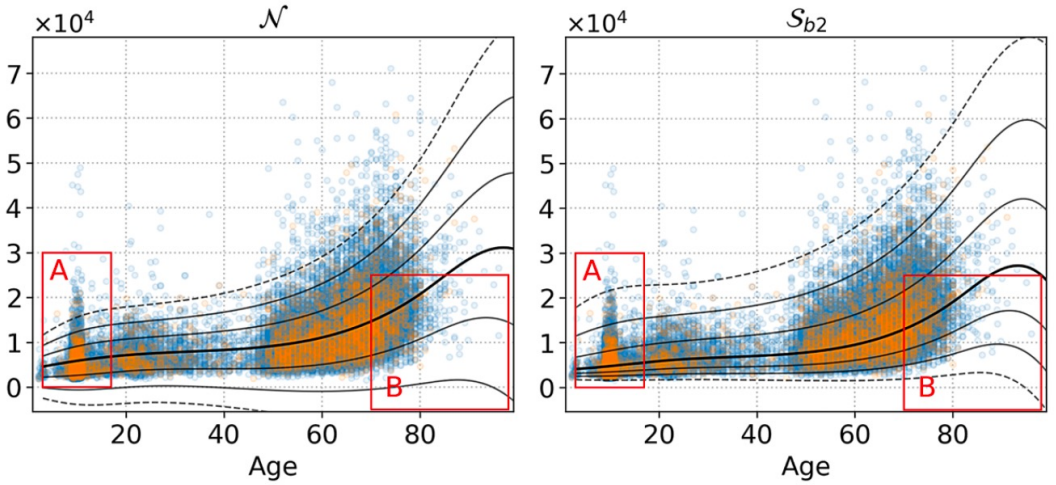
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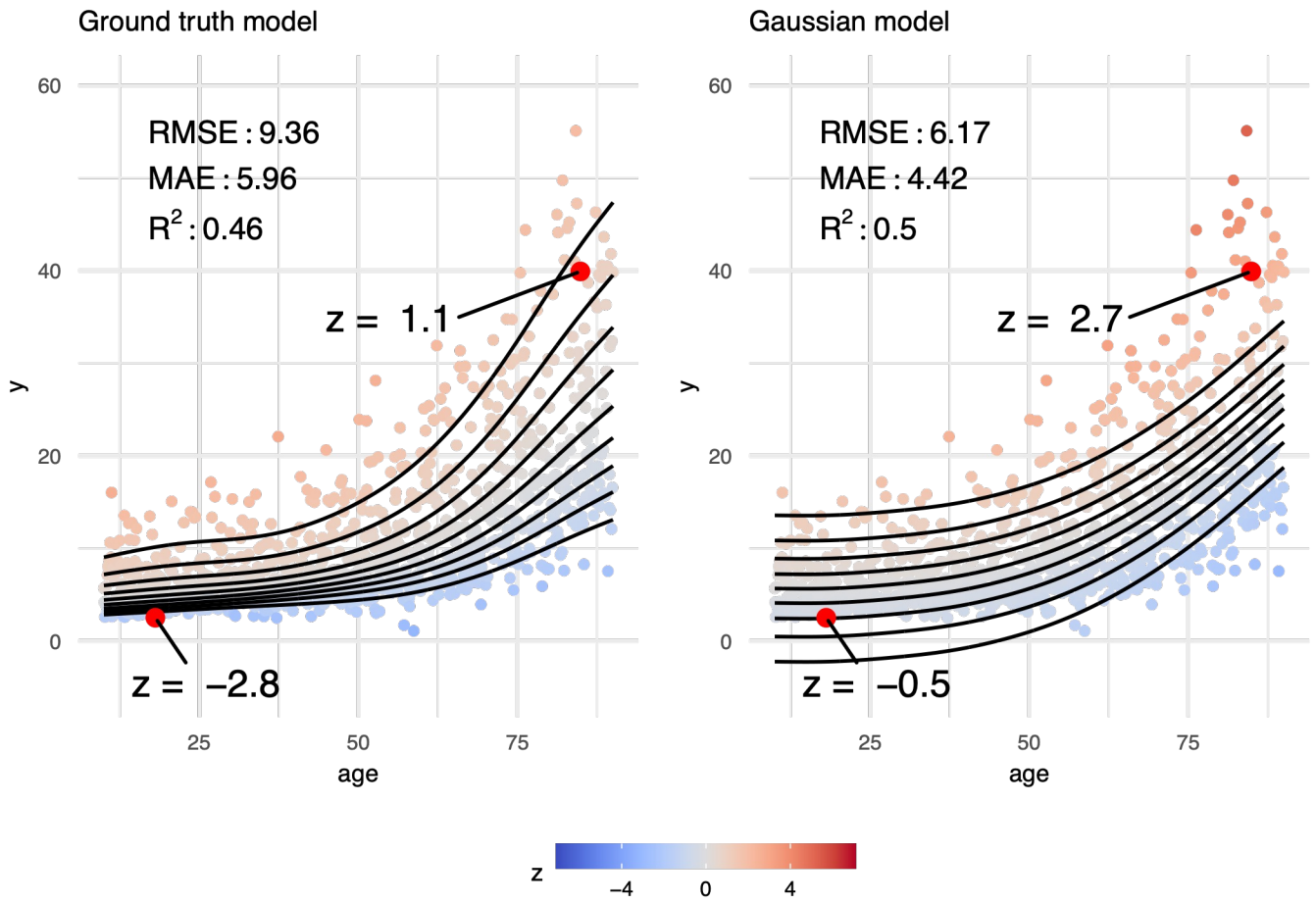






De Boer et al 2024

Modelling non-Gaussianity

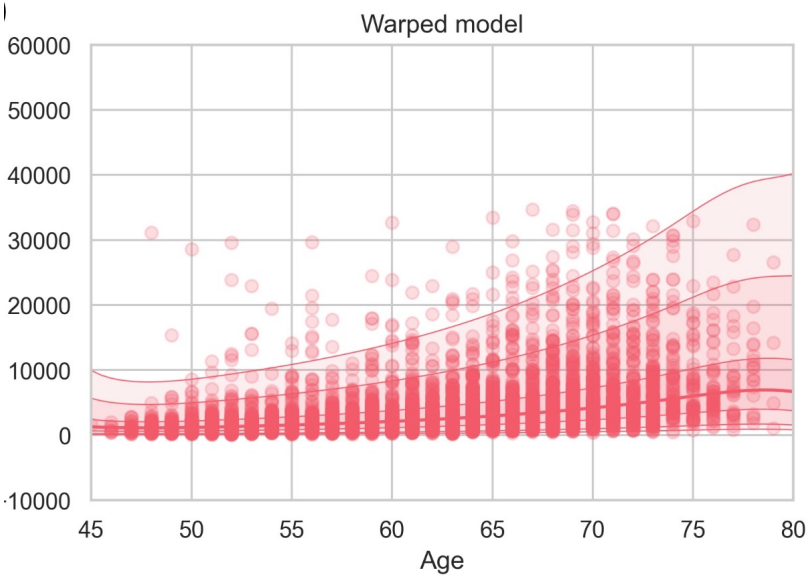


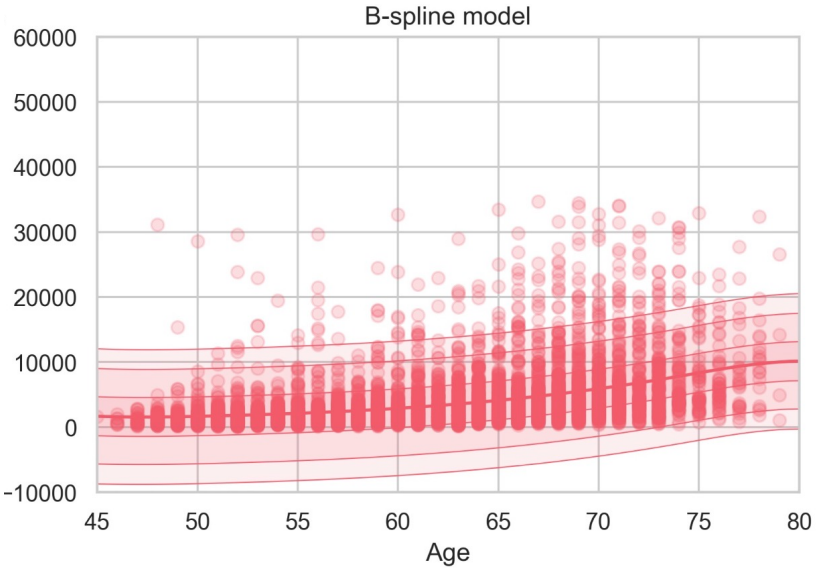
Marquand et al 2024

Modelling non-Gaussianity



Volume of white matter hypointensities

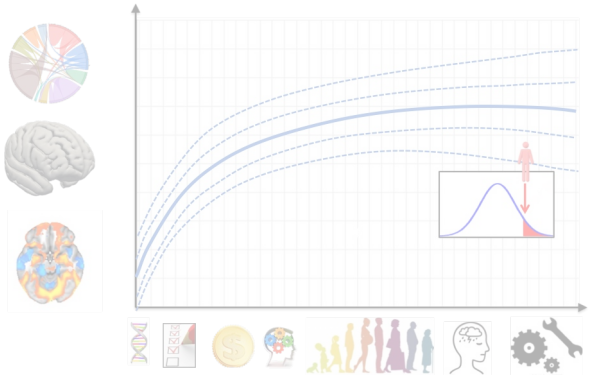




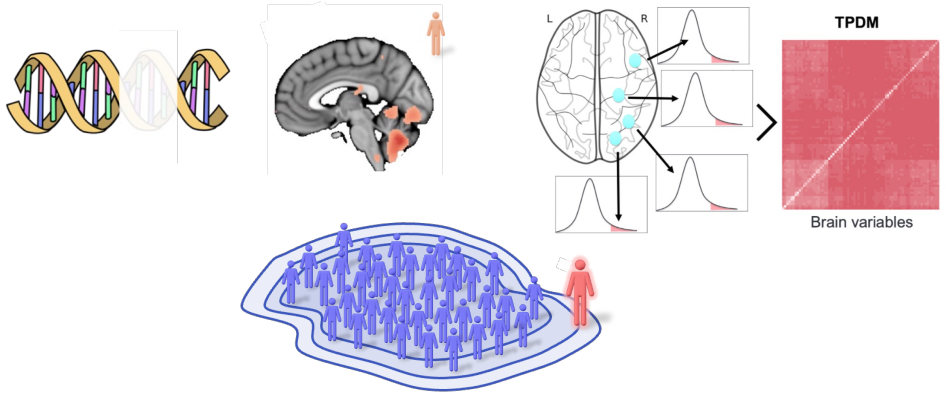
biobank uk

Fraza et al 2021

Overview



Parsing structured variation using normative models



From group effects to individual predictions

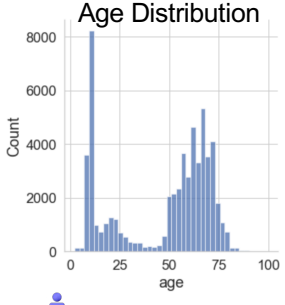


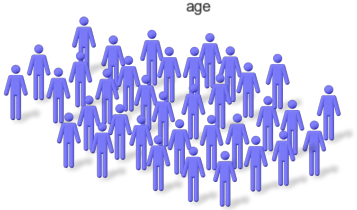
Combining multimodal data for an integrated perspective



N = 60,000 individuals

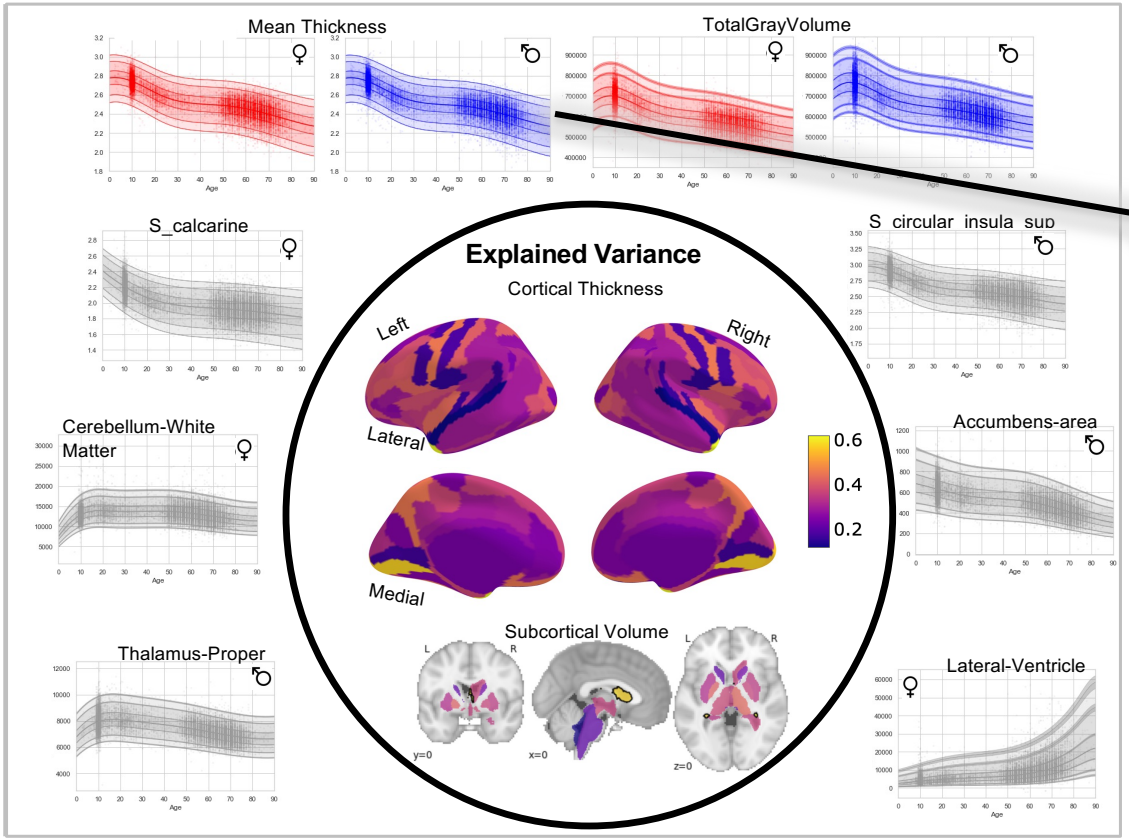
Full Sample
Age Distribution

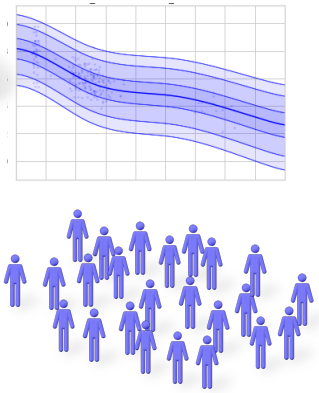




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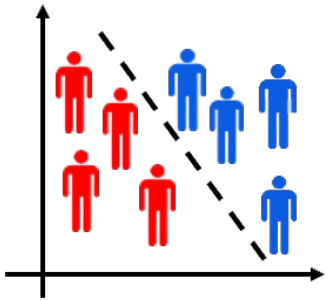




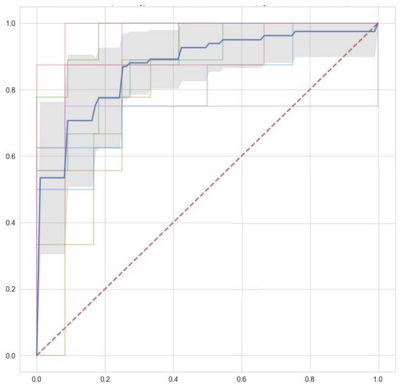


Rutherford et al 2022a (elife), 2022b (Nature Protocols)

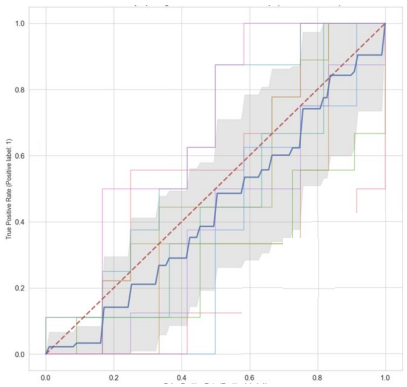
Predicts schizophrenia diagnosis more accurately than the raw data



Accuracy = 87%



Accuracy = 43%





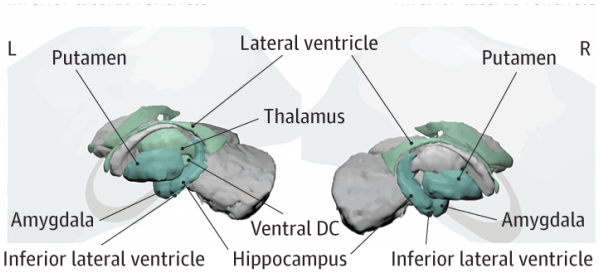


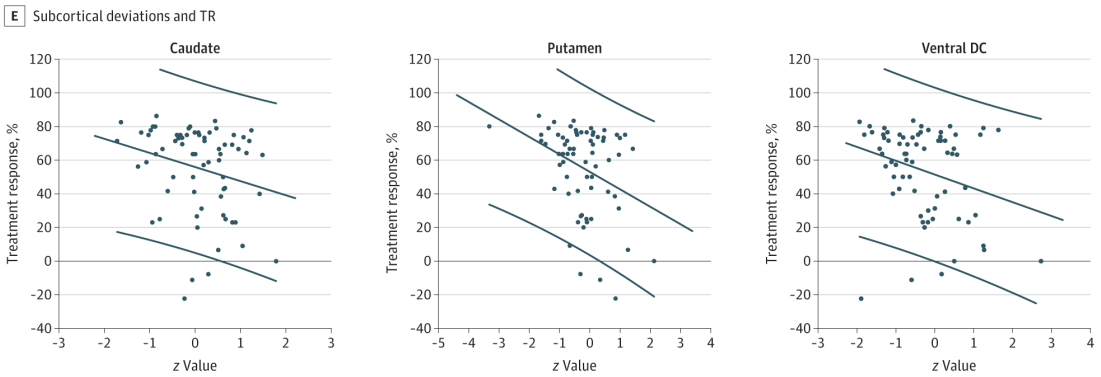


The Mind RESEARCH NETWORK
For Neurodiagnostic Discovery

UNIVERSITY OF MICHIGAN

Only normative deviations were associated with treatment response

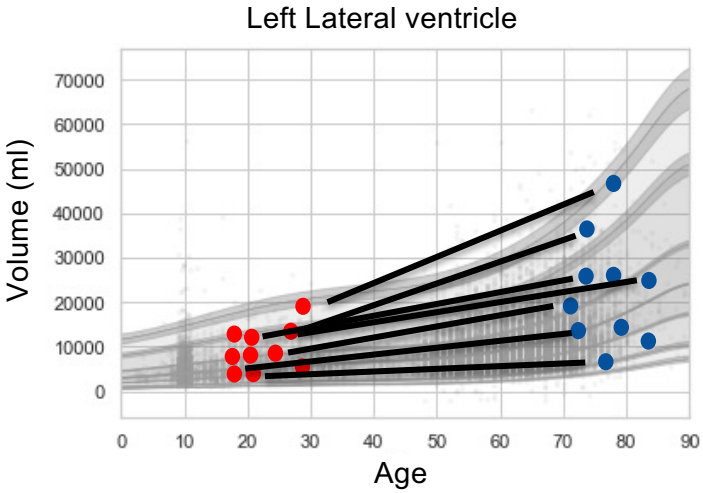




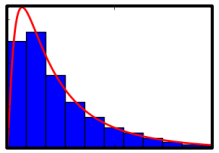
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

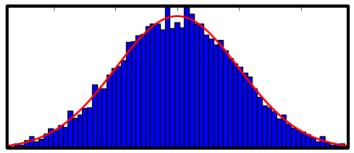
Rutherford et al 2023; Remiszewski et al 2023

Modelling longitudinal change

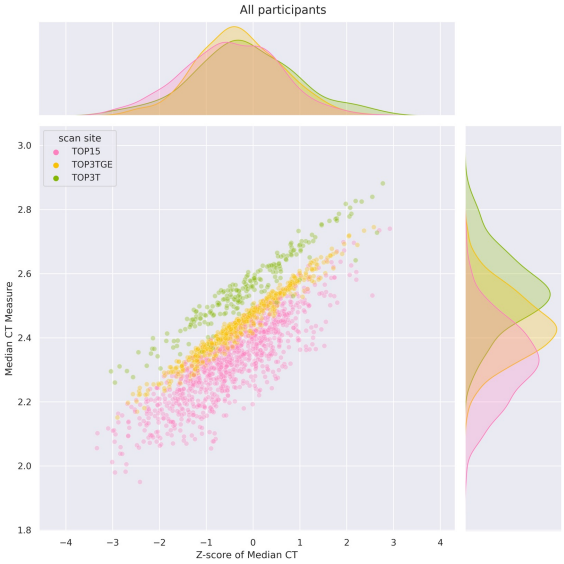


Raw values → Population centiles

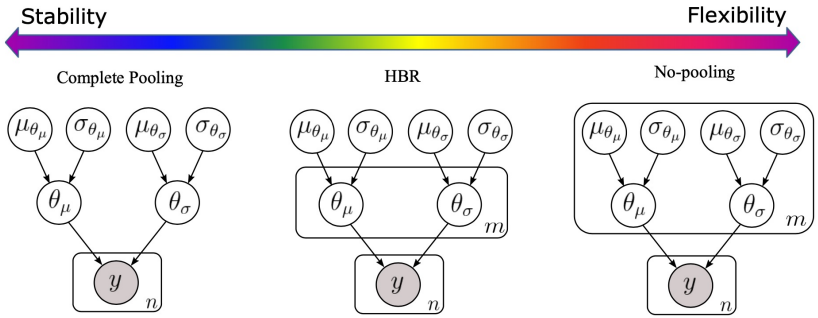




Meaningful comparisons **across scanners**



Hierarchical Bayesian regression



Kia et al 2020, 2021, Berthet et al 2024



Baseline

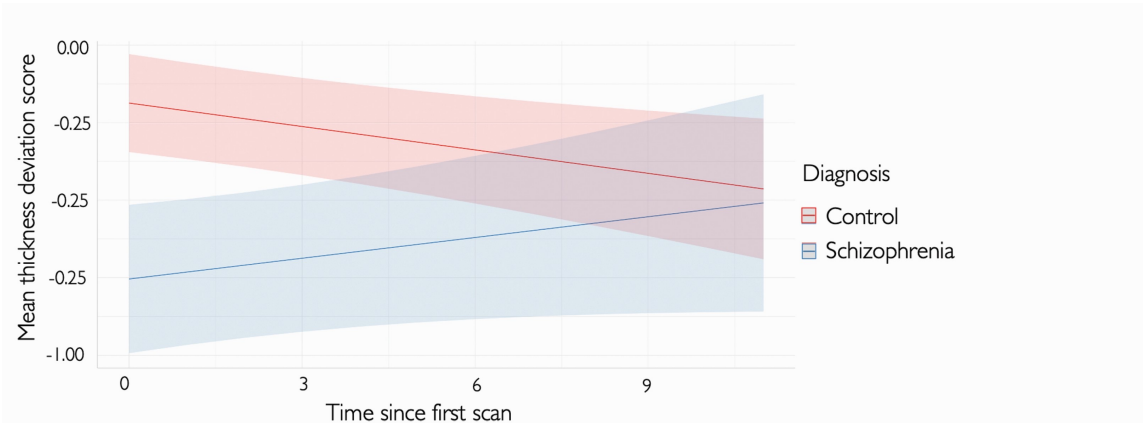
2 Years

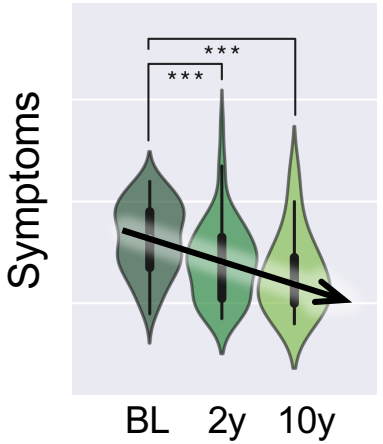
10 Years







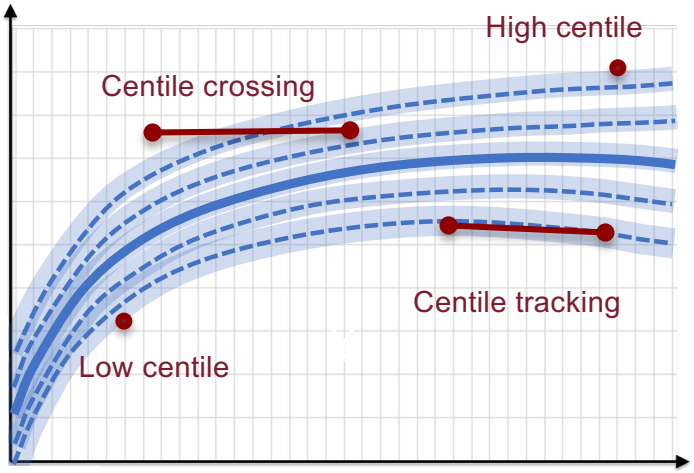




NORMENT
Norwegian Centre for
Mental Disorders Research

Berthet et al 2024

Sensitive detection of longitudinal change



$$\varphi(y^{(i)}) = \mathbf{w}^T \phi(\mathbf{x}^{(i)}) + \eta + \xi^{(i)}$$
$$\eta \sim \mathcal{N}(0, \sigma_\eta^2)$$
$$\xi^{(i)} \sim \mathcal{N}(0, \sigma_\xi^2)$$
$$\sigma^2 = \sigma_\eta^2 + \sigma_\xi^2$$

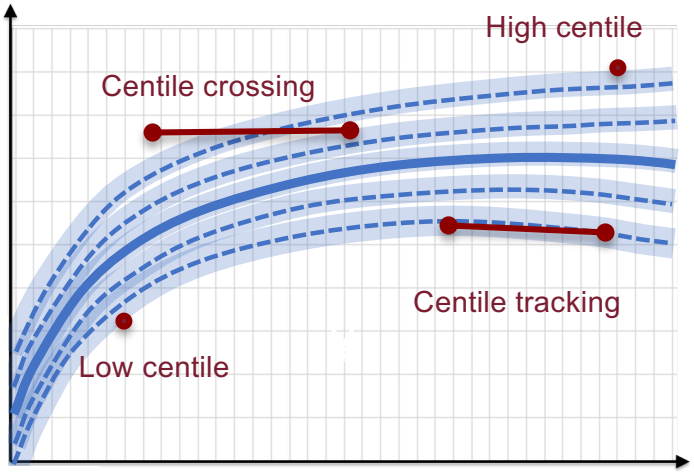
$$\mathbf{w}|\mathbf{y}, \mathbf{\Phi}; \omega^2, \sigma^2, \boldsymbol{\gamma} \sim \mathcal{N}(\bar{\mathbf{w}}, \mathbf{A}^{-1}),$$

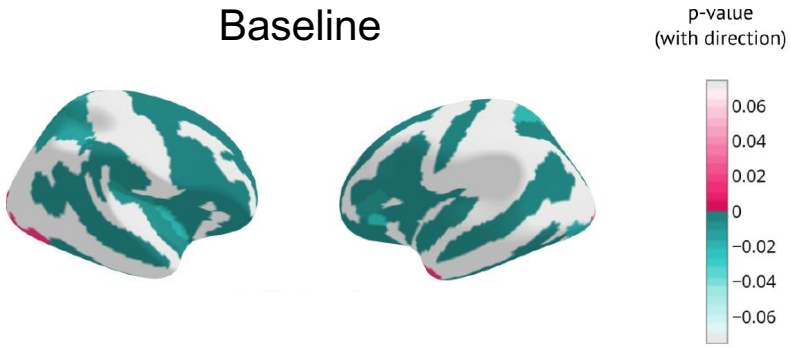
$$z = \frac{\varphi(y) - \bar{\mathbf{w}}^T \phi(\mathbf{x})}{\sqrt{\phi(\mathbf{x})^T \mathbf{A}^{-1} \phi(\mathbf{x}) + \sigma^2}},$$

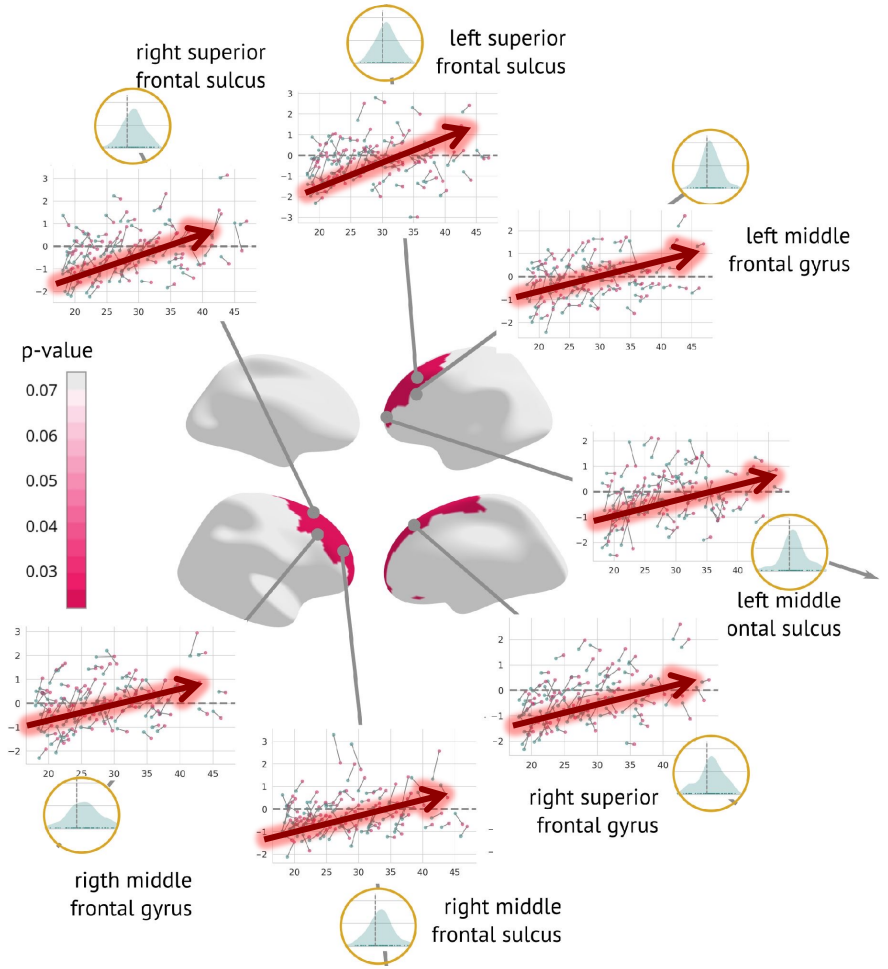
$$z\text{-}diff = \frac{[\varphi(y^{(2)}) - \varphi(y^{(1)})] - \bar{\mathbf{w}}^T [\phi(\mathbf{x}^{(2)}) - \phi(\mathbf{x}^{(1)})]}{\sqrt{[\phi(\mathbf{x}^{(2)}) - \phi(\mathbf{x}^{(1)})]^T \mathbf{A}^{-1} [\phi(\mathbf{x}^{(2)}) - \phi(\mathbf{x}^{(1)})] + 2\sigma_\xi^2}}$$

Rehák Bučková et al 2024

Sensitive detection of longitudinal change

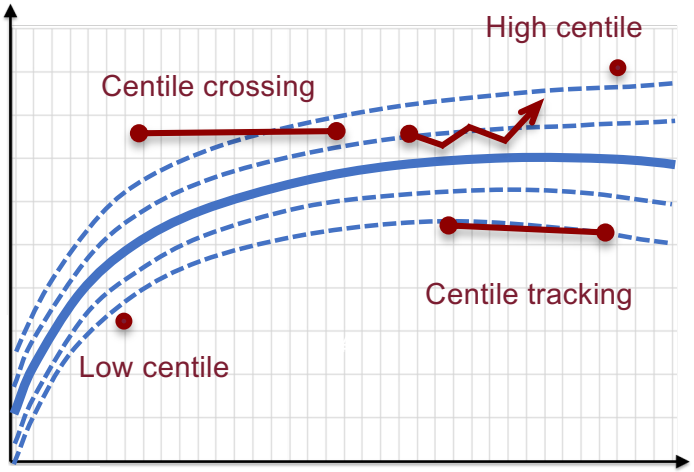


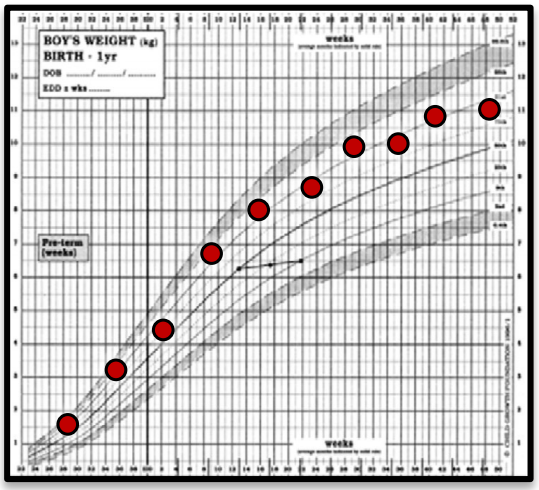




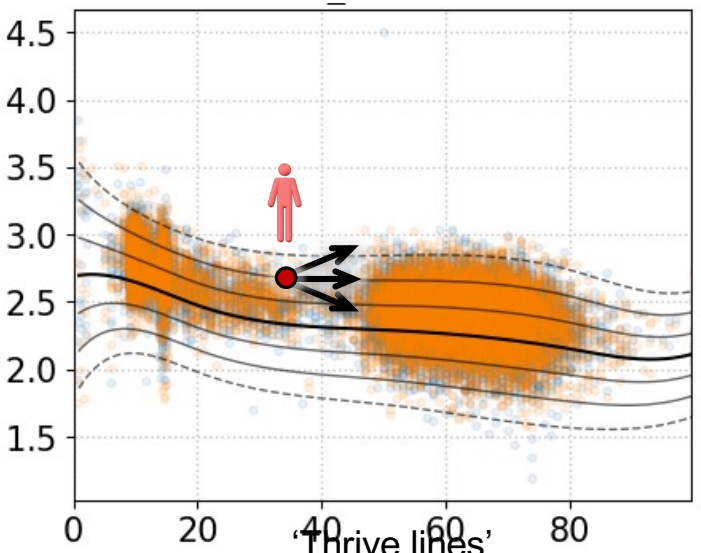
Rehák Bučková et al 2024

Sensitive detection of longitudinal change

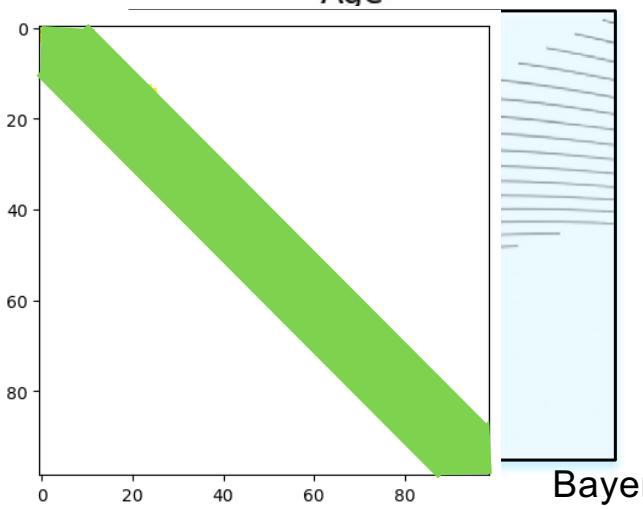






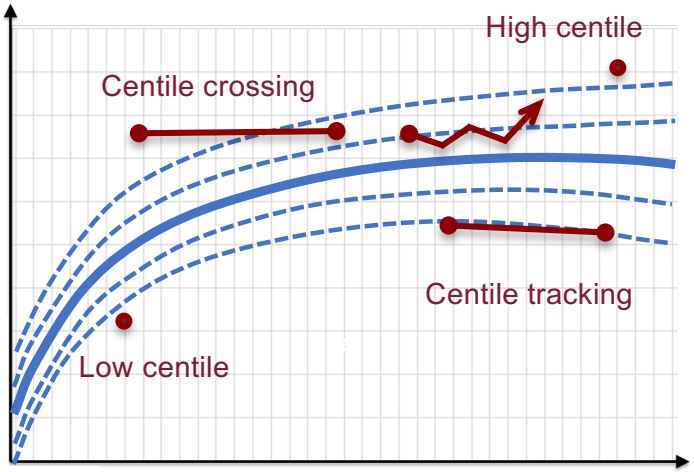


'Thrive lines'

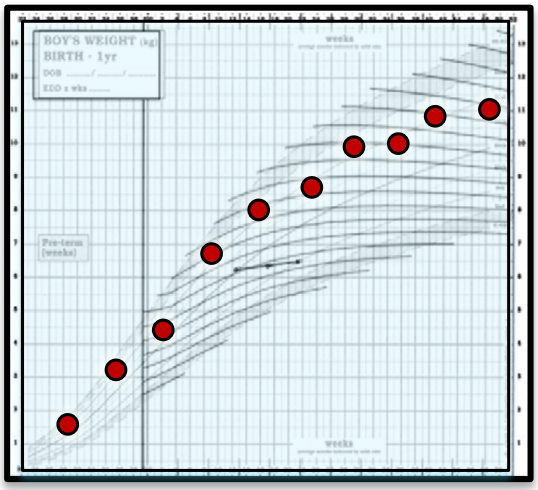


Bayer et al 2026

Sensitive detection of longitudinal change

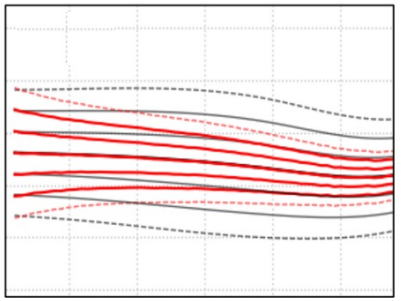


‘Thrive lines’



$$Z_g = \frac{Z_1 - Z_2}{\sigma}$$

$$\sigma = \sqrt{2 - 2r}$$



$$Z_g = \frac{Z_1 - rZ_2}{\sigma}$$

$$\sigma = \sqrt{1 - r^2}$$

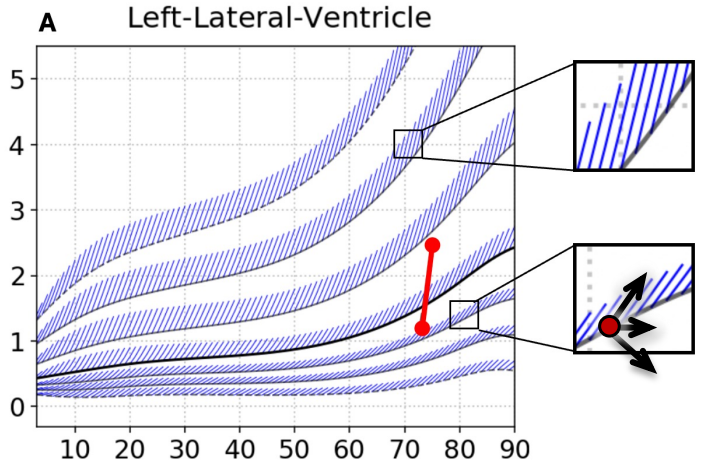
“Z gain”

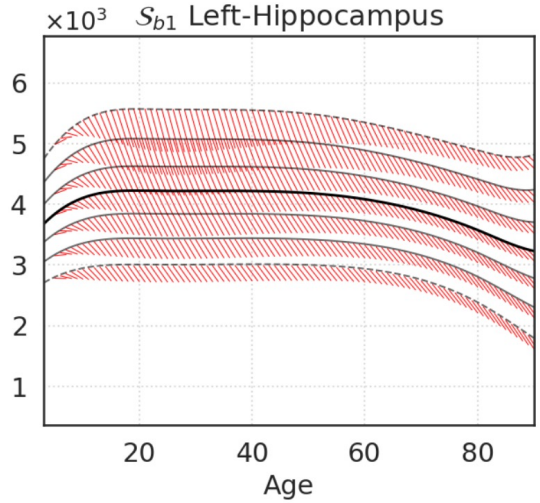


Bayer et al 2026

Sensitive detection of longitudinal change





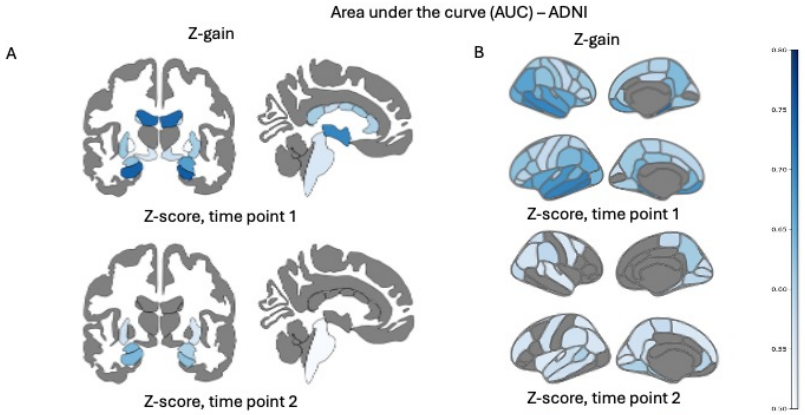


Bayer et al 2026

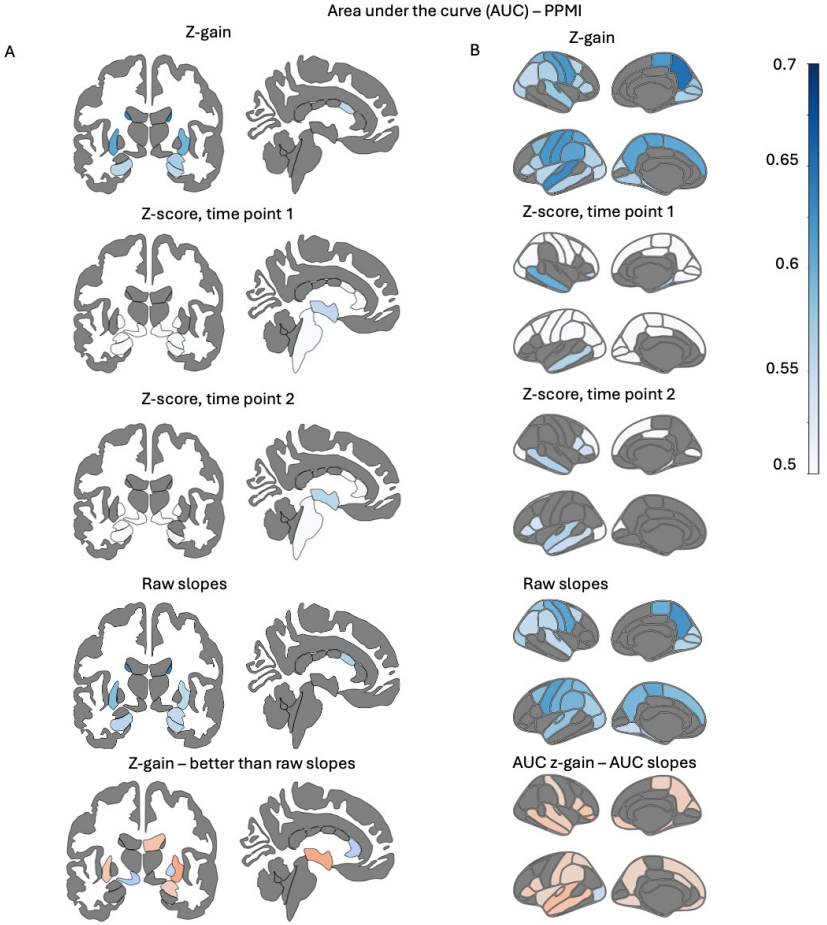
Sensitive detection of longitudinal change



Conversion to Dementia



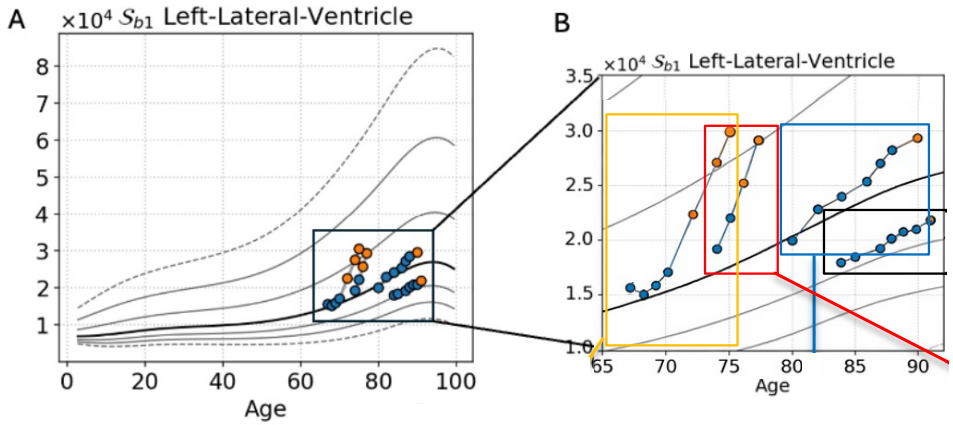
Onset of Parkinson's Disease



Bayer et al 2026

Sensitive detection of longitudinal change

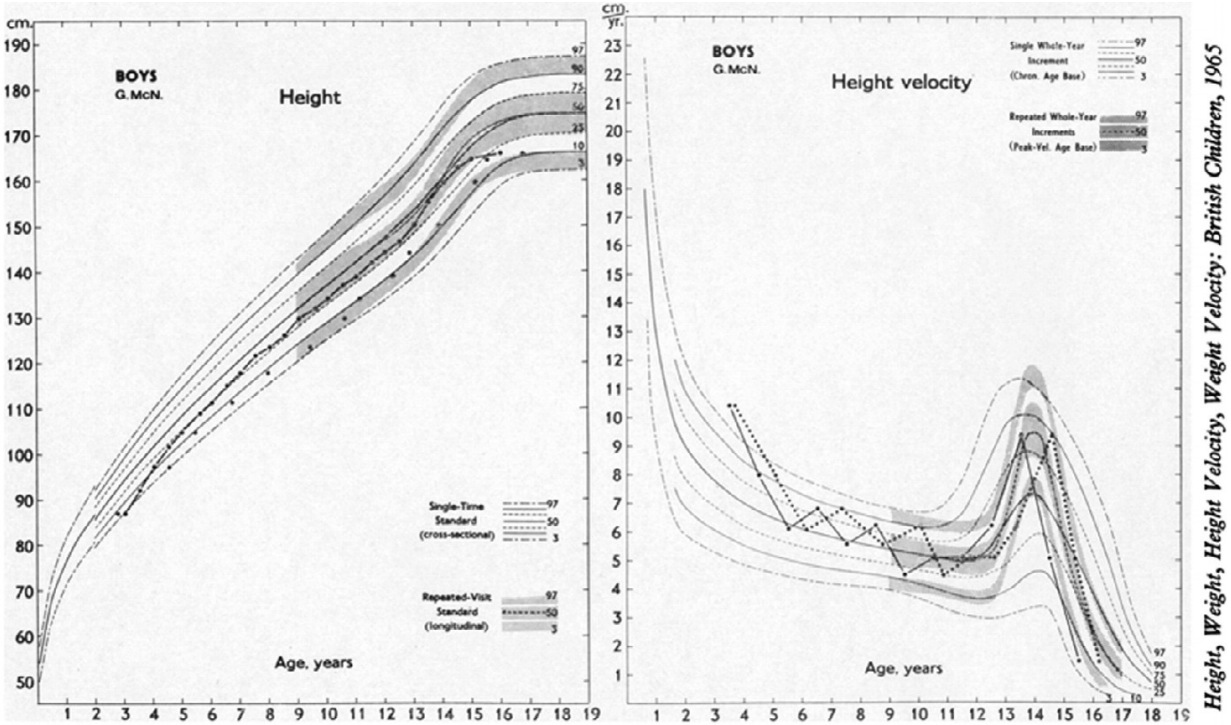




Bayer et al 2026

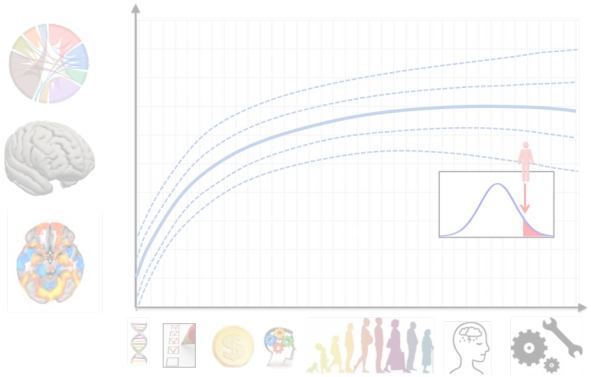
Sensitive detection of longitudinal change

Height of British children (1965)

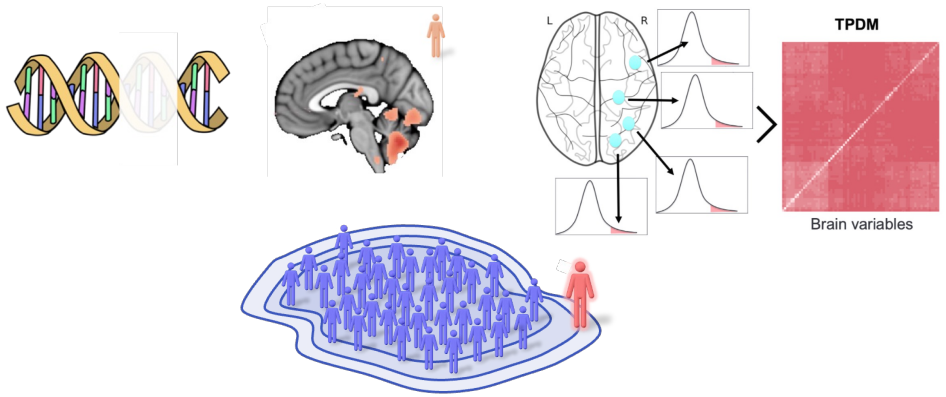


Cole et al 2012

Overview



Parsing structured variation using normative models



From group effects to individual predictions



Combining multimodal data for an integrated perspective

The science of extremes





Fraza et al (2023)

The science of extremes



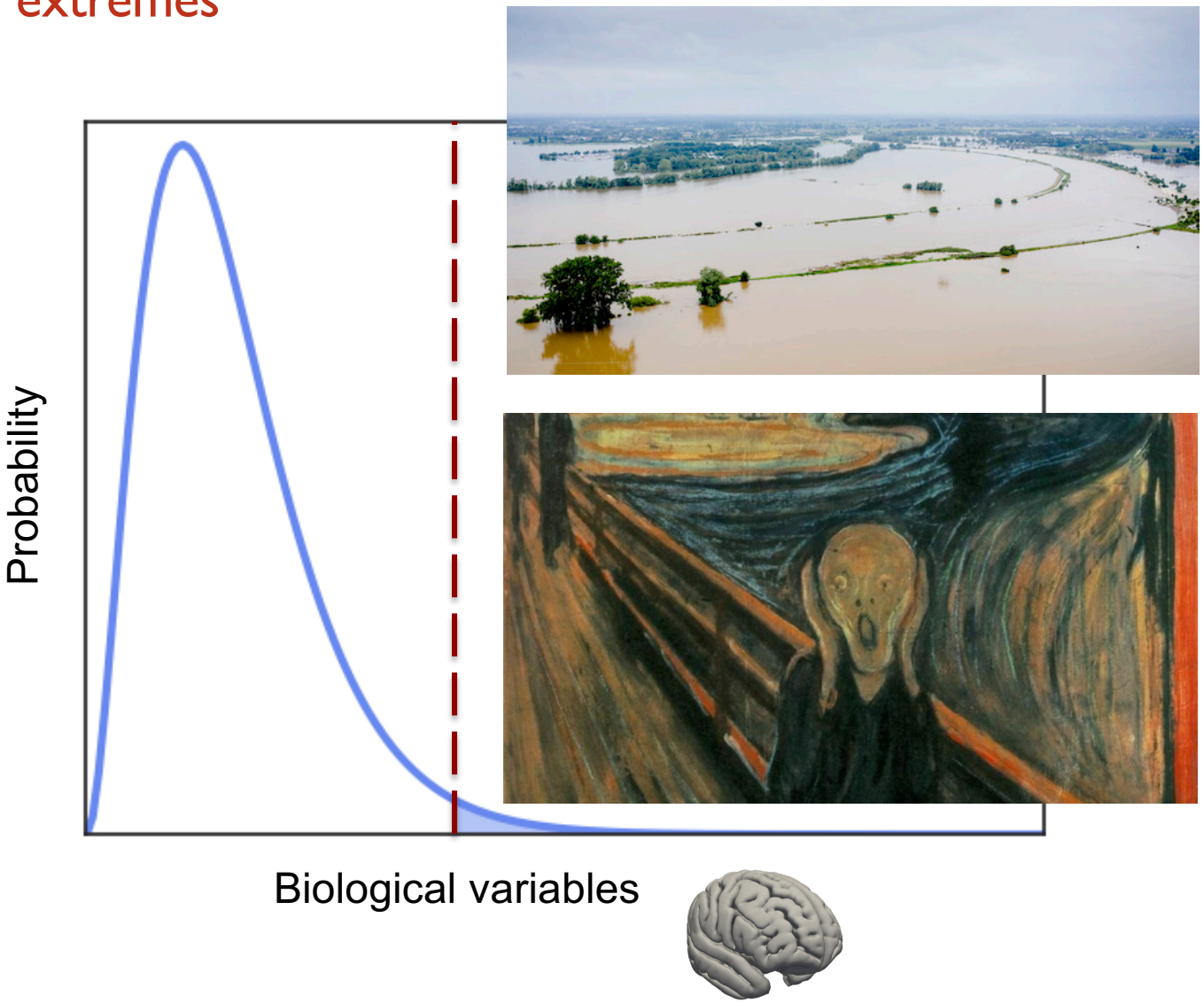


https://vimeo.com/109872288

Fraza et al (2023)

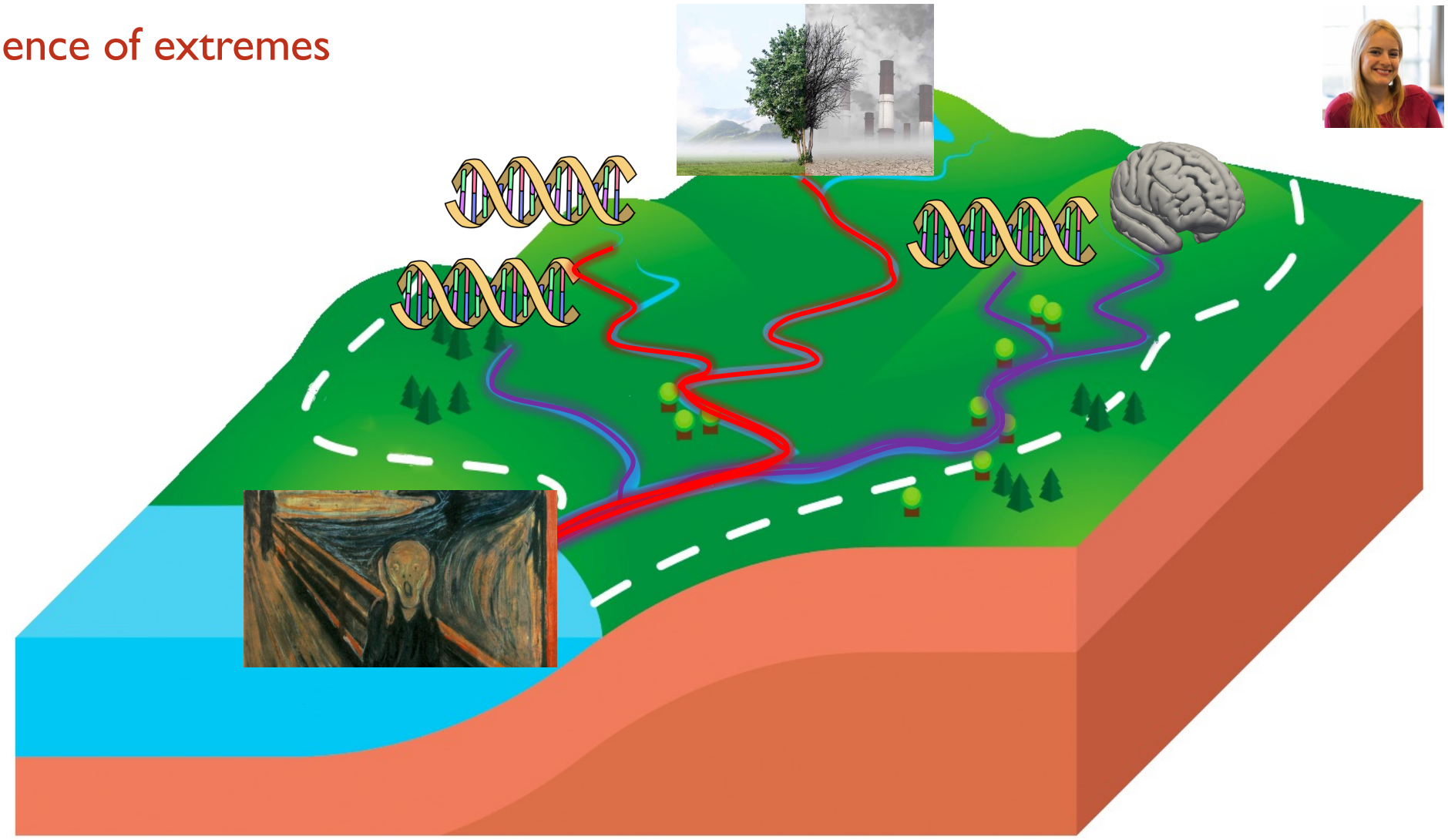
The science of extremes





Fraza et al (2023)

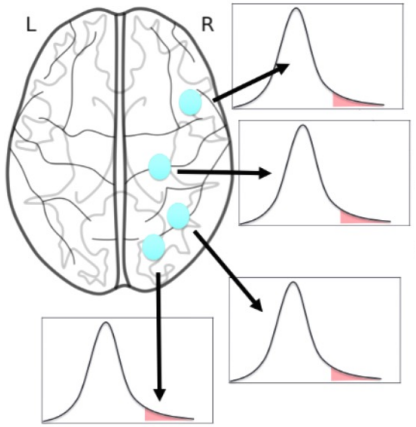
The science of extremes



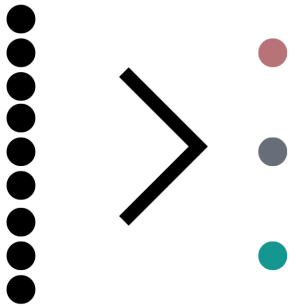
Fraza et al (2023)

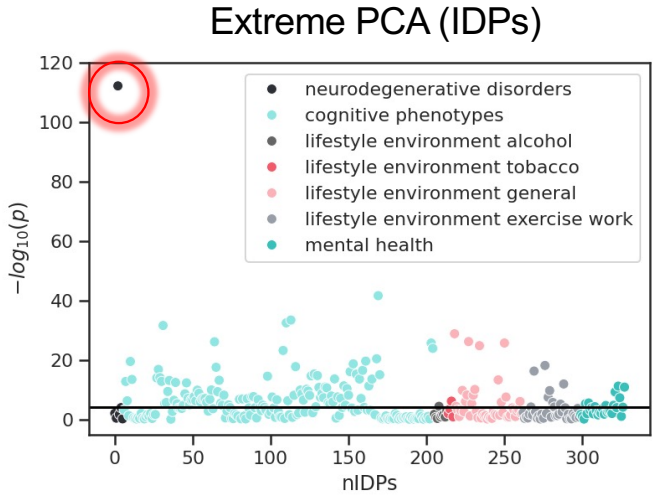
The science of extremes



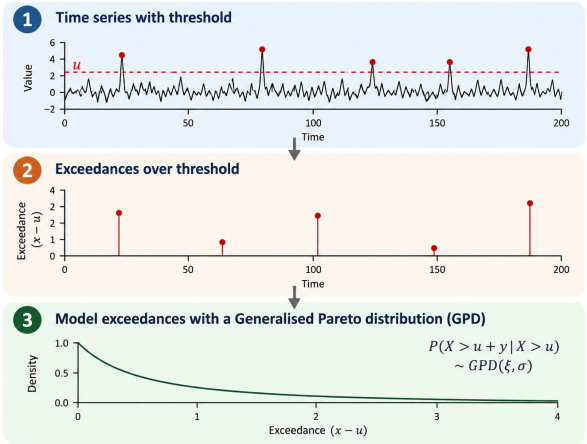


Tail pairwise dependency Matrix (TPDM)



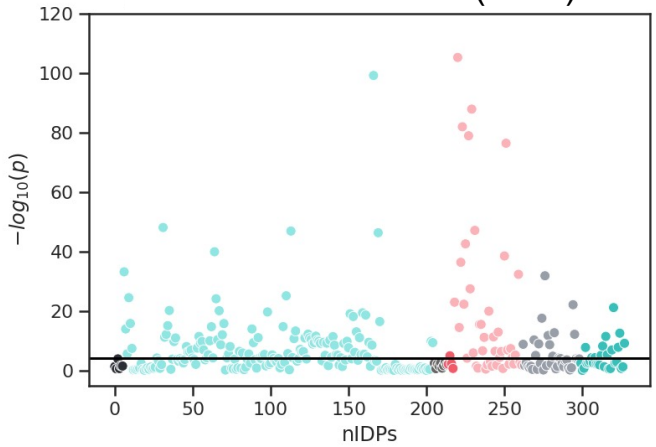


"Extreme PCA"



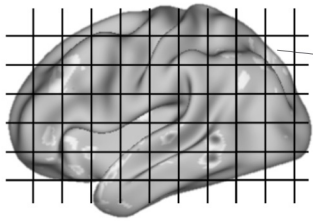
$$X \sim \mathrm{GPD}(\mu, \sigma, \xi)$$

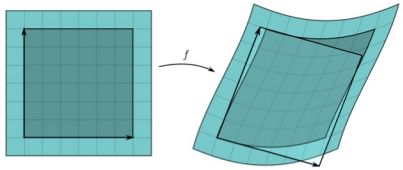
$$f_i(x) = \begin{cases} \frac{1}{\sigma}\left(1 + \xi\frac{x-\mu}{\sigma}\right)^{-1-1/\xi} & \text{for } \xi \neq 0, \\ \frac{1}{\sigma}\exp\left(-\frac{x-\mu}{\sigma}\right) & \text{for } \xi = 0, \end{cases}$$

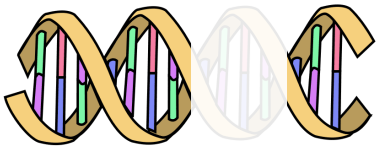


Fraza et al (2022)

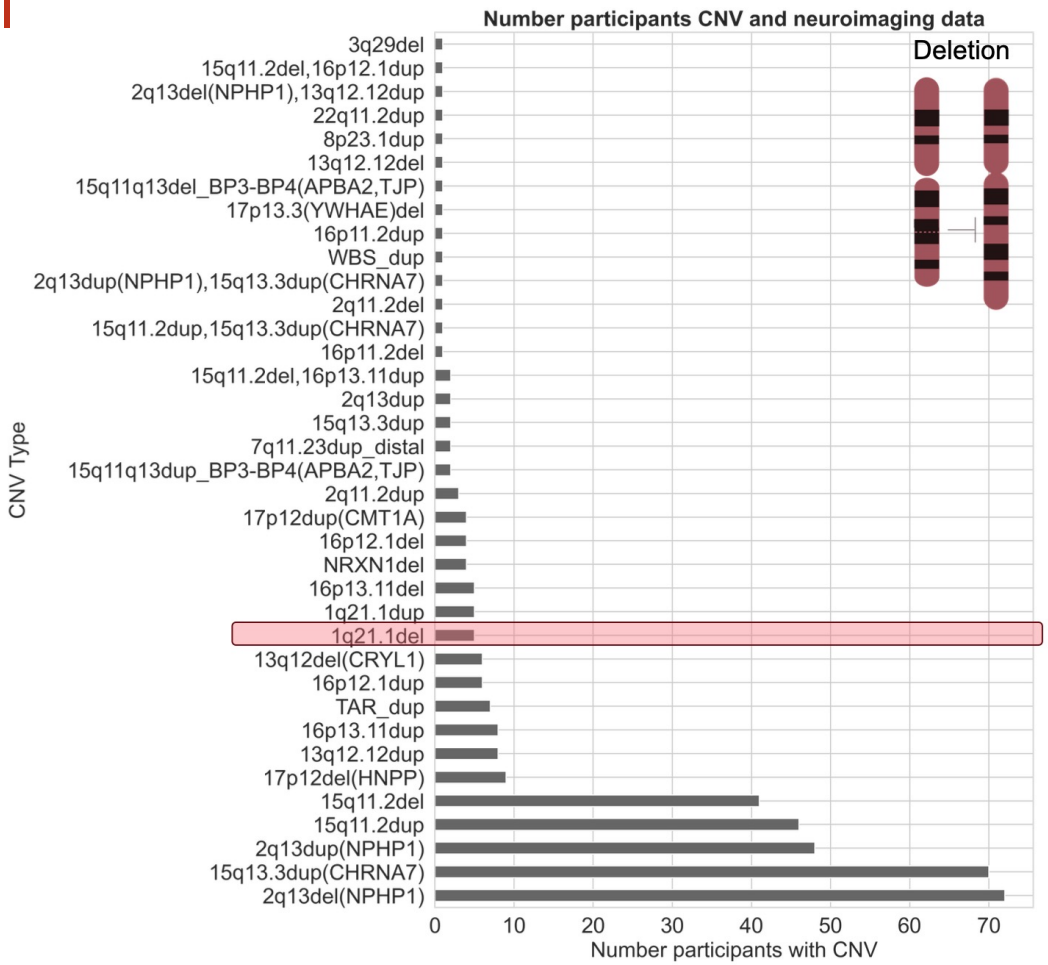
Imaging genetics at N=1







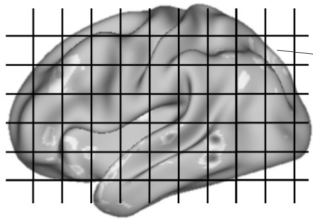
Deletion (1q21.1)

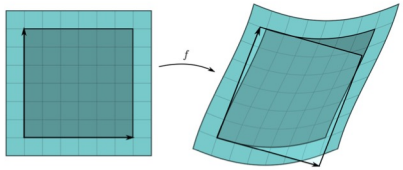


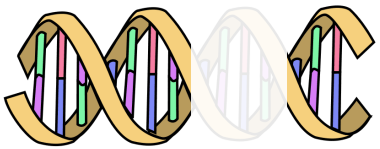


Fraza et al (2024)

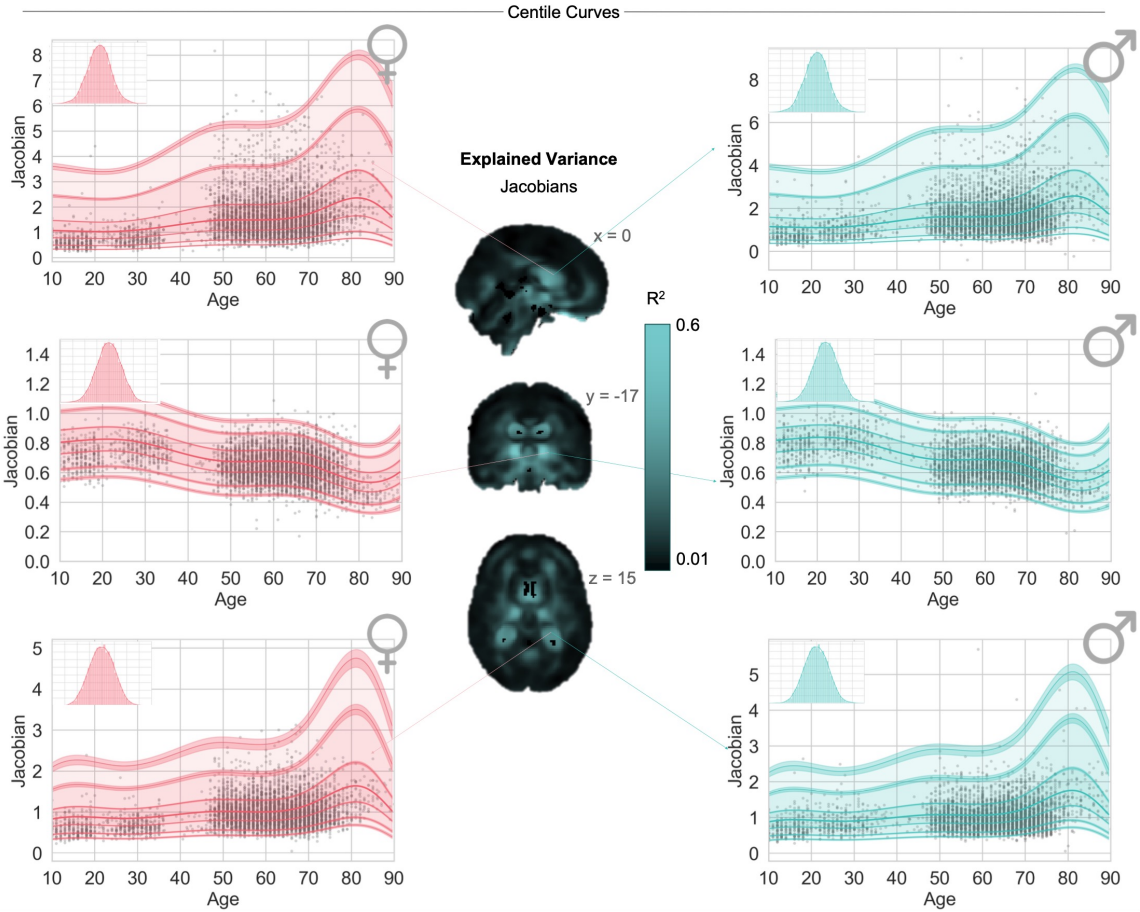
Imaging genetics at N=1







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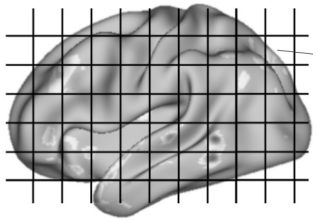


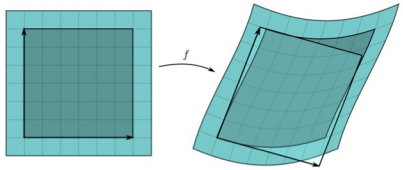


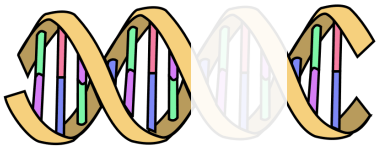
Fraza et al (2024)

Imaging genetics at N=1

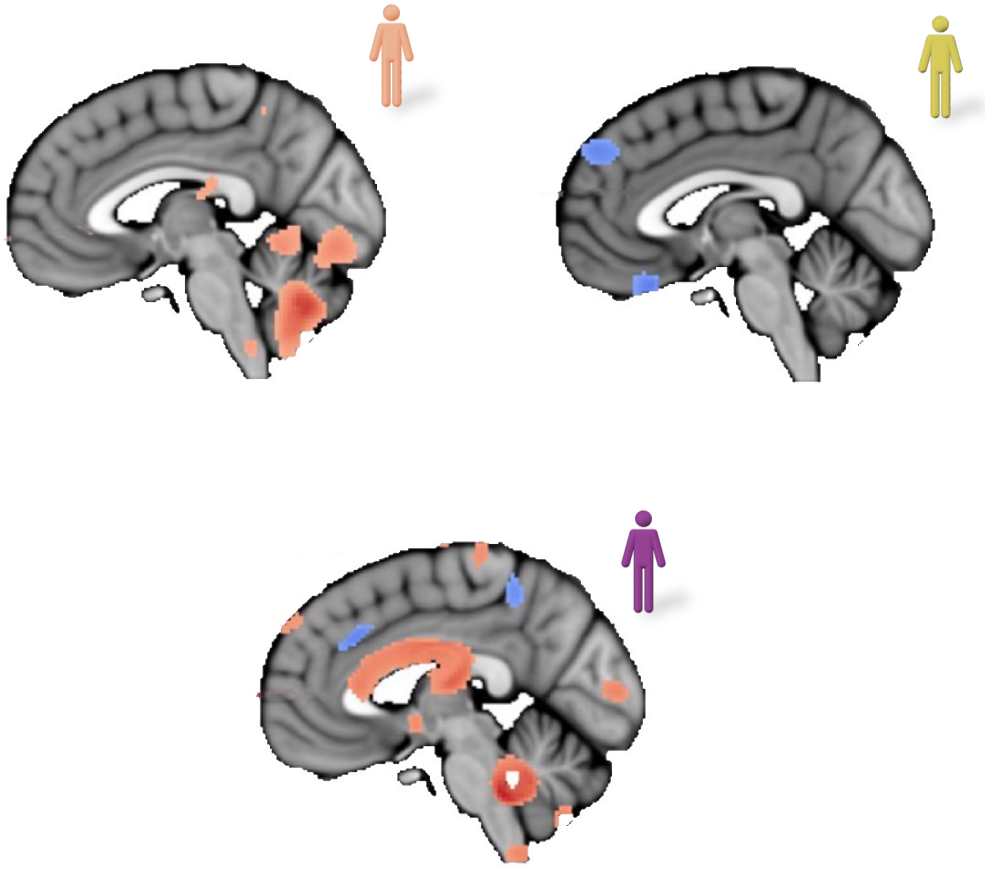






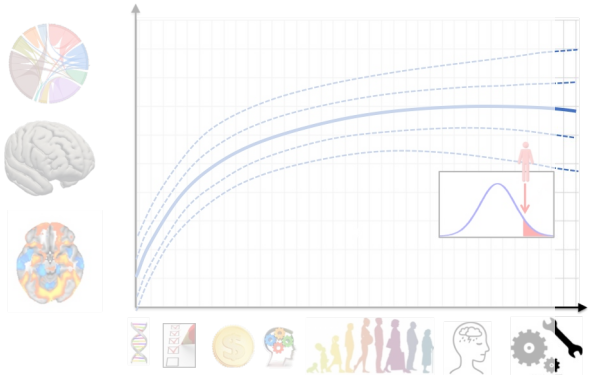


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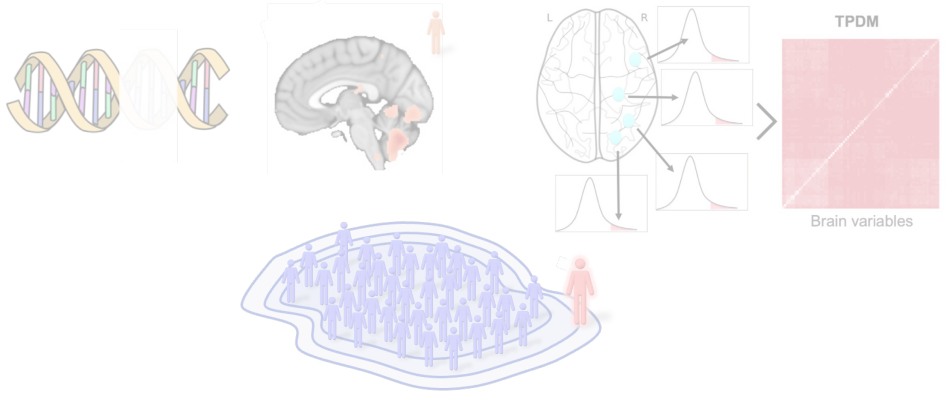


Fraza et al 2024

Overview



Parsing structured variation using normative models

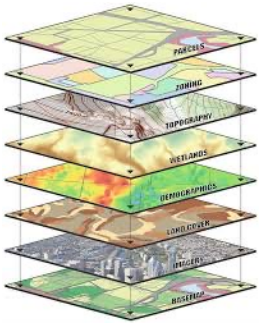


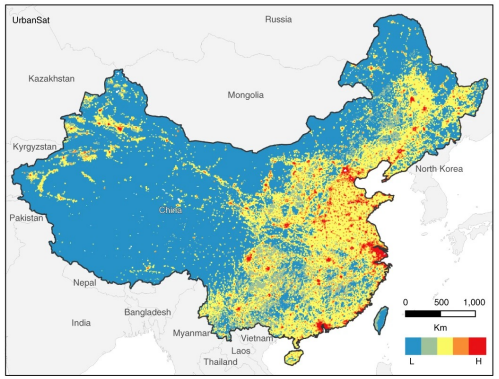
From group effects to individual predictions

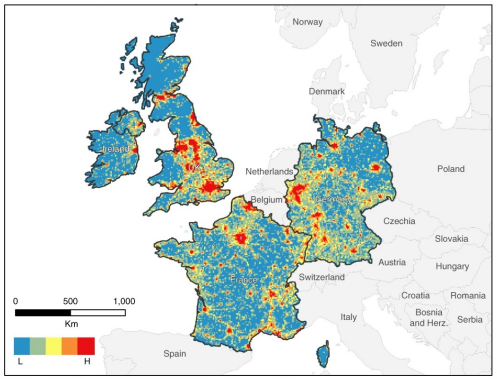


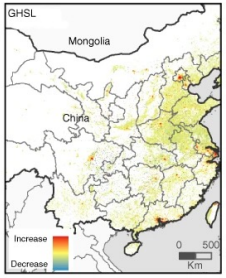
Combining multimodal data for an integrated perspective

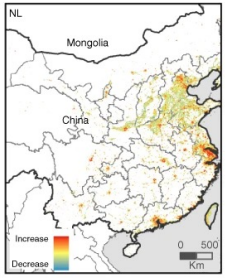


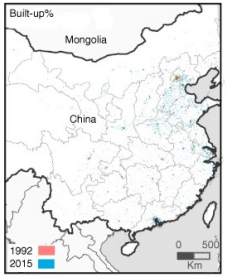


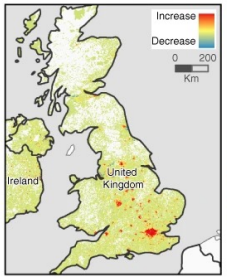


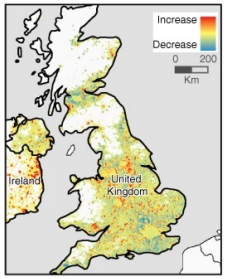


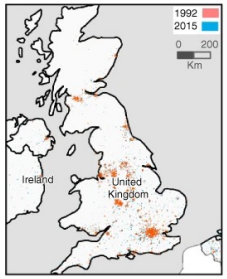






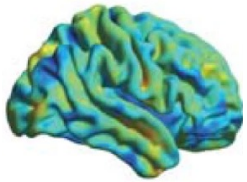




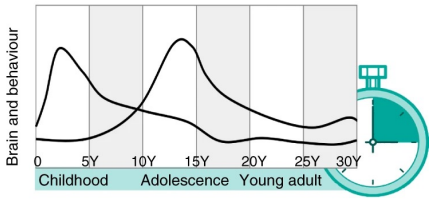




Effects of urbanicity on the brain

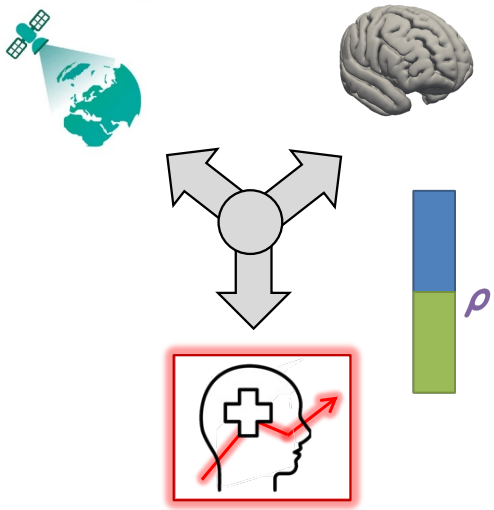


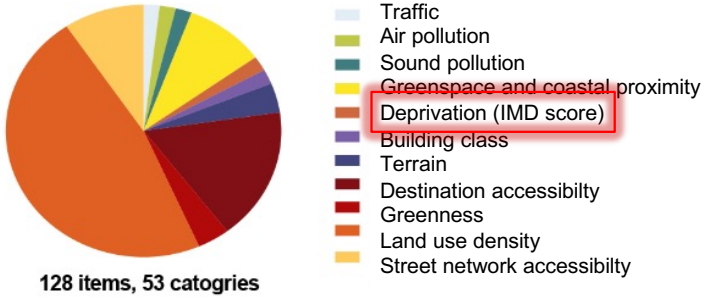
Sensitive periods for mental health

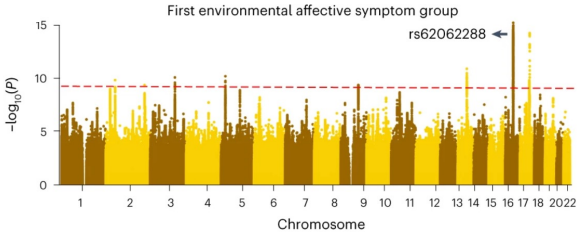


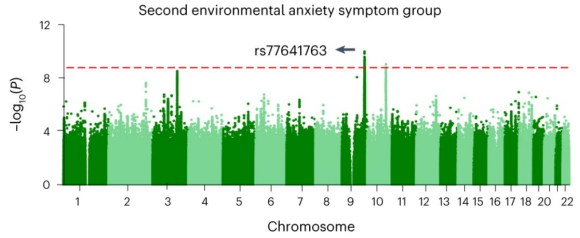
environ MENTAL

Xu et al 2022



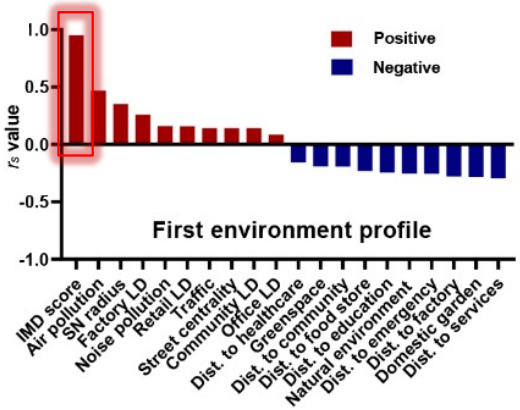


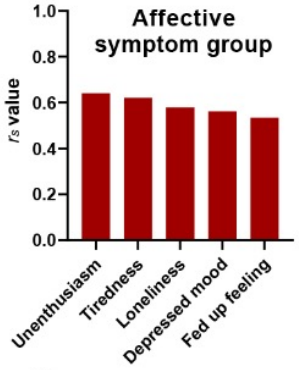


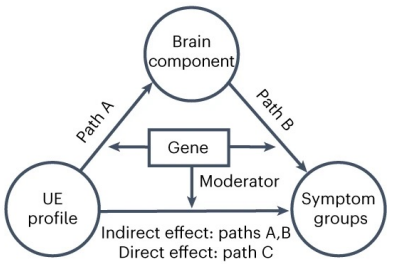


$$\max_{\mathbf{w}_1,..,\mathbf{w}_n} \mathbf{w}_1^{\mathrm{T}} X_1^{\mathrm{T}} \sum_{i=2}^{n} X_i \mathbf{w}_i$$

$$\|\mathbf{w}_1\|^2 = 1, \|\mathbf{w}_i\|^2 = 1, \|\mathbf{w}_1\|_1 \leq c_1 \text{ and } \|\mathbf{w}_i\|_1 \leq c_i$$

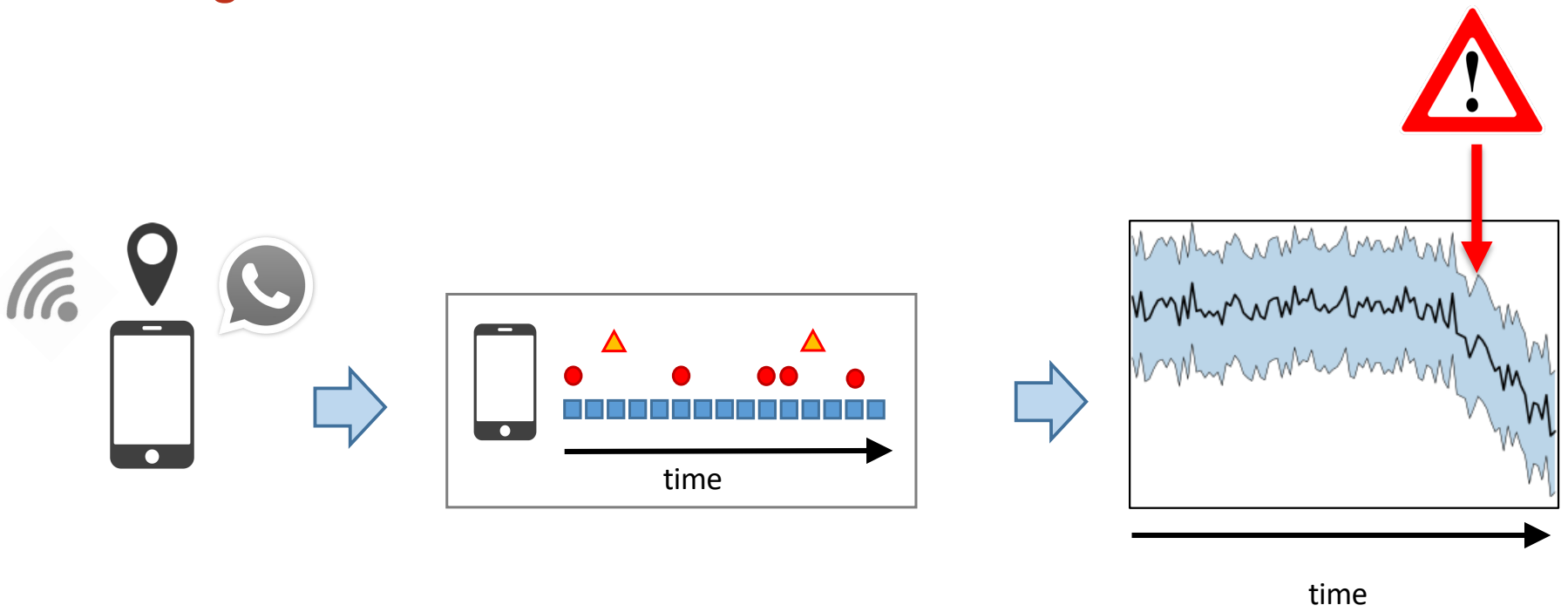






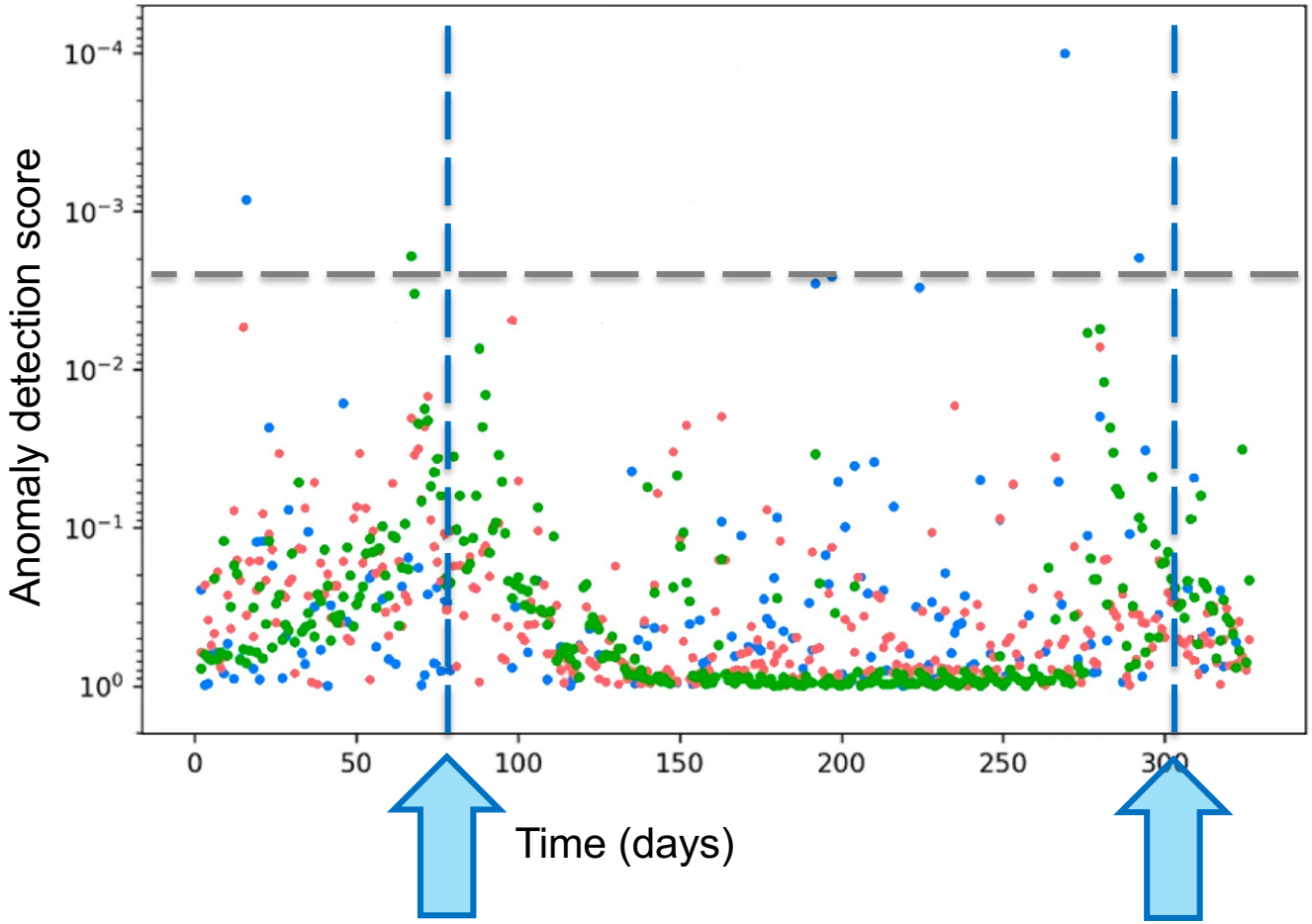
Xu et al 2023

Monitoring behaviour



Monitoring behaviour





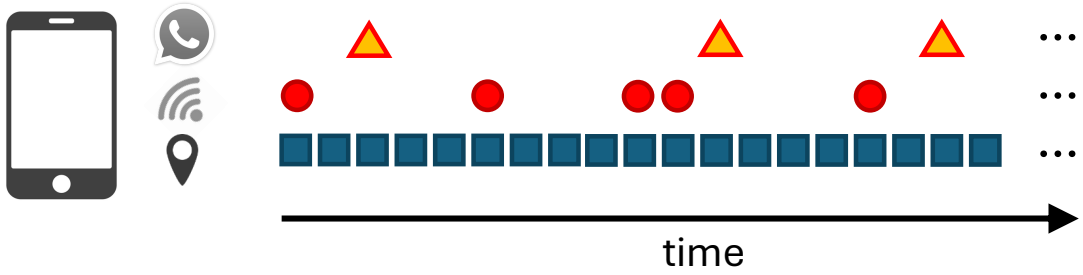
Cohen et al 2023

Monitoring behaviour

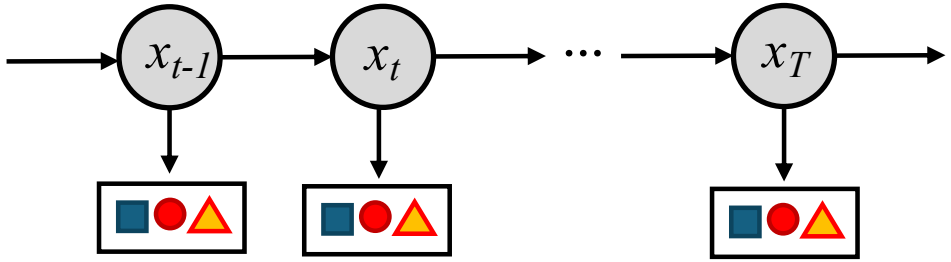




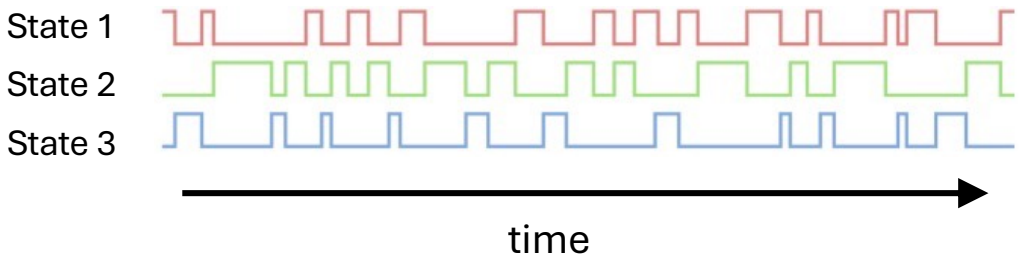
Sensor timeseries (social withdrawal)



Hidden Markov Model



Latent space time courses

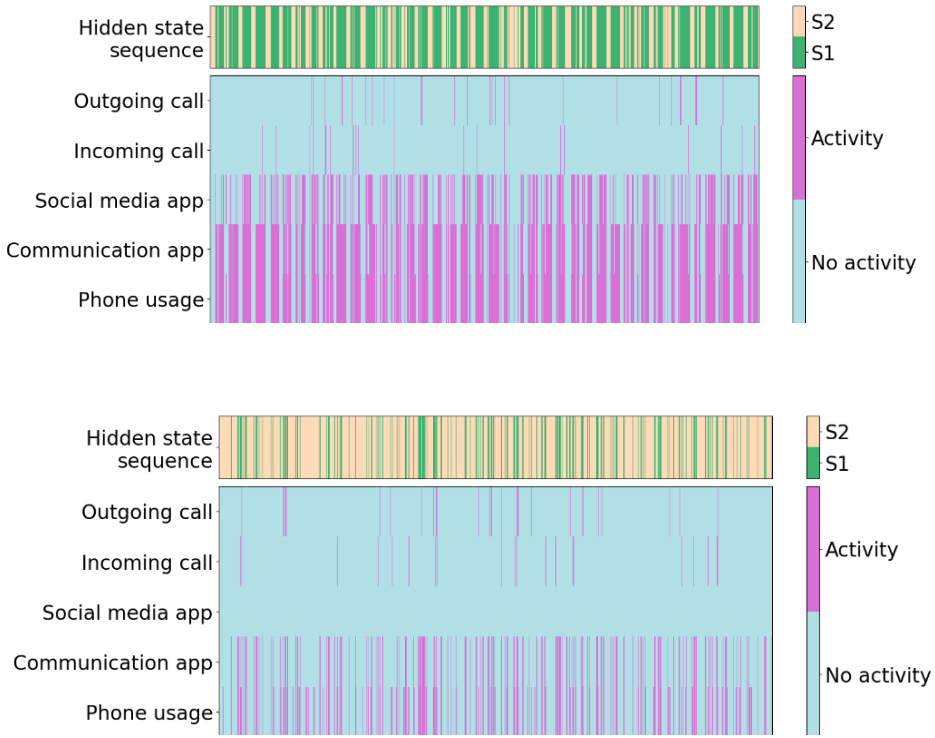


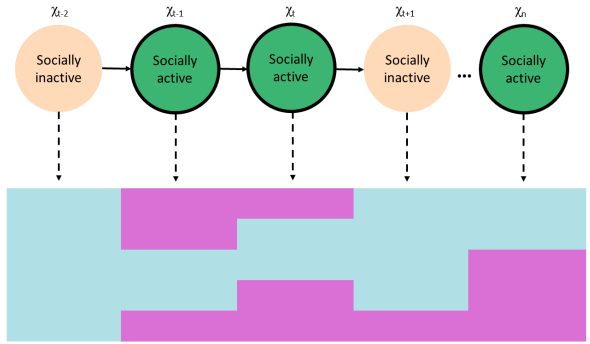
Leaning et al 2025

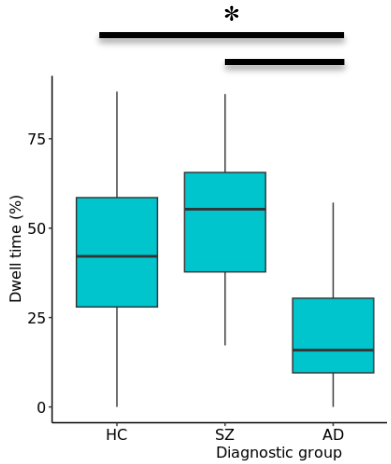
Monitoring behaviour











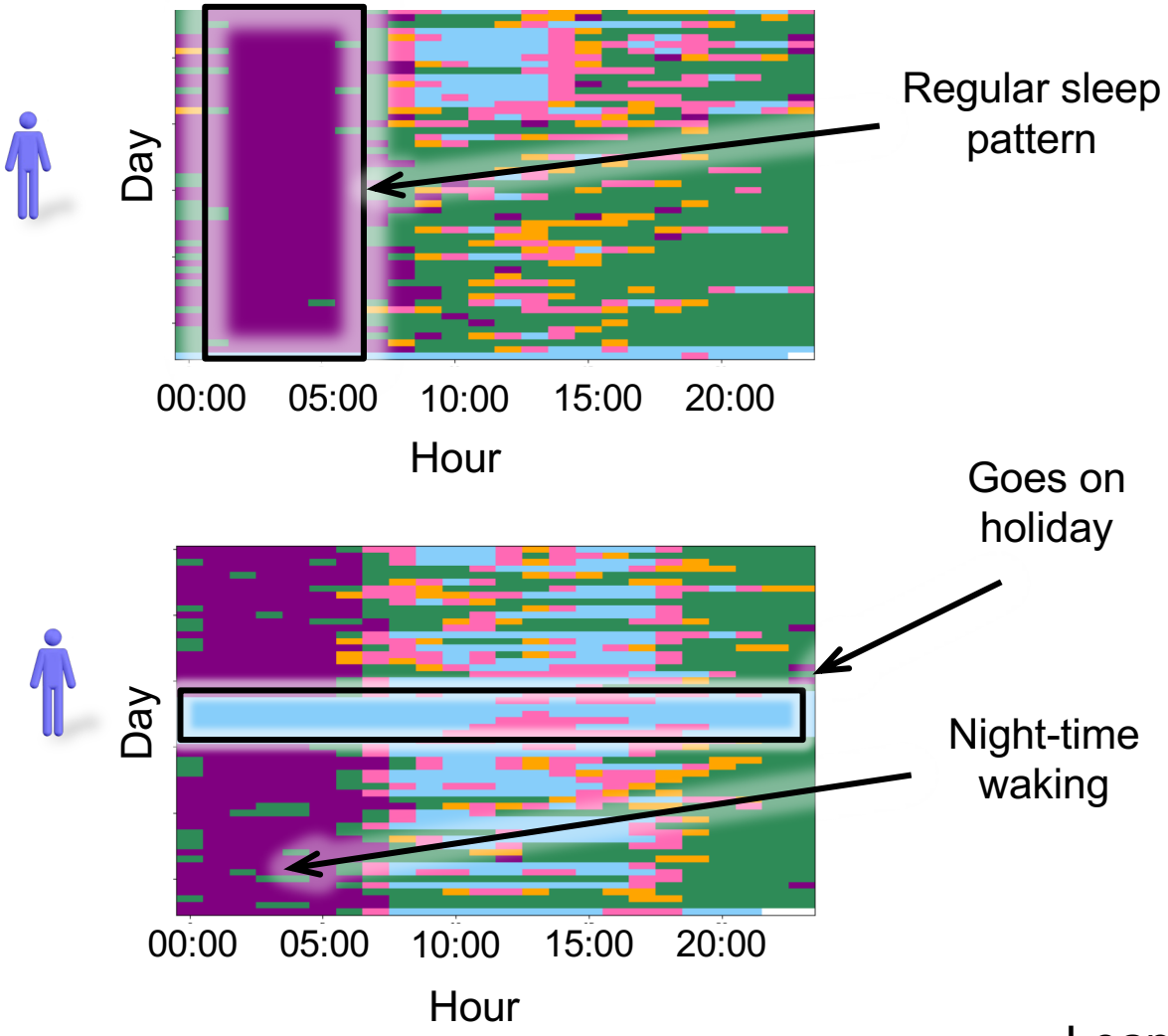
behapp

Leaning et al 2025

Monitoring behaviour





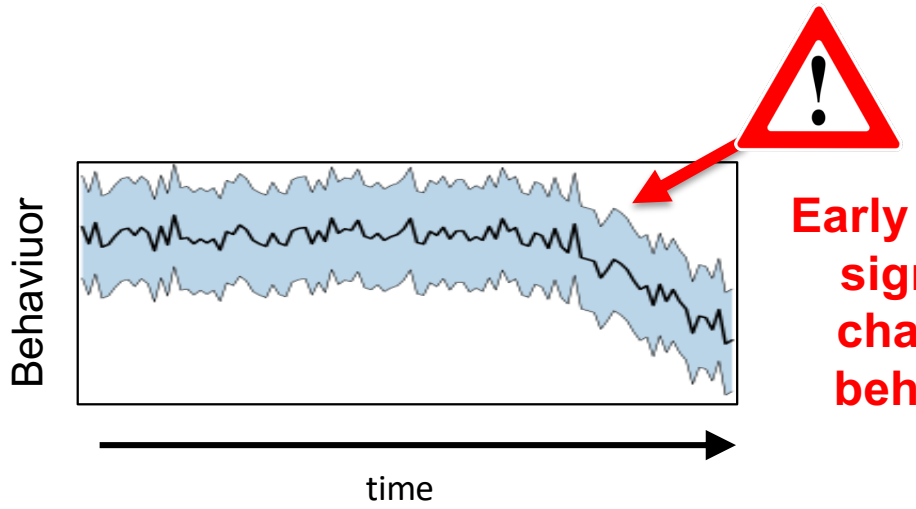


behapp

Leaning et al 2025b

Monitoring behaviour

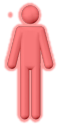


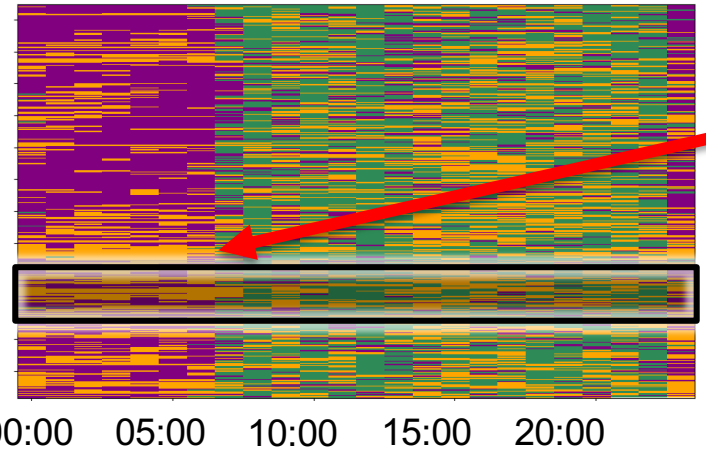


Early warning signal for change in behaviour









Change in sleeping pattern

Relapse

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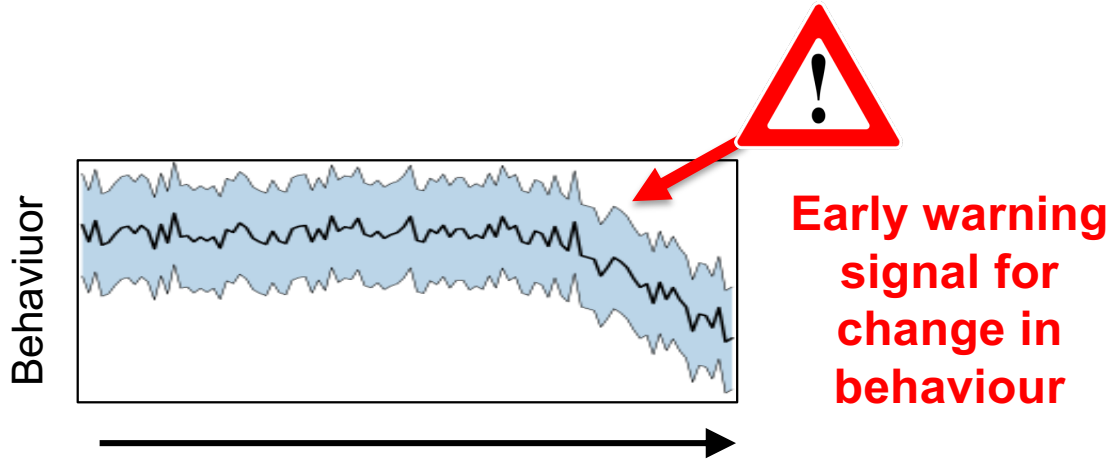
Leaning et al 2025b

Monitoring behaviour

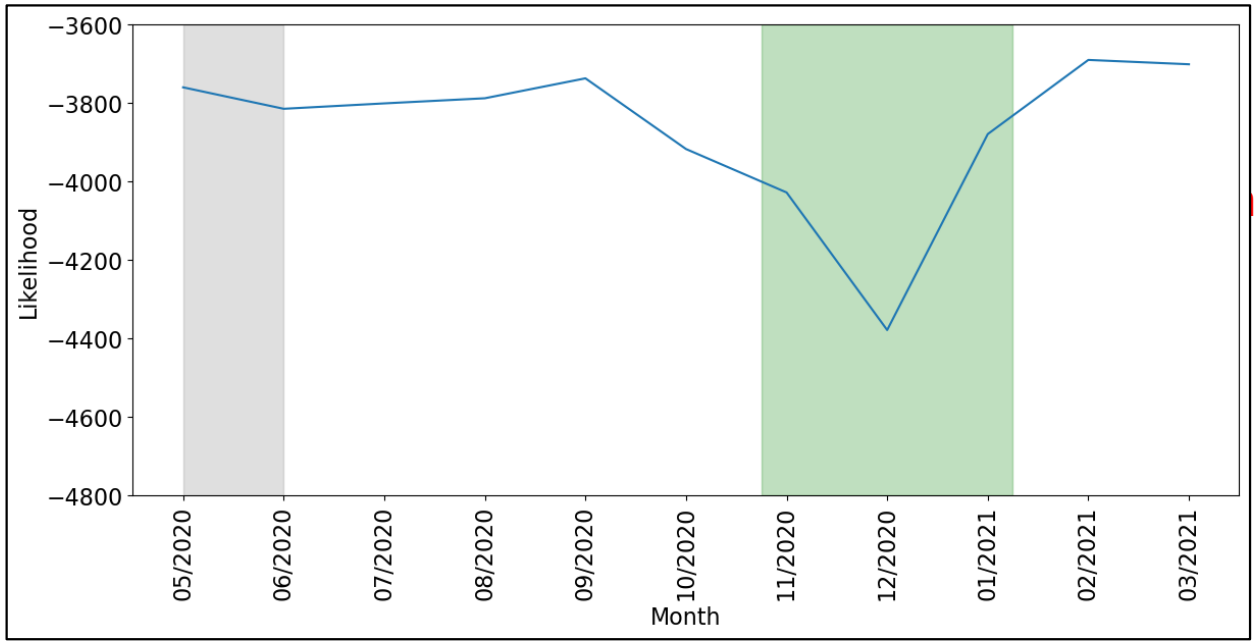








Early warning signal for change in behaviour



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Leaning et al 2025b

Monitoring behaviour



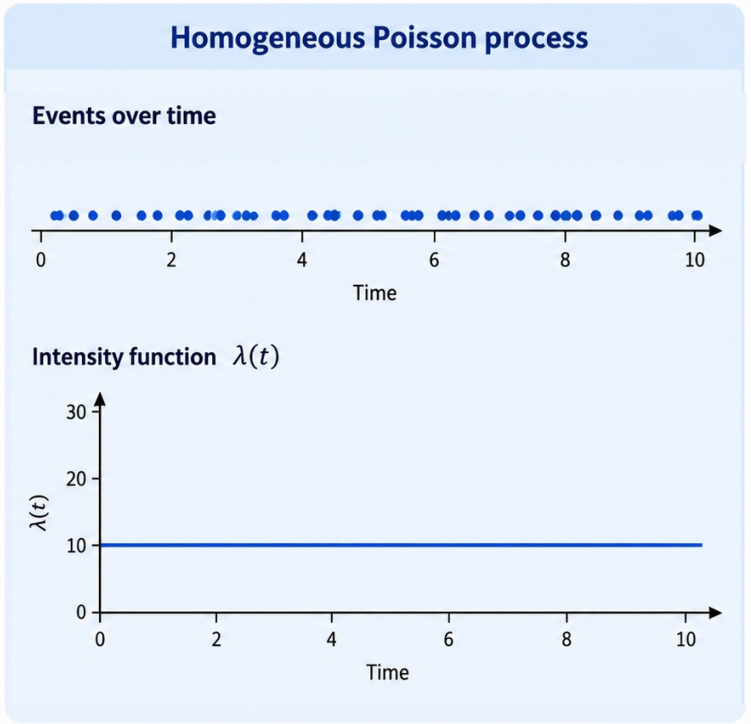


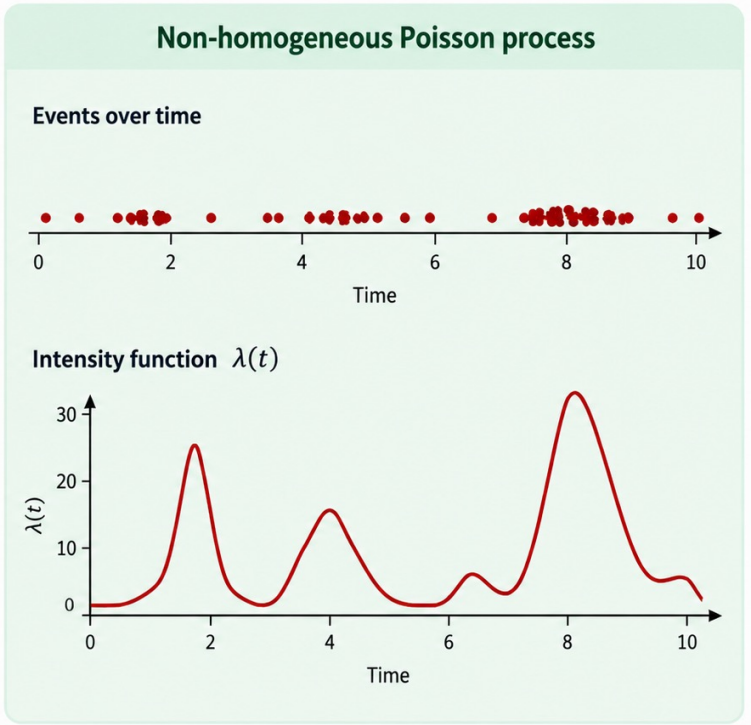
$$\Pr\{N(a,b] = n\} = \frac{[\lambda(b-a)]^n}{n!} e^{-\lambda(b-a)}$$

$$\Pr\{N(a,b] = n\} = \frac{[\Lambda(a,b)]^n}{n!} e^{-\Lambda(a,b)}$$

$$\Lambda(a,b) = \int_a^b \lambda(t)\,\mathrm{d}t$$





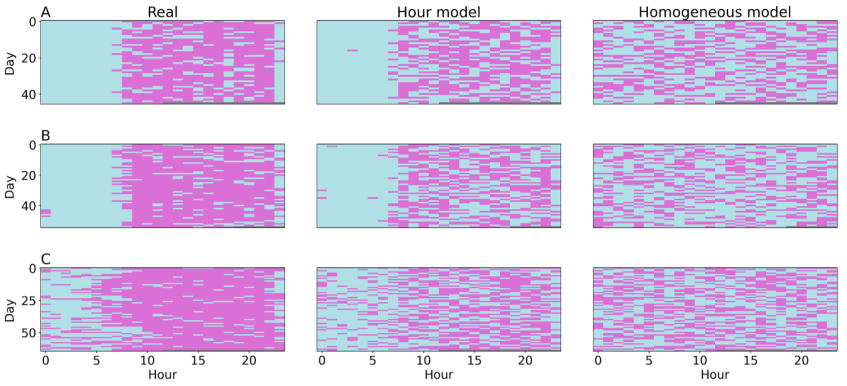


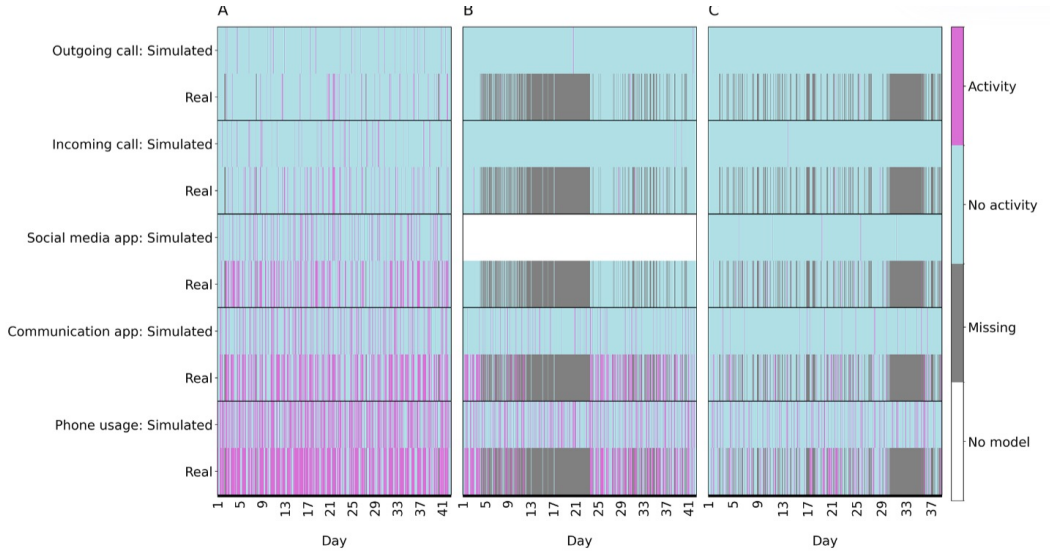
behapp

Leaning et al 2026

Monitoring behaviour











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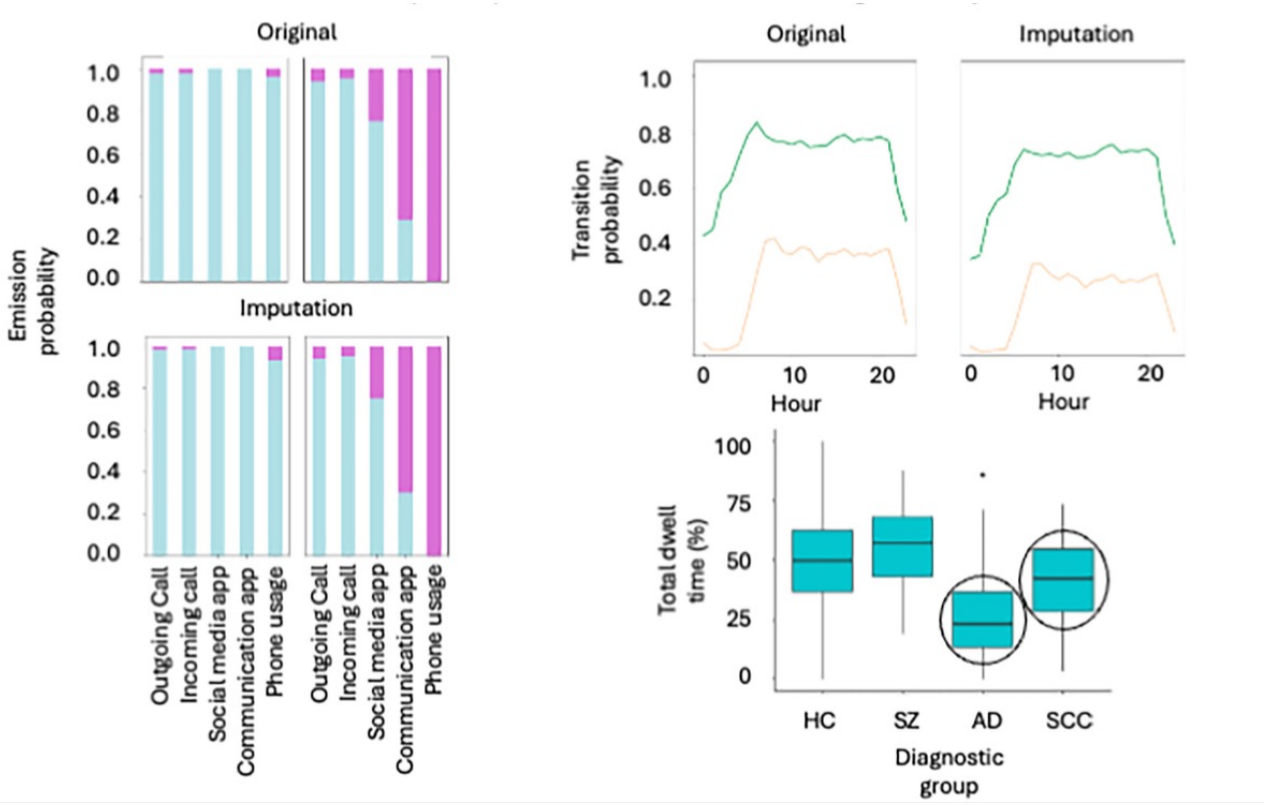
Leaning et al 2026

Monitoring behaviour





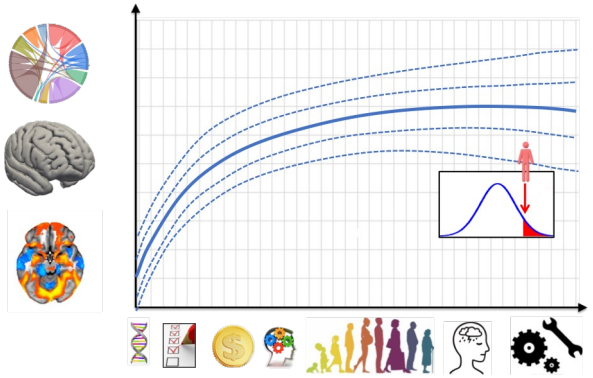




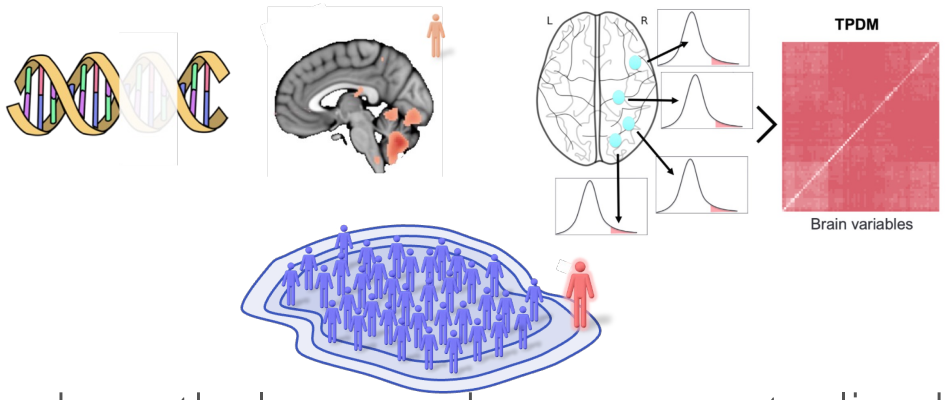
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Leaning et al 2026

Summary



Normative models are promising to parse variation in big data cohorts

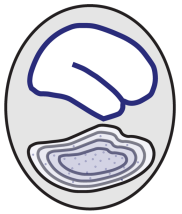


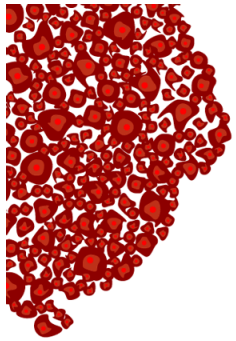
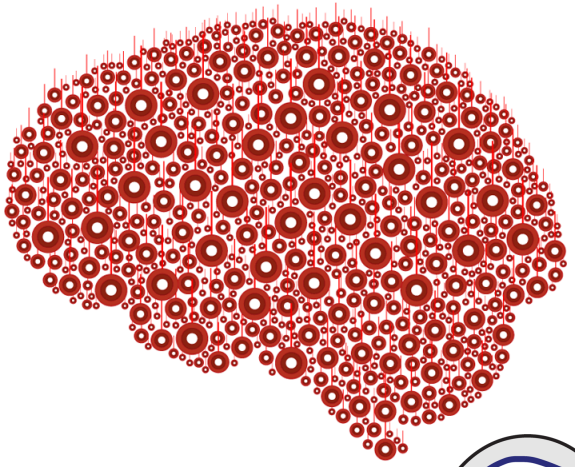
Psychopathology can be reconceptualized as extreme deviations for inference at N=1



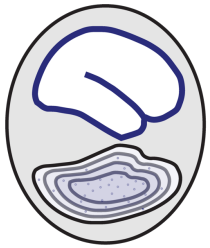
An integrated perspective is essential to make progress

GitHub

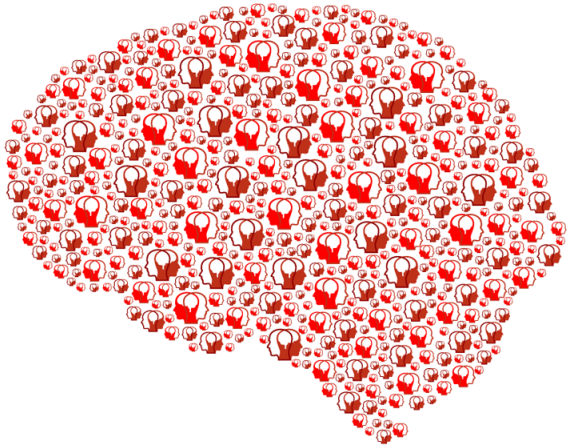


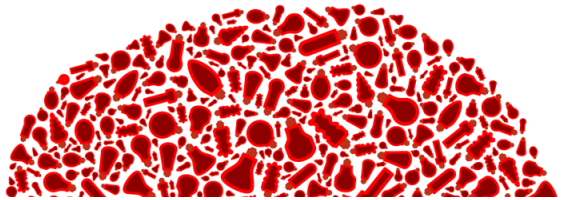




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