



**Validation of putative biomarkers
in clinical cohorts (II)**

Overview

- 1) Major challenges
- 2) Harmonization: HALFpipe
- 3) Transdiagnostic Markers: Ventral Striatal Activation
- 4) Connectomics: GraphVar and NBS-Predict)
- 5) Applications
 - 5.1. Prediction of Relapse (AUD Cohort)
 - 5.2. Prediction of Binge Drinking (IMAGEN)

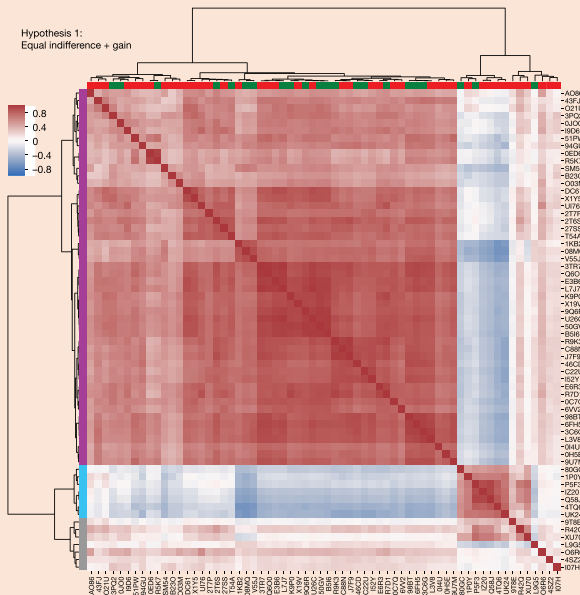
(1) Major Challenges for Biomarker Identification and Clinical Validation

- Heterogeneity (Data Acquisition/Structure/Analysis - Disorders)
- Sample Size
- Curse of Dimensionality
- Multi-Task-Prediction
- Data Access, Security and Communication Across Sites
- Clinical Translation
- Clinical Usability

(2) Harmonization: HALFPipe

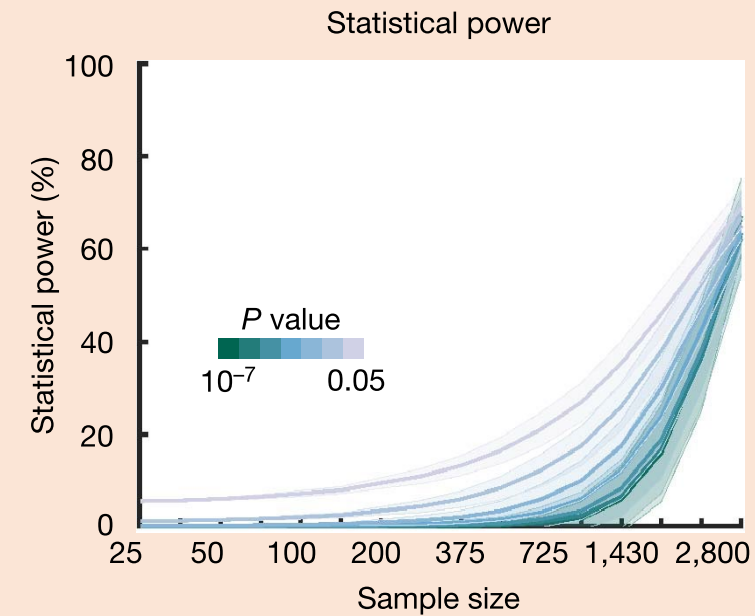
“No two teams chose identical workflows to analyze the data. This flexibility resulted in sizeable variation in hypothesis test results. ”

Botvinik-Nezer et al. (2020)



“As sample sizes grew into the thousands, replication rates began to improve and effect size inflation decreased. ”

Marek et al. (2022)



(2) Harmonization: HALFPipe











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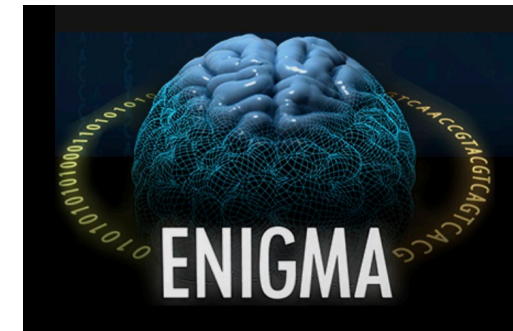
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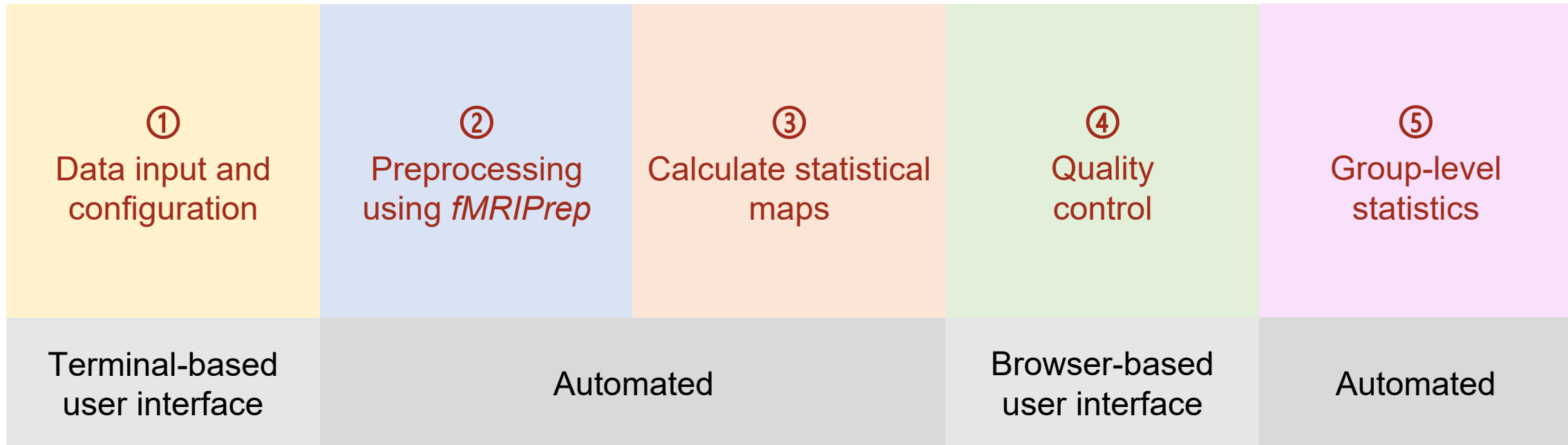
ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data

Lea Waller¹  | Susanne Erk¹  | Elena Pozzi^{2,3}  | Yara J. Toenders^{2,3}  |
Courtney C. Haswell⁴ | Marc Büttner¹  | Paul M. Thompson⁵  |
Lianne Schmaal^{2,3}  | Rajendra A. Morey^{4,6}  | Henrik Walter¹  | Ilya M. Veer^{1,7} 

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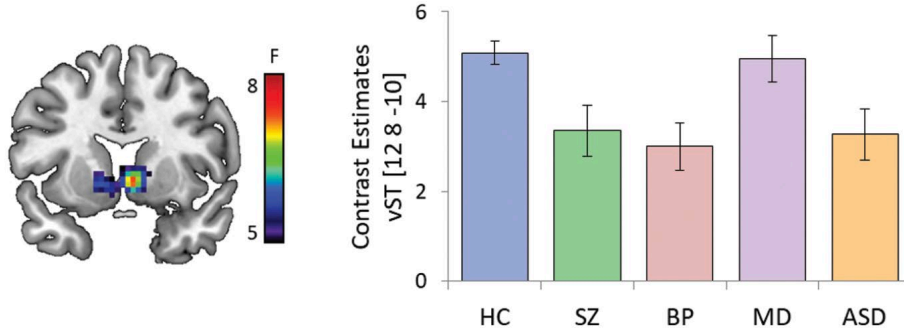


(2) Harmonization: HALFPipe



- Berlin project: Imaging genetics across affective/cognitive/social domains according to RDoC
- Currently: Similar tasks: WM, faces, reward: aiming at 10.000/task)
- Genetics with Sarah Medland
- Join by contacting enigma@charite.de
- Used already in MDD, PTSD (both rsfMRI) and OCD (tb fMRI)

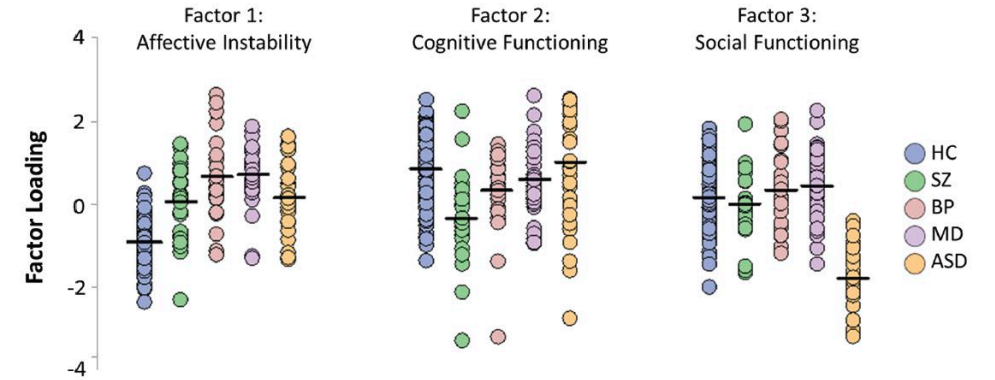
(3) Transdiagnostic Markers



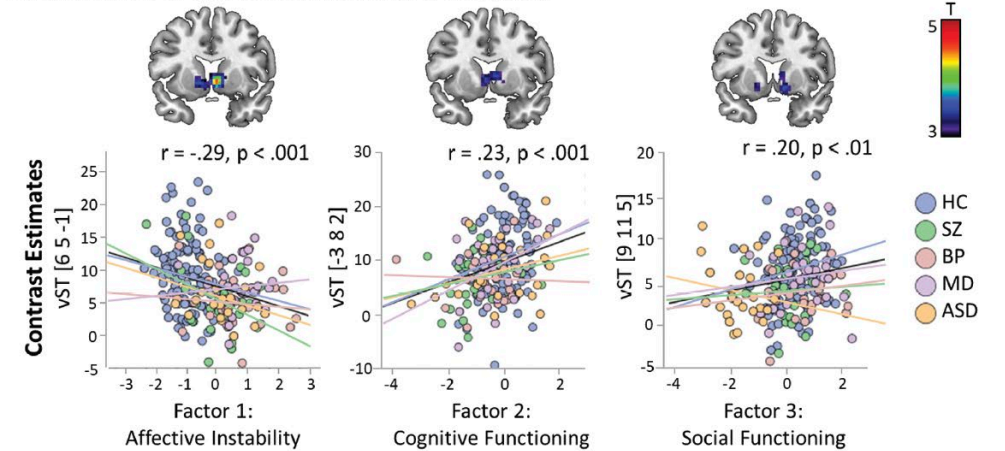
Ventral striatal (vST) activation is blunted across disorders (except MDD)

... and is differently related to affective, cognitive and social domains across disorders

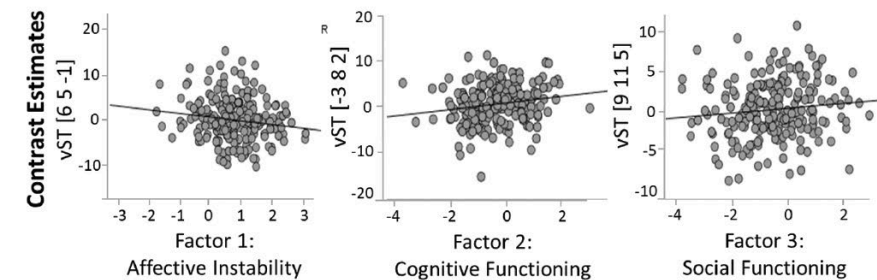
A) Principal Component analysis



B) Association of factor loadings with vST activation



C) Association of factor loadings with vST activation controlled for diagnostic group



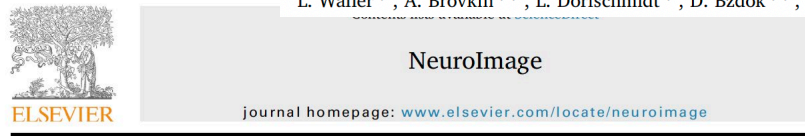
(4) Connectomic tools

From local activations to networks



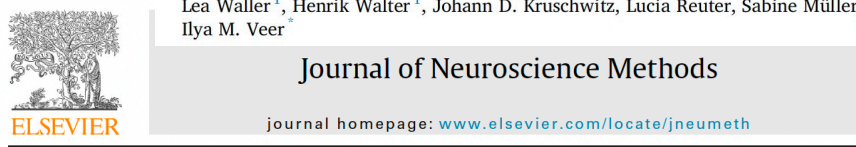
GraphVar 2.0: A user-friendly toolbox for machine learning on functional connectivity measures

L. Waller^{a,1}, A. Brovkin^{a,b,1}, L. Dorfschmidt^{a,b}, D. Bzdok^{c,d,e}, H. Walter^a, J.D. Kruschwitz^{a,b,*}



Evaluating the replicability, specificity, and generalizability of connectome fingerprints

Lea Waller¹, Henrik Walter¹, Johann D. Kruschwitz, Lucia Reuter, Sabine Müller, Susanne Erk, Ilya M. Veer^{*}



Computational Neuroscience

GraphVar: A user-friendly toolbox for comprehensive graph analyses of functional brain connectivity

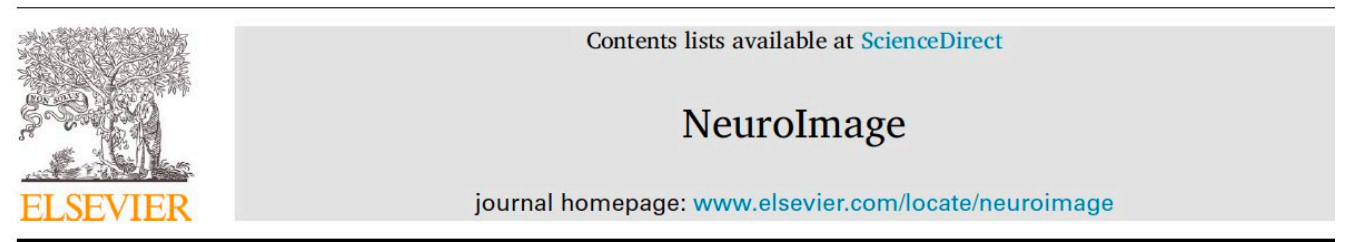
J.D. Kruschwitz^{a,b,*}, D. List^{a,b,*}, L. Waller^a, M. Rubinov^c, H. Walter^a

Combining connectomics & machine learning for prediction

- GitHub:
<https://github.com/eminSerin/NBS-Predict>

- NITRC:
<https://www.nitrc.org/projects/nbspredict/>

NeuroImage 244 (2021) 118625

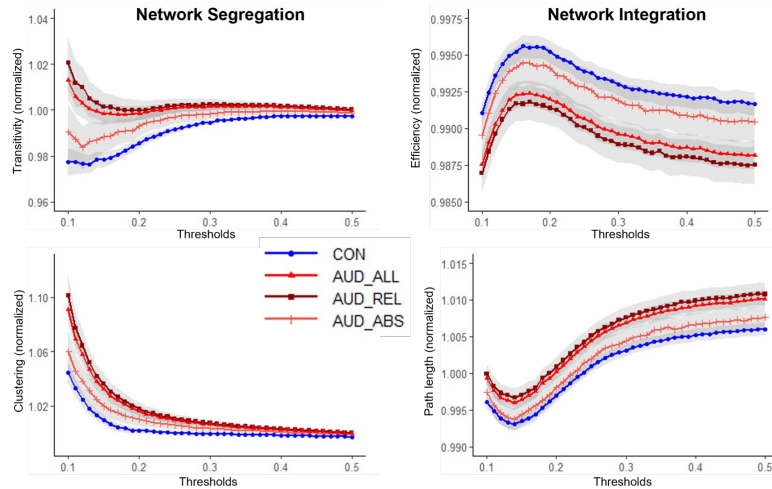


NBS-Predict: A prediction-based extension of the network-based statistic

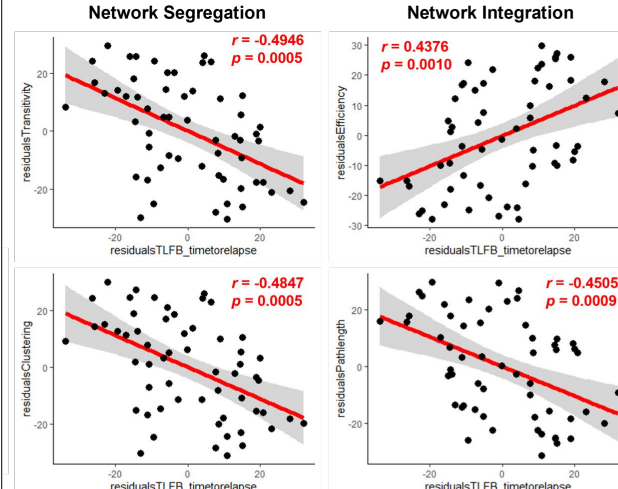
Emin Serin^{a,b,e,*}, Andrew Zalesky^c, Adu Matory^{d,e}, Henrik Walter^e, Johann D. Kruschwitz^{e,f}

(5.1) Application: Prediction of Relapse in AUD using Connectomics

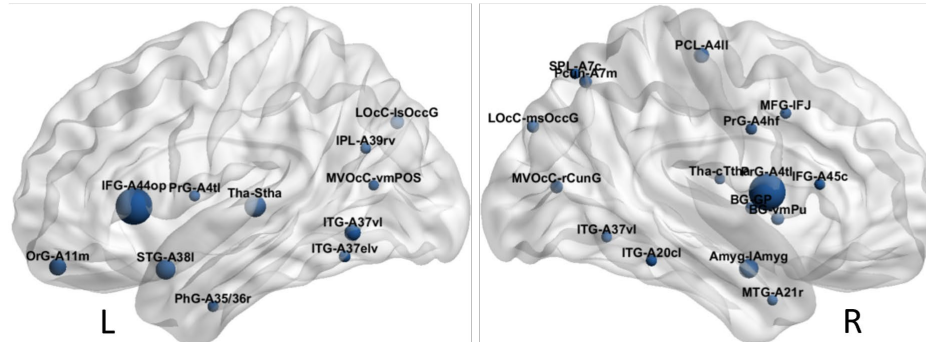
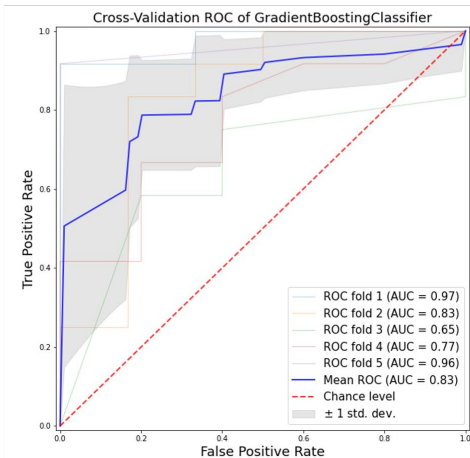
A) Global network organization



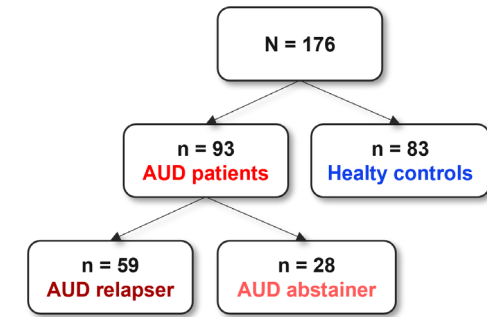
B) Brain-behavior relationships



C) Relapse prediction using measures of global and local network topology



- **Recently detoxified AUDs** ((for ≥ 3 years
- **Relapse** = occasion of $\geq 60/48$ g (male/female) pure alcohol intake within 48 weeks



A) **Relapsing AUDs: altered network organization (rsfMRI)**

B) **Abstaining AUD patients similar to healthy controls**

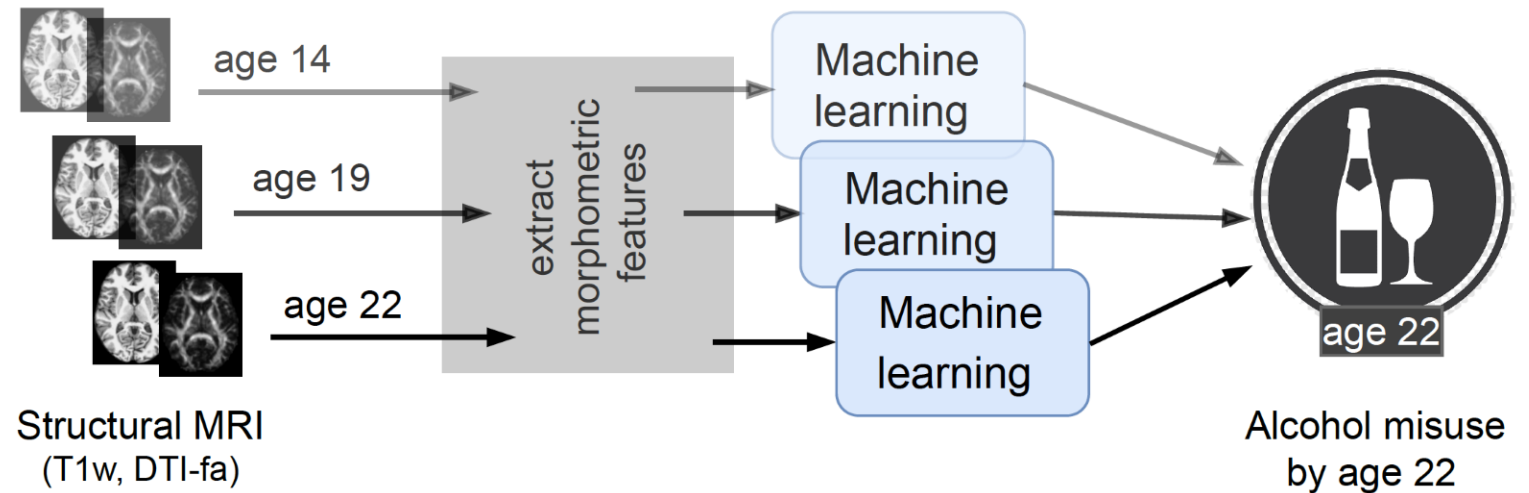
C) **Earlier relapse is associated with more segregated and less integrated networks in relapsing AUDs**

D) **Prediction of relapse: 81% balanced using Gradient Boosting Classifier.**

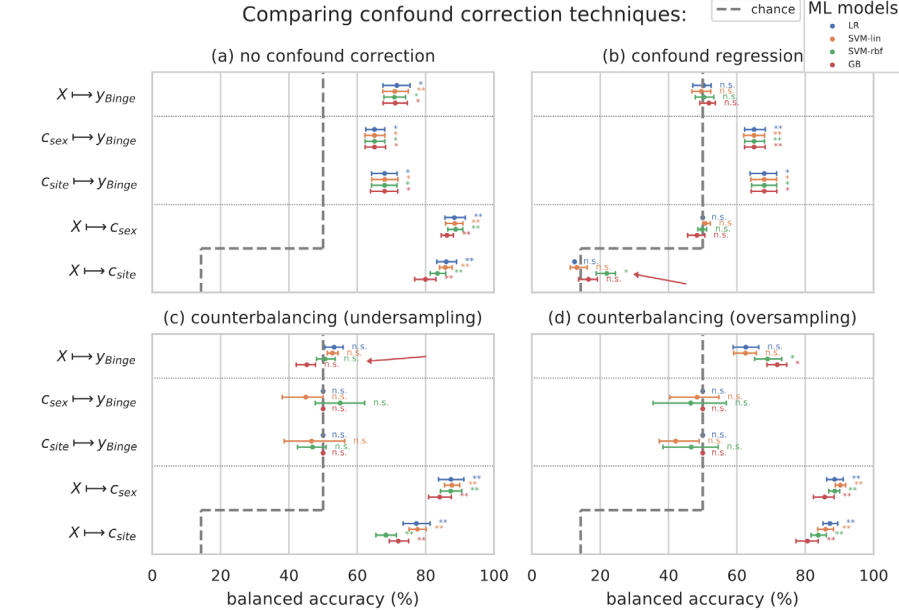
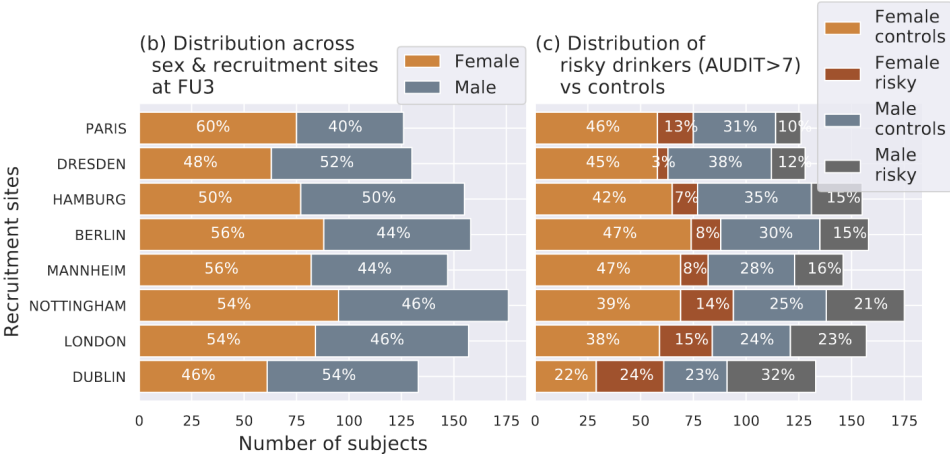
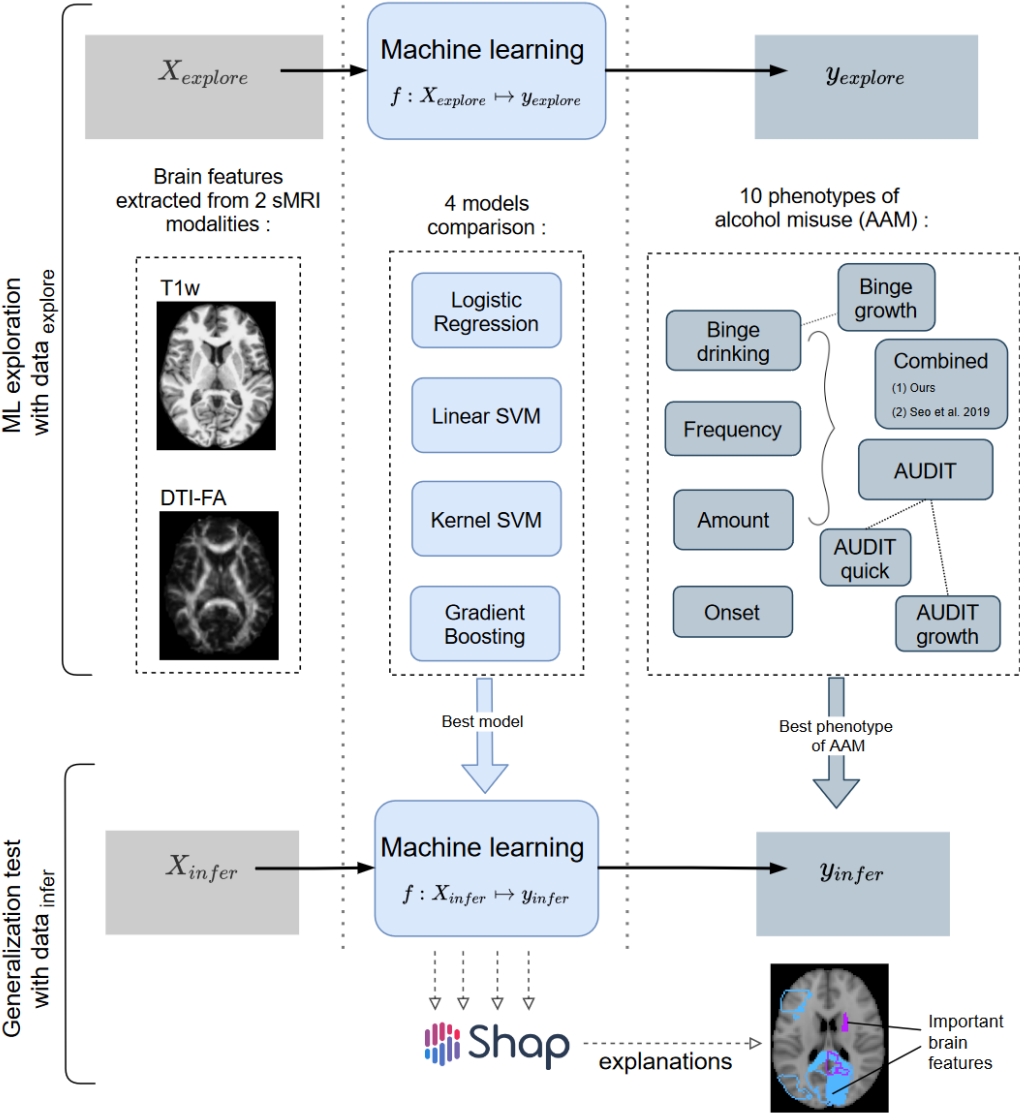
(5.2) Controlling for algorithms, confounds, clinical phenotypes in AUD

imagen dataset

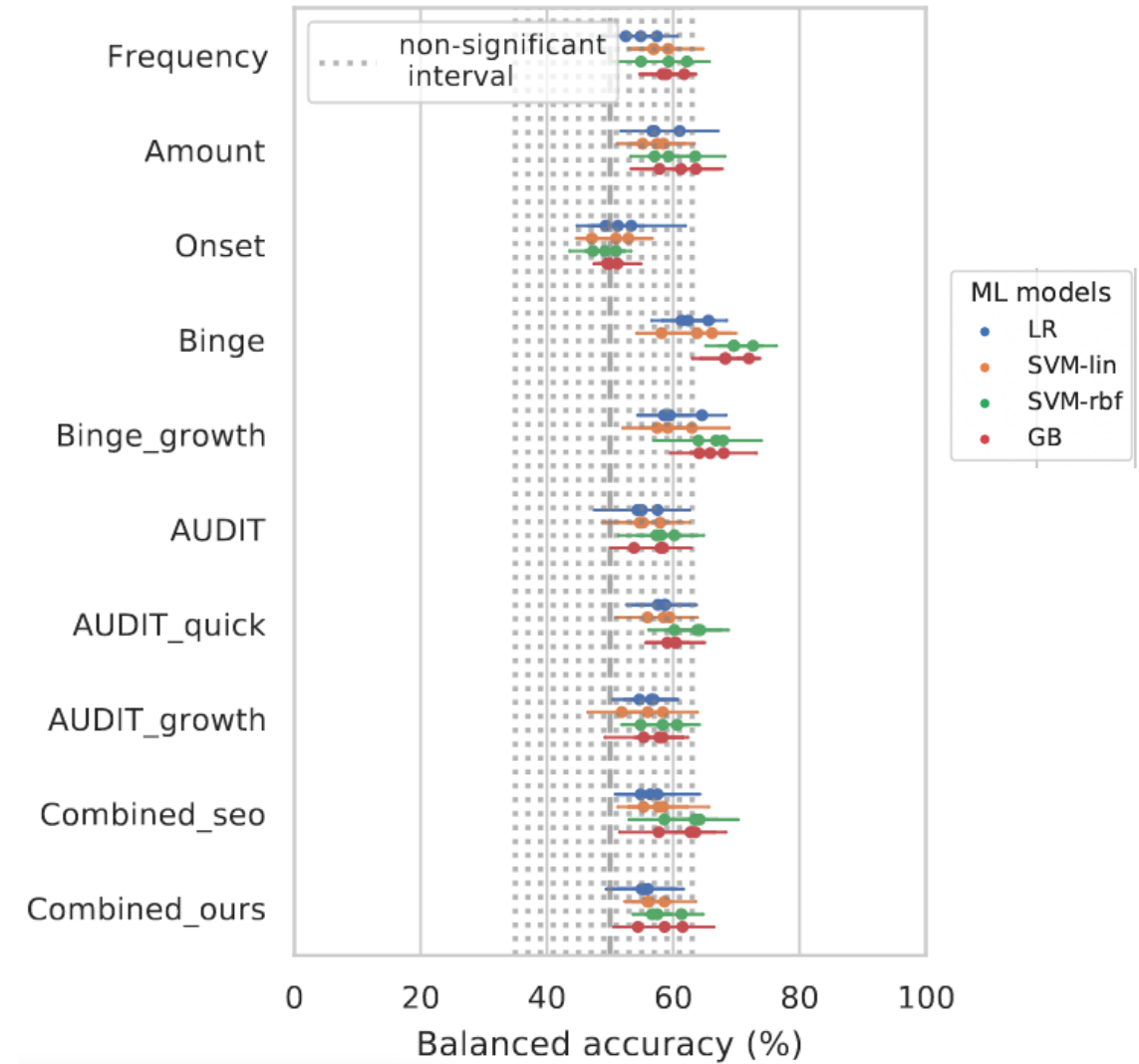
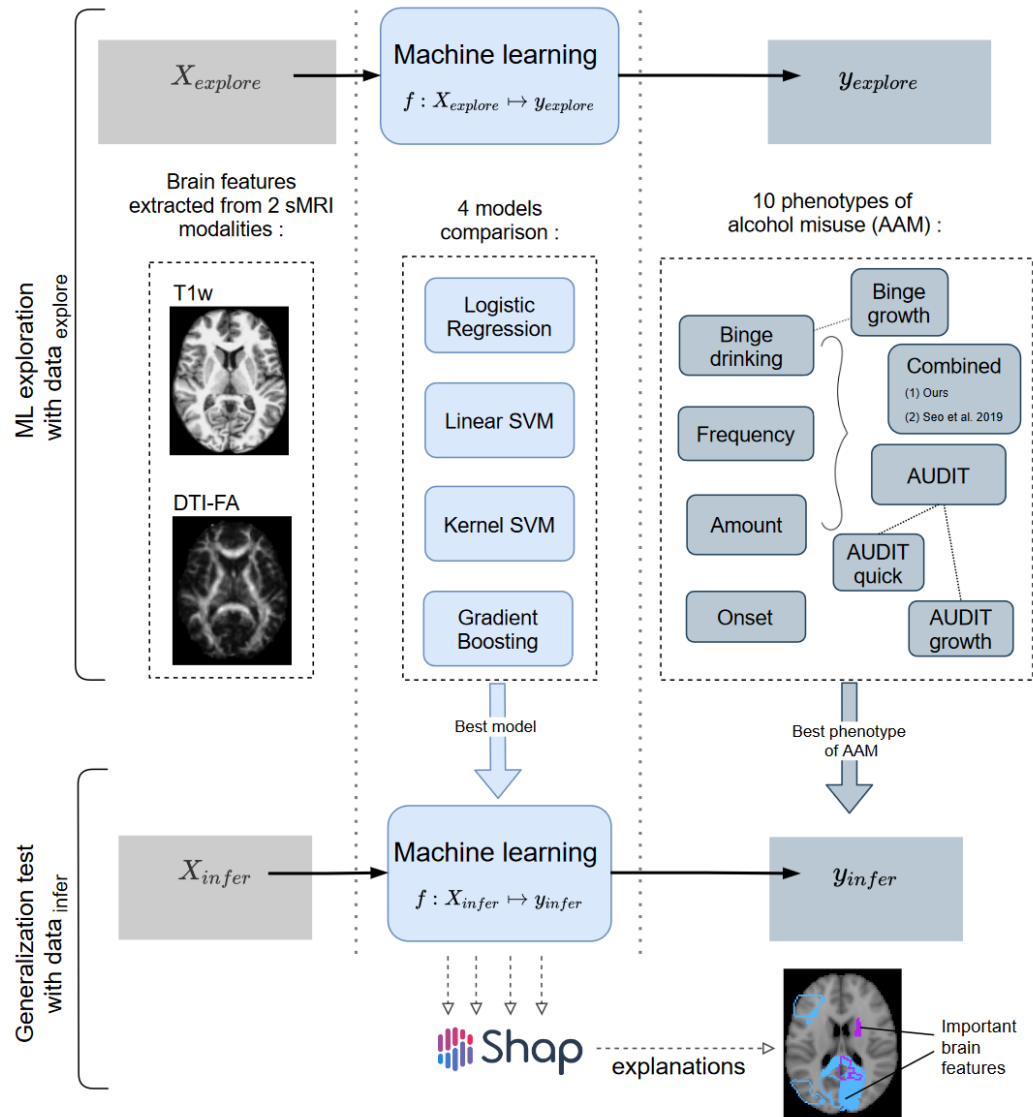
- Longitudinal study with baseline (BL) at age 14 and follow-ups at 16 (FU1), 19 (FU2) and 21 (FU3)
- IMAGING (structural and functional) and GENetic information
- + many questionnaires about personality, alcohol/drug use, health, family etc.
- Collected at 8 test centers in Europe
- N = 2462



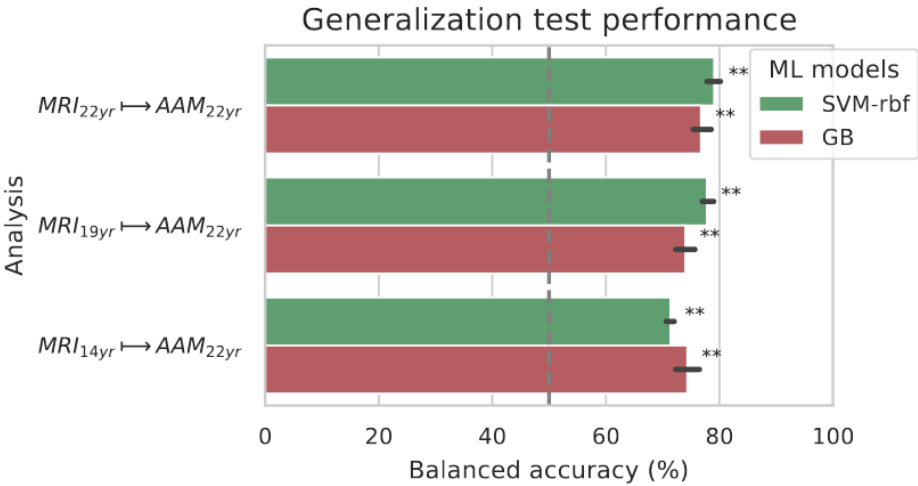
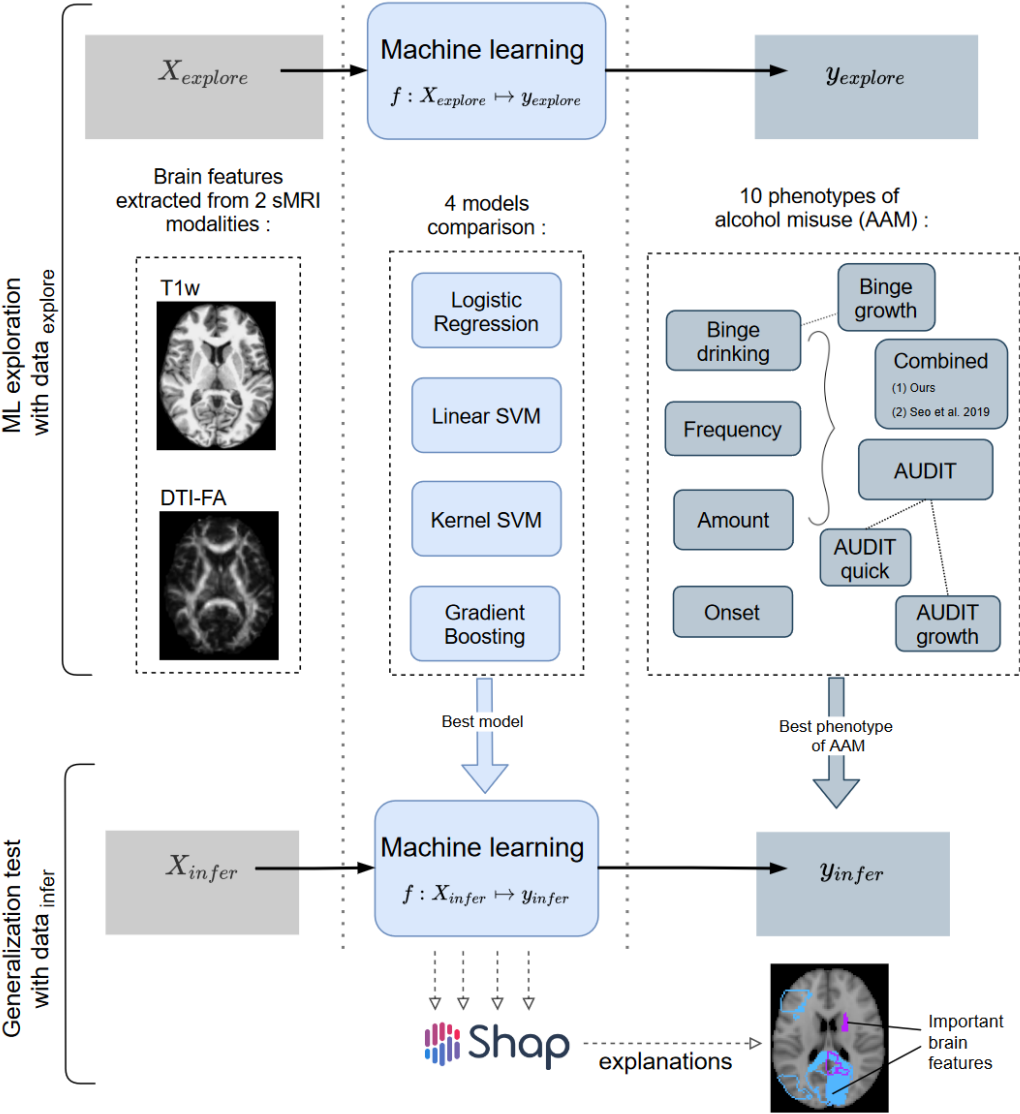
(5.2) Controlling for algorithms, confounds, clinical phenotypes in AUD



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(5.2) Controlling for algorithms, confounds, clinical phenotypes in AUD



Analysis	Mean balanced	Mean AUC
input	accuracy (%)	ROC (%)
X_{22yr}	78.0 ± 2.8	83.9 ± 1.9
X_{19yr}	75.5 ± 2.1	83.1 ± 1.9
X_{14yr}	73.1 ± 2.8	81.5 ± 1.5