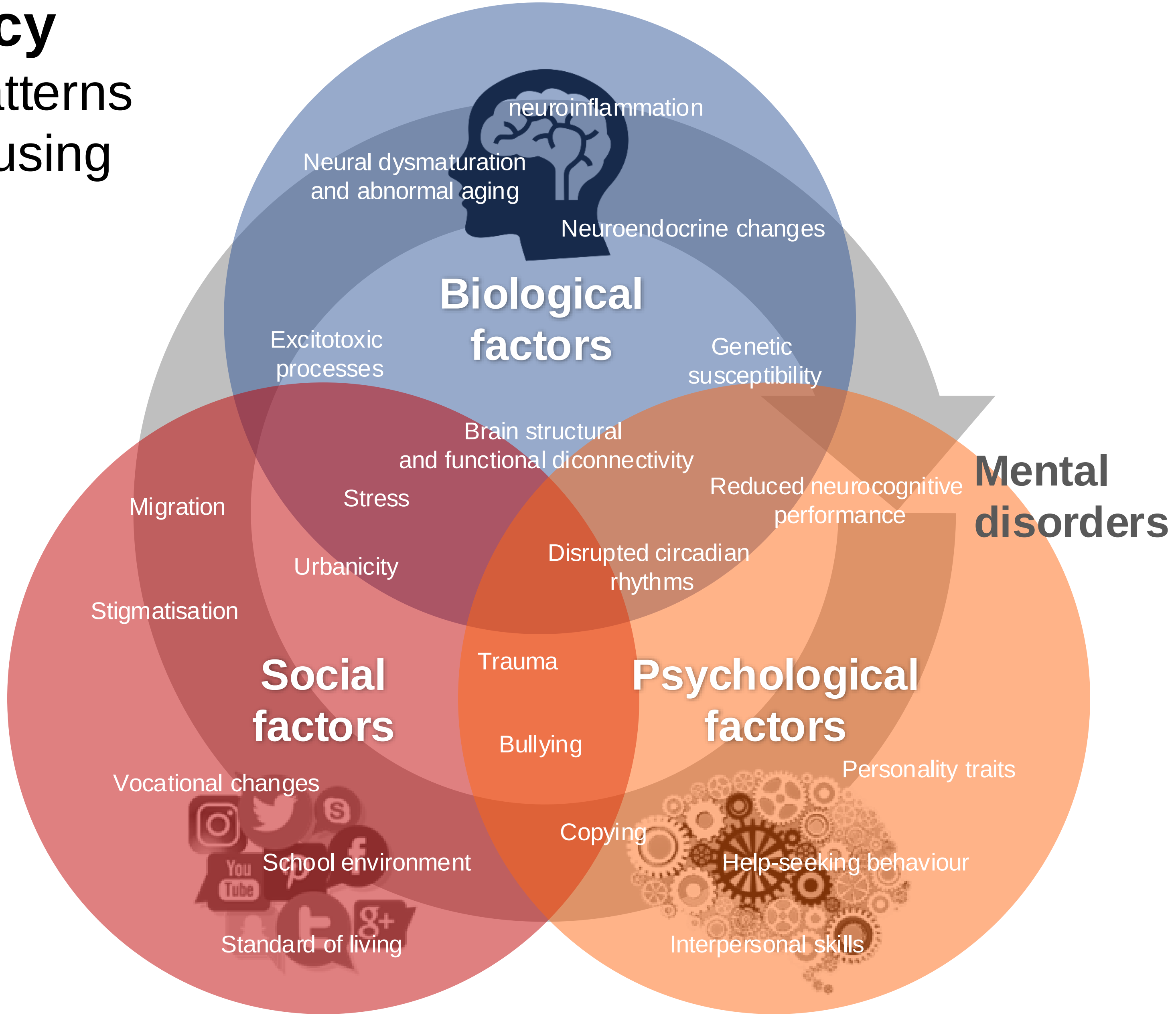
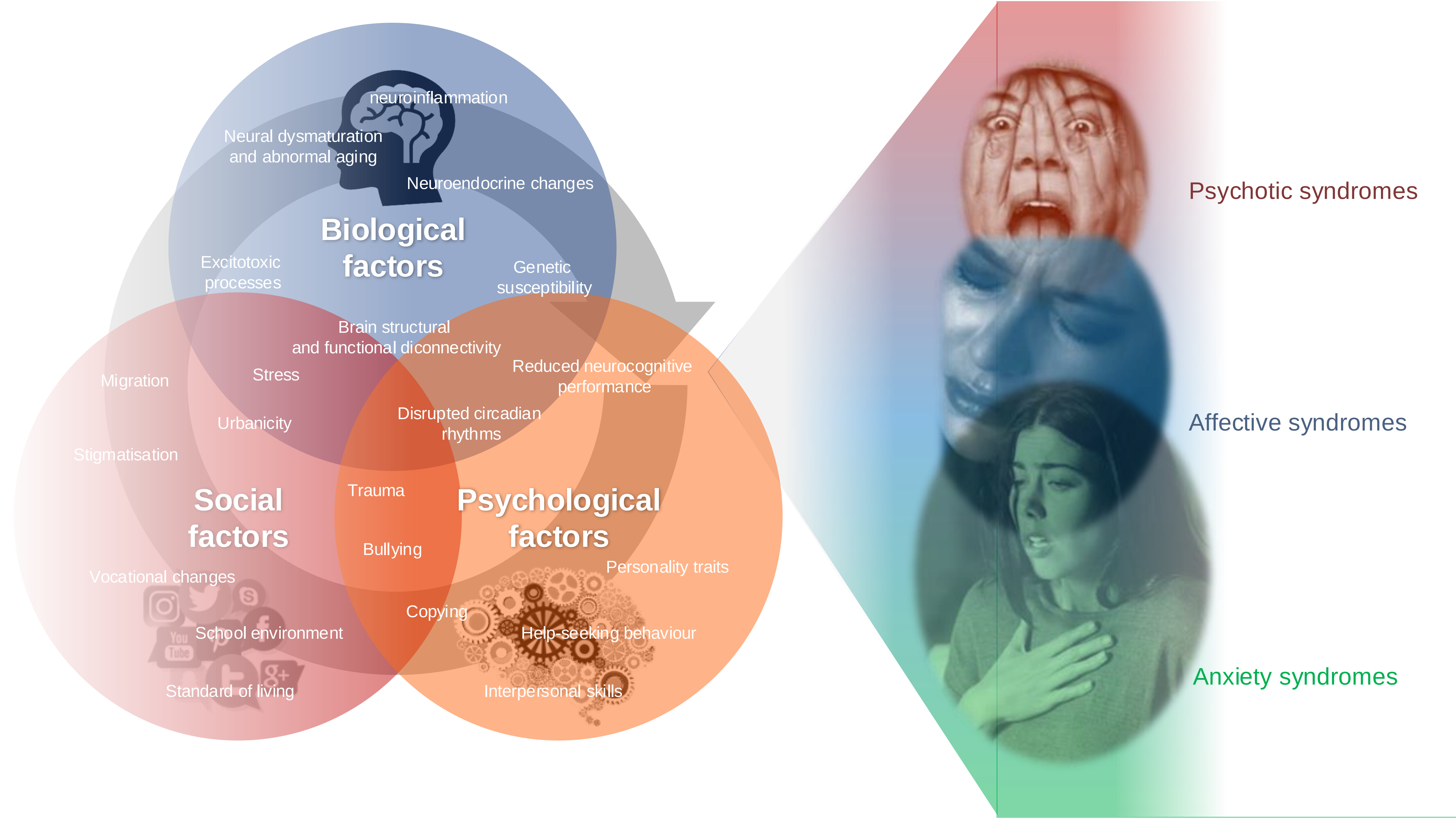
Beyond Accuracy

Unveiling hidden patterns of mental illnesses using machine learning

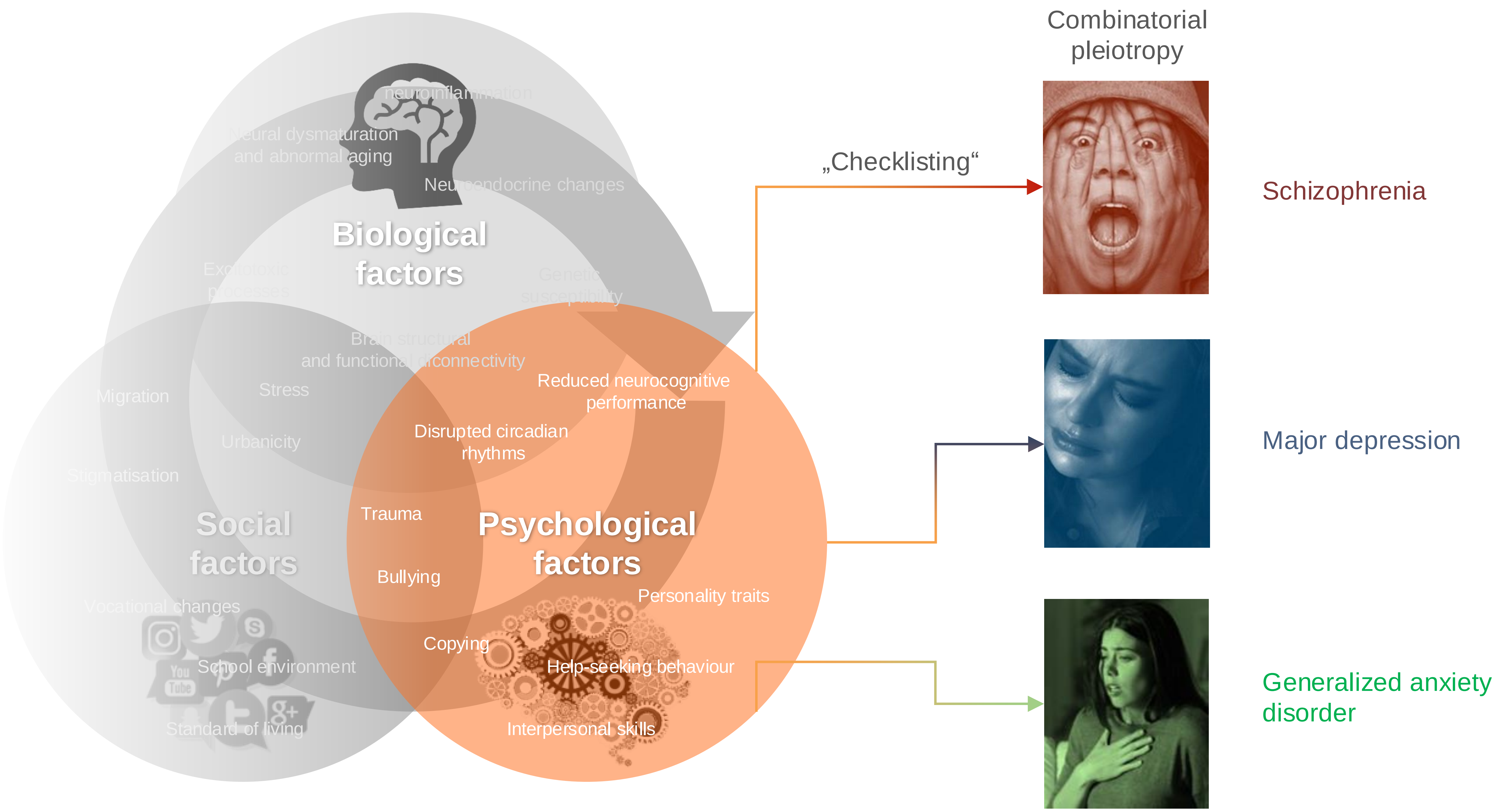
Computational Psychiatry Course
Zurich, 13/09/2023



Nikolaos Koutsouleris
Chair for Precision Psychiatry
LMU & King‘s College London
Max-Planck Fellow for Precision Psychiatry



neuroinflammation
Neural dysmaturation and abnormal aging
Neuroendocrine changes
Biological factors
Excitotoxic processes
Genetic susceptibility
Brain structural and functional diconnectivity
Migration
Stress
Reduced neurocognitive performance
Urbanicity
Disrupted circadian rhythms
Stigmatisation
Social factors
Trauma
Psychological factors
Bullying
Personality traits
Vocational changes
Copying
School environment
Help-seeking behaviour
Standard of living
Interpersonal skills
Psychotic syndromes
Affective syndromes
Anxiety syndromes


Combinatorial pleiotropy
„Checklisting“
Biological factors
neuroinflammation
Neural dysmaturation and abnormal aging
Neuroendocrine changes
Excitotoxic processes
Genetic susceptibility
Brain structural and functional disconnectivity
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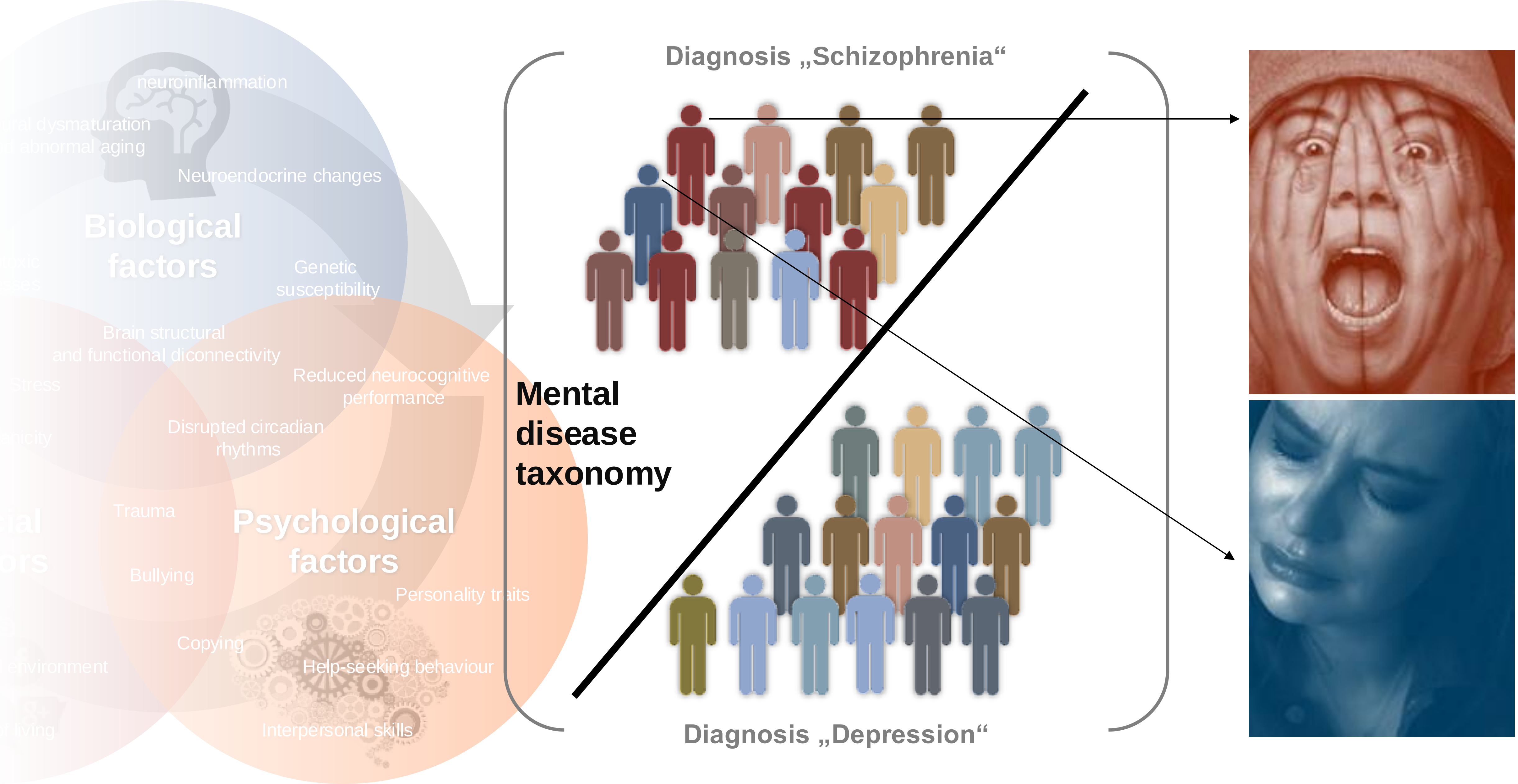
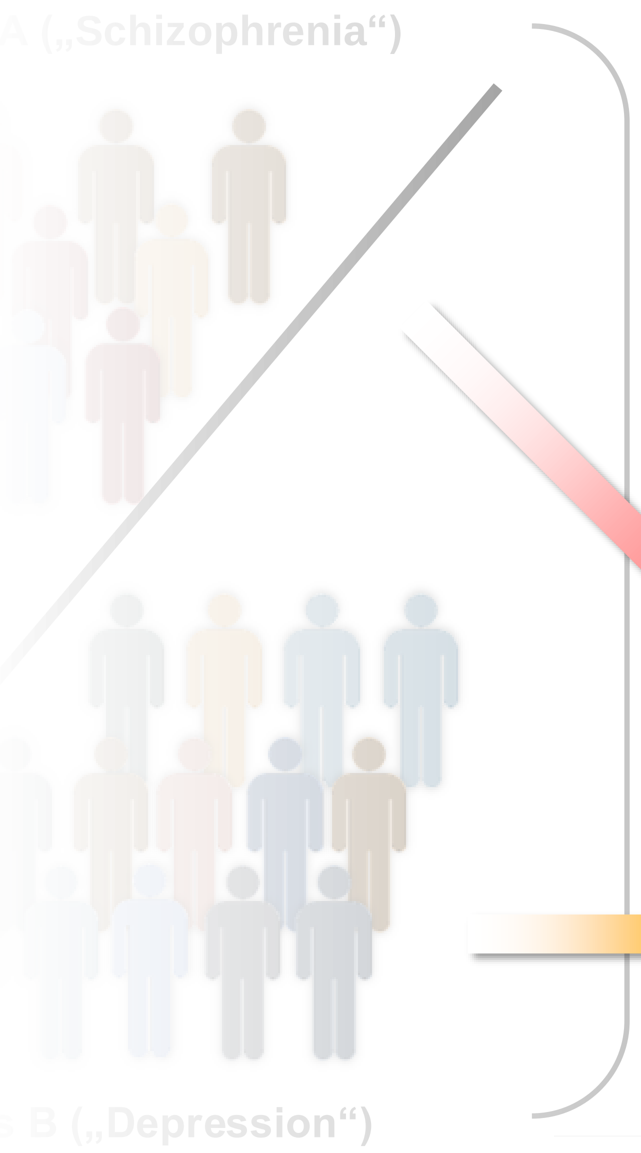
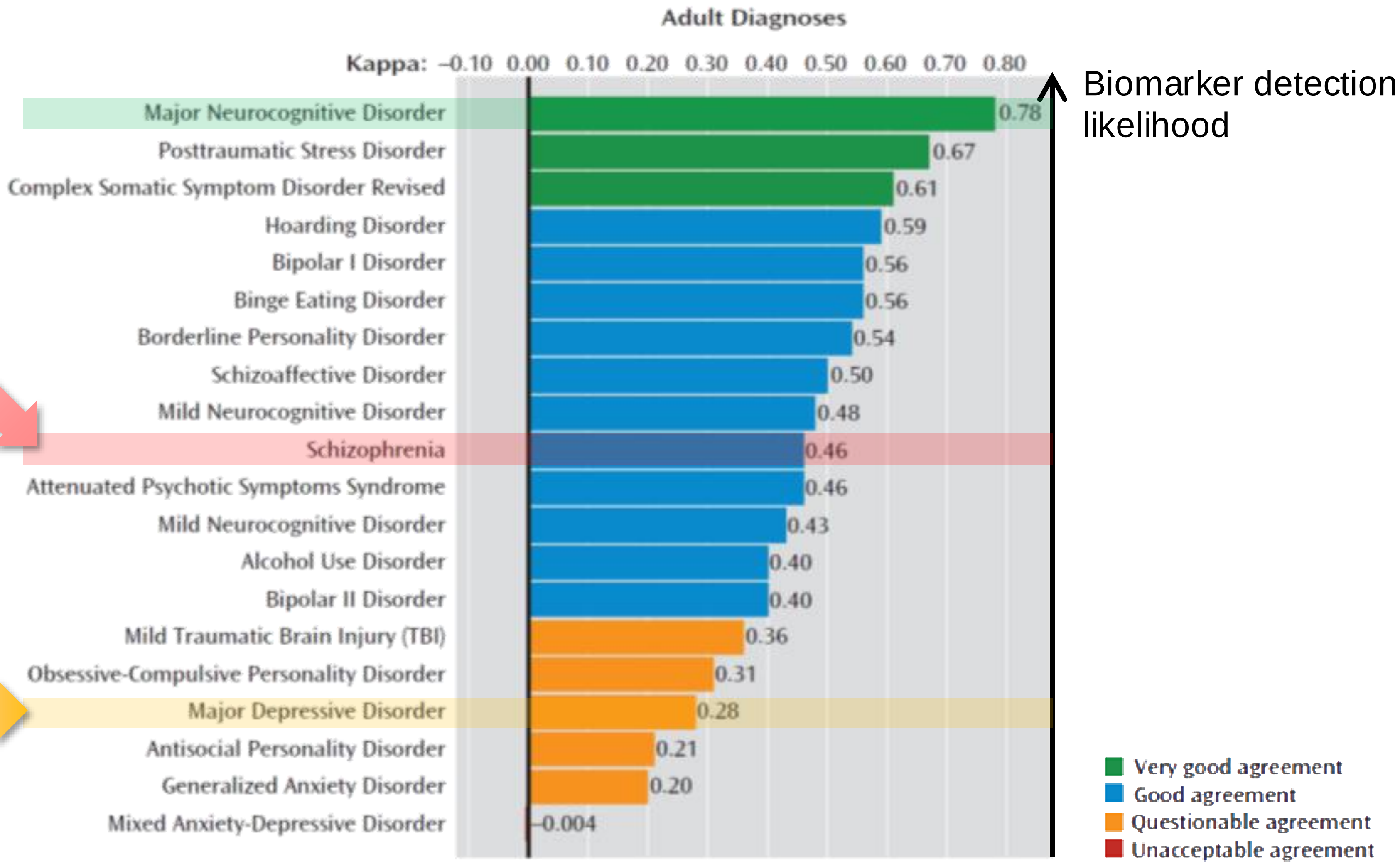
Trauma
Bullying
Copying
Psychological factors
Personality traits
Help-seeking behaviour
Interpersonal skills
Schizophrenia
Major depression
Generalized anxiety disorder



neuroinflammation
Neuroendocrine changes
Biological factors
Genetic susceptibility
Brain structural and functional diconnectivity
Stress
Reduced neurocognitive performance
Disrupted circadian rhythms
Trauma
Psychological factors
Bullying
Personality traits
Copying
Help-seeking behaviour
Interpersonal skills
Diagnosis „Schizophrenia“
Mental disease taxonomy
Diagnosis „Depression“

Inter-rater reliability of diagnoses in the DSM 5





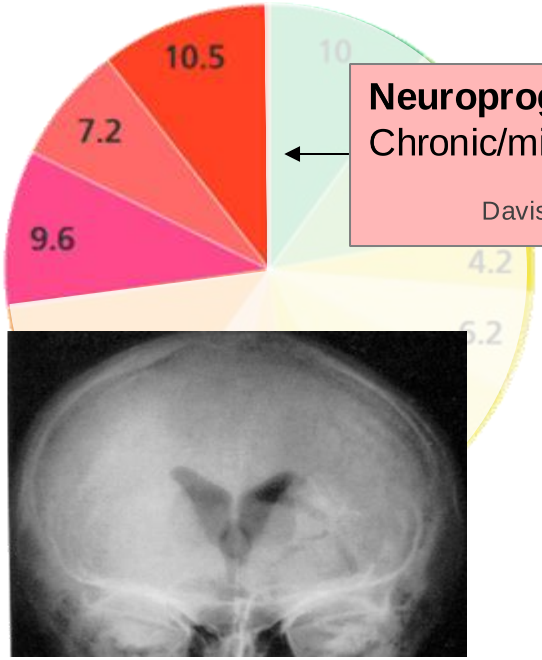
Freedman et al. 2013, AJP

The courses of schizophrenia are highly variable

… and for some patients they are debilitating

502 First-episode patients with psychosis followed over 20 years

Recovery of social functioning in % cases …



- Monophasisch
- Polyphasisch
- Chronisch halluzinatorisch

97-100%

66-90%

- Leicht-phasisch zum Residuum
- Einfach zum Residuum
- Polyphasisch zum Residuum

45-52%

- Polyphasisch zu gemischtem Residuum
- Monophasisch zu klarem Residuum
- Polyphasisch zu schizophrenen Residuum

2-25%

Neuroprogression hypothesis?
Chronic/mild encephalitis

Davis et al. 2014, Aust N Z J Psychiatry, 48(6):512-519

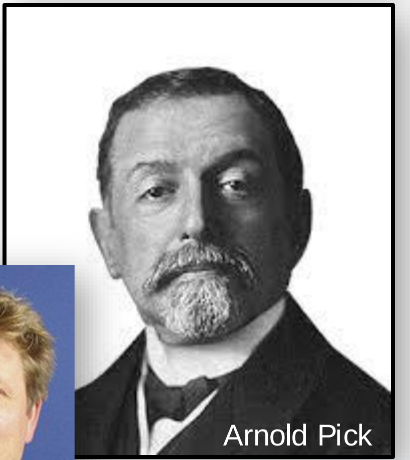
Huber et al. Schizophr Bull,1980;6:592–605.
Huber, Pneumencephalographische und psychopathologische Bilder bei endogenen Psychosen, p.27, 1957

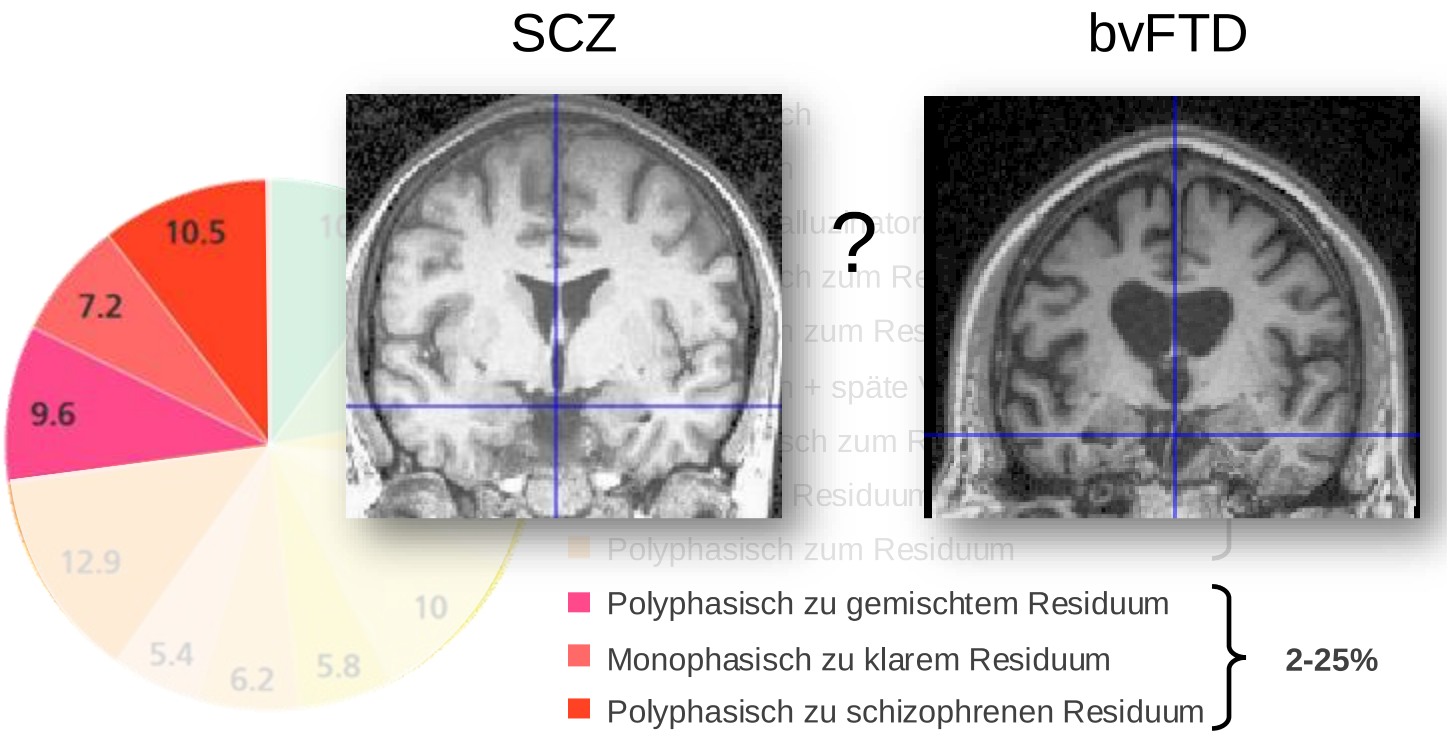
Stage 0 | Stage Ia | Stage Ib | Stage II | Stage III

Age

A century-old hypothesis linking psychosis to dementia


Emil Kraepelin


Arnold Pick



Huber et al. Schizophr Bull,1980;6:592–605.
Huber, Pneumencephalographische und psychopathologische Bilder bei endogenen Psychosen, p.27, 1957

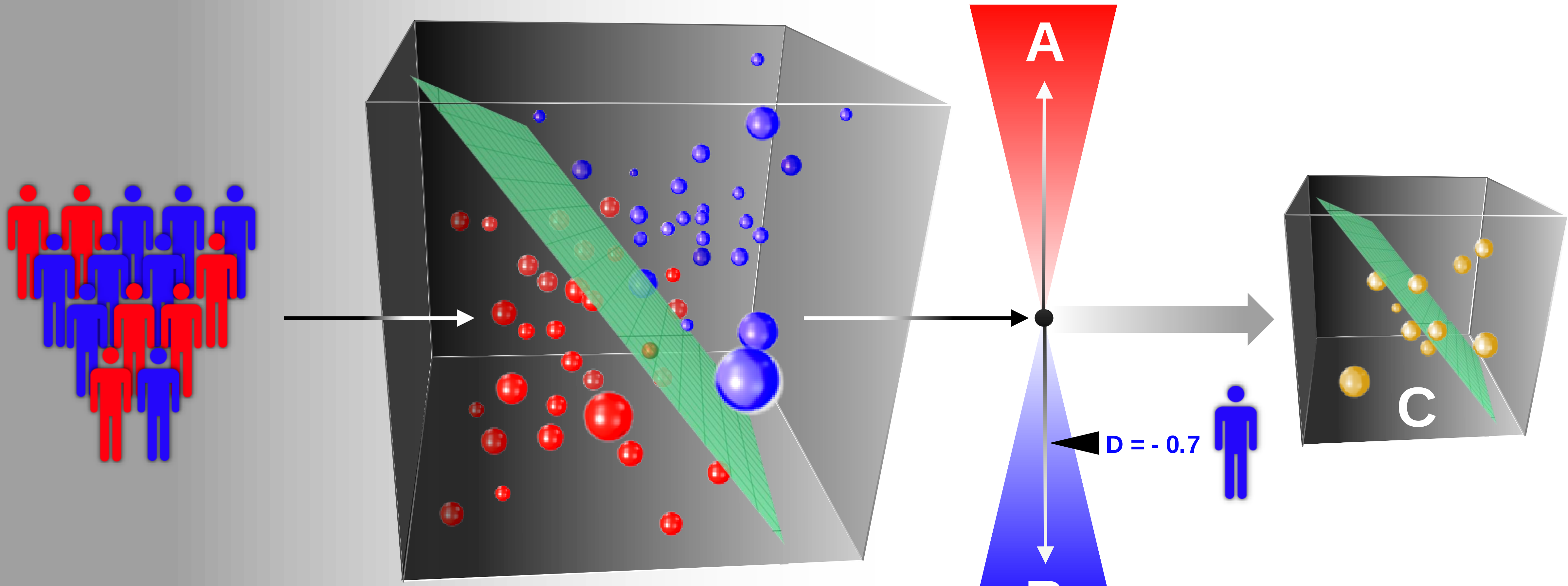
Collaboration with M. Schroeter
MPI for Human Cognitive and Brain Sciences, Leipzig

Stage 0 | Stage Ia | Stage Ib | Stage II | Stage III → Age

1 **Select normative phenotypes**
e.g. bvFTD vs. HC

2 **Develop and validate a multivariate surrogate (similarity) space**
e.g. using Support Vector Machines

3 **Apply similarity space to other phenotypes**
e.g. to schizophrenia

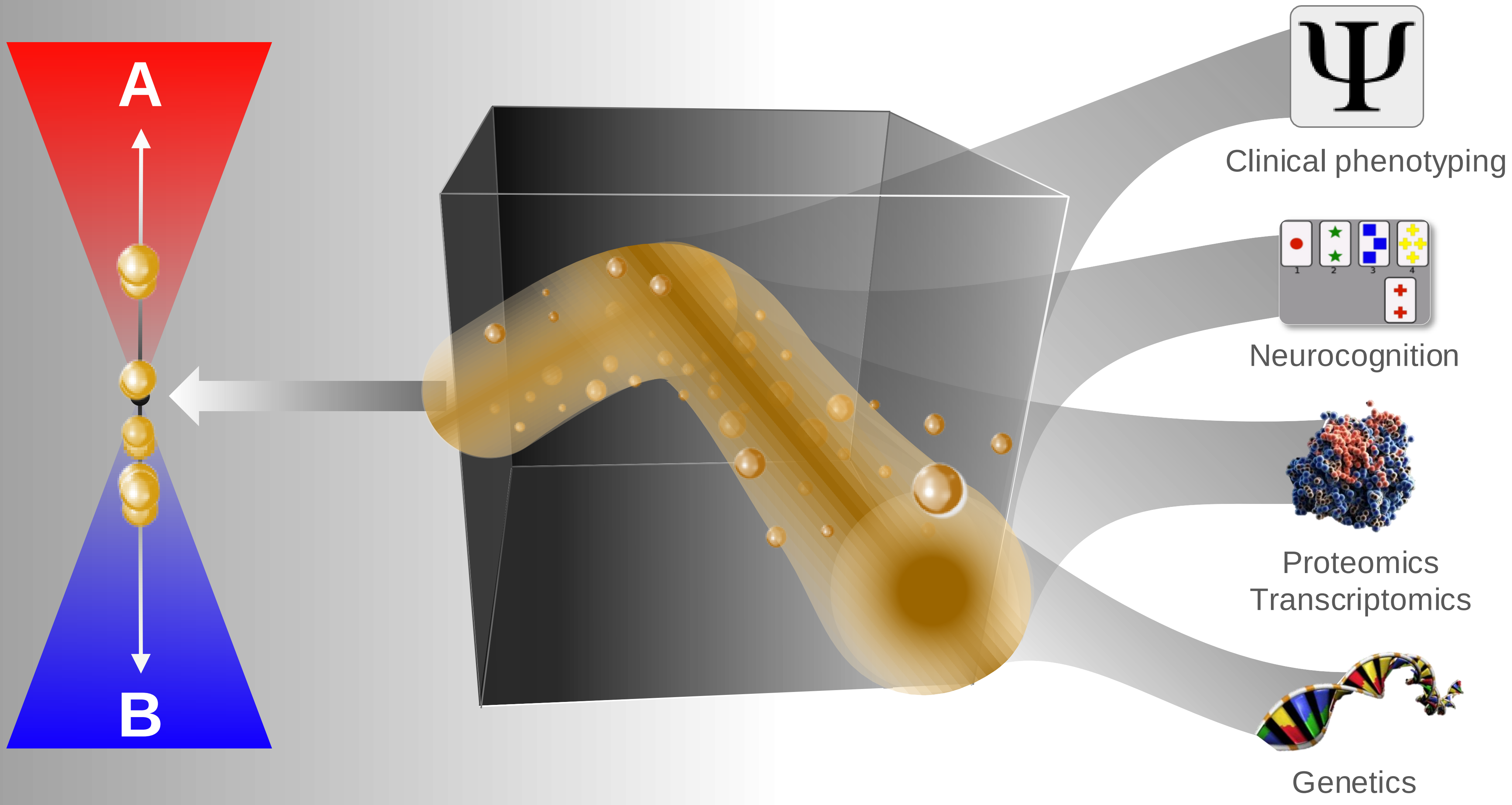


$$h(\boldsymbol{x}_i) = sign\left(\sum_{j=1}^{s} \alpha_j \; y_j \; K(\boldsymbol{x}_j, \boldsymbol{x}_i) + b \right)$$

$$K(\boldsymbol{v}, \boldsymbol{v}') = \exp\left(\frac{||\boldsymbol{v} - \boldsymbol{v}'||^2}{2\gamma^2}\right)$$

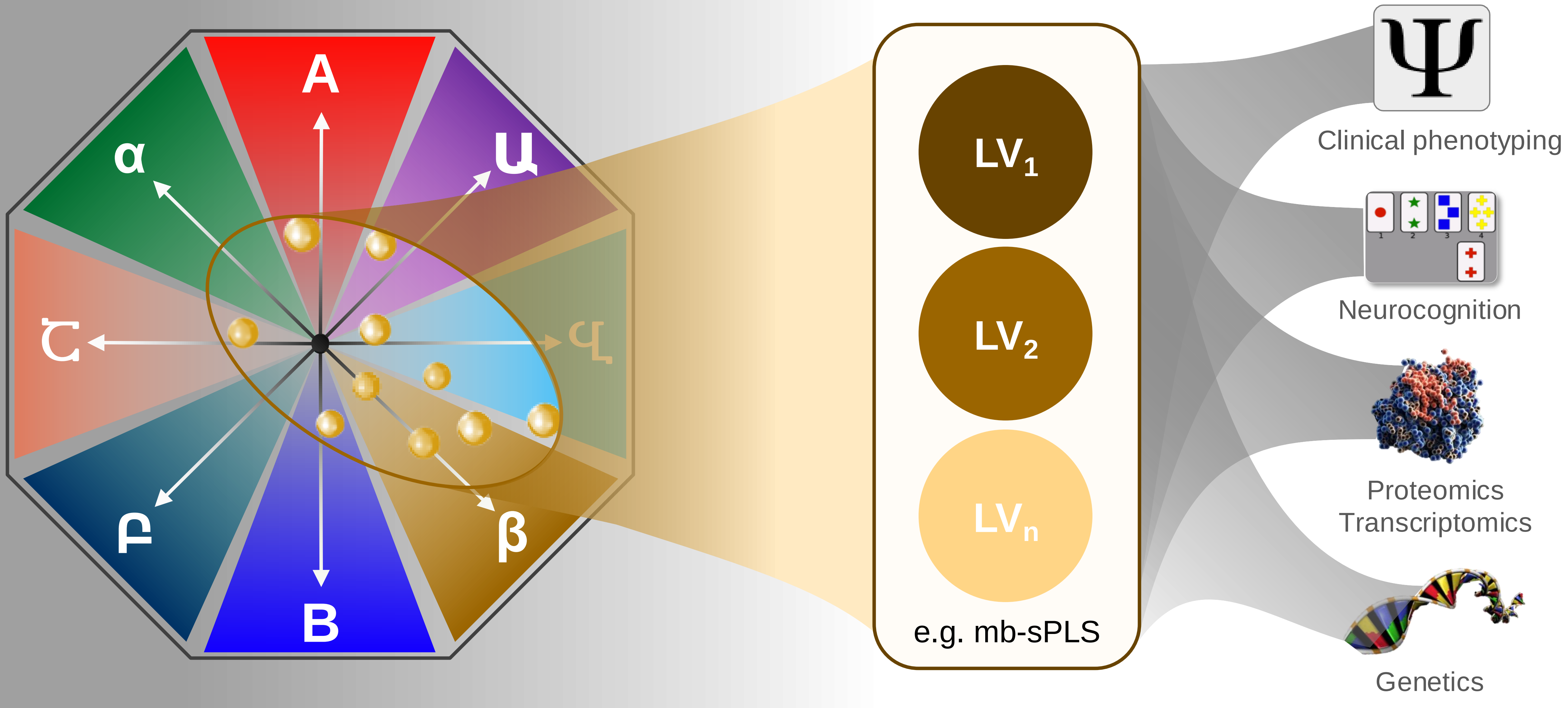
4a **Explain similarity by using biopsychosocial modelling that can predict expression scores at the individual level**

e.g. by using support vector regression

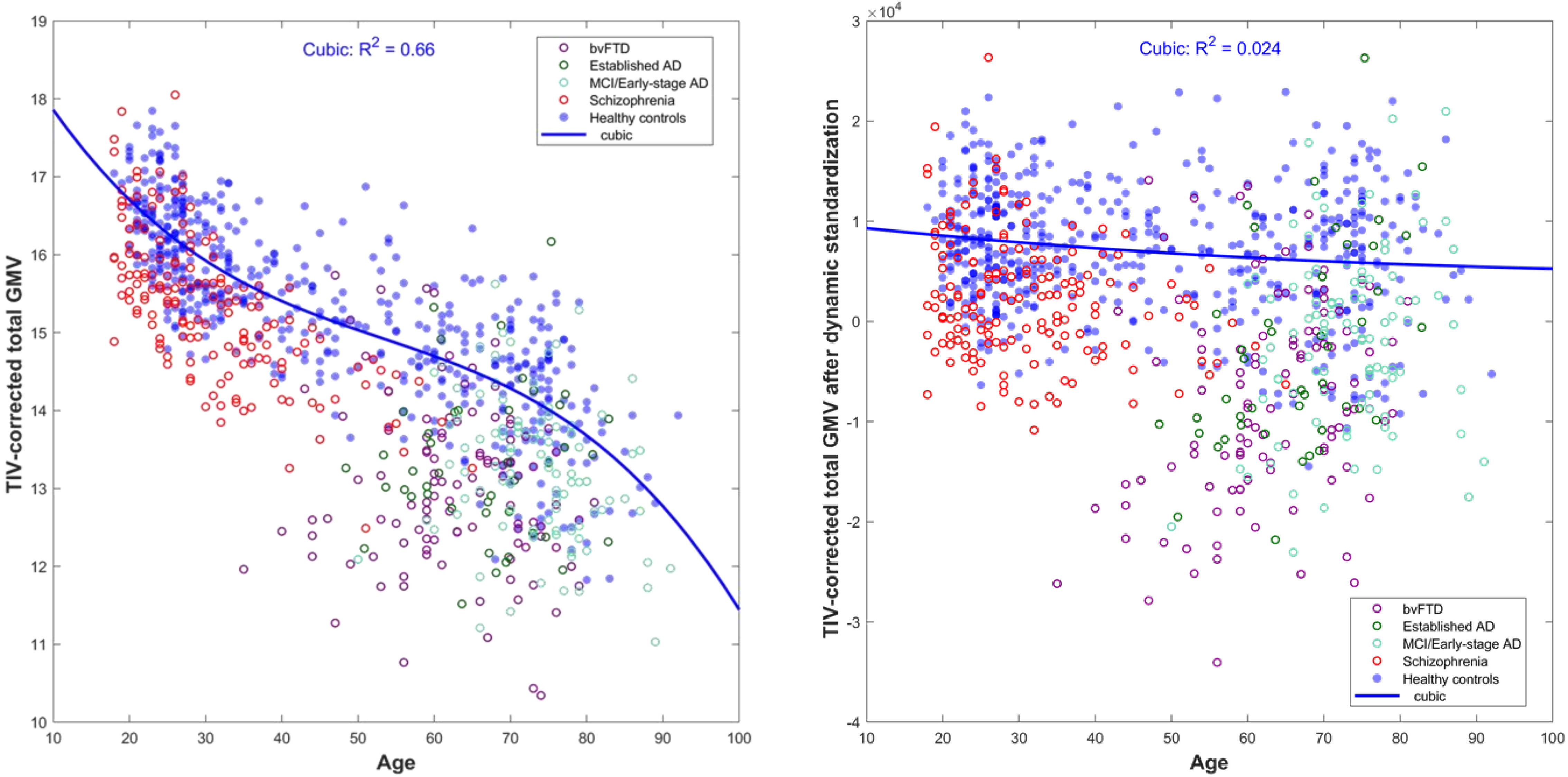


4b **Deconvolve heterogeneity by spanning multiple relevant similarity spaces**
e.g. bvFTD vs. HC, functional impairments, BrainAGE, etc.

5 **Model and understand biopsychosocial patterns embedded in mapping**
e.g. using factorization methods

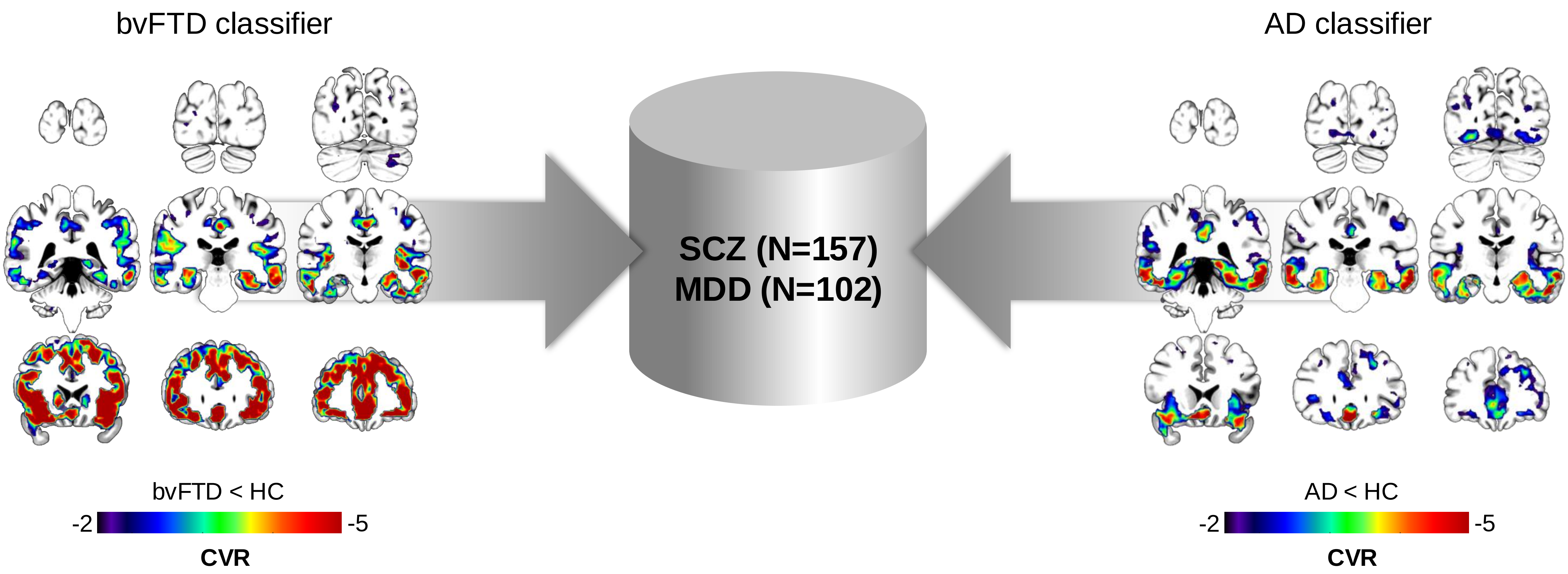


Adjusting for age effects is crucial



Comparing volumetric pattern expression across diagnoses

Do patients with SCZ (or MD) have an increased bvFTD (or AD) score?

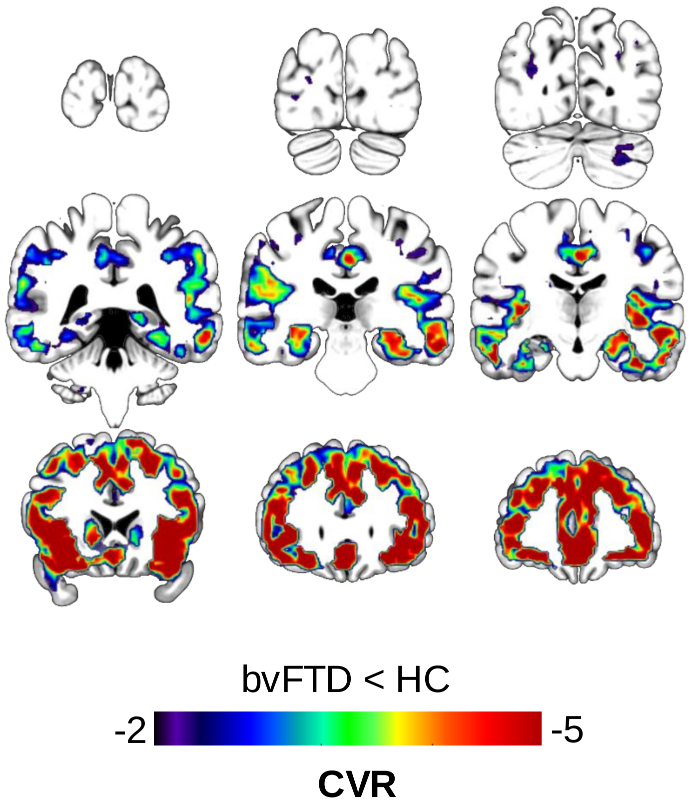


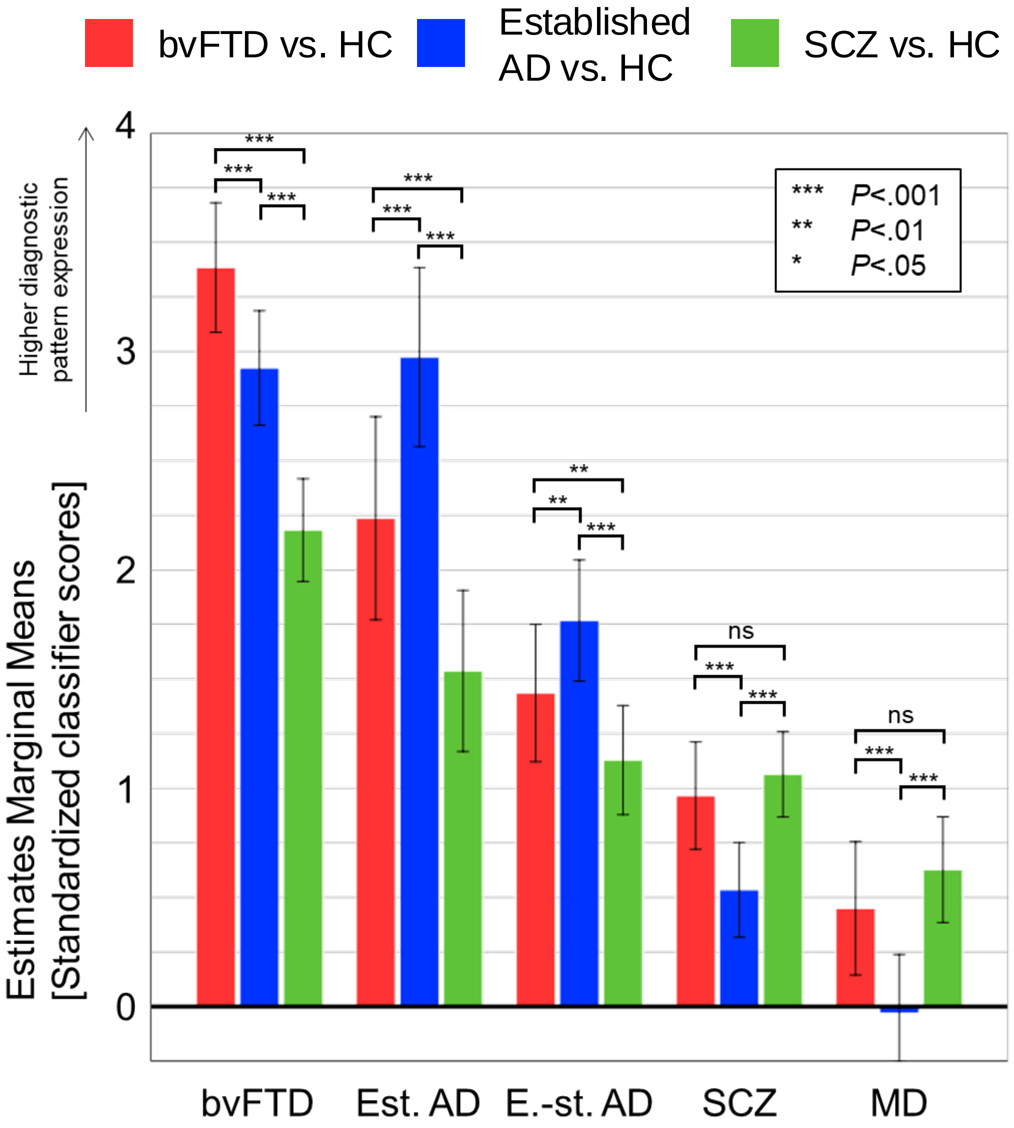
Koutsouleris et al. 2022, JAMA Psychiatry

Comparing volumetric pattern expression across diagnoses

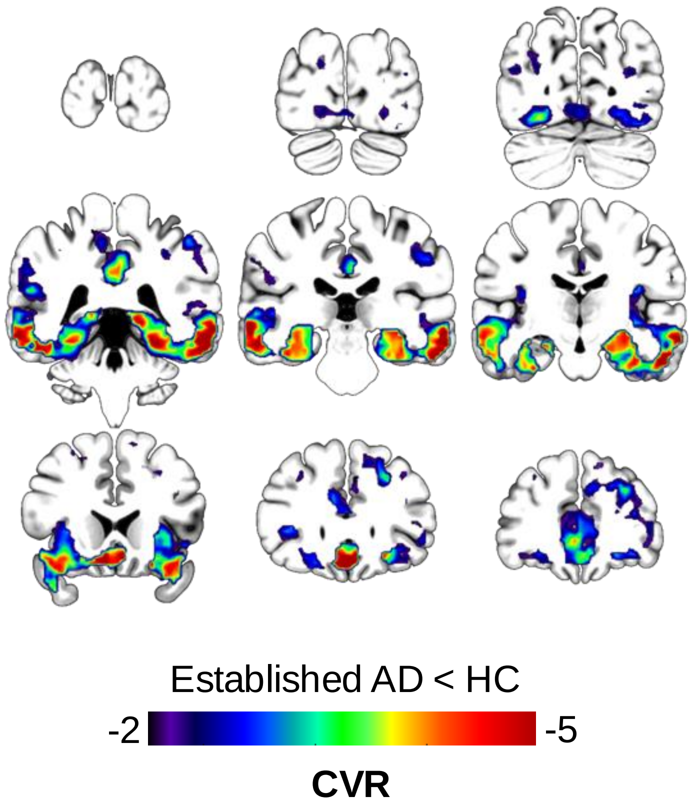
Do patients with SCZ (or MD) have an increased bvFTD score?

bvFTD classifier





AD classifier



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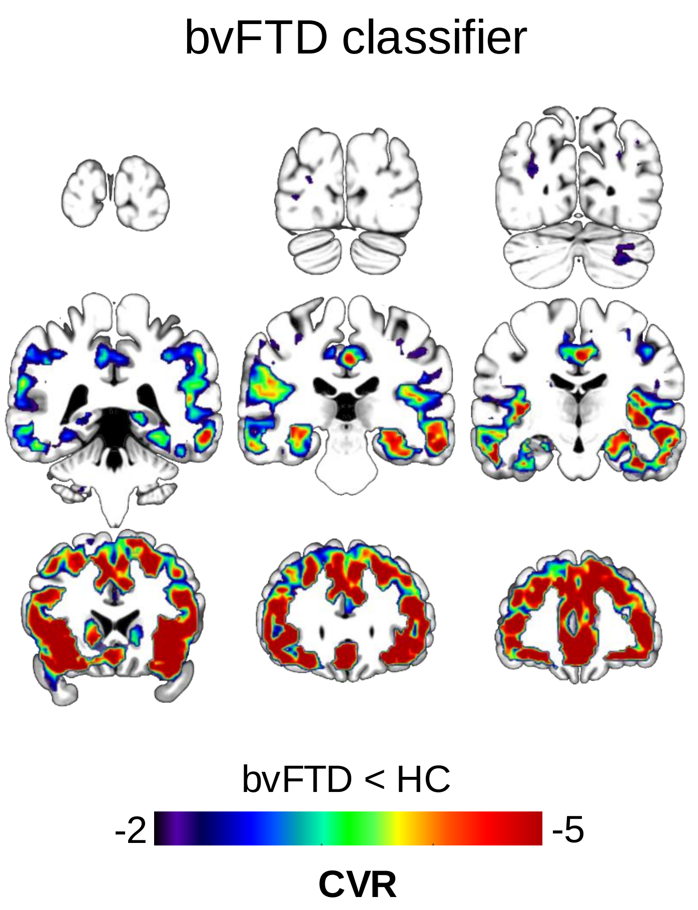
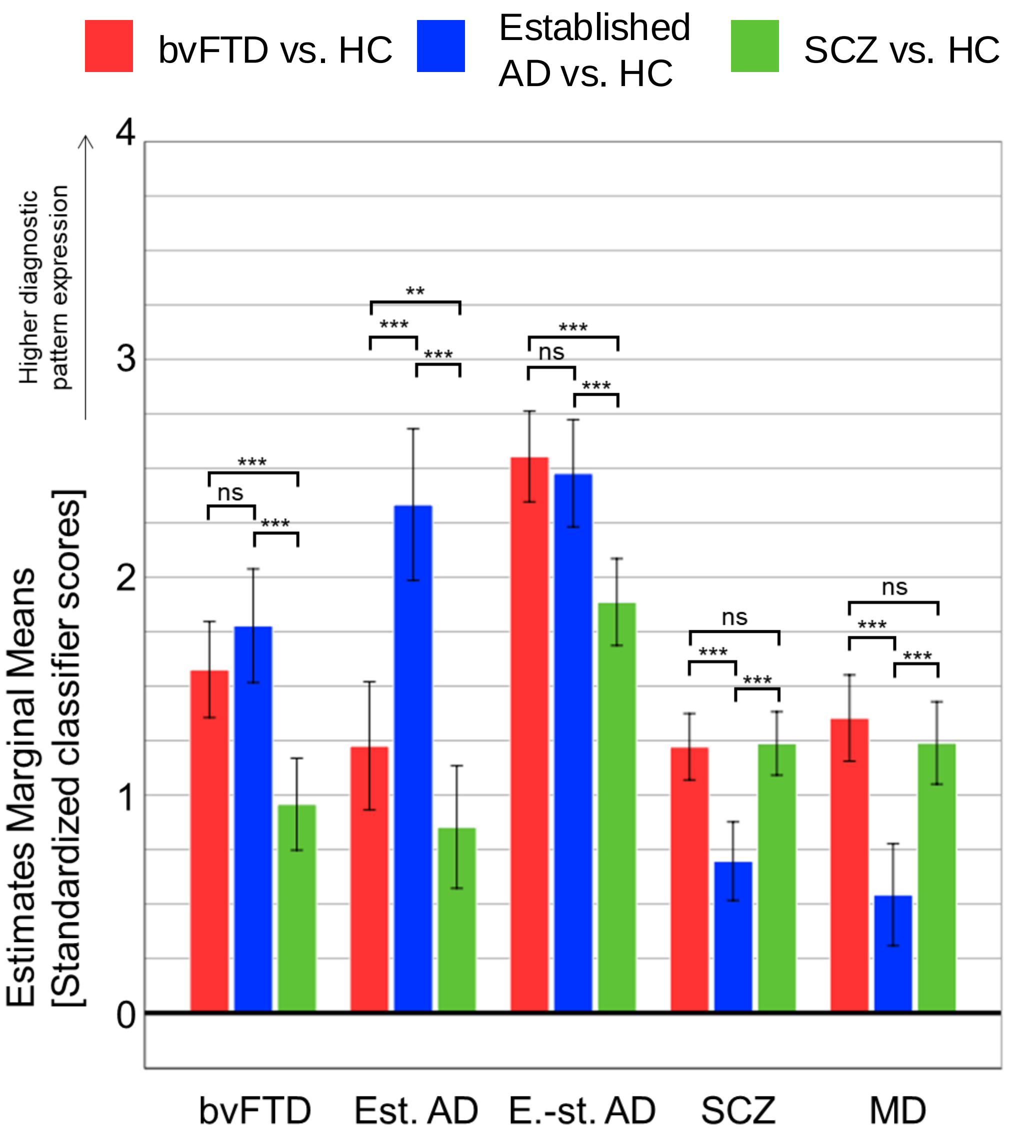
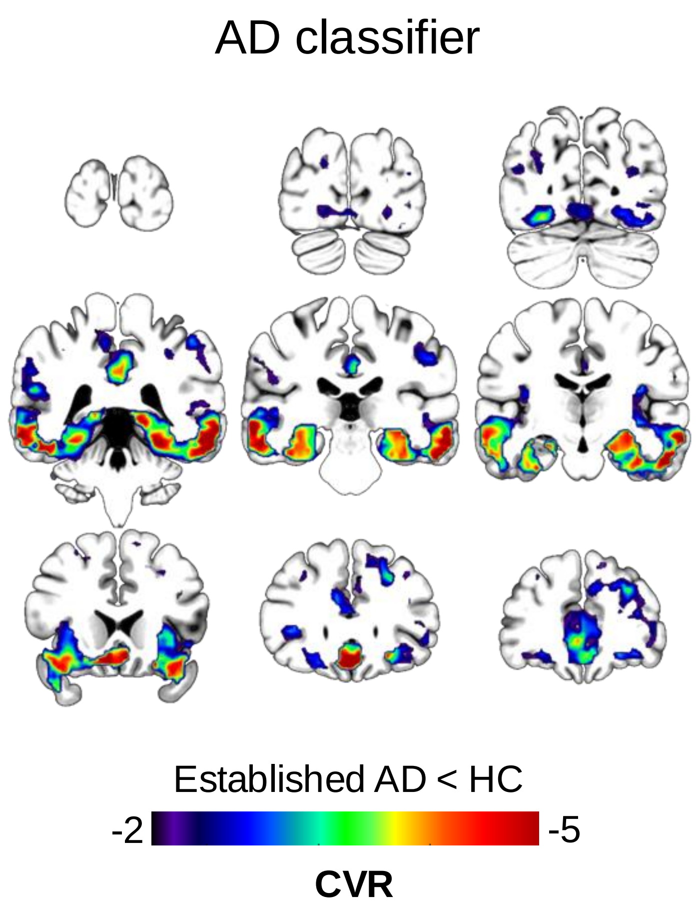


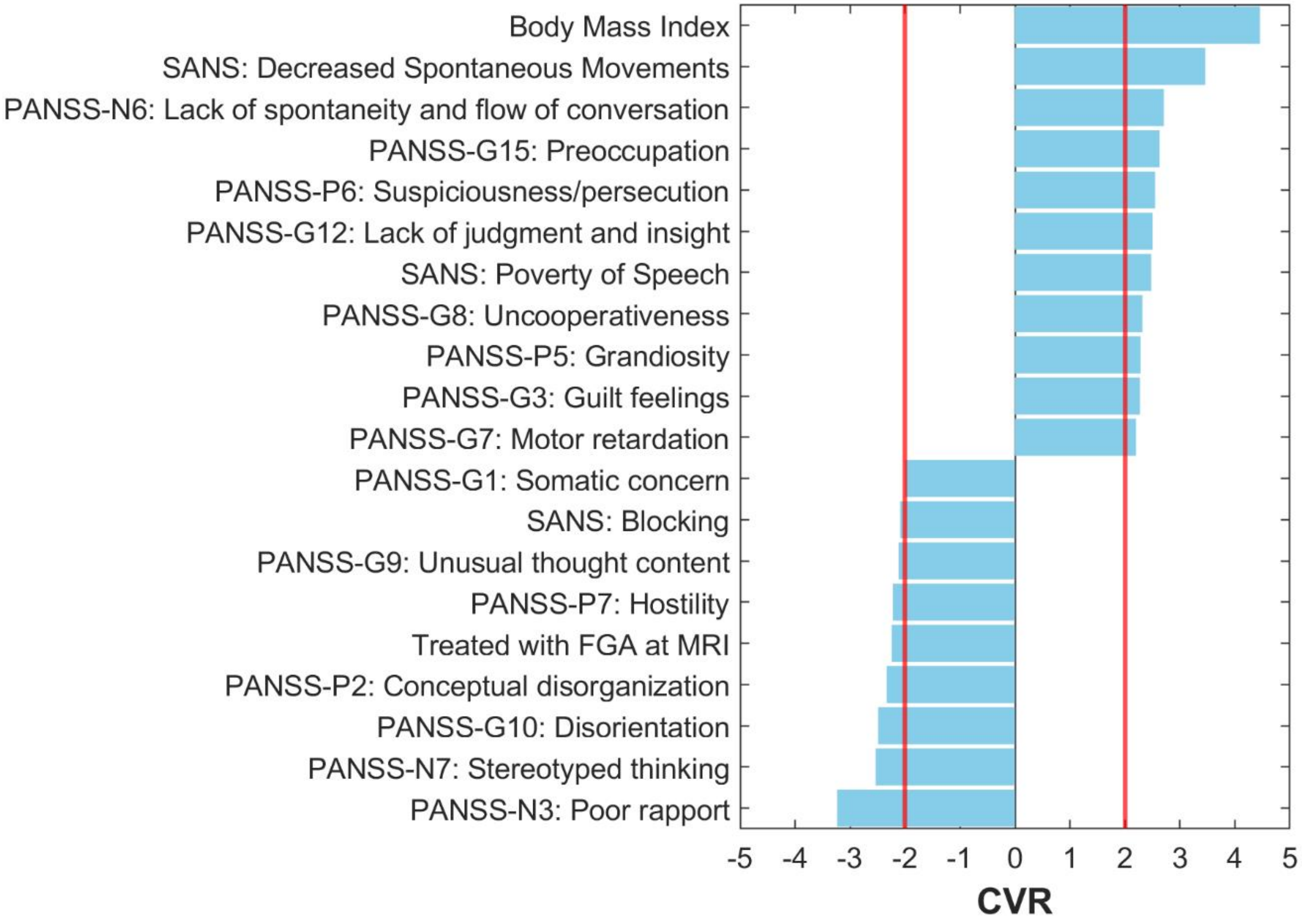


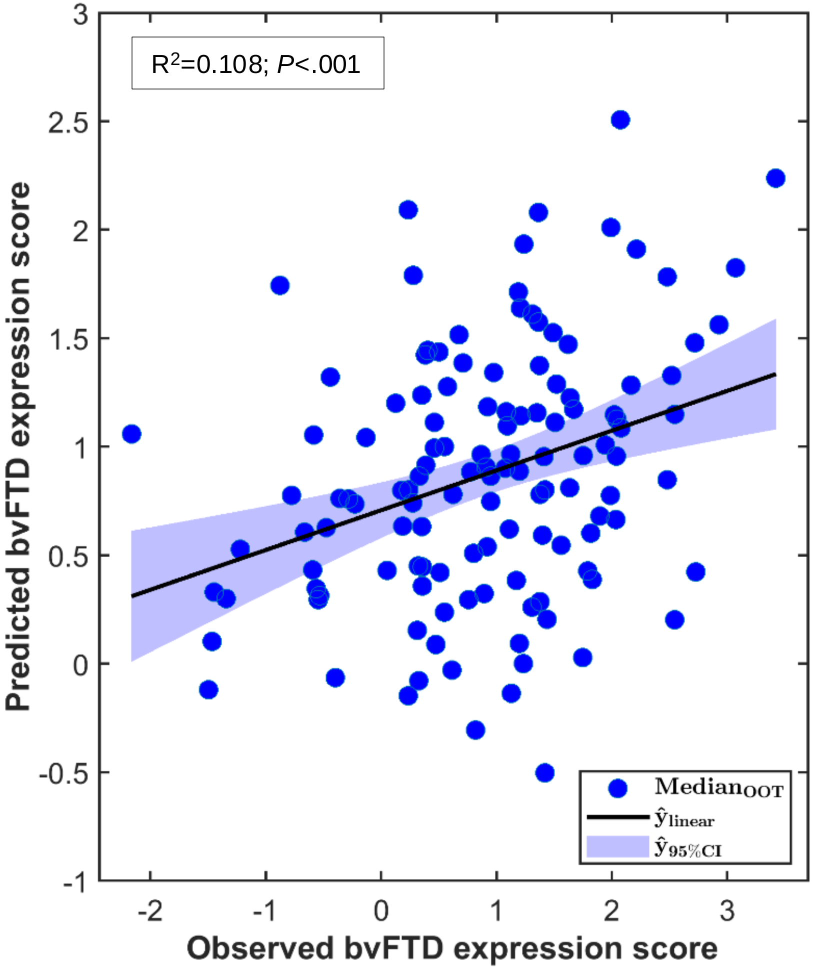


Koutsouleris et al. 2022, JAMA Psychiatry

Understanding clinical heterogeneity

… and what does an increased bvFTD expression mean for clinical phenotypes in SCZ?





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Understanding clinical heterogeneity

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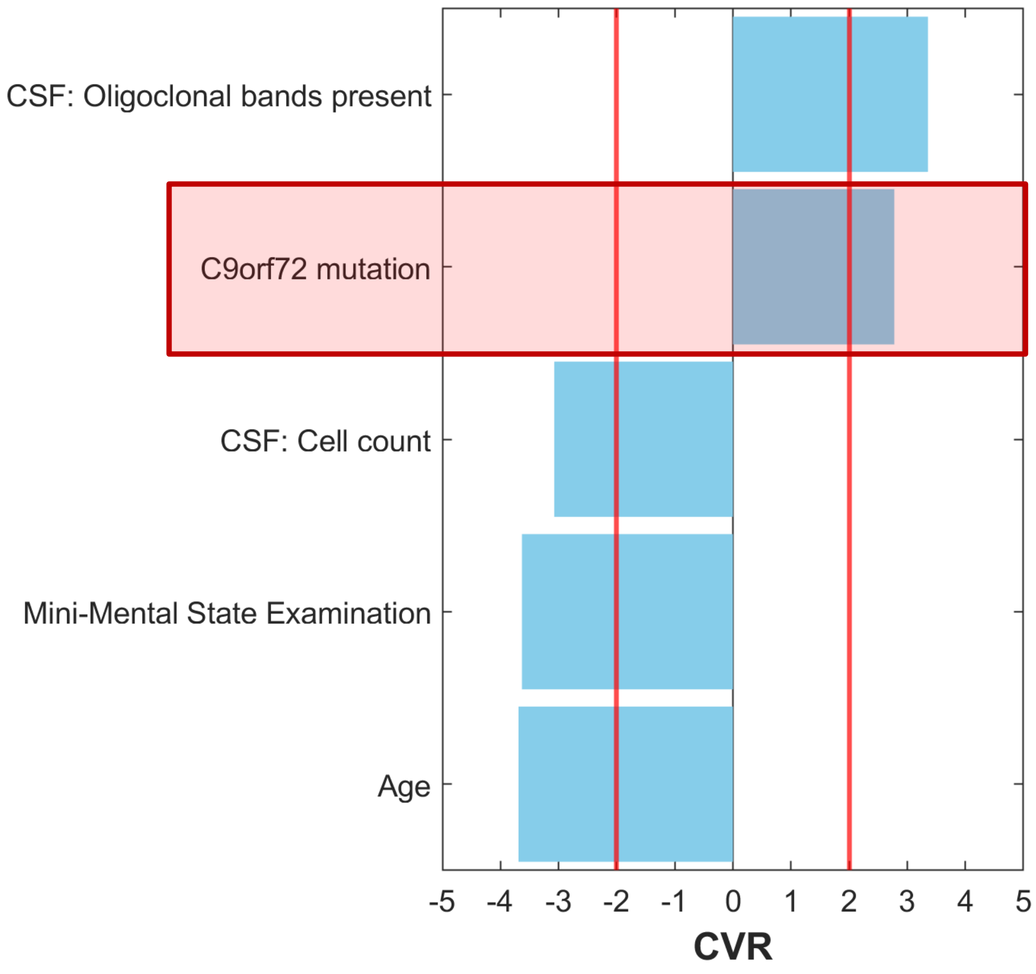
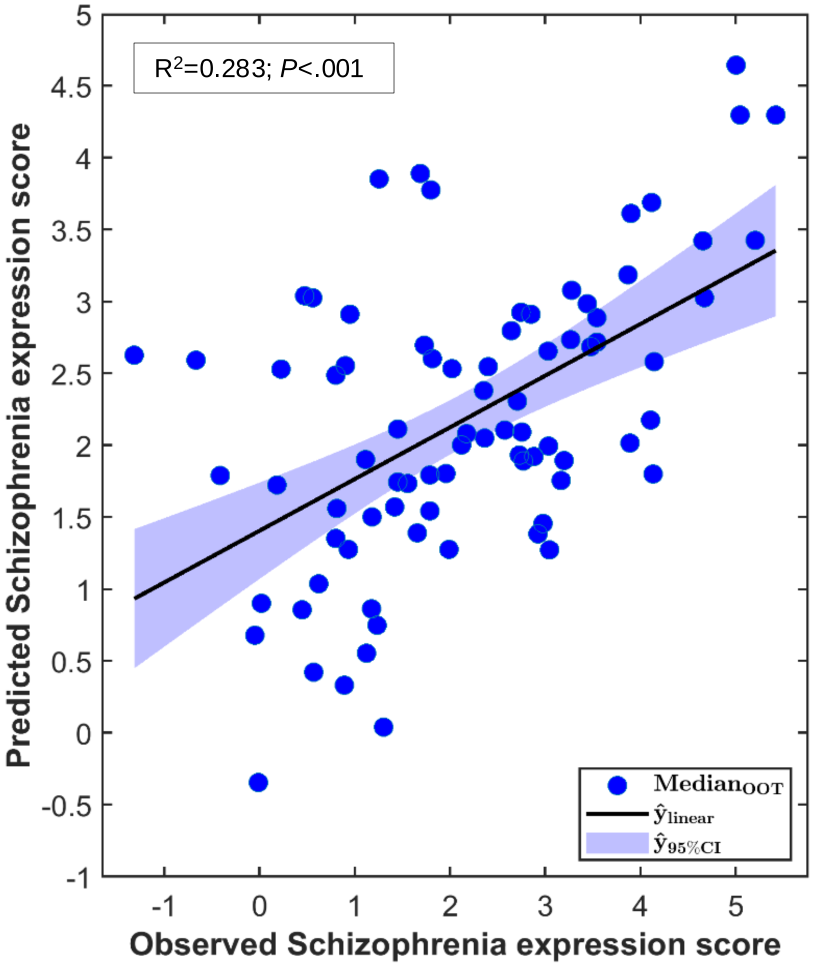
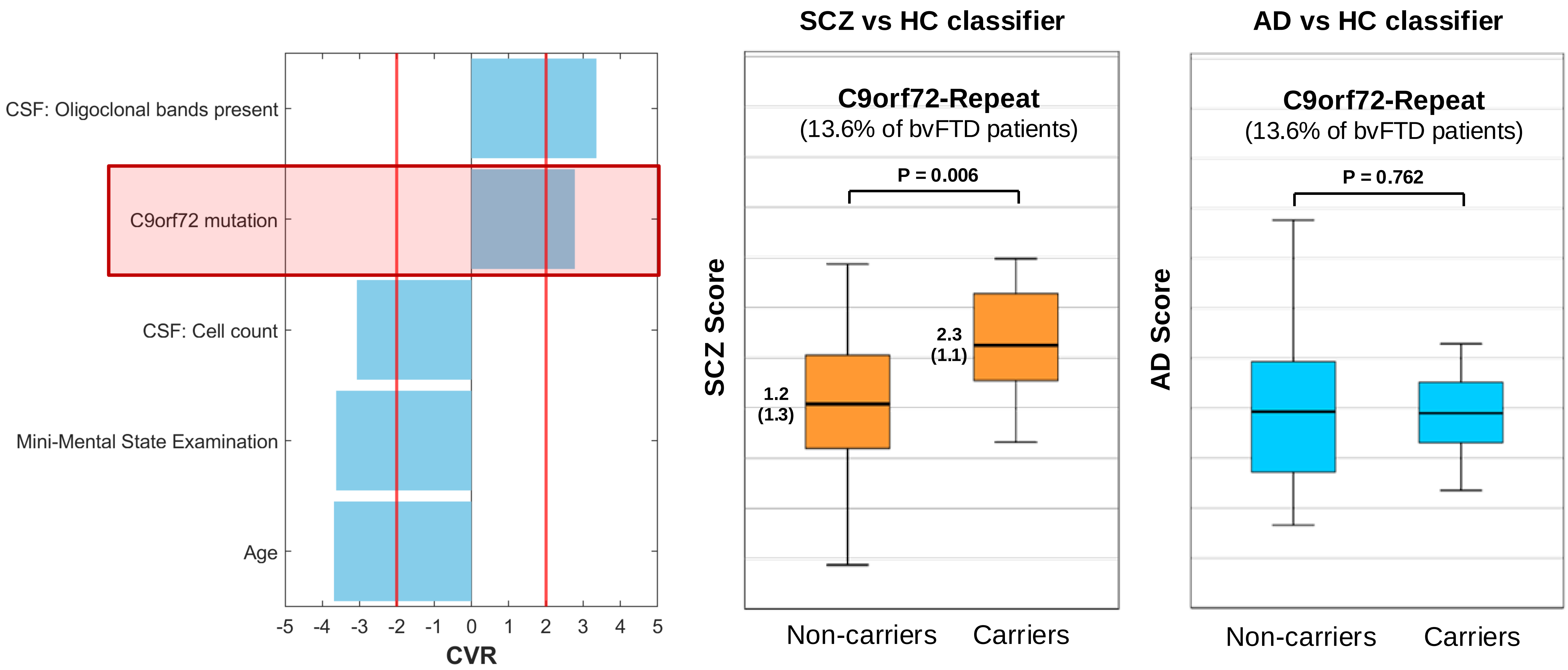




Koutsouleris et al. 2022, JAMA Psychiatry

Understanding clinical heterogeneity

The molecular underpinnings of an increased neuroanatomical SCZ likeness in bvFTD



Koutsouleris et al. 2022, JAMA Psychiatry

Understanding clinical heterogeneity

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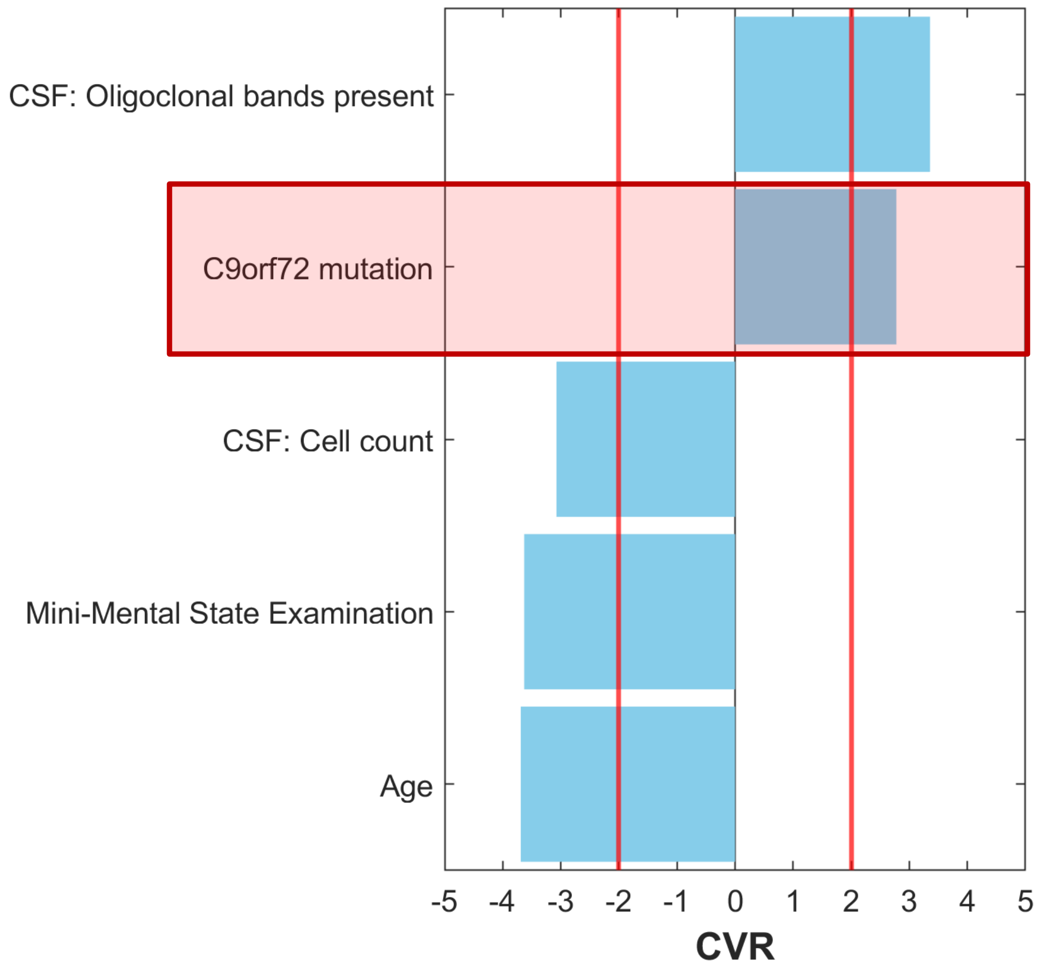



ARTICLE

Psychiatric disorders in *C9orf72* kindreds

Study of 1,414 family members

Emma M. Devenney, MBBChBAO, Rebekah M. Ahmed, MBBS, Glenda Halliday, PhD, Olivier Piguet, PhD, Matthew C. Kiernan, DSc, FRACP, and John R. Hodges, MD

Neurology® 2018;91:e1498-e1507. doi:10.1212/WNL.0000000000006344

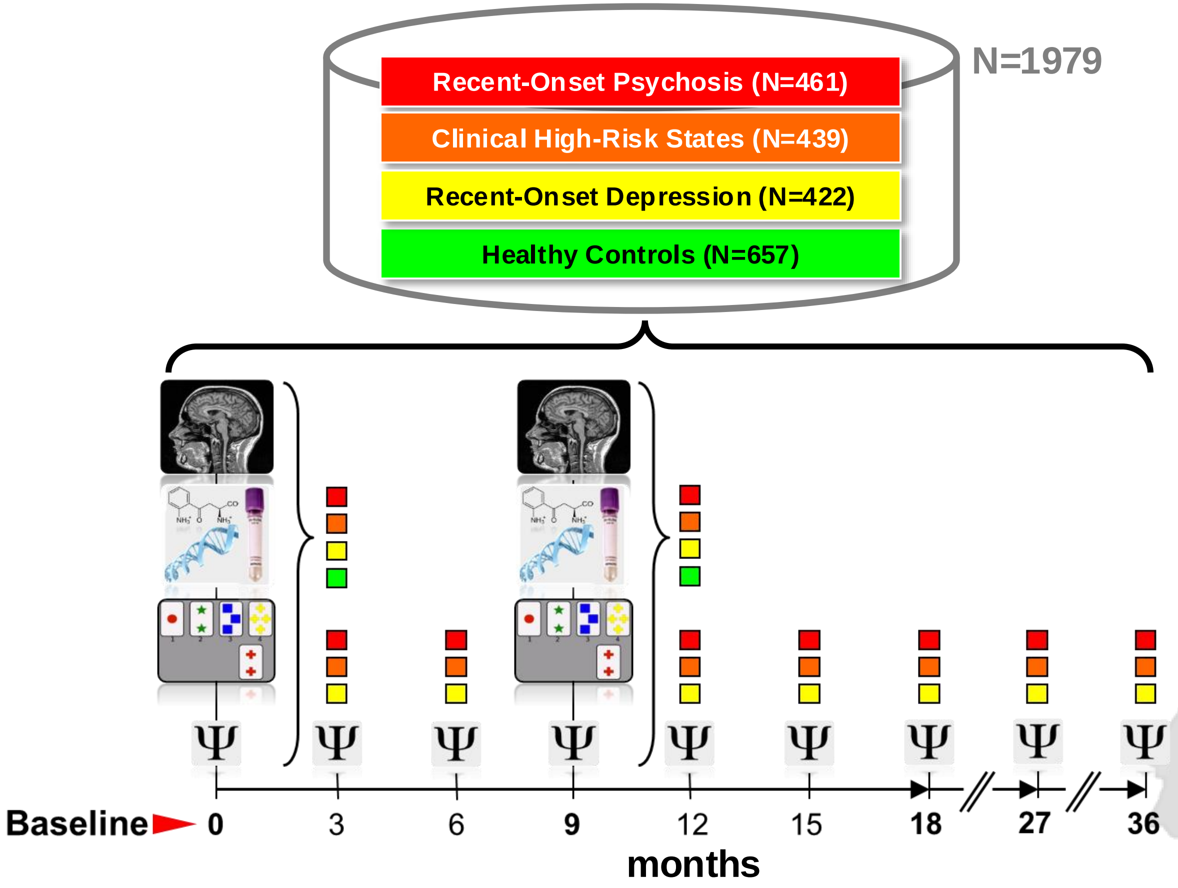
Correspondence
Dr. Devenney
Emma.devenney@sydney.edu.au

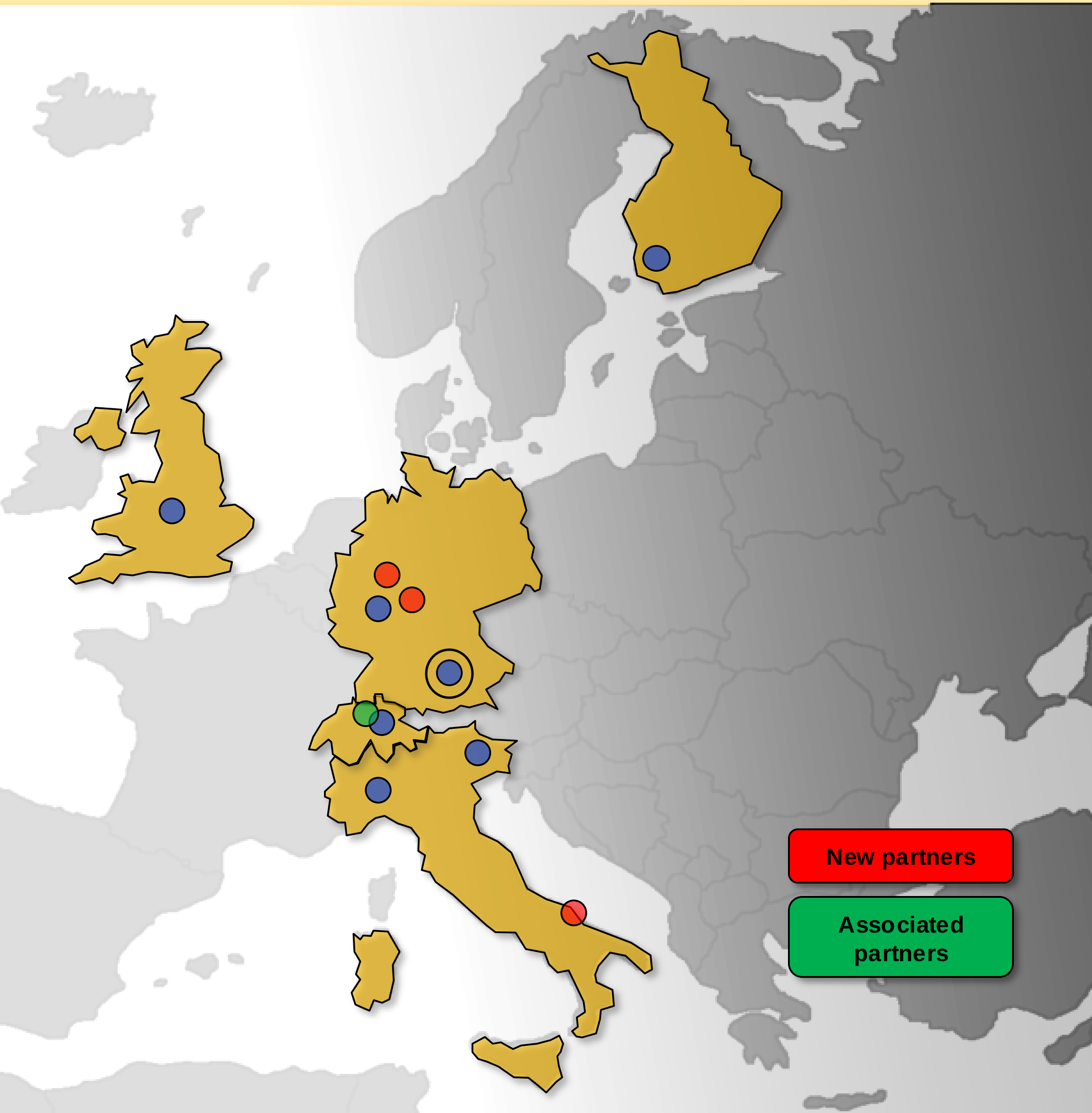
- The *Chromosome 9 open reading frame 72 (C9orf72)* - Expansion (>30 Repeats) is associated with psychotic/bipolar prodromes/courses of bvFTD.
- Hazard Ratio (HR) for schizophrenia is **4.9** and HR for psychosis is **17.9** in relatives of C9orf72-Carriern with bvFTD.

Koutsouleris et al. 2022, JAMA Psychiatry

Understanding the heterogeneity of early psychosis

Valid stratification models require representative training and validation cohorts

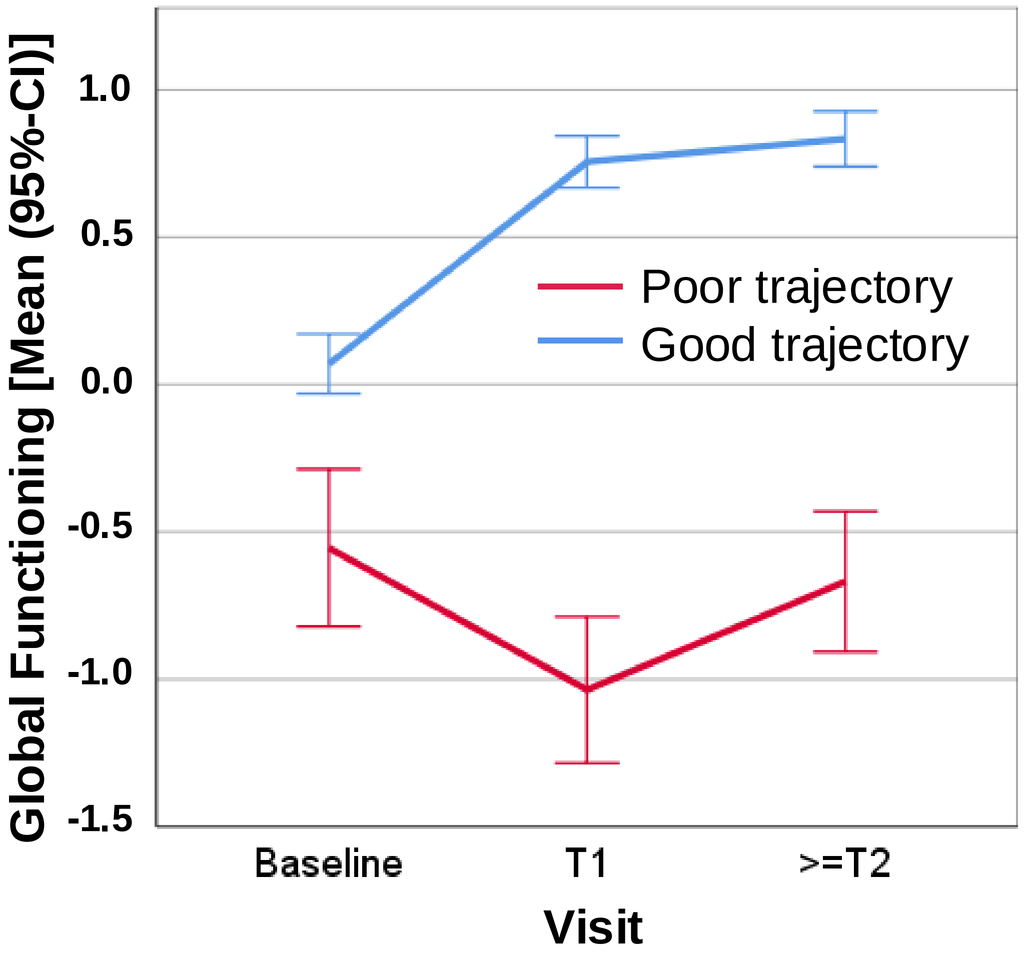




Understanding outcome heterogeneity

Can we link bvFTD pattern expression with very poor outcome in CHR / ROD patients ?

Poor trajectory: average follow-up functing score <= 25% percentile of the baseline sample



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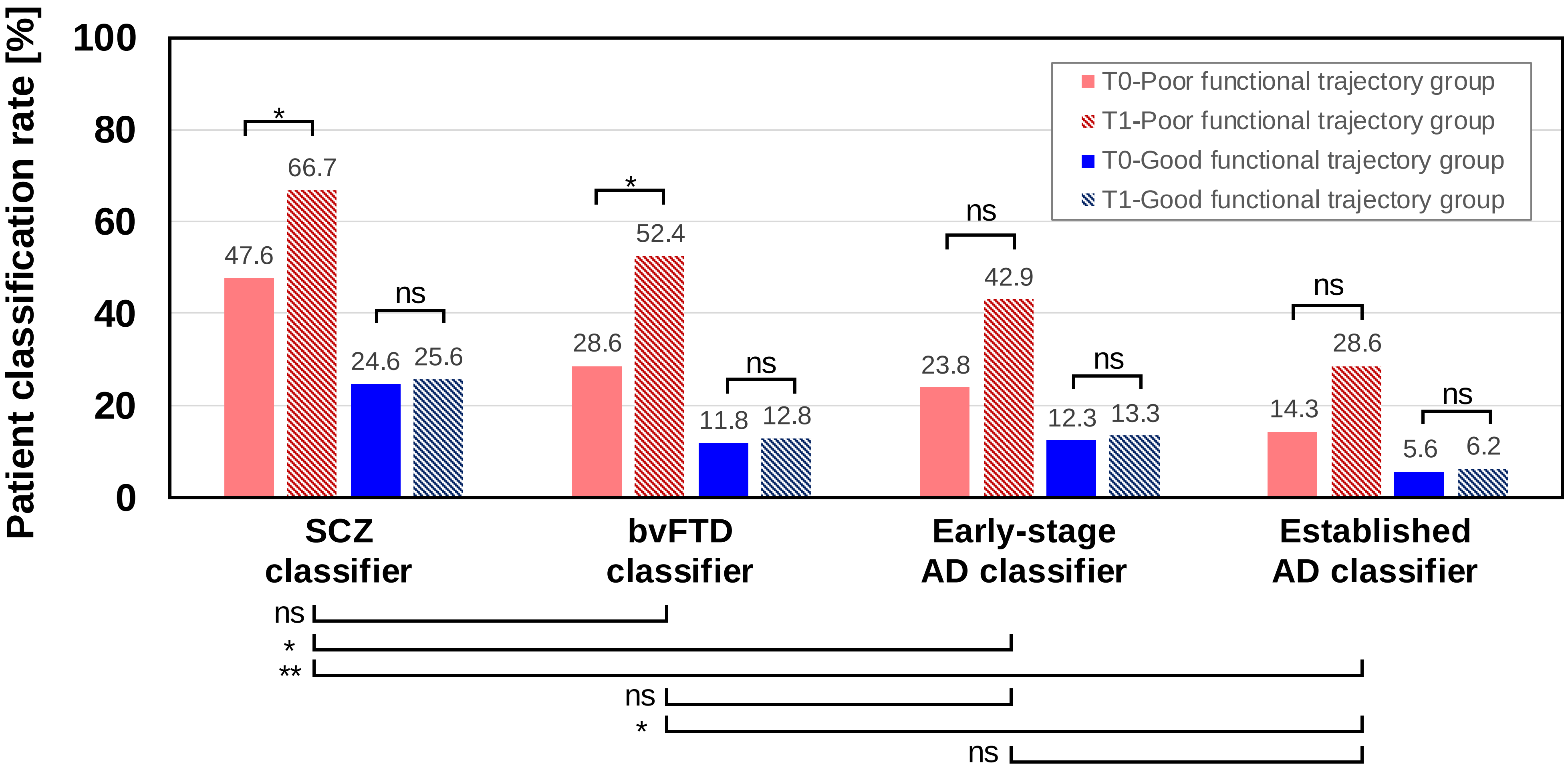
Understanding outcome heterogeneity

One way to look at this potential link is by testing the neuroprogression hypothesis



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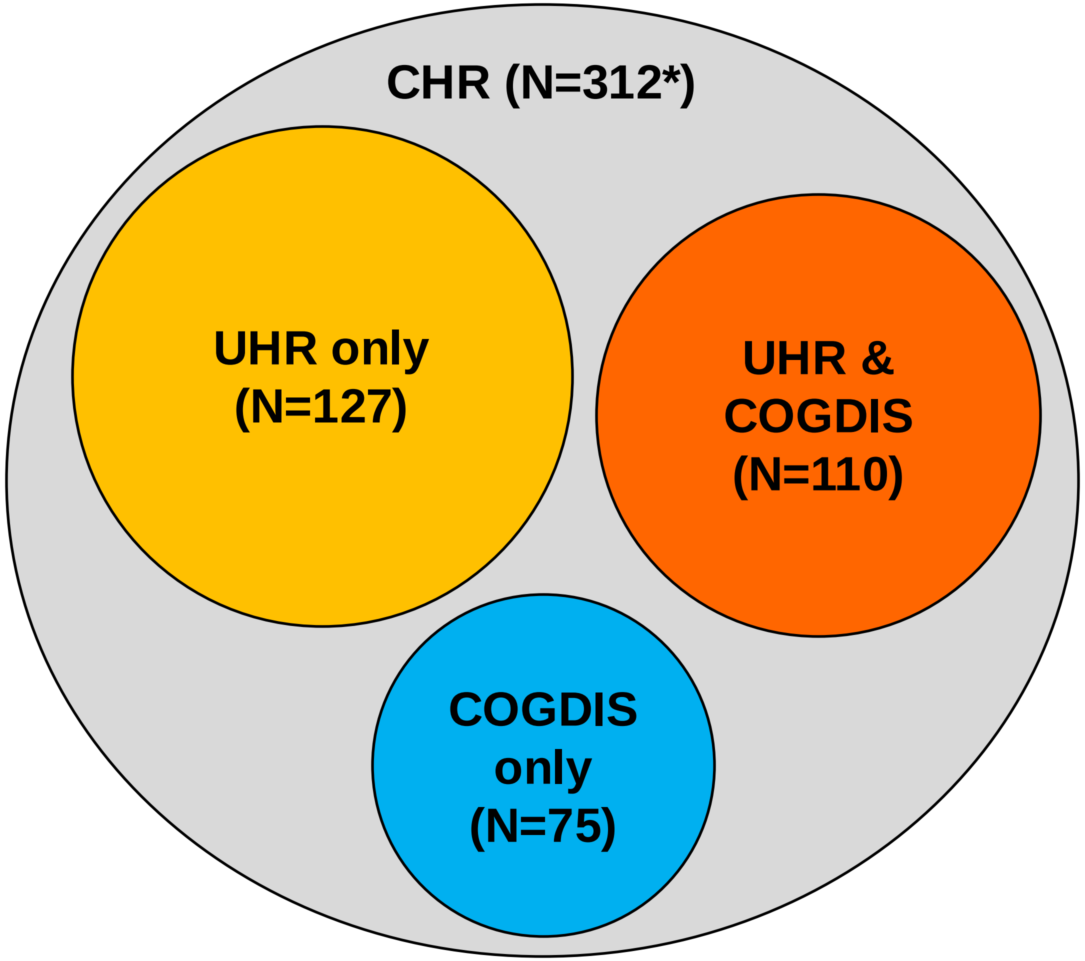
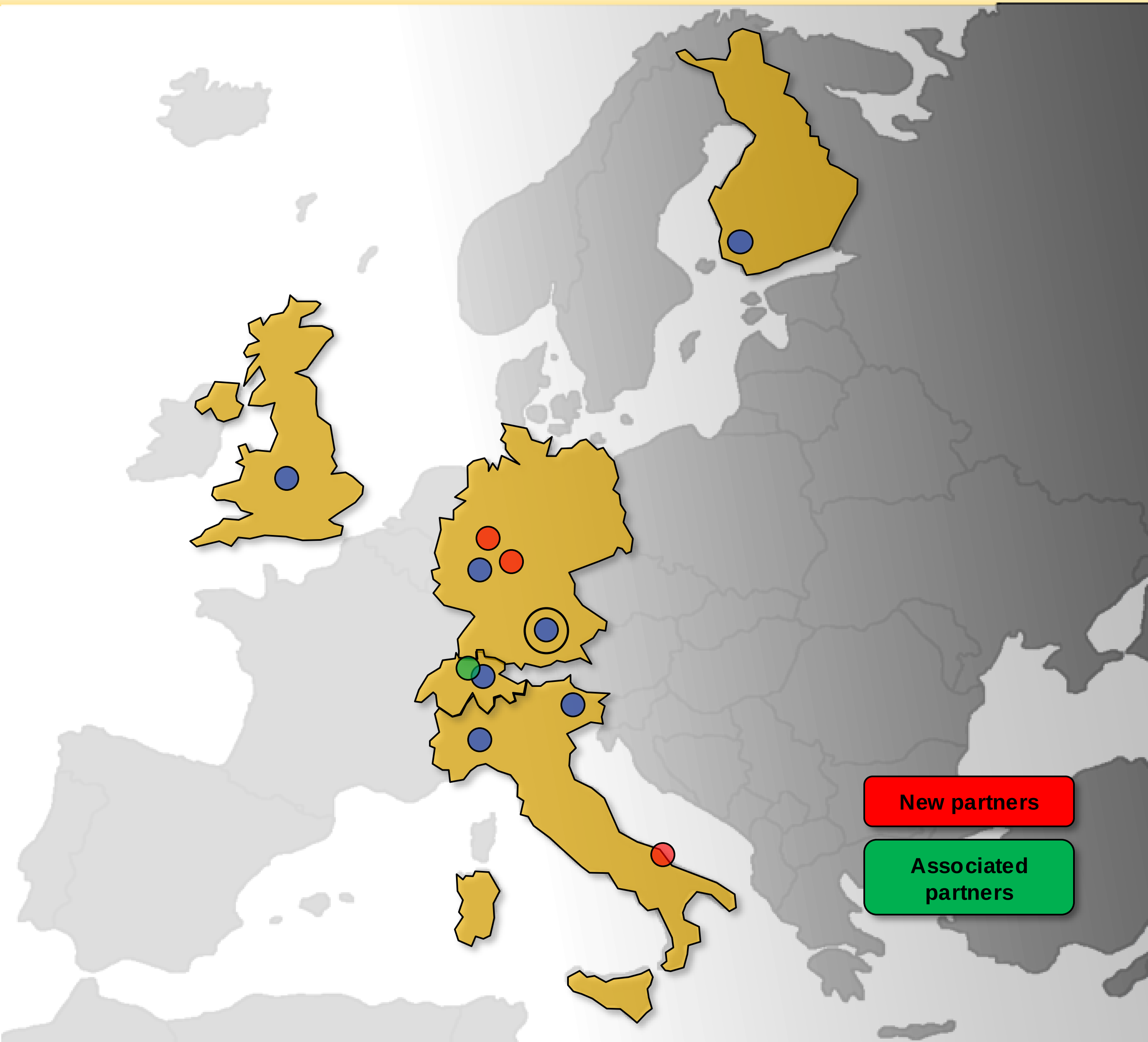
Understanding the heterogeneity of early psychosis

Investigating the neuroanatomical heterogeneity of psychosis risk syndromes



*patients with sufficient clinical data and MRI scans at baseline



JAMA Psychiatry | Original Investigation

Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis

ENIGMA Clinical High Risk for Psychosis Working Group

IMPORTANCE The lack of robust neuroanatomical markers of psychosis risk has been traditionally attributed to heterogeneity. A complementary hypothesis is that variation in neuroanatomical measures in individuals at psychosis risk may be nested within the range observed in healthy individuals.

OBJECTIVE To quantify deviations from the normative range of neuroanatomical variation in individuals at clinical high risk for psychosis (CHR-P) and evaluate their overlap with healthy variation and their association with positive symptoms, cognition, and conversion to a psychotic disorder.

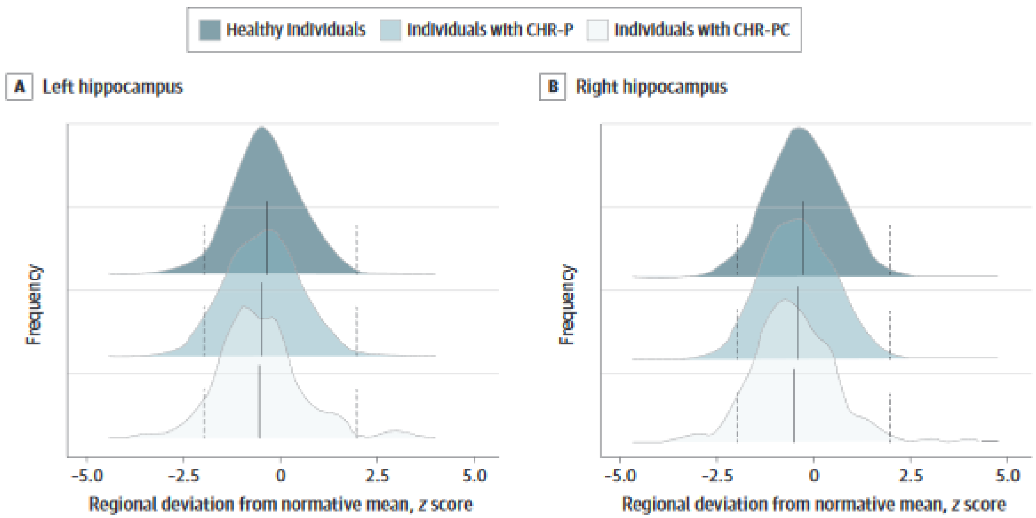
DESIGN, SETTING, AND PARTICIPANTS This case-control study used clinical-, IQ-, and neuroimaging software (FreeSurfer)–derived regional measures of cortical thickness (CT), cortical surface area (SA), and subcortical volume (SV) from 1340 individuals with CHR-P and 1237 healthy individuals pooled from 29 international sites participating in the Enhancing Neuroimaging Genetics Through Meta-analysis (ENIGMA) Clinical High Risk for Psychosis Working Group. Healthy individuals and individuals with CHR-P were matched by age and sex within each recruitment site. Data were analyzed between September 1, 2021, and November 30, 2022.

MAIN OUTCOMES AND MEASURES For each regional morphometric measure, deviation scores were computed as z scores indexing the degree of deviation from their normative means from a healthy reference population. Average deviation scores (ADS) were also calculated for regional CT, SA, and SV measures and globally across all measures. Regression analyses quantified the association of deviation scores with clinical severity and cognition, and 2-proportion z tests identified case-control differences in the proportion of individuals with infranormal ($z < -1.96$) or supranormal ($z > 1.96$) scores.

RESULTS Among 1340 individuals with CHR-P, 709 (52.91%) were male, and the mean (SD) age was 20.75 (4.74) years. Among 1237 healthy individuals, 684 (55.30%) were male, and the mean (SD) age was 22.32 (4.95) years. Individuals with CHR-P and healthy individuals overlapped in the distributions of the observed values, regional z scores, and all ADS values. For any given region, the proportion of individuals with CHR-P who had infranormal or supranormal values was low (up to 153 individuals [<11.42%]) and similar to that of healthy individuals (<115 individuals [<9.30%]). Individuals with CHR-P who converted to a psychotic disorder had a higher percentage of infranormal values in temporal regions compared with those who did not convert (7.01% vs 1.38%) and healthy individuals (5.10% vs 0.89%). In the CHR-P group, only the ADS SA was associated with positive symptoms ($\beta = -0.08$; 95% CI, -0.13 to -0.02; $P = .02$ for false discovery rate) and IQ ($\beta = 0.09$; 95% CI, 0.02-0.15; $P = .02$ for false discovery rate).

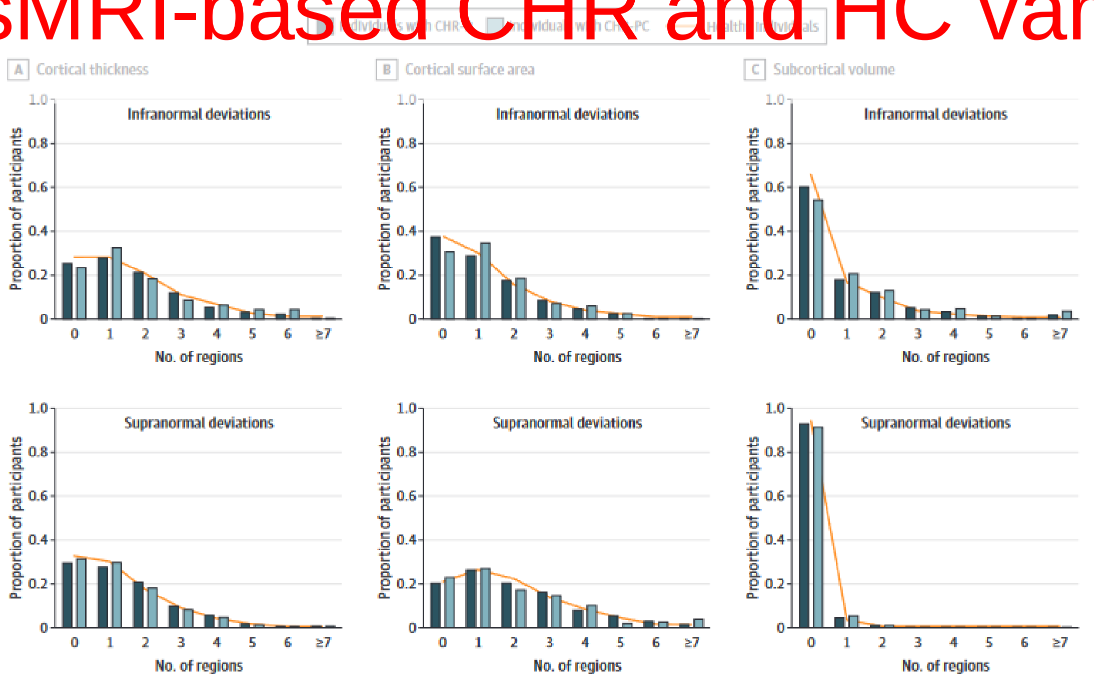
➔ Complete overlap between sMRI-based CHR and HC variation

Figure 1. Distribution of Hippocampal Subcortical Volume Normative z Scores in the Study Sample



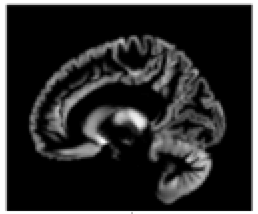
The hippocampus is used as an exemplar because the same pattern was observed for all regions (eFigures 4 and 5 in Supplement 1). The dotted vertical lines represent the cutoffs for infranormal ($z < -1.96$) and supranormal ($z > 1.96$) values. CHR-P indicates clinical high risk for psychosis; and CHR-PC, clinical high risk for psychosis converted to a psychotic disorder.

Figure 3. Distribution of the Total Number of Regions With Infra- or Supranormal Regional Normative z Scores



Structural brain pattern of clinical high-risk (CHR) for psychosis?

9 PRONIA sites; gray matter volume machine learning analysis



Generalization theory-based masking

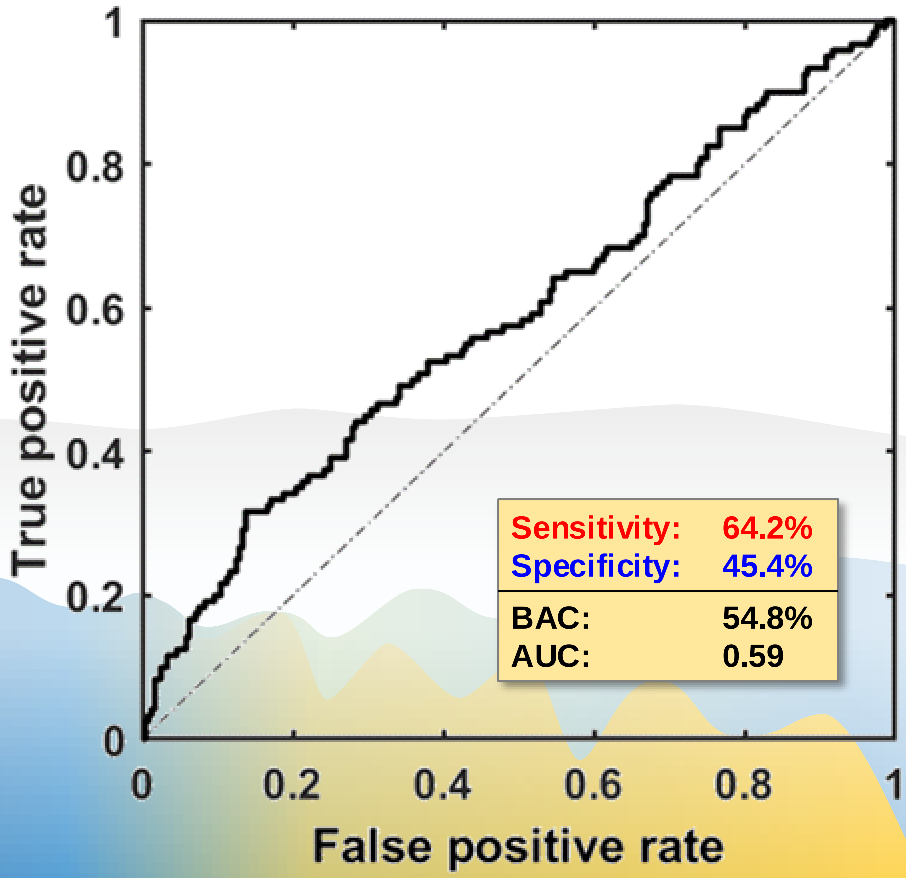
Weighting of voxels using F-score metric

Dimensionality reduction (PCA), number of eigenvariates [5:5:80]

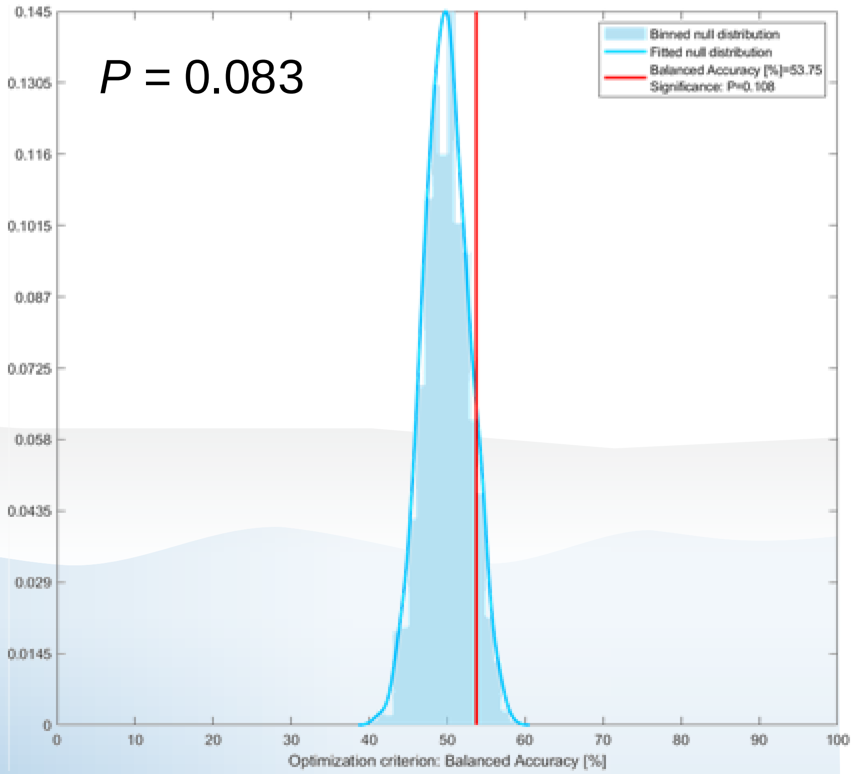
Standardization

Linear, non-kernelized L2-regularized, L1-loss SVM

120 CHR vs. 240 HC



1000 label permutations



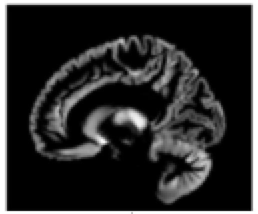
Koutsouleris et al., in preparation

Stage 0 | Stage Ia | Stage Ib | Stage II | Stage III

Age

Structural brain patterns of different CHR states ?

9 PRONIA sites | HC individuals matched one-to-one for site, age and sex to CHR patients



Generalization theory-based masking

Weighting of voxels using F-score metric

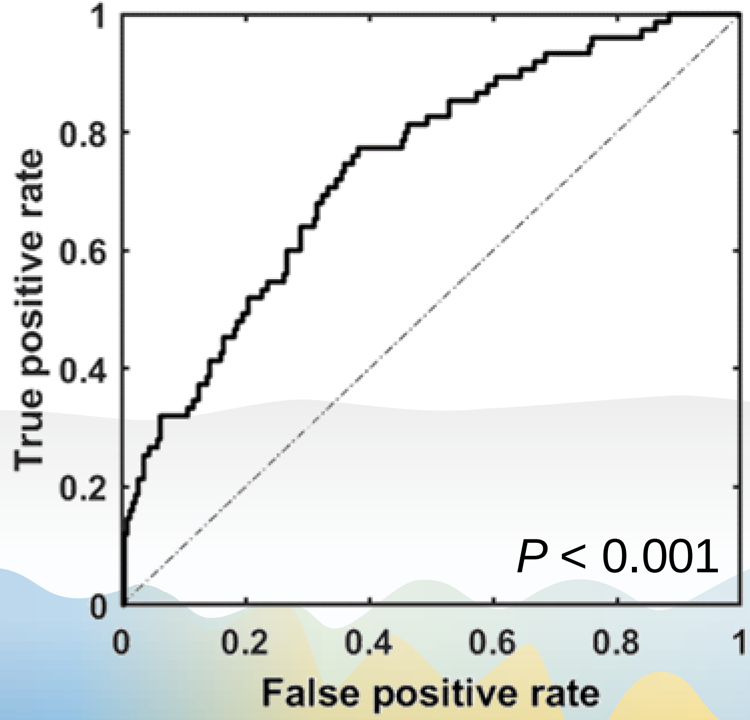
Dimensionality reduction (PCA), number of eigenvariates [5:5:80]

Standardization

Linear, non-kernelized L2-regularized, L1-loss SVM

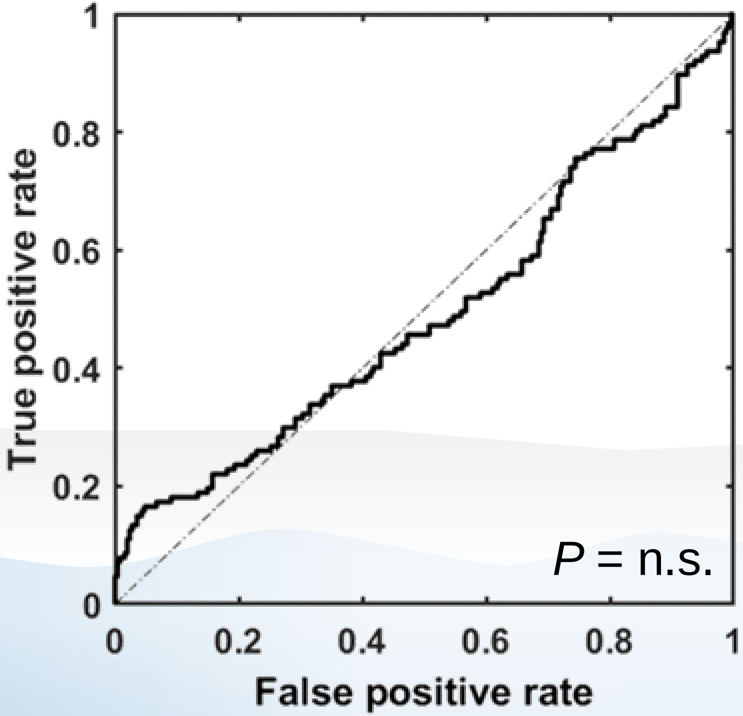
Koutsouleris et al., in preparation

75 COGDIS only vs. 225 HC



Sensitivity:	76.0%
Specificity:	61.8%
BAC:	68.9%
AUC:	0.74

127 UHR only vs. 254 HC



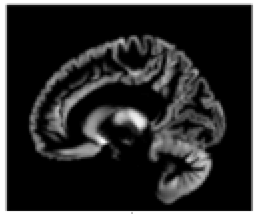
Sensitivity:	47.2%
Specificity:	46.5%
BAC:	46.9%
AUC:	0.49

Stage 0 | Stage Ia | Stage Ib | Stage II | Stage III

Age

Same separability of COGDIS and SCZ ?

9 PRONIA sites | HC individuals matched one-to-one for site, age and sex to CHR patients



Generalization theory-based masking

↓

Weighting of voxels using F-score metric

↓

Dimensionality reduction (PCA), number of eigenvariates [5:5:80]

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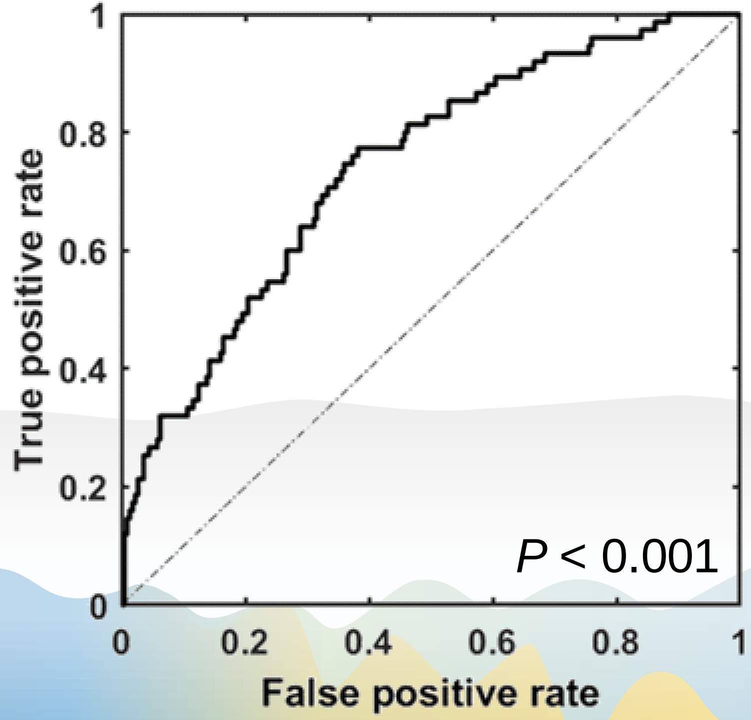
Standardization

↓

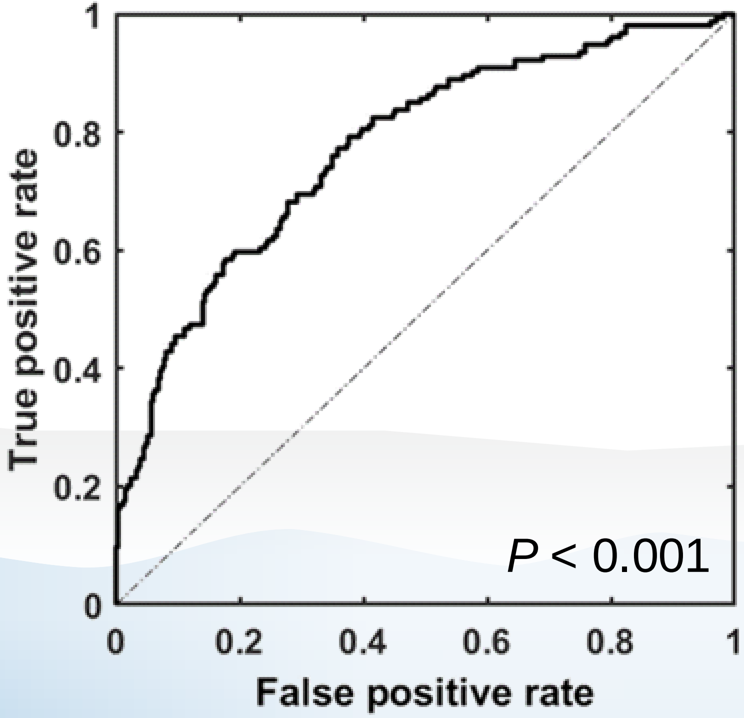
Linear, non-kernelized L2-regularized, L1-loss SVM

75 COGDIS only vs. 225 HC



Sensitivity:	76.0%
Specificity:	61.8%
BAC:	68.9%
AUC:	0.74

154 SCZ vs. 335 HC



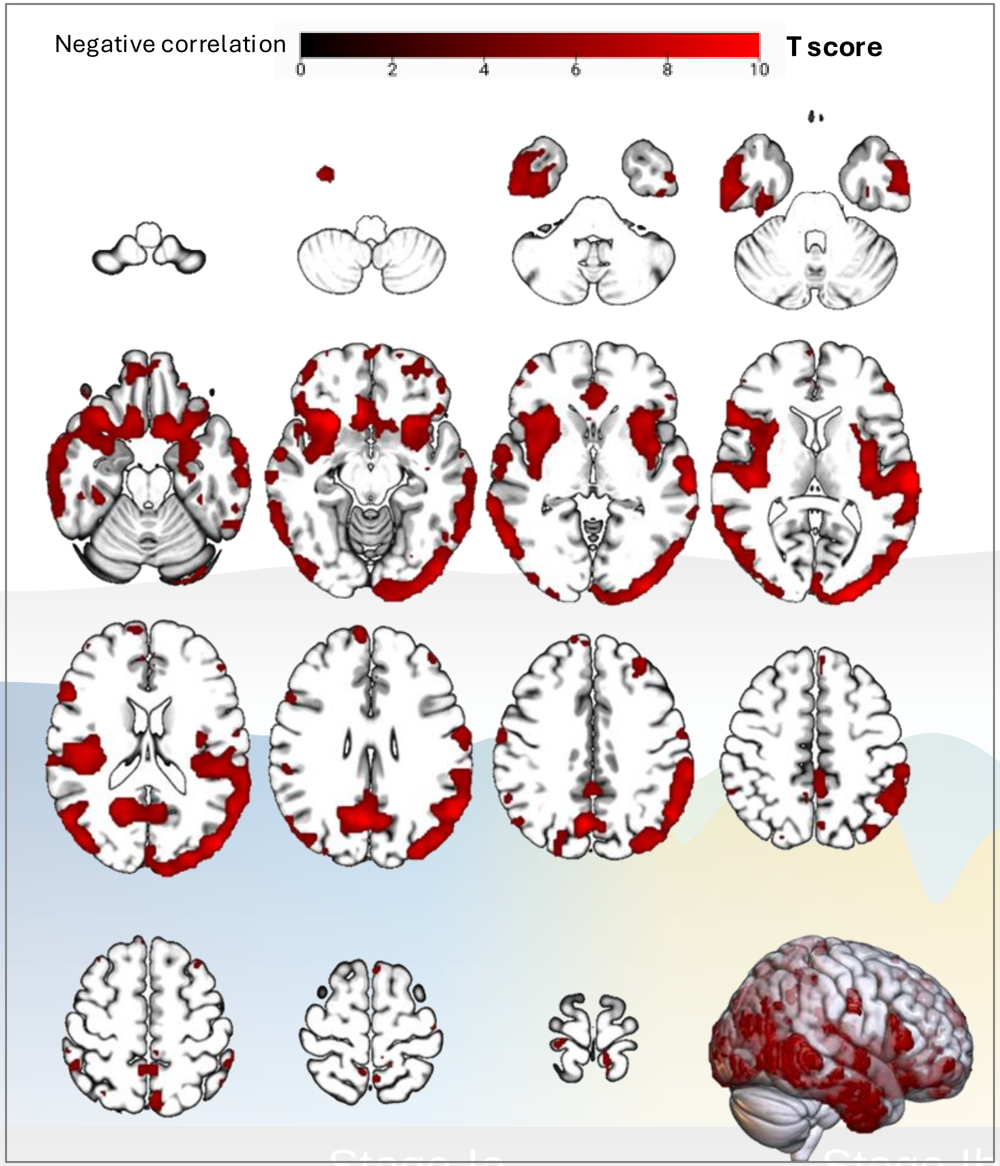
Sensitivity:	77.3%
Specificity:	63.6%
BAC:	70.4%
AUC:	0.77

Koutsouleris et al., in preparation

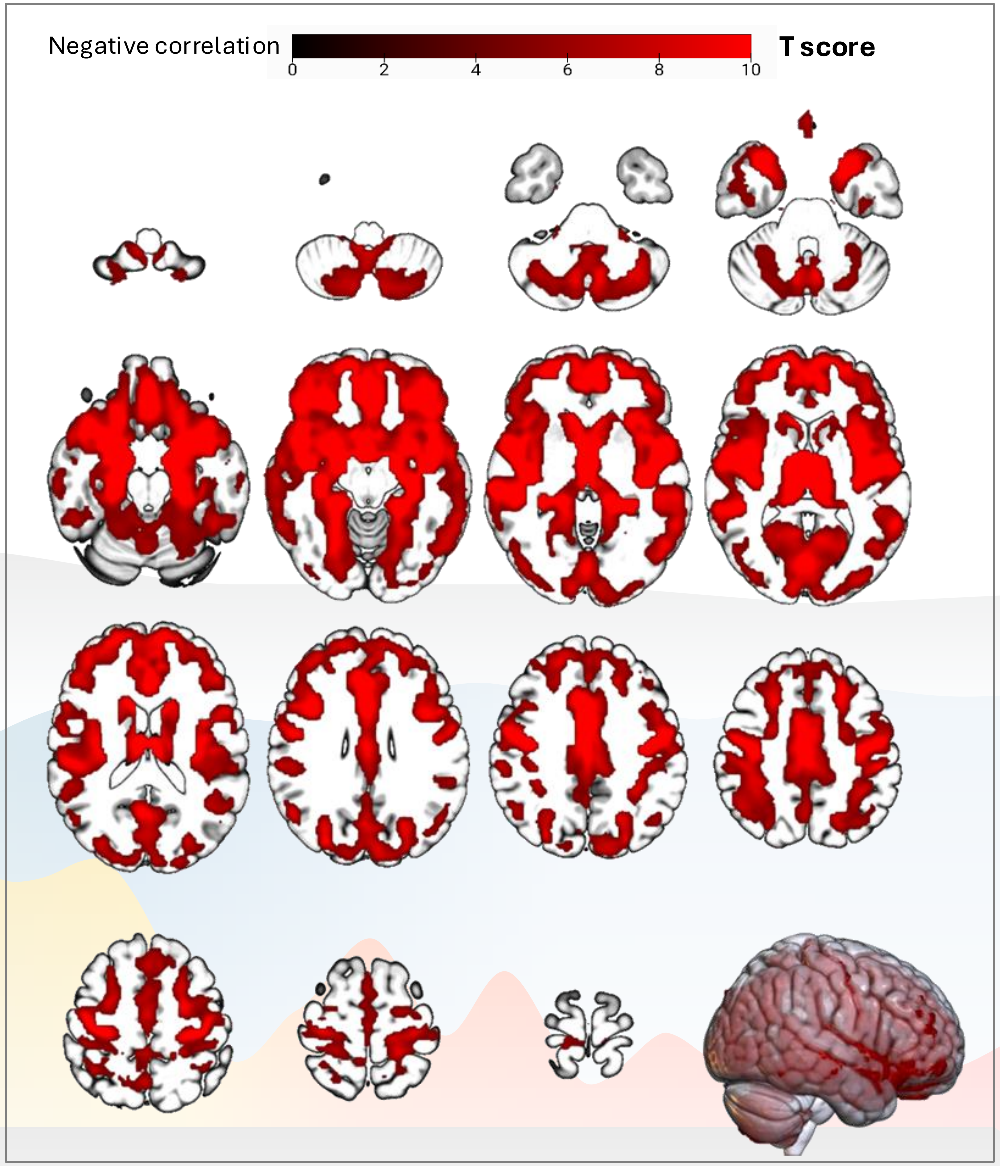
Stage 0 | Stage Ia | Stage Ib | Stage II | Stage III → Age

Where do COGDIS and SCZ patterns overap in the brain?

COGDIS pattern



Schizophrenia pattern

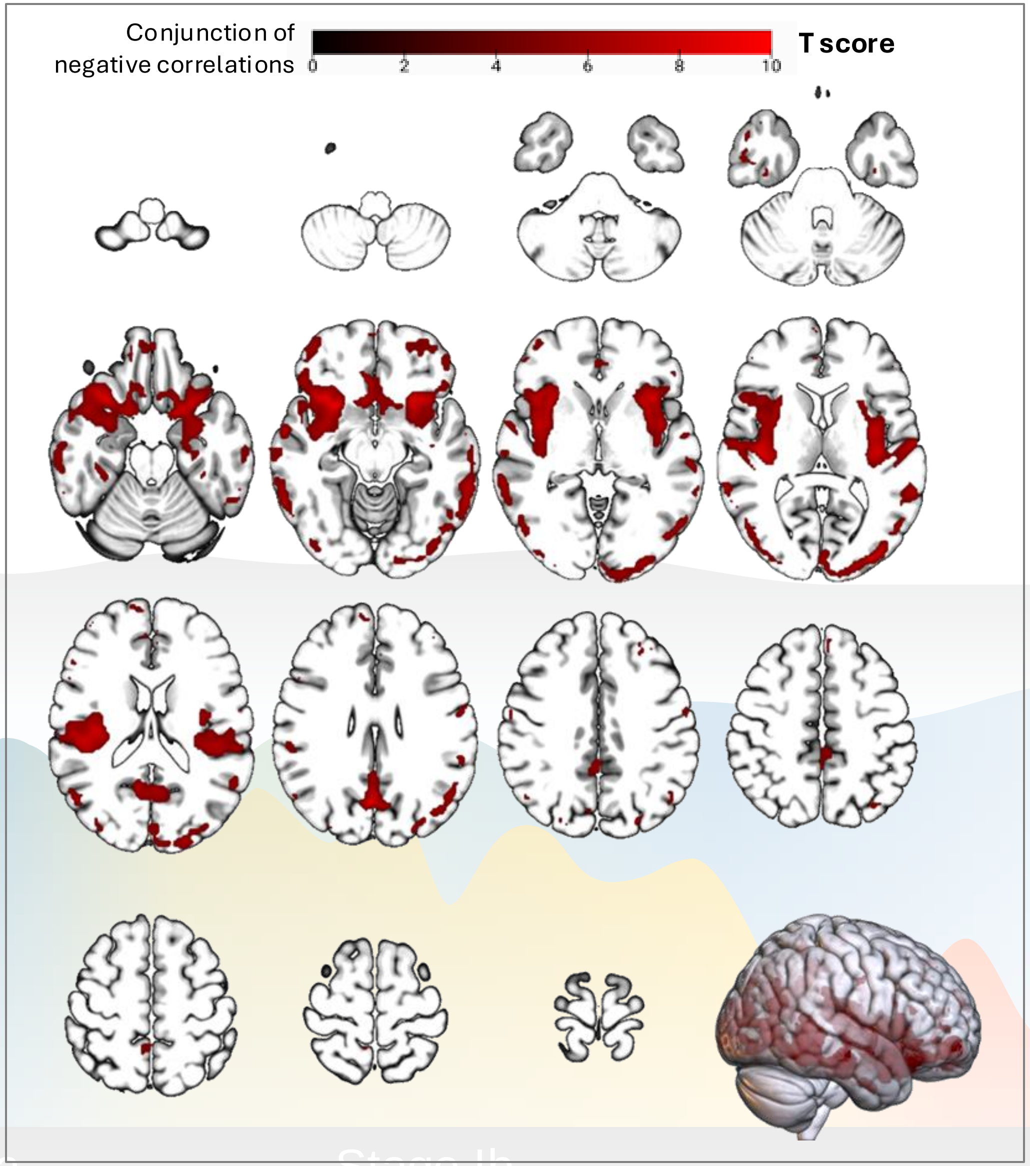


Stage 0 Stage Ia Stage Ib Age

Koutsouleris et al., in preparation

Where do COGDIS and SCZ patterns overap in the brain?

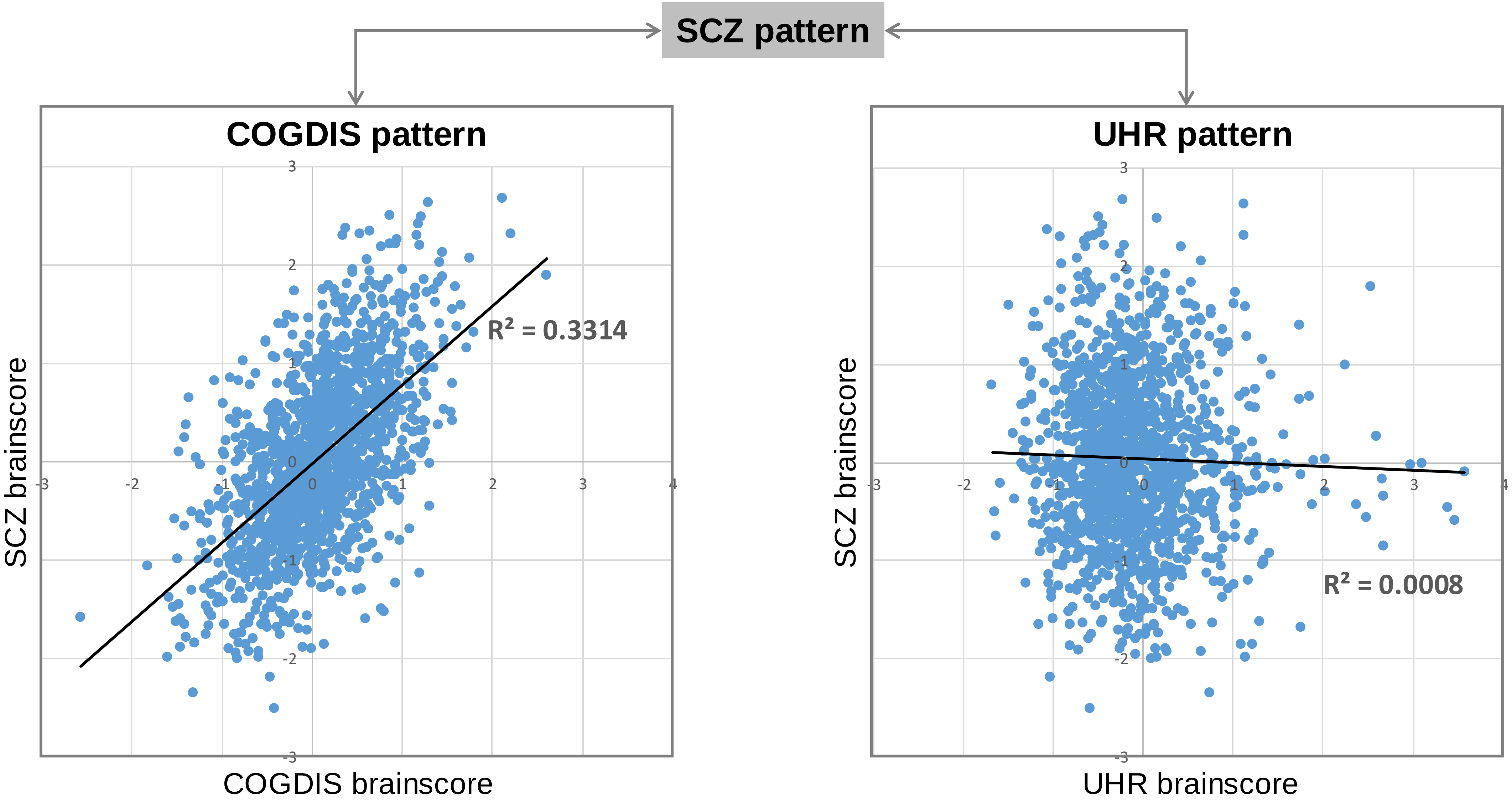
Spatial conjunction: COGDIS ∩ Schizophrenia



Koutsouleris et al., in preparation

Are COGDIS or UHR patterns co-expressed with the SCZ pattern?

Transdiagnostic brainscore correlation analysis (N=1440)

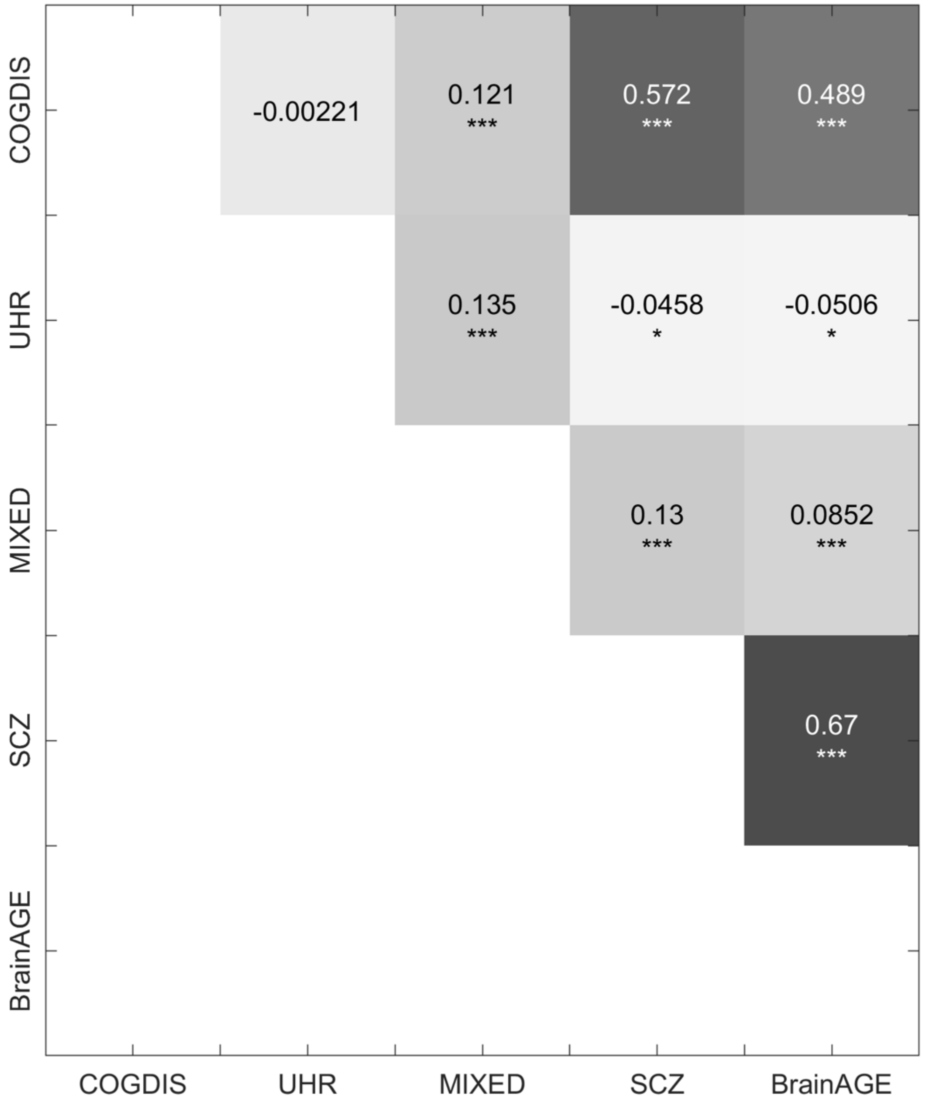


Koutsouleris et al., in preparation

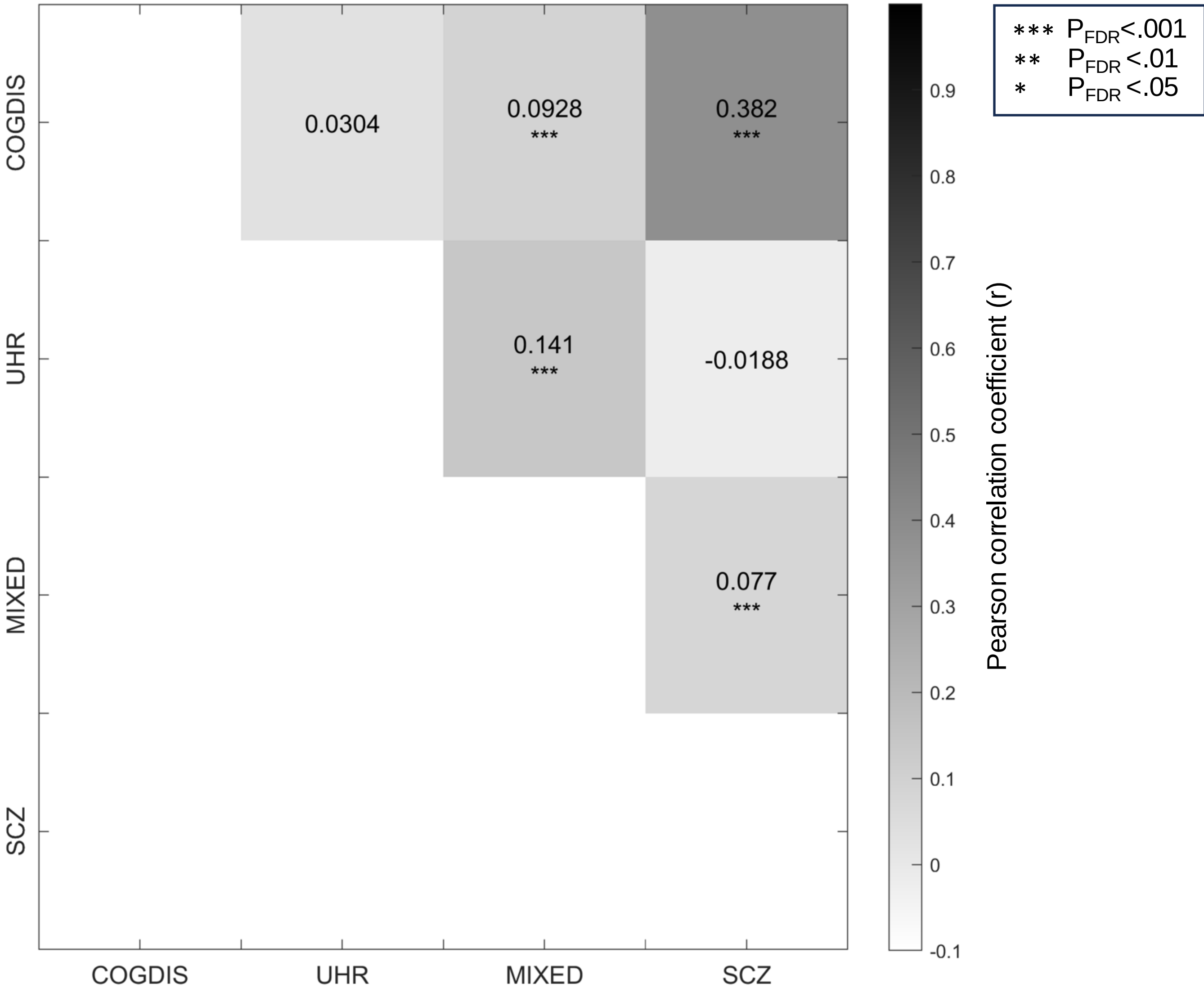
Are these correlations mediated by accelerated aging?

Transdiagnostic brainscore correlation analysis (N=1440)

Pairwise pattern correlations



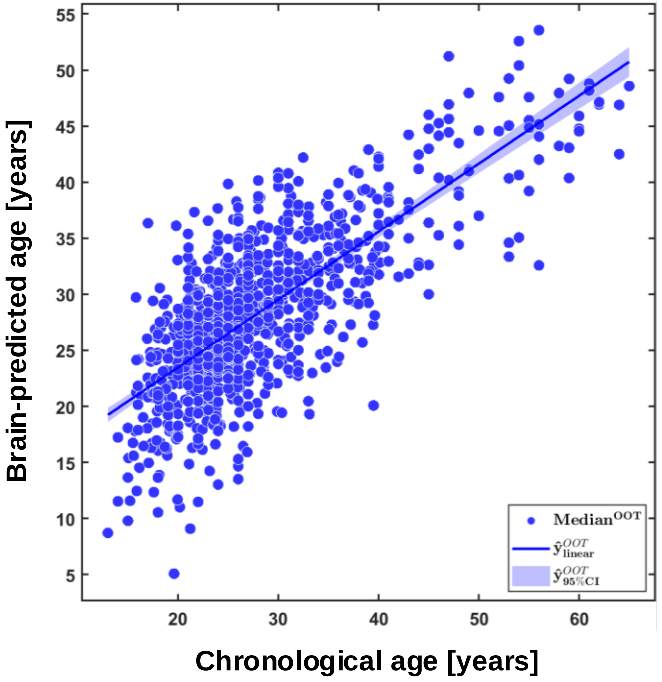
Pairwise correlations after BrainAGE correction

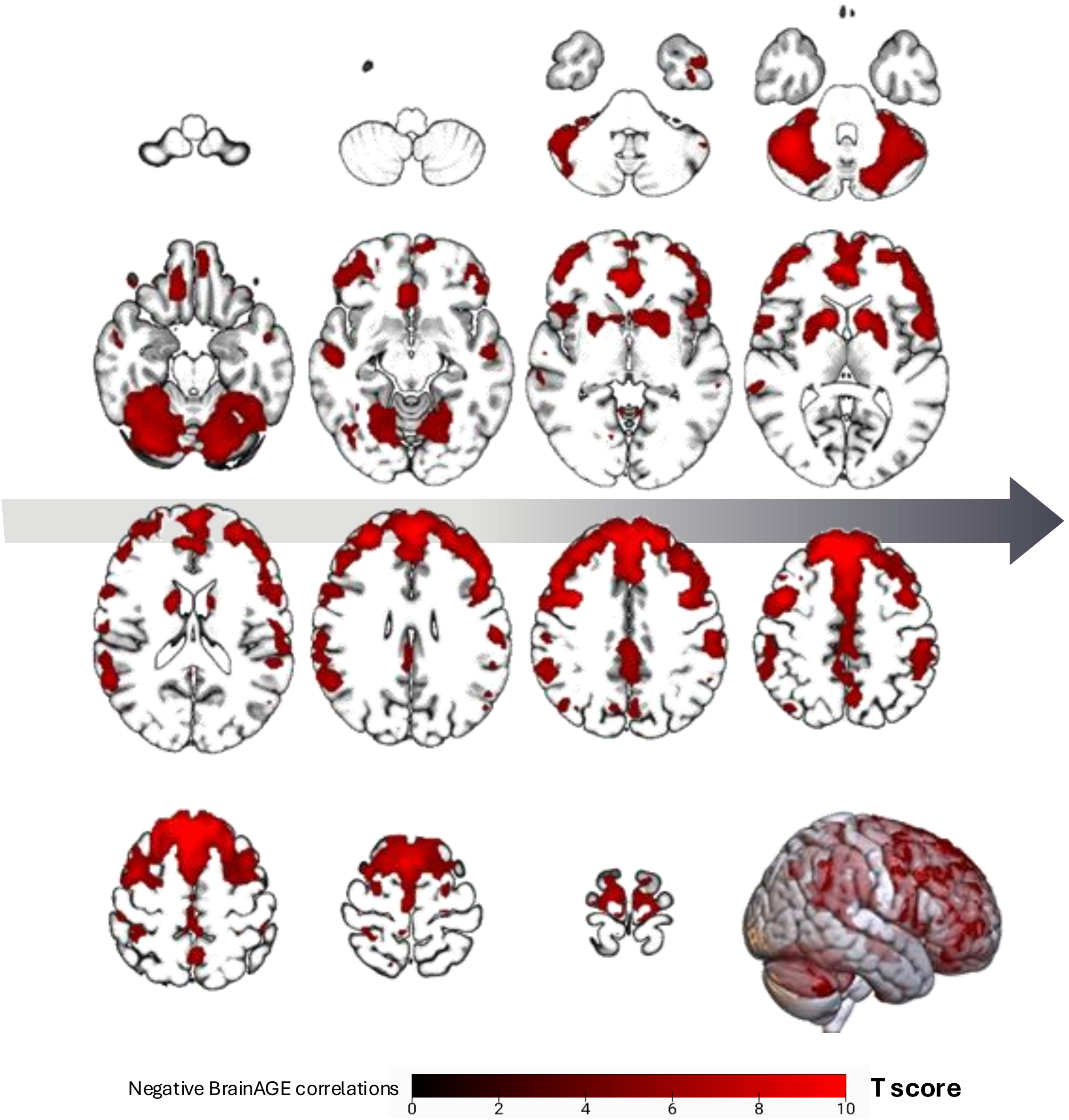


Koutsouleris et al., in preparation

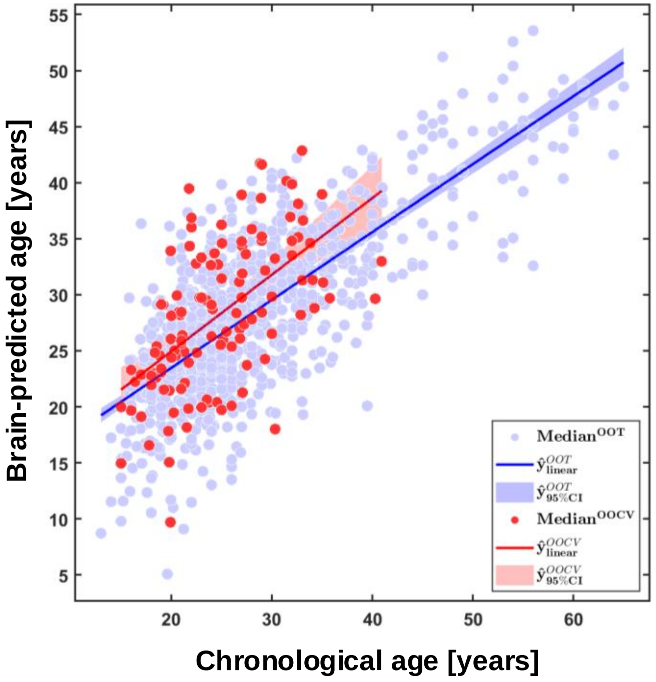
Transdiagnostic BrainAGE effects computed in the PRONIA data

907 HC from PRONIA, MUC and ZInEP



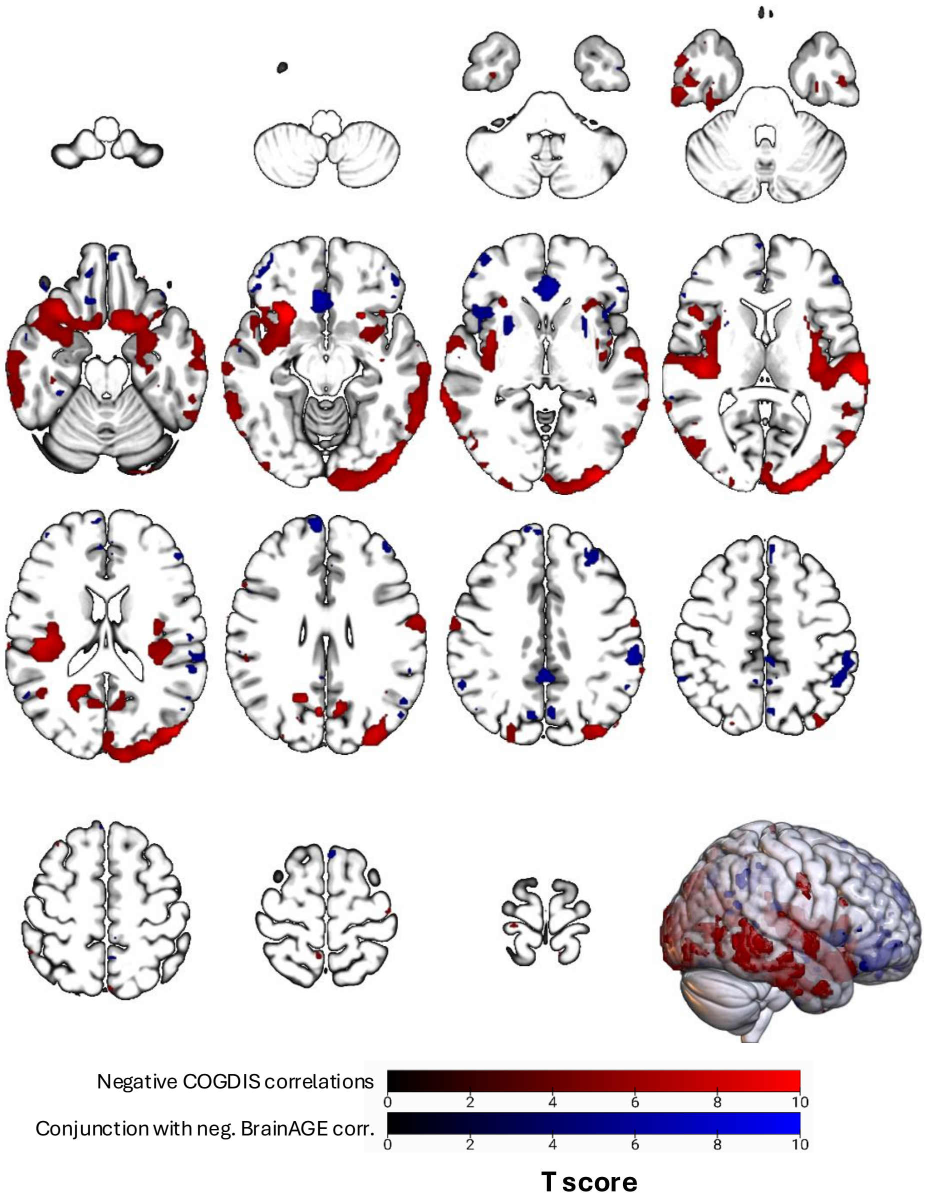


105 COGDIS patients from PRONIA and ZInEP

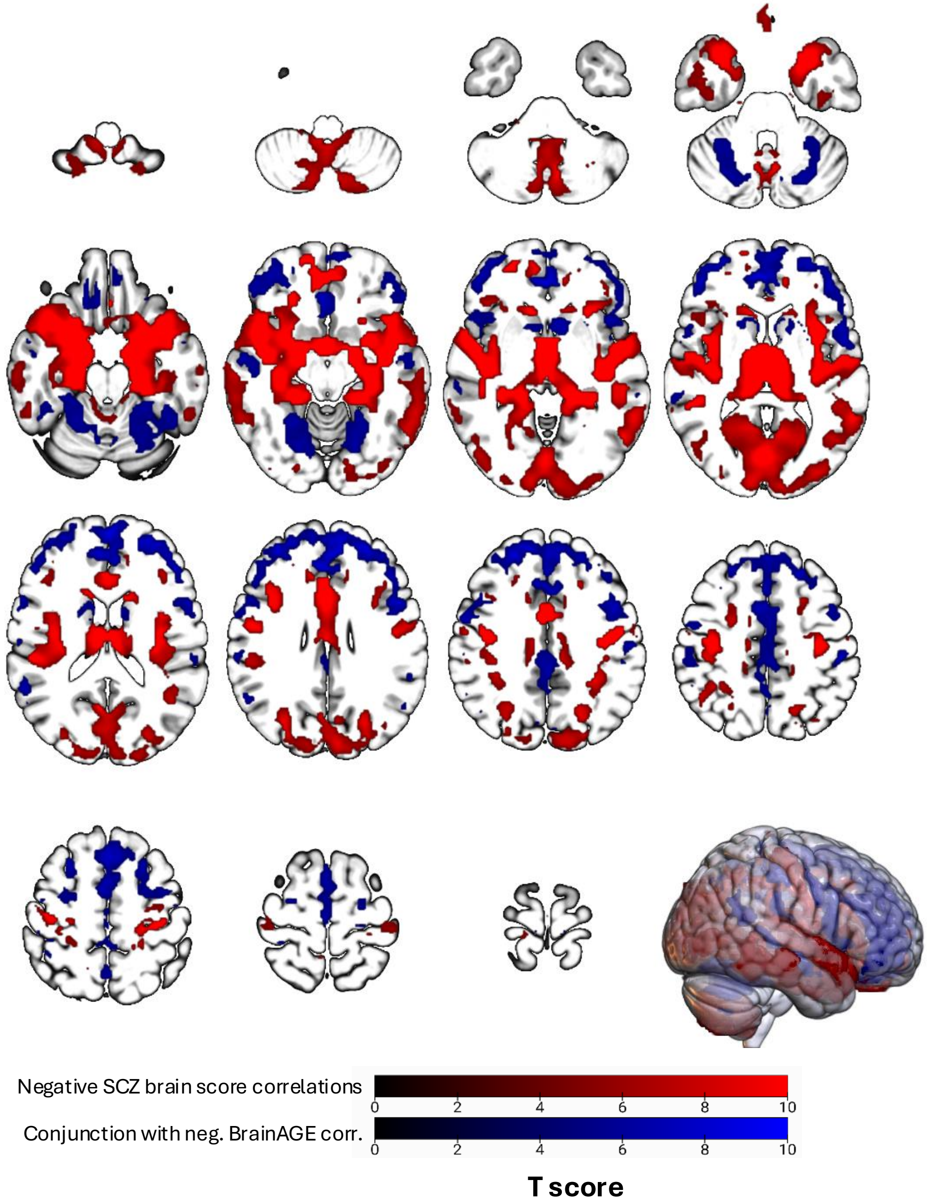


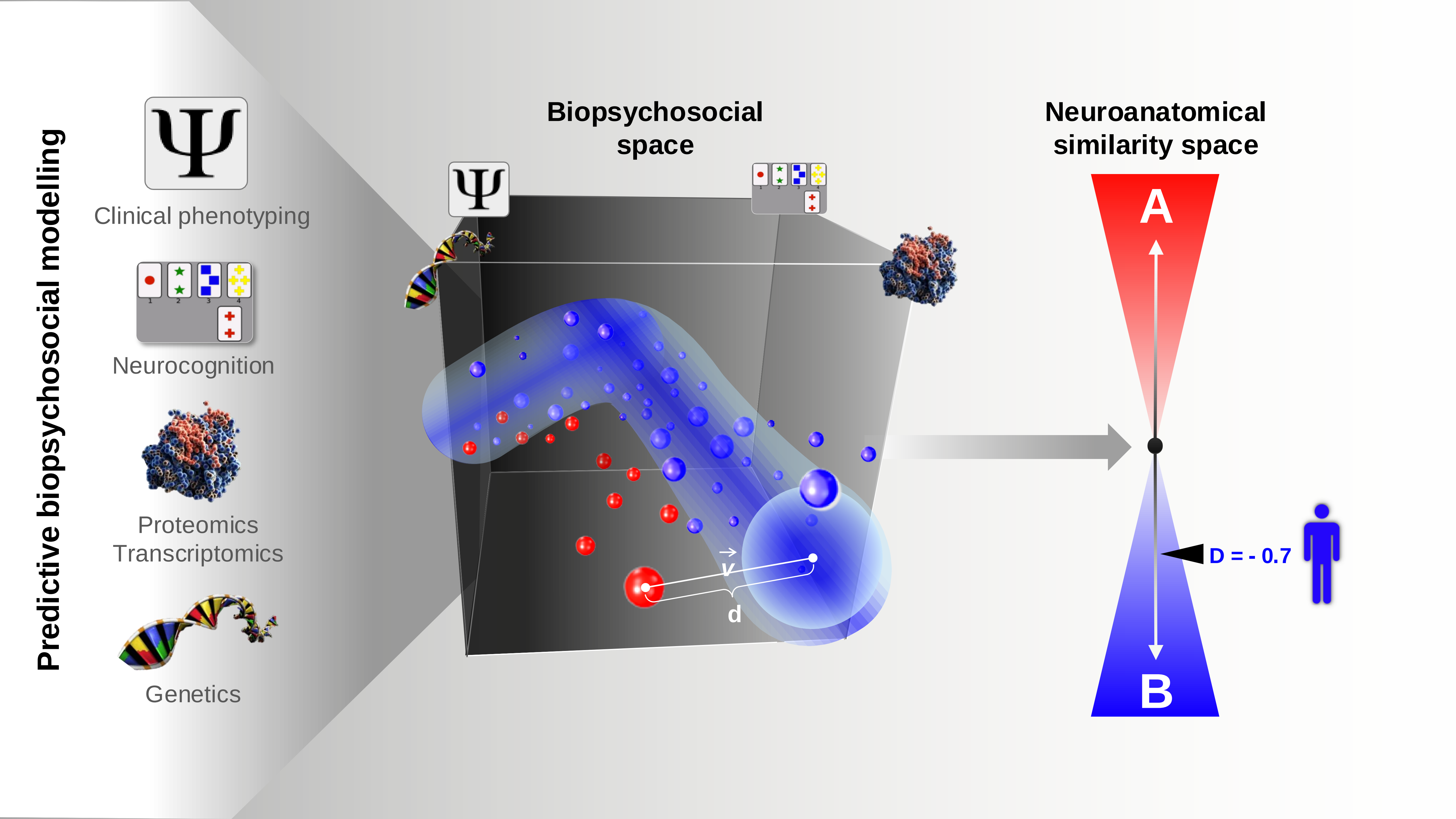
COGDIS, SCZ and BrainAGE overaps: State vs. Trait Markers?

Spatial conjunction: COGDIS ∩ BrainAGE



Spatial conjunction: Schizophrenia ∩ BrainAGE

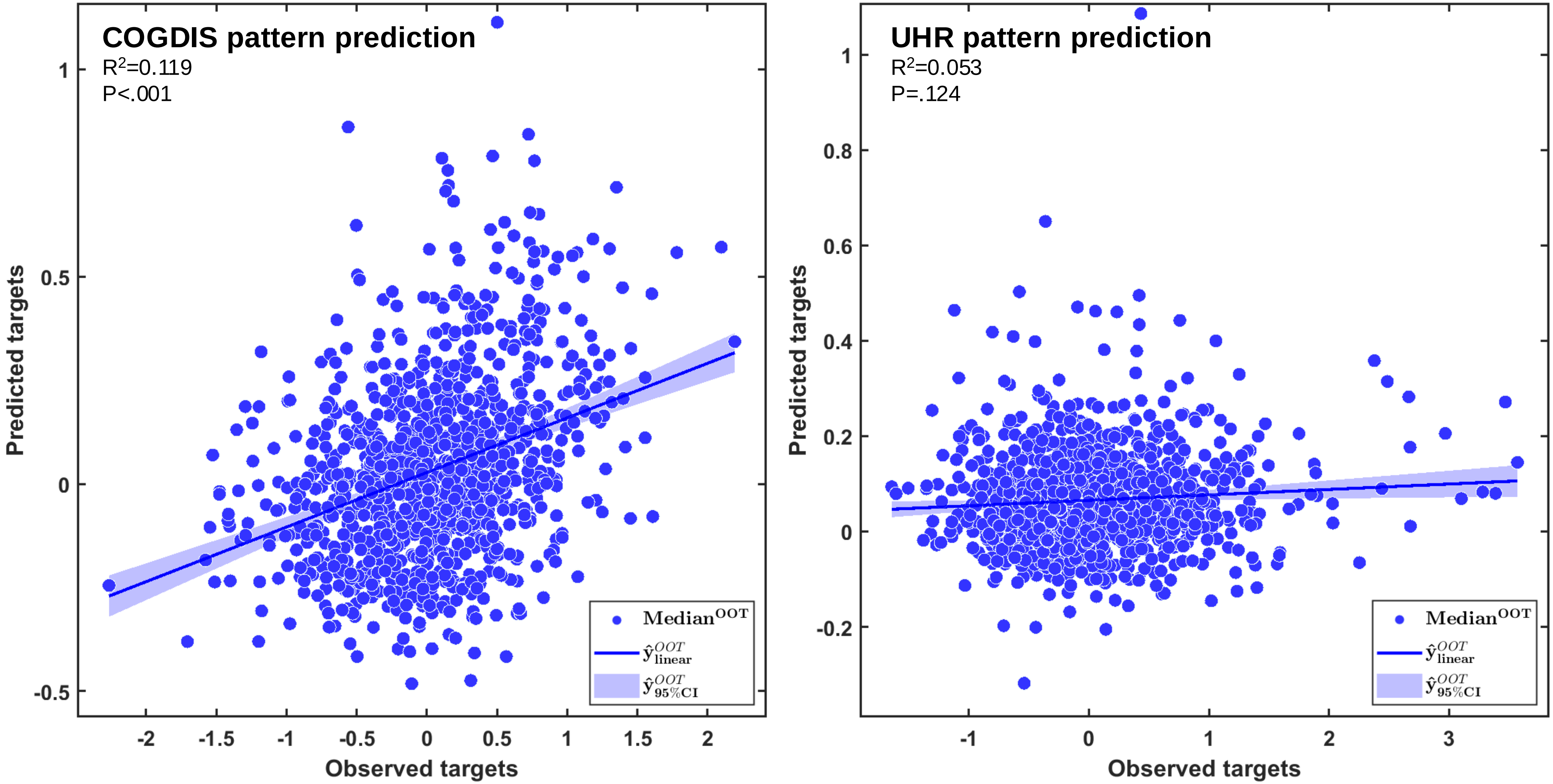




Predictive biopsychosocial modelling
Clinical phenotyping
Neurocognition
Proteomics
Transcriptomics
Genetics
Biopsychosocial
space
v
d
Neuroanatomical
similarity space
A
B
D = - 0.7

Can we predict COGDIS, UHR or schizophrenia brain pattern expression?

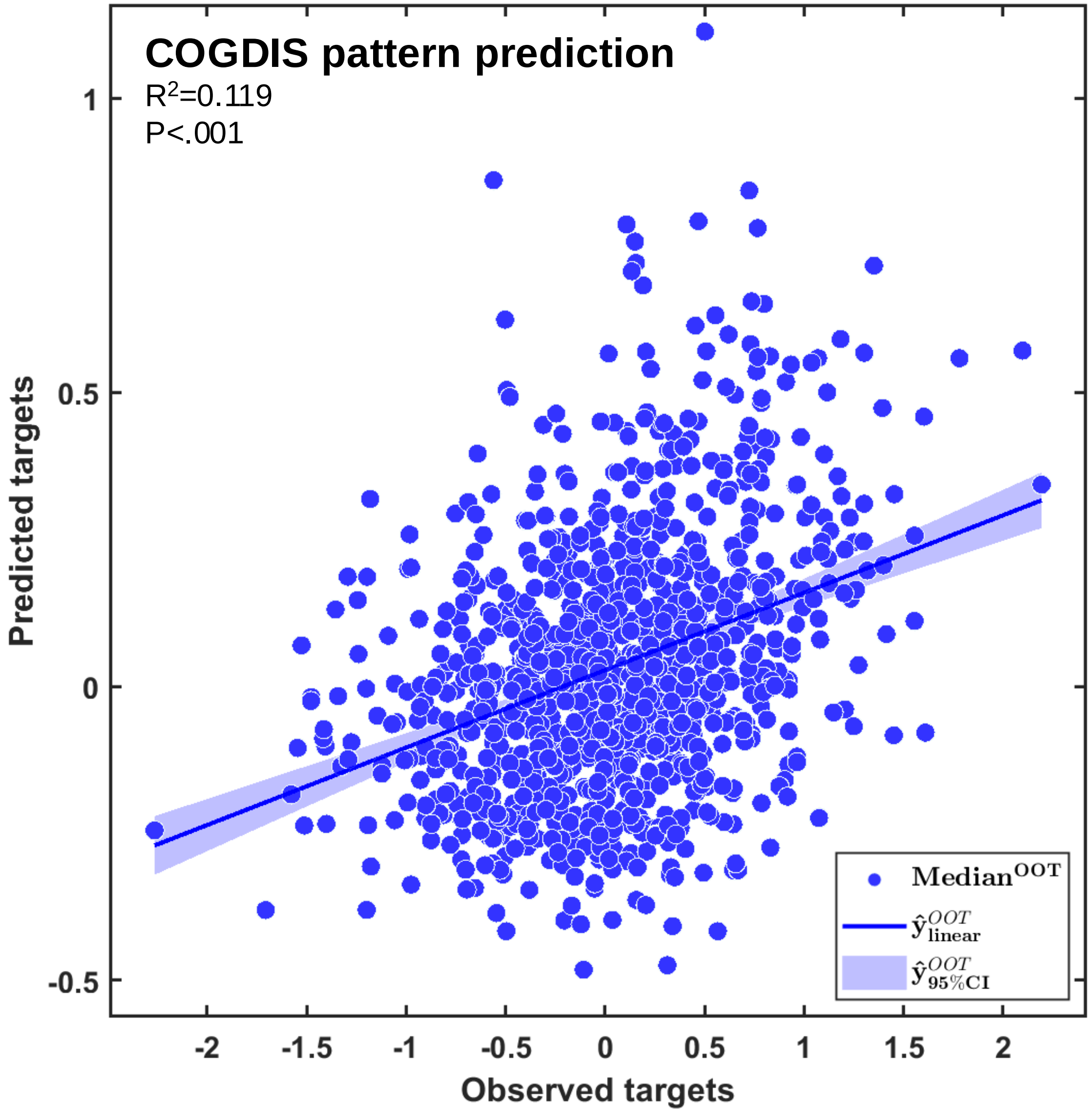
… by analyzing multimodal biopsychosocial data using SVR

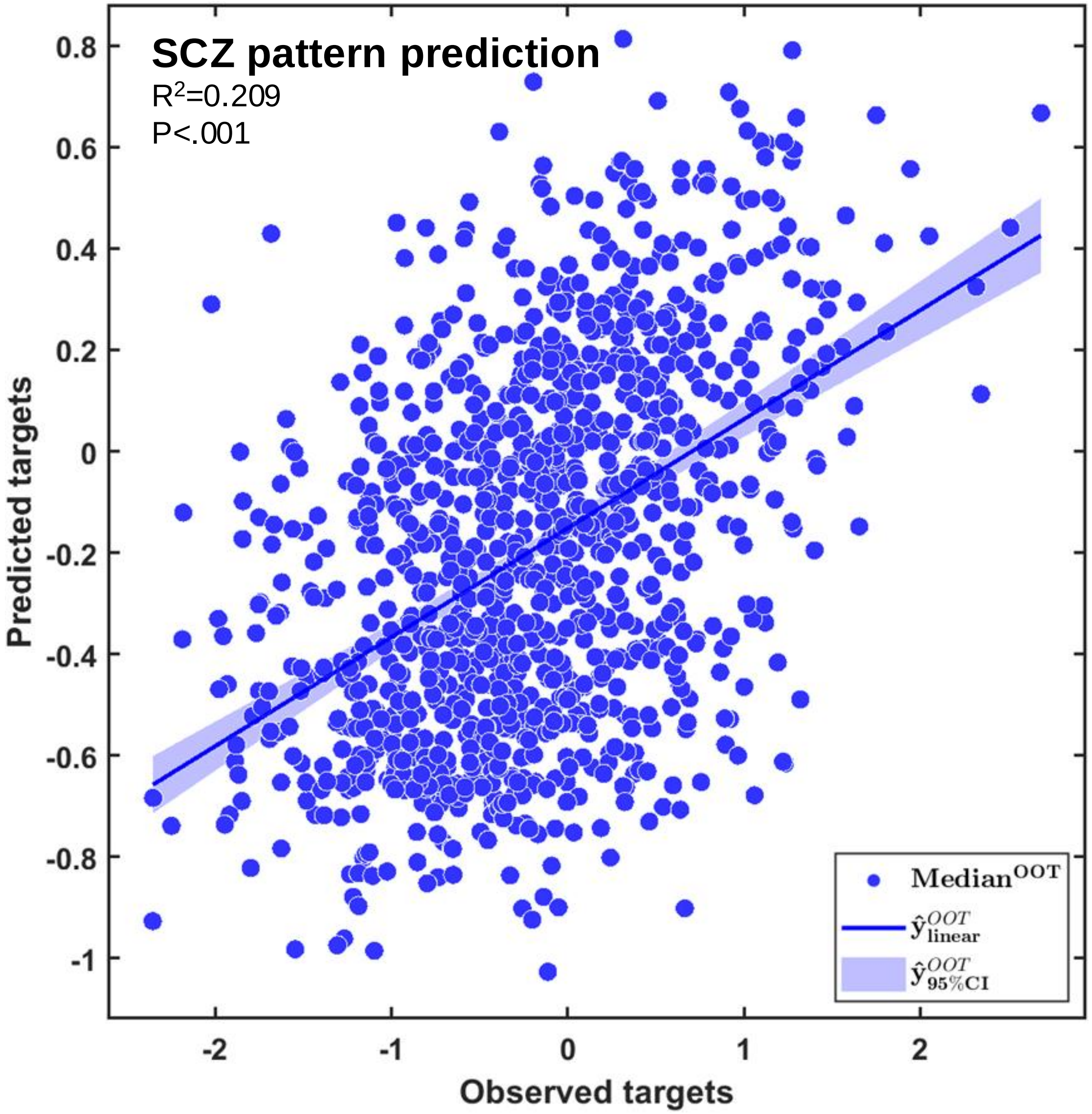


Koutsouleris et al., in preparation

Can we predict COGDIS, UHR or schizophrenia brain pattern expression?

… by analyzing multimodal biopsychosocial data using SVR





Koutsouleris et al., in preparation

Genomic pattern predictors

Co-expression of COGDIS and SCZ patterns does not emerge from an accidental spatial colocalization but from shared genetic fingerprints and likely upstream gene expression pathways.

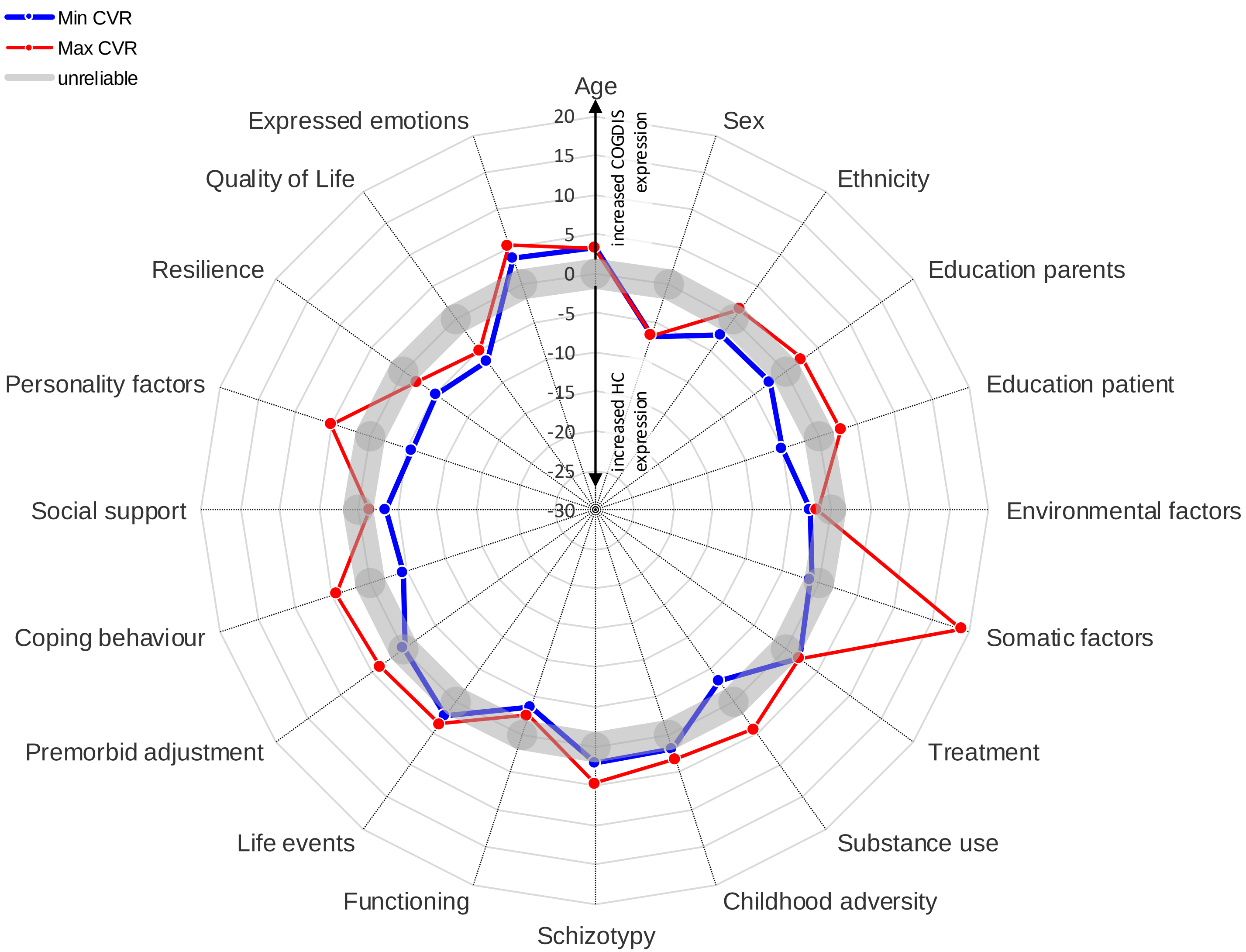
Koutsouleris et al., in preparation

Phenomenological predictors of the COGDIS pattern

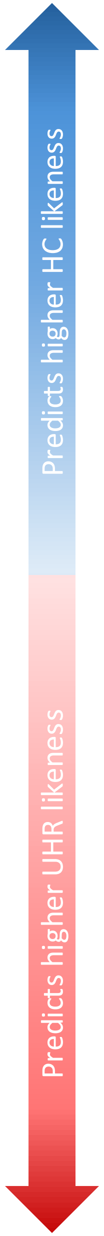
Predicts higher HC likeness

Predicts higher COGDIS likeness

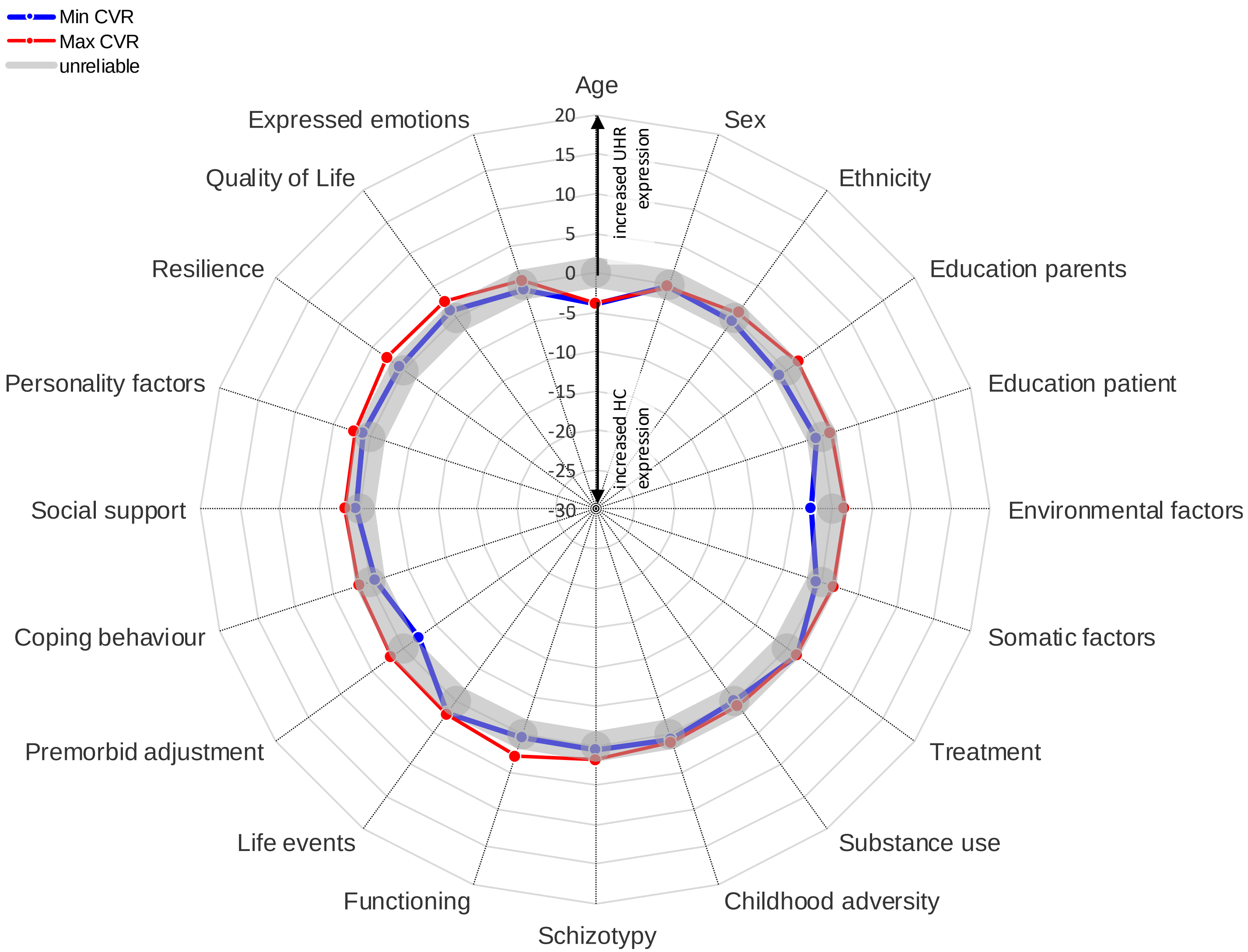
CVR	Variable
-6.81	WHOQoL-BREF: Overall quality of life
-6.75	Female Sex
-5.67	NEO-FFI: Agreeableness score
-5.06	RSA: Planned future score
-4.93	Graduation qualifying for university degree
-4.38	CISS: Task-oriented coping style score
-3.71	GF-R: Highest lifetime score
-3.45	MSPSS: Perceived social support by friends
-3.23	Alcohol consumption
-2.72	Low population at place of living
-2.6	GAF-S: Highest lifetime score
-2.56	White ethnicity
-2.42	Mother: With graduation
2.1	Current treatment for somatic disorder
2.54	Father: Without graduation
2.88	Participant: Other graduation
3.22	Age
3.27	CTQ: Emotional abuse score
3.57	CoLE: Burden due to events with effects on mental health
3.71	PAS (Childhood): scholastic performance
4.42	Average number of cigarettes per day
4.46	CISS: Emotion-oriented coping style score
4.68	WSS: Physical anhedonia score
5.19	NEO-FFI: Neuroticism score
5.28	LEE: Intrusiveness of significant other
18.9	Body-Mass Index



Phenomenological predictors of the UHR pattern



CVR	Variable
-3.93	Age
-2.74	Population density at place of living (inhabitants / km²)
-2.30	PAS (Childhood): adaptation to school
2.06	NEO-FFI: Extraversion score
2.20	CoLE: Burden due to events without effects on mental health
2.57	WHOQoL-BREF: Overall quality of health
2.65	RSA: Perception of self score
2.92	GAF-S: Highest lifetime score

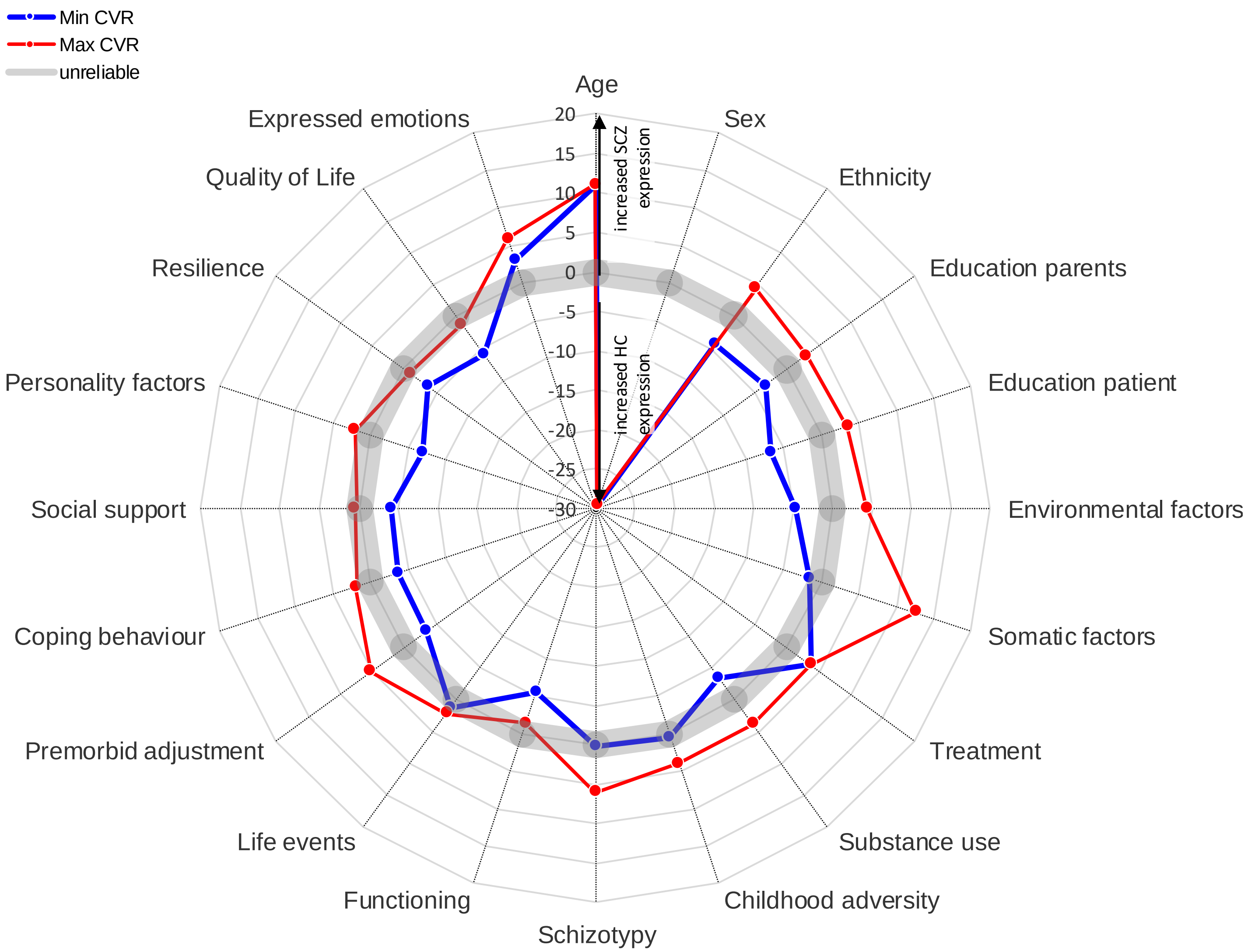


Phenomenological predictors of the Schizophrenia pattern

Predicts higher HC likeness

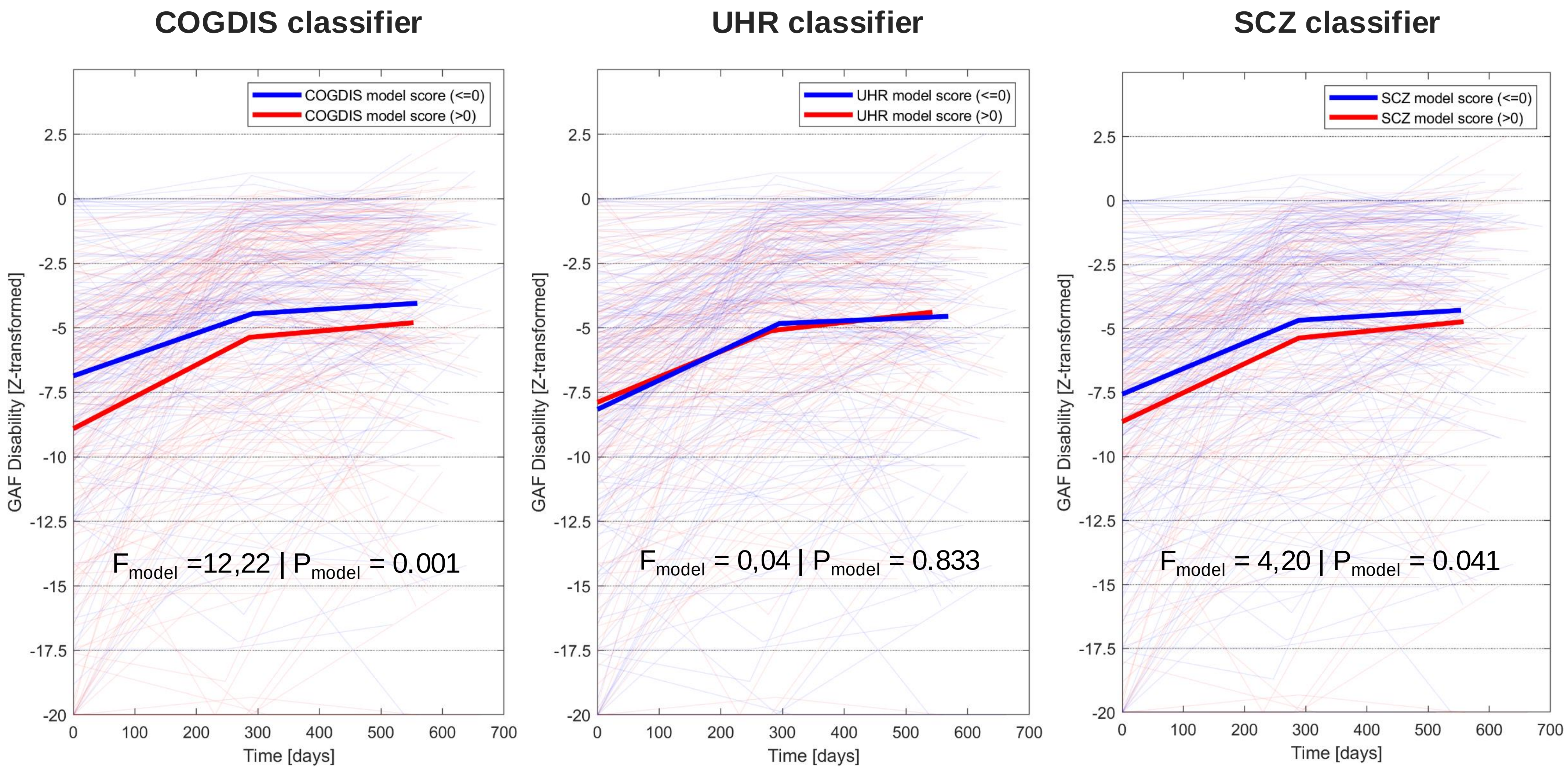
Predicts higher schizophrenia likeness

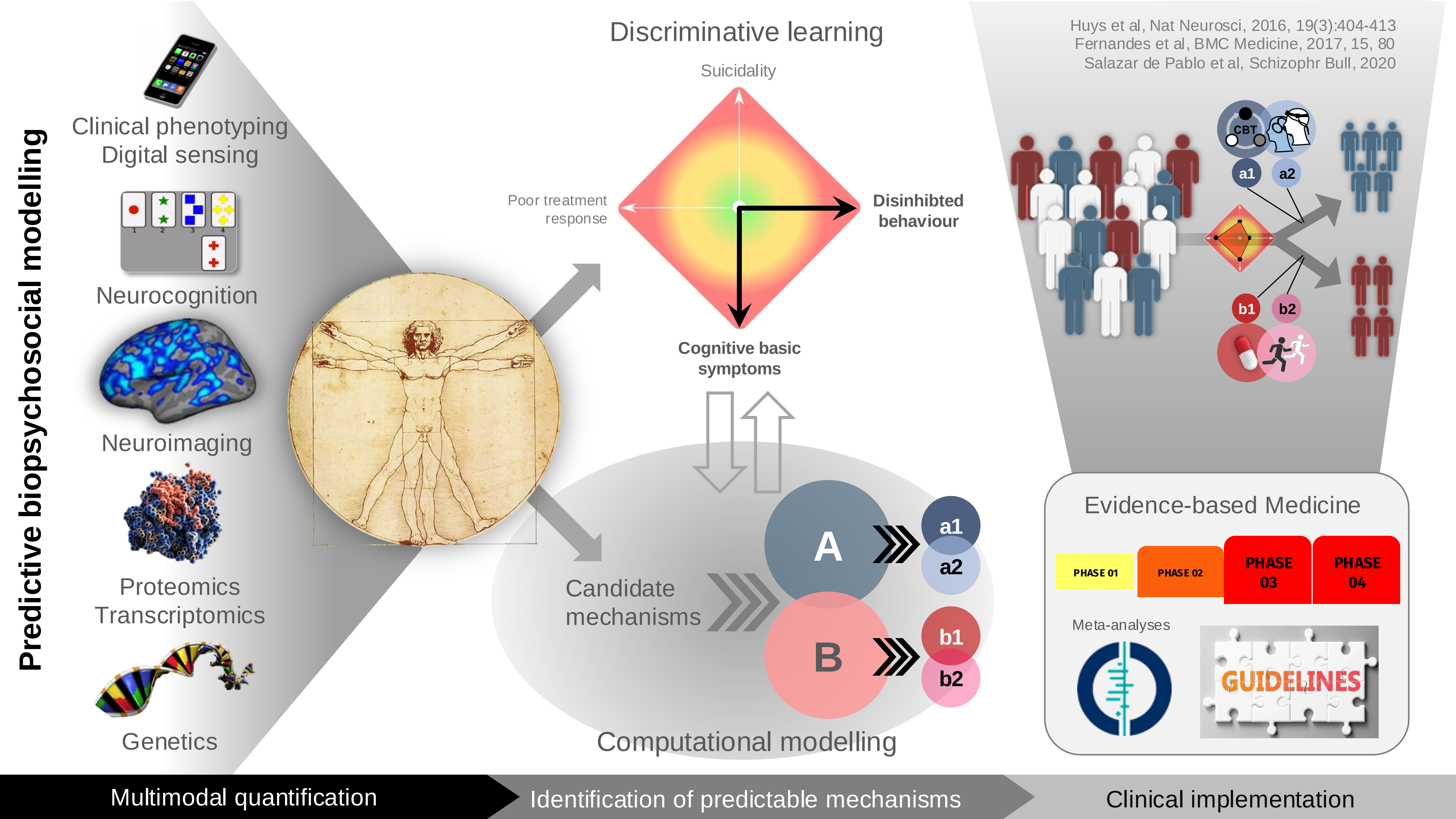
CVR	Variable
-29.44	Female sex
-6.88	NEO-FFI: Openness score
-6.75	Participant: Graduation qualifying for university degree
-6.01	WHOQoL-BREF: Overall quality of health
-5.46	GF-R: Highest lifetime score
-4.81	Low population density at place of living
-4.32	White ethnicity
-4.08	MSPSS: Perceived social support by significant others
-3.8	RSA: Social support score
-3.65	CISS: Social-diversion oriented coping style score
-3.48	PAS (General): Continuous employment or school functioning
-3.44	Mother: with graduation
-3.39	Alcohol consumption
2.01	CISS: Emotion-oriented coping style score
2.08	CoLE: Burden due to events with effects on mental health
2.09	NEO-FFI: Neuroticism score
2.95	Mother: No graduation qualifying for higher education degree
3.52	Participant: Other graduation
3.66	Current treatment for somatic disorder
3.79	Average number of cigarettes per day
3.98	CTQ: Sexual abuse score
4.27	Population density at place of living (inhabitants / km²)
4.42	Asian ethnicity
5.26	PAS (Childhood): Poor scholastic performance
5.95	LEE: Criticism by significant other
6.03	WSS: Magical ideation score
11.04	Age
12.57	Abdominal circumference



Stratification effects on functional trajectories (~600 days)

Mixed model analysis of GAF-Disability courses





Predictive biopsychosocial modelling
Clinical phenotyping
Digital sensing
Neurocognition
Neuroimaging
Proteomics
Transcriptomics
Genetics
Discriminative learning
Suicidality
Poor treatment response
Disinhibted behaviour
Cognitive basic symptoms
Candidate mechanisms
A
B
a1
a2
b1
b2
Computational modelling
Huys et al, Nat Neurosci, 2016, 19(3):404-413
Fernandes et al, BMC Medicine, 2017, 15, 80
Salazar de Pablo et al, Schizophr Bull, 2020
CBT
Evidence-based Medicine
PHASE 01
PHASE 02
PHASE 03
PHASE 04
Meta-analyses
GUIDELINES
Multimodal quantification
Identification of predictable mechanisms
Clinical implementation