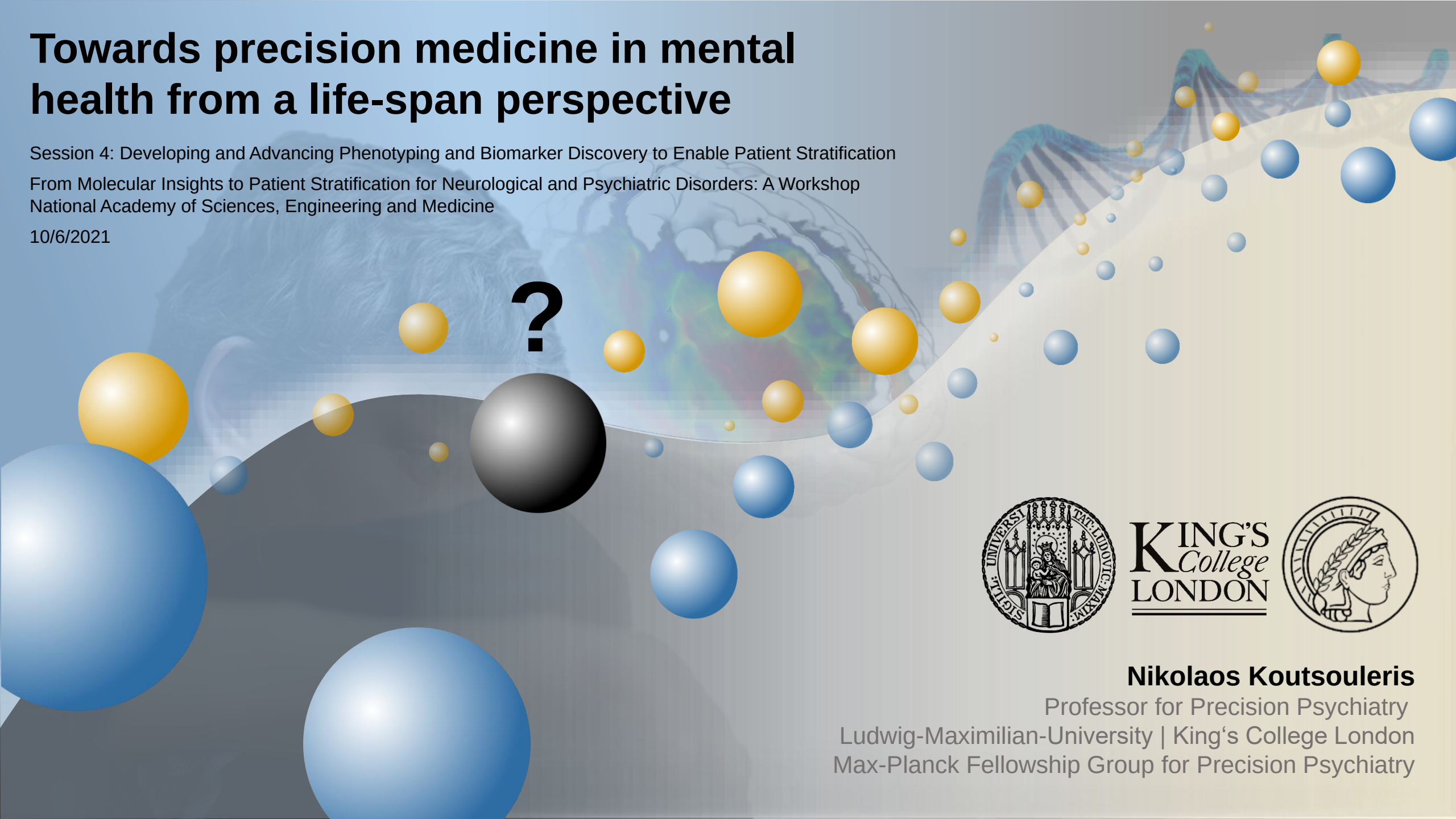
Towards precision medicine in mental health from a life-span perspective

Session 4: Developing and Advancing Phenotyping and Biomarker Discovery to Enable Patient Stratification

From Molecular Insights to Patient Stratification for Neurological and Psychiatric Disorders: A Workshop
National Academy of Sciences, Engineering and Medicine

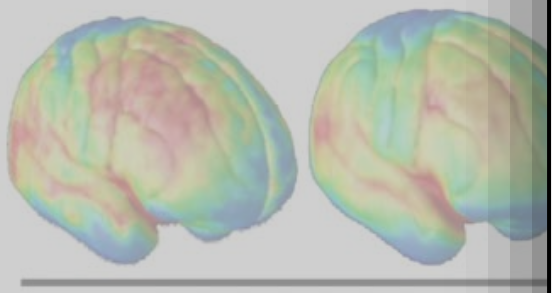
10/6/2021



Nikolaos Koutsouleris
Professor for Precision Psychiatry
Ludwig-Maximilian-University | King‘s College London
Max-Planck Fellowship Group for Precision Psychiatry

The challenge of longitudinal disease heterogeneity

Schizophrenia spectrum, bipolar a

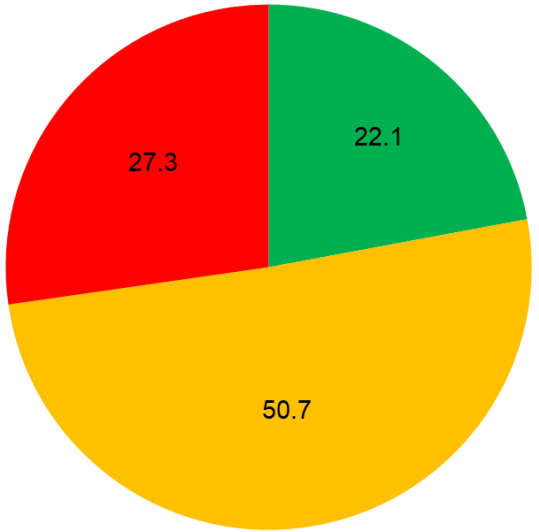


Healthy controls

5

Functioning

502 first-episode patients followed over 20 years



Social and occupational recovery in % of cases

Trajectory types

- episodic → **80-100%**
- intermediate → **25-80%**
- residual → **0-25%**

Huber et al. Schizophrenia Bulletin,1980;6:592–605.

Childhood | Adolescence | Early adulthood

time

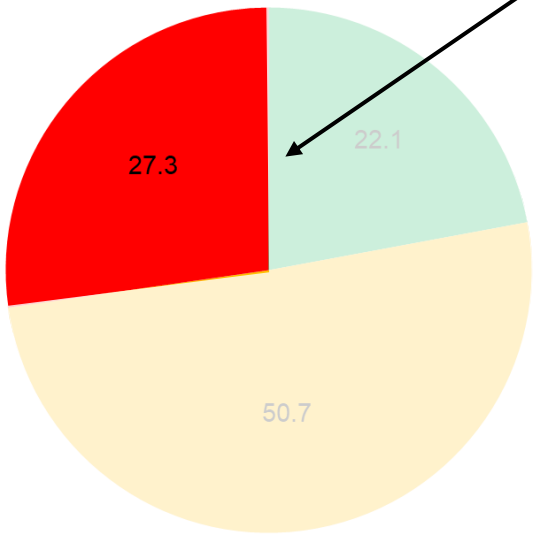
Gogtay and Thompson, Brain and Cognition, 72(1): 6–15

The challenge of longitudinal disease heterogeneity

Schizophrenia s

502 first-episode patients followed over 20 years

Neuroprogressive disease pathology?



Trajectory types

- episodic → 80-100%
- intermediate → 25-80%
- residual → 0-25%

Davis et al. Aust N Z J Psychiatry,2014;48(6):512–429
Schnack et al. AJP, 2016;173(6):607-616

Healthy controls

5

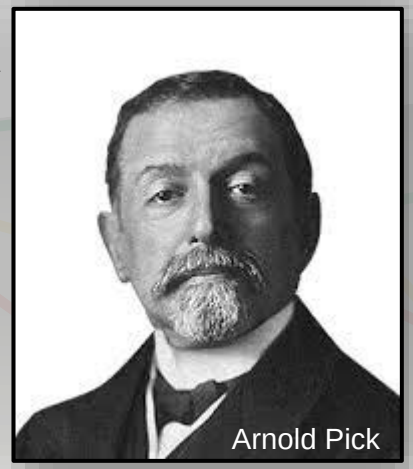
Functioning

Childhood | Adolescence | Early adulthood | time

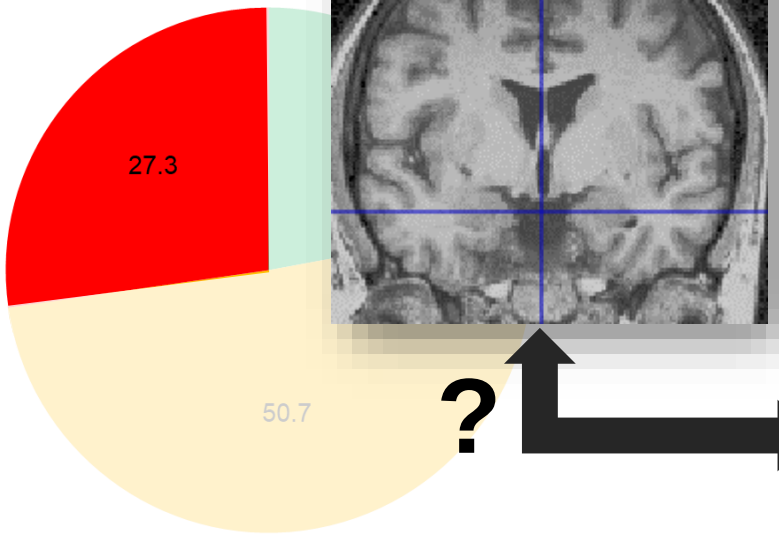
Gogtay and Thompson, Brain and Cognition, 72(1): 6–15

The challenge of longitudinal disease heterogeneity

Schizophrenia s… a…

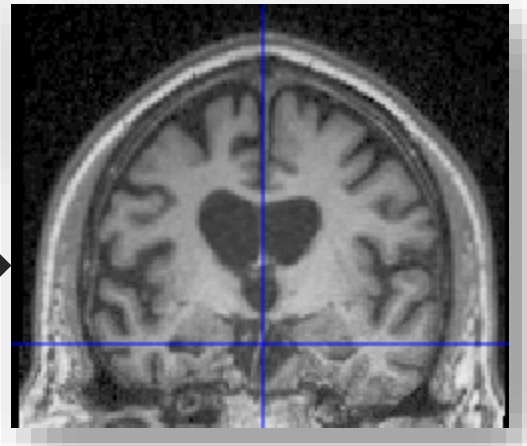


Schizophrenia / Dementia praecox



?

Behavioural-variant FTD



Healthy controls

5

Functioning

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

Adolescence

Early adulthood

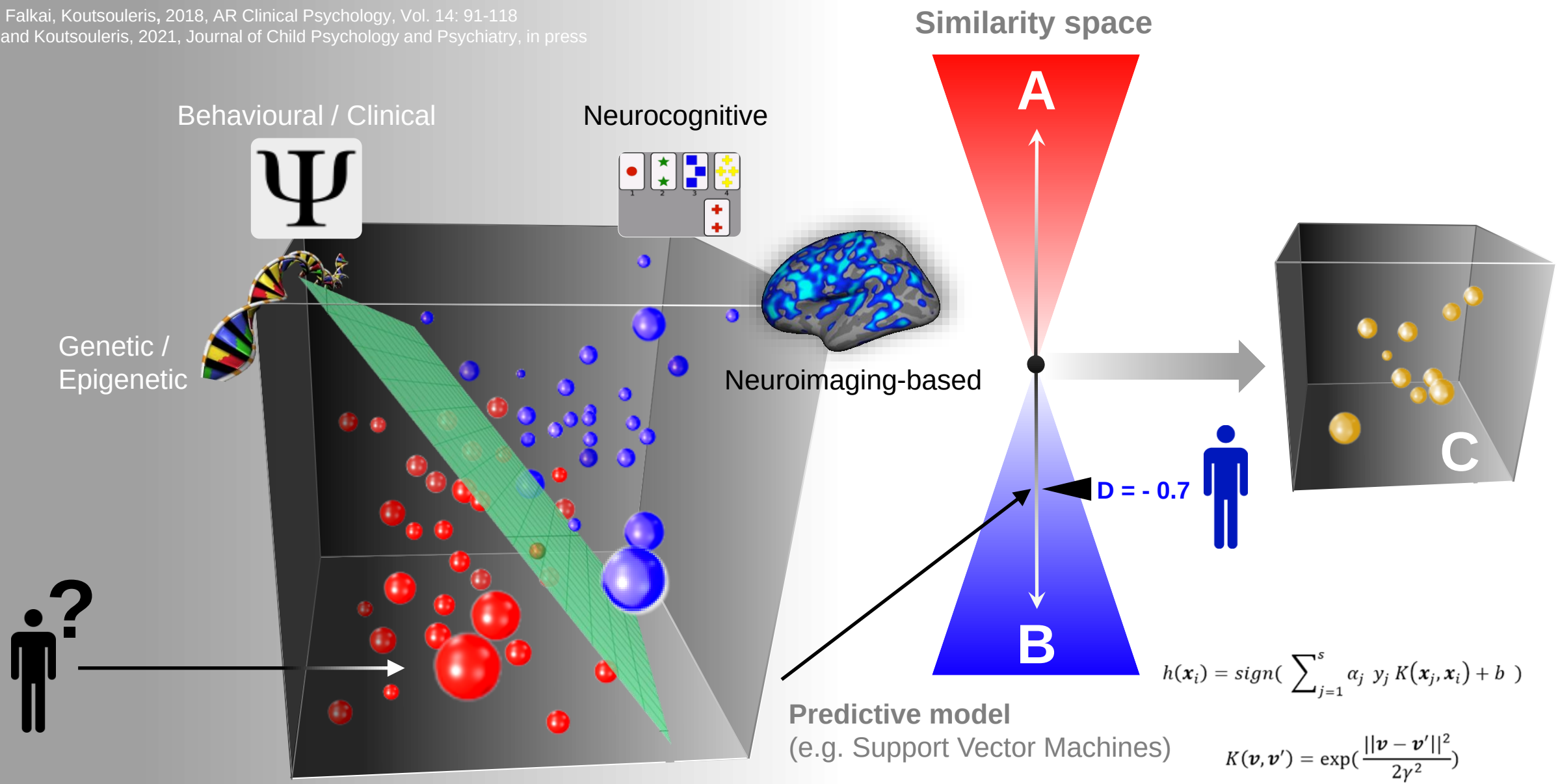
time

Gogtay and Thompson, Brain and Cognition, 72(1): 6–15

Understanding heterogeneity

Comparative neuroscience based on supervised machine learning

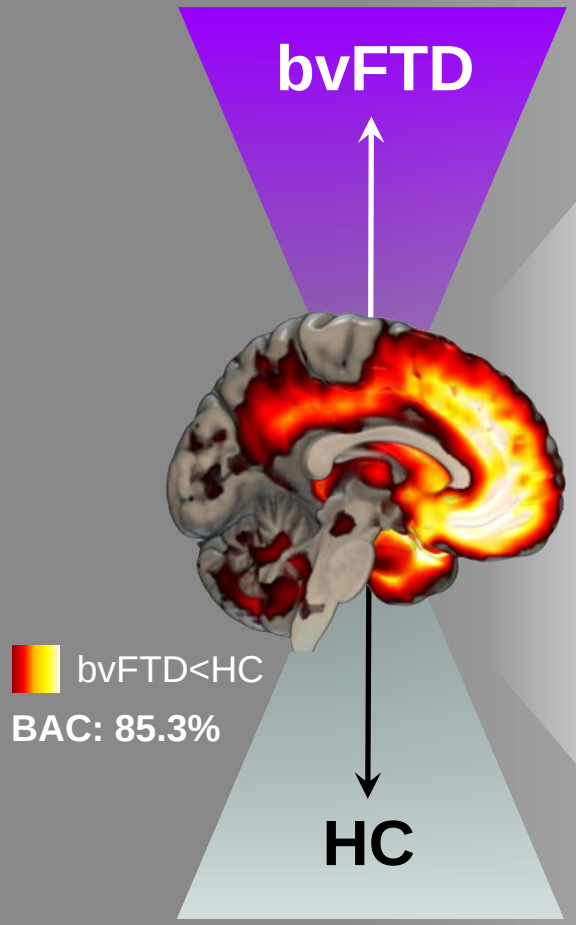
Dwyer, Falkai, Koutsouleris, 2018, AR Clinical Psychology, Vol. 14: 91-118
Dwyer and Koutsouleris, 2021, Journal of Child Psychology and Psychiatry, in press



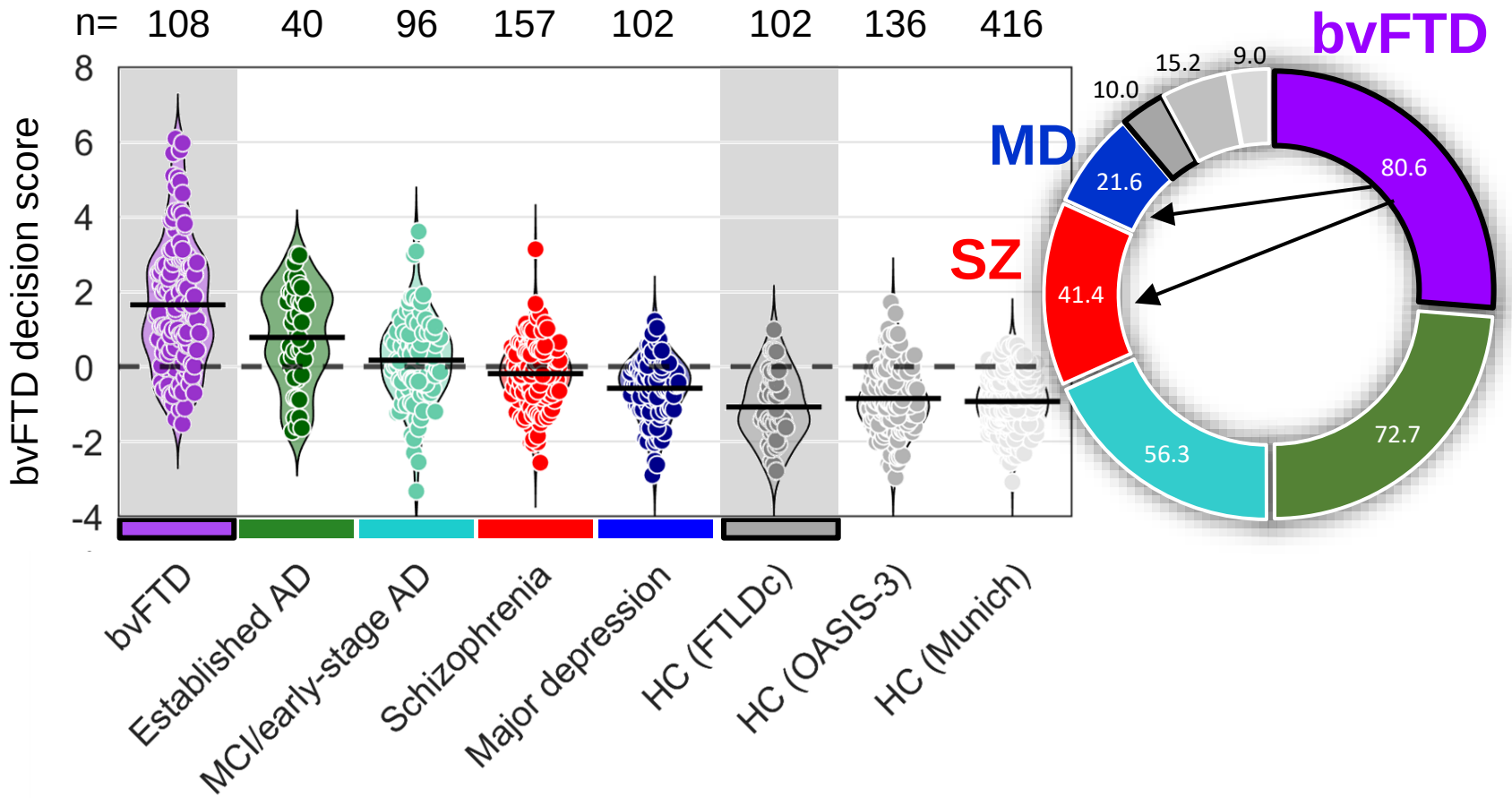
Understanding heterogeneity

Comparative neuroscience strategies crossing the borders between psychiatry and neurology

Trained neuroanatomical similarity model



sMRI-based bvFTD classifier applied across different diagnostic cohorts



Koutsouleris et al. 2014, Schizophrenia Bulletin, 40(5): 1140-115

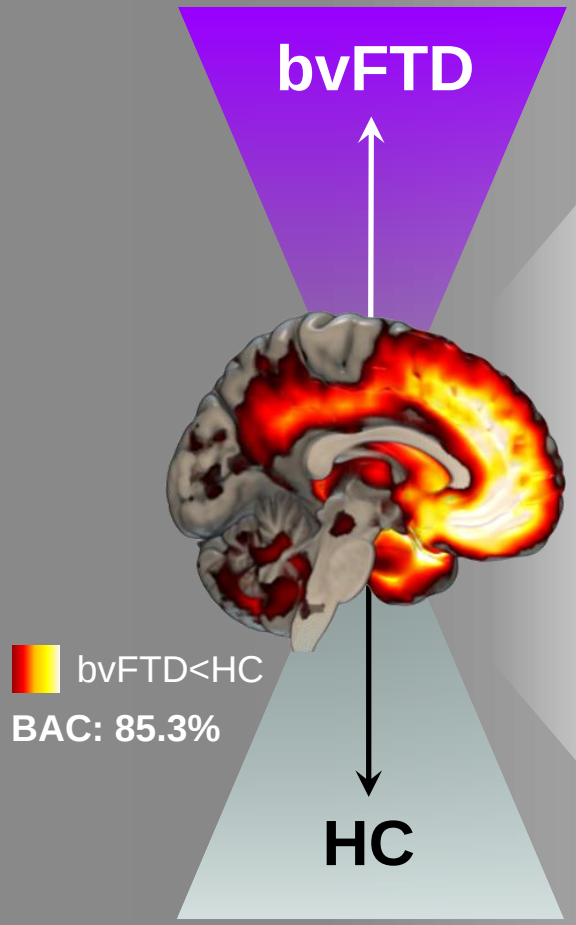
Koutsouleris et al. 2015, Brain, 138(Pt 7): 2059-2073

Koutsouleris et al. 2021, under review

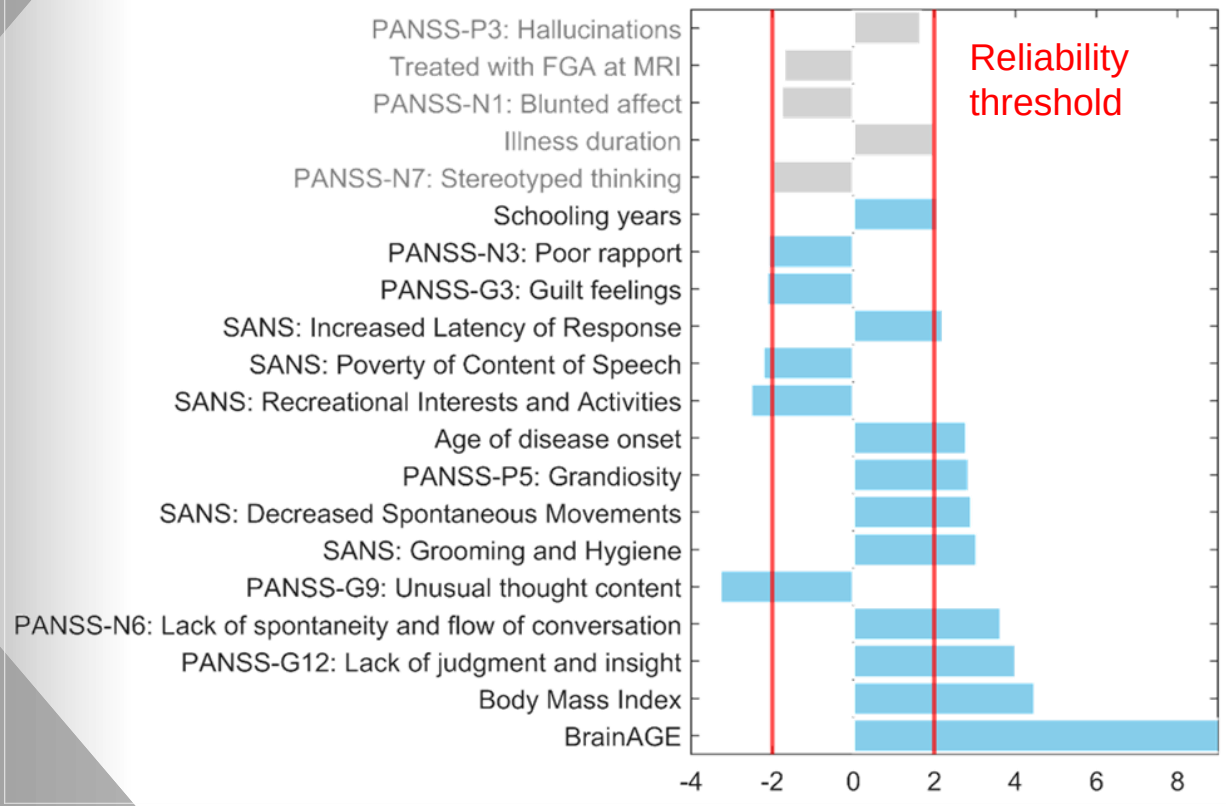
Understanding heterogeneity

Comparative neuroscience strategies revealing shared clinical phenotypes between SCZ and bvFTD

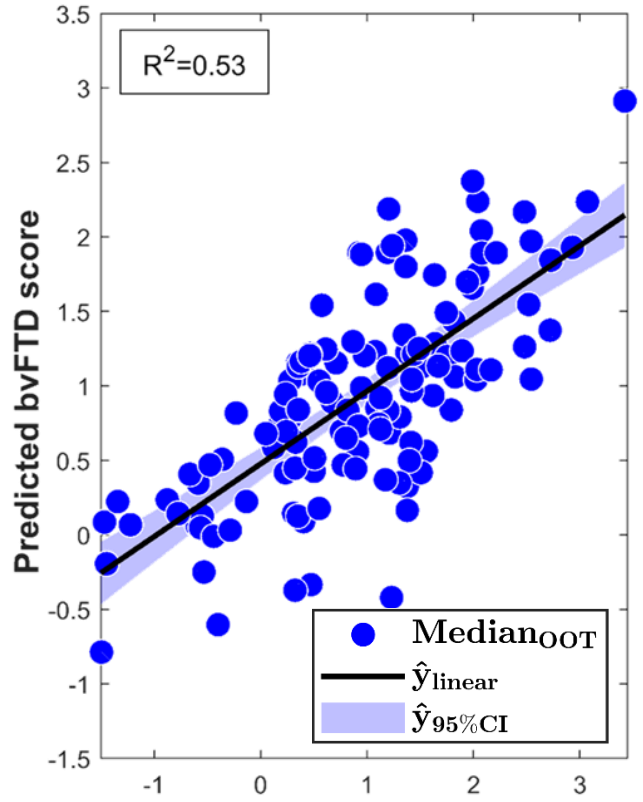
Trained neuroanatomical similarity model



Clinical and physical variables predicting high bvFTD scores in schizophrenia patients (n=127)



‚Mapping accuracy‘



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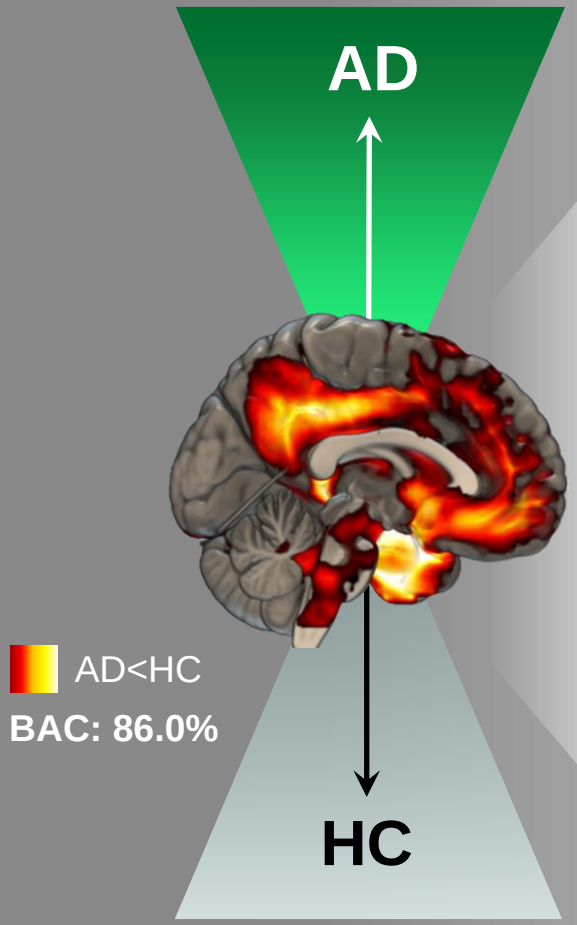
Koutsouleris et al. 2021, under review

Understanding heterogeneity

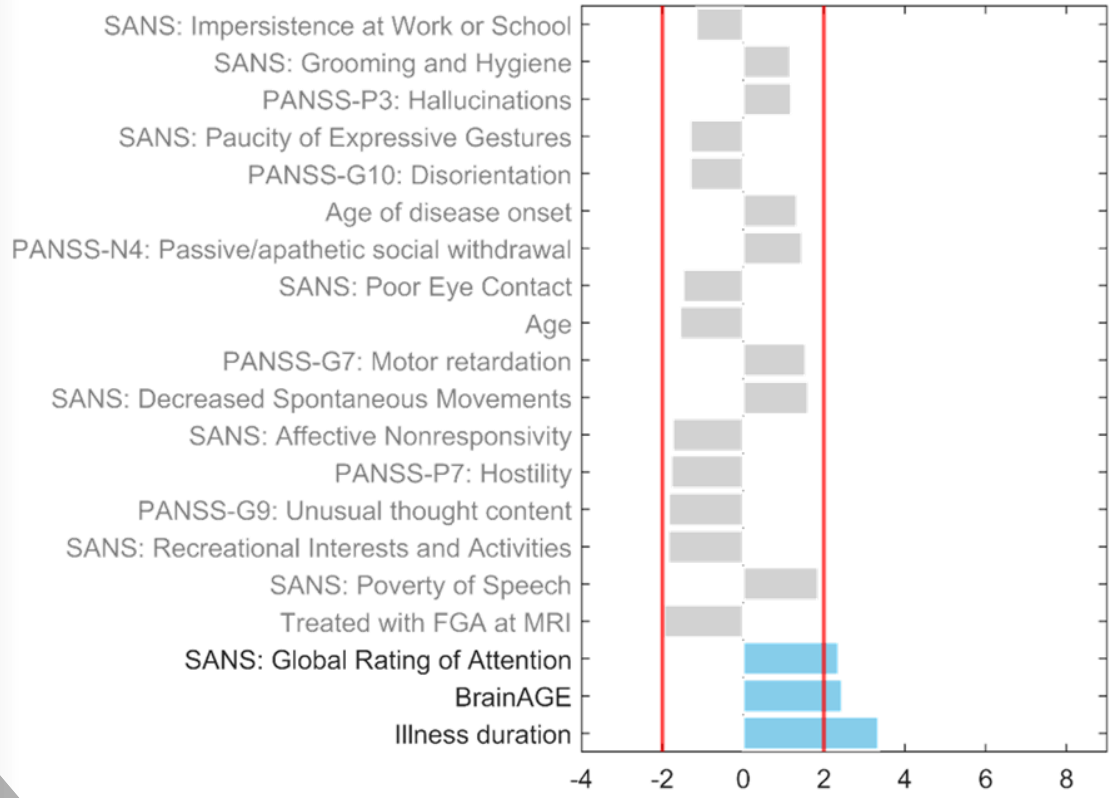
Comparative neuroscience strategies showing specific predictability of bvFTD brain patterns in SCZ

Trained neuroanatomical similarity model

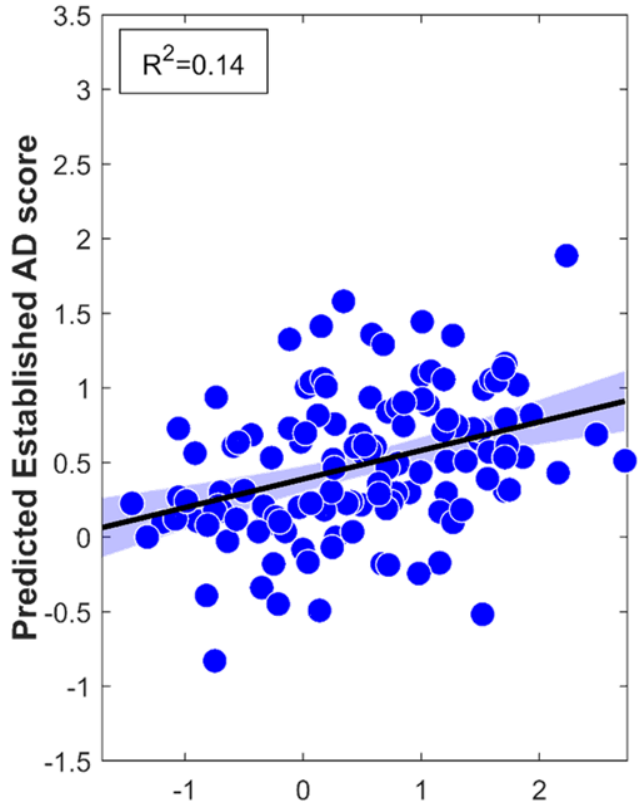


BAC: 86.0%

Clinical and physical variables predicting high AD scores in schizophrenia patients (n=127)



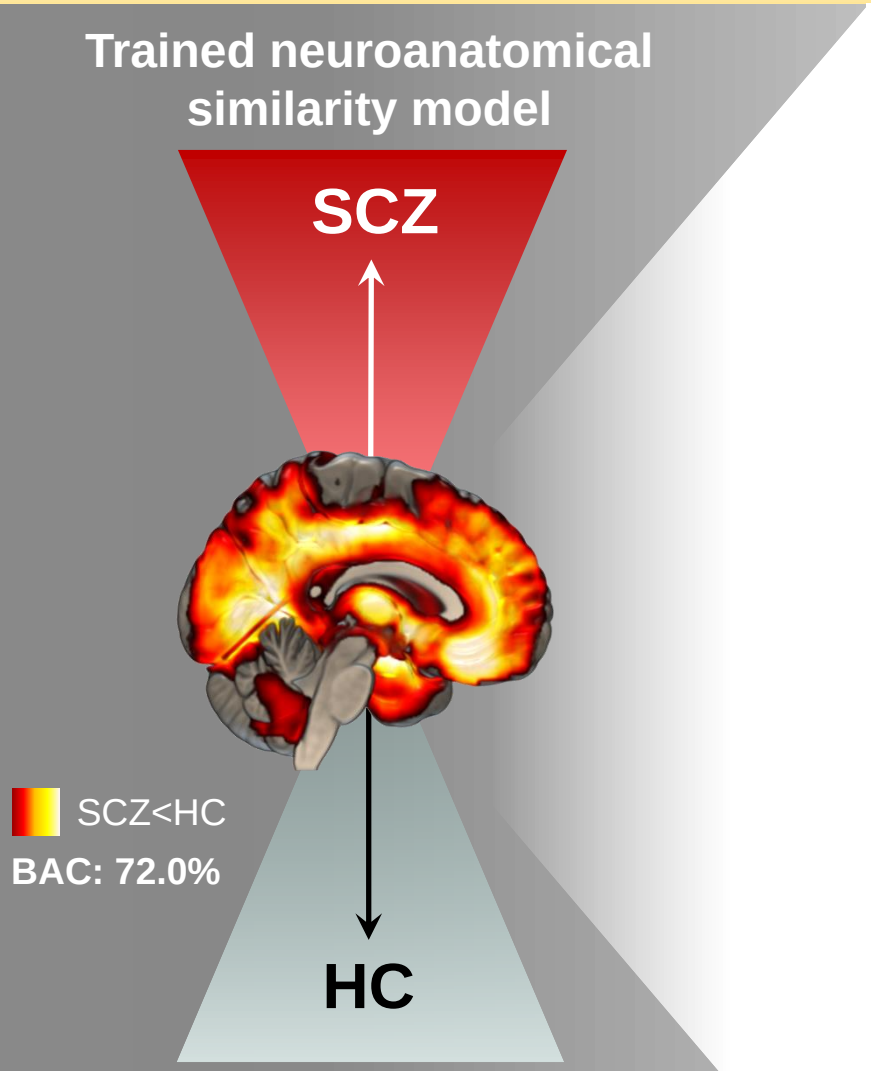
‚Mapping accuracy‘

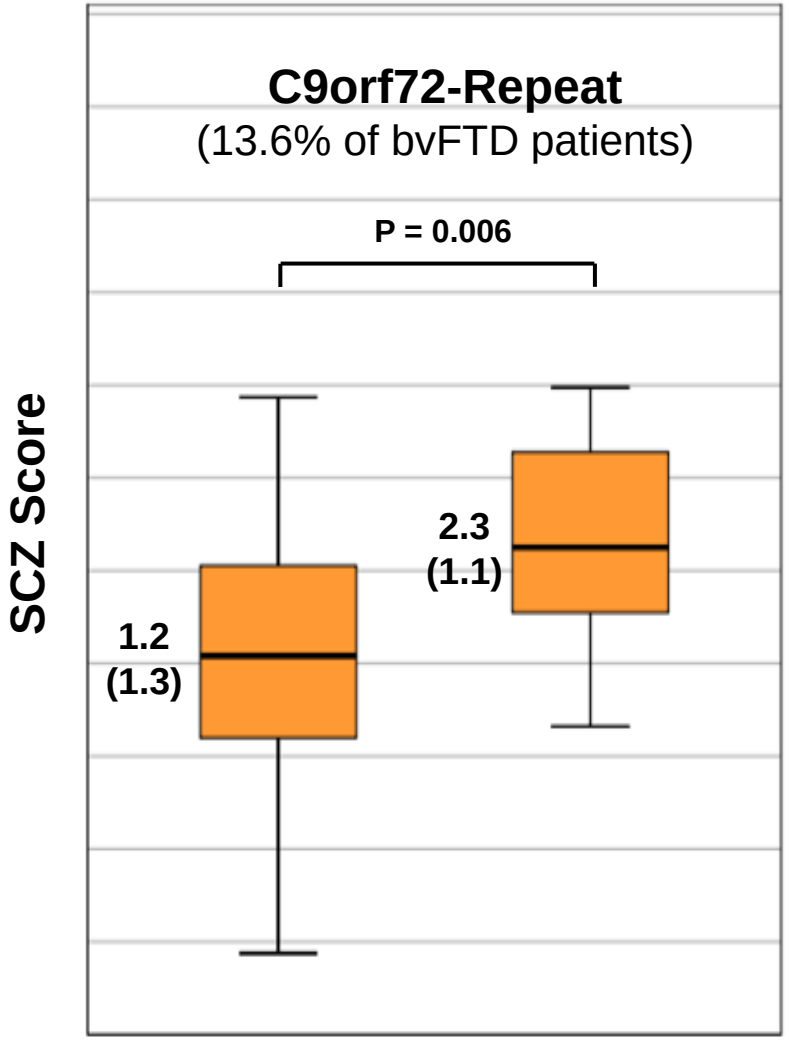


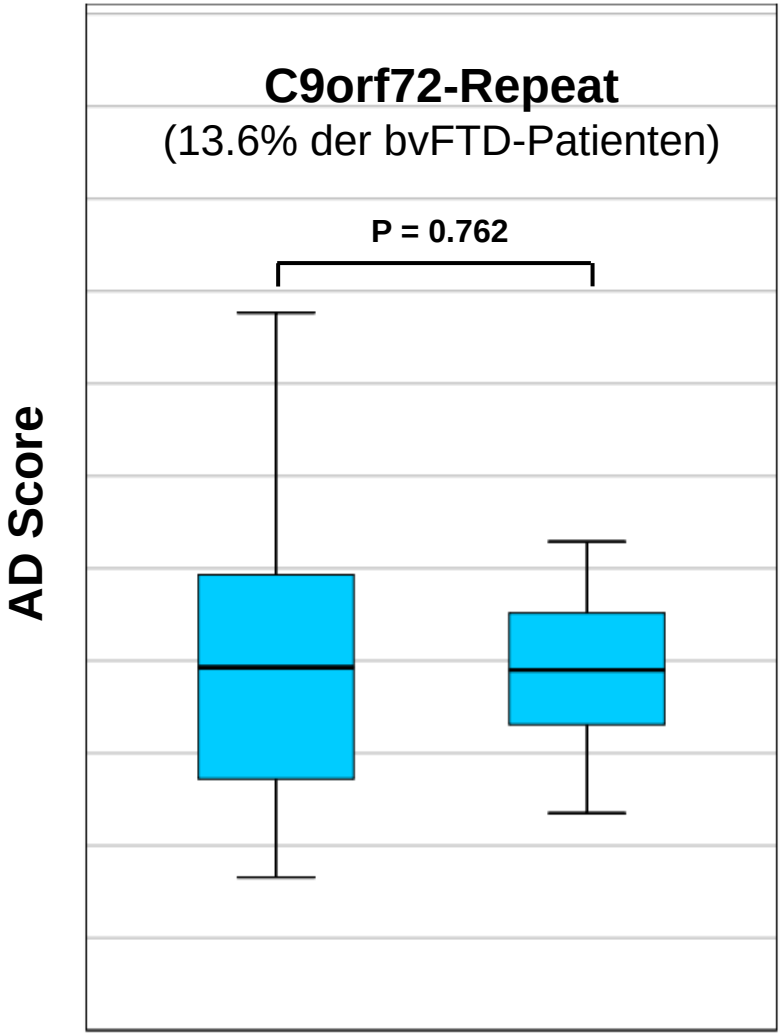
Koutsouleris et al. 2014, Schizophrenia Bulletin, 40(5): 1140-115
Koutsouleris et al. 2015, Brain, 138(Pt 7): 2059-2073
Koutsouleris et al. 2021, under review

Understanding heterogeneity

Comparative neuroscience strategies showing C9orf72 association of SCZ pattern expression in bvFTD





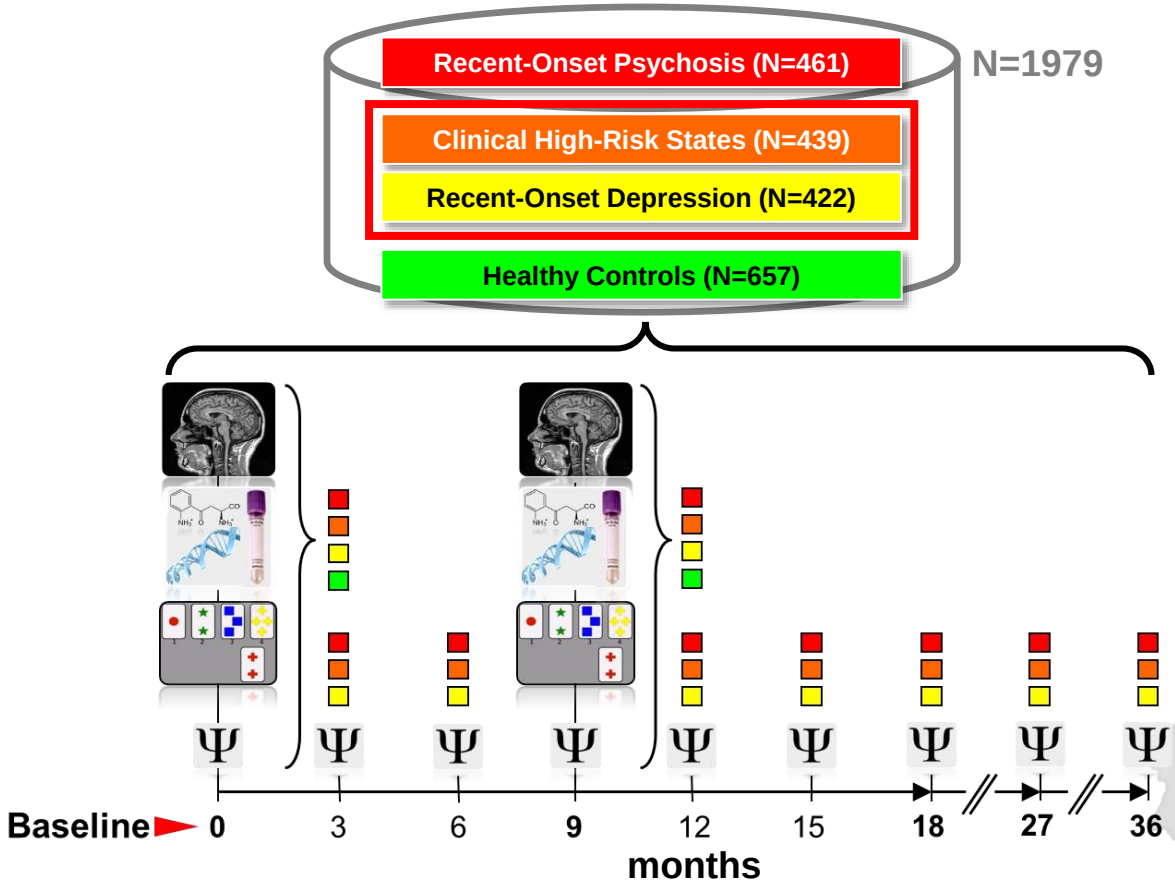


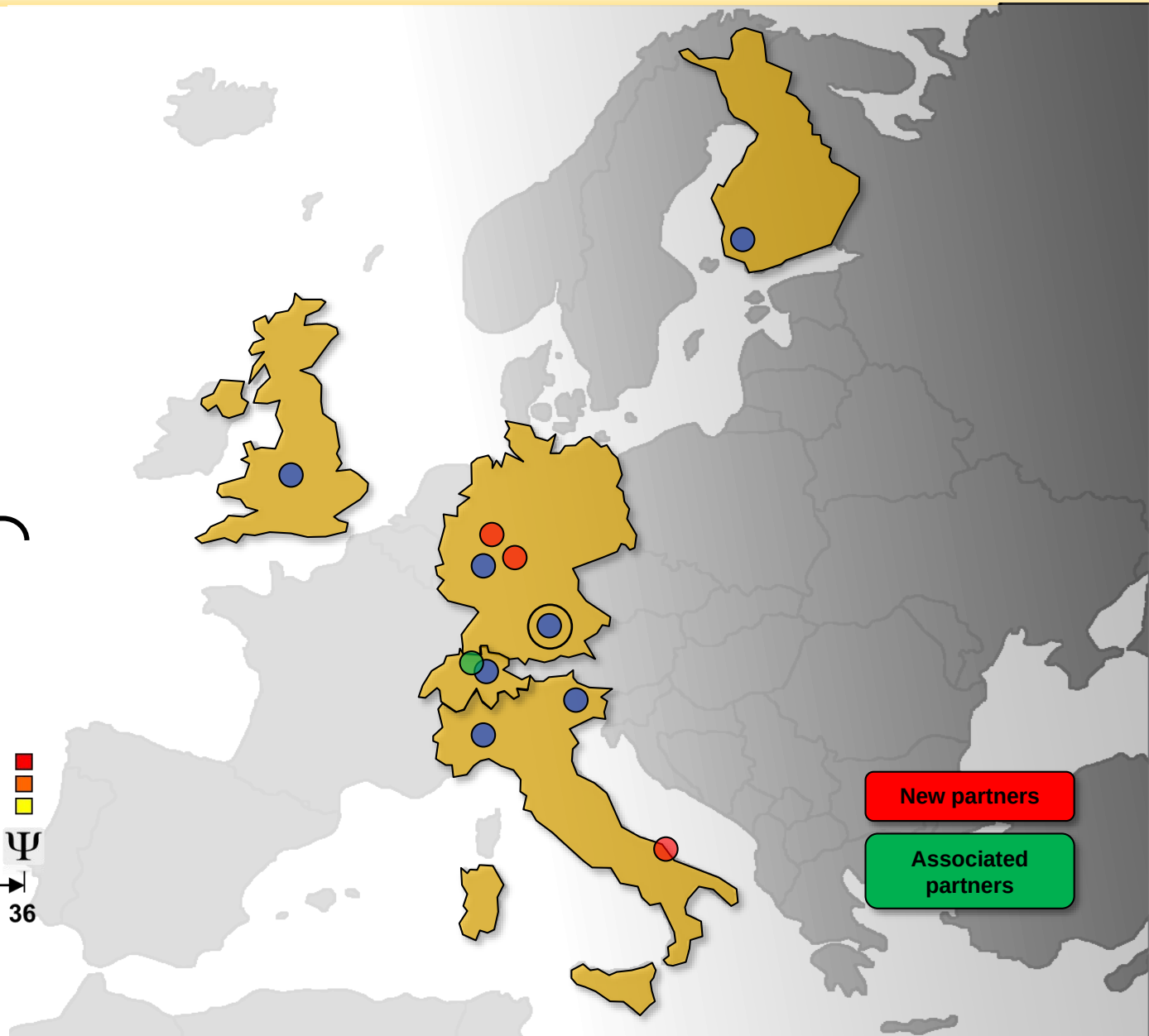
Koutsouleris et al. 2014, Schizophrenia Bulletin, 40(5): 1140-115
Koutsouleris et al. 2015, Brain, 138(Pt 7): 2059-2073
Koutsouleris et al. 2021, under review

Understanding longitudinal heterogeneity

Can we learning something from these cross-sectional analyses for predicting outcomes?

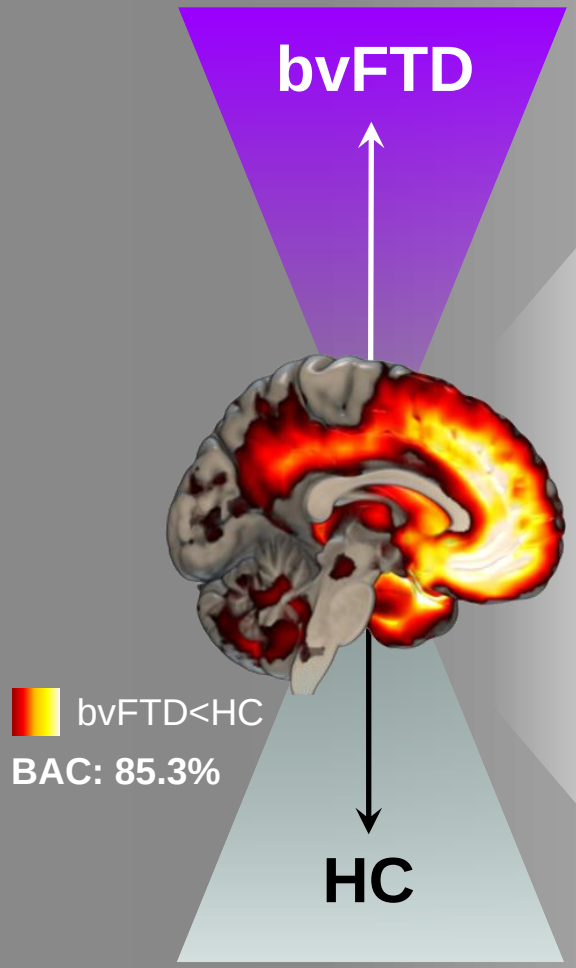
PRONIA

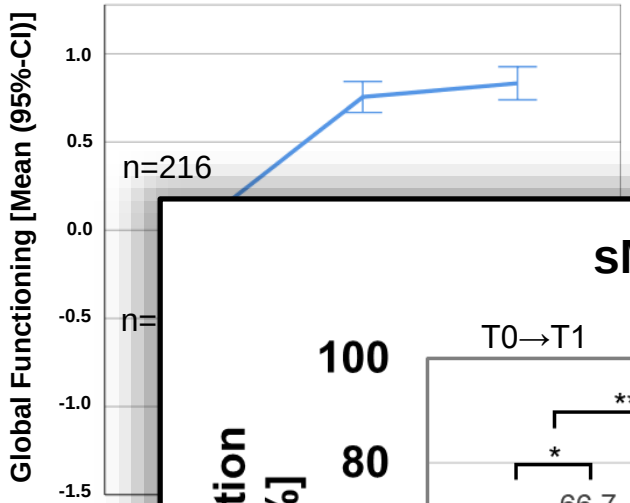




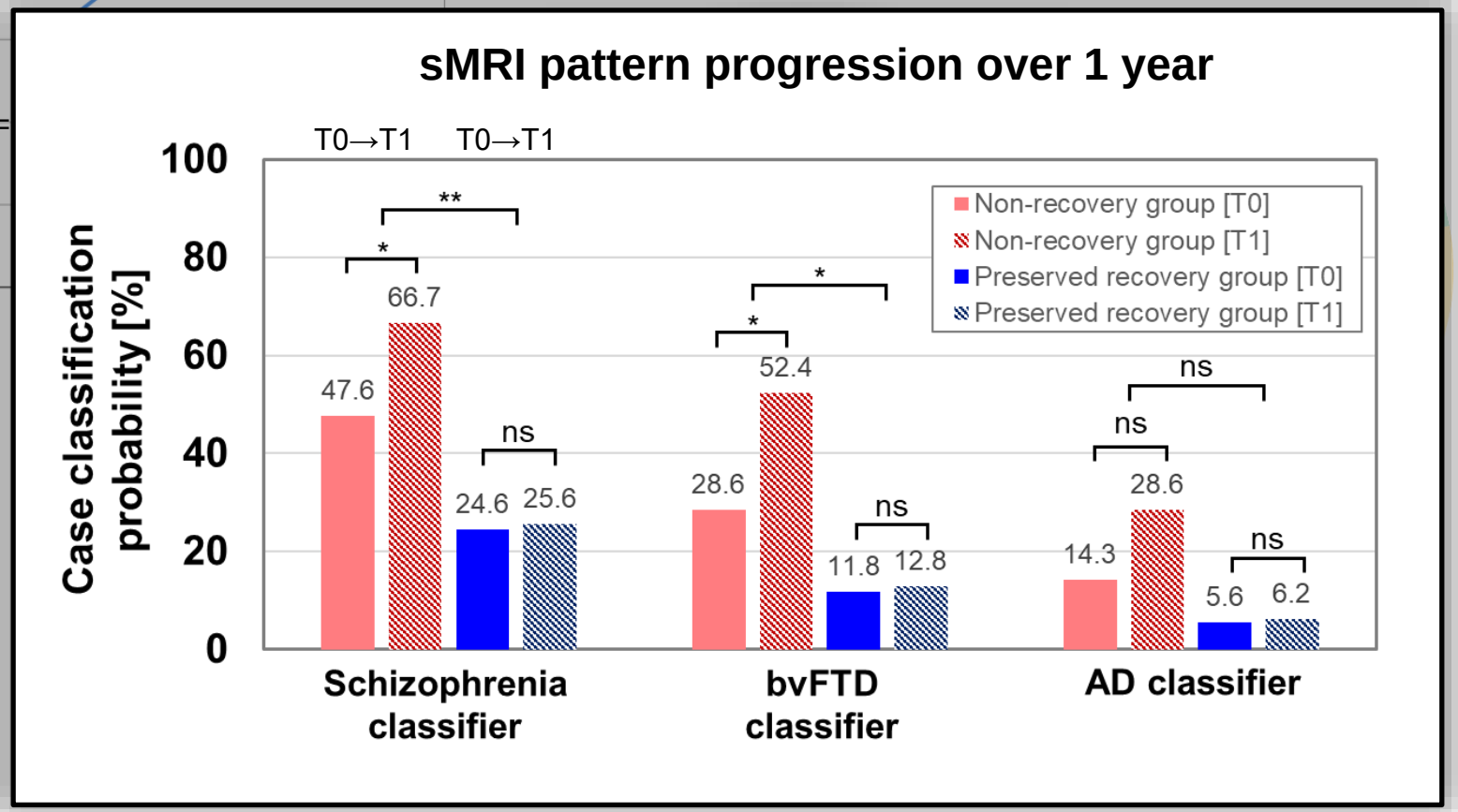
Understanding longitudinal heterogeneity

Testing the neuroprogression hypothesis in early-stage disease samples





Functional non-recovery: average follow-up functioning ≤ lower quartile of the baseline



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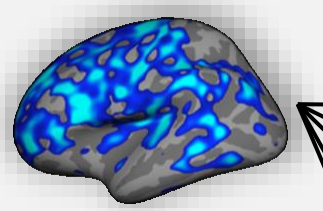
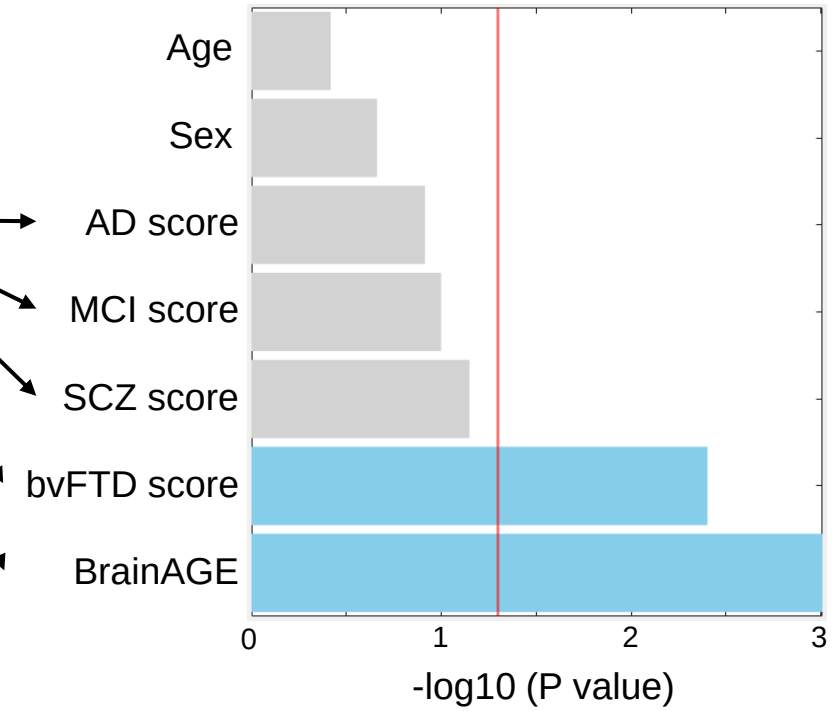
From promise to practice

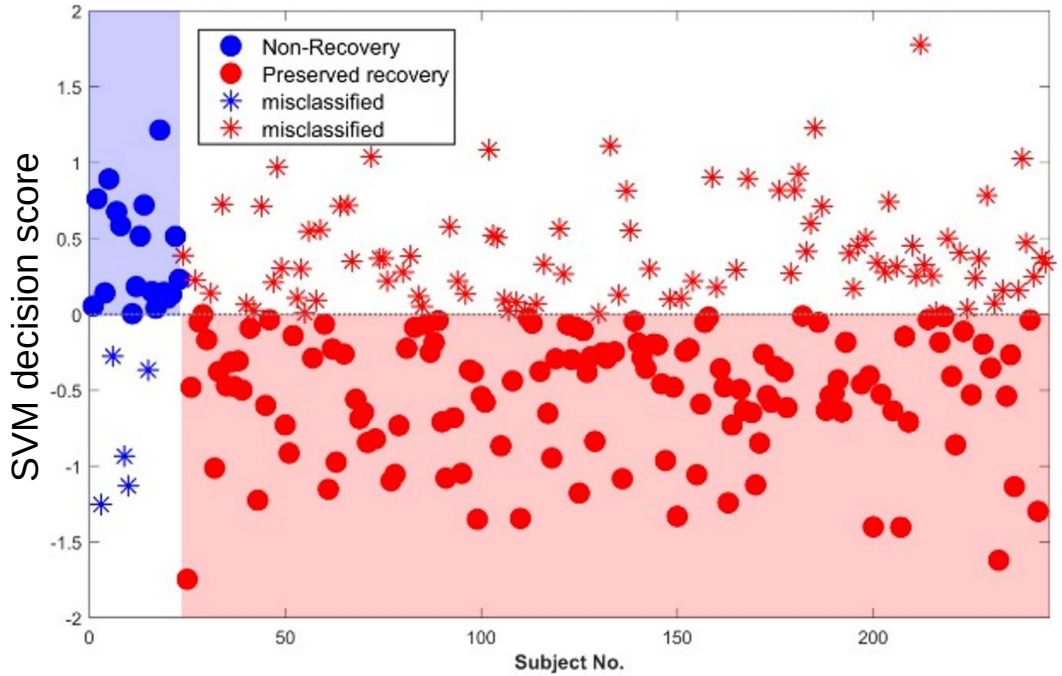
Using diagnostic decompositions to predict **2-years non-recovery courses** in CHR and ROD patients

Diagnostic decompositon model



Sensitivity:	**73.9%**
Specificity:	**59.3%**
BAC:	**66.6%**
AUC:	**0.67**





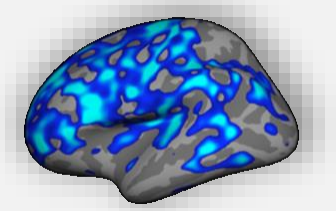
Koutsouleris et al. 2021, under review

PRONIA

From promise to practice

Using multiple data domains to predict **2-years non-recovery courses** in CHR and ROD patients

Diagnostic decomposition model

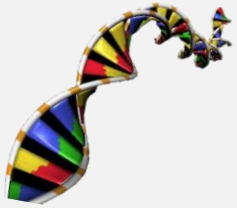


Sensitivity:	73.9%
Specificity:	59.3%
BAC:	66.6%
AUC:	0.67

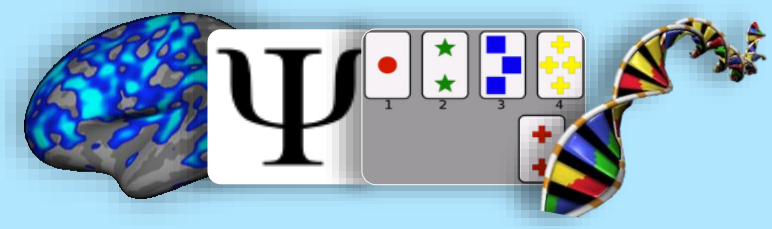
Clinical-neurocognitive risk calculator

Sensitivity:	69.6%
Specificity:	53.4%
BAC:	61.5%
AUC:	0.64

Poly-PRS-based risk calculator



Sensitivity:	77.3%
Specificity:	54.5%
BAC:	65.9%
AUC:	0.71



Sensitivity:	69.6%
Specificity:	**75.1%**
BAC:	**72.3%**
AUC:	**0.78**

Koutsouleris et al. 2021, under review

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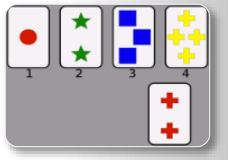
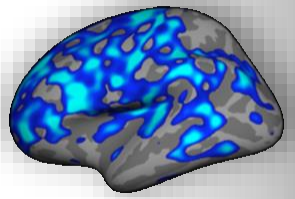
Toward the real-world implementation of biomarkers

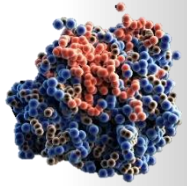
Clinical phenotyping
Digital sensing



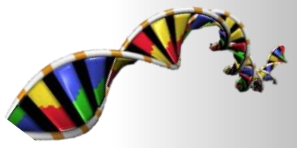
Neurocognition



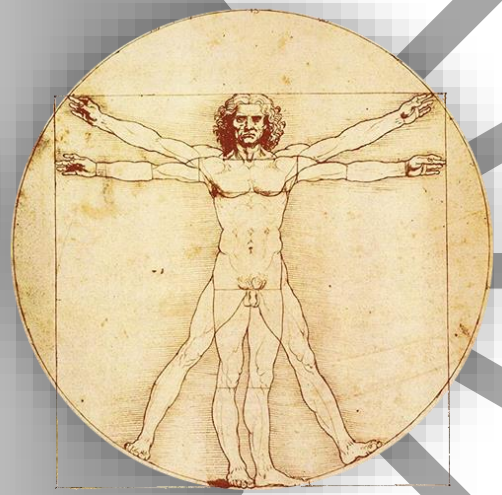
Neuroimaging



Proteomics
Transcriptomics



Genetics



To assess and compare data domains for their diagnostic, prognostic and theragnostic utility.

To test models across different phenotypes, patient populations and disease gradients/stages.

Based on lessons learned, to iteratively refine clinical applications areas for ‘algorithmic augmentation’.

To test clinical effectiveness of model-informed treatments in biomarker-stratified clinical trials.

To improve models and treatments via bedside-to-bench and bench-to-beside development cycles.