Developing imaging predictors and neurobehavioural phenotypes for externalising disorders.

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Reinforcement-related behaviour in normal brain function and psychopathology

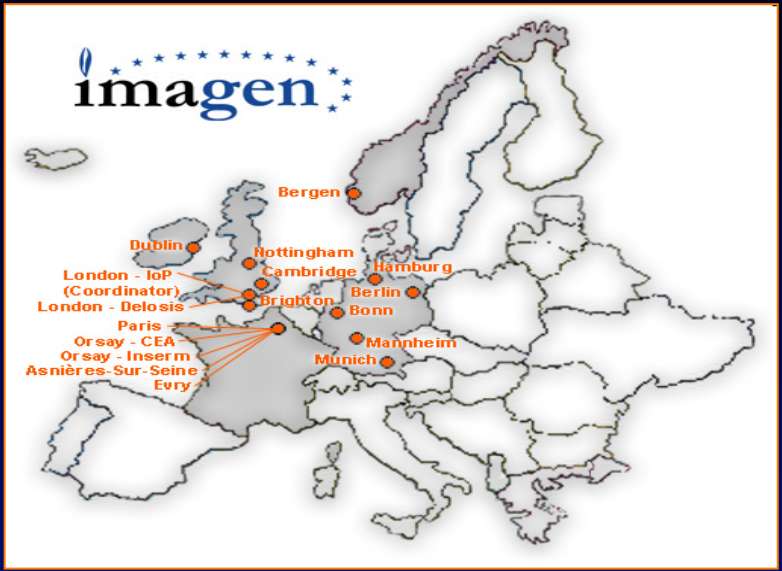
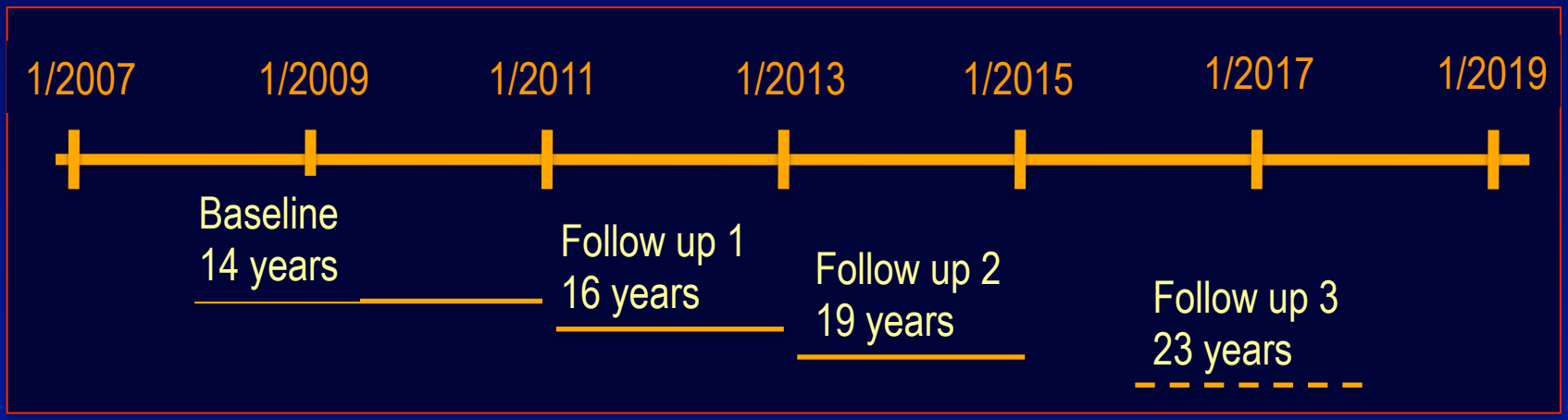
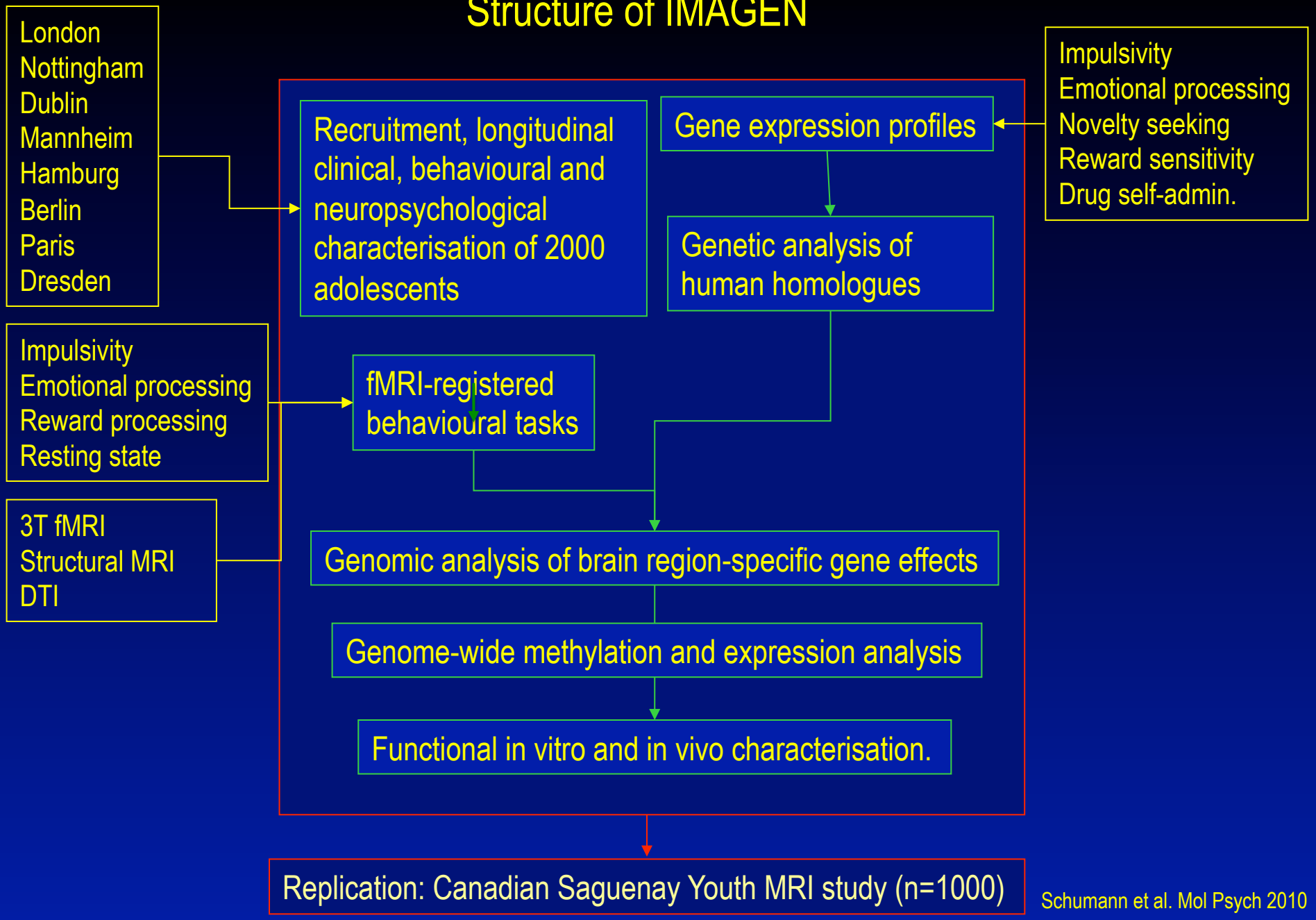


IMAGEN is a longitudinal, multi-centre functional and structural neuroimaging genetic study of a cohort of 2000+ adolescents, investigating the neurobiological basis of individual differences in brain activity during reward, impulsiveness and emotional reactivity at 14, 16 and 19 years



Schumann et al. Molecular Psychiatry 2010

Structure of IMAGEN



Schumann et al. Mol Psych 2010

History

Personality

Genetics

Brain

Cognition

Environment

Predictors of alcohol abuse:

"Neuropsychosocial profiles of current and future adolescent alcohol misusers"

Neuropsychosocial profiles of current and future adolescent alcohol misusers

115 Binge Drinker
Age 14 years

150 controls
(no alcohol at
14 and 16 years)

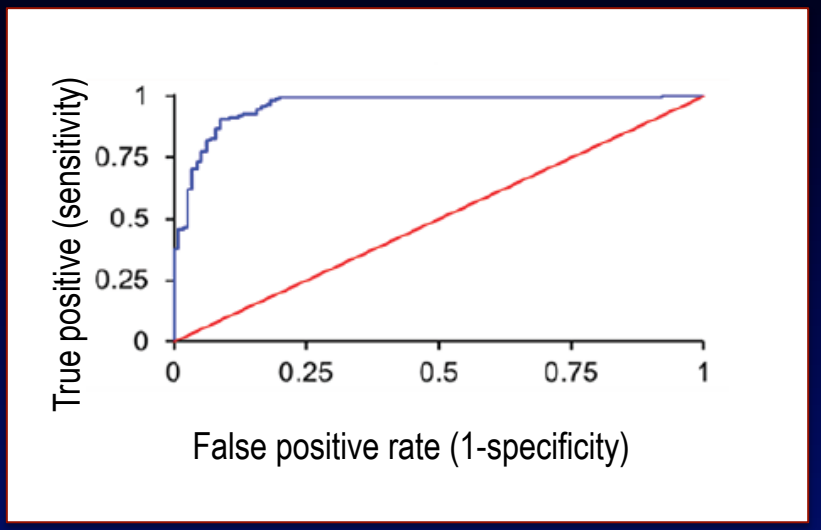
121 future binge drinkers
(16 years)

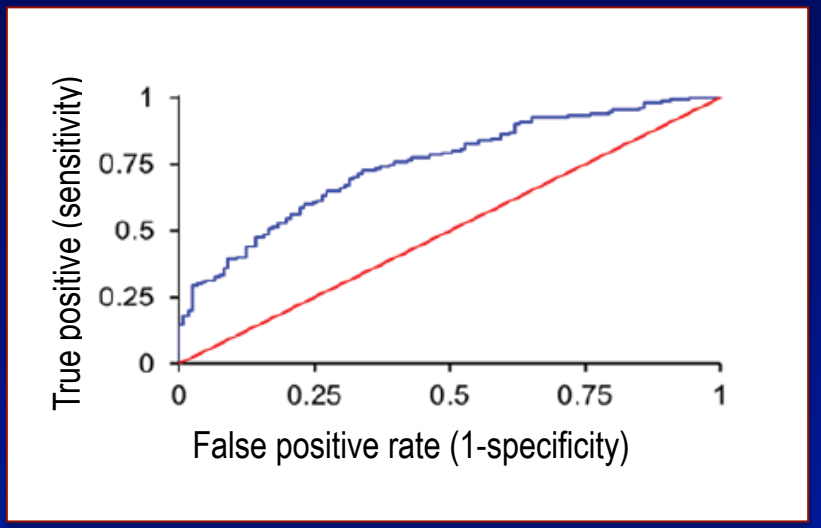
Classification

91% correct
($p=8 \times 10^{-61}$)

Prediction

66% correct
($p=4.2 \times 10^{-17}$)





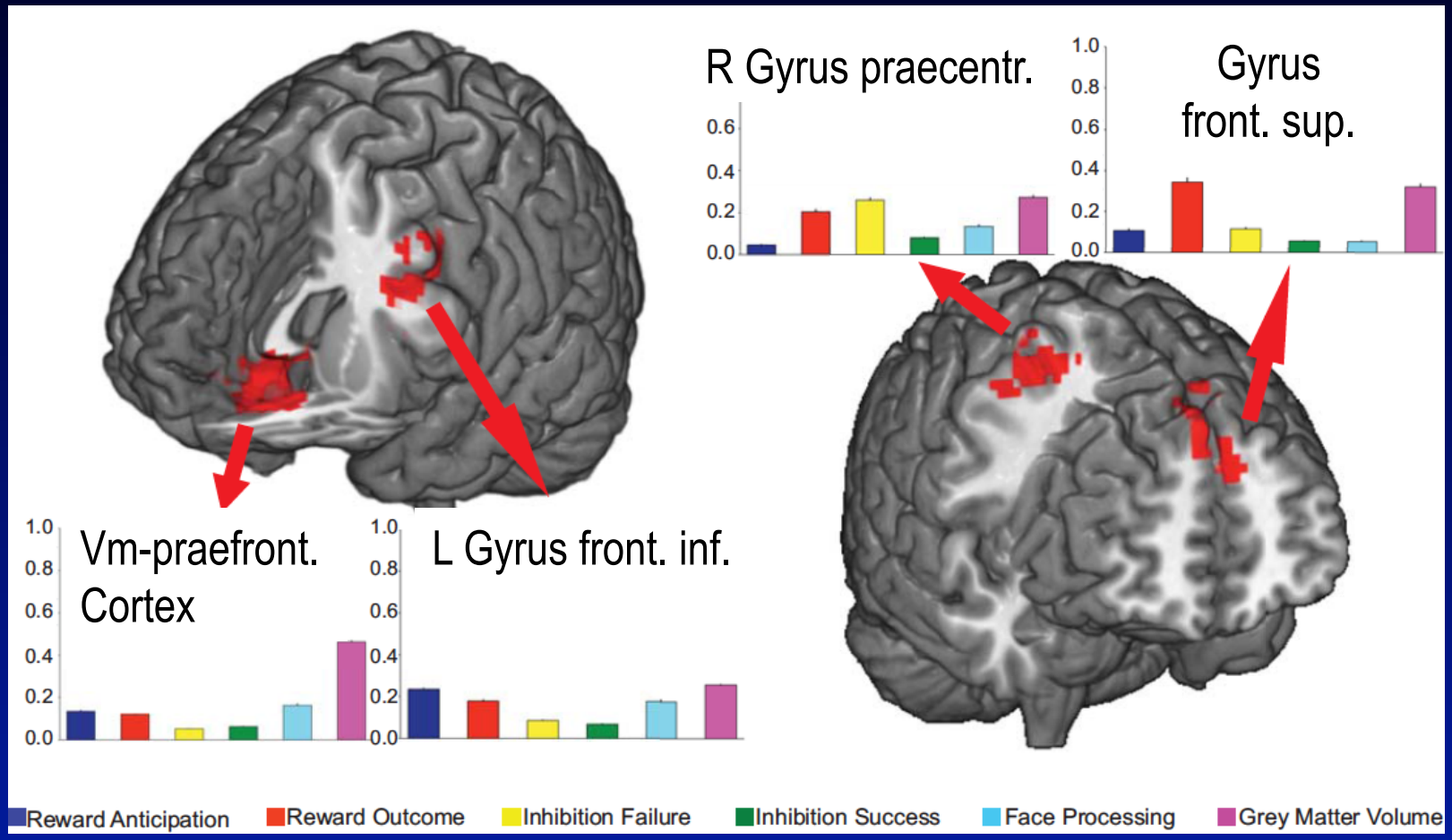
Regularised logistic regression

Whelan et al. Nature (2014)

Association of brain region und alcohol abuse

Classification (14 Jahre)

Prediction (16 Jahre)



Whelan et al. Nature (2014)

Neuropsychosocial profiles of alcohol misuse

History

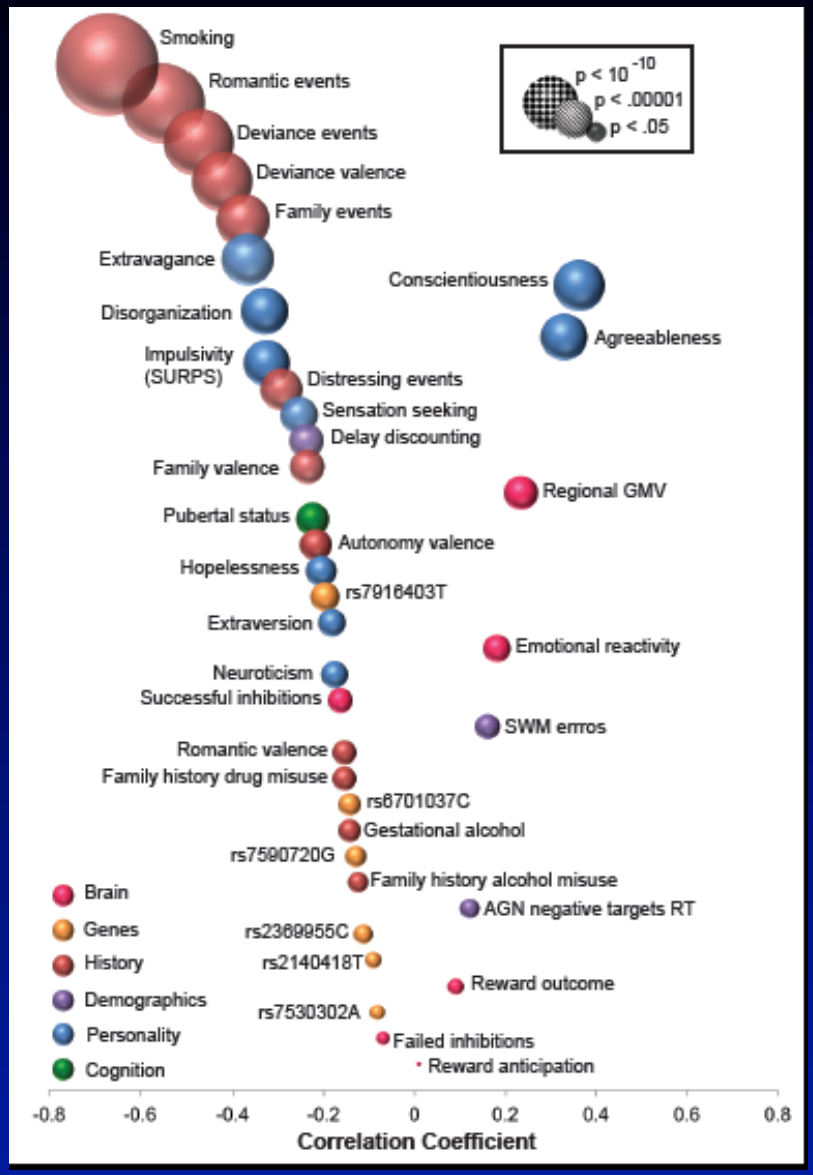
Personality

Genetics

Brain

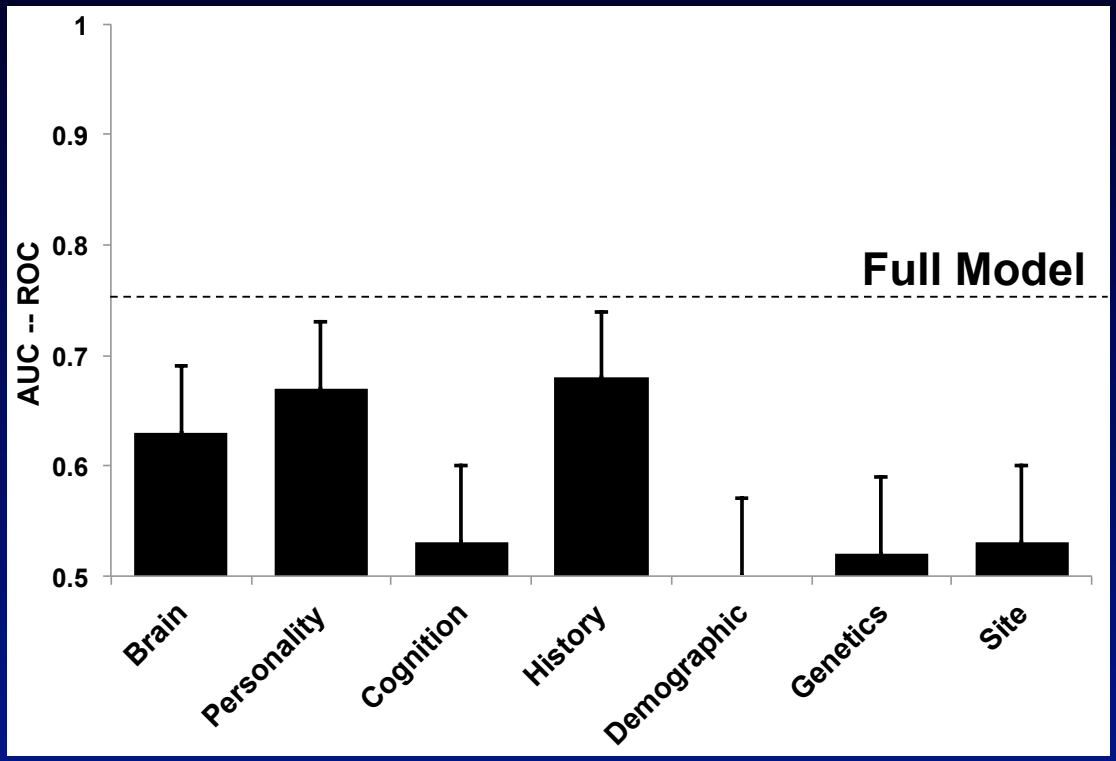
Cognition

Environment



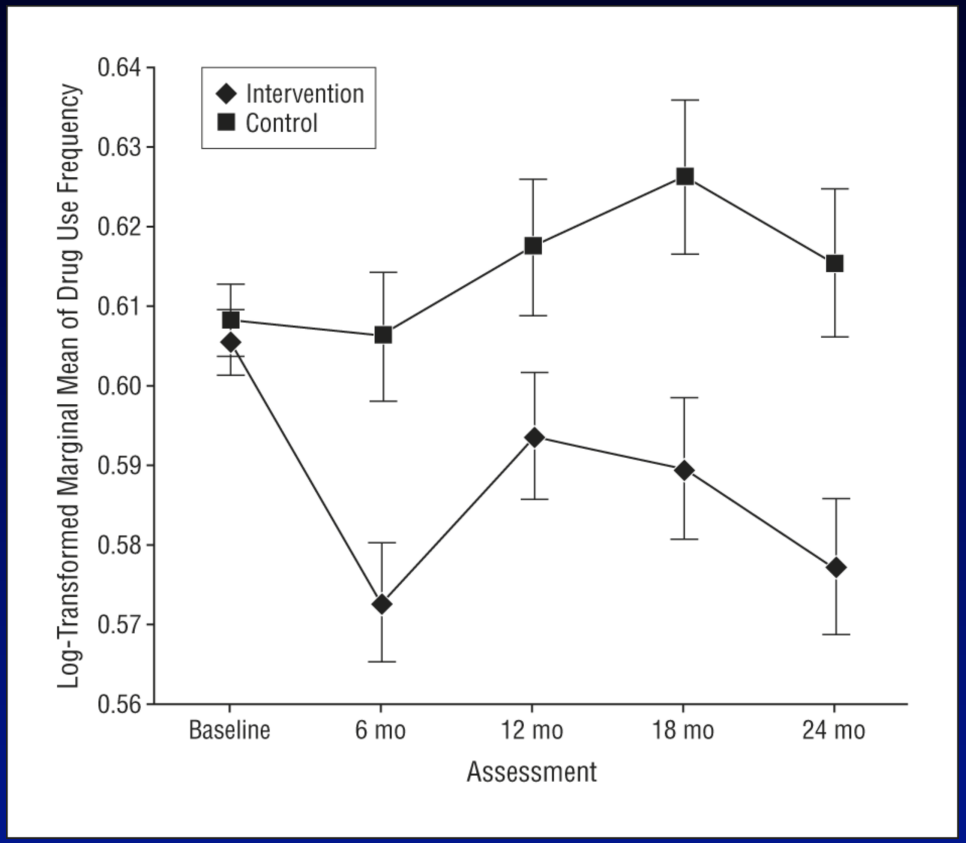
Whelan et al. Nature (i2014)

Binge Drinking Prediction - Domains



Whelan et al. Nature (2014)

Brief, Personality-Targeted Coping Skills Interventions and Survival as a Non–Drug User



N=732 fourteen year old adolescents;
Control condition is standard school drug education curriculum

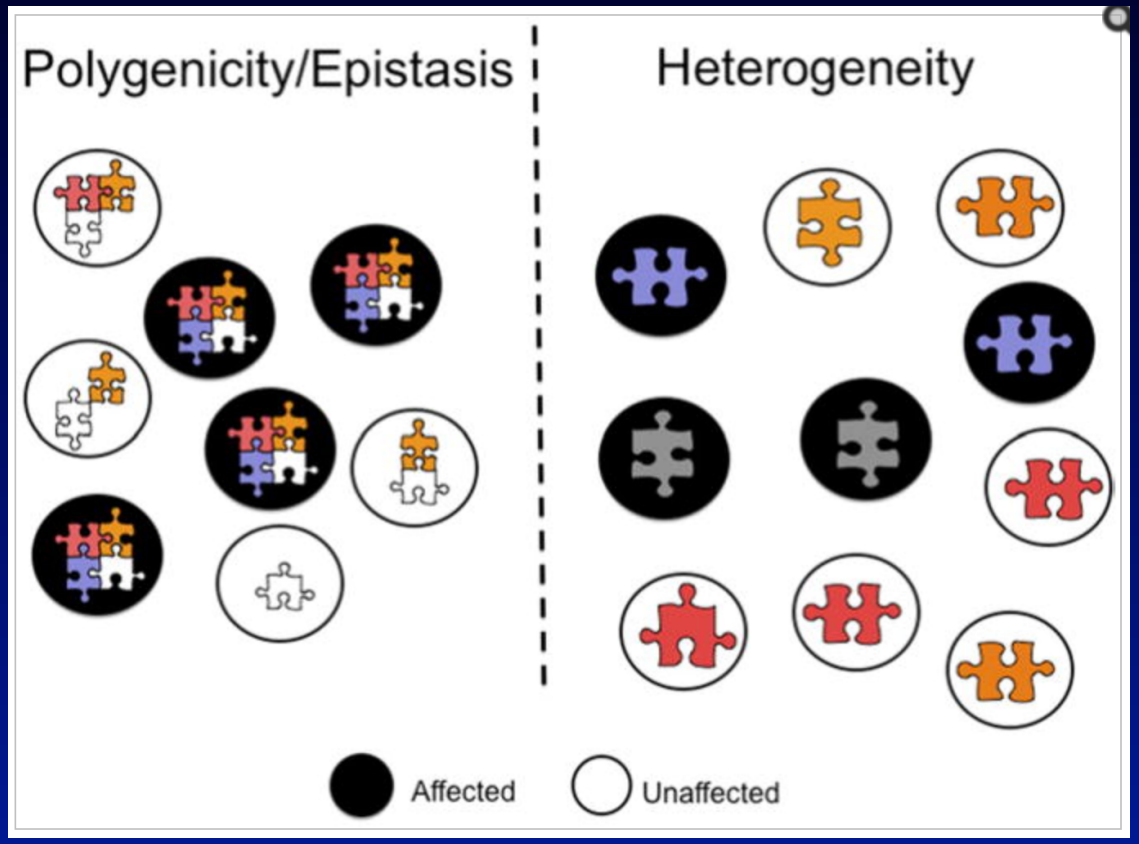
Conrod et al., Arch. Gen. Psychiatry 2010

(i) Multimodal predictors across different levels of observation, including neuroimaging can set a gold standard for predictions against which more widely applicable measures can be tested.

(ii) Depending on the phenotype predicted best predictors might not be the most mechanistically informative.

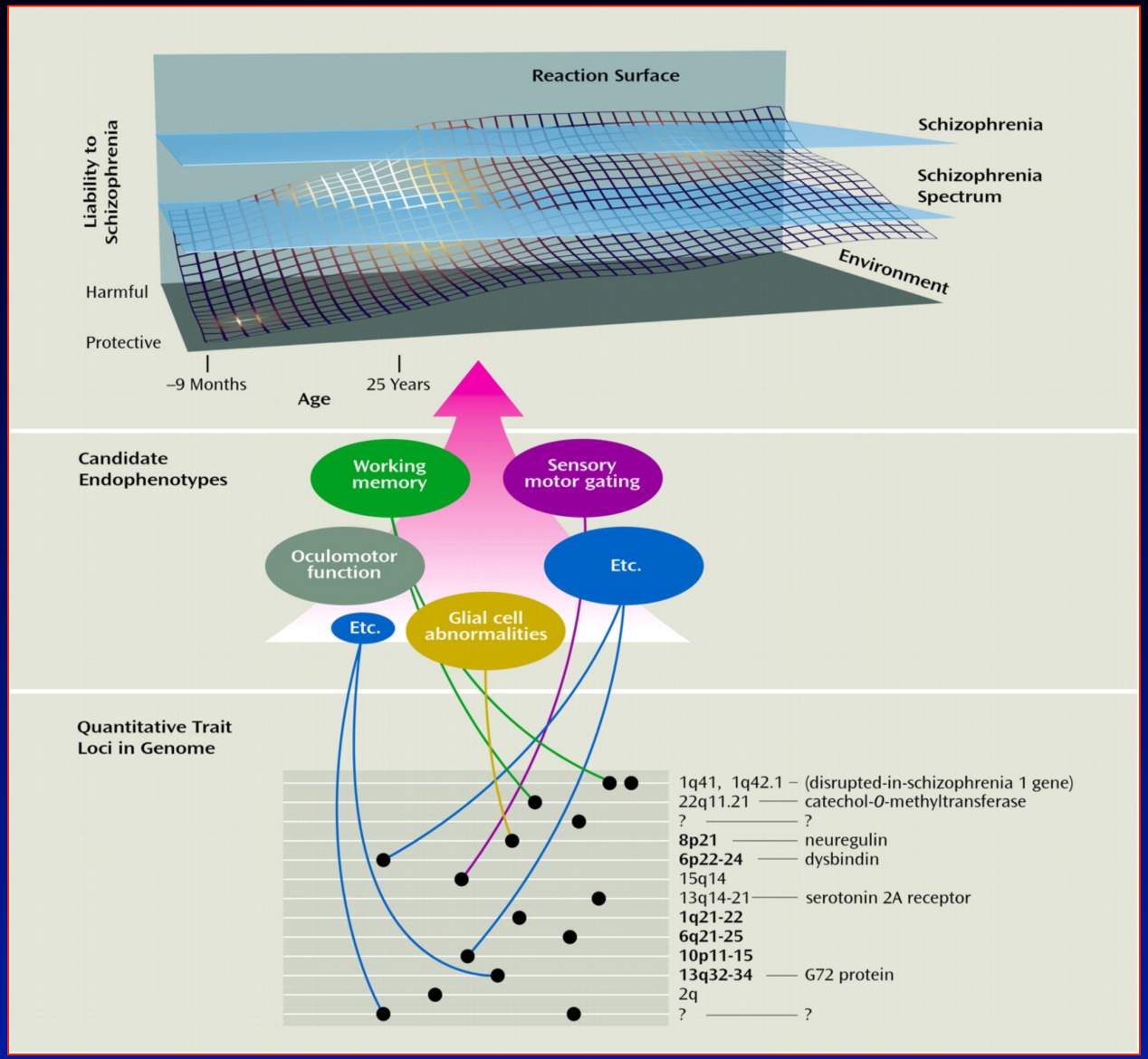
(iii) Due to the heterogeneity of the biological mechanisms underlying observable behaviour it might be more promising to predict quantifiable neurobiological phenotypes, which reflect clinically relevant psychopathology.

Polygenicity and heterogenetity limit the contribution of each single gene to the overall presentation.



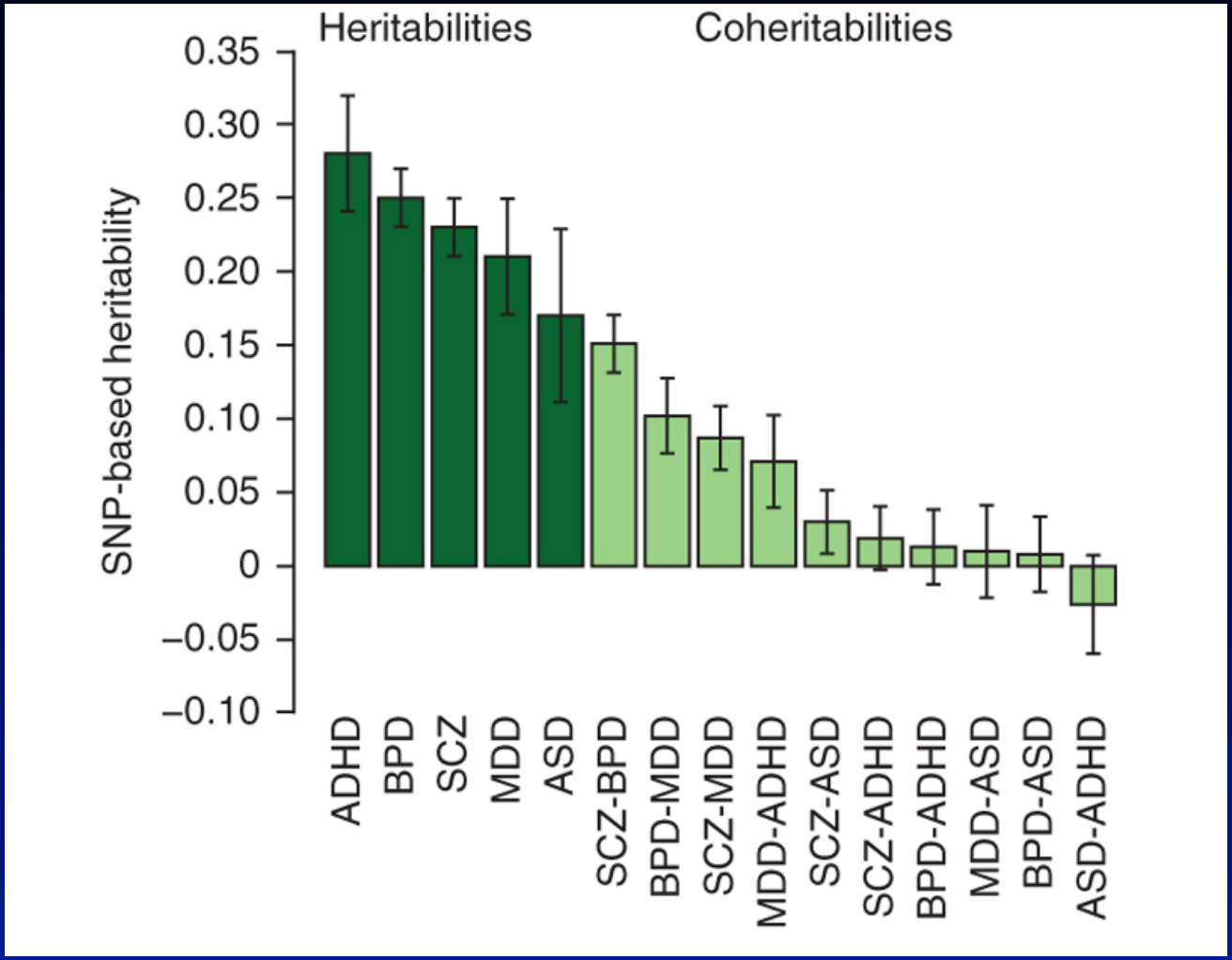
(Ducci and Goldman, 2012)

Endophenotype concept and heritability



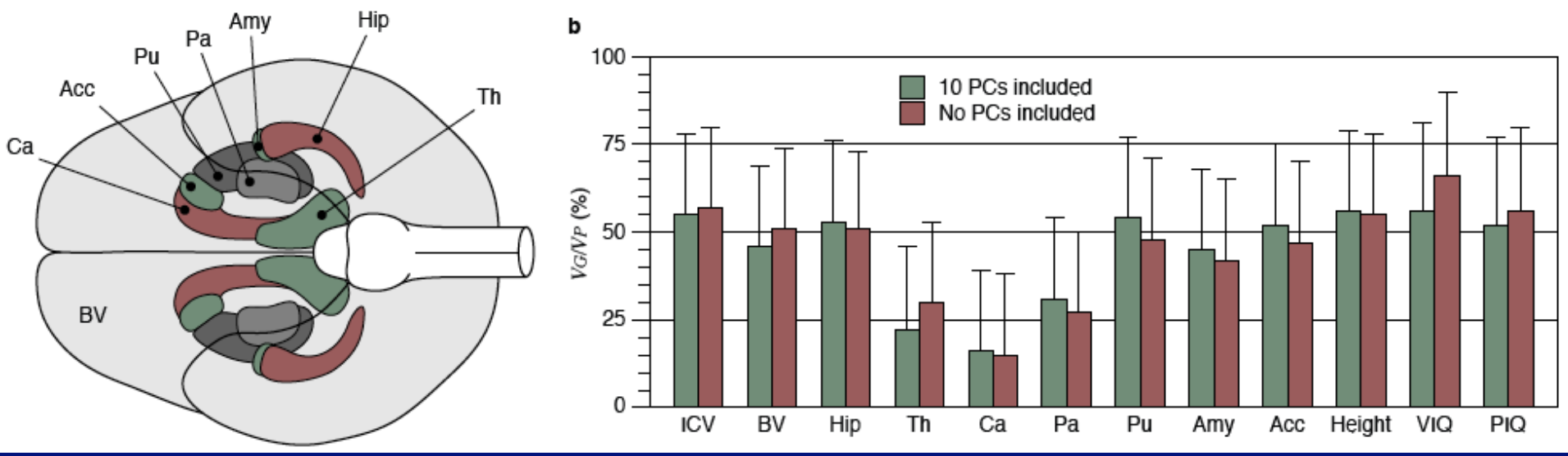
Gottesmann and Gould 2003

Genome-wide pleiotropy between psychiatric disorders.



Cross-Disorder Group of the Psychiatric Genomics Consortium
Nature Genetics **45**, 984–994 (2013)

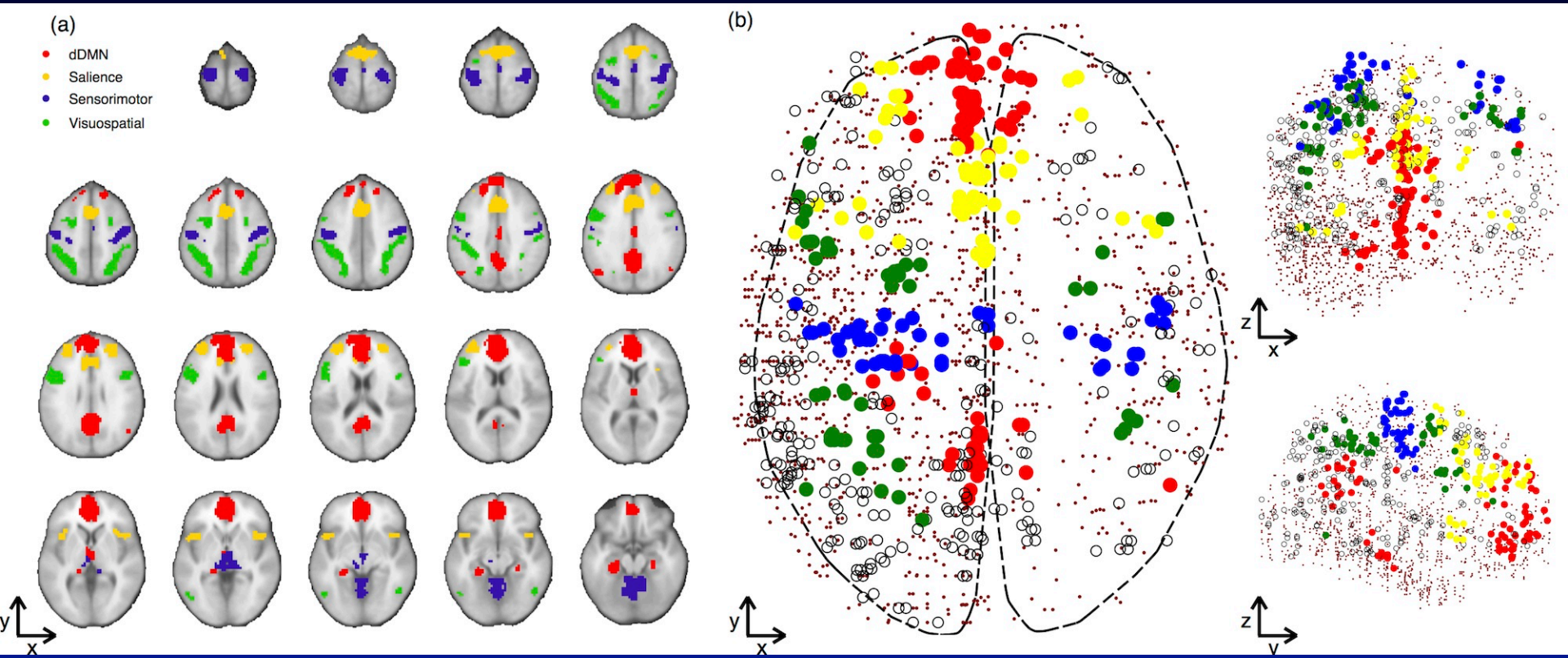
Genomic architecture of brain heritability



V_G/V_P: variance brain volume explained by genetic factors

Toro et al. Molecular Psychiatry 2015

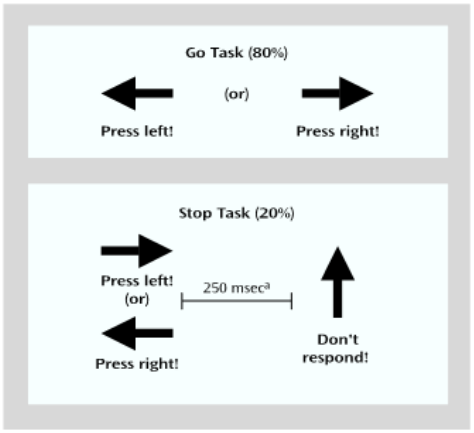
Functional networks in MRI and gene expression data



Richiardi et al. Science 2015

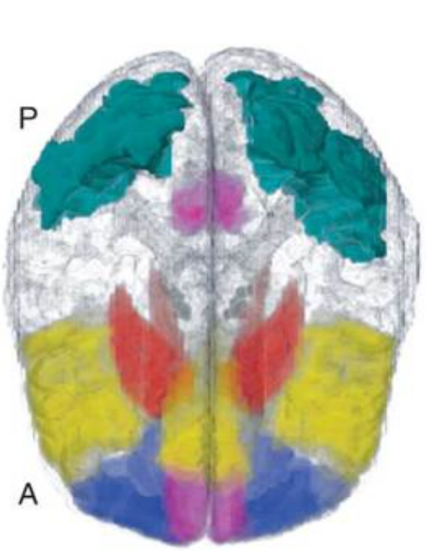
Impulsivity is a risk factor for substance abuse in adolescents

Stop signal task

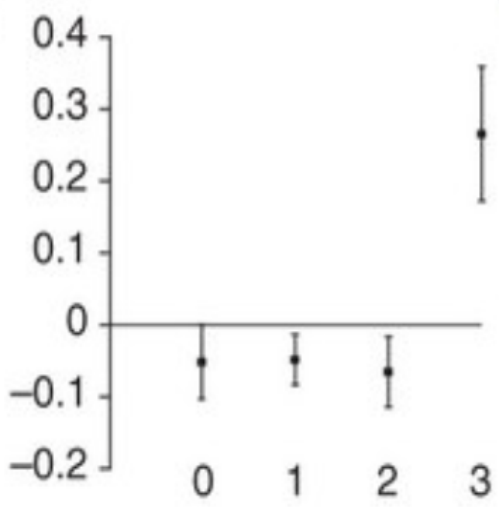


[a] The interval between horizontal and vertical arrows in the stop trials becomes smaller/larger in steps of 50 msec depending on each subject's performance to ensure 50% successful and 50% unsuccessful inhibition for each subject.

Stop success network



Factor score (frontal)

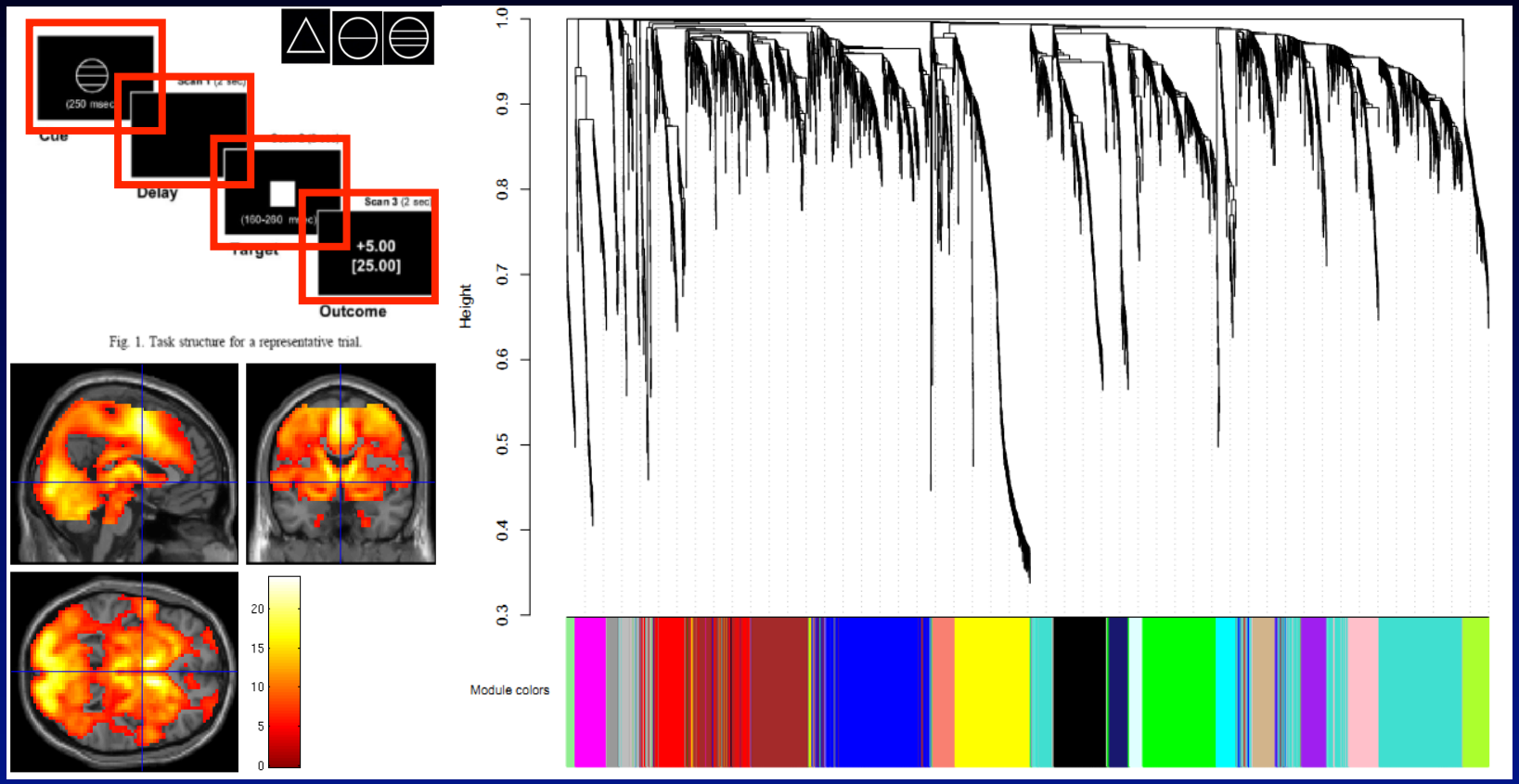


0 - no substances
1 - tried alcohol OR nicotine
2 - tried alcohol AND nicotine
3 - tried alcohol, nicotine AND illicit drug

Whelan et al., Nature Neuroscience, 2012

Brain activity networks during inhibition are associated with substance abuse in adolescents.

Reward anticipation in 1544 individuals activates 21 distinct brain regions



Weighted network analysis of brain activity during reward anticipation in 1544 individuals and subsequent bootstrapping.

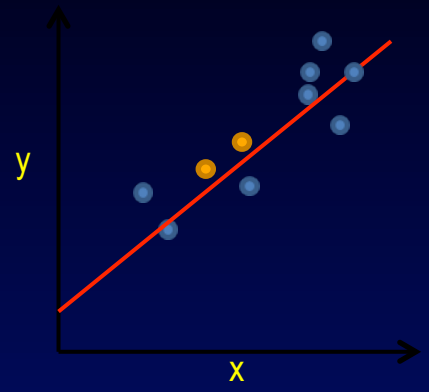
Jia et al. PNAS, in revision

We carried out several approaches to identify quantitative neurobiological phenotypes involving brain activation and structure, and genetic information.

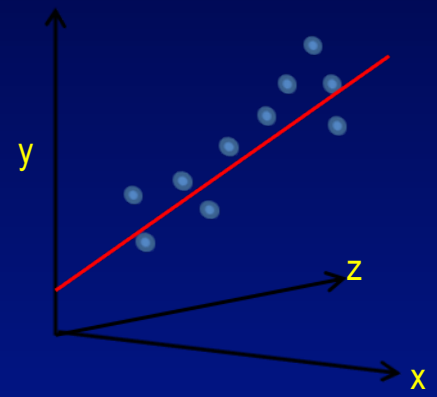
However, most of these approached suffer from a limited explanation of variance of behavioural or neuropsychiatric phenotypes, thus limiting their potential clinical utility.

Canonical Correlation Analysis

- a mathematical framework to understand linear relationships between two or more sets of variables.



Linear Regression,
one independent variable
(univariate, both modalities)



Linear Regression,
two independent variables
(multivariate, one modality)

$$y_1 \alpha_1 + y_2 \alpha_2 = C1$$

$$x_1 \beta_1 + x_2 \beta_2 = C2$$

Maximise correlation

Canonical Correlation Analysis
(multivariate, both modalities)

Canonical Correlation Issues

- Classical canonical correlation analysis requires more samples than features.
- In classical canonical correlation analysis, all features have non-zero weights, even if their contribution is negligible.

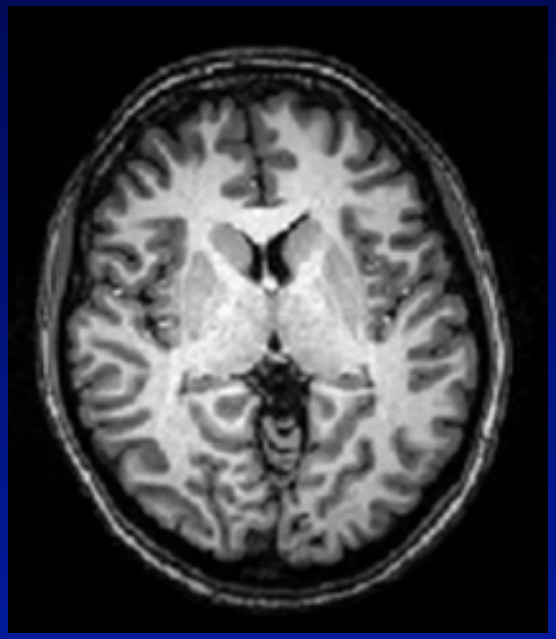


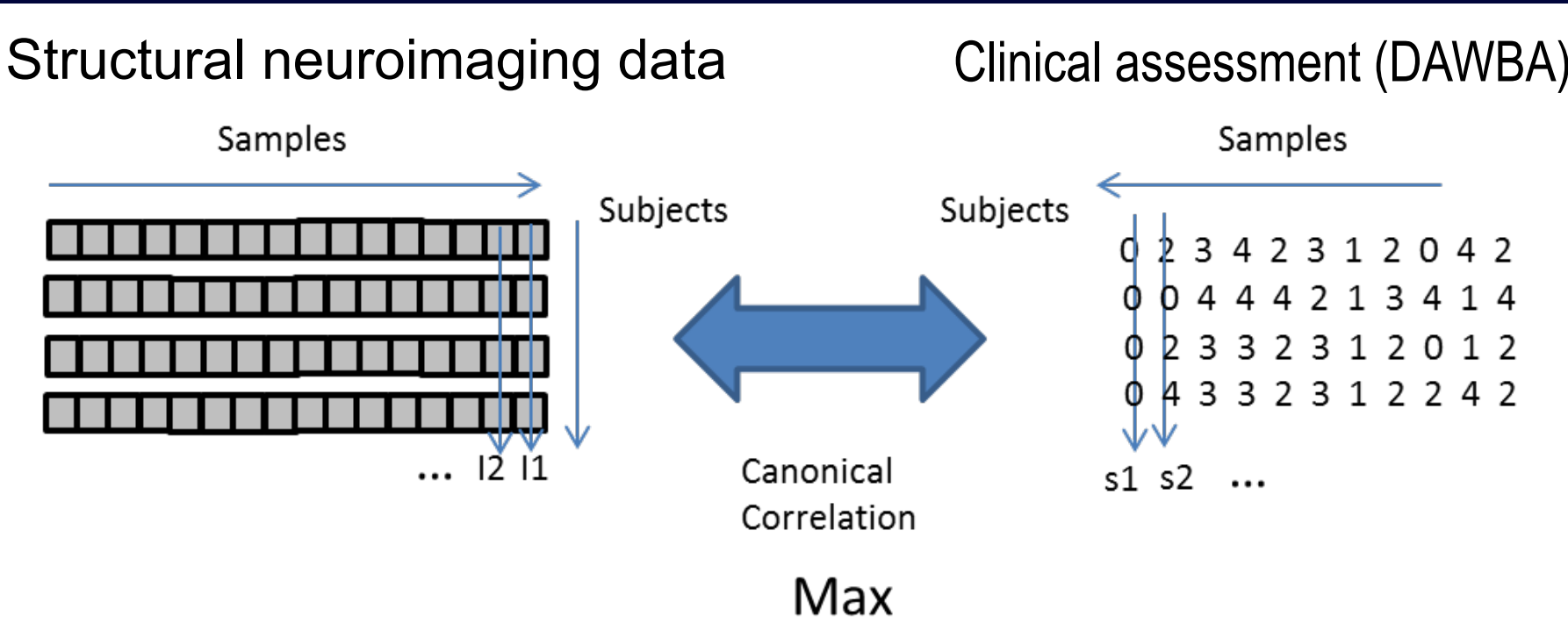
IMAGEN dataset:

Features ~ 500,000
Samples ~ 2000

Non-parametric/Kernel formulations can deal with this limitation:

1) Kernel Canonical Correlation
2) Sparse Canonical Correlation

Maximizing correlation of brain features with behavioural items using sparse Canonical Correlation Analysis



Ing et al. in preparation

- Defining a neurobehavioural phenotype by maximizing correlation of structural and/or functional brain characteristics with combinations of single behavioural items derived from deconstructed questionnaires is a promising way to identify neurobiologically-based behavioural symptom clusters.

- Neurobehavioural phenotypes thus defined might be more suitable for predictions than broad diagnostic or behavioural categories.

- However, this approach requires extensive replication to establish its robustness.

- It also requires empirical evaluations of the strengths and weaknesses of its applicability for clinical decision making and pharmaceutical research.

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