



POLYGENIC MEMORY SCORES AND SCHIZOPHRENIA

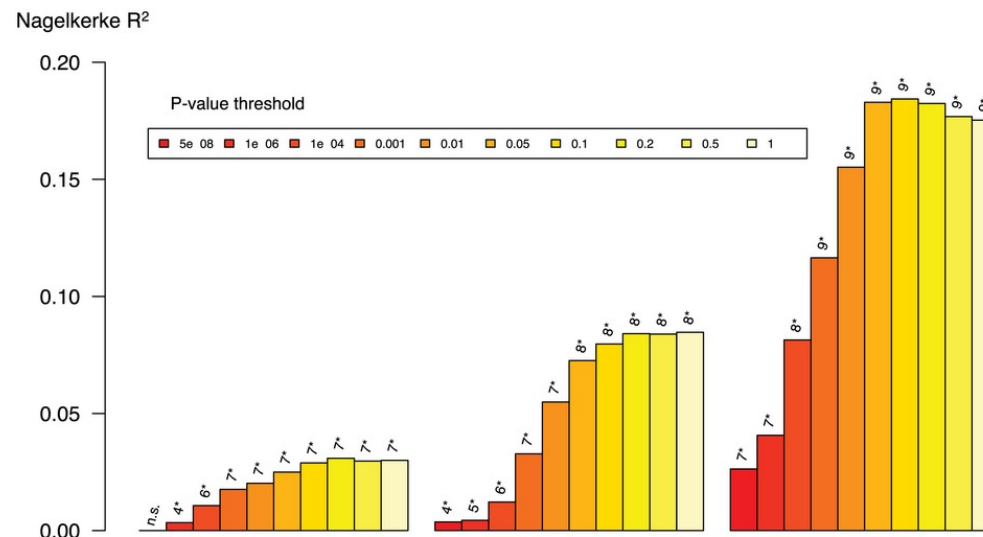
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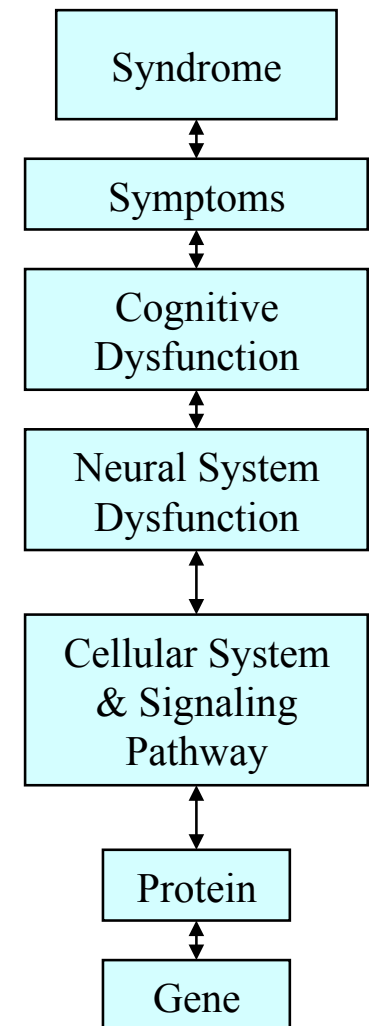
GENETIC ARCHITECTURE OF SCHIZOPHRENIA

- Highly polygenic (~8300 common variants)

- Polygenic risk scores for case-control status

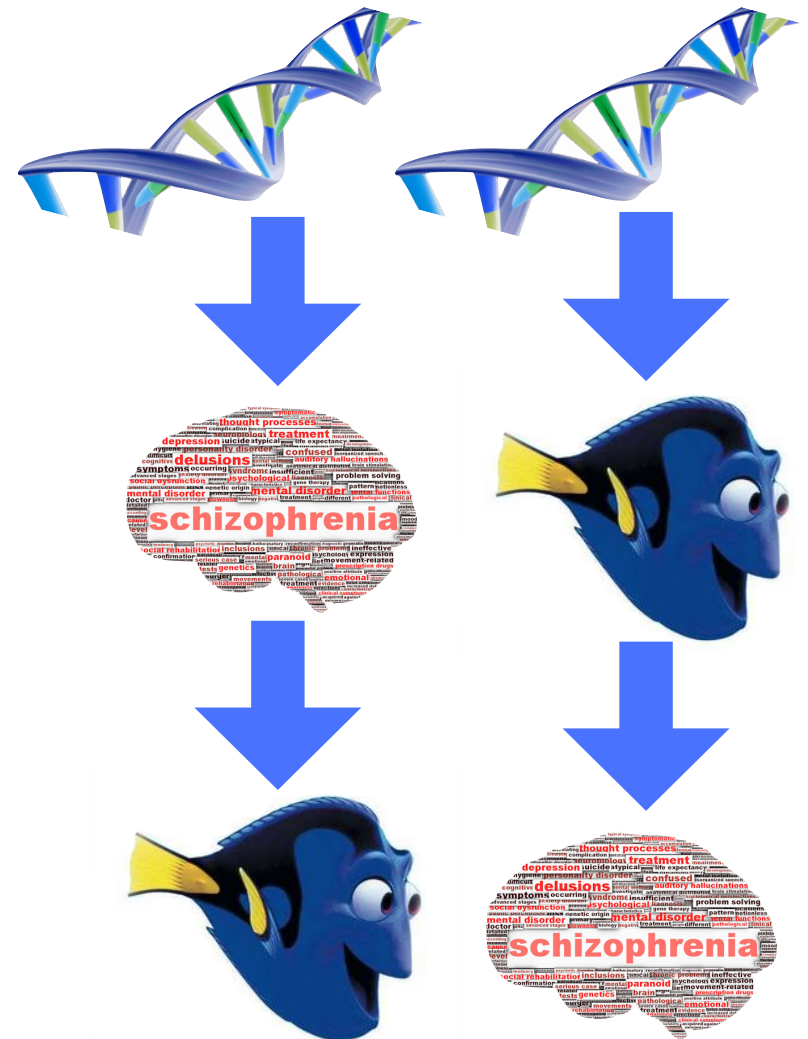


- Risk-associated variants may confer vulnerability via effects on cognitive domains



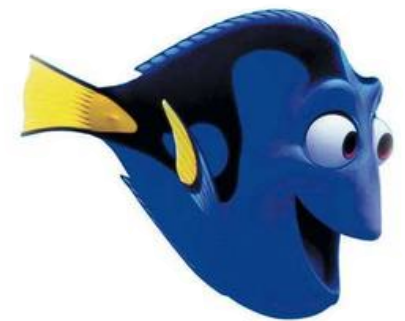
RISK SCORES & TRAITS

- **SCZ risk scores** have been used to predict many **endophenotypes**
 - IQ, structural MRI, working memory fMRI BOLD activation
- **Endophenotypes** have rarely been used to directly assay common genetic variance
 - General ability (Lencz et al., 2014)



MEMORY & SCHIZOPHRENIA

- Memory is one of the most profound cognitive impairments in schizophrenia
 - Related to specific neural networks
- California Verbal Learning Task (CVLT) is a robust measure for case-control separation
 - Heritable
 - Endophenotype

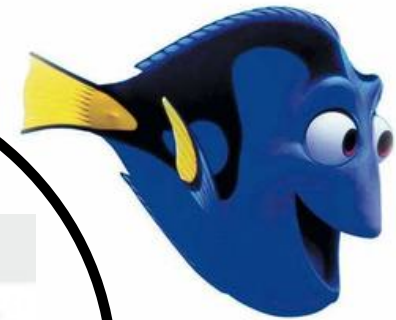
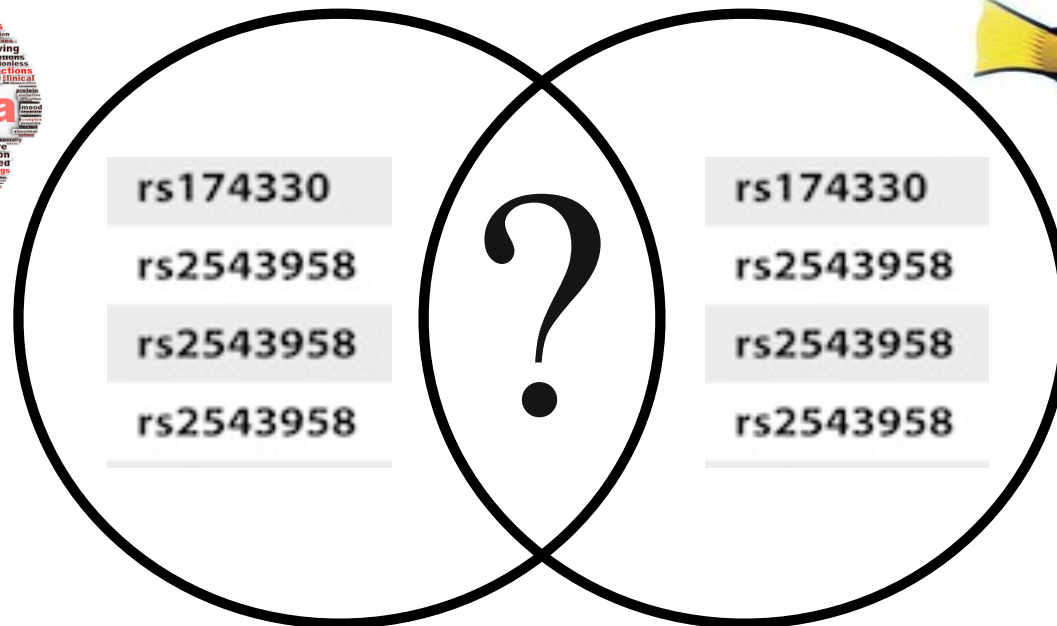


POLYGENIC SCORES FOR SCZ ENDOPHENOTYPES

Do genetic variants associated with an endophenotype for schizophrenia predict that phenotype in an independent sample?



Is polygenic risk for schizophrenia associated with genetic variants underlying memory impairment?



METHODS

ANALYSES OVERVIEW

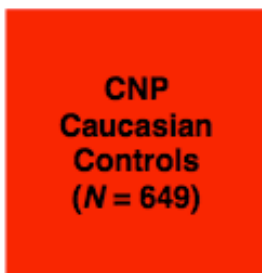
- Samples (case-control)
 - Discovery: Consortium for Neuropsychiatric Phenomics (UCLA)
 - Replication: Swedish twins (Karolinska)



Sample



Case/
Control

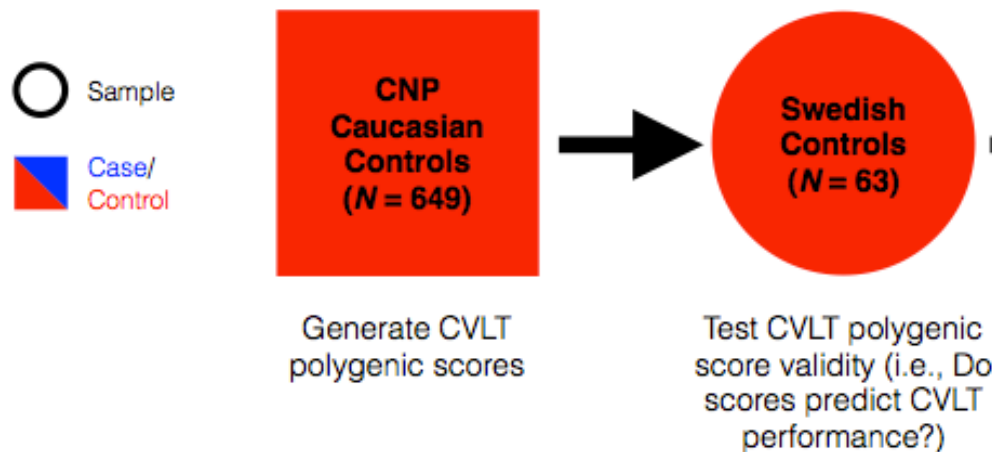


Generate CVLT
polygenic scores

ANALYSES OVERVIEW

○ Samples (case-control)

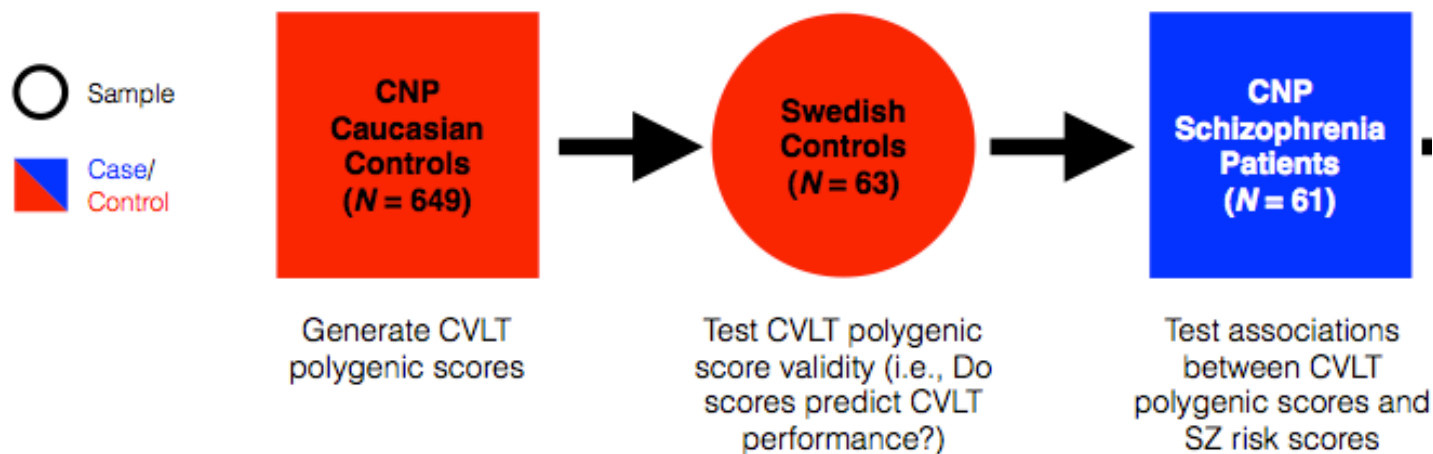
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ANALYSES OVERVIEW

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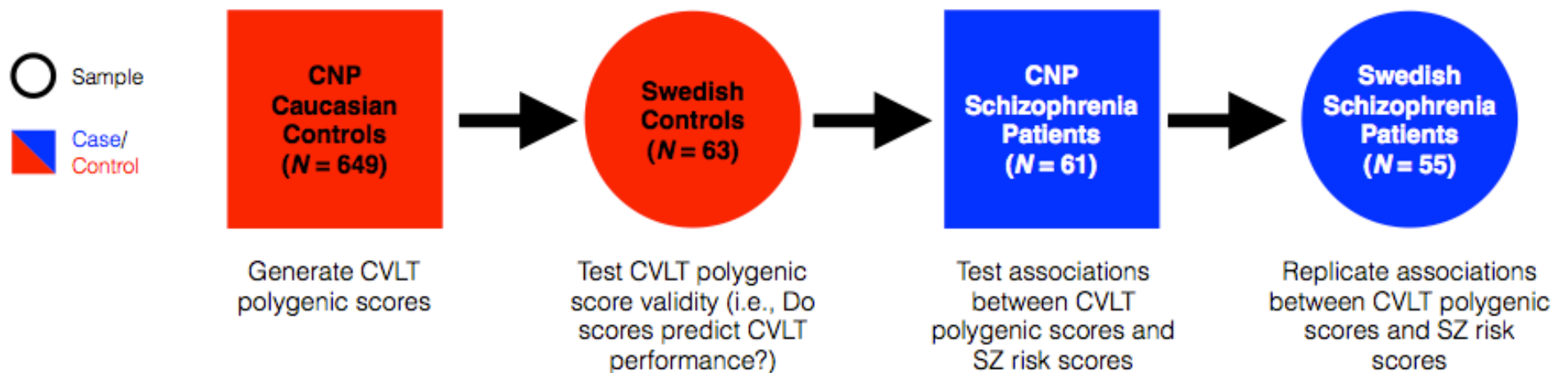
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ANALYSES OVERVIEW

- Samples (case-control)

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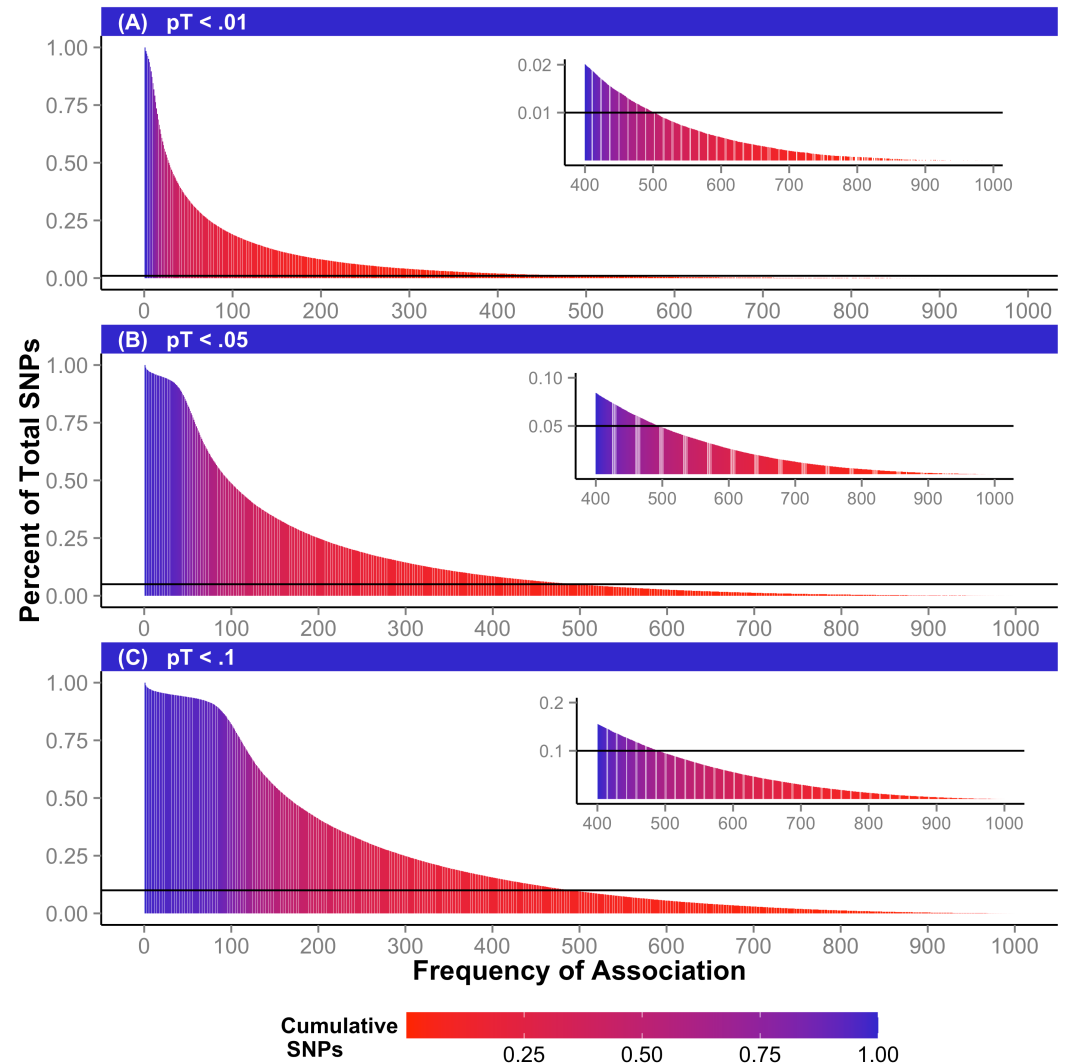
POLYGENIC SCORE GENERATION

- Polygenic memory scores derived from CNP controls (N = 649)
- GWAS of CVLT performance in 1000 samples randomly chosen with replacement (age, sex covariates)
- SNPs at nominal p-value thresholds that were associated with CVLT a minimum of 700 / 1000 times were included in polygenic memory scores
 - $p_T < .01, .05, .1$
 - Frequency of association cut-points = 700, 800, 900 / 1000
- Beta weights determined from full sample
- Polygenic memory scores and PGC SZ risk scores calculated according to Purcell et al. (2009)

RESULTS

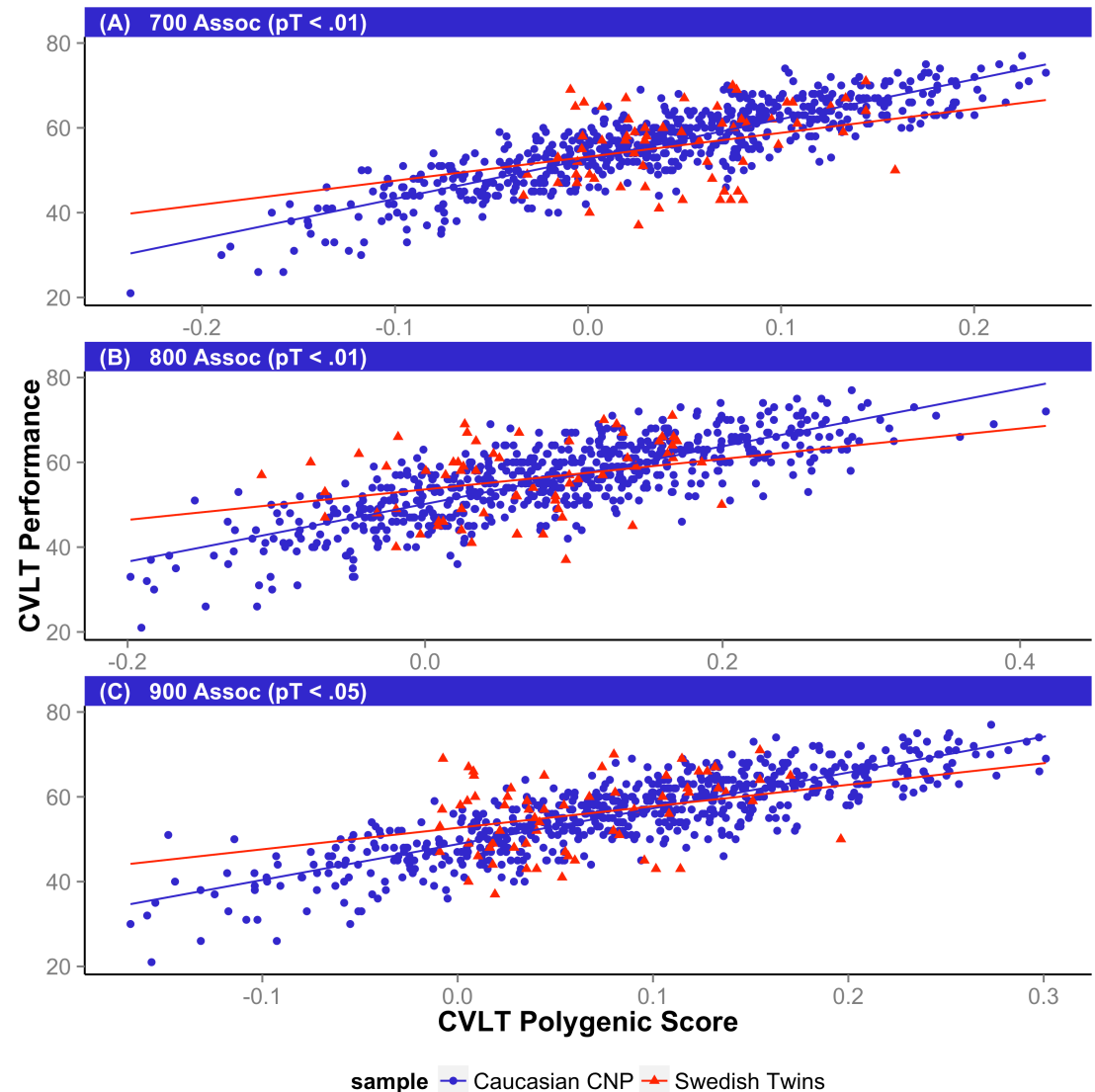
BOOTSTRAPPING

- Nominal significance thresholds
 - (A) $pT < .01$
 - (B) $pT < .05$
 - (C) $pT < .1$
- All frequency cut-points (700, 800, 900 associations) include significantly fewer SNPs than expected by chance
 - Increased SNR



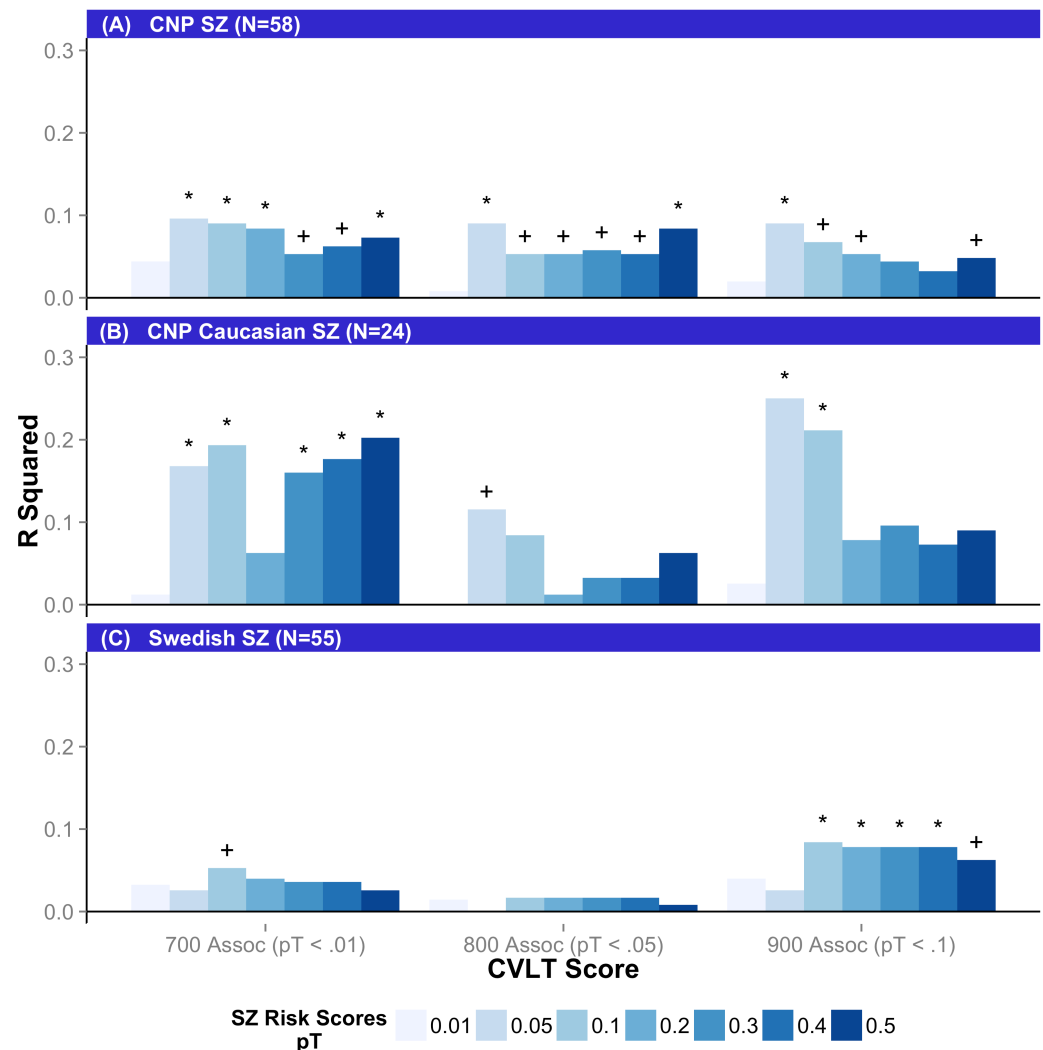
MEMORY SCORES PREDICT MEMORY PERFORMANCE

- CVLT scores derived from discovery sample predict memory performance in replication sample
 - True for all frequency cut-points



MEMORY SCORES ASSOCIATED WITH SZ RISK SCORES

- Polygenic memory scores associated with SZ risk scores
 - Negative correlation in discovery sample
 - Modest evidence of replication



CONCLUSIONS & LIMITATIONS

- Limitations

- Sample size
 - Specificity to memory?

- Schizophrenia-related variants can be ascertained in the general population via association with an endophenotype

THANK YOU!

