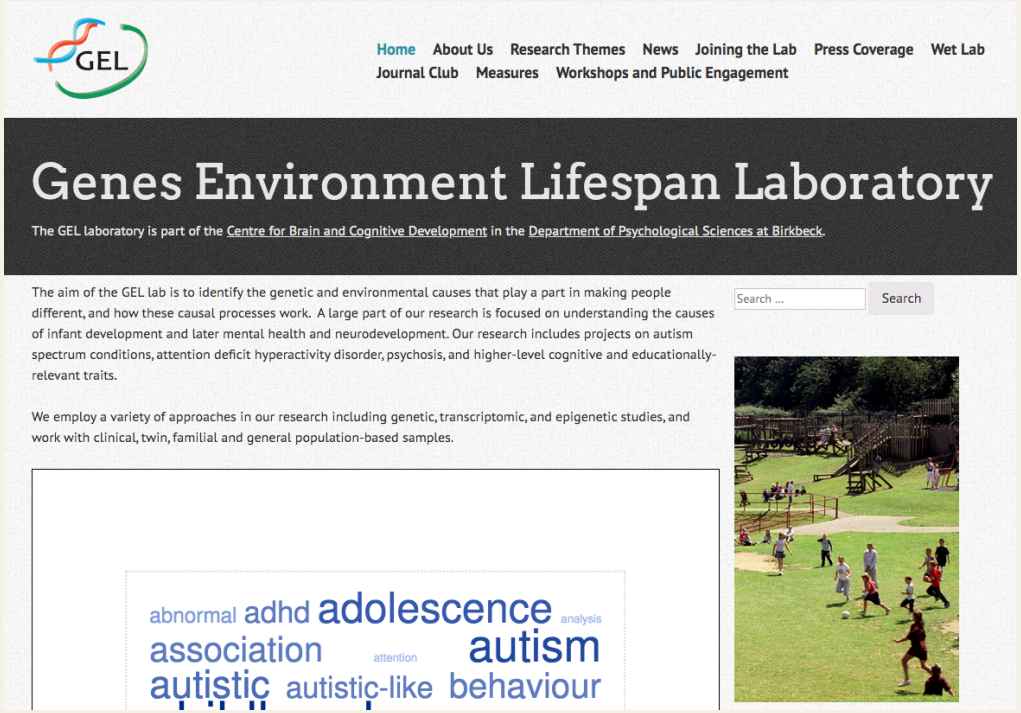
The first 10 years and beyond….

CBCD 20th Anniversary

Angelica Ronald

Joined CBCD in 2007



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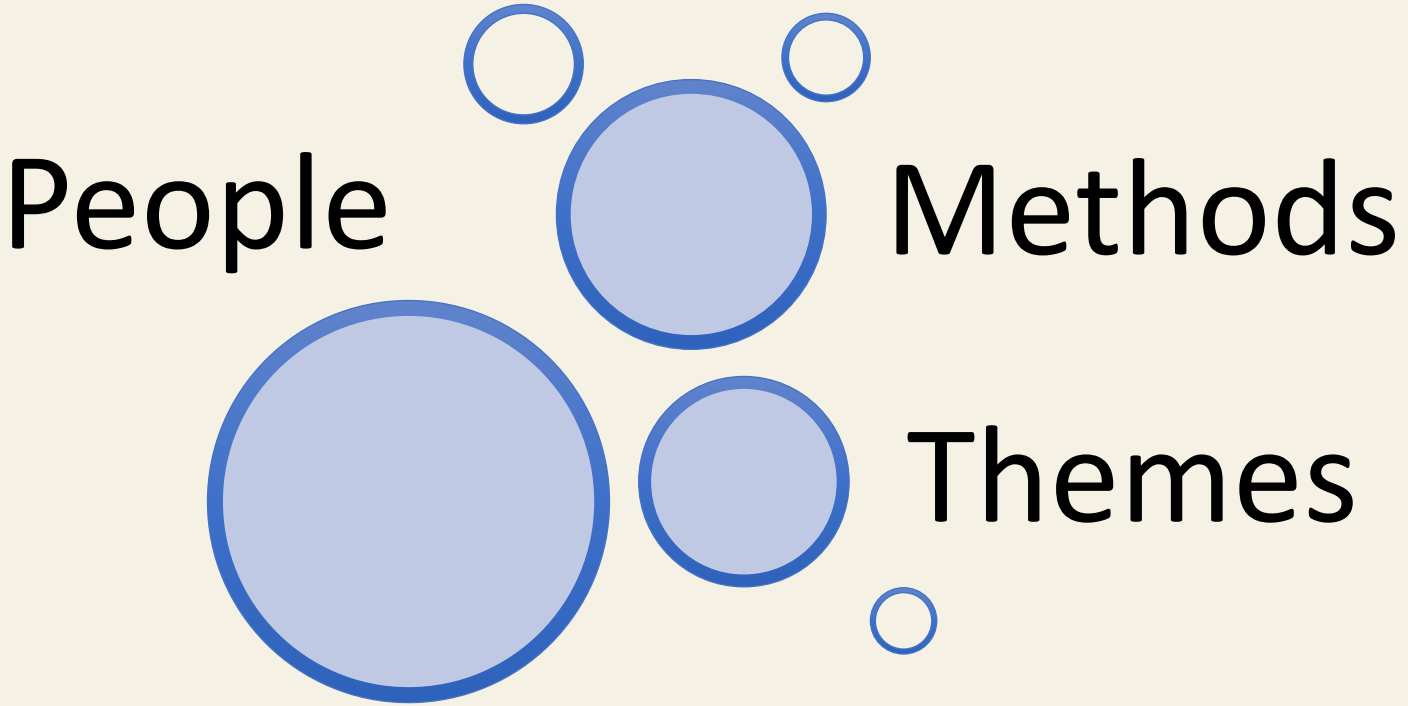

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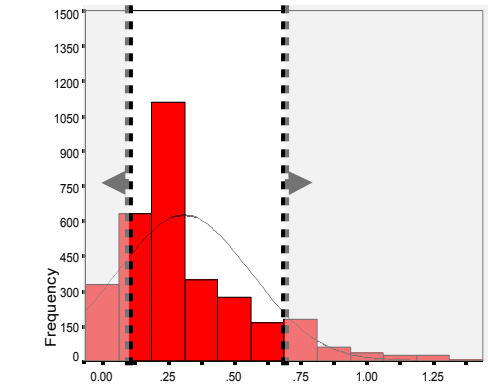
Back in 2007:

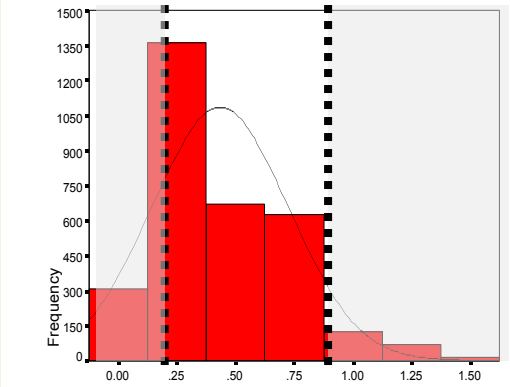
Behav Genet (2010) 40:31–45
DOI 10.1007/s10519-009-9308-6

ORIGINAL RESEARCH

A Genome-Wide Association Study of Social and Non-Social Autistic-Like Traits in the General Population Using Pooled DNA, 500 K SNP Microarrays and Both Community and Diagnosed Autism Replication Samples

Angelica Ronald · Lee M. Butcher · Sophia Docherty · Oliver S. P. Davis · Leonard C. Schalkwyk · Ian W. Craig · Robert Plomin





Ronald et al (2010) *Behavior Genetics*

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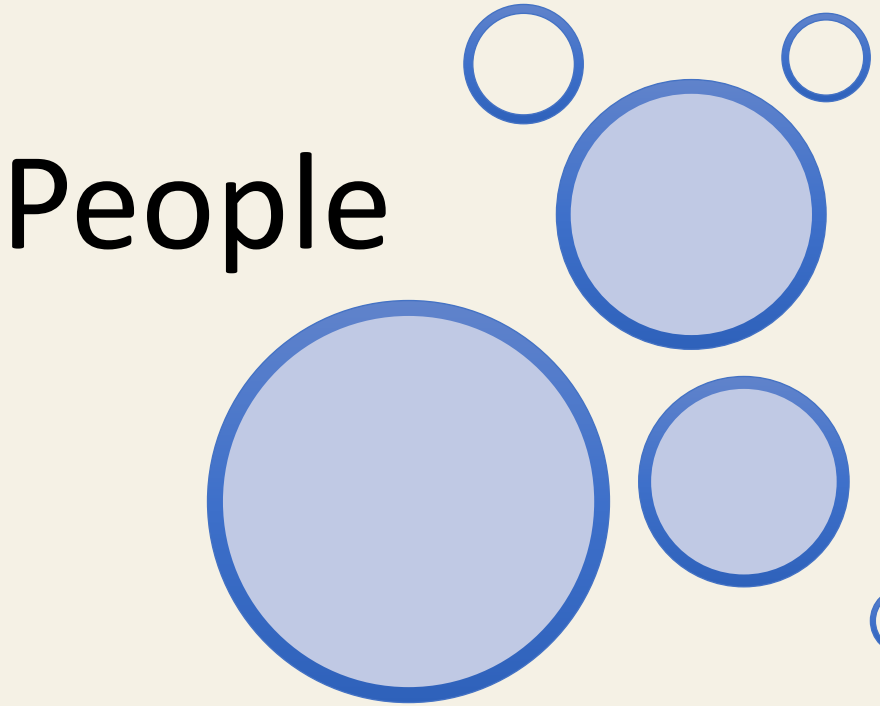

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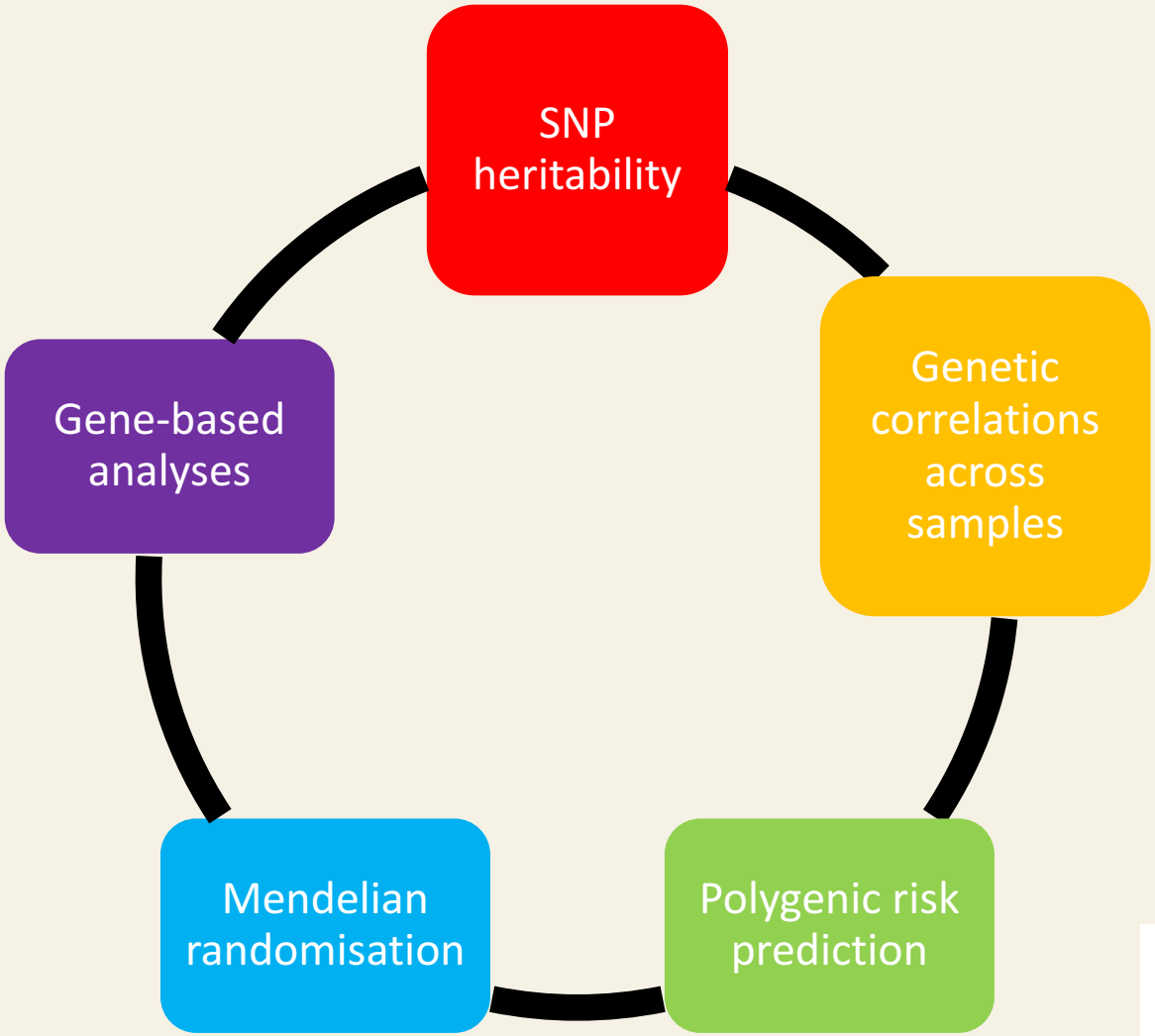
Methods



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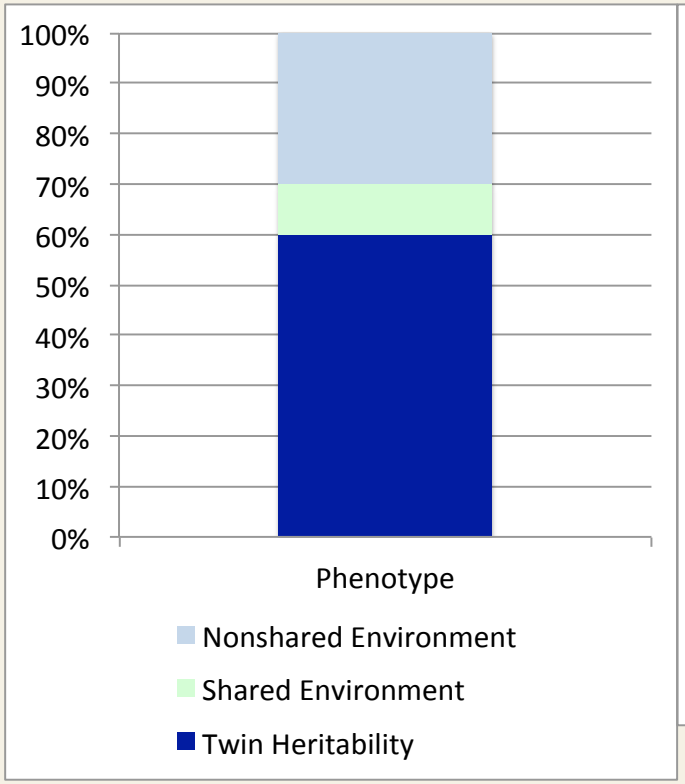
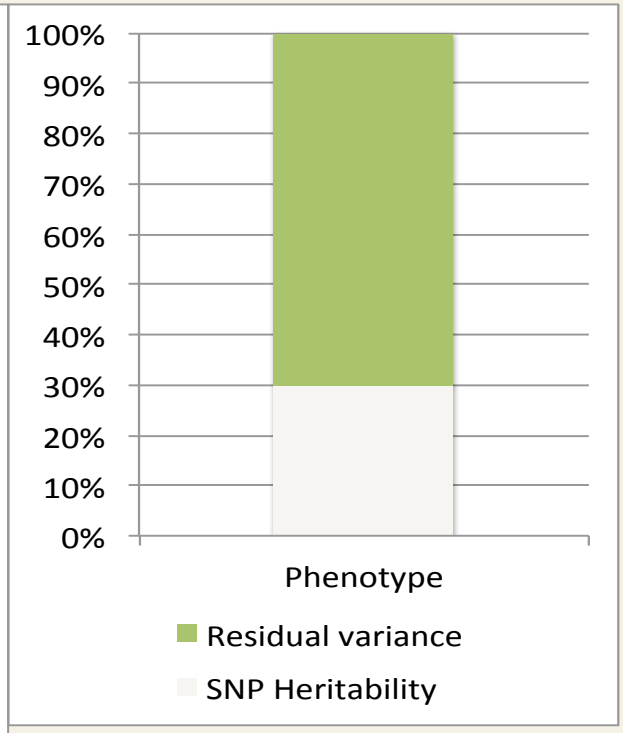
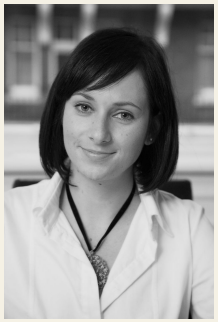
SNP Heritability

SNP; single nucleotide polymorphism







Dr Dominika Sieradzka

Dr Oliver Pain

Sieradzka et al 2015 *Behaviour Genetics;* Pain et al (2018) *Neuropsychiatric Genetics*

Method: Bulik-Sullivan et al (2015) *Nature Genetics;* Yang et al (2011) *Nature Genetics*

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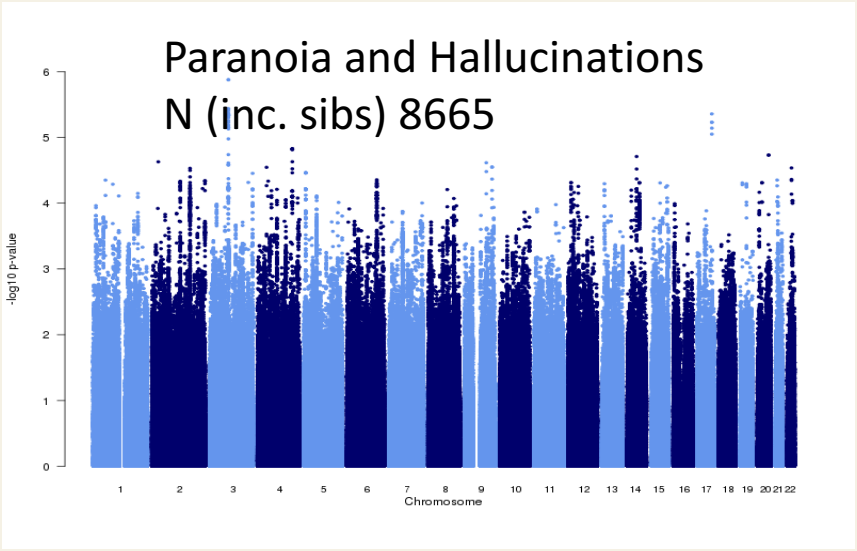
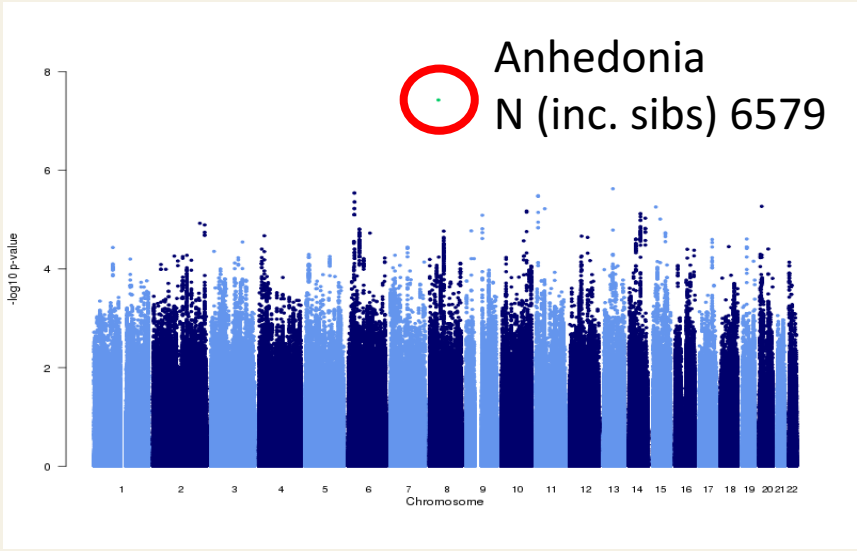
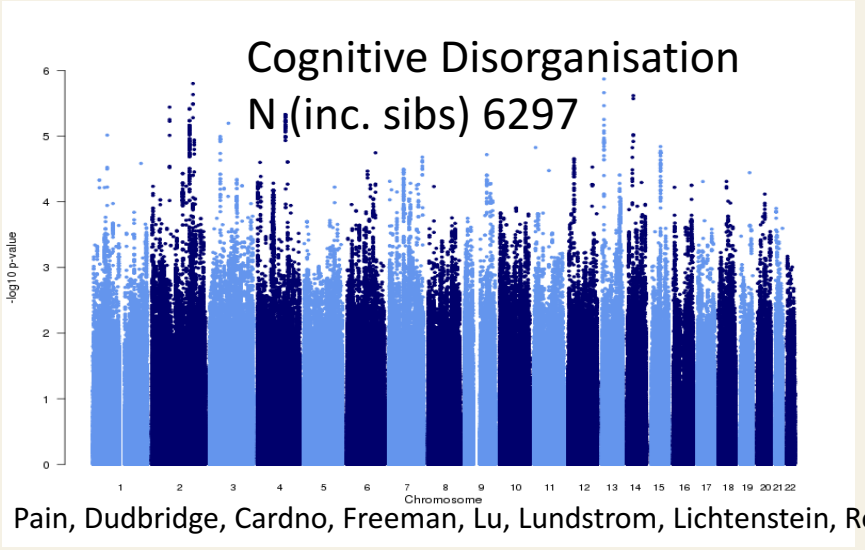
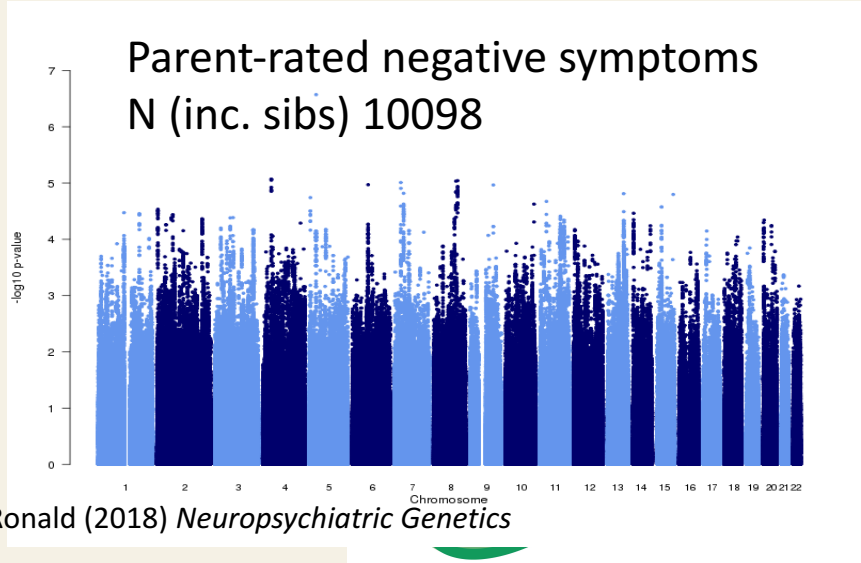
Gene discovery: Larger and cheaper





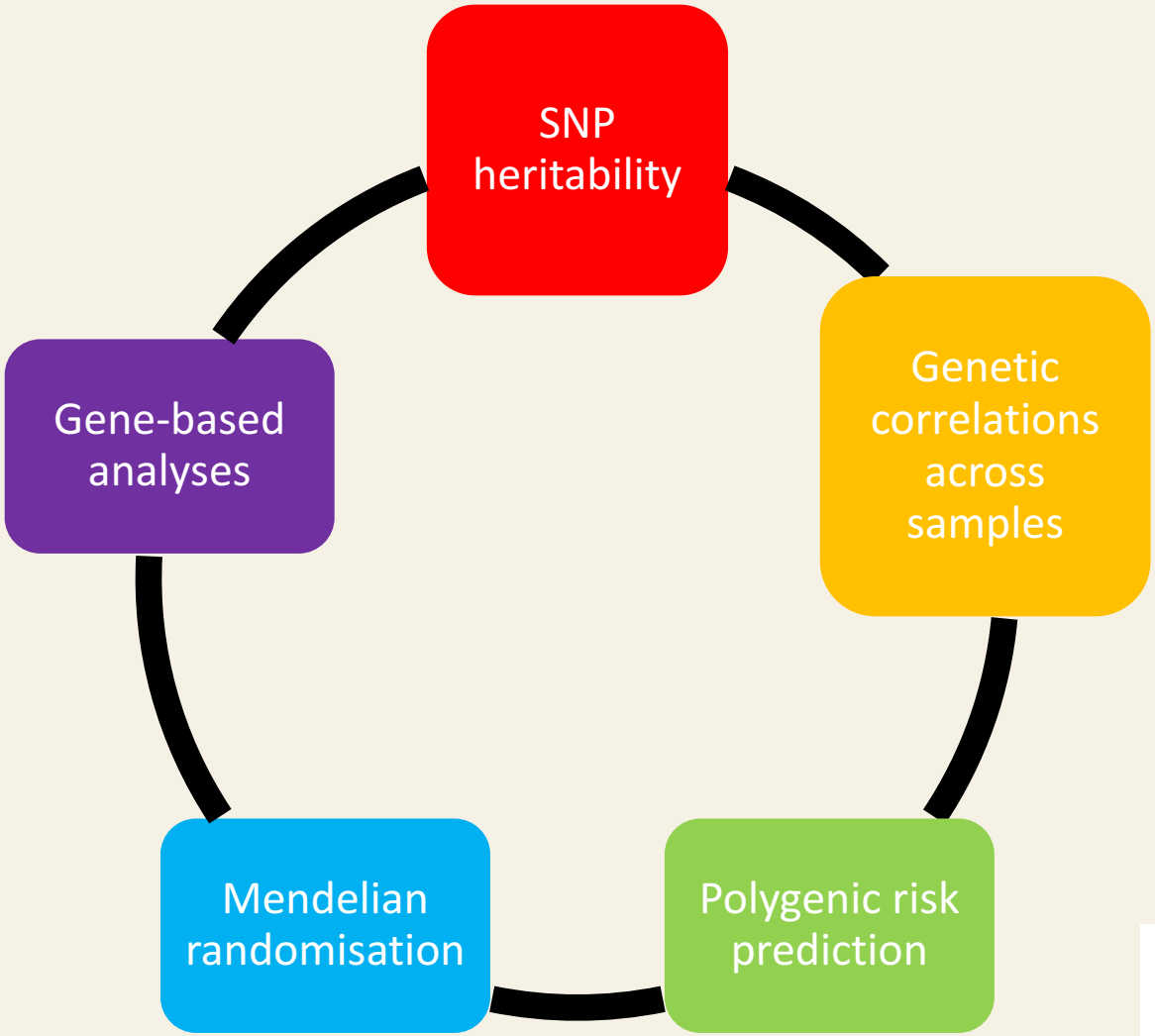




Pain, Dudbridge, Cardno, Freeman, Lu, Lundstrom, Lichtenstein, Ronald (2018) *Neuropsychiatric Genetics*

ifespan
oratory

Methods



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Wikus Barkhuizen

Genetic correlations across samples!

		Paranoia and hallucinations	Cognitive disorganisation	Anhedonia	Negative symptoms	Hypomania	Perceptual aberration	Physical anhedonia	Social anhedonia	Un-real voices	Un-real vision	Un-real conspiracy	Un-real communications
		Adolescent PENS				Schizotypy in adults				Positive PE in adults			
Adolescent PENS	Paranoia and hallucinations	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Cognitive disorganisation	NA	1	.47	NA	.08	-.19	-.06	-.28	.08	-.10	.36	-.10
	Anhedonia	NA	.47	1	NA	.43	.57	.11	.32	.58	-.01	.41	-.09
	Negative symptoms	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA
Schizotypy in adults	Hypomania	NA	.08	.43	NA	1	-.09	.02	.06	-.20	**.37***	.32	.12
	Perceptual aberration	NA	-.19	.57	NA	-.09	1	.08	.45	.26	.34	.10	.27
	Physical anhedonia	NA	-.06	.11	NA	.02	.08	1	**.54***	**-.42***	-.05	-.29	.12
	Social anhedonia	NA	-.28	.32	NA	.06	.45	**.54***	1	-.27	.18	.06	-.49
Positive PE in adults	Un-real voices	NA	.08	.58	NA	-.20	.26	**-.42***	-.27	1	**.95****	.50	**.93***
	Un-real vision	NA	-.10	-.01	NA	**.37***	.34	-.05	.18	**.95****	1	.64	**.83***
	Un-real conspiracy	NA	.36	.41	NA	.32	.10	-.29	.06	.50	.64	1	NA
	Un-real communications	NA	-.10	-.09	NA	.12	.27	.12	-.49	**.93***	**.83***	NA	1

1 .75 .5 .25 0 -.25 -.5 -.75 -1

Barkhuizen, Pain, Dudbridge & Ronald (2019) BioRxiv Preprint
https://www.biorxiv.org/content/10.1101/718015v1
Method: Bulik-Sullivan et al (2015) *Nature Genetics*

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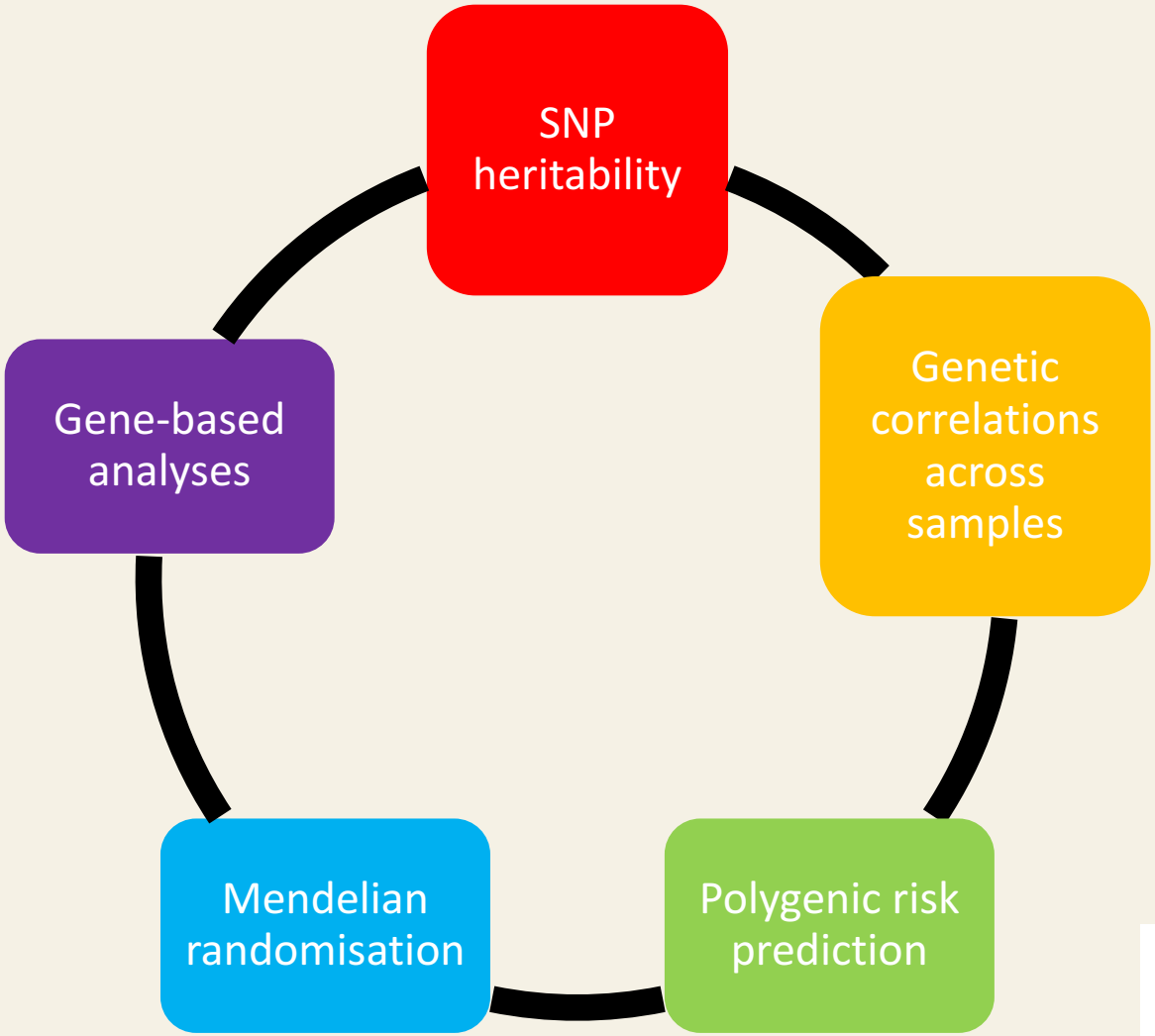
Methods



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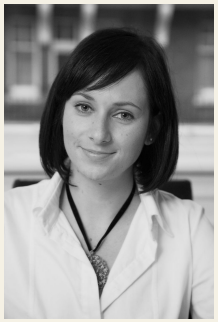
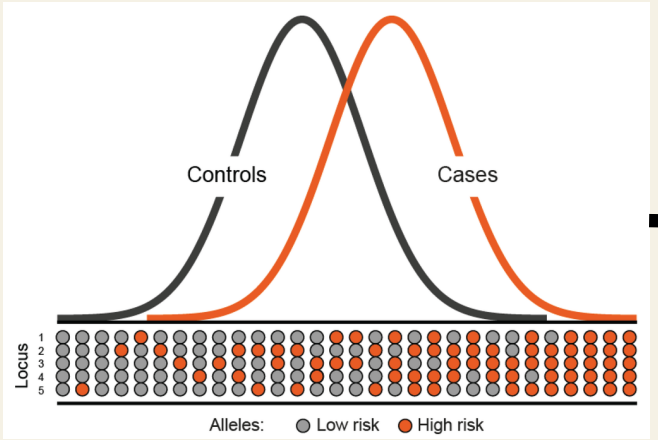
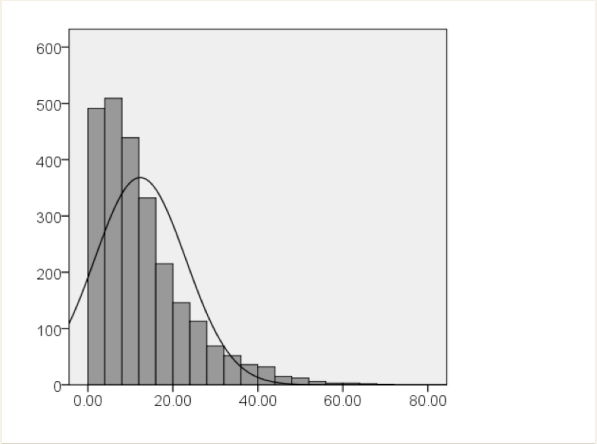
Polygenic Risk Score prediction



Dr Dominika Sieradzka



Polygenic risk score for each individual



Does the score predict a second phenotype

Dr Oliver Pain

Ronald & Pain (2018) *Human Molecular Genetics*
Sieradzka, Power, Freeman, … & Ronald (2014) *PLoS ONE*
Pain et al (2018) *Neuropsych Genetics*
Method: Purcell et al (2009)

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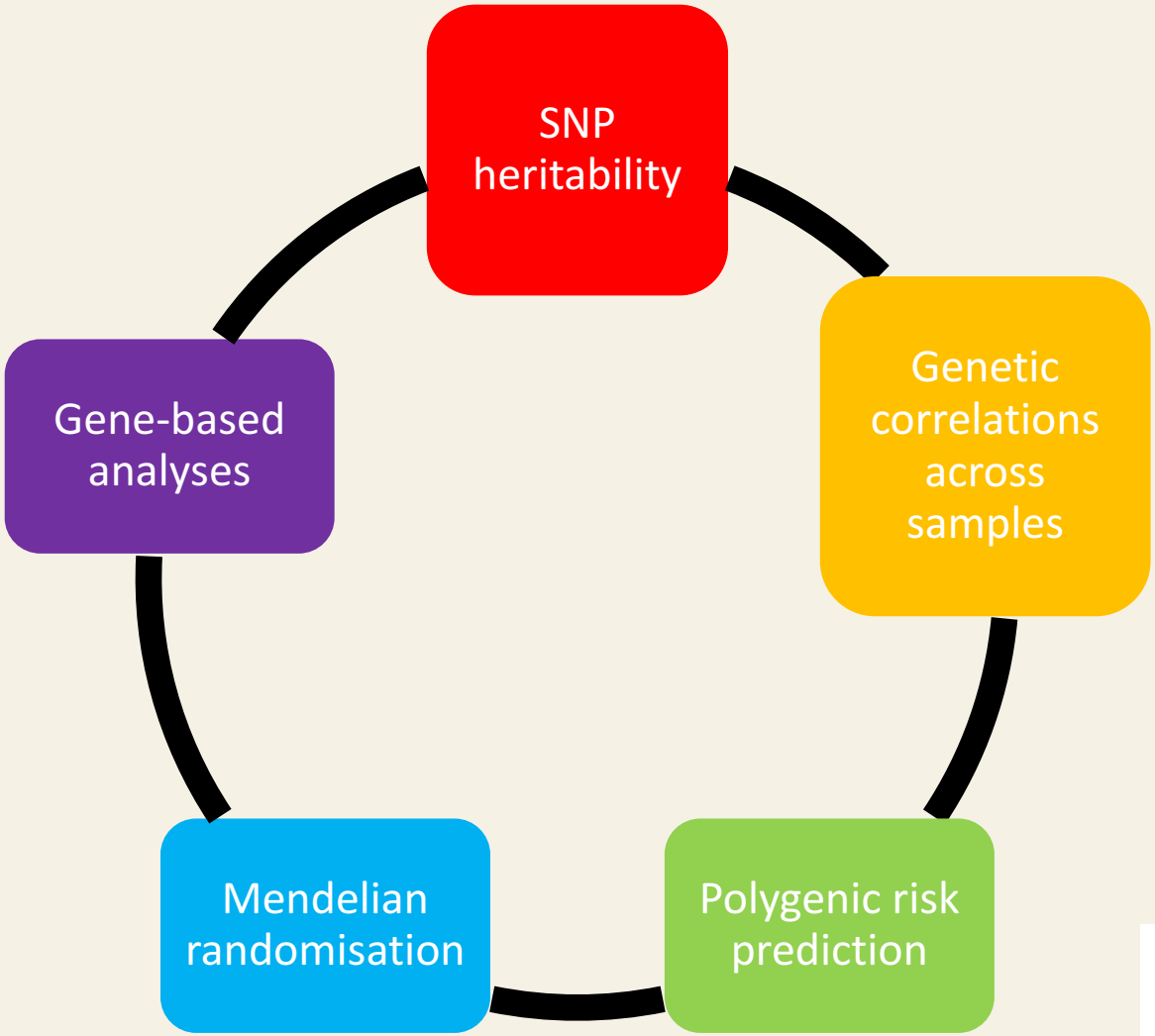
Methods



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Mendelian Randomisation

Wikus
Barkhuizen

Tobacco use → Psychiatric traits

Barkhuizen, Dudbridge & Ronald (in preparation)

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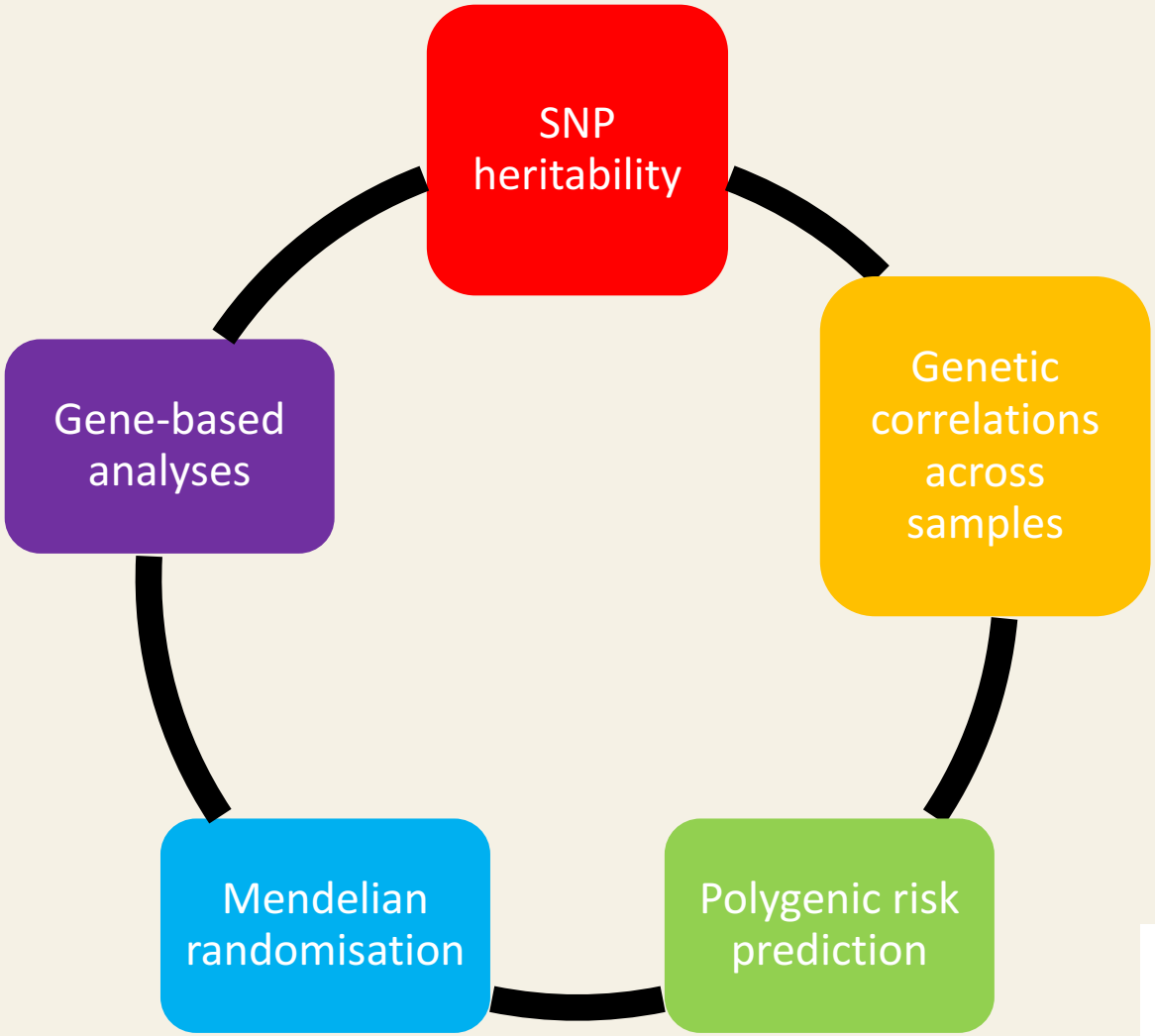
Methods



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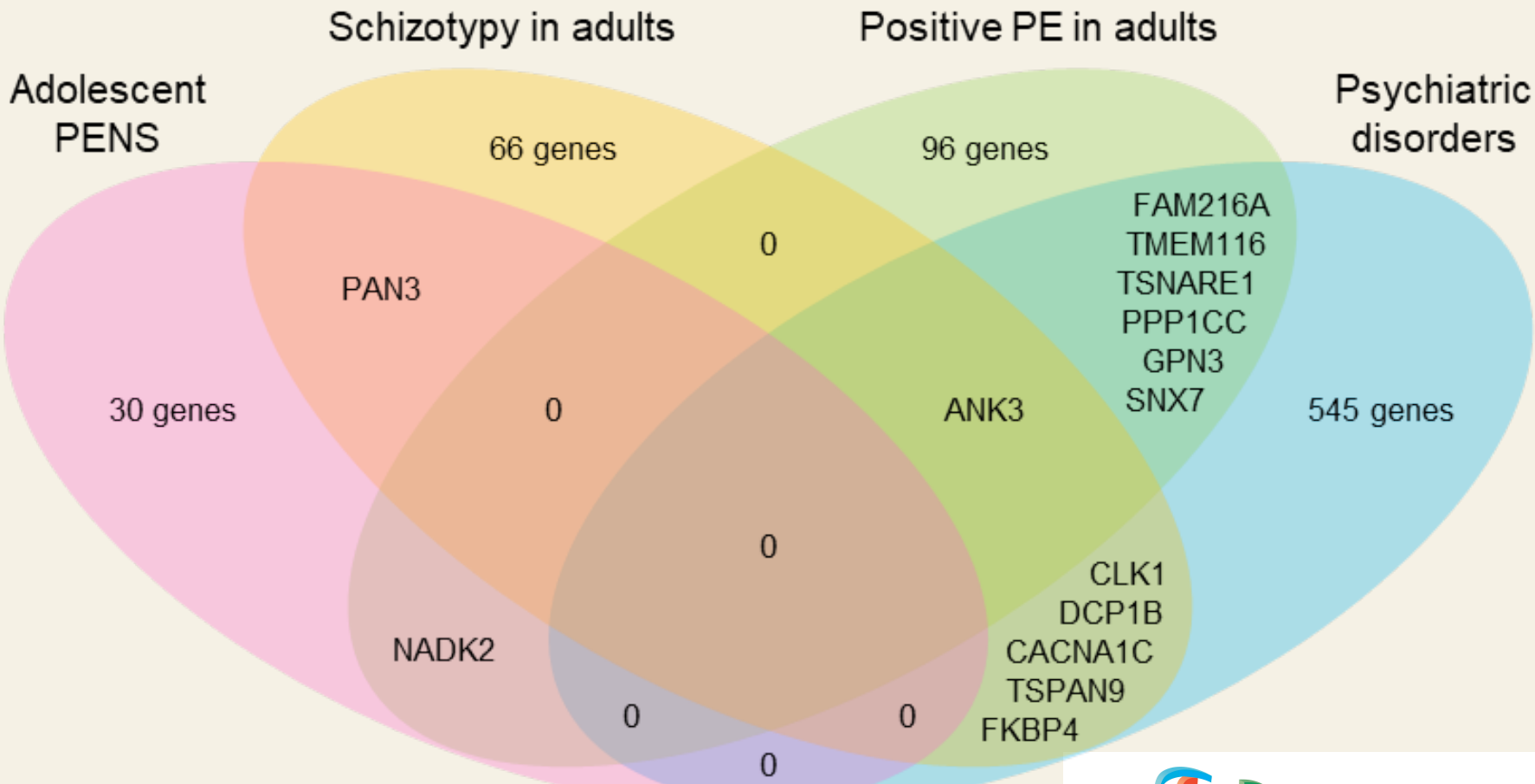
Gene-based analyses: Overlapping genes across age and with psychiatric disorders



Barkhuizen, Pain, Dudbridge & Ronald (2019) BioRxiv Preprint
https://www.biorxiv.org/content/10.1101/718015v1
Method: Watanabe et al (2017) *Nature Communication*

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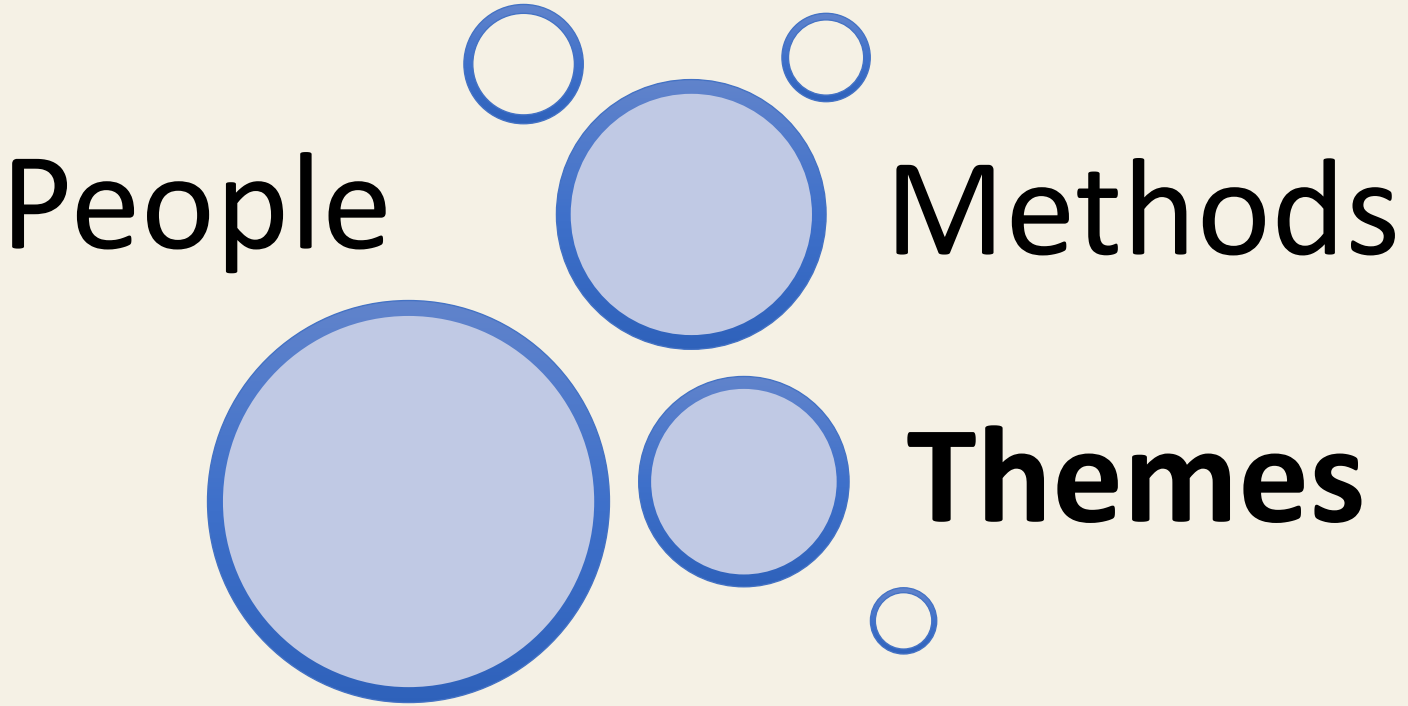

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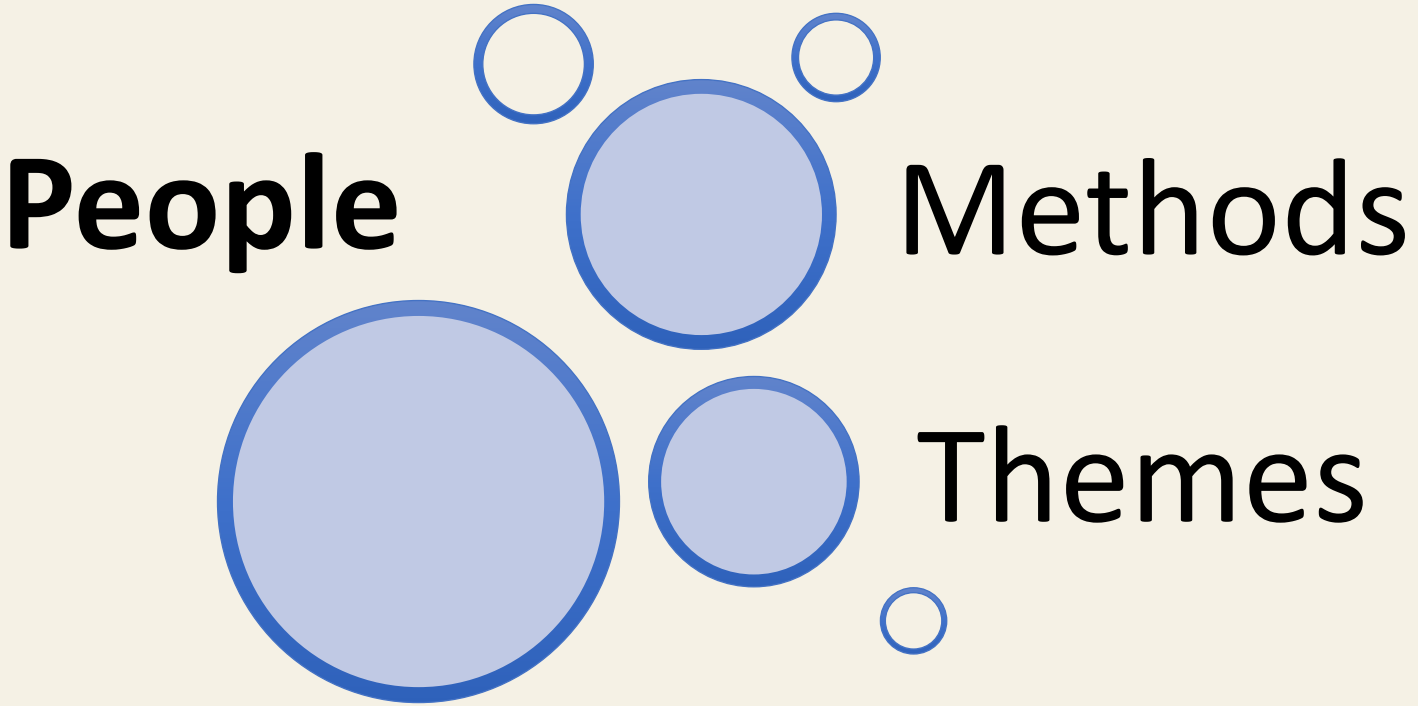
Themes

Dr Emma Meaburn, GEL lab co-director

GEL Genes Environment Lifespan laboratory



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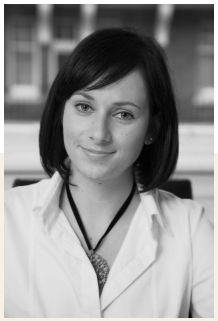
Past & present postdocs and PhD students

Dr Sania Shakoor

Dr Kostas Papageorgiou



Dr Dominika Sieradzka

Dr Helena Zavos

Dr Charlotte Willfors

Dr Elise Robinson

Dr Oliver Pain

Dr Mark Taylor

Aislinn Bowler

Chloe Austerberry

Wikus Barkhuizen

Monica Siqueiros

Dr Aline Scherff

Dr Karla Holmboe

Dr Victoria Hallett

Laura Havers

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Looking forward

Multi-method study of evocative parent-child effects

Chloe Austerberry*

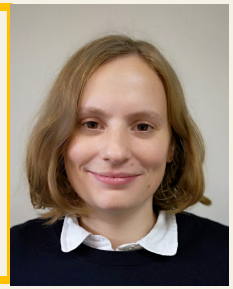
Longitudinal infant twin study in Stockholm

Monica Siqueiros*

Stability and change in psychotic experiences

Laura Havers*

iCASE PhD to develop app for cohort research



Aislinn Bowler

*See their posters today!

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Thank you

www.gel.bbk.ac.uk

Twitter @gelironald

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Acknowledgements

Research Team:

Wikus Barkhuizen

Professor Frank Dudbridge

Dr Oliver Pain

Funding

Camara-Rivers David grant fund

UK Medical Research Council

Wellcome Trust ISSF fund

Summary statistics: Samples and Resources

ALSPAC, CATSS and TEDS samples

Neale Lab *http://www.nealelab.is/uk-biobank*

UK Biobank

North Finland Birth Cohort

William Hennah and Alfreda Ortega-Alonso

Psychiatric Genomics Consortium www.med.unc.edu/pgc/results-and-downloads/

All the cohort teams and participants

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www.gel.bbk.ac.uk

MRC Medical Research Council Leading science for better health

TEDS

ALSPAC

The Child and Adolescent Twin Study in Sweden (CATSS)

- Notes on WCPG Guidelines: -
- Contact Information on final slide
- Use common fonts: Times New Roman, Arial, and Courier.
- Save versions in both 4:3 and 16:9!
- BEFORE YOU GO TO YOUR TALK DO THE FOLLOWING:
- After you put together your presentation save it. Then:
- a) Go to Design on the top Tab
- b) Go to Slide Size and click on it
- c) You will see the choice of 4:3 or 16:9
- d) Whatever size it currently isn't on, change to that size
- e) Save the presentation with another name or the name plus 4:3 or 16:9
- f) Go through the new presentation and correct the sizing and placement of your photos
- g) When you arrive at your talk determine whether you need a 4:3 or a 16:9 presentation and use the correct one.
- Regardless of whether you take your computer or a thumb drive include both your 4:3 and16:9 presentations.

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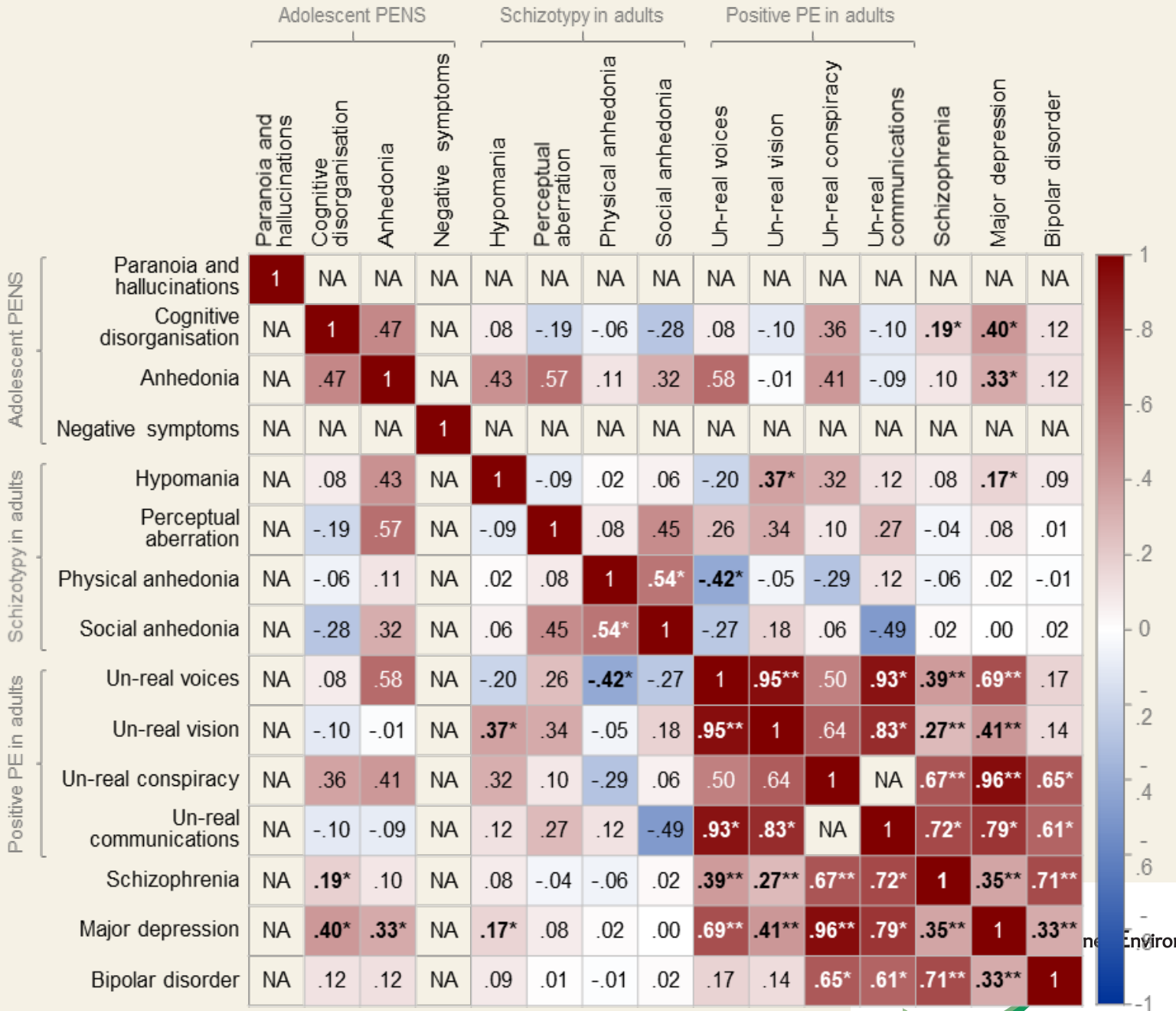
Adolescent PENS
Schizotypy in adults
Positive PE in adults
Paranoia and hallucinations
Cognitive disorganisation
Anhedonia
Negative symptoms
Hypomania
Perceptual aberration
Physical anhedonia
Social anhedonia
Un-real voices
Un-real vision
Un-real conspiracy
Un-real communications
Schizophrenia
Major depression
Bipolar disorder
Adolescent PENS
Schizotypy in adults
Positive PE in adults
Paranoia and hallucinations 1 NA NA NA NA NA NA NA NA NA NA NA NA NA NA
Cognitive disorganisation NA 1 .47 NA .08 -.19 -.06 -.28 .08 -.10 .36 -.10 .19* .40* .12
Anhedonia NA .47 1 NA .43 .57 .11 .32 .58 -.01 .41 -.09 .10 .33* .12
Negative symptoms NA NA NA 1 NA NA NA NA NA NA NA NA NA NA NA
Hypomania NA .08 .43 NA 1 -.09 .02 .06 -.20 .37* .32 .12 .08 .17* .09
Perceptual aberration NA -.19 .57 NA -.09 1 .08 .45 .26 .34 .10 .27 -.04 .08 .01
Physical anhedonia NA -.06 .11 NA .02 .08 1 .54* -.42* -.05 -.29 .12 -.06 .02 -.01
Social anhedonia NA -.28 .32 NA .06 .45 .54* 1 -.27 .18 .06 -.49 .02 .00 .02
Un-real voices NA .08 .58 NA -.20 .26 -.42* -.27 1 .95** .50 .93* .39** .69** .17
Un-real vision NA -.10 -.01 NA .37* .34 -.05 .18 .95** 1 .64 .83* .27** .41** .14
Un-real conspiracy NA .36 .41 NA .32 .10 -.29 .06 .50 .64 1 NA .67** .96** .65*
Un-real communications NA -.10 -.09 NA .12 .27 .12 -.49 .93* .83* NA 1 .72* .79* .61*
Schizophrenia NA .19* .10 NA .08 -.04 -.06 .02 .39** .27** .67** .72* 1 .35** .71**
Major depression NA .40* .33* NA .17* .08 .02 .00 .69** .41** .96** .79* .35** 1 .33**
Bipolar disorder NA .12 .12 NA .09 .01 -.01 .02 .17 .14 .65* .61* .71** .33** 1
1
.8
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0
-.2
-.4
-.6
-1
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Background/ 2 – traits and disorders

Psychopathology trait measures show genetic associations with disorders

Table 1. Effect Sizes of Genome-wide Polygenic Score Predictions for Four Psychiatric Disorders and Their Related Dimensional Traits

Disorder GPS	Related Trait	Variance Predicted in Disorder Itself by GPS (A)	Variance Predicted in Related Trait by Disorder GPS (B)	B/A
Autism	Autistic traits	1.13% (6)	0.1% (6)	9%
Schizophrenia	Negative symptom traits	7% (3)	0.7% (7)	10%
Depression	Depressive traits	0.72% (8)	0.11% (9)	15%
ADHD	ADHD traits	3.71% (10)	0.8% (10)	22%

ADHD, attention-deficit/hyperactivity disorder; GPS, genome-wide polygenic score.

Ronald (2019) *Biol Psych*

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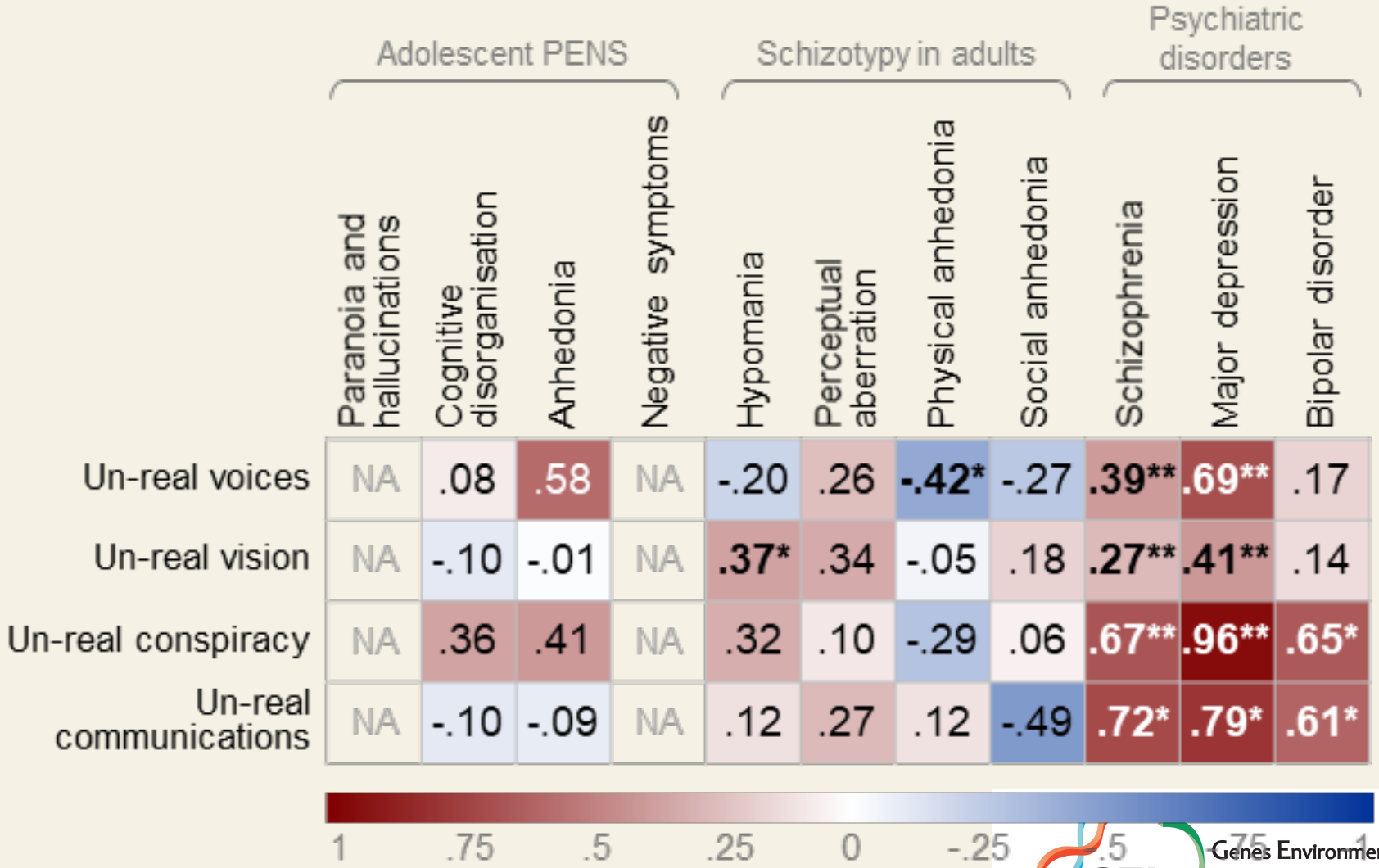
LD score regression with positive PE in older adults



**Survived correction for multiple testing *Nominally significant

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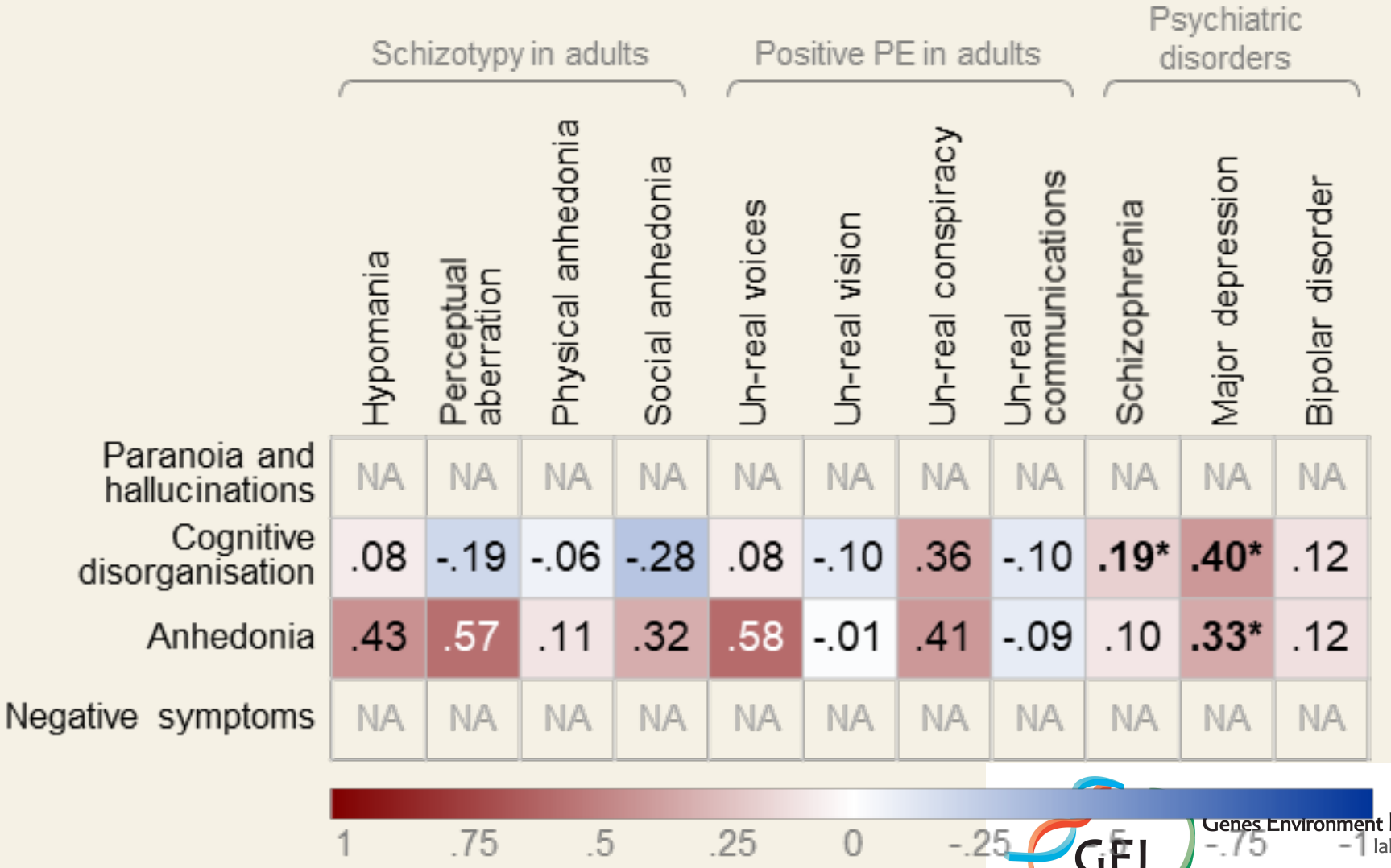
LD score regression with mid-adolescent PEs



**Survived correction for multiple testing *Nominally significant

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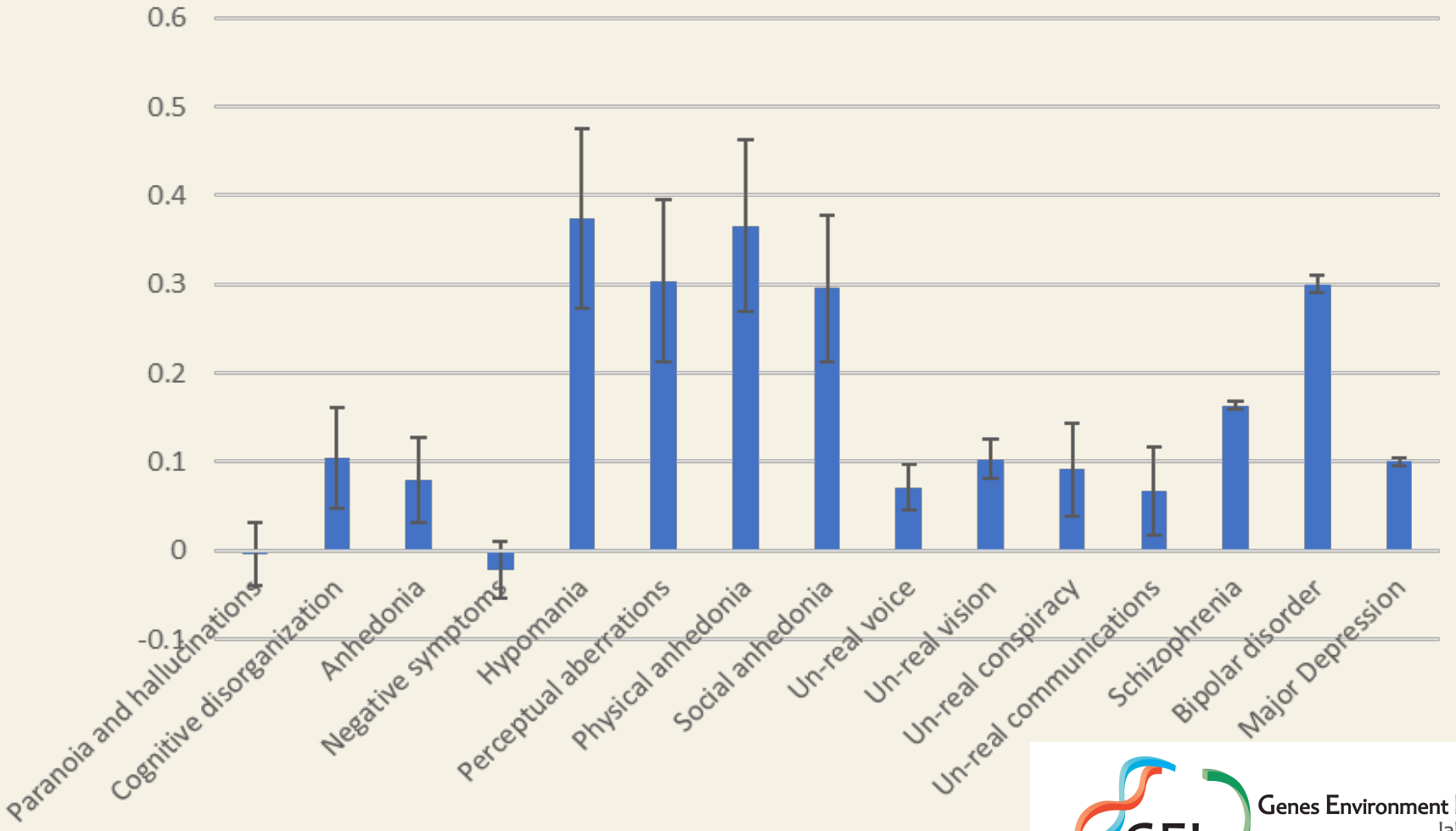
LD score regression: SNP h^2 estimates



Pain et al., 2018 *Neuropsych Gen*; Ortega-Alonso et al., 2017 *Schz Bull;* Wray et al 2018 *Nat Gen*; *www.nealelab.is/uk-biobank*; www.med.unc.edu/pgc;

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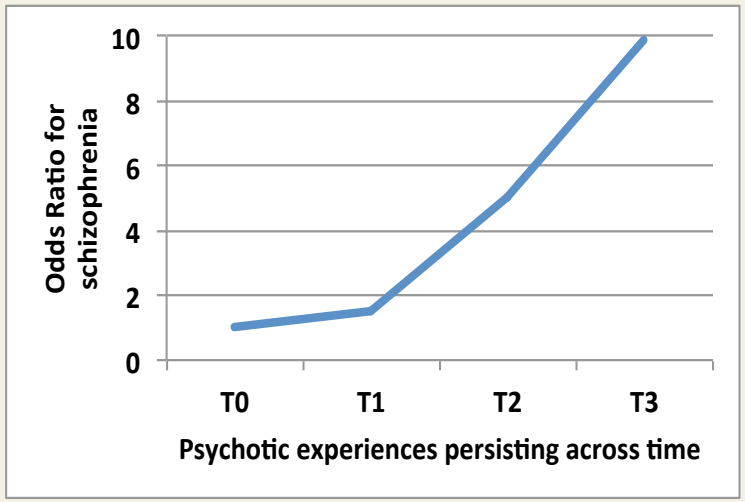
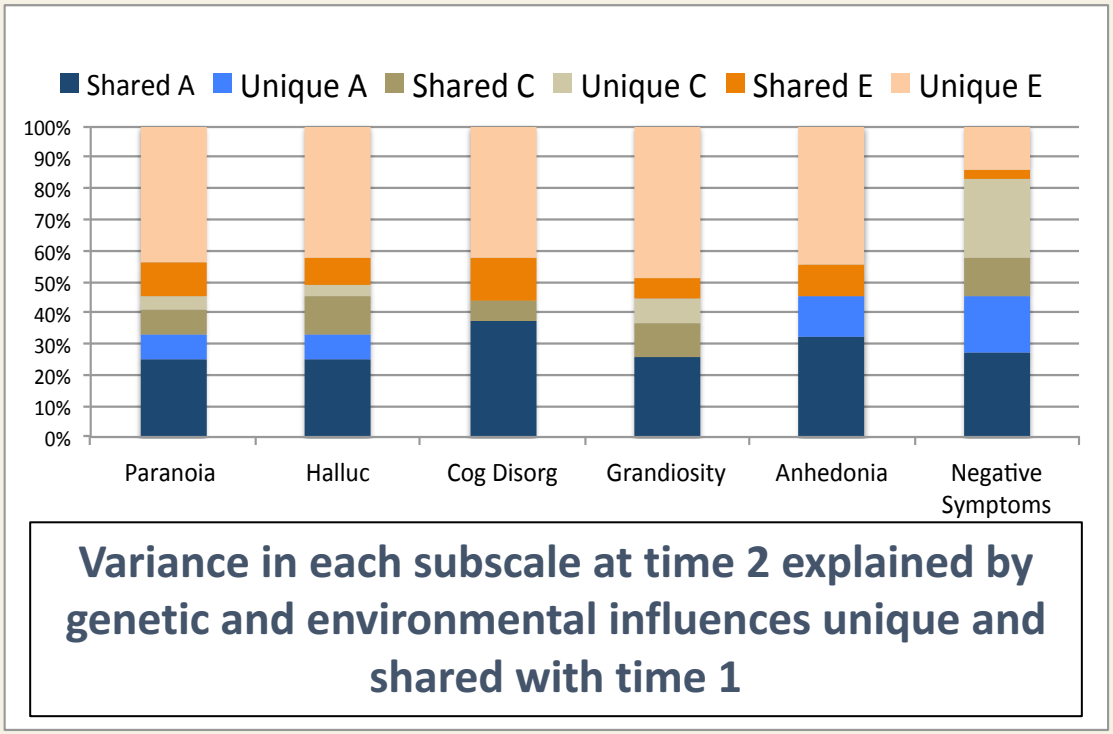
Stability and Change across Age



Dominguez et al (2011*) Schz Bull*



Variance in each subscale at time 2 explained by genetic and environmental influences unique and shared with time 1

Havers et al (2019*) Journal of Child Psychology and Psychiatry*

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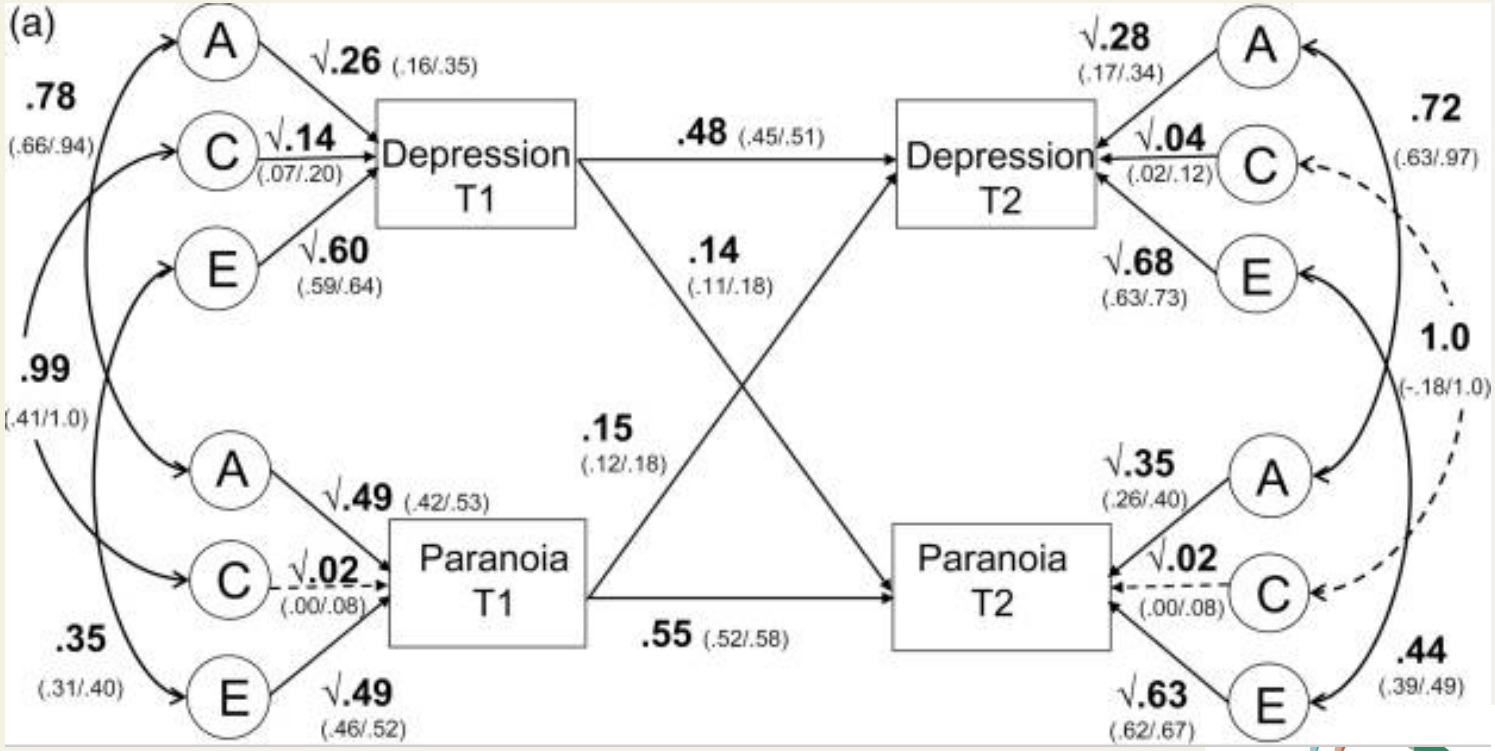
Causal Effects

Evidence of longitudinal causal effects between psychotic experiences and depression in adolescents



Zavos et al (2016*) Schz Bull*

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Aims

1. To evaluate genetic overlap between PE traits and clinical disorders

2. To explore stability of common genetic variation on PEs across adolescence → adulthood

3. Overlapping genes?

If genetic overlap:

3. Causal associations?

Analyses

LD score regression

→ **To assess degree of genome-wide genetic overlap**

FUMA

→ **Gene mapping**

- Positional
- Functional annotations

Mendelian randomization

→ **Generalized summary based MR**

- Sensitivity analyses using MR methods that make different assumptions
- Heidi-outliers removed from main and sensitivity MR

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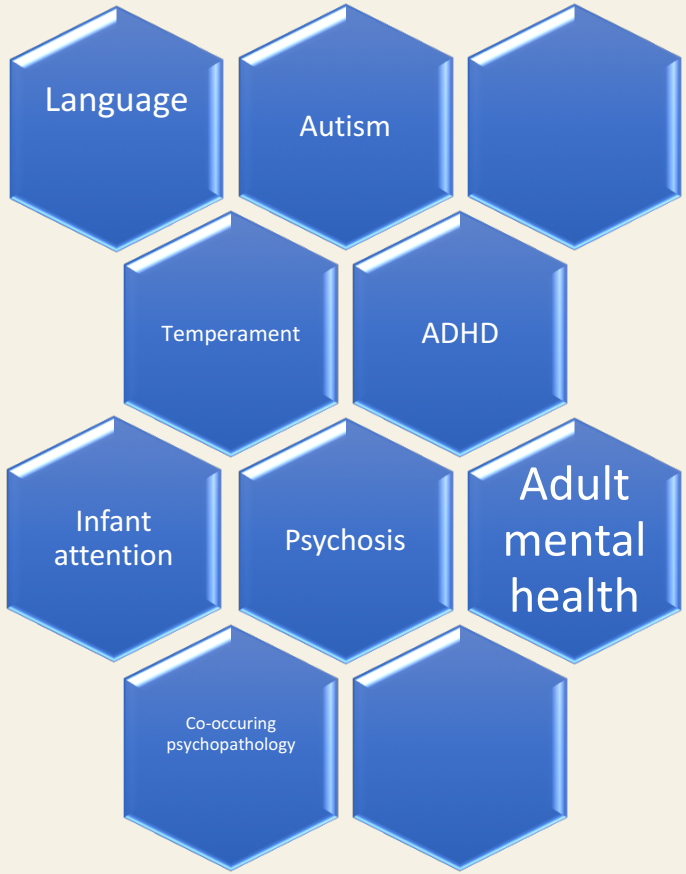
Themes



Development

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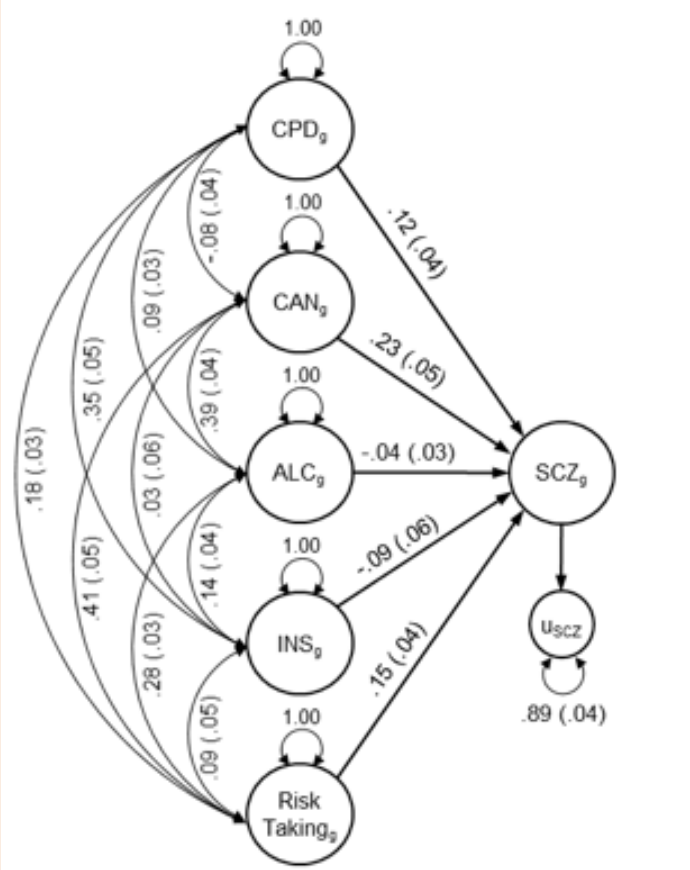
Genomic Structural Equation Modelling



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