The first 10 years and beyond…. 

CBCD 20th Anniversary

Angelica Ronald

Joined CBCD in 2007
Back in 2007:

Ronald et al (2010) *Behavior Genetics*
Methods

- SNP heritability
- Genetic correlations across samples
- Polygenic risk prediction
- Mendelian randomisation
- Gene-based analyses
SNP Heritability
SNP; single nucleotide polymorphism

Gene discovery: Larger and cheaper

Paranoia and Hallucinations
N (inc. sibs) 8665

Anhedonia
N (inc. sibs) 6579

Cognitive Disorganisation
N (inc. sibs) 6297

Parent-rated negative symptoms
N (inc. sibs) 10098

Methods

- SNP heritability
- Genetic correlations across samples
- Polygenic risk prediction
- Mendelian randomisation
- Gene-based analyses
Genetic correlations across samples!

<table>
<thead>
<tr>
<th></th>
<th>Adolescent PENS</th>
<th>Schizotypy in adults</th>
<th>Positive PE in adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paranoia and hallucinations</td>
<td>Cognitive disorganisation</td>
<td>Anhedonia</td>
</tr>
<tr>
<td>Paranoia and hallucinations</td>
<td>1.00</td>
<td>0.47</td>
<td>NA</td>
</tr>
<tr>
<td>Cognitive disorganisation</td>
<td>NA</td>
<td>0.88</td>
<td>-0.19</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>NA</td>
<td>0.47</td>
<td>1.00</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hypomania</td>
<td>NA</td>
<td>-0.19</td>
<td>-0.57</td>
</tr>
<tr>
<td>Perceptual aberration</td>
<td>NA</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Physical anhedonia</td>
<td>NA</td>
<td>-0.28</td>
<td>-0.32</td>
</tr>
<tr>
<td>Social anhedonia</td>
<td>NA</td>
<td>0.08</td>
<td>0.58</td>
</tr>
<tr>
<td>Un-real voices</td>
<td>NA</td>
<td>-0.10</td>
<td>-0.01</td>
</tr>
<tr>
<td>Un-real vision</td>
<td>NA</td>
<td>0.36</td>
<td>0.41</td>
</tr>
<tr>
<td>Un-real conspiracy</td>
<td>NA</td>
<td>-1.00</td>
<td>NA</td>
</tr>
<tr>
<td>Un-real communications</td>
<td>NA</td>
<td>-1.00</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

https://www.biorxiv.org/content/10.1101/718015v1
Methods

SNP heritability

Gene-based analyses

Genetic correlations across samples

Mendelian randomisation

Polygenic risk prediction
Polygenic Risk Score prediction

Polygenic risk score for each individual

Does the score predict a second phenotype

Ronald & Pain (2018) *Human Molecular Genetics*
Sieradzka, Power, Freeman, ... & Ronald (2014) *PLoS ONE*
Pain et al (2018) *Neuropsych Genetics*
Methods

SNP heritability

Gene-based analyses

Genetic correlations across samples

Mendelian randomisation

Polygenic risk prediction
Mendelian Randomisation

Tobacco use → Psychiatric traits

Wikus Barkhuizen

Barkhuizen, Dudbridge & Ronald (in preparation)
Methods

- SNP heritability
- Genetic correlations across samples
- Polygenic risk prediction
- Mendelian randomisation
- Gene-based analyses

GEL - Genes Environment Lifespan laboratory
Gene-based analyses: Overlapping genes across age and with psychiatric disorders

https://www.biorxiv.org/content/10.1101/718015v1
Themes

Dr Emma Meaburn, GEL lab co-director
Past & present postdocs and PhD students

Dr Sania Shakoor
Dr Kostas Papageorgiou
Dr Dominika Sieradzka
Dr Helena Zavos
Dr Charlotte Willfors
Dr Mark Taylor
Dr Aline Scherff
Dr Karla Holmboe
Dr Victoria Hallett
Dr Elise Robinson
Laura Havers
Wikus Barkhuizen
Monica Siqueiros
Aislinn Bowler
Chloe Austerberry
Genes Environment Lifespan laboratory
Looking forward

Chloe Austerberry*

Multi-method study of evocative parent-child effects

Longitudinal infant twin study in Stockholm

Monica Siqueiros*

Stability and change in psychotic experiences

iCASE PhD to develop app for cohort research

Laura Havers*

Aislinn Bowler

*See their posters today!
Thank you

www.gel.bbk.ac.uk
Twitter @gelironald
Acknowledgements

Research Team:
Wikus Barkhuizen
Professor Frank Dudbridge
Dr Oliver Pain

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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Camara-Rivers David grant fund
UK Medical Research Council
Wellcome Trust ISSF fund
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 and 16:9 presentations.
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

<table>
<thead>
<tr>
<th>Disorder GPS</th>
<th>Related Trait</th>
<th>Variance Predicted in Disorder Itself by GPS (A)</th>
<th>Variance Predicted in Related Trait by Disorder GPS (B)</th>
<th>B/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism</td>
<td>Autonomous traits</td>
<td>1.13% (6)</td>
<td>0.1% (6)</td>
<td>9%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Negative symptom traits</td>
<td>7% (3)</td>
<td>0.7% (7)</td>
<td>10%</td>
</tr>
<tr>
<td>Depression</td>
<td>Depressive traits</td>
<td>0.72% (8)</td>
<td>0.11% (9)</td>
<td>15%</td>
</tr>
<tr>
<td>ADHD</td>
<td>ADHD traits</td>
<td>3.71% (10)</td>
<td>0.8% (10)</td>
<td>22%</td>
</tr>
</tbody>
</table>

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

Ronald (2019) *Biol Psych*
LD score regression with positive PE in older adults

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**Survived correction for multiple testing  *Nominally significant
LD score regression with mid-adolescent PEs

**Survived correction for multiple testing**

*Nominally significant*
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;
Stability and Change across Age

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

Dominguez et al (2011) *Schz Bull*

Causal Effects

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

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
Genomic Structural Equation Modelling