Polygenic Risk for Psychiatric Disorder Reveals Distinct Association Profiles Across Social Behaviour in the General population

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Research aim

We investigate heterogeneity in genetic overlap of social behaviour with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), bipolar disorder (BP), major depression (MD) and schizophrenia (SCZ) across a spectrum of different social symptoms.

Polygenic risk scores (PRS)

ADHD-PRS, ASD-PRS, BP-PRS, MD-PRS, SCZ-PRS

PRS (clumping and thresholding approach) were based on genome-wide summary statistics[1] (N: 46,350 - 500,199). Here we study PRS based on a *P*-value selection threshold of $P_T \leq 0.1$.

Association analyses with social behaviour

Trait-specific:	Low prosociality vs peer problems
Reporter-specific:	Parent- vs teacher-reports
Age-specific:	4-17 years

In two UK population-based cohorts:

ALSPAC[2] (N≤6,174; 7-17 years; 14 scores)

We found evidence for association of social behaviour with ADHD-PRS, MD-PRS, and SCZ-PRS.

TEDS[3] (N≤7,112; 4-16 years; 15 scores)

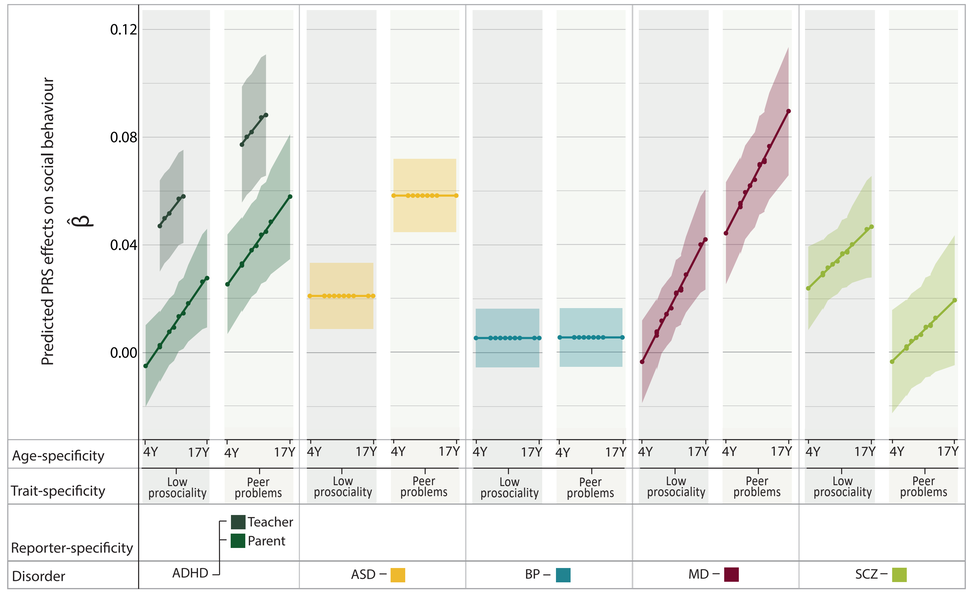
We found evidence for association of social behaviour with ADHD-PRS, ASD-PRS, MD-PRS, and SCZ-PRS.

Social behaviour was assessed using the Strength-and-Difficulties Questionnaire[4]. We performed 5 x 29 negative binomial regressions accounting for age, sex, ancestry informative PCs & cohort-specific covariates.

5 random-effects meta-regressions (R:metaphor,v2.1-0)[5] **of PRS effects accounting for age-, reporter-, and trait-specificity**

Sensitivity analyses with PRS effects adjusted for other disorders (cross-disorder adjusted).

Differences in trait-disorder overlap as predicted by age-, reporter- and trait-specific social behaviour



PRS estimates ($P_T \leq 0.1$) were modelled using random-effects meta-regression accounting for phenotypic correlations. The most parsimonious model for each disorder was identified using likelihood ratio tests (combining PRS effects without adjustment for cross-disorder PRS effects). 95% confidence interval bands are presented.

Meta-regression analysis of univariate PRS effects (non-adjusted and adjusted for cross-disorder effects)

	Non-adjusted for cross-disorder effects		Adjusted for cross-disorder effects	
Parameter	θ (SE)	*P*-value	θ (SE)	*P*-value
ADHD-PRS				
Intercept (Age 4, parent-reported, low prosociality)	-0.015 (0.010)	0.14	-0.017 (0.011)	0.13
Age (Centered at 4 years)	*0.0025 (0.00089)*	*0.0042*	*0.002 (0.001)*	*0.05*
Reporter (Teacher-reported)	0.044 (0.0085)	2.5×10^{-7}	0.046 (0.0083)	2.6×10^{-8}
Trait (Peer problems)	0.03 (0.0089)	7.3×10^{-4}	0.03 (0.0058)	2.0×10^{-7}
ASD-PRS				
Intercept (Low prosociality)	0.021 (0.0063)	7.7×10^{-4}	0.017 (0.0049)	4.8×10^{-4}
Trait (Peer problems)	0.037 (0.0083)	7.9×10^{-6}	0.025 (0.0054)	6.3×10^{-6}
BP-PRS				
Intercept	0.0054 (0.0056)	0.33	0.00056 (0.0054)	0.92
MD-PRS				
Intercept (Age 4, low prosociality)	-0.018 (0.011)	0.096	-0.021 (0.012)	0.09
Age (Centered at 4 years)	*0.0035 (0.00095)*	*1.9×10^{-4}*	*0.0027 (0.0011)*	*0.02*
Trait (Peer problems)	0.048 (0.0093)	2.8×10^{-7}	0.051 (0.0068)	8.8×10^{-14}
SCZ-PRS				
Intercept (Low prosociality)	0.017 (0.011)	0.12	0.026 (0.014)	0.06
Age (Centered at 4 years)	*0.0018 (0.00096)*	*0.063*	*0.0013 (0.0013)*	*0.32*
Trait (Peer problems)	-0.027 (0.0094)	0.0033	-0.043 (0.0076)	1.1×10^{-8}

Shared age-related association profile:

- The link between ADHD-, MD- and SCZ-PRS and social behaviour increased with age.

Disorder-specific profiles:

- ADHD-, MD-, and ASD-PRS were more strongly linked to peer problems than low prosociality.
- SCZ-PRS was associated with low prosociality only.
- ADHD-PRS was more strongly linked to teacher- than parent-reported social behaviour.

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Conclusion

We identified association profiles that suggest differences in the social genetic architecture across mental disorders.

[1] Cross-Disorder Group of the PGC 2019; [2] Fraser et al. 2013; [3] Rimfeld et al. 2019 ; [4] Goodman 1997; [5] Viechtbauer 2010

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