

Additional material

Shared genetic influences between dimensional ASD and ADHD symptoms during child and adolescent development

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Supplementary methods

Selection of SDQ-ADHD measures

Mother-reports on their children's hyperactive-impulsive and inattentive behaviour were obtained at 7, 10, 12, 13 and 17 years of age. An additional SDQ measure at 8 years of age was excluded due to potential bias. The administration of the questionnaire coincided with the recruitment of additional children into the study, resulting in late questionnaire returns (Jean Golding, personal communication). The reported age range for children using this questionnaire was considerably wider (7.83 to 14 years) and had approximately twice the variance ($\sigma^2=0.25$) than the observed age ranges and variances for children at slightly younger ages (7 year assessment: range 6.67 to 8.2 years; $\sigma^2=0.11$) and at slightly older ages (10 year assessment: range 9.5 years to 10.75 years; $\sigma^2=0.12$) (Table S1).

Meta-analysis of correlated test statistics from pathway analysis

Genetic variances of SCDC and SDQ-ADHD scores (four SCDC scores at 8, 11, 14 and 17 years and five SDQ-ADHD scores at 7, 10, 12, 13 and 17 years) were combined using an inverse variance weighted meta-analysis statistic, assuming multivariate normality [1],

$$S = \frac{e^T(RW)^{-1}B(e^T(RW)^{-1}B)^T}{e^T(WRW)^{-1}e} \quad (1)$$

which follows a χ^2 distribution with one degree of freedom. B is a vector of test statistics (B_1, \dots, B_K), where each test statistic is defined as the ratio of the additive genetic variance estimate explained by a selected pathway for measures K and its SE. R is approximated by the K x K phenotypic correlation matrix between all traits, i.e. rank-transformed SDQ-ADHD and SCDC scores. $e^T = (1, \dots, 1)$ has length K and W is a diagonal matrix of weights for the individual test statistics (inverse variance).

Additional references

1. Zhu X, Feng T, Tayo BO, Liang J, Young JH, Franceschini N, et al. Meta-analysis of Correlated Traits via Summary Statistics from GWASs with an Application in Hypertension. *Am. J. Hum. Genet.* 2015;96:21–36.
2. St Pourcain B, Skuse DH, Mandy WP, Wang K, Hakonarson H, Timpson NJ, et al. Variability in the common genetic architecture of social-communication spectrum phenotypes during childhood and adolescence. *Mol. Autism.* 2014;5:18.

Web resources

ALSPAC: <http://www.bris.ac.uk/alspac/>

PGC: <http://www.med.unc.edu/pgc/>

Supplementary tables

Table S1: Descriptives of SDQ-ADHD and SCDC scores in ALSPAC

Trait	Age(years)[range]	Male/Female	Mean(SD) [range]	Kurtosis	Skewness	N
SDQ-ADHD						
7	6.8(0.11)[6.7;8.2]	2864/2748	3(2.35)[0;10]	2.85	0.62	5612
10	9.7(0.12)[9.5;10.8]	2868/2810	3(2.24)[0;10]	3.31	0.83	5678
12	11.7(0.13)[11.6;13.8]	2613/2646	2(2.22)[0;10]	3.61	0.93	5259
13	13.2(0.18)[12.9;16.1]	2524/2548	3(2.22)[0;10]	3.25	0.78	5072
17	16.8(0.36)[16.5;18.3]	2019/2145	2(2.12)[0;10]	2.85	0.62	4164
SCDC						
8	7.7(0.14)[7.5;9.3]	2842/2709	2(3.71)[0;24]	9.12	2.19	5551
11	10.7(0.13)[10.5;13.8]	2751/2709	1(3.51)[0;24]	10.53	2.46	5460
14	13.9(0.15)[13.7;16.1]	2529/2531	1(3.59)[0;24]	9.08	2.20	5060
17	16.8(0.36)[16.5;18.3]	2024/2150	1(3.79)[0;24]	7.09	1.89	4174

ALSPAC - Avon Longitudinal Study of Parents and Children; SCDC - Social and Communication Disorders Checklist; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire; The kurtosis for the standard normal distribution is 3 and the skewness is 0

Table S2: Phenotypic correlations of SDQ-ADHD scores in ALSPAC

Age in years	7	10	12	13	17
7	1.00	0.65	0.60	0.56	0.46
10	0.66	1.00	0.67	0.63	0.52
12	0.61	0.68	1.00	0.69	0.55
13	0.57	0.63	0.70	1.00	0.59
17	0.46	0.52	0.56	0.59	1.00

ALSPAC - Avon Longitudinal study of Parents and Children; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire

Lower triangle: Spearman's rank correlation using pairwise complete observations;
Upper triangle: Pearson product moment correlation using rank-transformed scores adjusted for age, sex and the two most significant principal components

Table S3: Phenotypic correlations of SCDC scores in ALSPAC

Age in years				
	8	11	14	17
8	1.00	0.61	0.50	0.38
11	0.57	1.00	0.56	0.41
14	0.49	0.57	1.00	0.51
17	0.39	0.45	0.56	1.00

ALSPAC - Avon Longitudinal study of Parents and Children; SCDC - Social and Communication Disorders Checklist

Lower triangle: Spearman's rank correlation using pairwise complete observations;
Upper triangle: Pearson product moment correlation using rank-transformed scores adjusted for age, sex and the two most significant ancestry-informative principal components; Estimates correspond closely to previously published correlations[2]

Table S4: Univariate GREML of SDQ-ADHD scores in ALSPAC

Age in years	Rank-transformed			Untransformed scores			
	$h^2(\text{SE})$	Var_g	p	N	$h^2(\text{SE})$	p	N
7	0.10(0.07)	0.10(0.07)	0.070	5185	0.09(0.07)	0.095	5185
10	0.14(0.07)	0.14(0.07)	0.020	5235	0.14(0.07)	0.017	5235
12	0.19(0.07)	0.19(0.07)	0.0020 ^a	4886	0.15(0.07)	0.010	4886
13	0.18(0.07)	0.18(0.07)	0.0030 ^a	4735	0.16(0.07)	0.010	4735
17	0.15(0.09)	0.15(0.09)	0.04	3968	0.12(0.09)	0.079	3968

ALSPAC - Avon Longitudinal study of Parents and Children; GREML - Genetic-relationship-matrix restricted maximum likelihood; h^2 - heritability; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire; Rank-transformed - Rank-transformed scores; Untransformed - Untransformed scores (sensitivity analysis only); Var_g - Genetic variance; a - $p < 0.05$ after adjustment for multiple testing

All GREML- h^2 estimates were adjusted for age and sex and the two most significant ancestry-informative principal components. Differences compared with the total sample N are due to the exclusion of individuals with a relatedness of $\geq 2.5\%$. Note that for rank-transformed traits, estimates of SNP- h^2 are equivalent to estimates of Var_g , as the phenotypic variance has been standardised to one

Table S5: Univariate GREML of SCDC scores in ALSPAC

Age in years	Rank-transformed				Untransformed scores ^b		
	$h^2(\text{SE})$	Var_g	p	N	$h^2(\text{SE})$	p^a	N
8	0.24(0.07)	0.24(0.07)	7.0×10^{-5} ^a	5136	0.11(0.07)	0.043	5136
11	0.16(0.07)	0.16(0.07)	0.0050 ^a	5056	0.04(0.07)	0.28	5056
14	0.08(0.07)	0.08(0.07)	0.10	4735	0.07(0.07)	0.15	4735
17	0.45(0.08)	0.45(0.09)	3.0×10^{-9} ^a	3977	0.22(0.09)	0.0051 ^a	3977

ALSPAC - Avon Longitudinal study of Parents and Children; GREML - Genetic-relationship-matrix restricted maximum likelihood; h^2 - heritability; SCDC - Social and Communication Disorders Checklist; Rank-transformed - Rank-transformed scores; Untransformed - Untransformed scores (sensitivity analysis only); Var_g - Genetic variance; a - $p < 0.05$ after adjustment for multiple testing

All GREML- h^2 estimates were adjusted for age and sex and the two most significant ancestry-informative principal components. Differences compared with the total sample N are due to the exclusion of individuals with a relatedness of $\geq 2.5\%$. Note that for rank-transformed traits, estimates of SNP- h^2 are equivalent to estimates of Var_g , as the phenotypic variance has been standardised to one. Findings correspond closely to previously published estimates[2]

Table S6: Bivariate GREML of SDQ-ADHD scores in ALSPAC

r_g (SE), p (lower triangle) and Cov_g (upper triangle)					
Age	7	10	12	13	17
7	-	0.13(0.05)	0.09(0.05)	0.10(0.05)	0.07(0.06)
10	0.86(0.17), $p=8 \times 10^{-3}$ ^a	-	0.17(0.06)	0.13(0.06)	0.08(0.06)
12	0.65(0.21), $p=0.04$	0.94(0.13), $p=7 \times 10^{-4}$ ^a	-	0.15(0.06)	0.03(0.06)
13	0.73(0.25), $p=0.03$	0.76(0.17), $p=9 \times 10^{-3}$ ^a	0.76(0.13), $p=4 \times 10^{-3}$ ^a	-	0.13(0.06)
17	0.66(0.43), $p=0.10$	0.52(0.25), $p=0.07$	0.20(0.31), $p=0.30$	0.88(0.24), $p=0.01$ ^a	-

ALSPAC - Avon Longitudinal study of Parents and Children; Cov_g - Genetic covariance; GREML - Genetic-relationship-matrix restricted maximum likelihood; r_g - genetic correlation; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire (rank-transformed); a - $p < 0.05$ after adjustment for multiple testing

Table S7: Bivariate GREML of SCDC scores in ALSPAC

r_g (SE), p (lower triangle) and Cov_g (upper triangle)				
Age	8	11	14	17
8	-	0.18(0.05)	0.10(0.05)	0.17(0.06)
11	0.93(0.14), $p=1 \times 10^{-4}$ ^a	-	0.11(0.05)	0.11(0.06)
14	0.78(0.31), $p=0.02$	0.82(0.24), $p=0.02$	-	0.19(0.06)
17	0.50(0.14), $p=9 \times 10^{-4}$ ^a	0.38(0.16), $p=0.02$	0.95(0.34), $p=2 \times 10^{-7}$ ^a	-

ALSPAC - Avon Longitudinal study of Parents and Children; Cov_g - Genetic covariance; GREML - Genetic-relationship-matrix restricted maximum likelihood; GREML- r_g - Genetic correlation; SCDC - Social and Communication Disorders Checklist (rank-transformed); a - $p < 0.05$ after adjustment for multiple testing; r_g (SE), p are shown in the lower triangle and Cov_g in the upper triangle

Table S8: Bivariate GREML and Pearson correlations of SDQ-ADHD and SCDC scores in ALSPAC

r_g (SE), p^a					
Age	SCDC	8	11	14	17
SDQ					
7		0.80(0.25), $p=6 \times 10^{-3}$ ^a	1.00(0.35), $p=2 \times 10^{-3}$ ^a	1.00(0.79), $p=0.50$	0.52(0.29), $p=0.03$
10		0.62(0.20), $p=0.01$ ^a	0.74(0.23), $p=8 \times 10^{-3}$ ^a	0.89(0.40), $p=0.02$	0.53(0.19), $p=5 \times 10^{-3}$ ^a
12		0.39(0.19), $p=0.05$	0.44(0.21), $p=0.05$	0.48(0.30), $p=0.10$	0.13(0.19), $p=0.30$
13		0.72(0.19), $p=2 \times 10^{-3}$ ^a	1.00(0.26), $p=3 \times 10^{-4}$ ^a	0.80(0.34), $p=0.03$	0.42(0.17), $p=0.02$
17		0.73(0.37), $p=0.02$	0.92(0.43), $p=0.01$ ^a	1.00(0.43), $p=0.01$ ^a	0.80(0.26), $p=3 \times 10^{-3}$ ^a
Cov_g(SE)					
Age	SCDC	8	11	14	17
SDQ-ADHD					
7		0.13(0.05)	0.14(0.05)	0.07(0.05)	0.10(0.06)
10		0.11(0.05)	0.12(0.05)	0.10(0.05)	0.14(0.06)
12		0.09(0.05)	0.08(0.05)	0.07(0.05)	0.04(0.06)
13		0.15(0.05)	0.17(0.05)	0.10(0.05)	0.12(0.06)
17		0.11(0.06)	0.12(0.06)	0.12(0.06)	0.18(0.07)
r_p(SE)					
Age	SCDC	8	11	14	17
SDQ-ADHD					
7		0.43	0.36	0.3	0.27
10		0.44	0.41	0.37	0.33
12		0.39	0.40	0.37	0.32
13		0.40	0.41	0.42	0.35
17		0.34	0.36	0.39	0.50

Age - Age in years; ALSPAC - Avon Longitudinal study of Parents and Children; Cov_g - Genetic covariance; GREML - Genetic-relationship-matrix restricted maximum likelihood; r_g - Genetic correlation; r_p - Pearson product moment correlation based on rank-transformed traits; SCDC - Social and Communication Disorders Checklist(rank-transformed); SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire (rank-transformed); a - $p < 0.05$ after adjustment for multiple testing

Table S9: Pathway-based dissection of additive genetic variance in SDQ-ADHD and SCDC scores according to 50 molecular signatures database hallmark gene set collections (file A9.xlsx)

Table S10: Association between ADHD polygenic scores and SDQ-ADHD scores in ALSPAC

SDQ-ADHD	PGS bin	Beta (SE)	<i>p</i>	Adj-R ² (%)
7 y (N=5612)	P _T <0.001	0.002(0.01)	0.9	na
	P _T <0.01	0.009(0.01)	0.52	na
	P _T <0.05	0.014(0.01)	0.3	na
	P _T <0.1	0.022(0.01)	0.11	na
	P _T <0.3	0.035(0.01)	0.009	0.1
	P _T <0.5	0.033(0.01)	0.013	0.09
	P _T <0.7	0.032(0.01)	0.015	0.09
	P _T <0.9	0.032(0.01)	0.018	0.08
	P _T <1	0.032(0.01)	0.018	0.08
10 y (N=5678)	P _T <0.001	0.018(0.01)	0.18	na
	P _T <0.01	0.019(0.01)	0.16	na
	P _T <0.05	0.012(0.01)	0.38	na
	P _T <0.1	0.02(0.01)	0.14	na
	P _T <0.3	0.022(0.01)	0.093	na
	P _T <0.5	0.027(0.01)	0.042	0.05
	P _T <0.7	0.024(0.01)	0.067	na
	P _T <0.9	0.024(0.01)	0.072	na
	P _T <1	0.024(0.01)	0.07	na
12 y (N=5259)	P _T <0.001	0.005(0.01)	0.73	na
	P _T <0.01	0.01(0.01)	0.48	na
	P _T <0.05	0.016(0.01)	0.26	na
	P _T <0.1	0.021(0.01)	0.12	na
	P _T <0.3	0.021(0.01)	0.14	na
	P _T <0.5	0.024(0.01)	0.084	na
	P _T <0.7	0.024(0.01)	0.082	na
	P _T <0.9	0.024(0.01)	0.079	na
	P _T <1	0.024(0.01)	0.079	na
13 y (N=5072)	P _T <0.001	0.011(0.01)	0.45	na
	P _T <0.01	0.024(0.01)	0.085	na
	P _T <0.05	0.028(0.01)	0.046	0.06
	P _T <0.1	0.035(0.01)	0.014	0.1
	P _T <0.3	0.031(0.01)	0.031	0.07
	P _T <0.5	0.033(0.01)	0.017	0.09
	P _T <0.7	0.033(0.01)	0.02	0.09
	P _T <0.9	0.033(0.01)	0.02	0.09
	P _T <1	0.033(0.01)	0.019	0.09
17 y (N=4164)	P _T <0.001	-0.009(0.02)	0.55	na
	P _T <0.01	0.034(0.02)	0.032	0.09
	P _T <0.05	0.03(0.02)	0.054	na
	P _T <0.1	0.043(0.02)	0.0058	0.16
	P _T <0.3	0.037(0.02)	0.018	0.11
	P _T <0.5	0.042(0.02)	0.0073	0.15
	P _T <0.7	0.039(0.02)	0.013	0.12
	P _T <0.9	0.039(0.02)	0.013	0.13
	P _T <1	0.039(0.02)	0.012	0.13

Polygenic scores for risk-increasing alleles (PGS) in the PGC-ADHD sample were constructed in ALSPAC and then Z-standardised. Rank-transformed SDQ-ADHD scores were regressed on ADHD-PGS using linear regression, and are shown by PGS threshold (P_T); Adjusted regression R² (Adj-R²) is reported for signals with *p*<0.05; ALSPAC - Avon Longitudinal Study of Parents and Children; ADHD - Attention Deficit Hyperactivity Disorder; na - Not available; PGC - Psychiatric Genomics Consortium ; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire (rank-transformed); y - years

Table S11: Association between ASD polygenic scores and SDQ-ADHD scores in ALSPAC

SDQ-ADHD	PGS bin	Beta (SE)	<i>p</i>	Adj-R ² (%)
7 y (N=5612)	P _T <0.001	0.017(0.01)	0.2	na
	P _T <0.01	0.014(0.01)	0.3	na
	P _T <0.05	0.008(0.01)	0.57	na
	P _T <0.1	0.007(0.01)	0.62	na
	P _T <0.3	0.011(0.01)	0.41	na
	P _T <0.5	0.01(0.01)	0.46	na
	P _T <0.7	0.009(0.01)	0.52	na
	P _T <0.9	0.008(0.01)	0.54	na
	P _T <1	0.008(0.01)	0.54	na
	10 y (N=5678)	P _T <0.001	0.017(0.01)	0.2
P _T <0.01		-0.004(0.01)	0.78	na
P _T <0.05		-0.005(0.01)	0.72	na
P _T <0.1		-0.01(0.01)	0.45	na
P _T <0.3		-0.007(0.01)	0.61	na
P _T <0.5		-0.005(0.01)	0.71	na
P _T <0.7		-0.006(0.01)	0.63	na
P _T <0.9		-0.006(0.01)	0.63	na
P _T <1		-0.006(0.01)	0.63	na
12 y (N=5259)		P _T <0.001	0.023(0.01)	0.089
	P _T <0.01	-0.001(0.01)	0.96	na
	P _T <0.05	-0.006(0.01)	0.67	na
	P _T <0.1	-0.011(0.01)	0.42	na
	P _T <0.3	-0.006(0.01)	0.66	na
	P _T <0.5	-0.003(0.01)	0.81	na
	P _T <0.7	-0.004(0.01)	0.77	na
	P _T <0.9	-0.004(0.01)	0.77	na
	P _T <1	-0.004(0.01)	0.77	na
	13 y (N=5072)	P _T <0.001	0.029(0.01)	0.035
P _T <0.01		0(0.01)	0.98	na
P _T <0.05		0.004(0.01)	0.79	na
P _T <0.1		-0.001(0.01)	0.94	na
P _T <0.3		0(0.01)	0.98	na
P _T <0.5		0.006(0.01)	0.65	na
P _T <0.7		0.006(0.01)	0.7	na
P _T <0.9		0.006(0.01)	0.67	na
P _T <1		0.006(0.01)	0.67	na
17 y (N=4164)		P _T <0.001	0.006(0.02)	0.68
	P _T <0.01	0.001(0.02)	0.93	na
	P _T <0.05	0.002(0.02)	0.91	na
	P _T <0.1	-0.006(0.02)	0.7	na
	P _T <0.3	-0.007(0.02)	0.63	na
	P _T <0.5	-0.006(0.02)	0.7	na
	P _T <0.7	-0.006(0.02)	0.7	na
	P _T <0.9	-0.006(0.02)	0.71	na
	P _T <1	-0.006(0.02)	0.72	na

Polygenic scores for risk-increasing alleles (PGS) in the PGC-ASD sample were constructed in ALSPAC and then Z-standardised. Rank-transformed SDQ-ADHD scores were regressed on ASD-PGS using linear regression, and are shown by PGS threshold (P_T); Adjusted regression R² (Adj-R²) is reported for signals with *p*<0.05; ALSPAC - Avon Longitudinal Study of Parents and Children; ASD - Autism Spectrum Disorders; na - Not available; PGC - Psychiatric Genomics Consortium ; SDQ-ADHD - ADHD-subscale of the Strength and Difficulties Questionnaire (rank-transformed); y - years

Table S12: Association between ADHD polygenic scores and SCDC scores in ALSPAC

SCDC	PGS bin	Beta (SE)	<i>p</i>	Adj-R ² (%)
8 y (N=5551)	P _T <0.001	-0.001(0.01)	0.94	na
	P _T <0.01	0.004(0.01)	0.77	na
	P _T <0.05	0.001(0.01)	0.95	na
	P _T <0.1	-0.002(0.01)	0.91	na
	P _T <0.3	0.002(0.01)	0.87	na
	P _T <0.5	0.006(0.01)	0.68	na
	P _T <0.7	0.006(0.01)	0.65	na
	P _T <0.9	0.005(0.01)	0.69	na
	P _T <1	0.006(0.01)	0.68	na
	11 y (N=5460)	P _T <0.001	-0.014(0.01)	0.28
P _T <0.01		-0.002(0.01)	0.89	na
P _T <0.05		0.02(0.01)	0.14	na
P _T <0.1		0.023(0.01)	0.086	na
P _T <0.3		0.016(0.01)	0.23	na
P _T <0.5		0.021(0.01)	0.11	na
P _T <0.7		0.021(0.01)	0.12	na
P _T <0.9		0.021(0.01)	0.13	na
P _T <1		0.021(0.01)	0.12	na
14 y (N=5060)		P _T <0.001	-0.005(0.01)	0.74
	P _T <0.01	0.015(0.01)	0.3	na
	P _T <0.05	0.021(0.01)	0.14	na
	P _T <0.1	0.024(0.01)	0.085	na
	P _T <0.3	0.027(0.01)	0.053	na
	P _T <0.5	0.028(0.01)	0.049	0.06
	P _T <0.7	0.03(0.01)	0.035	0.07
	P _T <0.9	0.029(0.01)	0.039	0.06
	P _T <1	0.029(0.01)	0.038	0.07
	17 y (N=4174)	P _T <0.001	-0.01(0.02)	0.52
P _T <0.01		0.01(0.02)	0.52	na
P _T <0.05		0.012(0.02)	0.44	na
P _T <0.1		0.019(0.02)	0.23	na
P _T <0.3		0.017(0.02)	0.28	na
P _T <0.5		0.017(0.02)	0.28	na
P _T <0.7		0.017(0.02)	0.27	na
P _T <0.9		0.017(0.02)	0.27	na
P _T <1		0.018(0.02)	0.26	na

Polygenic scores for risk-increasing alleles (PGS) in the PGC-ADHD sample were constructed in ALSPAC and then Z-standardised. Rank-transformed SCDC scores were regressed on ADHD-PGS using linear regression, and are shown by PGS threshold (P_T); Adjusted regression R² (Adj-R²) is reported for signals with *p*<0.05; ALSPAC - Avon Longitudinal Study of Parents and Children; ADHD - Attention Deficit Hyperactivity Disorder; na - Not available; PGC - Psychiatric Genomics Consortium; SCDC - SCDC - Social and Communication Disorders Checklist (rank-transformed); y - years