Genetic and environmental contribution to the overlap between ADHD and ASD trait dimensions in young adults: a twin study

Laura Ghirardi[1], Erik Pettersson[1], Mark J. Taylor[1], Christine M. Freitag[2], Barbara Franke[3], Philip Asherson[4], Henrik Larsson[1,5] and Ralf Kuja-Halkola[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [2]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany; [3]Department of Human Genetics and Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands; [4]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK and [5]School of Medical Sciences, Örebro University, Örebro, Sweden

CAMBRIDGE
UNIVERSITY PRESS

Abstract

Background. Traits of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are strongly associated in children and adolescents, largely due to genetic factors. Less is known about the phenotypic and aetiological overlap between ADHD and ASD traits in adults.

Methods. We studied 6866 individuals aged 20–28 years from the Swedish Study of Young Adult Twins. Inattention (IA) and hyperactivity/impulsivity (HI) were assessed using the WHO Adult ADHD Self-Report Scale-V1.1. Repetitive and restricted behaviours (RRB) and social interaction and communication (SIC) were assessed using the Autism-Tics, ADHD, and other Comorbidities inventory. We used structural equation modelling to decompose covariance between these ADHD and ASD trait dimensions into genetic and shared/non-shared environmental components.

Results. At the phenotypic level, IA was similarly correlated with RRB ($r = 0.33$; 95% Confidence Interval (CI) 0.31–0.36) and with SIC ($r = 0.32$; 95% CI 0.29–0.34), whereas HI was more strongly associated with RRB ($r = 0.38$; 95% CI 0.35–0.40) than with SIC ($r = 0.24$; 95% CI 0.21–0.26). Genetic and non-shared environmental effects accounted for similar proportions of the phenotypic correlations, whereas shared environmental effects were of minimal importance. The highest genetic correlation was between HI and RRB ($r = 0.56$; 95% 0.46–0.65), and the lowest was between HI and SIC ($r = 0.33$; 95% CI 0.23–0.43).

Conclusions. We found evidence for dimension-specific phenotypic and aetiological overlap between ADHD and ASD traits in adults. Future studies investigating mechanisms underlying comorbidity between ADHD and ASD may benefit from exploring several symptom-dimensions, rather than considering only broad diagnostic categories.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are highly heritable neurodevelopmental disorders (Thapar *et al.*, 2017). ADHD is primarily characterized by age-inappropriate levels of inattention (IA), and/or hyperactivity and impulsivity (HI) (APA, 2013). ASD includes a group of disorders characterized by difficulties in social interaction and communication (SIC), and by the presence of stereotyped patterns of movements, behaviours, and interests (RRB) (APA, 2013). Despite the differences in the core symptoms of the disorders, several studies have reported elevated levels of autistic symptoms in children and adolescents diagnosed with ADHD (Clark *et al.*, 1999; Mulligan *et al.*, 2009; Grzadzinski *et al.*, 2011; Kroger *et al.*, 2011; Kotte *et al.*, 2013; Martin *et al.*, 2014; Grzadzinski *et al.*, 2016) and vice versa (Gadow *et al.*, 2006; Simonoff *et al.*, 2008; Yerys *et al.*, 2009). Family studies have shown that relatives of individuals with ASD are at higher risk of receiving a diagnosis of ADHD (Musser *et al.*, 2014; Jokiranta-Olkoniemi *et al.*, 2016; Ghirardi *et al.*, 2018), and that the magnitude of the risk changes as a function of the genetic relatedness (Ghirardi *et al.*, 2018), suggesting that ADHD and ASD might be influenced by partially shared familial factors that are likely to be of genetic origin.

These results are in line with what has been reported by twin studies, which have consistently found moderate to strong genetic correlations between traits related to ADHD and traits related to ASD in children and adolescents (Ronald *et al.*, 2008; Ronald *et al.*, 2010; Taylor *et al.*, 2015; Pinto *et al.*, 2016), although one study in 2-year-old children found considerably lower genetic correlations (Ronald *et al.*, 2010). Twin studies on traits related to ADHD and

ASD as measured on a continuous scale in the general population are based on the notion that ADHD (Larsson et al., 2012a; Middeldorp et al., 2016; Demontis et al., 2017) and ASD (Lundström et al., 2012; Colvert et al., 2015; Robinson et al., 2016) can be viewed as the extreme end of continuously distributed traits in the population and that such traits seem to be genetically correlated with dichotomous measures of the disorders, such as clinical diagnoses (for reviews on this topic see: Plomin et al., 2009, Martin et al., 2018). In addition, since from a clinical perspective, both ADHD and ASD are considered heterogeneous disorders, characterized by different presentations and severity (APA, 2013), it can be hypothesized that there might also be differences in how specific ADHD symptoms relate to specific ASD symptoms. Twin studies have tested this by estimating phenotypic and genetic associations across the different trait dimensions related to each disorder. Studies in children have reported stronger phenotypic and genetic correlations between ADHD traits of IA (Taylor et al., 2015) and HI (Taylor et al., 2015; Pinto et al., 2016), and ASD traits related to communication (Taylor et al., 2013; Taylor et al., 2015; Pinto et al., 2016) and social difficulties (Pinto et al., 2016). Findings from longitudinal twin studies from childhood to early adulthood on ADHD (Chang et al., 2013) and ASD (Taylor et al., 2017) traits suggest that there might be genetic effects uniquely related to the adult expression of these traits. Hence, the association between these traits may also differ phenotypically and aetiologically in adulthood (Lundstrom et al., 2011; Polderman et al., 2013; Polderman et al., 2014). One previous study investigated the overlap between total scores of ADHD and ASD symptoms using a DSM-IV-based scale in a large sample of Swedish adult twins from the general population and reported moderate phenotypic (0.44) and genetic (0.45) correlations (Lundstrom et al., 2011). Another study, in the same sample, explored heterogeneity in the genetic link between ADHD and ASD traits by estimating phenotypic and aetiological correlations between two trait dimensions related to ADHD, IA and HI, and two trait dimensions related to ASD, SIC and RRB (Polderman et al., 2014). IA was found to be associated with both dimensions of ASD at the phenotypic and genetic level, whereas HI was more strongly associated with RRB (Polderman et al., 2014), in contrast to what has been reported by studies in children and adolescents (Taylor et al., 2013; Taylor et al., 2015; Pinto et al., 2016).

Given that only one previous study investigated the dimension-specific overlap between ADHD and ASD traits in adults and considering the wide age range of the sample, in the present study, we aimed at estimating phenotypic and aetiological overlap between specific trait dimensions of ADHD and specific trait dimensions of ASD in a large population-based sample of young adult twins.

Material and methods

Participants

In February 2013, over 17 000 twins born in Sweden between 1 May 1985 and 30 June 1992 were identified from the Swedish Twin Register (Lichtenstein et al., 2002; Lichtenstein et al., 2006; Magnusson et al., 2012), corresponding to nearly all twins born in Sweden during that time period. After excluding individuals who had died, migrated, or acquired a secret identity ($n = 966$), and individuals who had opted out from the Swedish Twin Register or declined to be contacted ($n = 42$), 16 237individuals were invited to participate in the Young Adult Twin Swedish Study (YATSS) by filling out an online questionnaire (a paper version of the questionnaire was available upon request). Seven individuals were included at a later stage, after having requested to be re-included in the Swedish Twin Register, leading to a target population of 16 244 individuals. In a first wave, individuals received two reminders via letters and an additional reminder via phone call. In a second wave, a shorter version of the questionnaire was sent out to non-responders and to individuals who had not completed the parts of the original questionnaire included in the shorter version. For the second wave, individuals received two reminders, one via letter and one via phone call. All versions of the questionnaire (online complete version, online short version, paper version) included all the variables used in this study.

Of the target population ($n = 16 244$), 6866 individuals (42%) filled in the questionnaire. A comparison between participants and non-participants was performed (online Supplementary analysis S1). We found that non-participants were less likely to have completed upper secondary or post-secondary education or to be employed and more likely to have a diagnosis of any psychiatric disorder (online Supplementary Tables S1 and S2). Participants were between 20 and 28 years of age (mean = 24.32, standard deviation = 1.97) at the time of assessment. Among the participants, the response rate for all the ADHD and ASD dimensions was 74% ($n = 5082$). Among the respondents, 3110 were women, and 1972 were men. Individuals from complete and incomplete twin pairs were included in the twin analyses. Zygosity was established using standard physical similarity questions that have been validated through genotyping (Lichtenstein et al., 2002; Magnusson et al., 2012).

The project was reviewed and approved by the Regional Ethics Review Board in Stockholm. All participants provided informed consent.

Measures

ADHD trait dimensions were self-rated with the WHO Adult ADHD Self-Report Scale (ASRS), a questionnaire consisting of 18 items based on DSM-IV symptoms (Kessler et al., 2005; Adler et al., 2006). Each item has a five-point answer format (0 = 'never', 1 = 'rarely', 2 = 'sometimes', 3 = 'often' and 4 = 'very often'). Items were summed to create two sub-scales for ADHD: one measuring IA (nine items) and one measuring HI (nine items). Both subscales showed high internal consistency (Cronbach's α equal to 0.87 and 0.83, respectively) and good accuracy (Area under the curve equal to 0.81 and 0.79, respectively) in predicting a clinical diagnosis in this sample. More details on how accuracy was calculated can be found in online Supplementary analysis S2 and results are reported in online Supplementary Table S3.

Autistic trait dimensions were self-rated via 12 items of the Autism – Tics, AD/HD, and other Comorbidities inventory (A-TAC), which is based on DSM-IV symptoms (Hansson et al., 2005). Because this instrument has been developed for assessment of children, some of the items were adapted for adults. Each item has a three-point answer format (0 = 'no', 0.5 = 'yes, to some extent', and 1 = 'yes'). Items were summed to create two sub-scales for ASD, based on DSM-5 criteria: one measuring SIC (eight items) and one measuring RRB (four items). Both sub-scales had acceptable internal consistency given the small number of items (Cronbach's α equal to 0.62 and 0.65, respectively) (Cortina, 1993), and good accuracy (Area under the curve equal to 0.88 and 0.81, respectively) in predicting a clinical diagnosis in this sample (online Supplementary Table S3).

The English translation of all the items of the two questionnaires used in the survey is included in the online Supplementary Table S4. Following previous studies, if more than 20% of items in a sub-scale were missing (that is, >0 for RRB, >1 for SIC, >2 for IA and HI), the sub-scale was not considered reliable and coded as missing. If 20% or less of the items in a sub-scale were missing, the mean score for the remaining items in the sub-scale was used to replace the missing values (Polderman *et al.*, 2014). The distribution of all the variable under study was right-skewed. Hence, we investigated how different transformations, namely log transformation and square root transformation, affected the skewness and the kurtosis of the distribution of the variables (online Supplementary Table S5). Square root transformation was applied to the data before the analyses, as this resulted in values for skewness and kurtosis more similar to what expected for a normal distribution for the four variables of interest (online Supplementary Table S5).

Twin design

Information on monozygotic twins (MZ), who are in principle genetically identical, and dizygotic twins (DZ), who share on average 50% of their co-segregating alleles, was used to decompose the observed variance of ADHD and ASD trait dimensions and their covariance into the latent components: additive genetic influences (A); environmental influences shared by the members of the twin pair (C); dominance genetic effects (D); and environmental influences not shared by the members of the twin pair (E), including measurement error (Rijsdijk and Sham, 2002; Neale and Cardon, 2013). If a trait is influenced by genetics, the correlation between the members of a twin pair on this trait (also referred to as intra-class correlation, ICC) is expected to be greater in MZ than in DZ twins. This logic for within-trait correlations (univariate) can be extended to cross-trait correlations (bivariate/multivariate). The correlations of the score on trait 1 for twin 1 with the score of trait 2 score in twin 2 (cross-twin cross-trait correlations, CTCT) in MZ and DZ twin pairs can then be compared to estimate the relative importance of genetic and non-genetic effects for the phenotypic correlation between the two traits. Higher CTCT among MZ compared with DZ twins indicate that the covariation across traits is influenced by genetic effects.

When using data from twin pairs, it is not possible to estimate the C and the D components simultaneously, in addition to A and E, because the available information from MZ and DZ twin pairs would not suffice to estimate the parameters in the model. Hence, ADE (a model containing A-, D-, and E-sources of variance and covariance) and ACE solutions can only be fitted separately and subsequently compared.

Statistical analysis

All the analyses were conducted with structural equation modelling using OpenMx (Neale *et al.*, 2016). First, a saturated model was fitted to the data to obtain estimates of means, variances, and correlations, including age as a covariate on the means. Then, several sub-models were fitted in order to test several assumptions using likelihood ratio tests. We tested equality of means, variances, and correlations (phenotypic correlations, ICC and CTCT correlations) across twin order and sex. In addition, we tested equality of means and variances across zygosity (online Supplementary Table S6 and S7).

To investigate the relative influence of A, D, C, and E on the phenotypic correlations between traits, we fitted a model including the two subscales for ADHD, IA, and HI, and the two subscales for ASD, RRB, and SIC. In this model, we allowed the sources of (co)variance to correlate between traits, often referred to as correlated factors model. Since some of the correlations estimated in opposite-sex DZ twins were slightly lower than those estimated in same-sex DZ twins and some of the correlations estimated in male twins were lower than those estimated in female twins, we tested for potential sex differences in a set of sex-limitation models. First, we fitted an ADE model, allowing for quantitative and qualitative sex differences. The choice of an ADE model rather than an ACE model was based on the observation that most of the ICC and CTCT correlations in MZ twins were more than twice the correlations in DZ twins, suggesting a potential role of D. In this model A, D, and E components were free to differ between males and females for all traits under study (that is, allowing for quantitative sex differences). Further, the correlation between A for members of opposite-sex DZ twin pairs was free to be estimated between 0 and 0.5, instead of being fixed to 0.5 as it is for same-sex DZ twin pairs, for each of the traits under study (that is, allowing for qualitative sex differences). Then, we fitted a model in which A, D, and E parameters were allowed to differ between males and females, while constraining the genetic correlation between members of opposite-sex DZ twin pairs to be equal to 0.5, hence allowing for quantitative sex differences only. Thus, the relative contribution of the genetic and environmental sources of variation to the correlations across the traits under study was allowed to differ between males and females, but the sets of genes influencing them were assumed to be the same. In addition, a model in which no sex differences were allowed was fitted to the data. Two sub-models (AE and E models with no sex differences) were fitted to the data to evaluate whether they would explain the data significantly worse. The comparison of the AE model with the ADE model is a way to test the presence of the dominant genetic influences while the comparison of the E model with the AE model is a way to test for the presence of genetic influences. Likelihood ratio tests were used to test for a significant loss in the fit of the models. Akaike Information Criterion (AIC) was additionally used to assess the fit of each solution. In all models, we allowed for variance differences between males and females.

Three main sets of sensitivity analyses were performed. First, ACE model allowing for quantitative and qualitative sex differences was fitted to the data (online Supplementary Table S9), since some of the ICC and CTCT correlations suggested a potential role of shared environment. Second, ADE model allowing for quantitative and qualitative sex differences was fitted to the data, after excluding individuals with a diagnosis of ADHD and/or ASD (online Supplementary Table S10) to address the potential issue related to self-report quality in this group. Third, ADE model allowing for quantitative and qualitative sex differences and for variance differences across zygosity groups was fitted to the data (online Supplementary Table S11) since there was some evidence for this for HI (online Supplementary Table S6).

Results

Descriptive statistics

Descriptive statistics computed from non-transformed scores on the full sample are presented in Table 1, separately by sex. IA

and HI mean scores were significantly higher in females than in males ($p = 0.008$ and $p < 0.001$, respectively), whereas RRB and SIC mean scores were significantly higher in males than in females ($p < 0.001$ and $p = 0.006$, respectively). However, it should be noted that, although significant, the size of these differences was small, according to Cohen's d.

Saturated model

Overall, means and variances estimated from the saturated model could be equated across twin order, sex, and zygosity (online Supplementary Table S7). However, equating correlations across sex led to a significant decrease in the fit of the model (online Supplementary Table S7). ICC and CTCT correlations from the model allowing for differences between males and females are presented in Table 2. All correlations were higher for MZ than for DZ twins, suggesting that genetic effects may underlie variance of traits and covariance across traits.

Multivariate models

Results of the fit of the models testing for sex differences are presented in Table 3. We did not find evidence for sex differences. When we constrained the genetic correlation between members of opposite-sex twin pairs to be equal to 0.5 (as it is for same-sex DZ), there was not a significant loss in the fit of the model. When we constrained A, D, and E to be equal across sexes, no significant loss in the fit of the model was observed either.

The AE solution not allowing for sex differences was the most parsimonious without a statistically significant loss in fit according to the likelihood ratio test and it showed the best fit in terms of AIC (Table 3). Compared with the saturated model, the AE model not allowing for sex differences had a lower fit according to the likelihood ratio test ($p = 0.01$), but a better fit in terms of AIC. The estimate of the univariate heritability from this model were 44% (95% Confidence Interval (CI) 0.39–0.48%) for IA, 38% (95% CI 0.34–0.43%) for HI, 31% (95% CI 0.25–0.36%) for RRB, and 33% (95% CI 0.27–0.38%) for SIC. Phenotypic correlations and the relative contribution of additive genetic and non-shared environmental influences from the AE model not allowing for sex differences are presented in Fig. 1. IA was similarly correlated with RRB ($r = 0.33$; 95% CI 0.31–0.36) and with SIC ($r = 0.32$; 95% CI 0.29–0.34). HI was more strongly correlated with RRB ($r = 0.38$; 95% CI 0.35–0.40) than with SIC ($r = 0.24$; 95% CI 0.21–0.26). The phenotypic correlation between IA and HI was higher ($r = 0.61$; 95% CI 0.59–0.62) than the one between RRB and SIC ($r = 0.39$; 95% CI 0.36–0.41). As shown in Fig. 1, additive genetic and non-shared environmental contributions accounted for the same relative amount of co-variation across all the traits.

Additive genetic and non-shared environmental correlations from the AE model not allowing for sex differences are presented in Table 4. Overall, the pattern of aetiological correlations was similar to the pattern of phenotypic correlations. All correlations between genetic influences were significantly different from zero, and their magnitude ranged between low and moderate. Across ADHD and ASD traits, the strongest genetic correlation was estimated between HI and RRB ($r = 0.56$; 95% CI 0.46–0.65), whereas the weakest was estimated between HI and SIC ($r = 0.33$; 95% CI 0.23–0.43). The genetic correlation between HI and RRB was similar to the one between RRB and SIC ($r = 0.59$; 95% CI 0.49–0.70), and slightly lower than the one between IA and HI

Table 1. Descriptive statistics for females and males

	IA	HI	RRB	SIC
Females				
Mean	11.69	10.82	0.65	1.04
StD	6.55	6.01	0.78	1.13
N	3782	3780	3221	3512
Males				
Mean	11.25	9.59	0.73	1.13
StD	6.32	5.62	0.78	1.20
N	2054	2264	2054	2264
Cohen's d	0.07	0.21	−0.07	−0.11

IA, inattention; HI, hyperactivity; RRB, repetitive and restricted behaviours; SIC, social interaction and communication; StD, standard deviation; N, number of observations.
Note: Descriptive statistics were calculated from raw data. Cohen's d refers to the standardized difference between female and male mean score in each subscale.

($r = 0.66$; 95% CI 0.60–0.71). All the correlations between non-shared environmental influences were significantly different from zero but lower than the genetic correlations.

All the results from the sensitivity analyses were similar to the results from the main analyses (online Supplementary Tables S8, S9, S10 and S11).

Discussion

In this study, we aimed at estimating the phenotypic and aetiological overlap between self-rated trait dimensions of ADHD and ASD in a population-based sample of young adults. We found that HI was correlated more strongly with RRB, whereas IA was equally associated with both dimensions of ASD traits. This pattern of associations was also reflected at the aetiological level, where we found the strongest genetic correlation between HI and RRB and the weakest genetic correlation between HI and SIC. Non-shared environmental influences accounted for half of the phenotypic correlations, suggesting that environmental exposures may be as important as genetic risk factors for the overlap between the traits examined in this adult sample. We did not find evidence for quantitative or qualitative sex differences. Overall, the findings are in line with the only previous study exploring phenotypic and aetiological associations between dimensions of ADHD and ASD in an independent sample of Swedish older adults, using different measures for ADHD and ASD traits (Polderman *et al.*, 2014), indicating the robustness of this pattern of findings. This suggests that future research aiming at understanding the aetiology of ADHD, ASD, and their overlap may benefit from analysing their respective symptom-domains, rather than focusing only on broader diagnostic categories.

Although we found moderate genetic correlations across all ADHD and ASD traits, HI and RRB were more strongly correlated than HI and SIC. Notably, the genetic (and the phenotypic) correlation between HI and RRB was equal to the correlation between RRB and SIC. Evidence of a genetic link between ADHD and ASD has been found in several family studies using data on clinical diagnoses (Musser *et al.*, 2014; Jokiranta-Olkoniemi *et al.*, 2016; Grove *et al.*, 2017; Ghirardi *et al.*, 2018) and in one recent genome-wide association study (Grove *et al.*, 2017). However, in these studies, the different symptom-dimensions of disorders were not investigated. Results from

Table 2. Intra-class correlations (on the diagonal) and cross-twin cross-trait correlations (above the diagonal) for MZ, DZ same-sex and DZ opposite-sex

	r (95% CI)	r (95% CI)	r (95% CI)	r (95% CI)
	MZ			
	IA	HI	RRB	SIC
IA	0.44 (0.39–0.49)	0.28 (0.24–0.33)	0.20 (0.16–0.25)	0.15 (0.11–0.20)
HI		0.40 (0.35–0.45)	0.21 (0.16–0.25)	0.11 (0.07–0.16)
RRB			0.33 (0.26–0.39)	0.19 (0.14–0.24)
SIC				0.34 (0.29–0.40)
	DZ same-sex			
	IA	HI	RRB	SIC
IA	0.23 (0.14–0.31)	0.08 (0.01–0.15)	0.06 (−0.01 to 0.12)	0.03 (−0.04 to 0.10)
HI		0.09 (0.01–0.18)	0.09 (0.02–0.16)	0.03 (−0.04 to 0.10)
RRB			0.08 (−0.02 to 0.17)	0.02 (−0.06 to 0.09)
SIC				0.09 (−0.01 to 0.19)
	DZ opposite-sex			
	IA	HI	RRB	SIC
IA	0.18 (0.10–0.26)	0.15 (0.08–0.22)	0.01 (−0.05 to 0.08)	0.08 (0.02–0.15)
HI		0.23 (0.15–0.31)	0.03 (−0.04 to 0.10)	0.06 (−0.01 to 0.12)
RRB			0.11 (0.01–0.21)	0.10 (0.03–0.17)
SIC				0.12 (0.03–0.21)

IA, inattention; HI, hyperactivity; RRB, repetitive and restricted behaviours; SIC, social interaction and communication; MZ, monozygotic twins; DZ, dizygotic twins; r, correlation coefficient; 95% CI, 95% Confidence Interval.
Note: correlations were estimated from Model 7 in online Supplementary Table S7.

Table 3. Fitting measures of the sex-limitation multivariate models including IA, HI, RRB, and SIC

	−2LL	DF	Δ -2LL	Δ DF	*p* value	AIC
Saturated model	46 976.00	22 002				2972.00
ADE[a] qualitative and quantitative sex differences	47 165.97	22 144	189.97	142	<0.01	2877.97
ADE[b] only quantitative sex differences	47 178.31	22 154	12.34	10	0.26	2870.31
ADE[b] no sex differences	47 202.23	22 180	36.54	36	0.44	2842.51
AE[c] no sex differences	47 210.12	22 190	7.61	10	0.67	2830.12
E[d] no sex differences	47 795.91	22 200	585.79	10	<0.01	3395.91

−2LL, -2LogLikelihood; DF, degrees of freedom; Δ -2LL, difference in -2LogLikelihood between the two models compared; Δ DF, difference in degrees of freedom between the two models compared; *p* value, *p* values for likelihood ratio test between the two models compared.
Note: Means adjusted for age.
[a]Compared with Saturated model;
[b]Compared with ADE allowing for qualitative and quantitative sex differences;
[c]Compared with ADE no sex differences;
[d]Compared with AE no sex differences.

the current study suggest that the genetic overlap between ADHD and ASD may be further differentiated between the symptom-dimensions of the disorders. In addition, the fact that one of the correlations between traits related to different disorders (i.e. HI and RRB) was equal to the correlation between traits related to the same disorder (i.e. RRB and SIC) suggests that certain symptoms may be expressed across current diagnostic boundaries.

Non-shared environment accounted for approximately half of the covariation across all the ADHD and ASD traits. A number of studies have shown that low birth weight is associated with an increased risk of several neurodevelopmental disorders, even after controlling for potential shared genetic liability using family-

based designs (Hultman *et al.*, 2007; Losh *et al.*, 2011; Pettersson *et al.*, 2015). Thus, it is possible that such environmental risk factors influence multiple ASD and ADHD dimensions. However, it should be noted that the contribution of the non-shared environment also includes measurement error that correlates between the measures under study, for example in the case participants tend to rate themselves similarly across different traits due to factors that are not shared by the members of the twin pair.

Our findings differ from what has been reported in other studies on the dimension-specific overlap between ADHD and ASD traits in childhood and adolescence (Taylor *et al.*, 2013; Taylor *et al.*, 2015; Pinto *et al.*, 2016). In childhood, the SIC problems
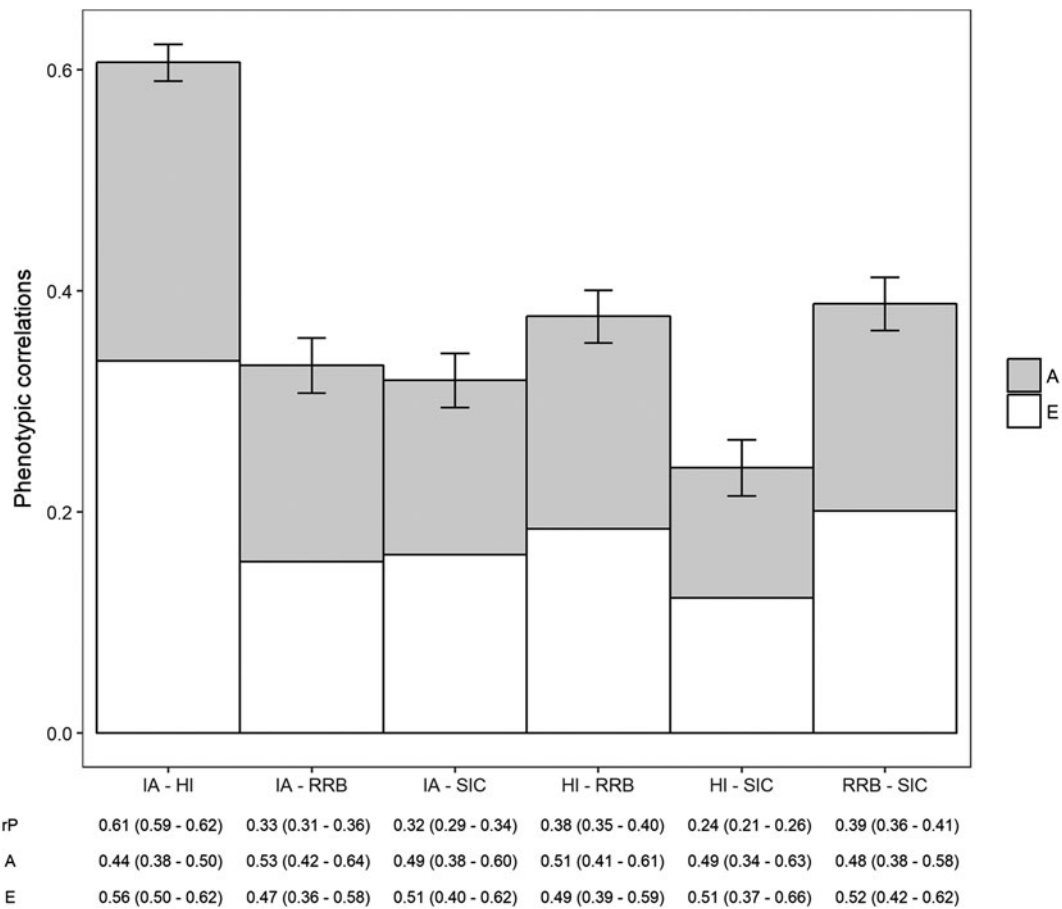
Fig. 1. Phenotypic correlations and contribution of additive genetic and non-shared environmental sources of co-variation. IA, inattention; HI, hyperactivity; RRB, repetitive and restricted behaviours; SIC, social interaction and communication; rP, phenotypic correlation; A, additive genetic contribution; E, non-shared environmental contribution. Note: A and E refer to the proportions of the phenotypic correlation explained by additive genetics and non-shared environment.

Table 4. Additive genetic (below the diagonal) and non-shared environmental (above the diagonal) correlations

	IA	HI	RRB	SIC
	r (95% CI)	r (95% CI)	r (95% CI)	r (95% CI)
IA		0.57 (0.53–0.61)	0.25 (0.19–0.30)	0.28 (0.23–0.33)
HI	0.66 (0.60–0.71)		0.26 (0.21–0.31)	0.19 (0.14–0.24)
RRB	0.49 (0.39–0.58)	0.56 (0.46–0.65)		0.29 (0.24–0.35)
SIC	0.42 (0.33–0.51)	0.33 (0.23–0.43)	0.59 (0.49–0.70)	

IA, inattention; HI, hyperactivity; RRB, repetitive and restricted behaviours; SIC, social interaction and communication; r, correlation coefficient; 95% CI, 95% Confidence Interval.

seem to be more strongly associated with all traits of ADHD, whereas our results suggest that HI may be more specifically linked to RRB in adults, in accordance with a previous study (Polderman *et al.*, 2014). These results may be important for future research evaluating different neurocognitive processes implicated in ADHD, ASD, and other neurodevelopmental disorders (for a review on the topic see e.g. Rommelse *et al.*, 2011). In addition, the observation that young adults are more prone to manifest HI and RRB together may be relevant for the assessment of ADHD and ASD symptoms in this age group and, potentially, for designing interventions aimed at targeting deficits in these domains. However, this aspect warrants further investigation,

particularly as our findings on self-rated dimensional traits may not directly extend to individuals meeting clinical criteria for ADHD and ASD.

The results should be considered in the context of some strengths and limitations. The questionnaire used for the assessment of IA and HI problems has been designed to screen for ADHD symptoms in adults (Kessler *et al.*, 2005; Adler *et al.*, 2006). While the short version including six items has been shown to have high sensitivity for DSM-IV and DSM-5 diagnoses (Kessler *et al.*, 2005; Kessler *et al.*, 2007; Ustun *et al.*, 2017), some inherent inaccuracy is expected with reliance in self-ratings alone. However, the subscales used in this study had high internal

consistency and good accuracy in predicting a clinical diagnosis of ADHD (see online Supplementary Table S3). Although the questionnaire used for the assessment of RRB and SIC has been developed for parent-rating of symptoms of several domains during childhood, it showed good accuracy in predicting a clinical diagnosis of ASD (see online Supplementary Table S3). Overall, the assessment of different traits related to ADHD and ASD can help in understanding more about the manifestation and the aetiology of neurodevelopmental problems appearing or continuing during adulthood, even if they do not satisfy the criteria for a diagnosis (Faraone *et al.*, 2006). The main limitation of our study was the response rate to the survey, which was low. Non-participants were more likely to have lower education, to be unemployed, and to have a diagnosis of psychiatric disorders. This suggests that we might not be capturing the full range of variation of traits related to ADHD and ASD in the population, as the ones with more severe symptoms are less likely to have responded to the survey. In addition, information from self-report only was used. Univariate heritability estimates for ADHD traits were in line with what has been reported in other studies using total scores of self-rated ADHD traits in adults (Boomsma *et al.*, 2010; Larsson *et al.*, 2012*b*; Park *et al.*, 2017), whereas for ASD traits, estimates were somewhat lower than reported in other studies (Hoekstra *et al.*, 2007; Park *et al.*, 2017). Associations across relatives using self-rated symptom scores tend to be lower compared with estimates obtained using other informants, e.g. parent reports. Lower than expected cross-twin correlations may lead to an inflation of the non-shared environmental component, which captures any source of dissimilarity between the twins, including measurement error. This may, in turn, lead to an underestimation of the true genetic contribution (Chang *et al.*, 2013; Brikell *et al.*, 2015). In a multivariate setting, the non-shared environmental contribution could be inflated by a tendency (not of genetic origin) of an individual to systematically under- or over-report their behaviours or symptoms. Whether such bias is contributing to the observed overlap is, however, impossible to evaluate with the available information and may be considered a limitation to self-reported data in general. Another limitation is the lower power to test for potential sex differences as compared with a previous study (Polderman *et al.*, 2014), which limits our ability to clarify whether there might be sex differences in the genetic link between ADHD and ASD traits in young adults. Nevertheless, it should be noted that our results are in line with what reported in the previous study (Polderman *et al.*, 2014). Last, we observed a significant loss of the fit between the saturated model and the ADE and AE models according to the likelihood ratio test, however, the ADE and AE models had a better fit in terms of AIC, an index that, by penalizing the model for the number of parameters, better reflects the fit of the model in terms of parsimony.

Conclusions

We found that, although all traits related to ADHD and ASD were correlated, the phenotypic and genetic correlations varied in strength. This suggests that the overlap between ADHD and ASD may be, at least partially, dimension-specific in adults. Hence, it will be important for future studies to explore specific dimensions, rather than only considering broad diagnostic categories. This approach may lead to a better understanding of the mechanisms underlying comorbidity between ADHD and ASD.

References

Adler LA, Spencer T, Faraone SV, Kessler RC, Howes MJ, Biederman J and Secnik K (2006) Validity of pilot Adult ADHD Self- Report Scale (ASRS) to Rate Adult ADHD symptoms. *Annals of Clinical Psychiatry* **18**, 145–148.

American Psychological Association (APA) (2013) *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Arlington: American Psychiatric Publishing.

Boomsma DI, Saviouk V, Hottenga JJ, Distel MA, de Moor MH, Vink JM, Geels LM, van Beek JH, Bartels M, de Geus EJ and Willemsen G (2010) Genetic epidemiology of attention deficit hyperactivity disorder (ADHD index) in adults. *PLoS One* **5**, e10621.

Brikell I, Kuja-Halkola R and Larsson H (2015) Heritability of attention-deficit hyperactivity disorder in adults. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **168**, 406–413.

Chang Z, Lichtenstein P, Asherson PJ and Larsson H (2013) Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry* **70**, 311–308.

Clark T, Feehan C, Tinline C and Vostanis P (1999) Autistic symptoms in children with attention defcit-hyperactivity disorder. *European Child and Adolescent Psychiatry* **8**, 50–55.

Colvert E, Tick B, McEwen F, Stewart C, Curran SR, Woodhouse E, Gillan N, Hallett V, Lietz S, Garnett T, Ronald A, Plomin R, Rijsdijk F, Happé F and Bolton P (2015) Heritability of autism spectrum disorder in a UK population-based twin sample. *JAMA Psychiatry* **72**, 415–423.

Cortina JM (1993) What is coefficient alpha? An examination of theory and applications. *Journal of Applied Psychology* **78**, 98.

Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Belliveau R, Bybjerg-Grauholm J, Bækved-Hansen M, Cerrato F, Chambert K, Churchhouse C, Dumont A, Eriksson N, Gandal M, Goldstein J, Grove J, Hansen CS, Hauberg M, Hollegaard M, Howrigan DP, Huang H, Maller J, Martin AR, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Ripke S, Robinson EB, Satterstrom FK, Stevens C, Turley P, Won H,

Andreassen OA, Burton C, Boomsma D, Cormand B, Dalsgaard S, Franke B, Gelernter J, Geschwind D, Hakonarson H, Haavik J, Kranzler H, Kuntsi J, Langley K, Lesch K-P, Middeldorp C, Reif A, Rohde LA, Roussos P, Schachar R, Sklar P, Sonuga-Barke E, Sullivan PF, Thapar A, Tung J, Waldman I, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Daly MJ, Faraone SV, Børglum AD and Neale BM (2017) Discovery of the first genome-wide significant risk loci for ADHD. *bioRxiv*. (https://www.biorxiv.org/content/early/2017/06/03/145581). Accessed 1 August 2018.

Faraone SV, Biederman J and Mick E (2006) The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine* **36**, 159–165.

Gadow KD, DeVincent CJ and Pomeroy J (2006) ADHD symptom subtypes in children with pervasive developmental disorder. *Journal of Autism and Developmental Disorders* **36**, 271–283.

Ghirardi L, Brikell I, Kuja-Halkola R, Freitag CM, Franke B, Asherson P, Lichtenstein P and Larsson H (2018) The familial co-aggregation of ASD and ADHD: a register-based cohort study. *Molecular Psychiatry* **23**, 257–262.

Grove J, Ripke S, Als TD, Mattheisen M, Walters R, Won H, Pallesen J, Agerbo E, Andreassen OA, Anney R, Belliveau R, Bettella F, Buxbaum JD, Bybjerg-Grauholm J, Bækved-Hansen M, Cerrato F, Chambert K, Christensen JH, Churchhouse C, Dellenvall K, Demontis D, De Rubeis S, Devlin B, Djurovic S, Dumont A, Goldstein J, Hansen CS, Hauberg ME, Hollegaard MV, Hope S, Howrigan DP, Huang H, Hultman C, Klei L, Maller J, Martin J, Martin AR, Moran J, Nyegaard M, Nærland T, Palmer DS, Palotie A, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Pourcain BS, Qvist P, Rehnström K, Reichenberg A, Reichert J, Robinson E, Roeder K, Roussos P, Saemundsen E, Sandin S, Satterstrom FK, Smith GD, Stefansson H, Stefansson K, Steinberg S, Stevens C, Sullivan PF, Turley P, Walters GB, Xu X, Geschwind D, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Neale BM, Daly MJ and Børglum AD (2017) Common risk variants identified in autism spectrum disorder. *bioRxiv*. (https://www.biorxiv.org/content/early/2017/11/27/224774). Accessed 1 August 2018.

Grzadzinski R, Di Martino A, Brady E, Mairena MA, O'Neale M, Petkova E, Lord C and Castellanos FX (2011). Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? *Journal of Autism and Developmental Disorders* **41**, 1178–1191.

Grzadzinski R, Dick C, Lord C and Bishop S (2016) Parent-reported and clinician-observed autism spectrum disorder (ASD) symptoms in children with attention deficit/hyperactivity disorder (ADHD): implications for practice under DSM-5. *Molecular Autism* **7**, 7.

Hansson SL, Röjvall AS, Rastam M, Gillberg C, Gillberg C and Anckarsäter H (2005) Psychiatric telephone interview with parents for screening of childhood autism–tics, attention-deficit hyperactivity disorder and other comorbidities (A–TAC). *The British Journal of Psychiatry* **187**, 262–267.

Hoekstra RA, Bartels M, Verweij CJ and Boomsma DI (2007) Heritability of autistic traits in the general population. *Archives of Pediatrics & Adolescent Medicine* **161**, 372–377.

Hultman CM, Torrang A, Tuvblad C, Cnattingius S, Larsson JO and Lichtenstein P (2007) Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *Journal of the American Academy of Child and Adolescent Psychiatry* **46**, 370–377.

Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, Suominen A, Gyllenberg D, Chudal R, Leivonen S, Gissler M, Brown AS and Sourander A (2016) Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders. *JAMA Psychiatry* **73**, 622–629.

Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB and Walters EE (2005) The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychological Medicine* **35**, 245–256.

Kessler RC, Adler LA, Gruber MJ, Sarawate CA, Spencer T and Van Brunt DL (2007) Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *International Journal of Methods in Psychiatric Research* **16**, 52–65.

Kotte A, Joshi G, Fried R, Uchida M, Spencer A, Woodworth KY, Kenworthy T, Faraone SV and Biederman J (2013) Autistic traits in children with and without ADHD. *Pediatrics* **132**, e612–e622.

Kroger A, Hanig S, Seitz C, Palmason H, Meyer J and Freitag CM (2011) Risk factors of autistic symptoms in children with ADHD. *European Child Adolescent Psychiatry* **20**, 561–570.

Larsson H, Anckarsater H, Rastam M, Chang Z and Lichtenstein P (2012a) Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8500 twin pairs. *Journal of Child Psychology and Psychiatry* **53**, 73–80.

Larsson H, Asherson P, Chang Z, Ljung T, Friedrichs B, Larsson JO and Lichtenstein P (2012b) Genetic and environmental influences on adult attention deficit hyperactivity disorder symptoms: a large Swedish population-based study of twins. *Psychological Medicine* **43**, 197–207.

Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P and Pedersen NL (2002) The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *Journal of Internal Medicine* **252**, 184–205.

Lichtenstein P, Sullivan PF, Cnattingius S, Gatz M, Johansson S, Carlstrom E, Björk C, Svartengren M, Wolk A, Klareskog L, de Faire U, Schalling M, Palmgren J and Pedersen NL (2006) The Swedish Twin Registry in the third millennium: an update. *Twin Research and Human Genetics* **9**, 875–882.

Losh M, Esserman D, Anckarsäter H, Sullivan PF and Lichtenstein P (2011) Lower birth weight indicates higher risk of autistic traits in discordant twin pairs. *Psychological Medicine* **42**, 1091–1102.

Lundstrom S, Chang Z, Kerekes N, Gumpert CH, Rastam M, Gillberg C, Lichtenstein P and Anckarsäter H (2011) Autistic-like traits and their association with mental health problems in two nationwide twin cohorts of children and adults. *Psychological Medicine* **41**, 2423–2433.

Lundström S, Chang Z, Råstam M, Gillberg C, Larsson H, Anckarsäter H and Lichtenstein P (2012) Autism spectrum disorders and autistic-like traits: similar etiology in the extreme end and the normal variation. *Archives of General Psychiatry* **69**, 46–52.

Magnusson PKE, Almqvist C, Rahman I, Ganna A, Viktorin A, Walum H, Halldner L, Lundström S, Ullén F, Långström N, Larsson H, Nyman A, Gumpert CH, Råstam M, Anckarsäter H, Cnattingius S, Johannesson M, Ingelsson E, Klareskog L, de Faire U, Pedersen NL and Lichtenstein P (2012) The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin Research and Human Genetics* **16**, 317–329.

Martin J, Hamshere ML, O'Donovan MC, Rutter M and Thapar A (2014) Factor structure of autistic traits in children with ADHD. *Journal of Autism and Developmental Disorders* **44**, 204–215.

Martin J, Taylor MJ and Lichtenstein P (2018) Assessing the evidence for shared genetic risks across psychiatric disorders and traits. *Psychological Medicine* **48**, 1759–1774.

Middeldorp CM, Hammerschlag AR, Ouwens KG, Groen-Blokhuis MM, Pourcain BS, Greven CU, Pappa I, Tiesler CMT, Ang W, Nolte IM, Vilor-Tejedor N, Bacelis J, Ebejer JL, Zhao H, Davies GE, Ehli EA, Evans DM, Fedko IO, Guxens M, Hottenga JJ, Hudziak JJ, Jugessur A, Kemp JP, Krapohl E, Martin NG, Murcia M, Myhre R, Ormel J, Ring SM, Standl M, Stergiakouli E, Stoltenberg C, Thiering E, Timpson NJ, Trzaskowski M, van der Most PJ, Wang C, EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium, Psychiatric Genomics Consortium ADHD Working Group, Nyholt DR, Medland SE, Neale B, Jacobsson B, Sunyer J, Hartman CA, Whitehouse AJO, Pennell CE, Heinrich J, Plomin R, Smith GD, Tiemeier H, Posthuma D and Boomsma DI (2016) A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. Journal of the American Academy of Child and Adolescent Psychiatry 55, 896–905. e6.

Mulligan A, Anney RJ, O'Regan M, Chen W, Butler L, Fitzgerald M, Buitelaar J, Steinhausen HC, Rothenberger A, Minderaa R,

Nijmeijer J, Hoekstra PJ, Oades RD, Roeyers H, Buschgens C, Christiansen H, Franke B, Gabriels I, Hartman C, Kuntsi J, Marco R, Meidad S, Mueller U, Psychogiou L, Rommelse N, Thompson M, Uebel H, Banaschewski T, Ebstein R, Eisenberg J, Manor I, Miranda A, Mulas F, Sergeant J, Sonuga-Barke E, Asherson P, Faraone SV and Gill M (2009) Autism symptoms in attention-deficit/ hyperactivity disorder: a familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *Journal of Autism and Developmental Disorders* **39**, 197–209.

Musser ED, Hawkey E, Kachan-Liu SS, Lees P, Roullet JB, Goddard K, Steiner RD and Nigg JT (2014) Shared familial transmission of autism spectrum and attention-deficit/hyperactivity disorders. *Journal of Child Psychology and Psychiatry* **55**, 819–827.

Neale M and Cardon L (2013) *Methodology for Genetic Studies of Twins and Families*. Doordrecht: Springer Science & Business Media.

Neale MC, Hunter MD, Pritikin JN, Zahery M, Brick TR, Kirkpatrick RM, Estabrook R, Bates TC, Maes HH and Boker SM (2016) Openmx 2.0: extended structural equation and statistical modeling. *Psychometrika* **81**, 535–549.

Park S-H, Guastella AJ, Lynskey M, Agrawal A, Constantino JN, Medland SE, Song YJC, Martin NG and Colodro-Conde L (2017) Neuroticism and the overlap between autistic and ADHD traits: findings from a population sample of young adult Australian twins. *Twin Research and Human Genetics* **20**, 319–329.

Pettersson E, Sjolander A, Almqvist C, Anckarsater H, D'Onofrio BM, Lichtenstein P and Larsson H (2015) Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. *Journal of Child Psychology and Psychiatry* **56**, 453–459.

Pinto R, Rijsdijk F, Ronald A, Asherson P and Kuntsi J (2016) The genetic overlap of attention-deficit/hyperactivity disorder and autistic-like traits: an investigation of individual symptom scales and cognitive markers. *Journal of Abnormal Child Psychology* **44**, 335–345.

Plomin R, Haworth CM and Davis OS (2009) Common disorders are quantitative traits. *Nature Reviews Genetics* **10**, 872–878.

Polderman TJ, Hoekstra R, Vinkhuyzen A, Sullivan PF, van der Sluis S and Posthuma D (2013) Attentional switching forms a genetic link between attention problems and autistic traits in adults. *Psychological Medicine* **43**, 1985–1996.

Polderman TJ, Hoekstra RA, Posthuma D and Larsson H (2014) The co-occurrence of autistic and ADHD dimensions in adults: an etiological study in 17770 twins. *Translational Psychiatry* **4**, e435.

Rijsdijk FV and Sham PC (2002) Analytic approaches to twin data using structural equation models. *Briefings in Bioinformatics* **3**, 119–133.

Robinson EB, St Pourcain B, Anttila V, Kosmicki JA, Bulik-Sullivan B, Grove J, Maller J, Samocha KE, Sanders SJ, Ripke S, Martin J, Hollegaard MV, Werge T, Hougaard DM, iPSYCH-SSI-Broad Autism Group, Neale BM, Evans DM, Skuse D, Mortensen PB, Børglum AD, Ronald A, Smith GD and Daly MJ (2016) Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. *Nature Genetics* **48**, 552–555.

Rommelse NN, Geurts HM, Franke B, Buitelaar JK and Hartman CA (2011) A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neuroscience & Biobehavioral Reviews* **35**, 1363–1396.

Ronald A, Simonoff E, Kuntsi J, Asherson P and Plomin R (2008) Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *Journal of Child Psychology and Psychiatry* **49**, 535–542.

Ronald A, Edelson LR, Asherson P and Saudino KJ (2010) Exploring the relationship between autistic-like traits and ADHD behaviors in early childhood: findings from a community twin study of 2-year-olds. *Journal of Abnormal Child Psychology* **38**, 185–196.

Simonoff E, Pickles A, Charman T, Chandler S, Loucas T and Baird G (2008) Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry* **47**, 921–929.

Taylor MJ, Charman T, Robinson EB, Plomin R, Happe F, Asherson P and Ronald A (2013) Developmental associations between traits of autism spectrum disorder and attention deficit hyperactivity disorder: a genetically informative, longitudinal twin study. *Psychological Medicine* **43**, 1735–1746.

Taylor MJ, Charman T and Ronald A (2015) Where are the strongest associations between autistic traits and traits of ADHD? evidence from a community-based twin study. *European Child and Adolescent Psychiatry* **24**, 1129–1138.

Taylor MJ, Gillberg C, Lichtenstein P and Lundstrom S (2017) Etiological influences on the stability of autistic traits from childhood to early adulthood: evidence from a twin study. *Molecular Autism* **8**, 5.

Thapar A, Cooper M and Rutter M (2017) Neurodevelopmental disorders. *The Lancet. Psychiatry* **4**, 339–346.

Ustun B, Adler LA, Rudin C, Faraone SV, Spencer TJ, Berglund P, Gruber MJ and Kessler RC (2017) The world health organization adult attention-deficit/hyperactivity disorder self-report screening scale for DSM-5. *JAMA Psychiatry* **74**, 520–526.

Yerys BE, Wallace GL, Sokoloff JL, Shook DA, James JD and Kenworthy L (2009) Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. *Autism Research* **2**, 322–333.