Open Research Online

The Open University's repository of research publications
and other research outputs

The co-occurrence of autistic and ADHD dimensions in adults: an etiological study in 17 770 twins

Journal Item

How to cite:

Polderman, T. J. C.; Hoekstra, R. A.; Posthuma, D. and Larsson, H. (2014). The co-occurrence of autistic and ADHD dimensions in adults: an etiological study in 17 770 twins. Translational Psychiatry, 4(9), article no. e435.

For guidance on citations see FAQs.

© 2014 Macmillan Publishers Limited

Version: Version of Record

Link(s) to article on publisher's website:
http://dx.doi.org/doi:10.1038/tp.2014.84

Copyright and Moral Rights for the articles on this site are retained by the individual authors and/or other copyright owners. For more information on Open Research Online's data policy on reuse of materials please consult the policies page.

oro.open.ac.uk

OPEN

Citation: Transl Psychiatry (2014) 4, e435; doi:10.1038/tp.2014.84
© 2014 Macmillan Publishers Limited All rights reserved 2158-3188/14
www.nature.com/tp

ORIGINAL ARTICLE

The co-occurrence of autistic and ADHD dimensions in adults: an etiological study in 17 770 twins

TJC Polderman[1], RA Hoekstra[2], D Posthuma[1,3] and H Larsson[4]

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) often occur together. To obtain more insight in potential causes for the co-occurrence, this study examined the genetic and environmental etiology of the association between specific ASD and ADHD disorder dimensions. Self-reported data on ASD dimensions social and communication difficulties (ASDsc), and repetitive and restricted behavior and interests (ASDr), and ADHD dimensions inattention (IA), and hyperactivity/impulsivity (HI) were assessed in a community sample of 17 770 adult Swedish twins. Phenotypic, genetic and environmental associations between disorder dimensions were examined in a multivariate model, accounting for sex differences. ASDr showed the strongest associations with IA and HI in both sexes (r_p 0.33 to 0.40). ASDsc also correlated moderately with IA (females r_p 0.29 and males r_p 0.35) but only modestly with HI (females r_p 0.17 and males r_p 0.20). Genetic correlations ranged from 0.22 to 0.64 and were strongest between ASDr and IA and HI. Sex differences were virtually absent. The ASDr dimension (reflecting restricted, repetitive and stereotyped patterns of behavior, interests and activities) showed the strongest association with dimensions of ADHD, on a phenotypic, genetic and environmental level. This study opens new avenues for molecular genetic research. As our findings demonstrated that genetic overlap between disorders is dimension-specific, future gene-finding studies on psychiatric comorbidity should focus on carefully selected genetically related dimensions of disorders.

Translational Psychiatry (2014) **4,** e435; doi:10.1038/tp.2014.84; published online 2 September 2014

INTRODUCTION

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) are neurodevelopmental disorders, typically diagnosed in childhood. ASD is characterized by deficits in social interaction and social communication (ASDsc), and by restricted, repetitive and stereotyped patterns of behavior, interests and activities (ASDr)[1] and is generally considered a lifelong condition.[2] ADHD is characterized by inattention (IA) and by hyperactive/impulsive (HI) symptoms[1] that also show a substantial degree of persistence into adulthood.[3] According to the first prevalence study in adults, ~1% of the population has a diagnosis of ASD.[4] For ADHD ~2.5% of adults meets diagnostic criteria.[5] Studies in clinical- and population-based samples of children showed that both ASD[6] and ADHD[7] are among the most heritable conditions in psychiatry with heritability estimates of ~75%. Only a few studies focused on the heritability of ASD[8] and ADHD traits[9,10] in adults, suggesting heritability estimates of 30–50% for both traits.

ASD and ADHD often co-occur; roughly 28–44% of adults diagnosed with ASD also meet criteria for ADHD.[11] Both conditions can have a large negative impact on the daily life of affected individuals and their families,[12] in particular when both conditions co-occur.[13] A better understanding of the etiology of this co-occurrence is therefore important. It might reveal shared causal mechanisms, and it could provide clues for enhanced treatment options, for example, counseling of the comorbid presentation of symptoms instead of the separate treatment of disorders.

One explanation for the frequent co-occurrence of disorders may be a shared genetic vulnerability; that is, genetic factors that have a role in the development of ASD also affect the development of ADHD traits. Studies in community samples of children, from the United States of America,[14] United Kingdom[15] and Sweden,[16,17] showed that the genetic factors on ASD and ADHD traits become increasingly intertwined with age, suggesting that shared genetic factors indeed have an important role in the co-occurrence of ASD and ADHD traits, especially in later phases of childhood. The few studies in adults showed similar results with genetic correlations between ASD and ADHD traits of ~0.60.[18,19] However, both ASD and ADHD are characterized by a heterogeneous pattern of behavioral symptoms, and this likely reflects an equally heterogeneous genetic etiology. Twin studies of ASD in childhood suggested genetic specificity for the three dimensions of ASD,[20,21] whereas studies of IA and HI in children,[22,23] as well as in adults,[10] suggested a considerable genetic overlap but also genetic specificity. Consequently, the previously observed genetic correlations between ASD and ADHD may be due to overlap in particular disorder dimensions.

A recent study by Polderman *et al.*[24] investigated specific patterns in the co-occurrence of ASD and ADHD traits in adults. Five trait-based dimensions of ASD (social skill impairments, strong routine preferences, attentional switching problems, imagination impairments and a strong fascination for numbers and patterns), and two dimensions of ADHD (IA and HI) were jointly examined in a population-based adult sample from the

[1]Department of Functional Genomics, Complex Trait Genetics, Center for Neurogenomics and Cognitive Research (CNCR), VU University Amsterdam, Amsterdam, The Netherlands; [2]Department of Life, Health and Chemical Sciences, Faculty of Science, The Open University, Milton Keynes, UK; [3]Department of Complex Trait Genetics, Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands and [4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. Correspondence: Dr TJC Polderman, Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research (CNCR), VU University Amsterdam, Neuroscience Campus Amsterdam (NCA), De Boelelaan 1085, Amsterdam 1081 HV, The Netherlands.
E-mail: tinca.polderman@vu.nl
Received 4 July 2014; accepted 26 July 2014

Netherlands. HI problems did not correlate substantially with the ASD trait dimensions, whereas IA problems correlated only with the ASD dimension assessing attentional switching difficulties. Importantly, this finding was replicated in an independent Dutch twin-sibling sample in which Attention Problems (measuring mainly IA problems) again showed a specific association with the ASD dimension attentional switching only. Genetic analyses in the latter sample revealed that this association was entirely explained by genetic factors, leading the authors to suggest that switching attention problems in particular are pivotal in explaining the (genetic) link between ASD and ADHD traits.

No studies thus far examined the etiology of the associations between ASD and ADHD dimensions in adults based on symptoms as used in clinical practice. In addition, previous studies were underpowered to investigate sex differences in the etiology and associations of ASD and ADHD dimensions. Sex differences are important to consider, as the prevalence of both ASD[4] and ADHD[5] is higher in males than in females. The current study aimed to fill this gap in the literature by addressing the phenotypic, genetic and environmental associations between DSM-5-based ASD (ASDr and ASDsc) and ADHD dimensions (IA and HI) in a multivariate twin model. Data from a large Swedish adult twin sample ($n = 17\,770$) provided sufficient statistical power to examine potential sex differences.

MATERIALS AND METHODS

Participants

A sample of 42 582 Swedish twins was recruited from the population-representative *Swedish Twin Registry*. The sample included all twin pairs born in Sweden between 1959 and 1985 in which both individuals survived their first birthday. Of this target sample, 25 485 (60%) individuals took part in the Swedish Twin study of Adults: Genes and Environments (STAGE).[25] Twins were sent a letter inviting them to participate in the study and were given a personal login to the study web page, on which they were asked to complete an online questionnaire. Non-responders were approached with up to three reminders. Twins could also choose to complete the questionnaire via telephone interview with a trained test administrator who recorded the responses using a computer-based questionnaire, supplemented with a self-administered paper questionnaire for sensitive topics. Most responders (72%) completed the questionnaire via the web; 28% of the responders preferred the telephone interview, of which 12% also completed the paper questionnaire (including the items on ASD and ADHD). Compared with responders, the non-responders more often were male, were less educated and were more often convicted for crime, or diagnosed with a psychiatric disorder. There were no differences regarding age, birth weight or whether they had been diagnosed with a neurological disorder.[26]

Questionnaire data and zygosity were available for 21 913 individuals. The response rate for the ASD and ADHD dimension assessments in this sample was 81% ($n = 17\,770$), of whom 40% ($n = 7085$) were men and 60% ($n = 10\,685$) were women. Participants were between 20 and 46 years of age (mean = 33.73, s.d. = 7.63) at the time of assessment. Individuals ($n = 6864$) from incomplete twin pairs as well as individuals ($n = 10\,906$) from complete twin pairs were included in the twin analyses resulting in 2676 monozygotic (MZ) male twins, 2206 dizygotic (DZ) male twins, 4240 MZ female twins, 3164 DZ female twins and 5484 DZ opposite-sex twins. Zygosity was established using standard physical similarity questions that have been validated previously through genotyping.[25]

The project has been reviewed and approved by the regional ethics committee of the Karolinska Institutet. All participants provided informed consent.

Measures

Autistic trait dimensions were assessed via a self-reported questionnaire of 12 items, based on ASD DSM-5 symptoms. Each item had a three-point answer format (0 = 'no', 1 = 'yes, to some extent' and 2 = 'yes').[19] Items were summed to create two dimensions of ASD: social and communication difficulties (ASDsc, eight items) and repetitive and restricted behavior and interests (ASDr, four items), following the dyadic structure used in the DSM-5. Cronbach's alpha for the measured dimensions were moderate but acceptable (0.53 and 0.49, respectively), given the low number of items per scale.[27]

ADHD trait dimensions were assessed via a self-report questionnaire of the 18 DSM-5 symptoms, consisting of nine IA items, and nine HI items. Each item had a three-point answer format (0 = 'no', 1 = 'yes, to some extent' and 2 = 'yes'). The 18 DSM-5 items were slightly modified to fit adults and to assess current ADHD symptoms. The items were summed to create two scales, IA and HI.[10] Cronbach's alphas for the measured scales were 0.78 for both the IA and HI scales.

The items to assess the ASD and ADHD trait dimensions are presented in Supplementary Table 1. If >20% of the items in a scale were missing (that is, >0 for ASDr, >1 for ASDsc and >2 for IA and HI), the scale was deemed unreliable and coded as missing for the individual concerned. Missing items of ASRsc, and the ADHD dimensions were replaced by the mean score of an individual on those dimension items if the number of missing items on that dimension was 1 (ASDsc), or <3 (IA and HI). ASD and ADHD scales were positively skewed and were therefore independently transformed ($\log_{10}(x+1)$) before analyses to approach normality of their distributions (scenes ranging from 0.24 to 0.28).

Twin design

Information of MZ and DZ twins was used to decompose the observed variance of a particular ASD or ADHD dimension, as well as the covariance between dimensions, into latent genetic and environmental variance components. These components are additive genetic influences (A, additive effects of genes at multiple loci), dominant genetic influences (D, interaction of genetic effects at the same loci), environmental influences that are shared among family members (C, common, shared environmental effects) and non-shared environmental influences that are unique for a person (E). The latter also includes measurement error and is therefore always included in the statistical models. As (MZ) twins are genetically identical, they share all their additive and dominant genetic effects, whereas DZ twins on average share half of their segregating genes,[28] and thus share on average half of their additive genetic effects and a quarter of their dominant genetic effects. All twins in this sample grew up in the same family and thus shared their family environment.

The effects of C and D cannot be estimated simultaneously in the classical twin model. The decision for fitting either an ACE or ADE model is usually based on the MZ and DZ within pair correlations. MZ correlations twice as high as DZ correlations indicate the presence of additive genetic influences (AE model). As dominant genetic influences (D) reduce the expected phenotypic resemblance in DZ twins relative to MZ twins, DZ correlations lower than half the MZ correlations suggest the presence of dominant genetic influences (ADE model). Common environmental effects (C) make family members more similar. Therefore, DZ correlations higher than half the MZ correlations indicate shared environmental influences (ACE model) and MZ correlations that are of similar magnitude as DZ correlations indicate that only environmental influences have a role (CE model).[29] The genetic and environmental variance explained is usually reported in a standardized form, by dividing this part of the variance by the total phenotypic variance. The proportion of variance that is explained by genetic effects (A and D) is called the broad-sense heritability estimate (that is, heritability is calculated as genetic variance divided by the total phenotypic variance). It was tested whether additive genetic, dominant genetic and shared and non-shared environmental factors contributed significantly to the total variance of ASD and ADHD dimensions, and to the total covariance between the five dimensions. On the basis of the cross trait-cross twin correlations (CTCT: for example, the correlation of the ASDr dimension of twin 1 with the IA dimension of twin 2), genetic and environmental correlations among dimensions were estimated. These are used to indicate to what extent different trait dimensions are influenced by the same genetic or environmental factors.

Statistical analyses

All analyses were conducted with structural equation modelling in Mx.[30] Mx provides parameter estimates by maximizing the likelihood using raw data, so that all data, even data from individuals with some missing observations, can be included. A multivariate model, including the two ASD and two ADHD trait dimensions, was applied to the data. Estimates of the means, variances, phenotypic and twin correlations were obtained from a saturated model in which the phenotypic variance was not decomposed into genetic or environmental factors. Age was included as covariate on the means. Within subject correlations between phenotypes

© 2014 Macmillan Publishers Limited

were constrained to be equal across first and second born twin in same-sex twin pairs, and it was tested whether phenotypic correlations were equal for males and females. Twin correlations and CTCT correlations were estimated for each zygosity group, and subsequently tested for quantitative and qualitative sex differences within the MZ, DZ and DOS groups.

Specific hypotheses were evaluated using hierarchical likelihood ratio (χ^2) tests. The χ^2 statistic is computed by taking twice the difference between the log-likelihood of a reference model and the log-likelihood of a nested submodel with certain constraints (for example, equal means for males and females), whereas the associated degrees of freedom are computed as the difference in the number of estimated parameters between the two models.[31] Akaike's Information Criterion and Bayesian Information Criteria were additionally used to assess model fit, with lower (negative) estimates suggesting better model fits. To avoid oversimplification, and reduce multiple testing,[32] we only fitted multivariate models, and a limited set of nested models with type-I error rate set at 0.01.

RESULTS

The means ($\chi^2 = 36.688$, df = 4, $P < 0.000$) and phenotypic correlations ($\chi^2 = 33.283$, df = 6, $P < 0.000$) differed significantly between males and females, whereas variances were considered equal in both genders ($\chi^2 = 12.849$, df = 4, $P = 0.012$). Although significant, the magnitude of the sex differences in the mean scores and correlation patterns was only small. The correlations between ASD and ADHD dimensions were marginally stronger in males; however, the confidence intervals for the correlation of ASDr and HI overlapped for both genders (see Table 1). ASDr correlated moderately with both IA (0.39 in males and 0.33 in females) and HI (0.40 in both males and females). ASDsc also correlated moderately with IA (0.35 and 0.29 in males and females, respectively) but only modestly with HI (0.20 and 0.17 in males and females, respectively).

Genetic modeling

Table 2 presents the twin correlations and heritability estimates. Given the pattern of twin correlations (with DZ correlations generally being lower than half the MZ correlations), ADE models were fitted to the data. Estimates of A and D were moderate for males and females. However, non-additive genetic influences on the variance and covariance could be removed from the genetic model for both males ($\chi^2 = 15.126$, df = 10, $P = 0.128$) and females ($\chi^2 = 14.415$, df = 10, $P = 0.155$), resulting in heritability estimates between 23 and 37%.

Twin correlations and CTCT correlations were equal for males and females for MZ twin pairs ($\chi^2 = 9.192$, df = 4, $P = 0.056$, and $\chi^2 = 8.619$, df = 6, $P = 0.196$, respectively), DZ same-sex twin pairs ($\chi^2 = 2.483$, df = 4, $P = 0.648$, and $\chi^2 = 6.344$, df = 6, $P = 0.386$, respectively), and were similar between DZ same-sex and DOS (MF and FM) twin pairs ($\chi^2 = 7.618$, df = 12, $P = 0.814$ and ($\chi^2 = 19.998$, df = 18, $P = 0.333$, respectively), indicating that quantitative and qualitative sex differences in genetic or environmental (co)variation were negligible. Therefore, Table 3 summarizes the CTCT correlations for all MZ versus all DZ twin pairs. MZ CTCT correlations were generally higher than DZ CTCT correlations, suggesting that genetic influences partly explained the phenotypic correlations between ASD and ADHD dimensions. However, MZ CTCT correlations were lower than the within-person phenotypic correlations, suggesting that non-shared environmental influences also affect the overlap between ASD and ADHD dimensions.

Parameters of males and females were equal for genetic ($\chi^2 = 7.897$, df = 10, $P = 0.640$) and unique environmental ($\chi^2 = 20.126$, df = 10, $P = 0.028$) variance and covariance (see Table 4). Genetic and unique environmental correlations based on a reduced AE model, equalized for males and females, are presented in Table 5. Genetic correlations were strongest between ASDr and both IA and HI ($r_g > 0.60$). This correlation was also substantial between the ASDsc dimension and IA ($r_g = 0.50$) but lower between ASDsc and HI ($r_g = 0.22$). Unique environmental correlations were generally modest ($r_g < 0.34$) but still explained a considerable proportion of the phenotypic correlations.

Table 1. Untransformed estimated means for males and females, and phenotypic correlations for males (above diagonal) and females (below diagonal)

	ASDr	*ASDsc*	*IA*	*HI*
Males				
Mean	2.06	2.44	3.25	3.31
s.d.	1.42	2.04	2.70	2.84
N	6357	6764	7049	7052
Females				
Mean	2.08	2.44	3.15	3.33
s.d.	1.38	1.91	2.75	2.85
N	9571	10 245	10 621	10 636
Phenotypic correlations				
ASDr		0.28 (0.27–0.29)	0.39 (0.38–0.39)	0.40 (0.39–0.41)
ASDsc	0.25 (0.25–0.26)		0.35 (0.34–0.35)	0.20 (0.20–0.21)
IA	0.33 (0.32–0.33)	0.29 (0.29–0.30)		0.45 (0.44–0.45)
HI	0.40 (0.40–0.41)	0.17 (0.17–0.18)	0.43 (0.43–0.44)	

Abbreviations: ASD, autism spectrum disorder; ASDr, ASD repetitive and restricted behavior and interests; ASDsc, ASD social and communication difficulties; HI, hyperactive/impulsive problems; IA, inattention. Note: Means corrected for age. The applied model is $\mu = \alpha + \beta_{age}$; β is based on raw data, where age is coded as actual age in years. 95% Confidence intervals in parentheses.

DISCUSSION

This study presents novel findings regarding the etiology of the co-occurrence of ASD and ADHD dimensions in adults, and is the first study adequately powered to assess potential sex differences in the associations between both conditions. The ASDr dimension, reflecting restricted, repetitive and stereotyped patterns of behavior, interests and activities, was mostly associated with IA and HI. This hints at an important role for ASDr in the co-occurrence of ASD and ADHD. The four items that represented ASDr in our questionnaire do not overlap with items of IA or HI; therefore, item overlap cannot explain these associations. Remarkably, a previous study in Dutch adults, which used different (less clinical) measures of ASD and ADHD traits than the scales used here, showed that difficulties with attention switching, which might conceivably be aggravated by ASDr, were substantially associated with IA (*r* 0.47). In the same study, 'a strong fascination for numbers and patterns', another manifestation of ASDr, was modestly but significantly associated with HI (*r* 0.17),[24] whereas no other ASD scale was associated with HI. We observed a similar picture in the current study where, of two ASD dimensions, only ASDr correlated substantially with HI. In addition, the correlations between ASDsc and IA were moderate, suggesting that the co-occurrence between ASD and ADHD traits is primarily based on IA problems, rather than HI problems. An exception is ASDr, which is associated with both IA and HI.

It has been argued that ASDr in ASD[33] and ADHD[34,35] are due to a lack of inhibitory control, although contrasting findings have also been reported.[36] A recent magnetic resonance imaging study on ASD and ADHD traits in a sample of typical adults showed a correlation of ASD and ADHD traits with gray matter volume in the inferior frontal gyrus, a region previously associated with

© 2014 Macmillan Publishers Limited

Table 2. Twin correlations per dimension, for each zygosity group, and estimates for additive genetic (A) and unique environmental (E) influences equalized for males and females

	MZM	*DZM*	*MZF*	*DZF*	*DOSMF*	*DOSFM*	*A*	*E*
ASDr	0.31(0.29–0.33)	0.05 (0.02–0.06)	0.22 (0.21–0.24)	0.13 (0.11–0.14)	0.04 (0.02–0.05)	0.08 (0.06–0.09)	23 (21–24)	77 (76–79)
ASDsc	0.40 (0.39–0.41)	0.12 (0.10–0.14)	0.35 (0.33–0.36)	0.17 (0.16–0.18)	0.18 (0.17–0.19)	0.08 (0.07–0.09)	35 (34–36)	65 (64–66]
IA	0.34 (0.32–0.35)	0.11 (0.09–0.14)	0.38 (0.38–0.40)	0.14 (0.12–0.19)	0.09 (0.07–0.12)	0.09 (0.07–0.12)	34 (32–35)	66 (65–68]
HI	0.37 (0.35–0.37)	0.15 (00.13–0.17)	0.39 (00.39–0.41])	0.17 (0.16–0.17)	0.13 (0.11–0.14)	0.08 (0.06–0.09)	37 (35–38)	63 (62–66]

Abbreviations: ASD, autism spectrum disorder; ASDr, ASD repetitive and restricted behavior and interests; ASDsc, ASD social and communication difficulties; DOS, DZ opposite-sex; DZF, dizygotic female; DZM, dizygotic female; HI, hyperactive/impulsive problems; IA, inattention; MZF, monozygotic female; MZM, monozygotic male. Note: The twin correlations and estimates of A and E were based on models with the means corrected for age. 95% Confidence intervals in parentheses.

Table 3. Cross-trait cross-twin correlations (CTCT) for MZ twin pairs above diagonal, and for DZ twin pairs below diagonal, with 95% confidence intervals in parentheses

	ASDr	ASDsc	IA	HI
ASDr		0.13 (0.12–0.14)	0.18 (0.17–0.18)	0.19 (0.18–0.19)
ASDsc	0.05 (0.04–0.05)		0.18 (0.18–0.18)	0.07 (0.07–0.08)
IA	0.07 (0.05–0.07)	0.06 (0.05–0.06)		0.23 (0.21–0.23)
HI	0.07 (0.06–0.07)	0.05 (0.04–0.05)	0.08 (0.07–0.09)	

Abbreviations: ASD, autism spectrum disorder; ASDr, ASD repetitive and restricted behavior and interests; ASDsc, ASD social and communication difficulties; DOS, DZ opposite sex; DZ, dizygotic; HI, hyperactive/impulsive problems; IA, inattention; MZ, monozygotic. Note: CTCT correlations were equal for MZ males and MZ females, and between DOS twin pairs and DZ same-sex twin pairs.

Table 4. Model fitting results of multivariate genetic models with ASDr, ASDsc, IA and HI

Model	*−2LL*	X^2	*df*	*P*	*Sample size-adjusted BIC*	*AIC*
Saturated	19 053.151				−20 3295.57	
[a]ADE	19 070.093	16.942	20	0.66	−20 3349.51	−23.058
[b]AE males	19 085.218	15.126	10	0.13	−20 3373.15	−4.874
[b]AE females	19 084.507	14.415	10	0.16	−20 3373.51	−5.585
[b]A males = A females	19 077.990	7.897	10	0.64	−20 3376.77	−12.103
[b]E males = E females	19 090.219	20.126	10	0.03	−20 3370.65	0.126
[b]AE males = AE females	19 099.946	29.853	20	0.07	−20 3396.99	−10.147

Abbreviations: AIC, Akaike's information criterion; ASD, autism spectrum disorder; ASDr, ASD repetitive and restricted behavior and interests; ASDsc, ASD social and communication difficulties; BIC, Bayesian information criteria; df, degrees of freedom; HI, hyperactive/impulsive problems; IA, inattention; −2LL, −2log likelihood. Note: [a]Compared with saturated model. [b]Compared with ADE model. X^2 = Chi square (difference in −2log likelihoods). The models were based on means corrected for age.

Table 5. Genetic (below diagonal) and unique environmental (above diagonal) correlations between dimensions for males and females, with 95% confidence intervals in parentheses

	ASDr	*ASDsc*	*IA*	*HI*
ASDr		0.20 (0.19–0.23) (54%)	0.25 (0.24–0.28) (51%)	0.31 (0.30–0.31) (54%)
ASDsc	0.43 (0.35–0.47) (46%)		0.22 (0.21–0.24) (45%)	0.17 (0.16–0.19) (57%)
IA	0.61 (0.56–0.64) (49%)	0.50 (0.48–53) (55%)		0.33 (0.33–0.36) (49%)
HI	0.64 (0.63–0.65) (46%)	0.22 (0.18–0.24) (43%)	0.63 (0.59–0.66) (51%)	

Abbreviations: ASD, autism spectrum disorder; ASDr, ASD repetitive and restricted behavior and interests; ASDsc, ASD social and communication difficulties; HI, hyperactive/impulsive problems; IA, inattention. Note: additive genetic and unique environmental variance and covariance was equal between males and females; therefore, correlations are based on the sex-equated AE model. The percentage of the phenotypic correlations that is because of genetic and environmental effects. 95% Confidence intervals in parentheses.

inhibitory control.[37] As our data indicate that ASDr explains a substantial part of the co-occurrence of ASD and ADHD traits, one might speculate whether interventions targeting this dimension specifically (for example, by training inhibitory control) might be beneficial to patients with comorbid ASD and ADHD. Surely, this hypothesis warrants further detailed study of ASDr, as this dimension encompasses a range of characteristics including motor stereotypes, restricted interests, sensory sensitivities and difficulty with change. Further studies should examine which aspects of ASDr are most related to ADHD. Moreover, the current findings were based on community-based data, and therefore clinical studies need to confirm the important role of ASDr in the co-occurrence of ASD and ADHD.

Heritability estimates for ASD and ADHD dimensions were moderate, in line with previous studies of ASD and ADHD traits and dimensions in adults.[8–10,18,19,24] We observed substantial

© 2014 Macmillan Publishers Limited

genetic correlations between ASDr, IA and HI, and moderate genetic correlations between the other ASD scale and IA, suggesting that genetic pleiotropy partly explains the phenotypic associations between ASD and ADHD dimensions. Several rare genetic variants that have been found to be associated with ASD[38] have also been implicated in the risk for ADHD[39] (see Taurines *et al.*[40] for an overview). However, a recent study that investigated the overlap of common variants between ASD and ADHD failed to identify genetic overlap.[41] Our study might shed some light on these findings as we observed genetic correlations between ASDr and HI, but not between the ASDsc dimension and HI. These results suggest that genetic overlap between ASD and ADHD is dimension-specific, and thus highlight the importance of carefully selecting specific dimensions (for example, ASDr and HI) when searching for pleiotropic genes that may explain psychiatric comorbidity.

Apart from a genetic contribution, unique environmental variation accounted for approximately half of the phenotypic correlations. A couple of studies provided evidence for an association between increasing paternal age and psychiatric outcomes such as ASD and ADHD in offspring, probably due to new genetic mutations during spermatogenesis.[42,43] Non-genetically mediated low birth weight and related delayed brain maturation[44] have also been associated with both ASD,[45,46] and ADHD,[47,48] even after strict correction for potential confounders,[49] but the underlying risk mechanism is still unclear. The negative impact of toxins such as air pollutants, tobacco, heavy metals and pesticides on ASD[50] and ADHD[51] has been studied rather extensively in animals, and to a much lesser extent in humans. Yet, results so far are mixed, and these findings should therefore be treated with great caution. A recent epigenetic study showed that MZ twins discordant for ASD and related traits differed on DNA methylation profiles.[52] Interestingly, apart from CpG alterations affecting ASD in general, a substantial number of associated CpG sites were specific for dimensions of ASD, again suggesting heterogeneity in the risk factors affecting the different disorder dimensions.

Genetic factors could be equalized for males and females, indicating neither quantitative nor qualitative sex differences on ASD and ADHD dimensions. These results mirror previous studies that examined total scores of ASD[19] and ADHD traits.[9,10] Moreover, we did not find evidence for sex differences in the genetic or environmental factors affecting the co-occurrence of ASD and ADHD traits. The lack of sex-specific genetic influences on ASD and ADHD and their co-occurrence, together with the observation that the prevalence for both conditions is markedly higher in males[4,5] suggests that the effect of genetic risk factors may be different in males and females. This is line with the 'female protective model' proposing that females are relatively protected from genetic mutations that cause neurodevelopmental conditions in males.[53]

Limitations

This study should be considered in the light of its limitations. First, data were derived from a general population sample and, as such, our results might not be extrapolated directly to clinical settings. However, previous studies have suggested the etiology to be similar in the extreme end and in the normal variation of both ASD[54,55] and ADHD traits.[56] Moreover, the availability of much larger population samples when using a quantitative measure approach in general population samples provides significantly more statistical power in genetic studies.[57] Second, the internal consistency of the ASD dimensions was relatively low, perhaps due to the low number of items (in particular for the ASDr dimension), or heterogeneity among the dimension items. Low alphas for ASD dimensions have been reported before, especially for dimensions assessing restricted repetitive behaviors,[58–61] and future studies should aim to optimize the collection of autistic trait dimensions in the general population. Third, to avoid multiple testing and oversimplification of the data, we limited our analyses to omnibus testing. However, future studies could test additional models in which, for example, sibling interaction, reciprocal causation between dimensions or dimension-specific sex differences are also examined. Fourth, females were slightly over-represented in our sample, whereas people who reported a psychiatric diagnosis were underrepresented. Men with ASD or ADHD symptoms may have difficulty completing the questionnaire, and be especially unlikely to take part; we can therefore not exclude that this group is underrepresented. Fifth, our measures were based on self-reports only. Although this approach is common practice in adult population research, multiple informants would have allowed behavioral variation in different social conditions to be taken into account. In addition, there is evidence that lower heritability estimates in adult samples are partly because of self-reported measures of ASD and ADHD traits.[62]

To summarize, we have found evidence for strong phenotypic and genetic associations between ASDr and both ADHD dimensions. ASDsc primarily correlated with IA, and only modestly with HI. These findings suggest that it is especially ASDr problems that form an important link between ASD and ADHD comorbidity; if replicated in a clinical sample, this knowledge may help to direct future counseling in the treatment of both conditions. In addition, we argue that gene-finding strategies could benefit from a focus on the genetic overlap between specific dimensions of ASD and ADHD, when searching for pleiothopic genes that may drive psychiatric comorbidity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the participants of STAGE. TJCP and DP would like to acknowledge financial support from the Netherlands Organization for Scientific research (NWO Brain & Cognition: 433-09-228), and the Neuroscience Campus Amsterdam. HL would like to acknowledge financial support from the Swedish research council.

REFERENCES

1 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th edn, American Psychiatric Publishing: Arlington, VA, USA, 2013.
2 Billstedt E, Gillberg IC, Gillberg C. Autism in adults: symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. *J Child Psychol Psychiatry* 2007; **48**: 1102–1110.
3 Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006; **36**: 159–165.
4 Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J *et al.* Epidemiology of autism spectrum disorders in adults in the community in England. *Arch Gen Psychiatry* 2011; **68**: 459–465.
5 Simon V, Czobor P, Bálint S, Mészáros A. Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009; **194**: 204–211.
6 Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: a decade of new twin studies. *Am J Med Genet Part B Neuropsychiatr Genet* 2011; **156B**: 255–274.
7 Nikolas MA, Burt SA. Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: a meta-analysis. *J Abnorm Psychol* 2010; **119**: 1–17.
8 Hoekstra RA, Bartels M, Verweij CJH, Boomsma DI. Heritability of autistic traits in the general population. *Arch Pediatr Adolesc Med* 2007; **161**: 372–377.
9 Boomsma DI, Saviouk V, Hottenga J-J, Distel MA, de Moor MHM, Vink JM *et al.* Genetic epidemiology of attention deficit hyperactivity disorder (ADHD index) in adults. *PLoS ONE* 2010; **12**: e10621.
10 Larsson H, Asherson P, Chang Z, Ljung T, Friedrichs B, Larsson J-O *et al.* Genetic and environmental influences on adult attention deficit hyperactivity disorder

© 2014 Macmillan Publishers Limited

symptoms: a large Swedish population-based study of twins. *Psychol Med* 2013; **43**: 197–207.
11 Lai M-C, Lombardo MV, Baron-Cohen S. Autism. *Lancet* 2014; **383**: 896–910.
12 Holden SE, Jenkins-Jones S, Poole CD, Morgan CL, Coghill D, Currie CJ. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). *Child Adolesc Psychiatry Mental Health* 2013; **7**: 34.
13 Anckarsäter H, Stahlberg O, Larson T, Hakansson C, Jutblad S-B, Niklasson L *et al.* The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *Am J Psychiatry* 2006; **163**: 1239–1244.
14 Ronald A, Edelson LR, Asherson P, Saudino KJ. Exploring the relationship between autistic-like traits and ADHD behaviors in early childhood: findings from a community twin study of 2-year-olds. *J Abnorm Child Psychol* 2010; **38**: 185–196.
15 Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry* 2008; **49**: 535–542.
16 Lichtenstein P, Carlström E, Råstam M, Gillberg C, Anckarsäter H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry* 2010; **167**: 1357–1363.
17 Ronald A, Larsson H, Anckarsäter H, Lichtenstein P. Symptoms of autism and adhd: a Swedish twin study examining their overlap. *J Abnorm Psychol* 2014; **123**: 440–451.
18 Reiersen AM, Constantino JN, Grimmer M, Martin NG, Todd RD. Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Res Hum Genet* 2008; **11**: 579–585.
19 Lundström S, Chang Z, Kerekes N, Gumpert CH, Råstam M, Gillberg C *et al.* Autistic-like traits and their association with mental health problems in two nationwide twin cohorts of children and adults. *Psychol Med* 2011; **41**: 2423–2433.
20 Happé F, Ronald A. The "fractionable autism triad": a review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychol Rev* 2008; **18**: 287–304.
21 Ronald A, Larsson H, Anckarsäter H, Lichtenstein P. A twin study of autism symptoms in Sweden. *Mol Psychiatry* 2011; **16**: 1039–1047.
22 Greven CU, Rijsdijk FV, Plomin R. A twin study of ADHD symptoms in early adolescence: hyperactivity-impulsivity and inattentiveness show substantial genetic overlap but also genetic specificity. *J Abnorm Child Psychol* 2011; **39**: 265–275.
23 McLoughlin G, Rijsdijk F, Asherson P, Kuntsi J. Parents and teachers make different contributions to a shared perspective on hyperactive-impulsive and inattentive symptoms: a multivariate analysis of parent and teacher ratings on the symptom domains of ADHD. *Behav Genet* 2011; **41**: 668–679.
24 Polderman TJC, Hoekstra RA, Vinkhuyzen AAE, Sullivan PF, van der Sluis S, Posthuma D. Attentional switching forms a genetic link between attention problems and autistic traits in adults. *Psychol Med* 2013; **43**: 1985–1996.
25 Lichtenstein P, Sullivan PF, Cnattingius S, Gatz M, Johansson S, Carlström E *et al.* The Swedish Twin Registry in the third millennium: an update. *Twin Res Hum Genet* 2006; **9**: 875–882.
26 Furberg H, Lichtenstein P, Pedersen NL, Thornton L, Bulik CM, Lerman C *et al.* The STAGE cohort: A prospective study of tobacco use among Swedish twins. *Nictone Tob Res* 2008; **10**: 1727–1735.
27 Cortina JM. What is coefficient alpha? An examination of theory and applications. *J Appl Psychol* 1993; **78**: 98–104.
28 Hall JG. Twinning. *Lancet* 2003; **362**: 735–743.
29 Plomin R, DeFries JC, McClearn GE, McGuffin P. *Behavior Genetics* 5th edn., Worth: New York, USA, 2008.
30 Neale MC Boker SM Xie G Maes HHM. *Mx:Statistical Modeling*. Department of Psychiatry, Virginia Common Wealth University: Richmond, VA, 2006.
31 Rijsdijk F. Statistical genetics: gene mapping through linkage and association. In: Ferreira M, Neale B, Medland S, Posthuma D (eds). *Statistical Genetics: Gene Mapping through Linkage and Association*. London: Taylor & Francis, 2007, pp 43–58.
32 Sullivan PF, Eaves LJ. Evaluation of analyses of univariate discrete twin data. *Behav Genet* 2002; **32**: 221–227.
33 Mosconi MW, Kay M, D'Cruz A-M, Seidenfeld A, Guter S, Stanford LD *et al.* Impaired inhibitory control is associated with higher-order repetitive behaviors in autism spectrum disorders. *Psychol Med* 2009; **39**: 1559–1566.
34 Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry* 2005; **57**: 1336–1346.
35 Lipszyc J, Schachar R. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. *J Int Neuropsychol Soc JINS* 2010; **16**: 1064–1076.
36 Rommelse NNJ, Geurts HM, Franke B, Buitelaar JK, Hartman CA. 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. *Neurosci Biobehav Rev* 2011; **35**: 1363–1396.
37 Geurts HM, Ridderinkhof KR, Scholte HS. The relationship between grey-matter and ASD and ADHD traits in typical adults. *J Autism Dev Disord* 2013; **43**: 1630–1641.
38 Ronemus M, Iossifov I, Levy D, Wigler M. The role of de novo mutations in the genetics of autism spectrum disorders. *Nat Rev Genet* 2014; **15**: 133–141.
39 Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R *et al.* Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet* 2010; **376**: 1401–1408.
40 Taurines R, Schwenck C, Westerwald E, Sachse M, Siniatchkin M, Freitag C. ADHD and autism: differential diagnosis or overlapping traits? A selective review. *Atten Deficit Hyperact Disord* 2012; **4**: 115–139.
41 Lee SH, Ripke S, Neale BM, Faraone SV *et al.* Cross-Disorder Group of the Psychiatric Genomics Consortium Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* 2013; **45**: 984–994.
42 D'Onofrio BM, Rickert ME, Frans E, Kuja-Halkola R, Almqvist C, Sjölander A *et al.* Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry* 2014; **71**: 432–438.
43 Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G *et al.* Rate of *de novo* mutations and the importance of father's age to disease risk. *Nature* 2012; **488**: 471–475.
44 Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009; **8**: 110–124.
45 Losh M, Esserman D, Anckarsäter H, Sullivan PF, Lichtenstein P. Lower birth weight indicates higher risk of autistic traits in discordant twin pairs. *Psychol Med* 2012; **42**: 1091–1102.
46 Ronald A, Happé F, Dworzynski K, Bolton P, Plomin R. Exploring the relation between prenatal and neonatal complications and later autistic-like features in a representative community sample of twins. *Child Dev* 2010; **81**: 166–182.
47 Groen-Blokhuis MM, Middeldorp CM, van Beijsterveldt CEM, Boomsma DI. Evidence for a causal association of low birth weight and attention problems. *J Am Acad Child Adolesc Psychiatry* 2011; **50**: e2.
48 Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 2002; **288**: 728–737.
49 D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry* 2013; **70**: 1231–1240.
50 Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. *Transl Psychiatry* 2014; **4**: e360.
51 Elia J, Laracy S, Allen J, Nissley-Tsiopinis J, Borgmann-Winter K. Epigenetics: genetics versus life experiences. *Curr Top Behav Neurosci* 2012; **9**: 317–340.
52 Wong CCY, Meaburn EL, Ronald A, Price TS, Jeffries AR, Schalkwyk LC *et al.* Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. *Mol Psychiatry* 2014; **19**: 495–503.
53 Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S *et al.* A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. *Am J Hum Genet* 2014; **94**: 415–425.
54 Lundström S, Chang Z, Råstam M, Gillberg C, Larsson H, Anckarsäter H *et al.* Autism spectrum disorders and autistic like traits: similar etiology in the extreme end and the normal variation. *Arch Gen Psychiatry* 2012; **69**: 46–52.
55 Robinson EB, Koenen KC, McCormick MC, Munir K, Hallett V, Happé F *et al.* Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). *Arch Gen Psychiatry* 2011; **68**: 1113–1121.
56 Larsson H, Anckarsater H, Råstam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. *J Child Psychol Psychiatry* 2012; **53**: 73–80.
57 Van der Sluis S, Posthuma D, Nivard MG, Verhage M, Dolan CV. Power in GWAS: lifting the curse of the clinical cut-off. *Mol Psychiatry* 2013; **18**: 2–3.
58 Ronald A, Happé F, Bolton P, Butcher LM, Price TS, Wheelwright S *et al.* Genetic heterogeneity between the three components of the autism spectrum: a twin study. *J Am Acad Child Adolesc Psychiatry* 2006; **45**: 691–699.
59 Ronald A, Happé F, Price TS, Baron-Cohen S, Plomin R. Phenotypic and genetic overlap between autistic traits at the extremes of the general population. *J Am Acad Child Adolesc Psychiatry* 2006; **45**: 1206–1214.
60 Hoekstra RA, Vinkhuyzen AAE, Wheelwright S, Bartels M, Boomsma DI, Baron-Cohen S *et al.* The construction and validation of an abridged version of the autism-spectrum quotient (AQ-Short). *J Autism Dev Disord* 2011; **41**: 589–596.
61 Lecavalier L, Aman MG, Scahill L, McDougle CJ, McCracken JT, Vitiello B *et al.* Validity of the autism diagnostic interview-revised. *Am J Ment Retard* 2006; **111**: 199–215.
62 Chang Z, Lichtenstein P, Asherson PJ, Larsson H. Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry* 2013; **70**: 311–318.

© 2014 Macmillan Publishers Limited

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-nd/3.0/

Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)