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ORIGINAL ARTICLE

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

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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.

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) and is generally considered a lifelong condition. ADHD is characterized by inattention (IA) and by hyperactive/impulsive (HI) symptoms that also show a substantial degree of persistence into adulthood. According to the first prevalence study in adults, ~1% of the population has a diagnosis of ASD. For ADHD ~2.5% of adults meets diagnostic criteria. Studies in clinical- and population-based samples of children showed that both ASD and ADHD are among the most heritable conditions in psychiatry with heritability estimates of ~75%. Only a few studies focused on the heritability of ASD and ADHD traits in adults, suggesting heritability estimates of 30–50% for both traits. ASD and ADHD often co-occur; roughly 24–44% of adults diagnosed with ASD also meet criteria for ADHD. Both conditions can have a large negative impact on the daily life of affected individuals and their families, in particular when both conditions co-occur. 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, United Kingdom and Sweden, 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. 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, whereas studies of IA and HI in children, as well as in adults, 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. 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...
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 and ADHD 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). 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 telephone interview, whereas 28% of the respondents 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.

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.

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’). Items were summed to create two dimensions of ASD: social and communication difficulties (ASDr, 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.

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 adult context. To assess current ADHD symptoms, we asked the respondents 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 ASD, > 1 for ASDsc and > 2 for IA and HI), the scale was deemed unreliable and coded as missing for the individual concerned. The items to assess the ASD traits were the language and the communication problems as used in clinical practice. In addition, previous studies showed 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.

In the current study, the authors aimed to examine potential sex differences. 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 and ADHD 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.
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 (χ²) tests. The χ² 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. Akaike Information Criterion and Bayesian Information Criteria were additionally used to assess model fit, with lower (negative) estimates suggesting better model fit. To avoid oversimplification, and reduce multiple testing, we only fitted multivariate models, and a limited set of nested models with type-I error rate set at 0.01.

RESULTS
The means (χ² = 36.688, df = 4, P < 0.000) and phenotypic correlations (χ² = 33.283, df = 6, P < 0.000) differed significantly between males and females, whereas variances were considered equal across both genders (χ² = 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 both IA (0.39 in males and 0.33 in females) and HI (0.40 in both males and females). ASDr and both IA and HI (r = 0.20–0.45) 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 (rG = 0.50) but lower between ASDsc and HI (rG = 0.22). Unique environmental correlations were generally modest (rE < 0.34) but still explained a considerable proportion of the phenotypic correlations.

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 (χ² = 15.126, df = 10, P = 0.128) and females (χ² = 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 (χ² = 9.192, df = 4, P = 0.056, and χ² = 8.619, df = 6, P = 0.196, respectively), DZ same-sex twin pairs (χ² = 2.483, df = 4, P = 0.648, and χ² = 6.344, df = 6, P = 0.386, respectively), and were similar between DZ same-sex and DOS (MF and FM) twin pairs (χ² = 7.618, df = 12, P = 0.148 and χ² = 19.998, df = 18, P = 0.033, 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.

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 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), 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 and ADHD are due to a lack of inhibitory control, although contrasting findings have also been reported. 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
inhibitory control. 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.6–10,18,19,24 We observed substantial
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 have also been implicated in the risk for ADHD (see Taurines et al. for an overview). However, a recent study that investigated the overlap of common variants between ASD and ADHD failed to identify genetic overlap. 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. Non-genetically mediated low birth weight and related delayed brain maturation have also been associated with both ASD and ADHD, even after strict correction for potential confounders, but the underlying risk mechanism is still unclear. The negative impact of toxins such as air pollutants, tobacco, heavy metals and pesticides on ASD and ADHD 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. 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 and ADHD traits. 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 females, 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.

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 and ADHD traits. 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. 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, 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.

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 pleiotropic genes that may drive psychiatric comorbidity.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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