Autistic traits in a population-based ADHD twin sample

Angela M. Reiersen, 1 John N. Constantino,1,2 Heather E. Volk,3 and Richard D. Todd1,4

1Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; 2Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA; 3Doctoral Program in Public Health Studies, St. Louis University School of Public Health, St. Louis, MO, USA; 4Department of Genetics, Washington University School of Medicine, St. Louis, MO, USA

Background: Most diagnostic nomenclatures do not allow for the concurrent diagnosis of autism and attention-deficit/hyperactivity disorder (ADHD). Clinic-based studies suggest autistic symptoms are common in children with ADHD, but such studies are prone to referral bias. This study assesses whether children with ADHD selected from the general twin population have elevated levels of autistic traits. Methods: Nine hundred forty-six twins identified by Missouri birth records were assigned to DSM-IV ADHD diagnoses and seven population-derived ADHD subtypes defined through latent class analysis of DSM-IV ADHD symptoms. The Social Responsiveness Scale (SRS) was used as a quantitative measure of autistic traits. Linear regression was used to evaluate whether mean SRS scores differed between ADHD diagnostic groups. Results: Mean SRS scores for DSM-IV predominantly inattentive subtype and combined subtype ADHD groups were significantly higher than for subjects without DSM-IV ADHD (p < .001, both comparisons). Five of the population-derived ADHD subtypes (talkative-impulsive, mild and severe inattentive, mild and severe combined) had significantly higher mean SRS scores compared to the latent class subtype with few ADHD symptoms (p < .001, all comparisons). DSM-IV combined subtype and the population-derived severe combined subtype had the highest mean total SRS scores and the highest mean scores for each of the three autism symptom domains, with a substantial proportion of individuals scoring in the clinically significant range. Conclusions: This study provides population-based evidence for clinically significant elevations of autistic traits in children meeting diagnostic criteria for ADHD. These results have implications for the design and interpretation of studies of both disorders. Keywords: ADHD, autism, PDD, Social Responsiveness Scale.

The present version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) does not allow ADHD to be diagnosed if symptoms occur only during the course of a pervasive developmental disorder (PDD) (American Psychiatric Association, 1994). As a result of this exclusion requirement, modern treatment and etiological studies of ADHD and autism exclude subjects who meet criteria for both disorders. However, recent clinic-based studies indicate that clinically significant symptoms consistent with ADHD are present in 59–75% of children with PDD (Goldstein & Schwabach, 2004; Sturm, Fernell, & Gillberg, 2004; Yoshida & Uchiyama, 2004). Additionally, characteristics of autism spectrum disorders have been found in children with DSM-IV ADHD (Clark, Feehan, Tinline, & Vostanis, 1999) and in ICD-10 hyperkinetic disorder (HKD), a diagnosis similar to DSM-IV combined type ADHD (Santosh & Mijovic, 2004). From a molecular genetics perspective, there is evidence of overlap between some linkage peaks for autism and ADHD (Smalley, Loo, Yang, & Cantor, 2005), suggesting that some genes may influence both ADHD and autism. However, it is possible that such overlap in linkage peaks is due to diagnostic misspecification (Todd, 2005).

Previously, we reported on the development of the Social Responsiveness Scale (SRS), a 65-item parent- or teacher-rated questionnaire designed to assess autistic traits in a quantitative manner, with an emphasis on deficits in reciprocal social behavior (Constantino & Gruber, 2005a; Constantino, Przybeck, Friesen, & Todd, 2000). The scale includes items from all three DSM-IV autism symptom domains, including social impairment, communication impairment, and stereotyped behavior. Scores on the SRS are continuously distributed in the general population, and are highly heritable (Constantino & Todd, 2003c, 2005b). A study comparing the SRS to the Autism Diagnostic Interview-Revised (ADI-R) showed high correlations between SRS scores and the ADI-R algorithm scores for DSM-IV autism criteria (Constantino et al., 2003a). In an epidemiological study of 219 male twin pairs (438 individuals), linear regression using Child Behavior Checklist (CBCL) syndrome scales to predict SRS score found evidence of an association between the CBCL attention problems scale and total SRS score (Constantino, Hudziak, & Todd, 2003b). Structural equation modeling using the same sample suggested that the genetic factors influencing SRS score were separate from those influencing attention problems, but that within-individual interactions between SRS score and attention problems (reciprocal causation) may account for the relationship between these two measures.
Prior work with our Missouri Twin Study sample assigned subjects to population-derived ADHD subtypes defined through latent-class analysis (LCA) of the DSM-IV ADHD symptom items (Neuman et al., 2005; Volk, Neuman, & Todd, 2005). LCA, a non-parametric version of cluster analysis, works to separate subjects into phenotypically homogenous groups. These population-derived subtypes differ with respect to comorbidity profiles (Volk et al., 2005), academic progress and cognitive problems (Todd et al., 2002), and associations with candidate genes (Todd et al., 2005; Todd, Lobos, Sun, & Neuman, 2003). In this and two other samples, both DSM-IV and population-derived ADHD subtypes showed evidence of familiality, but only population-derived subtypes appeared genetically independent (Rasmussen et al., 2004; Todd et al., 2001; Volk et al., 2005). Considering the above, the population-derived ADHD subtypes have special relevance for genetic and other etiological studies.

Most studies suggesting co-occurrence of ADHD and autistic symptoms have been based on relatively small and highly selected clinical samples, which can be prone to referral bias. In order to determine whether symptoms of ADHD and autism naturally cluster in children from the general population, it is important to examine these associations in larger, population-based samples. If children with ADHD in the general population frequently have clinically significant autistic symptoms, this would have important practical implications for clinical assessment and treatment as well as relevance in terms of defining phenotypes for etiological studies of ADHD and autism. Such a finding would also call into question the generalizability of studies which exclude one or the other diagnosis. The current study examines the overlap of these disorders in a population-based twin sample using both DSM-IV and population-derived ADHD subtypes and a quantitative measure of autistic traits (the SRS). We hypothesized that subjects with ADHD would have elevated levels of autistic traits as measured by the SRS, and expected to find differences in mean SRS score among different ADHD subtypes.

Methods

This study was conducted using a population-based twin sample (1647 individuals) originally collected as part of an epidemiologic study of ADHD (Neuman et al., 2005). Twin pairs were selected for the study if parent response to a brief screening interview indicated endorsement of three or more present or past inattentive symptoms in at least one twin of the pair. As a result, the sample was enriched 4-fold for ADHD. The Child Behavior Checklist (CBCL, 1991 version) – a parent questionnaire that examines behavior and functioning of children (Achenbach, 1991) – was completed by mail for subjects who were screened for the study (n = 7239). The sample also includes 183 twin pairs randomly selected across birth years and 104 twin pairs selected based on CBCL anxious/withdrawn subscale scores greater than the 95th percentile. These subjects were included to serve as controls and to maintain the blindness of the interviewers since many of the children had been selected for ADHD-related characteristics (Neuman et al., 2005). Twin pairs where one twin had died or with parent-reported mental retardation or autism were excluded from the study.

A semi-structured interview, the Missouri Assessment of Genetics Interview for Children (MAGIC), was used to obtain information on DSM-IV diagnoses for all subjects included in the study (n = 1647). This interview has shown excellent interrater reliability in obtaining DSM-IV diagnoses, including ADHD (Todd, Joyner, Heath, Neuman, & Reich, 2003). The ADHD data examined here was obtained from parent interviews. Wechsler Intelligence Scale for Children-Third Edition (WISC-III) vocabulary scores were obtained as part of a prior study of cognitive function in ADHD subtypes (Todd et al., 2002), and were used as an estimate of IQ in the current study. The WISC-III vocabulary test was administered by trained interviewers, either in person or by phone. We did not obtain full WISC-III data, but we were able to obtain WISC-III vocabulary scores on the majority of subjects because it was possible to administer this subtest by phone.

The Social Responsiveness Scale (SRS) is a 65-item parent/teacher questionnaire for assessing autistic traits (Constantino & Gruber, 2005a; Constantino et al., 2000). Each SRS item rates the frequency of a particular behavior on a 4-point Likert scale (0 to 3 points for each item), making possible scores range from zero to 195, with higher scores indicating a higher degree of autistic symptoms. Previous research with the SRS indicates that it is largely independent of other major domains of psychopathology (Constantino et al., 2003b). An SRS score greater than 2.5 standard deviations above the mean suggests a ‘severe interference in everyday social interactions’ (Constantino & Gruber, 2005a).

Previously published SRS means are 35.3 ± 22.0 for boy twins (Constantino & Todd, 2003c), 27.5 ± 18.4 for girl twins (Constantino & Todd, 2003c), 101.5 ± 23.6 for children with PDD-NOS (Constantino et al., 2000) and 51.1 ± 32.9 for children with ADHD (Constantino et al., 2000). Additional information regarding psychometric properties, reliability, and validity of the SRS have been reported elsewhere (Constantino et al., 2003a; Constantino & Gruber, 2005a; Constantino et al., 2000).

For the current study, the SRS forms were separately mailed to all families, and completed by the parent (usually the mother). SRS scores were considered invalid if 12 or more items (≥18%) were unanswered. For those subjects with fewer than 12 items missing, the SRS total score algorithm

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included correction for the number of missing items. The SRS items were also separated into 3 mutually exclusive categories based on the 3 DSM-IV autism symptom domains of social impairment (47 items), communication impairment (6 items: numbers 10, 12, 19, 35, 51, 53), and stereotyped behaviors (12 items: numbers 4, 8, 14, 20, 24, 28, 29, 31, 39, 49, 50, 63). We also created an ‘ADHD-like’ subscale including 8 items that seemed most likely to be directly affected by ADHD symptoms (items 1, 35, 41, 45, 52, 55, 56, 65), a 57-item ‘non-ADHD’ subscale that excluded these 8 items, and a ‘key autism’ subscale including only 9 items that seemed very specific for autism spectrum disorders (item numbers 10, 15, 16, 20, 33, 39, 50, 51, 53). All subscale scores were considered invalid if 18% or more of the subscale items were missing. Raw subscale scores were divided by the maximum possible raw subscale score for the number of items answered, and then multiplied by 100 in order to produce scores that could be meaningfully compared to other scores. Also, for comparison to subscale scores, a ‘total SRS percent’ score was created by expressing the total SRS score as percent of the highest possible SRS score.

A total of 1018 subjects had both MAGIC and SRS data. Of these 1018 subjects, 38 were excluded due to incomplete or invalid SRS data or incomplete ADHD diagnostic data. Of the remaining 980 subjects, 34 were excluded due to WISC-III vocabulary scores that were less than 4, indicating probable mental retardation. The current analysis includes 946 subjects – 451 complete twin pairs and 44 individual subjects.

In the group of 946 subjects, ages ranged from 7 to 19 years when MAGIC interview and WISC-III data were obtained (mean 12.4 ± 3.0), but ranged from 8 to 25 years at the time of the SRS rating (mean 14.0 ± 4.2). Seventy-eight percent of SRS forms were obtained within 2 years of the MAGIC, but some SRS forms were obtained as much as 3 years before or 7 years after the MAGIC. Sixty-two percent of subjects are male, and 92% are European American. Fourteen percent had a DSM-IV ADHD diagnosis based on the MAGIC. WISC-III vocabulary scaled score mean was 9.5 ± 2.6 for the 780 subjects who were tested.

Because parents returned SRS questionnaires for only 62% of the 1647 subjects who participated in MAGIC interviews, an evaluation for possible response bias was done by comparing the 1018 SRS responders to the 629 non-responders on a number of demographic variables obtained via self-report or from year 2000 United States of America census data describing the population living within the subject’s postal service area (zip code). There were small but significant differences between groups for race, age, and socioeconomic status variables. For SRS responders versus non-responders: percent European American was 91% vs. 75% (p < .001); mean age at MAGIC was 12.4 vs. 13.8 years (p < .001); mean percentage African American in subject’s zip code was 9% vs. 12% (p = .006); and mean income for subject’s zip code was $34,896 vs. $33,033 (p = .04). Mean WISC-III vocabulary test scaled scores were slightly higher for subjects whose parents returned the SRS forms (9.1 vs. 8.3, p < .001). Importantly, there were no significant differences in sex or proportion of subjects with a DSM-IV ADHD diagnosis between SRS responders and non-responders.

Written informed consent (or assent for youth under age 18 years) was obtained from participants and legal guardians prior to participation. The study protocol was approved by the Washington University School of Medicine Human Studies Committee.

**Statistical analyses**

Subjects were assigned to population-derived ADHD subtypes based on latent-class analysis (LCA) of the 18 DSM-IV ADHD symptoms obtained from the MAGIC interview. Briefly, LCA can be used to identify homogenous subtypes of individuals based on response to a set of correlated items, here symptom profiles. The method of assigning latent-class ADHD diagnoses to subjects in this population has been described elsewhere (Neuman et al., 2005; Todd et al., 2002; Volk et al., 2005). The LCA examined clustering of the 18 DSM-IV ADHD symptoms and an inattention screener status variable. The screener status variable indicated whether each subject screened positive (≥3 past or present inattentive symptoms) or negative (<3 inattentive symptoms) for ADHD. It was included in the LCA to remove any variation induced by the screener, so selection based on screener response would not affect latent class membership. Latent class models were fit using the software program LCAP (http://hardy.wustl.edu), which uses the EM algorithm to find maximum likelihood estimates of latent class parameters. The Bayesian Information Criteria (BIC) was used to determine the number of classes. The BIC is calculated from the log-likelihood value (LL) and the number of parameters (p) estimated in the model times natural log of the sample size (n) according to the formula (-2LL + p ln n) (Schwartz, 1978). Seven ADHD categories resulted from LCA: mild and severe inattentive, mild and severe combined, talkative-impulsive, hyperactive, and a class showing few ADHD symptoms (Volk et al., 2005).

Mean SRS scores were calculated for subjects in DSM-IV and latent-class subtypes. Linear regression was used to determine whether mean total SRS scores differed between ADHD diagnostic groups defined by DSM-IV or latent class subtypes. Standard errors were adjusted to account for family clustering (non-independence of observations within twin pairs) using the ‘cluster’ option available in STATA 8.2 (College Station, TX). Subject age at SRS, sex, zygosity, and WISC-III vocabulary score were included in the models to remove any differences in mean score by these factors. For analyses utilizing DSM-IV diagnostic subtypes, subjects without DSM-IV ADHD were used as the
reference group. For analyses involving population-defined ADHD subtypes, the few ADHD symptoms subtype was used as the reference group. Using this method, the regression coefficient ($\beta$) for each ADHD subtype variable indicates the covariate-corrected change in the mean SRS score compared to the reference group mean, and the associated $p$-value indicates the significance level of this difference. The regression coefficient ($\beta$) for each covariate indicates the average change in SRS score associated with a unit change in the covariate. For example, the unit change for age is one year. We used post-hoc comparisons to test for differences in mean SRS score (differences in $\beta$) between symptomatic ADHD subtypes. The Bonferroni correction for multiple testing was used for all post-hoc comparisons.

In order to estimate the proportion of subjects likely to have clinically significant autistic traits, the percent of subjects meeting a threshold total SRS score was calculated for each ADHD subtype. Because our study involves twins, we calculated our own cut-offs based on previously reported mean SRS scores for male and female twins (Constantino & Todd, 2003c). These twin-based thresholds were calculated as the sex-specific mean plus 2.5 times the standard deviation (Total SRS $\geq 91$ for boys, $\geq 74$ for girls).

### Results

Mean total SRS and various subscale scores for each diagnostic group are shown in Table 1. Total SRS scores and all subscale scores were highest for DSM-IV combined subtype and the severe combined latent class.

Figure 1 illustrates covariate-corrected comparisons of mean SRS scores between ADHD subtypes. The figure shows the actual total SRS mean scores for each group and indicates which groups showed statistically significant differences based on the linear regression analyses.

In the analysis involving DSM-IV subtypes (Figure 1, top), only the predominantly inattentive and combined subtypes showed significantly higher SRS means than the non-ADHD group ($p < .001$ for each). The $\beta$-coefficients indicated covariate-corrected mean SRS score increases of 16.97 and 35.26, respectively. Although the SRS mean for the predominantly hyperactive-impulsive subtype was somewhat elevated compared to the reference group, the $p$-value did not reach statistical significance ($\beta = 11.89$, $p = .055$). Post-hoc tests for differences between mean SRS scores of DSM-IV ADHD subtypes showed that the combined type ADHD group had a significantly higher mean SRS score than the predominantly inattentive ($p = .0095$) and predominantly hyperactive-impulsive ($p = .0079$) subtypes. SRS means were not significantly different between the predominantly inattentive and predominantly hyperactive-impulsive subtypes.

In the similar analysis using population-defined (LCA-based) ADHD subtypes (Figure 1, bottom), the SRS mean for the hyperactive subtype was not sig-
Figure 1 Covariate-corrected comparisons of Mean SRS scores between ADHD subtypes. Top graph shows DSM-IV subtypes (* = significantly different from ‘No ADHD’ and ‘Combined’; ** = significantly different from all other groups). Bottom graph shows latent class groups (* = significantly different from ‘FEW’ and ‘HCMB’ groups; ** = significantly different from ‘FEW’, ‘HYPER’, and ‘HCMB’ groups; *** = significantly different from all other groups). Latent classes: FEW = few symptoms; HYPER = hyperactive; TALK = talkative; MIA = mild inattentive; HIA = severe inattentive; MCMB = mild combined; HCMB = severe combined.

Table 2 Percent of subjects meeting a threshold for clinically significant autistic symptoms (n = 946 subjects)

<table>
<thead>
<tr>
<th>DSM-IV classes:</th>
<th>Number in diagnostic group (males/females)</th>
<th>Percent of males meeting threshold (SRS &gt; 91)</th>
<th>Percent of females meeting threshold (SRS &gt; 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ADHD</td>
<td>468/344</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>11/3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inattentive</td>
<td>63/12</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>Combined</td>
<td>41/4</td>
<td>32</td>
<td>75</td>
</tr>
<tr>
<td>Latent classes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few symptoms</td>
<td>260/247</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hyperactive</td>
<td>20/11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Talkative</td>
<td>32/29</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mild inattentive</td>
<td>84/31</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Severe inattentive</td>
<td>98/21</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Mild combined</td>
<td>48/13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Severe combined</td>
<td>41/11</td>
<td>29</td>
<td>73*</td>
</tr>
</tbody>
</table>

*For the severe combined latent class, the proportion of subjects meeting the threshold differed significantly between female and male groups (Fisher’s exact test, p = 0.014).
subtype if only raw mean SRS scores were considered (data not shown), but using the sex-specific threshold is more appropriate in terms of evaluating the presence of clinically significant social impairment compared to same-sex peers.

Discussion

DSM-IV does not allow ADHD to be diagnosed if symptoms occur only during the course of a PDD (American Psychiatric Association, 1994). Similarly, many neurobiological, genetic, and treatment studies of these disorders exclude participants with evidence of both disorders. Both of these practices may be inappropriate given the frequent co-occurrence of ADHD and PDD symptoms in clinical samples. The current study adds to existing literature by demonstrating that 1) autistic traits — measured quantitatively using the SRS — are elevated in children with ADHD ascertained from the general population, and 2) different ADHD subtypes are associated with markedly different levels of social impairment.

Previous studies mentioned in the introduction found evidence that children with ADHD or HKD have increased rates of impairment in all three autism symptom domains of social deficits, communication impairment, and stereotyped behaviors (Clark et al., 1999; Santosh & Mijovic, 2004). In the current study, examination of DSM-IV-based autism symptom scales derived from the SRS demonstrates that the DSM-IV combined and population-defined severe combined ADHD subtypes have the highest mean scores for each of the three autism symptom domains (Table 1). Given these results, it appears that children with severe forms of ADHD, like children with autism, have clinically significant symptoms in all three autism symptom domains.

It is possible that a subset of SRS items might be misconstrued as describing ADHD symptoms. Examples include items related to shared attention, fidgeting in social situations, and walking between people who are talking. To address this issue, we created an ‘ADHD-like’ subscale including eight items that might be directly affected by inattention, impulsivity, or general hyperactivity, and a 57-item ‘non-ADHD’ subscale that excludes these eight items. Since some additional SRS items might be endorsed due to anxiety disorders, non-autistic social impairment, or other factors that may be unrelated to autism, we also created a short scale including only nine key autism-related items. As with the total SRS score, the mean scores on each of these subscales were highest for the DSM-IV combined and population-defined severe combined ADHD subtypes (Table 1). We also repeated the linear regression analyses using each of these three modified scales, and in each case the results were essentially unchanged compared to analyses using the total SRS score: the exact same ADHD subtypes had significantly higher mean SRS scores than the reference groups (data not shown). These sub-analyses further support the presence of true autistic symptomatology in children with ADHD and the use of total SRS scores.

Despite the above findings, it is still difficult to say whether the mildly elevated mean SRS scores (in the range of 40–50) seen in some ADHD subtypes indicate true autistic traits versus general impairment in social functioning. Other work examining general social competence in children with ADHD using the Child Behavior Checklist (CBCL) social competency scale showed that that severe inattentive, severe combined and mild combined latent classes had similar scores and that these groups were significantly more impaired than the other latent classes. Also, the social problems syndrome scale indicated the most severe levels of impairment in these same three subtypes (Volk, Henderson, Neuman, & Todd, 2006). Since the CBCL social problems and social competency scales may measure elements of social competency that are largely independent of autistic symptoms, we repeated our linear regression analyses using these two CBCL subscales as additional covariates. When we controlled for these two CBCL subscale scores, our basic results did not change except that the SRS mean for one of the latent classes (talkative-impulsive class) no longer showed a significant difference compared to the few symptoms class (p-value increased from <.001 to .055). This suggests that the elevated SRS scores in ADHD subjects are not due solely to any components of non-autistic social deficits measured by these two CBCL scales.

This study has some limitations. We obtained the parent-rated SRS questionnaires from only a subgroup of the original subjects, and comparisons between SRS responders and non-responders suggested a small degree of response bias related to socioeconomic status, IQ, race and age, but no response bias related to sex or ADHD diagnosis. Based on these results, we found that parents of poorer minority subjects or subjects with decreased IQ were less likely to complete the SRS. This may be due to stigma regarding research participation among minority subjects, or selection bias on the familial level regarding education and general socioeconomic status. We emphasize that there was no evidence of response bias based on sex or ADHD status, which would have been more likely than other variables to influence our results if response bias were present. Also, a twin sample may be somewhat different from non-twin samples in terms of the rates of attention problems and autistic traits or the degree that perinatal factors influence these symptoms. A recent preliminary study showed that in males – but not females – SRS scores are higher in twins than in non-twins (Ho, Todd, & Constantino, 2005). In contrast, there is little evidence for different prevalences...
of ADHD or ADHD subtypes in twins versus non-twins (Neuman et al., 2005).

Issues related to our sampling scheme and enrichment for ADHD may also limit the generalizability of our study. Most twin pairs were selected based on a screen for inattentive symptoms. In order to maintain blindness of the interviewers, a small subset of study subjects was selected based on high endorsement of anxious/withdrawn symptoms on the CBCL, and another subset was randomly selected. While our sample is not prone to the referral bias that can occur with clinical samples, the method of sample selection should be considered when interpreting the results. Further studies using different population-based samples and alternative types of control groups could be used in future studies. For example, it may be useful to use a group of normal functioning children without ADHD as a control group when comparing the level of autistic traits in children with ADHD versus control subjects.

SRS scores were not collected at the same time as the MAGIC interviews. However, 78% of SRS forms were completed within two years of the MAGIC and 93% within five years of the MAGIC. In this study, older age at SRS was associated with a slightly lower SRS score, but this effect of age appeared very small compared to the range of possible scores on the SRS. Also, prior work suggests that SRS scores are highly stable over time (Constantino & Todd, 2005b), thus the time difference between measurement of SRS score and ADHD status likely had minimal effect on the results of this study. Since this study is essentially cross-sectional, it is not possible to examine temporal developmental paths, and any direction of effect of one symptom on the other cannot be determined.

To enhance reliability in measurement of autistic features, it would have been useful to obtain teacher-rated SRS forms and direct observational measures of autistic symptoms such as the Autism Diagnostic Observation Schedule (ADOS). Although we did not use the ADOS for this specific study, six Missouri twin subjects with both MAGIC and SRS data were evaluated using the ADOS in a separate study (Constantino, J.N., unpublished data). All six were males with SRS scores greater than 70. Of these six individuals, two were diagnosed with autism based on the ADOS, and the other four were categorized as being in the autism spectrum. Notably, all six had either population-defined inattentive (one mild, two severe) or combined (one mild, two severe) ADHD. This suggests that the SRS measures true autistic symptomatology and that there is an association between true autistic symptoms and ADHD. We do not think the lack of teacher reports is a major limitation since parent and teacher SRS scores have been shown to be highly correlated (Constantino et al., 2003a). Also, parent-rated SRS scores correlate highly with other measures of autistic traits such as the ADI-R (Constantino et al., 2003a). The use of both parent- and teacher-rated SRS scores plus other standard measures of autistic symptoms would help to confirm our findings.

Our estimate of IQ was based only on the WISC-III vocabulary score, a verbal IQ measure. We did not include a measure of performance IQ in the current analyses. It may be useful to include measures of both verbal and performance IQ plus additional neurocognitive tests in future studies of the association between ADHD and autism.

Conclusions

The current study shows evidence of association between ADHD and autistic symptoms in children ascertained from the general twin population. The strongest evidence for this association is found in combined subtype ADHD subjects. Among children with ADHD, girls may be even more likely to exhibit clinically significant social impairment than boys. Our finding that nearly one-third of boys and three-fourths of girls with population-defined severe combined subtype ADHD meet clinical cutoffs for autistic symptomatology suggests that gene association, genetic linkage, and imaging studies of autism and ADHD that have excluded participants based on co-occurrence of symptoms have tremendously skewed sampling frames. Whether the apparent association of ADHD and autistic symptoms is due to genetic and environmental causes influencing both disorders, measurement overlap due to imperfect diagnostic instruments, or other factors, it appears important to consider the presence of both ADHD symptoms and autistic features in studies of either disorder.

In our own clinical experience, children with a combination of ADHD symptoms and autistic traits are generally much more difficult to treat than children with ADHD alone. These children may benefit from treatment of both disorders, and revision of DSM diagnostic criteria to allow the diagnosis of both ADHD and PDD in the same individual might reinforce the importance of treating both disorders when they co-occur. Treatment studies involving children with these characteristics may be useful in defining the most appropriate treatment strategies for these patients.

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**Correspondence to**

Angela M. Reiersen, Department of Psychiatry, Box 8134, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110-1093, USA; Tel: (314) 747-6769; Fax: (314) 747-6777; Email: reiersa@psychiatry.wustl.edu

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