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What About the Girls? Sex-Based Differences in Autistic Traits and Adaptive Skills

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ABR collected the data, ran the analyses, and wrote the paper. LK served as co-principal investigator for one site of the project, collected the data, helped design the analyses, and wrote the paper. BEY served as co-principal investigator for one site of the project, collected the data, provided feedback on analyses, and wrote the paper. JB provided insight and feedback on the interpretation of analyses and edited the paper. ATW collected the data and edited the paper. SWW served as co-principal investigator for one site of the project, collected the data, provided feedback on analyses, and edited the paper. GLW collected the data, helped design the analyses, and edited the paper. CP collected the data, provided feedback on analyses, and wrote the paper. RTS collected the data, provided feedback on analyses, and edited the paper. THO collected the data, provided feedback on analyses, and edited the paper. AS collected the data, provided feedback on analyses, and edited the paper. SS collected the data, managed the database, and edited the paper. KR-B provided feedback on analyses and edited the paper. AM served as co-principal investigator for one site of the project, collected the data, provided feedback on analyses, and edited the paper. LGA served as co-principal investigator for one site of the project, collected the data, helped design the analyses, and edited the paper.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Abstract

There is growing evidence of a camouflaging effect among females with autism spectrum disorder (ASD), particularly among those without intellectual disability, which may affect performance on gold-standard diagnostic measures. This study utilized an age- and IQ-matched sample of school-aged youth (n = 228) diagnosed with ASD to assess sex differences on the ADOS and ADI-R, parent-reported autistic traits, and adaptive skills. Although females and males were rated similarly on gold-standard diagnostic measures overall, females with higher IQs were less likely to meet criteria on the ADI-R. Females were also found to be significantly more impaired on parent reported autistic traits and adaptive skills. Overall, the findings suggest that some autistic females may be missed by current diagnostic procedures.

Keywords

Autism spectrum disorder; Sex differences; Diagnosis; Adaptive skills

Introduction

Autism spectrum disorder (ASD) is identified in females at a substantially lower rate than in males, with most epidemiological studies reporting approximately a 4:1 male to female ratio (Fombonne 2009). However, a recent meta-analysis of epidemiological studies found that the true ratio is likely closer to 3:1, with findings suggesting that autistic females[1] are more likely to be missed (Loomes et al. 2017). These authors and others have hypothesized that autistic traits may be “camouflaged”[2] in females and that current diagnostic procedures may be biased against females (Kirkovski et al. 2013; Lai et al. 2016). This contrasts strongly to the longstanding belief that females are simply at reduced risk for developing ASD, based on the consistent finding of lower prevalence rates among females.

Studies exploring the etiological basis of ASD have found some support for the observed sex differences in diagnostic rates. Many in the field have described a female protective effect (e.g., Robinson et al. 2013), by which female sex in some way directly reduces the risk of ASD. For instance, there is a higher rate of ASD recurrence in families of female probands than in those of male probands, as well as higher rates of autistic traits in the families of female probands (Robinson et al. 2013). There are also reports that autistic females carry a

[1]Identity-first language rather than person-first language is used in this manuscript, consistent with practice among autistic self-advocates (Brown 2011).

[2]Researchers and female self-advocates have used the terms “masking” and “camouflaging” to describe the phenomenon of autistic women and girls being missed by current diagnostic procedures. The authors chose the term camouflaging, and placed it in quotes for its initial use, to describe this phenomenon which can occur both when autistic women/girls actively seek to hide social communication difficulties, as well as when clinicians fail to accurately diagnose them, due to societal expectations that are believed by many to result in diagnostic bias.

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higher mutational burden, including a higher frequency of both copy number variants (CNVs) and single-nucleotide variants (SNVs) (Gilman et al. 2011; Jacquemont et al. 2014). These findings suggest that there may be a higher genetic threshold for ASD in females relative to males. Hormonal effects have also been hypothesized to play a role in the etiology of ASD and in the observed sex differences in prevalence. Elevated levels of fetal testosterone have been implicated in the development of ASD, and there have been some findings of higher levels of testosterone in autistic females as compared to typically developing females (Auyeung et al. 2009; Bejerot et al. 2012; Knickmeyer and Baron-Cohen 2006). Although studies of animal models of ASD have not yet placed a strong emphasis on investigating sex differences, some of these studies have reported lower rates of autistic behaviors in female animal models as compared to males (e.g., Kataoka et al. 2013; Schoch et al. 2017). Although animal models of ASD have obvious limitations, these findings are notable, as it would be difficult to explain sex differences among animal models as resulting from camouflaging or diagnostic bias.

Taken together, the etiological literature suggests that it is unlikely that ASD is equally common among males and females. However, there is growing evidence that current diagnostic procedures may fail to capture the female manifestation of ASD and thus exaggerate the sex imbalance in prevalence rates (Halladay et al. 2015; Kirkovski et al. 2013; Loomes et al. 2017). Females have been found to be diagnosed with ASD at significantly later ages and to experience greater delays in the time from an initial evaluation to receiving a clinical ASD diagnosis (Begeer et al. 2013; Shattuck et al. 2009; Siklos and Kerns 2007). Interestingly, data from the Center for Disease Control's Autism and Developmental Disabilities Monitoring (ADDM) Network show that the sex imbalance in diagnostic rates has grown over time, from approximately 3.5:1 in 2000 to 4.5:1 in 2010 (Boat and Wu 2015). Although the factors driving this phenomenon are not yet fully known, it is notable that this coincides with a period of time in which rates of ASD have been increasing overall, with particular expansion among children without co-occurring intellectual disability (ID) (Boat and Wu 2015). It is also well-established that the sex imbalance in prevalence varies with cognitive ability, with a smaller male to female ratio of approximately 2:1 among individuals with co-occurring ID and a much larger ratio of as much as 6:1 among those with average to above average IQ (Fombonne 2009; Kirkovski et al. 2013; Loomes et al. 2017; Volkmar et al. 1993). This pattern may indicate that as the autism spectrum has expanded to include more individuals without co-occurring ID, females in this group have not been adequately identified.

Some prior studies have also found that even when presenting with comparable levels of socio-communicative impairment females are less likely than males to be diagnosed with ASD and are more likely to be able to "camouflage" their social impairments on performance-based measures (Dworzynski et al. 2012; Lai et al. 2016; Wilson et al. 2016). This is particularly true in the case of females without co-occurring ID (Giarelli et al. 2010; Hiller et al. 2016). Qualitative self-report data have also supported the theory that females may be under-diagnosed, as many females who were diagnosed with ASD late (i.e., in adolescence or adulthood) report that they received a series of inaccurate diagnoses prior to their ASD diagnosis (Bargiela et al. 2016; Cridland et al. 2014; Trubanova et al. 2014). Given this mounting evidence that ASD is not adequately identified in females without co-

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occurring ID, many have theorized that there may be sex differences in the manifestation of autistic traits in this group, which could in turn contribute to diagnostic disparities (Kreiser and White 2014; Lai et al. 2015).

Sex differences in the manifestation of autistic traits have been investigated in a range of studies over the past few decades. Early work in this field generally found that autistic females were more severely impaired than their male counterparts, presenting with lower IQs and more prominent autistic traits (Lord and Schopler 1985; Lord et al. 1982; McLennan et al. 1993; Tsai and Beisler 1983). Subsequent studies have found that overall, particularly after controlling for IQ, there are not significant differences by sex in the degree of social-communication impairment, but that restricted/repetitive behaviors (RRBs) are more prominent in males (Mandy et al. 2012; Pilowsky et al. 1998; Van Wijngaarden-Cremers et al. 2014; Volkmar et al. 1993). However, important sex differences have been identified in the ways in which socio-communicative impairments manifest, particularly among those without co-occurring ID. Autistic females without ID tend to show more developmentally appropriate vocabulary and core language skills than their male counterparts (Halladay et al. 2015; Hiller et al. 2016; Messinger et al. 2015), though not always (Hartley and Sikora 2009). Given that language delays are the most commonly reported first concern among parents of children with ASD (Chawarska et al. 2007), this difference may have important implications for diagnostic timing and accuracy. Autistic females without ID are also more likely to have intact play and imitation skills, which are often considered core impairments in ASD (Kirkovski et al. 2013; Knickmeyer et al. 2008; Lord et al. 1982). Additionally, in contrast to the social isolation classically described among autistic boys, girls are more likely to be described as “clingy” or overly concerned with being liked by peers (Hiller et al. 2016; Kirkovski et al. 2013). Furthermore, some studies have found that parents rate females as being more socially impaired than their male counterparts, even when differences are not apparent on performance-based measures of social-communication skills (Halladay et al. 2015; Holtmann et al. 2007; Kirkovski et al. 2013). Additionally, some authors have noted that sex differences in RRBs may also be driven by clinician bias, as females may have restricted interests in more “normative” content areas (e.g., books, celebrities, animals) (Halladay et al. 2015; Kirkovski et al. 2013). It is also worth noting that prior studies describe patterns of sex differences among males and females identified by currently available measures. As described above, the camouflaging effect may mean that there are some autistic females who are not identified by current measures and thus are excluded from these studies.

Differences in the manifestation of autistic traits have lent support to the theory of camouflaging in autistic females, which hypothesizes that females are able to mask socio-communicative impairments due to increased sensitivity to social pressure to fit in, gendered expectations for social behavior, and strengths in some social-communication skills (Lai et al. 2015, 2016). The camouflaging theory has been supported by qualitative interview data from autistic females (Bargiela et al. 2016; Cridland et al. 2014). A recent quantitative study also supported the camouflaging theory, finding that autistic females displayed greater discrepancies between clinician-rated and self-rated autistic traits and core social cognitive abilities, with females showing less impairment on clinician ratings (Lai et al. 2016). This pattern of findings may indicate that current diagnostic tools are not as well-suited for

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evaluating ASD in females and may lead to a higher rate of false negatives among females. There have been relatively few studies to date examining sex differences among school-age youth in performance on the gold-standard diagnostic measures: the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2001) or its recent revision, the ADOS-2 (Lord et al. 2012) and the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al. 2003), which are both widely used to evaluate ASD traits in both clinical and research settings. The school-age period (i.e., age 6–17) is of critical importance in understanding sex differences among those without co-occurring ID, as many of these individuals, particularly females, are first diagnosed with ASD during this time (Daniels and Mandell 2014; Giarelli et al. 2010). Of the studies identified in our literature review, two reported higher rates of RRBs in males on these measures, consistent with broader findings among autistic individuals (Bölte et al. 2011; Mandy et al. 2012), while two found no sex differences in any of the domains (Holtmann et al. 2007; Mandic-Maravic et al. 2015). Due to the field's heavy reliance on these measures for both clinical diagnosis and research case ascertainment, understanding sex differences on these measures is vital, as this may contribute to diagnostic disparities.

In contrast to the relatively rich literature on sex differences in autistic traits, fewer studies have focused on sex differences in adaptive behavior in autistic individuals. It is well-established that autistic individuals have lower adaptive behavior than their typically developing peers, and that adaptive skills are often well below expectations based on IQ (Bölte and Poustka 2002; Klin et al. 2007; Pugliese et al. 2015; Volkmar et al. 1987). Furthermore, adaptive behavior has been shown to be a stronger predictor of overall well-being than both autistic traits and IQ, making it a critical domain in understanding the daily experience of individuals with ASD (Farley et al. 2009; Kanne et al. 2011). Mixed findings have been reported by the few studies that have examined sex differences in adaptive behavior, with some finding that parents rate autistic females as having lower adaptive skills (Carter et al. 2007; Frazier et al. 2014a; Howe et al. 2015), while others find no differences (Andersson et al. 2013; Banach et al. 2009; Mandic-Maravic et al. 2015; Reinhardt et al. 2015). Notably, all of these studies have included participants both with and without co-occurring ID/cognitive delay, and many used early childhood samples. There has not yet been a specific focus on sex differences in adaptive behavior among individuals without co-occurring ID, among whom sex differences in autistic traits appear to be strongest.

The goal of the present study was to expand upon prior research on sex-based differences in autistic traits in individuals without co-occurring ID who meet criteria for ASD on at least one gold-standard diagnostic measure (the ADOS or ADI-R). We aimed to examine sex differences in autistic traits and adaptive functioning. Based on the requirement that all participants meet criteria on at least one gold-standard diagnostic measures, we predicted that our sample would not detect differences in total scores, but that item-level differences would emerge for specific skills. Specifically, we hypothesized that autistic females would show significantly lower levels of RRBs than males and better play and conversation skills than males on performance-based measures, based on prior findings. Consistent with the camouflaging theory, we expected that despite similar performance on gold-standard diagnostic measures, females would show greater impairments than males in adaptive skills and in parent-report of daily social skills. Furthermore, we hypothesized that sex differences in adaptive skills and parent-report of social skills would be reduced among participants who

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met criteria on both the ADOS and ADI-R relative to participants who met criteria on only one measure. For this study, we focused specifically on school-age youth (ages 6–16) who had been evaluated using Module 3 of the ADOS/ADOS-2 (a play-based and conversation-based assessment of social communication skills and autistic traits), as many children without co-occurring ID, particularly girls, are first diagnosed in the school-age period (Daniels and Mandell 2014; Giarelli et al. 2010).

Methods

Participants

Participants were identified from clinic-based and research-recruited samples at four different sites across the United States: the Center for Autism Spectrum Disorders at Children's National (Rockville, MD), the National Institute of Mental Health Laboratory of Brain and Cognition (Bethesda, MD), the Center for Autism Research at Children's Hospital of Philadelphia (Philadelphia, PA) and research and clinical programs at Virginia Tech, including the Center for Autism Research (Blacksburg, VA). From across these sites, an initial sample of 816 participants (n= 125 females) was identified who had item-level data available on the Module 3 of the ADOS, a full-scale IQ > 70, and met criteria for ASD based on the following: (1) a diagnosis of ASD from a trained clinician based on DSM-IV-TR (American Psychiatric Association 2000) and DSM-5 (American Psychiatric Association 2013) diagnostic criteria, and (2) met ASD criteria on the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2012) or its recent revision, the ADOS-2 (Lord et al. 2012), and/or the Autism Diagnostic Interview-Revised (ADI-R; Rutter et al. 2003). In this sample, approximately 89% (n = 735) participants met criteria on the ADOS/ADOS-2, 78% (n = 636) met criteria on the ADI-R, and 70% (n = 573) met criteria on both measures. As noted above, all met criteria on at least one of these two measures. The authors recognize that requiring participants to meet criteria on one gold-standard measure may limit the generalizability of findings and the likelihood of identifying sex differences on these measures. The goal of the present study was to focus on sex differences within the population of those with ASD who meet criteria commonly used in research to better understand this targeted population. This limitation will be further addressed in the discussion.

From the initial sample of 816 participants, a final matched sample of 228 children (n = 114 females) was created. Participants were matched on full-scale IQ (within five points) and age (within 1 year) using the case-control matching feature ("fuzzy" command) in SPSS 22. The male and female groups selected by this procedure were not statistically different in age or full-scale IQ, which was assessed using a variety of measures, including the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler 2011; n = 39), the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II; Wechsler and Hsiaopin 2011; n= 32), the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler 2003; n = 67), the Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V; Wechsler 2014; n = 10), the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler 2008; n= 1), the Wechsler Preschool and Primary Scales of Intelligence-Fourth Edition (WPPSI-IV; Wechsler 2011; n = 1) and the Differential Ability Scales-Second Edition (DAS-II; Elliot

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2007; $n = 78$). Average age in the matched sample was 10.11 years (SD = 2.16; range 6.0–16.25 years); full-scale IQ fell in the average range overall (M = 101.09, SD = 18.87; range 71–145). There were no significant differences in maternal education ($\chi^2 = 5.51$, *ns*) or ethnic distribution ($\chi^2 = 6.48$, *ns*) by sex (see Table 1).

Measures

Gold-Standard Diagnostic Measures—All participants were assessed using Module 3 of the ADOS (Lord et al. 2001) or its revision, the ADOS-2 (Lord et al. 2012). The ADOS is a play-based and conversation-based assessment of social communication skills and autistic traits, designed to be administered by a trained clinician. Module 3 of the ADOS is designed for children and adolescents with fluent speech. Following administration of the ADOS, the clinician rates the child on several different behaviors (or items), using an ordinal scale, where 0 indicates no evidence of impairment, 1 indicates mild impairment, and 2–3 indicates significant impairment. In the most recent version (the ADOS-2), scores from selected items are then summed to create a Social Affect score and a restricted/repetitive behaviors score. These two summary scores are then totaled to generate a total algorithm score, which is compared to two cutoff scores: one for "Autism" and another for "Autism Spectrum." Although one new item was added to the Module 3 in the ADOS-2, this new item was not included in the total algorithm, and thus all participants were compared using the ADOS-2 algorithm, regardless of the version of the ADOS that was administered. Participants were considered to have met research criteria for ASD on the ADOS/ADOS-2 if their score was at or above the "Autism Spectrum" cutoff of 7. In addition to the diagnostic algorithm, the ADOS-2 also calculates a Comparison Score, which provides a severity ranking of 1–10 (1: minimal-to-no evidence, 10: high) based on the individual's diagnostic algorithm score and age.

The Autism Diagnostic Interview-Revised (ADI-R; Rutter et al. 2003) is a semi-structured diagnostic interview, designed to be administered by a trained clinician with a parent or caregiver. The ADI-R gathers information on both current and historical functioning, focusing on the year between the child's fourth and fifth birthdays. Parent responses to items asking about specific ASD traits are coded on an ordinal scale that parallels the ADOS, where 0 indicates no evidence of impairment, 1 indicates mild impairment, and 2–3 indicates significant impairment. Scores for selected items are then summed to create algorithm scores for four domains: Reciprocal social interaction, communication, Restricted, Repetitive, and Stereotyped Patterns of Behavior, and Abnormalities of Development at or before 36 months. For the present study, the algorithm scores based on historical information (i.e., behaviors between ages 4–5 years) were used because these scores have been determined to best discriminate ASD from non-ASD (Boelte and Poustka 2000). Participants are considered to have met criteria for ASD on the ADI-R if their algorithm scores meet or exceed cutoff criteria in each of the four domains.

Parent-Reported ASD Traits—The Social Responsiveness Scale (SRS; Constantino and Gruber 2005), and its update the Social Responsiveness Scale-2 (SRS-2; Constantino and Gruber 2012), are sex-normed parent-report measures of autistic traits for children ages 4–18. Parents rate their children on several different behaviors, using a Likert scale of 1–4. T-

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scores are generated within five domains of ASD traits: social awareness, social cognition, social motivation, social communication, and restricted/repetitive behaviors, as well as a total score, where higher scores indicate higher levels of autistic traits.

Parent-Reported Adaptive Behavior—Adaptive behavior was assessed using the Vineland Adaptive Behavior Scales, Second Edition, Survey Interview (Vineland-II; Sparrow et al. 2005). The Vineland-II is a sex-normed and age-normed measure that assesses adaptive behavior skills in individuals from birth to age 90 and divides adaptive behavior into three broad domains in this age group: communication skills, daily living skills, and social skills. Standard scores are generated for each domain, as well as for the adaptive behavior composite (ABC).

Data Analysis

Item-level data were available for all participants on the ADOS. Complete data (i.e., domain scores) were available for 85% (n= 193 total, n = 95 females) of the matched sample on the ADI-R, for 80% (n= 182 total, n= 91 females) of the sample on the SRS, and for 76% (n= 174 total, n= 77 females) of the sample on the Vineland-II. Individuals for whom the data were not available on particular measures were excluded from those specific analyses, such that the samples for these analyses were not statistically matched. However, there were still no statistical differences in age (p values range .267–.624) or IQ (p values range .495–.916) by sex among these reduced samples. To evaluate our hypothesis that males and females would show similar levels of ASD traits on gold-standard measures by sex, Pearson Chi square analyses were used to assess sex differences in rates of meeting ASD criteria on the ADOS and the ADI-R, and t tests were used to assess sex differences in the ADOS Comparison Score (an indicator of number of ASD traits). Pearson Chi square analyses of item-level data on the ADOS were used to evaluate the hypothesis that females would show fewer RRBs and better conversation and play skills than males. Additional exploratory analyses using Pearson chi-squares were then undertaken to investigate other potential sex differences in item-level performance on the ADOS. Effect sizes for Chi square analyses were calculated using Cramer's phi (Φ) coefficient; by convention, Φ = 0.10 is interpreted as a small effect size, Φ = 0.30 as a medium effect size, and Φ = 0.50 is considered a large effect (Cohen 1988). One-way ANOVAs were used to analyze differences by sex in scores on both the SRS and the Vineland-II, evaluating the hypothesis that females would show greater levels of parent-reported difficulty with social and adaptive skills. Two-way ANOVAs were used to assess the hypothesis that participants who met diagnostic criteria on both the ADOS and ADI-R would show fewer sex differences than participants meeting on only one measure (the ADOS). Effect sizes for ANOVAs were calculated using Cohen's d. The false discovery rate procedure (Benjamini and Hochberg 1995) was used to control for Type I error rate in all analyses.

Results

Sex Differences on Gold-Standard Diagnostic Measures

Overall, approximately 90% of females and 94% of males in this sample met "Autism Spectrum" cutoff criteria on the ADOS/ADOS-2, using the ADOS-2 diagnostic algorithm

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(Pearson χ^2 = 0.965, *ns*; Table 1). Consistent with our hypotheses, there were no significant sex differences in the ADOS-2 Comparison Score (t= 0.830, *ns*; Table 1), indicating similar levels of overall autistic traits across sexes. Similarly, there were no significant differences in likelihood of meeting ASD criteria on the ADI-R by sex (Pearson χ^2 = 0.208, *ns*), with 72.63% of females (n= 69) and 75.51% (n = 74) of males meeting criteria. Performance on gold-standard measures was further explored through item-level analyses of the ADOS. Consistent with our hypotheses, females showed less evidence of RRBs, as evidenced by lower scores on the Excessive Interests item of the ADOS (Pearson χ^2= 5.799, p = .055), with a small effect size (Φ = 0.159). Contrary to hypotheses, no significant sex differences were found in play skills (Imagination/Creativity, Pearson χ^2 = 0.971, *ns*) or conversation skills (Conversation, Pearson χ^2= 2.483, *ns*) on the ADOS. Females were less likely to direct a range of facial expressions towards the examiner during the ADOS (Facial Expressions, Pearson χ^2= 9.049, p = .01), with a small effect size (Φ = 0.199). At the trend level, females out-performed males in identifying and sharing emotions with others (Empathy, Pearson χ^2= 4.754, p = .09), with a small effect size (Φ = 0.144), and showed lower rates of hyperactivity (Overactivity, Pearson χ^2= 5.535, p = .063), with a small effect size (Φ = 0.156). However, none of these findings survived corrections for multiple comparisons, indicating that overall, performance on the ADOS was similar between males and females.

Due to the unexpected finding of a relatively low percentage of participants overall meeting ASD cutoff criteria on ADI-R (74.09%, n = 143 of 193 available), post-hoc analyses were undertaken to further explore this finding. Among the 193 participants who received the ADI-R, sociodemographic characteristics were consistent with the full sample. Logistic regression was used to determine whether domain scores related differentially to likelihood of meeting criteria on the ADI-R, with meeting ASD criteria on the ADI-R as the binary outcome, and scores on each of the four domains (reciprocal social interaction, communication, restricted/repetitive behaviors, early developmental abnormalities) as the predictors. To meet criteria on the ADI-R algorithm, an individual must obtain a score of 10 out of 30 possible points on the Reciprocal Social Interaction domain (33%), 8 out of 26 on the communication domain (31%), 3 out of 12 on the restricted/repetitive behaviors domain (25%) and 1 out of 5 on the Early Developmental Abnormalities domain (20%). Thus, although the point totals differ by domain, the proportion of points required to pass each domain is roughly equal, with the Early Developmental Abnormalities domain as the “easiest” criterion to pass by proportion. In the full sample, all domain scores were significant predictors of meeting criteria on the ADI-R, as expected, with the exception of the communication domain (Table 2). Early Developmental Abnormalities were the strongest overall by sex, Early Developmental Abnormalities was the only domain to significantly predict meeting ADI-R criteria overall among females. Among males, the communication and restricted/repetitive behaviors domains were both significant predictors of meeting ADI-R criteria.

Because early developmental delays are predictive of later intellectual ability, and this domain emerged as a key predictor for females, an additional exploratory analysis was conducted to examine whether IQ at the time of the ADOS related to likelihood of meeting criteria on the ADI-R. A hierarchical logistic regression was performed to predict meeting

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ADI-R criteria, with all four ADI-R domain scores entered in the first block, and sex, full-scale IQ, and the interaction of sex and IQ in the next block. After accounting for the effects of domain scores, sex significantly predicted likelihood of meeting criteria on the ADI-R (β = − 4.46, Wald criterion = 3.82, p = .051), such that females were significantly less likely to meet criteria. The interaction of sex and IQ was also significant (β = 0.041, Wald criterion = 3.58, p = .058), such that females with higher IQs were the least likely to meet criteria on the ADI-R.

Parent Report of Daily Functioning

One-way ANOVAs revealed significant differences on all five domains of the SRS. Females were rated as having significantly stronger autistic traits across all domains, with effect sizes ranging from small to large (Table 3; Fig. 1). On the Vineland-II, one-way ANOVAs (Table 3; Fig. 2) revealed that females had significantly lower daily living skills [F(1,172) = 4.77, p = .03] than males, with a small effect size (Cohen's d = 0.335). Social skills were also more impaired in females, at the trend level [F(1,172) = 2.93, p= .09]. No significant differences were found for communication skills. All findings on the SRS-2 retained significance after controlling for multiple comparisons, as well as the differences on the Vineland-II daily living scale. Since both the SRS and the Vineland-II are sex-normed measures, this pattern of findings indicates that autistic females were rated as more impaired with respect to typically developing females than autistic males were when compared to typically developing males. Raw score data were not available for all participants to assess whether the significant difference in normed scores corresponded to a significant difference in raw scores as well, which would indicate that autistic females showed stronger autistic traits and greater adaptive impairments than autistic males. However, when the sample mean was compared to the normative tables to determine the corresponding raw score for each scale, the female raw score was consistently higher across all subscales (Table 4). Although standard deviations could not be calculated to examine this statistically, this pattern of findings is consistent with hypotheses that autistic females would show stronger autistic traits and greater adaptive skill impairments than autistic males. For the Vineland-II, the normative table for ages 10:0–10:11 was used, based on the average age of participants. The SRS is not age-normed. The raw score associated with the mean score for females was higher across all subscales of the SRS and lower across all subscales of the Vineland-II, consistent with hypotheses.

To assess the hypothesis that participants who met diagnostic criteria on both the ADOS and the ADI-R would show fewer sex differences than those meeting criteria on only one measure, participants who had received both measures (n = 193) were then divided into three groups, based on whether they met diagnostic criteria on ADOS only (n= 22 males, 23 females), on ADI-R only (n = 2 males, 8 females), or on both measures (n = 72 males, 62 females). This distribution did not differ significantly by sex (Pearson χ^2= 4.322, p = .115). Given the very small number of participants who met criteria on the ADI-R only, further analyses focused on comparison of those who met on ADOS only versus those who met on both measures. Two-way ANOVAs were used to analyze the effects of sex and number of measures on which ASD criteria were met (i.e., both the ADOS and ADI-R versus the ADOS alone) on parent-reported functioning. For the SRS, results were largely consistent

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with results of the one-way ANOVAs (Table 4). There was a main effect of sex on all domains of the SRS, with the exception of social motivation. The effects of meeting criteria on one versus two measures were significant for the restricted/repetitive behaviors domain and at the trend level for the Social Cognition domain, such that participants who met criteria on both measures were rated as having stronger autistic traits in these domains. There were no significant interaction effects on any items. On the Vineland-II, results were also generally consistent with the one-way ANOVAs. For the daily living skills domain, there was a significant main effect of meeting criteria on one versus two measures, such that participants who met on both the ADOS and the ADI-R had lower skills on average. There was also a main effect of sex at the trend level, with females showing lower skills. The interaction was not significant. On the Social domain, there was a significant main effect of sex, such that females had lower skills on average. The main effect of meeting ASD criteria on one versus two measures was not significant; however, there was an interaction effect at the trend level, such that there were greater sex differences among those who met on the ADOS only, consistent with our hypotheses. On the communication domain, there was a trend-level effect of meeting criteria on one versus two measures, such that participants who met on both measures showed greater impairments. The main effect of sex and the interaction effect were both non-significant. Again, controlling for multiple comparisons retained all significant findings on both the SRS and the Vineland-II (Table 5).

Discussion

This study was the first investigation of sex differences in both adaptive behavior and daily social skills among school-age youth diagnosed with ASD without co-occurring ID. Results supported our hypotheses, based on the camouflaging theory, that autistic females would be more impaired on parent-reported measures of adaptive behavior and daily social functioning, despite similar overall performance on gold-standard diagnostic measures. Females were rated as having stronger autistic traits by their parents than their male counterparts in comparison to their typically developing peers. Additionally, autistic females were rated as having lower daily living skills than autistic males, when compared to a normative sample. Although statistical analysis of raw scores was not possible, corresponding raw score data were also indicative of stronger autistic traits and lower daily living skills among autistic females than autistic males. Overall, this pattern of findings suggests that the females who ultimately met criteria on gold-standard diagnostic measures were more severely affected in real-world settings than their male counterparts. This may be an indication that females required a stronger manifestation of autistic traits in order to meet criteria on gold-standard measures. However, it is also possible that parents respond to these measures differently when reporting about their daughters as compared to their sons. Parents may expect girls to be more socially competent, for example, and thus see their daughters as more impaired by social differences due to their higher expectations. However, this possibility seems less likely, given that both the Vineland-II and the SRS are sex-normed, and thus should already account for societal differences in parental expectations. It is also notable that both the Vineland-II and the SRS are sex-normed measures, using continuous rating scales, while the ADOS and ADI-R are best conceptualized as symptom-count measures, which were developed on predominantly male samples without sex-specific

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cutoffs or algorithms. The use of sex norms likely makes the SRS and the Vineland more sensitive to possible sex differences. Additionally, the use of the continuous rating scale in the SRS, as opposed to the ordinal scale of the ADOS, allows for greater variability in scores, and potentially a stronger ability to capture more subtle sex-based differences in the intensity of autistic traits. However, the findings on the separate sub-scales of the SRS should be interpreted with some caution, as there is stronger support for the two-factor structure in the SRS-2 (social-communication index and restricted/repetitive behaviors scale) than for the five-factor structure utilized in both the SRS and SRS-2 (Frazier et al. 2014b). There are also indications that non-ASD clinical samples may also have elevated scores on the SRS (Pine et al. 2008; Yerys et al. 2009), and thus it is possible that these findings are not uniquely indicative of stronger autistic traits, but rather of greater clinical impairment overall.

The findings also raise questions about the sensitivity of gold standard autism diagnostic tools for females. A notable minority of this sample failed to meet diagnostic criteria on the ADI-R, despite meeting ASD criteria on both the ADOS-2 algorithm and in the judgment of an experienced clinician. Females with higher cognitive ability were at the greatest risk of failing to meet ADI-R criteria. Notably, analyses revealed that a failure to show early developmental differences was the strongest predictor of failing to meet ADI-R criteria in the sample, particularly among females, and that this was particularly true for females with higher intellectual ability. This result raises concerns that individuals without ID of both sexes, but particularly females, may not receive accurate clinical diagnoses and may also be unnecessarily excluded from research trials if inclusion criteria are tightly tethered to exceeding threshold on these standardized tools. Of note, early developmental delays have been removed from the clinical diagnostic criteria for ASD in the DSM-5; the diagnostic algorithm of the ADI-R may also need to be updated to be consistent with the DSM-5. Moreover, if the females in this sample represent only the girls with the strongest autistic traits, this necessarily raises the question of whether there are girls with less intense autistic traits who may not meet strict cutoff criteria on gold-standard measures, but who nonetheless meet DSM-5 criteria for ASD. The variability in the sex ratio in ASD by cognitive ability, from 2:1 among those with ID to as high as 6:1 among those without ID, also raises the question of whether females with higher cognitive abilities may be missed, consistent with the findings in the present sample that females were less likely to meet ADI-R criteria as intellectual ability increased. There is no clear theoretical reason why the female protective effect would be stronger as cognitive ability increases, and thus it seems likely that current diagnostic procedures fail to adequately identify females with higher intellectual abilities. There are indications that this disparity impacts even early screening procedures, as prior studies have found that parents' first concerns differ by sex (Hiller et al. 2016; Little et al. 2016), and at least one recent study has found sex differences at the item-level on the Modified Checklist for Autism in Toddlers (M-CHAT), one of the most widely-used early ASD screening instruments (Øien et al. 2017).

The findings in this study provide an initial indication of potential sex differences in the profile of autistic traits; however, additional research is needed to further investigate the manifestation and experience of ASD across the gender spectrum. Further evaluation of the camouflaging hypothesis is also needed to understand if this is an important factor in

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explaining sex differences in diagnostic rates. Cognitive interviewing techniques (Beatty and Willis 2007) are a well-established methodology for gathering additional information from participants about how they understand and respond to psychological surveys and measures. Use of cognitive interviewing with the ADOS will allow researchers to explore and better understand the ways in which autistic individuals experience the ADOS, as well as how well they feel the ADOS captures their daily social functioning. This type of structured, qualitative data provides valuable information to guide our understanding of the effectiveness of our measures with this population, which may not be well characterized currently. It will also be important to explore diagnostic pathways in future research. As described above, autistic females have been found to be vulnerable to inaccurate and delayed diagnoses. Researchers have begun paying increased attention to female self-advocates, who have described their experiences of being misdiagnosed for several years prior to obtaining a diagnosis of ASD, and the deleterious effects that inappropriate behavioral, educational, and psychiatric treatments have had on their lives (Bargiela et al. 2016). We need more information about the inaccurate diagnoses that autistic females most often receive prior to being accurately diagnosed, as well as information about how they are ultimately able to obtain a diagnosis of ASD, in order to understand the limitations of our current diagnostic methodologies and pathways to treatment. It will also be important to evaluate sex differences in other age groups, particularly at younger ages, in light of the ADI-R findings in this sample. Longitudinal studies on children who eventually develop ASD, who develop other clinical conditions (e.g., ADHD, anxiety), and of typically developing children are also needed to study developmental pathways over time, to understand when and how males and females begin to manifest autistic traits differently. Longitudinal studies could also provide prospective data on the potential effects of later diagnosis on females' development and well-being (e.g., missed opportunities for early intervention and supports).

This study was limited, as are most studies in the field, by its reliance on the ADOS and ADI-R for case ascertainment. Some authors investigating sex differences have noted that using stringent cutoff scores on standardized measures as inclusion criteria may overly restrict our samples, limiting our ability to capture true sex differences in the manifestation of ASD (e.g., Lai et al. 2016). Having been developed with a predominantly male sample, the ADOS and the ADI-R likely are best at capturing autistic traits as they are most commonly manifested in males. Thus, females currently included in studies like this one may be those with autistic trait profiles that are closest to the prototypical male profile of ASD. Autistic females who show a different pattern of autistic traits or who evidence less readily apparent socio-communicative impairments may not be appropriately captured by currently available diagnostic tools. It is quite possible that there exists a group of autistic females who do not fit the "classic" (i.e., male) profile of ASD, and who are often able to mask their autistic traits, and thus are never identified and never receive appropriate supports. A broader sampling of autistic females, who may not meet criteria on gold-standard measures but do meet DSM-5 criteria, would likely yield greater sex differences. We assert that the over-reliance on these measures in research trials, including in the present study, creates a self-perpetuating cycle, by which females whose autistic traits may not align with the ADOS and ADI-R, or who may be able to "pass" an ADOS, are excluded from research. Researchers then fail to find sex differences in their studies because the very

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females who we are most interested in studying cannot be included. While the ADOS and ADI-R are powerful tools, strict adherence to these measures as the only acceptable way of validating an ASD diagnosis inherently restricts our research samples and limits our ability to understand sex differences in ASD. Because research informs clinical practice, this emphasis on the ADOS/ADI-R may also lead to an over-reliance on these measures among clinicians, such that females who do not meet criteria on these measures are never diagnosed, and thus do not gain access to valuable services and appropriate interventions. Innovative methodologies are needed to develop reliable and valid methods of accurately identifying these autistic girls and women to enable access to needed clinical services and participation in research.

It should also be noted that this study investigated sex-based differences in ASD, as defined by biological sex assigned at birth. However, there are higher rates of gender variance in autistic individuals (Strang et al. 2014). Although biological sex traits may drive differences in the manifestation of autistic traits, gender identity will almost certainly influence the manifestation of autistic traits as well. Future research needs to consider not only sex-based differences, but also the role that gender identity, including gender non-conformity, may play in the manifestation of ASD.

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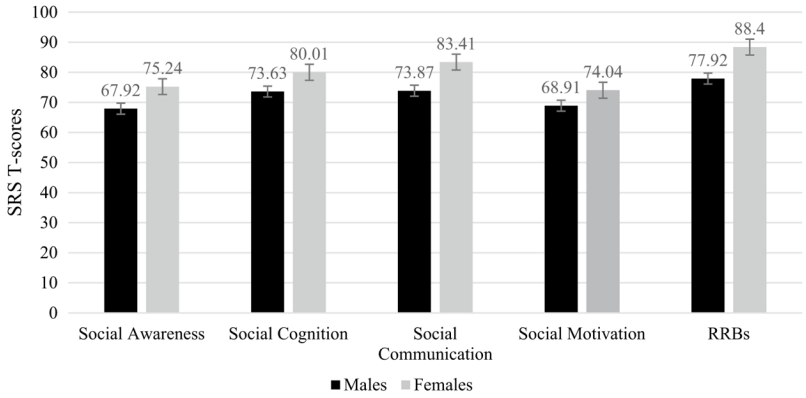

Fig. 1.

Sex differences in parent-reported autistic traits on the Social Responsiveness Scale. Note: results shown with standard error bars

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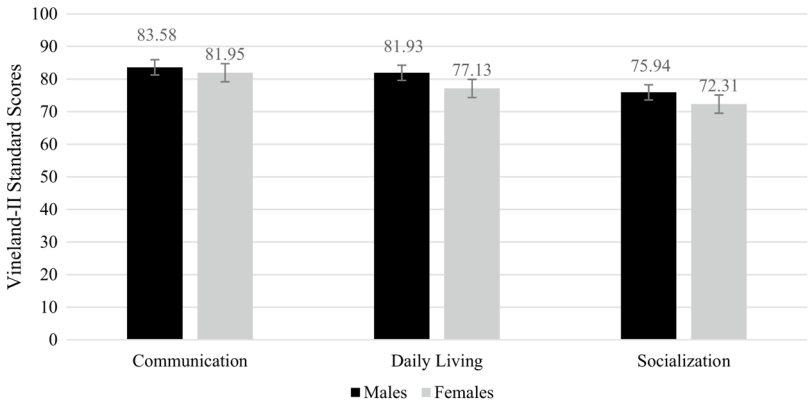

Fig. 2.

Sex differences in parent-reported adaptive functioning on the Vineland-II Adaptive Behavior Scales. Note: results shown with standard error bars

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Table 1

Demographics

	Males (*N* = 114)	Females (*N* = 114)	Statistic, p value
Maternal education			χ^2= 5.51 (*ns*)
Graduate degree	38	35	
College degree	30	34	
Associate's degree/partial college	19	7	
High school diploma	5	5	
Partial high school	5	3	
Other/unknown	17	30	
Race			χ^2= 6.48 (*ns*)
White	88	79	
Black	4	12	
Asian	3	7	
Latino/a	6	6	
Other/unknown	13	10	
Age	10.12 (2.15)	10.11 (2.19)	*t* = 0.025 (*ns*)
Full-scale IQ (mean/SD)	101.03 (18.67)	101.16 (19.14)	*t* = − 0.053 (*ns*)
ADOS-2 (*N*)	114	114	
ADOS-2: overall (mean/SD)	13.40 (5.51)	12.60 (4.97)	n/a
ADOS-2: social affect (mean/SD)	10.07 (4.57)	9.76 (4.27)	n/a
ADOS-2: restricted/repetitive behavior (mean/SD)	3.33 (2.13)	2.83 (1.88)	n/a
ADOS-2: comparison score (mean/SD)	7.37 (1.98)	7.14 (2.17)	0.830 (*ns*)
ADI-R (*N*)	99	96	
ADI-R: reciprocal social interaction (mean/SD)	17.79 (5.82)	17.86 (5.54)	n/a
ADI-R: communication (mean/SD)	14.90 (4.46)	14.94 (4.81)	n/a
ADI-R: restricted/repetitive behavior (mean/SD)	5.55 (2.32)	5.50 (2.66)	n/a

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Table 2

Logistic regression of Autism Diagnostic Interview-Revised

	B	Wald criterion	*p* value	Exp. (β)
Total sample				
Reciprocal social interaction	0.107	4.787	.029	1.113
Communication	0.105	2.683	.101	1.111
Restricted/repetitive behavior	0.229	6.961	.008	1.258
Abnormal development	0.464	9.215	.002	1.591
Females only				
Reciprocal social interaction	0.114	2.311	.128	1.121
Communication	0.030	0.112	.738	1.030
Restricted/repetitive behavior	0.178	2.889	.089	1.195
Abnormal development	0.515	6.597	.010	1.673
Males only				
Reciprocal social interaction	0.125	3.182	.074	1.133
Communication	0.208	4.323	.038	1.232
Restricted/repetitive behavior	0.289	3.659	.056	1.335
Abnormal development	0.405	2.585	.108	1.499

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Table 3

Parent report of daily functioning

Social Responsiveness Scale (T-scores)	**Males** **M (SD)** ***N* = 91**	**Females** **M (SD)** ***N* = 91**	***F* (1,180)/*p* value**	**Cohen's *d***
Social awareness	67.92 (13.64)	75.24 (12.32)	14.425 ($p = .0001$)	0.566
Social cognition	73.63 (13.05)	80.01 (13.58)	10.451 ($p = .001$)	0.482
Social communication	73.87 (12.72)	83.41 (13.56)	23.958 ($p = .0001$)	0.730
Social motivation	68.91 (13.93)	74.04 (14.93)	5.745 ($p = .02$)	0.357
Autistic mannerisms/RRBs	77.92 (15.85)	88.40 (17.51)	17.895 ($p = .0001$)	0.631
Vineland Adaptive Behavior Scales-II (standard scores)	Males M (SD)	Females M (SD)	$F(1, 172)/p$ value	Cohen's *d*
	N = 97	*N* = 77		
Communication	83.58 (14.04)	81.95 (14.47)	0.563 (*ns*)	0.115
Daily living	81.93 (14.13)	77.13 (14.70)	4.77 ($p = .03$)	0.335
Socialization	75.94 (14.70)	72.31 (12.59)	2.93 ($p = .09$)	0.263

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Table 4

Raw scores corresponding to sample means by sex

Social Responsiveness Scale	**Males T-score mean**	**Males corresponding raw score**	**Females T-score mean**	**Females corresponding raw score**
Social awareness	67.92	11	75.24	13
Social cognition	73.63	19	80.01	21
Social communication	73.87	33	83.41	38
Social motivation	68.91	15	74.04	16
Autistic mannerisms/RRBs	77.92	21	88.40	23
Vineland Adaptive Behavior Scales-II	Males standard score mean	Males corresponding raw score	Females standard score mean	Females corresponding raw score
Communication	83.58	37	81.95	36
Daily living	81.93	37	77.13	34
Socialization	75.94	32	72.31	30

Determination of raw scores was performed by rounding T-scores and standard scores to nearest whole number, following usual conventions (< 0.5: round down, > 0.5: round up). When the exact T-score mean did not appear in the normative table, the nearest T-score below the rounded mean was used and the nearest Standard Score above the mean was used, for conservative estimation (i.e. assuming weaker autistic traits and higher adaptive skills)

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Table 5

Two-way ANOVAs of parent-reported daily functioning by sex and diagnostic criteria met

	Main effect of sex	Main effect of diagnostic criteria (ADOS only vs. ADOS + ADI-R)	Interaction effect
Social Responsiveness Scale			
Social awareness	$F(1,143) = 10.166$, $p = .002$	$F(1,143) = 1.089$, *ns*	$F(1,143) = 0.011$, *ns*
Social cognition	$F(1,143) = 9.382$, $p = .003$	$F(1,143) = 2.910$, $p = .090$	$F(1,143) = 0.262$, *ns*
Social communication	$F(1,143) = 12.634$, $p = .001$	$F(1,143) = 1.870$, *ns*	$F(1,143) = 0.649$, *ns*
Social motivation	$F(1,143) = 1.507$, *ns*	$F(1,143) = 0.676$, *ns*	$F(1,143) = 0.936$, *ns*
Autistic mannerisms/RRB	$F(1,143) = 6.774$, $p = .010$	$F(1,143) = 4.732$, $p = .031$	$F(1,143) = 1.171$, *ns*
Vineland-II			
Communication	$F(1,138) = 1.581$, *ns*	$F(1,138) = 3.249$, *ns*	$F(1,138) = 0.360$, *ns*
Daily living	$F(1,138) = 3.118$, $p = .080$	$F(1,138) = 4.182$, $p = .043$	$F(1,138) = 0.157$, *ns*
Socialization	$F(1,138) = 5.291$, $p = .023$	$F(1,138) = 1.609$, *ns*	$F(1,138) = 3.070$, $p = .082$