Gender Differences in Autism Spectrum Disorders: Divergence Among Specific Core Symptoms

Anita Beggiato, Hugo Peyre, Anna Maruani, Isabelle Scheid, Maria Rastam, Frederique Amsellem, Carina I. Gillberg, Marion Leboyer, Thomas Bourgeron, Christopher Gillberg, and Richard Delorme

Community-based studies have consistently shown a sex ratio heavily skewed towards males in autism spectrum disorders (ASD). The factors underlying this predominance of males are largely unknown, but the way girls score on standardized categorical diagnostic tools might account for the underrecognition of ASD in girls. Despite the existence of different norms for boys and girls with ASD on several major screening tests, the algorithm of the Autism Diagnosis Interview-Revised (ADI-R) has not been reformulated. The aim of our study was to investigate which ADI-R items discriminate between males and females, and to evaluate their weighting in the final diagnosis of autism. We then conducted discriminant analysis (DA) on a sample of 594 probands including 129 females with ASD, recruited by the Paris Autism Research International Sibpair (PARIS) Study. A replication analysis was run on an independent sample of 1716 probands including 338 females with ASD, recruited through the Autism Genetics Resource Exchange (AGRE) program. Entering the raw scores for all ADI-R items as independent variables, the DA correctly classified 78.9% of males and 72.9% of females ($P < 0.001$) in the PARIS cohort, and 72.2% of males and 68.3% of females ($P < 0.0001$) in the AGRE cohort. Among the items extracted by the stepwise DA, four belonged to the ADI-R algorithm used for the final diagnosis of ASD. In conclusion, several items of the ADI-R that are taken into account in the diagnosis of autism significantly differentiates between males and females. The potential gender bias thus induced may participate in the underestimation of the prevalence of ASD in females. *Autism Res* 2016, 00: 000–000. © 2016 International Society for Autism Research, Wiley Periodicals, Inc.

**Keywords:** autism spectrum disorders; sex; gender; autism diagnosis interview-revised

**Introduction**

Autism spectrum disorders (ASD) are disabling developmental disorders characterized by aberrations in the domain of social communication and stereotyped or repetitive behavioral patterns, with a prevalence of about 1% in the general population [Baird et al., 2006]. Beneath this unifying definition lies an extreme degree of clinical heterogeneity, ranging from mild to severe impairments. Community-based studies has shown for a longtime a sex ratio heavily skewed towards males, 4 to 1 across the entire spectrum, rising to 8 to 1 of average intelligent patients [Fombonne, 2003]. Although this asymmetry in the male-female ratio has been known for many years, the underlying factors remain largely unknown and this proportion is actually broadly known for many years, the underlying factors remain largely unknown and this proportion is actually broadly revised [Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015]. While the disproportionately high rate of ASD in males has usually been ascribed to either a genetic [Mandy et al., 2011] or a sex-hormone-related etiology [Cicchetti, Lord, Koenig, Klin, & Volkmar, 2008], cognitive or neuroanatomical factors could also play a role [Constantino, Zhang, Frazier, Abbacchi, & Law, 2010]. Moreover, the difficulty in assessing symptoms of autism in females may contribute to a mis- or under-diagnosis of ASD in these patients [Kothari, Skuse, Wakefield, & Micali, 2013].

Many studies suggest that autistic symptoms differ according to gender [Mandy et al., 2011]. For example, boys with ASD appear more impaired than girls in terms of early social development and have a higher reported rate of restrictive repetitive behaviors [Lai et al., 2015; Supekar, & Menon, 2015; Szatmari et al., 2012], suggesting a need for gender-specific items or norms for boys and girls with ASD [Baron-Cohen et al., 2009; Kopp et al., 2011]. However, the effect size of these differences...
seems small and not clinically relevant [Zwaigenbaum et al., 2012] leading the DSM IV-TR or DSM-5 criteria (APA) to consider that the core symptoms of ASD are identical in males and females. Such conclusions were based on screening or diagnostic tools developed and validated mostly in male subjects [Tadevosyan-Leyfer et al., 2003]. Thus, males are more prone to present with symptoms detected with such tools, and supporting the possibility that the rate of ASD might be underestimated in girls, thereby skewing the male/female ratio [Baron-Cohen et al. 2009; Kopp, Beckung, & Gillberg, 2010]. In this line, the most recent epidemiological studies—specifically based on general and nationwide population—reported that the ratio between male and female could be weaker than previously suggested with a range of approximately 3:1 male:female [Hinkka-Yli-Salomaki et al., 2014; Jensen, Steinhausen, & Lauritsen, 2014; Kim et al., 2011; Semaundsen, Magnusson, Georgsdottir, Eglisson, & Rafnsson, 2013] and a lack of association between gender ratio and intellectual disability (ID) [Irding et al., 2012; Mattila et al., 2011], while clinical or school based-population studies reported a wider predominance of boys over girls (5:1) [Hiller, Young, & Weber, 2014]. A longitudinal study of high-risk individuals also found a lower relative risk of ASD in males than in females, as well as limited gender differences in phenotypical features such as symptom severity, intellectual ability and adaptive skills [Zwaigenbaum et al., 2012].

Among the widely used diagnostic tools for ASD, the Autism Diagnostic Interview-Revised Version: Score (ADI-R) [Lord, Rutter, & Le Couteur, 1994] does not take into account the variability of autistic symptoms by gender, and may thus be unable to detect subtle gender-specific symptoms. Indeed, gender differences were not taken into account in the construction and the validation of ADI [Le Couteur et al., 1989] and ADI revised version [Lord et al., 1994]. Only the intellectual impairment was considered in the norming samples with the aim to discriminate autistic from nonautistic subjects with intellectual deficit. For example, the use of quantitative criteria based on the total score on the Social Responsiveness Scale, rather than using categorically defined diagnoses, leads to improved detection of ASD features in females [Constantino, Zhang, Frazier, Abbacchi, & Law, 2010]. The delayed assessment and diagnosis of ASD in girls is an important issue as it not only contributes to the delay in the initiation of specific therapeutic strategies [Giarelli et al., 2010], but also to the difficulty in identifying specific segregation patterns in multiplex families [Sato et al., 2012].

Against this background, the aim of our study was to investigate how raw scores on ADI-R items might vary according to gender. More specifically we wanted to know to what extent ADI-R symptom profiles discriminated females from males in a large ASD sample. We therefore conducted a discriminant analysis (DA) on 594 probands, including 129 (22%) females with ASD, recruited by the Paris Autism Research International Sib-pair (PARIS) Study. To validate our results, we then ran a similar analysis on an independent sample of 1716 probands (338 (20%) females) with ASD, recruited by the Autism Genetics Resource Exchange (AGRE) Program.

Methods

Samples

The exploratory phase of the study was conducted on a sample of 594 probands (465 males and 129 females) with ASD, recruited by the PARIS consortium at specialized clinical centers in France and Sweden. Diagnosis was based on clinical evaluation by experienced clinicians, using DSM-IV-TR criteria (APA, 2000) and the ADI-R. In multiplex families, only index cases were included in the present analysis in order to ensure unbiased estimates of the coefficients of the correlation matrix. The reliability of the ADI-R scores and diagnosis across centers and raters was verified. Patients were included after a clinical and medical check-up including psychiatric and neuropsychological examinations, standard karyotyping, negative blood test results for Fragile-X, brain imaging and EEG whenever possible. The presence of associated ID was assessed using the Wechsler Intelligence Scale for Children, 3rd or 4th edition, or the Wechsler Preschool and Primary Scale of Intelligence. For patients with moderate to profound ID or those who were non-verbal, cognitive level was estimated using the Psycho-Educational-Profile Revised or Raven’s Progressive Matrices [Steerneman, Muris, Merckelbach, & Willems, 1997].

A replication analysis was conducted on data obtained from the AGRE program [Geschwind et al., 2001]. AGRE enrolled families with more than one child diagnosed with ASD. Experts made the final diagnosis by combining the information from the ADI-R, the ADOS and from clinical records. The procedure leading to the diagnostic consensus is described in the web page of the AGRE Program (http://research.agre.org/program/diag.cfm). The ADI-R score sheets of 1716 individuals (1378 males and 338 females) were downloaded. Only data from the index case of each family, with a positive diagnosis of autism on the ADI-R and with an assessment of his/her cognitive function (either with Raven’s Progressive Matrices or the Stanford-Binet), were included in the replication analysis.

Autism Diagnostic Interview-Revised Version: Score Adjustment

A total of 138 items that were similar or comparable between the two versions (1995 and 2003) of the ADI-R...
were included in the DA. We modified several items of the ADI-R in accordance with previous studies [Tadevosyan-Leyfer et al., 2003] (for details, see Supporting Information Table S1). Specifically, language-related items with a maximum score of 8 (i.e., items not applicable because of insufficient language abilities) were systematically replaced by items with three as the most severe rating. Also, items with a maximum score of 4 were replaced by items with a score of 3 in order to consistently use the 0–3 scale for all items. Scores of up to 7 for some items were also changed to a score of 0–3 depending on the nature of the question and how it reflected severity with respect to that specific item. Scores of 8 or 9 for other items (excluding those from the spoken language subgroup), indicating that the item was not asked about or not applicable, were replaced with blanks to reflect that no information was available for that item. Finally, the mean score of each item replaced blanks across the sample, so that missing values would not contribute to the DA. For items that had both “ever” and “current” ratings, both were entered into the analysis to compensate for missing items and to provide the redundancy necessary for the robustness of our DA. The inclusion of both types of items also helped to discriminate between cases that did or did not show improvement over time.

Data Analyses

The demographic and clinical characteristics of the patients and ADI-R scores were compared between groups using the Student’s t-test and the Fisher X² test for continuous and discrete variables, respectively. All tests were two-tailed with a significance level of \( P \leq 0.05 \). The degree to which ADI-R data predicted whether a patient belonged to the male or female ASD subgroup was ascertained using a linear DA [Green, 1978]. DA estimates membership in a group derived from observed values of several continuous variables. This method estimates a classification of the variables into different groups based on known continuous responses. All variables were first entered together in the analysis, with the prior probability of belonging to a specific group fixed at 0.5. Subsequently, a stepwise discriminant function analysis was performed to determine which ADI-R items were the strongest discriminators between the male and female groups. A threshold of \( F = 3.84 \) (\( P = 0.05 \)) was used to enter variables in the model, and \( F = 2.71 \) (\( P = 0.1 \)) was used to remove variables. The \( F \) value for a variable indicates its statistical significance for discrimination between groups, i.e., it is a measure of the extent to which a variable makes a unique contribution to the prediction of group membership. Finally, standardized canonical function coefficients (SCFC) are given for each variable in each discriminant function. They are used to compare the relative importance of the independent variables. The larger the SCFC, the greater is the contribution of the respective variable to the discrimination between groups. In particular, when SCFC is positive, it implies higher item scores for males than for females and when negative, coefficients have the opposite meaning.

The major estimate of the effect size that we provided in the DA is the percentage of people properly classified in each group. The significance of the observed differences between male and female is estimated by the value of Wilks’ lambda [Green, Salkind, & Akey, 2008].

To confirm the statistical validity of the DA to explore the gender differences in ASD, we conducted an addition exploration using logistic regression. We measured the relationship between gender and the ADI-R extracted variables from the DA in order to estimate the probably of males and females to be properly classified by the logistic regression. In the PARIS ASD group, 16 variables were considered and in the AGRE cohort, 20 variables were included.

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL); figures were created using JMP 9.0 (SAS Inc., Cary, NC).

Results

The demographic characteristics of the PARIS ASD group are summarized in Table 1. Males and females included in the analysis did not differ in terms of age, IQ, or main diagnosis at the time of ADI-R completion. When all 138 ADI-R items were entered as independent variables in the analysis, the DA accurately classified 78.9% of the males and 72.9% of the females (Wilks’ lambda = 0.67, \( F = 195.12, \) df = 138, \( P < 0.001 \), Fig. 1). In order to determine the ADI-R items that were the strongest discriminators between males and females, a stepwise DA was performed. This DA identified 16 variables that accurately classified 71.6% of the males and 65.1% of the females (Wilks’ lambda = 0.84, \( F = 101.31, \) df = 16, \( P < 10^{-4} \)) (Table 2). Among these variables, six are taken into account by the ADI-R algorithm for the diagnosis of autism: one item (“range of facial expressions used to communicate”) indicates qualitative impairments in reciprocal social interaction, two items (“social vocalization,” “imaginative play”) indicate qualitative impairments in communication and three items indicate repetitive and stereotyped behaviors (“unusual preoccupations,” “circumscribed interests,” and “hand and finger mannerisms”). Most of the remaining ADI-R items extracted were related to the domain of repetitive and stereotyped behaviors (“unusual attachments to objects,” “purposive hand movements,” “mid-line hand movements”), and to the
domain of communication impairments (“regression in constructive or imaginative play,” “attention to voice”). An additional item, related to an unusual ability to draw, discriminated between males and females (with females having better skills than males).

To confirm the validity of our results, we conducted a replication analysis with an independent population composed of patients from the AGRE cohort (demographic characteristics in Table 1). Using the same methods, the DA resulted in the accurate classification of 72.2% of the males and 68.3% of the females (Wilks’ lambda = 0.82, F = 320.16, df = 138, P < 10^{-4}, Fig. 2). The stepwise DA extracted 20 variables that led to the accurate classification of 71.6% of the males and 65.1% of the females (Wilks’ lambda = 0.88, F = 225.42, df = 20, P < 10^{-4}, Table 3). Among these items, eleven were included in the diagnostic algorithm. They belonged to the three main dimensions of autism, i.e., social impairments (“range of facial expressions used to communicate”), communication deficits (“nodding,” “head shaking,” “stereotyped utterances” and “delayed echolalia,” “spontaneous imitation of actions” and “imaginative play”) and stereotyped or repetitive behavior patterns (“circumscribed interests,” “unusual preoccupations” and “repetitive use of objects” or “interest in parts of objects”). Interestingly, 6 of the 20 ADI-R items were similarly extracted in the stepwise DA based on the PARIS cohort (Fig. 3): the item evaluating the range of facial expressions used to communicate in the social impairments domain (AGRE: SCFC = 0.209; PARIS: SCFC = 0.285), imaginative play in the communication deficit domain, (AGRE: SCFC = 0.241; PARIS: SCFC = 0.263), and items assessing circumscribed interests and unusual preoccupations, in the domain of repetitive and stereotyped behaviors (AGRE: SCFC = 0.472; PARIS: SCFC = 0.355). The last two items, “self-injury” (AGRE: SCFC = 0.166; PARIS: SCFC = 0.315) and “unusual drawing skills” (AGRE: SCFC = 0.186; PARIS: SCFC = 0.245), were more pronounced in females but were not taken into account by the algorithm.

Finally the statistical validity of the DA to explore the gender differences in ASD was confirm by using a logistic regression approach. The logistic regression conducted in the PARIS ASD group (16 variables; see
Supporting Information Table S2) accurately classified 70.8% of the males and 68.8% of the females. In the AGRE cohort (20 variables; see Supporting Information Table S3), logistic regression accurately classified 73.5% of the males and 72.1% of the females.

**Discussion**

An increasing number of studies, based on large-scale epidemiological or longitudinal data, reports a lack of agreement within the literature regarding sex differences in autism spectrum [Lai et al., 2015]. In particular, the higher prevalence of ASD in males seems to be lower and not dependent to the intellectual ability, at the opposite of what was previously found. However, gender specificity in core autistic symptoms have been strongly suggested in many studies [Hartley, & Sikora, 2009; Mandy et al., 2011; Szatmari et al., 2012] and may affect the ability to identify girls with ASD [Giarelli et al., 2010; Kopp, Beckung, & Gillberg, 2010]. The way girls score on standardized categorical diagnostic instruments might account for the under recognition of ASD in females. Clinicians and researchers increasingly use standardized categorical diagnostic tools (such as the ADI-R) in ASD assessment. If such instruments do not take gender differences in clinical presentation into account in their diagnostic algorithms, this is likely going to contribute to under-recognition of ASD in females.

Given that the ADI-R is currently one of the most commonly used diagnostic tools, we investigated how the raw scores of individual ADI-R items differentiated between males and females. Both in the PARIS and

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### Table 2. Description of Extracted ADI-R Items that are Mostly Involved in the Gender Specificity of Core Autistic Symptoms (PARIS Sample), and Their Discriminant Function Coefficients

<table>
<thead>
<tr>
<th>Item</th>
<th>Item label</th>
<th>Rating time</th>
<th>Item description</th>
<th>ADI-R related domains</th>
<th>ADI-R algorithm sub-domains</th>
<th>Standardized canonical function coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>CRFACEX</td>
<td>Current</td>
<td>Range of facial expressions used to communicate</td>
<td>B</td>
<td>B1</td>
<td>−0.285</td>
</tr>
<tr>
<td>99</td>
<td>ELPLAY</td>
<td>Ever</td>
<td>Regression in constructive or imaginative play</td>
<td>B</td>
<td></td>
<td>0.192</td>
</tr>
<tr>
<td>16</td>
<td>CCHAT</td>
<td>Current</td>
<td>Social vocalization/“chat”</td>
<td>C</td>
<td>C2V</td>
<td>0.432</td>
</tr>
<tr>
<td>34</td>
<td>AVOICE5</td>
<td>Ever</td>
<td>Attention to voice</td>
<td>C</td>
<td>C3V</td>
<td>0.315</td>
</tr>
<tr>
<td>22</td>
<td>EINAPPQ</td>
<td>Ever</td>
<td>Inappropriate questions or statements</td>
<td>C</td>
<td>C3V</td>
<td>−0.252</td>
</tr>
<tr>
<td>63</td>
<td>PLAYS</td>
<td>Ever</td>
<td>Imaginative play</td>
<td>C</td>
<td>C4</td>
<td>0.263</td>
</tr>
<tr>
<td>70</td>
<td>CIRINT</td>
<td>Current</td>
<td>Circumscribed interests</td>
<td>D</td>
<td>D1</td>
<td>0.355</td>
</tr>
<tr>
<td>71</td>
<td>EUNPROC</td>
<td>Ever</td>
<td>Unusual preoccupations</td>
<td>D</td>
<td>D1</td>
<td>0.403</td>
</tr>
<tr>
<td>78</td>
<td>CABINR</td>
<td>Current</td>
<td>Abnormal idiosyncratic negative response to specific sensory stimuli</td>
<td>D</td>
<td></td>
<td>−0.359</td>
</tr>
<tr>
<td>76</td>
<td>CUATT</td>
<td>Current</td>
<td>Unusual attachment to objects</td>
<td>D</td>
<td></td>
<td>−0.306</td>
</tr>
<tr>
<td>82</td>
<td>CMLHAND</td>
<td>Current</td>
<td>Mid-line hand movements</td>
<td>D</td>
<td></td>
<td>−0.299</td>
</tr>
<tr>
<td>21</td>
<td>ELHAND</td>
<td>Ever</td>
<td>Purposive hand movements</td>
<td>D</td>
<td></td>
<td>−0.270</td>
</tr>
<tr>
<td>81</td>
<td>CHFMAN</td>
<td>Current</td>
<td>Hand and finger mannerisms</td>
<td>D</td>
<td></td>
<td>0.264</td>
</tr>
<tr>
<td>73</td>
<td>CCHANGE</td>
<td>Ever</td>
<td>Difficulties with minor changes in subject’s own routines or personal environment</td>
<td>D</td>
<td>D3</td>
<td>0.245</td>
</tr>
<tr>
<td>90</td>
<td>CSLFINJ</td>
<td>Current</td>
<td>Self injury</td>
<td>D</td>
<td></td>
<td>−0.315</td>
</tr>
<tr>
<td>109</td>
<td>CDRAW</td>
<td>Current</td>
<td>Drawing skill (unusually skilled use of perspective or creative approach)</td>
<td>D</td>
<td></td>
<td>−0.245</td>
</tr>
</tbody>
</table>

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*The number of each item refers to the number used in the ADI-R (1995).

*The label of each item refers to the name used in the AGRE database.

Positive coefficients mean that males had higher item scores than females; negative coefficients mean the opposite; B: “social impairments” domain (B1: “failure to use nonverbal behaviors to regulate social interaction” sub-domain); C: “communication deficits” domain (C2V: “relative failure to initiate or sustain conversational interchange” sub-domain; C3V: “stereotyped, repetitive or idiosyncratic speech” sub-domain; C4: “lack of varied spontaneous make-believe or social imitative play” sub-domain); D: “stereotyped or repetitive behavior patterns” domain (D1: “encompassing preoccupation or circumscribed pattern of interest” sub-domain; D3: “stereotyped and repetitive motor mannerisms” sub-domain).
AGRE cohorts, our results suggest that males and females score differently on six items of the ADI-R including four, which account in the diagnosis algorithm for ASD. The “range of facial expressions used to communicate” (from the domain of reciprocal social interactions, where girls scored higher than boys), “imaginative play” (from the domain of communication impairments, where girls have a more imaginative play) and “circumscribed interests” and “unusual preoccupations” (from the domain of repetitive and stereotyped behaviors, less pronounced in girls) consistently differentiated males from females in both cohorts. Since these four items influenced the algorithm scores of the ADI-R, correction factors depending of the sex of the subject should be applied to avoid a gender bias in the diagnosis of ASD when using the ADI-R.

Regarding items that were the best discriminators between males and females in our study, we confirmed the results of previous reports showing less repetitive and stereotyped behaviors in girls than in boys [Baron-Cohen et al., 2009; Knickmeyer, Wheelwright, & Baron-Cohen, 2008; Kopp, Beckung, & Gillberg, 2010; Szatmari et al., 2012]. In the largest of these studies [Szatmari et al., 2012], items related to the insistence on sameness and circumscribed interests dimensions [Lam, Bodfish, & Piven, 2008] differentiated between the two groups. Similarly, items related to circumscribed interests and unusual interests were the main discriminators between males and females in our study. These converging findings should be addressed in future version of the diagnostic algorithm of the ADI-R, so as to make the diagnosis of ASD in girls more consistent with the “typical girl phenotype” of autism. Specifically, the scoring weights of items related to restricted behaviors may be different according to patient’s gender.

Interestingly, the results of our study suggested that some items related to the social communication dimension, specifically “the range of facial expressions used to communicate” and “imaginative play,” might be good discriminators. Imaginative play was also reported as being more severely impaired in boys than in girls in a smaller sample using the ADI [McLennan, Lord, & Schopler, 1993]. The difference in imaginative play is also consistent with a study examining gender-typical play in children with ASD. Girls with ASD engage in more pretend play than boys, suggesting that pretense is relatively preserved in females [Knickmeyer et al., 2008]. Although imaginative play appeared as a discriminant item between gender in our study, we observed that female were more severely affected than males (AGRE: SCFC $-0.209$; PARIS: SCFC $-0.285$). Our results contrast with previous findings [Lord, Schopler, & Revicki, 1982]. Several studies have reported that the prevalence of spontaneous mimicry depends on both gender and autistic traits [Hermans, van Wingen, Bos, Putman, & van Honk, 2009; McIntosh, Reichmann-Decker, Winkielman, & Wilbarger, 2006]: males in the general population exhibit reduced spontaneous mimicry when compared to females; a similar difference has been found between females and males with high scores on the Autism Spectrum Quotient, as well as between females and males with low scores [Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Hermans et al., 2009]. However, the range of facial expressions used to communicate seems extremely variable in male and in female (based on the observed intra-group variability) in both PARIS and AGRE cohorts, with average higher scores in females. The variability was not related to IQ ($r = -0.02$ for PARIS and $r = -0.06$ for AGRE) and factors that may influence this variability not identified.

Our study further reinforces the suggestion of a gender bias in the diagnosis of ASD. In both of our samples, the items that were the strongest discriminators were among those included in the diagnostic algorithm of the ADI-R, which may make females less likely to be identified as having ASD. Some scores from all three ADI-R domains appeared to be gender-dependent: the “range of facial expressions” item is taken into account in the domain of reciprocal social
interactions, the “imaginative play” item scores for communication impairments and both “circumscribed interests” and “unusual preoccupations” items measure repetitive and stereotyped behaviors. Aiming to improve the ability to properly delineate the autism phenotype in girls, gender-specific items or different norms for boys and girls with ASD have been elaborated in quantitative tools such as the Autism Spectrum Screening Questionnaire and the Social Responsiveness Scale [Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Kopp, & Gillberg, 2011]. Our results add to existing evidence gathered in previous studies suggesting

Table 3. Description of Extracted ADI-R Items that are Mostly Involved in the Gender Specificity of Core Autistic Symptoms (AGRE Sample), with Their Discriminant Function Coefficients

<table>
<thead>
<tr>
<th>Itema</th>
<th>Item labelb</th>
<th>Rating time</th>
<th>Item description</th>
<th>ADI-R related domains</th>
<th>ADI-R algorithm sub-domains</th>
<th>Standardized canonical function coefficients c</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>RFACEXS</td>
<td>Ever</td>
<td>Range of facial expressions used to communicate</td>
<td>B</td>
<td>B1</td>
<td>−0.209</td>
</tr>
<tr>
<td>56</td>
<td>CSOCDIS</td>
<td>Current</td>
<td>Social disinhibition</td>
<td>B</td>
<td></td>
<td>−0.215</td>
</tr>
<tr>
<td>14</td>
<td>ARTIFIC5</td>
<td>Ever</td>
<td>Articulation/ pronunciation</td>
<td>C</td>
<td></td>
<td>0.143</td>
</tr>
<tr>
<td>18</td>
<td>CSTEREO</td>
<td>Current</td>
<td>Stereotyped utterances and delayed echolalia</td>
<td>C</td>
<td>C3V</td>
<td>0.377</td>
</tr>
<tr>
<td>18</td>
<td>ESTEREO</td>
<td>Ever</td>
<td>Stereotyped utterances and delayed echolalia</td>
<td>C</td>
<td>C3V</td>
<td>−0.287</td>
</tr>
<tr>
<td>24</td>
<td>CNEOID</td>
<td>Current</td>
<td>Neologisms/idosyncratic language</td>
<td>C</td>
<td>C3V</td>
<td>−0.289</td>
</tr>
<tr>
<td>29</td>
<td>CIMIT</td>
<td>Current</td>
<td>Spontaneous imitation of actions</td>
<td>C</td>
<td>C4</td>
<td>0.325</td>
</tr>
<tr>
<td>63</td>
<td>CPLAY</td>
<td>Current</td>
<td>Imaginative play</td>
<td>C</td>
<td>C4</td>
<td>0.241</td>
</tr>
<tr>
<td>32</td>
<td>NODS</td>
<td>Ever</td>
<td>Nodding</td>
<td>C</td>
<td>C1</td>
<td>−0.179</td>
</tr>
<tr>
<td>33</td>
<td>CHSHAKE</td>
<td>Current</td>
<td>Head shaking</td>
<td>C</td>
<td>C1</td>
<td>0.263</td>
</tr>
<tr>
<td>36</td>
<td>ENOISE</td>
<td>Ever</td>
<td>Undue general sensitivity to noise</td>
<td>D</td>
<td></td>
<td>−0.150</td>
</tr>
<tr>
<td>70</td>
<td>ECIRINT</td>
<td>Ever</td>
<td>Circumscribed interests</td>
<td>D</td>
<td>D1</td>
<td>0.472</td>
</tr>
<tr>
<td>71</td>
<td>EUNPROC</td>
<td>Ever</td>
<td>Unusual preoccupations</td>
<td>D</td>
<td>D1</td>
<td>0.244</td>
</tr>
<tr>
<td>72</td>
<td>EUSEOBJ</td>
<td>Ever</td>
<td>Repetitive use of objects or interest in parts of objects</td>
<td>D</td>
<td>D4</td>
<td>0.428</td>
</tr>
<tr>
<td>90</td>
<td>ESLFINJ</td>
<td>Ever</td>
<td>Self injury</td>
<td></td>
<td></td>
<td>−0.166</td>
</tr>
<tr>
<td>91c</td>
<td>EAGGOTH</td>
<td>Ever</td>
<td>Aggression to non-caretakers or non-family members</td>
<td></td>
<td></td>
<td>0.256</td>
</tr>
<tr>
<td>86</td>
<td>CGAIT</td>
<td>Current</td>
<td>Gait</td>
<td></td>
<td></td>
<td>−0.146</td>
</tr>
<tr>
<td>92</td>
<td>CFAINT</td>
<td>Current</td>
<td>Faints/fits/blackouts</td>
<td></td>
<td></td>
<td>−0.163</td>
</tr>
<tr>
<td>109</td>
<td>CDRAW</td>
<td>Current</td>
<td>Drawing skill (unsually skilled use of perspective or creative approach)</td>
<td></td>
<td></td>
<td>−0.186</td>
</tr>
<tr>
<td>111</td>
<td>CCOMPU</td>
<td>Current</td>
<td>Computational ability (e.g., Mental arithmetic)</td>
<td></td>
<td></td>
<td>0.208</td>
</tr>
</tbody>
</table>

a The number of each item refers to the number used in the ADI-R (1995).

b The label of each item refers to the name used in the AGRE database.

c Positive coefficients mean that males had higher item scores than females; negative coefficients mean the opposite; B: “social impairments” domain (B1: “failure to use nonverbal behaviors to regulate social interaction” sub-domain); C: “communication deficits” domain (C1: “lack of, or delay in, spoken language and failure to compensate through gesture” sub-domain; C3V: “stereotyped, repetitive or idiosyncratic speech” sub-domain; C4: “lack of varied spontaneous make-believe or social imitative play” sub-domain); D: “stereotyped or repetitive behavior patterns” domain (D1: “encompassing preoccupation or circumscribed pattern of interest” sub-domain; D4: “preoccupations with part of objects or non-functional elements of material” sub-domain).
that the algorithm scores of the ADI-R should be re-evaluated in order to take into account the clinical variability in autistic symptoms across males and females.

A caveat to keep in mind is that the gender-specific profile of a patient, based on the ADI-R, may to some extent be the result of a lack of agreement between raters for some items when assessing symptoms in a girl. Indeed, in a study of the reliability of the ADI-R in which seven clinical examiners evaluated a 3-year-old girl, the items “range of facial expressions used to communicate,” “unusual preoccupations” and “repetitive use of objects or interest in parts of objects,” showed very poor reliability (weighted kappa values = 0.25, 0.1, and 0.03, respectively) [Cicchetti et al., 2008]. This contrasts with the results of the first study of reliability of the ADI-R, which was conducted in a mostly male sample (80%), showing good inter-rater reliability for all items (weighted kappa for all pairs of raters exceeded 0.63) [Lord et al., 1994]. This suggests that the difference in scores may be partially driven by a different perception of symptoms depending on the gender of the subject. Another potential bias could be related to the assessment of autistic symptoms with the ADI-R. The presence of a greater social impairment in females with ASD may depend from the parental interpretation of the observed behaviors in their child [Crick, & Zahn-Waxler, 2003]. Using direct observation methods like the ADOS, Holtmann and collaborators [Holtmann, Bölte, & Poustka, 2007] did not reported any discrepancies in autism core features between males and females, even if parental reports showed more social communication impairments in females. Parents may be influenced by the expectation of more social abilities from their daughters than their sons.

One major limitation of our article is the difficulty to bridge the gap between our theoretical findings and their clinical applications. Our study contributes to identify subdomains that are more gender-specific and provides the direction of these differences. With our current analysis, we were not able to determine precisely which and how items should be re-scored depending on gender. Further studies including subjects around the threshold of ASD assessed with standardized methods will provide a gender-neutral ADI-R algorithm. In the specific context of ID, the modification of the ADI algorithm could be less effective to discriminate autistic symptoms from those related to the cognitive deficit. Finally another limitation is that the ADI-R gives an empirically derived algorithm only for the diagnosis of Autism, excluding Asperger and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) individuals (based on DSM-IVTR). Differently from PARIS, the AGRE cohort made a diagnostic classification in which the disorders belonging to the broad spectrum were established combining the ADI-R and other diagnostic instruments such as the ADOS. Thus, the gold-standard diagnostic classification in AGRE may introduce a sex-bias since females are less represented in Asperger or PDD-NOS cohorts.

In conclusion, converging studies show less repetitive and stereotyped behaviors in girls [Supekar, & Menon, 2015], raising concerns about the risk of underestimating ASD in females when using the diagnostic algorithm of the ADI-R. The DSM-5 criteria for ASD may probably reinforce this bias, since diagnosis requires two out of four symptoms of the “restricted and repetitive behaviors” category to be present [Hiller et al., 2014]. In contrast, DSM-IV criteria only required one single symptom from this category for a diagnosis of Asperger’s syndrome or autism, and none for a diagnosis of PDD-NOS. However, sensory sensitivity issues, which are also included under the restricted and

Figure 3. Six ADI-R items were similarly extracted by both stepwise discriminant analyses. The black and grey squares represent standardized canonical function coefficients extracted from the PARIS and the AGRE cohorts, respectively. Positive coefficients mean that males have higher item scores than females; negative coefficients mean the opposite. Four of these items are included in the ADI-R algorithm and count towards the diagnosis of autism: one is used to evaluate social impairments (“range of facial expressions used to communicate” of the ADI-R algorithm, “failure to use nonverbal behaviors to regulate social interaction” sub-domain), one for communication deficits (“imaginative play” of the ADI-R algorithm, “lack of varied spontaneous make-believe or social imitative play” sub-domain) and two for repetitive and stereotyped behaviors (both “circumscribed interests and unusual preoccupations” of ADI-R algorithm, “encompassing preoccupations or circumscribed pattern of interest” sub-domain).
repetitive behaviors category in the DSM-5, were not gender discriminators in our study. In this respect, our results have important implications for tailoring clinical assessment measures of ASD in girls and for diminishing the perceived differences in prevalence between males and females.

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References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Rescoring of the ADI-R Items Included in the Analysis.

**Table S2.** Description of Extracted ADI-R Items that are Mostly Involved in the Gender Specificity of Core Autistic Symptoms (PARIS Sample) Using Discriminant Analysis and Logistic Regression.

**Table S3.** Description of Extracted ADI-R Items that are Mostly Involved in the Gender Specificity of Core Autistic Symptoms (AGRE sample) Using Discriminant Analysis and Logistic Regression.
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