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Gender differences in high-functioning autism: implications in everyday life and clinical settings

Martina Micai[1], Angela Caruso[1], Laura Maria Fatta[1,2], Francesca Fulceri[1], Maria Luisa Scattoni[1]

[1] Research Coordination and Support Service, Italian National Institute of Health, Rome, Italy; [2] Department of Developmental and Social Psychology, Sapienza University of Rome. *Received 4 January 2019; accepted 13 March 2019.*

Summary. Gender differences in autism spectrum disorder have been extensively investigated; however, reviews on gender differences in individuals with high-functioning autism spectrum conditions are still limited. This review summarizes gender differences in intelligence quotient, functional adaptation, executive function, social and cultural expectations, language and pragmatic skills, core symptoms (communication/social interaction, and restricted/repetitive patterns of behavior, interests or activities), neurobiology and their implications on diagnosis and treatment selection. Current literature shows the need to identify precise diagnostic tools that may reduce the gender bias in the diagnosis of autism spectrum disorders. A lack of diagnosis or a misdiagnosis leads to inappropriate treatment that may have negative consequences on the individual's development. Directions for future research focuses are provided and the implications in clinical settings are discussed with the aim of identifying points for consideration in order to improve the everyday life of females and males with a high-functioning autism spectrum condition.

Key words. Autism spectrum disorder, high functioning autism, Asperger syndrome, gender differences.

Differenze di genere nelle persone con autismo ad alto funzionamento: implicazioni nella vita quotidiana e nei contesti clinici

Riassunto. Le differenze di genere nel disturbo dello spettro autistico sono state ampiamente studiate, tuttavia sono ancora limitate le revisioni sulle differenze di genere nelle persone con autismo ad alto funzionamento. Questa review presenta i risultati e le implicazioni per clinici e ricercatori sulle differenze di genere negli individui con autismo ad alto funzionamento su quoziente intellettivo, funzionamento adattivo, funzioni esecutive, aspettative sociali e culturali, abilità linguistiche e pragmatiche, sintomi nucleari (comunicazione/interazione sociale, e comportamenti, interessi o attività ristretti/ripetitivi) e neurobiologia. Dalla letteratura attuale emerge la necessità di individuare precisi strumenti diagnostici che possano ridurre l'impatto delle differenze di genere nella diagnosi di disturbo dello spettro autistico. Una mancanza di diagnosi o una diagnosi errata porta ad un trattamento non appropriato che può avere conseguenze negative sullo sviluppo dell'individuo. Vengono fornite indicazioni per i futuri focus di ricerca e vengono discusse le implicazioni nei contesti clinici con l'obiettivo di raccogliere spunti di riflessione per migliorare la vita quotidiana di donne e uomini con autismo ad alto funzionamento.

Parole chiave. Disturbo dello spettro autistico, autismo ad alto funzionamento, sindrome di Asperger, differenze di genere.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with persistent deficits in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities[1]. Clinical manifestations of ASD vary depending on the severity of core symptoms, developmental level, and chronological age[1]. Recent epidemiological data reported a prevalence rate of ASD in the USA and Europe ranging from 1:59 to 1:100 and that varies with sex and race/ethnicity[2-5].

In this narrative review, we present gender differences in a subgroup of individuals with a high-functioning autism spectrum condition. Data included individuals with autism spectrum disorder but without cognitive impairments (according to DSM 5[1]), and individuals diagnosed with Asperger syndrome and pervasive developmental disorder according to DSM IV-TR[6].

Professionals should be aware of gender differences in high-functioning autism in order to improve diagnostic and treatment practices and the etiological understanding of the disorder.

Methods

A literature search was conducted between October 23 and November 22, 2018 using the PubMed electronic database. The search terms used were: (high functioning autism [Title/Abstract] OR PDD [Title/Abstract] OR child development disorders, pervasive [Title/Abstract] OR asperger syndrome [Title/Abstract]) AND (sex characteristics OR gender differences OR sex differences). The search was not limited by language or publication date. Given the narrative nature of this review, we selected the literature that we considered useful to describe the clinical and neurobiological aspects of the gender bias in the ASD population.

Prevalence of the gender bias

ASD occurs about 4 times more often in males than in females[7], and in high-functioning autism (HFA) ranges from 6:1[8] to 10:1[9]. Hiller, Young and Weber[10] observed that pre-diagnosis concerns were also significantly different between the sexes, to the detriment of females. It is worth noticing that there is an underrepresentation of females with ASD in the scientific studies analyzed[11]. The several discrepancies in the gender ratio in pre-diagnosis concerns, diagnosis and research may in part due to false negatives or misdiagnosis of females with ASD, that are often classified as affective disorders, anxiety disorders, personality disorders or eating disorders[12]. Neurobiological factors may also play a role in the prevalence of the male:female ratio; possible implications are discussed in a dedicated paragraph below.

In addition, females with Asperger syndrome under 18 years of age tend to obtain a diagnosis later than their male peers[13]. One interpretation of this diagnosis gap between males and females with ASD is provided by the camouflage hypothesis[14]. Girls seem to be more capable than boys of masking ASD symptoms and in compensating social behavior flaws[15-17]. Dean and colleagues described the camouflage hypothesis in children with ASD without intellectual disabilities in the school setting[14]. Females tended to stay in closer proximity to peers and to be more involved in activities, whereas males tended to play alone (unlike typically developing children who played in organized games). In addition, females generally tended to play games that imply functional social skills such as dolls or that imitate complex behavioral schemes[10].

A recent systematic review approached this issue by analyzing 54 studies including 13,784,284 participants. Findings revealed that in children meeting the criteria for ASD, the true male-to-female ratio is closer to 3:1. Thus, girls who met the criteria for ASD had a disproportionate risk of not receiving a clinical diagnosis[18].

Neuropsychological profile

The risk of females being underdiagnosed is particularly true for girls without intellectual disabilities or with an intelligent quotient (IQ) over 70[19-21]. However, the diagnosis of intellectual disability should be based on both clinical assessment and standardized testing of intellectual and adaptive functions[1]. Thus, although there is no evidence that adaptive skills differ with gender[22,23], it is important to study these areas further, because they play a crucial role in programming an adequate support for individuals with ASD. The influence of higher IQs in the gender discrepancy of HFA diagnosis may be due to the previously described camouflage hypothesis: females with higher IQ, are more capable of adopting strategies that make them more socially functional.

The executive function (e.g. initiation, sustained attention, shifting, inhibition and planning skills) of females with ASD may contribute to a social functional advantage. There is a limited number of studies on gender differences in the executive function of individuals with HFA and the results vary greatly. Lehnhardt and colleagues[24] showed that females diagnosed late in life had higher processing speed and executive function scores, whereas males had better verbal abilities. In addition, females with ASD scored better than males for attention to detail and dexterity involving executive function[25]. Again, these results may support the camouflage hypothesis. However, in other studies, executive function difficulties were observed more frequently in females than in males with HFA. Kiep and Spek[26] observed that females with HFA performed worse than males for working memory and had more perseverative errors on the Wisconsin Card Sorting Test[27], but fewer perseverative errors and completed more strategies in the same test. In addition, the same performance between genders was seen in planning abilities. Parents also reported deficits in executive function and everyday life skills more often for females with HFA than for males[28]. Inhibition skills have been observed to be poorer in females with HFA than in males[29]. The heterogeneity of these results urges further exploration considering that the methodology may have an impact on the performance of individuals with HFA. For example, they may benefit from using computerized executive function tests, or parent-reports may be biased by parent expectations that in turn may differ between the genders.

Language and pragmatic skills

The diagnosis of ASD is based on behavioral measurements that involve verbal, nonverbal and pragmatic skills. For this reason, it is fundamental to consider these skills when studying the gender gap in people with HFA. The previously cited camouflage hypothesis was also observed with regard to the linguistic and pragmatic skills in a recent study[30] in which females with HFA used pragmatic expressions and conversational pauses in a more similar way to typical population compared to males with HFA. Pragmatic skills are also supported by better scores in verbal fluency in girls with HFA, with more detailed emotional autobiographical memories[31] and more frequent use of internal state language[32], and gestures[33], abilities which are important for social functioning and provide a wealth of knowledge that is crucial to adequately address future social situations[34,35]. Linguistic and pragmatic skills in ASD, and specifically in subjects with HFA, is a field of research that needs to be more widely investigated, because it may be one of the keys for understanding the gender bias in the diagnosis of ASD.

Social communication and social interaction

The results regarding ASD gender differences in social communication and interaction vary and few studies evaluate social skills in individuals with HFA. In these studies, the parents of girls with HFA reported more social problems than the parents of boys[36], showing females to be more socially anxious[37,38], to have greater difficulties making friends[36,39], worse communication skills[33], and to lack of a true understanding of interactional meaning when playing[40]. However, females with HFA tend to feel a stronger desire to develop friendships than their male peers[41]. These results may be partly due to the cultural expectations that society has of the female prototype[36,39,42]. Indeed, it may be useful to consider cultural backgrounds and social expectations when exploring gender differences in people with HFA in future research.

Sociocultural influences on ASD diagnosis also influence the gender ratio and delay in diagnosis. Females with HFA may be seen as 'shy', instead of considering their social flaws part of the symptoms of a developmental condition. This may explain why parents and teachers may ask for a clinical opinion later in time. In addition, consistently with the camouflage hypothesis, females with HFA may learn gender-related normative behavior, but they tend to maintain problems with the true understanding of the social meaning of context, rules, and relationships[43]. Not only the individual gender differences seem to have a fundamental influence on the gender bias in diagnosis, but also the social context plays an important role. Females tend to be accompanied by 'protective same-age friendships' that play an inclusive role. These behaviors would allow females with HFA to appear more socially included in the peer group[43]. Another important aspect is the clinician's expectation bias: given the gender ratio of ASD, clinicians may expect to meet more males with ASD than females and this fact may influence the lower inclination to diagnose a girl with ASD[44,45]. Additionally, practitioners are using diagnostic criteria and interpreting the clinical signs on the basis of ASD research conducted on predominantly male samples[12].

Restricted, repetitive patterns of behavior, interests or activities

Again, results are controversial when we talk about gender differences in individuals with a high functioning autism spectrum condition in restricted, repetitive patterns of behavior, interests or activities. On the one hand, it has been observed for males to adopt more frequent repetitive behaviors[46,47] and restricted interests[47] than females, and higher rates of support at school due to hyperactive behavior[48]. On the other hand, no gender differences have been observed for repetitive and restricted behaviors in HFA[19,39] or stereotyped behaviors[39], even when IQ was used as a covariate[49]. In another study, stereotyped behaviors in males decrease during their lifetime, whereas for females they remained constant[33]. To explain the gender bias in the repetitive and restricted behavior area, one recent hypothesis considers that females may display a different phenotype or different patterns of stereotyped behaviors[50,51], with more socially appropriate interests, in line with the camouflage theory[52]. Future research should seek to pinpoint the reasons for these discrepancies (e.g. differences in restricted, repetitive patterns of behavior, interests or activity types between genders) and potentially identify an *ad hoc* assessment tools for evaluating female and male behaviors.

Neurobiology

Since no single neurobiological marker is known to have an integral role, it has been hypothesized that an interplay between genetic alterations, prenatal environments and epigenetic effects may be responsible for the striking gender bias in ASD[53-57]. Here, we summarize the possible etiological protective and risk factors responsible for the gender bias in HFA.

A considerable number of studies report the "female protective effect" theory, according to which females with ASD carry a higher heritable mutational "load" than ASD males[58]. In favor of this, the siblings of females with ASD have higher autistic trait scores and a higher recurrence risk than the siblings of males with ASD[59]. Although some studies need to be replicated, other findings indicate that the male preponderance of ASD, including HFA, is linked to autosomal and sex-specific genetic alterations, such as single nucleotide polymorphisms (SNPs), single-nucleotide variants (SNVs) and copy number variants (CNVs)[60-63]. For example, Sato and colleagues[64] discovered an inherited mutation with a clear male-biased penetrance in the SHANK1 gene that is involved in neuronal synaptic function and plays a role in mediating social behavior, particularly when it affects higher social cognitive functioning. They described HFA in males carrying a microdeletion in the SHANK1 gene, whereas female relatives carrying the same microdeletion show anxiety but did not meet the diagnostic criteria for ASD[64]. This sex-dependent genotype effect is in line with the data collected in ASD animal models: SHANK1 deletion causes specific ASD-related deficits, with a focus on social recognition and cognitive functioning, only in male mice, whereas females display severe social anxiety levels[65].

Another phenomenon that could provide substantial information for understanding the biological basis of gender differences in ASD regards the genetic heterogeneity related to the X chromosome. As a part of this sex chromosome theory, two specific conditions have been

proposed: in females, possessing an increased X-chromosome gene dosage is protective, whereas in males, the expression of Y-chromosome genes represents a higher risk factor for developing ASD. As females have double the dose of X-chromosome genes of males, humans have developed an X-inactivation process, which may or may not occur randomly. The possibility of a preferential X-inactivation chromosome may protect females from expressing X-linked mutations in genes associated with ASD[66]. In one study, an example of a lack of a protective effect associated with preferential X inactivation in females was observed. The authors hypothesized that mutations in the FMR1 allele, known to cause intellectual disability and autistic behavior, might also contribute to the etiology of HFA, especially in women[67].

In males, the Y chromosome contains the SRY gene, which plays an important role during development because it regulates the production of testosterone, a key factor for the masculinization process[68]. Many studies have demonstrated that high levels of fetal testosterone are associated with the development of ASD, with some findings of higher levels of testosterone in autistic females than in typically developing peers[69,70]. Research by the Baron-Cohen group[71] provided evidence that serum and amniotic levels of testosterone are higher in the ASD population, notably among females[71,72]. Moreover, they identified sex-specific biomarker fingerprints for males and females with HFA: males showed altered levels of cytokines and other inflammatory molecules, whereas females presented altered levels of several biomarkers, including growth factors and hormones[73,74]. These findings revealed the effect of prenatal sex hormones and the immune system associated with the development of ASD, assuming them to be secondary environmental candidates in modulating gender differences in HFA.

Human neuroimaging findings explore the brain characteristics of ASD, reporting substantial structural and functional differences between males and females[75-77]. The extreme male brain theory (EMB) describes the 'ASD brain' as an extreme and hypermasculinized variant of the male brain. According to this theory, males are better able to analyze or construct systems (systemizing quotient), whereas females achieve higher scores for empathy, language skills, and social cognition (empathy quotient)[78]. In support of the EMB theory, females characterized by a male-typical organization of brain anatomy were significantly more likely to be diagnosed with HFA than female individuals with a female-typical brain phenotype[79]. More specifically, when investigating the neuroanatomical features of the gray and white matter regions, suggestive evidence of neuroanatomical 'masculinization' was observed in some areas of the brain of females with HFA, compared to males[76]. Gender differences in the behavioral phenotype may also be explained by differences in brain connectivity. Nevertheless, the studies addressing structural connectivity and gender differences in HFA are limited and substantially controversial. Recently, Zeestraten and colleagues reported frontal lobe alterations in males with HFA that are not observed in females with HFA, which supports the disconnection of the frontal lobe from higher-order association areas in ASD[80]. Contrary to expectations, Kirkovski and collaborators found no effects of biological sex differences when investigating white matter integrity in individuals with HFA, thereby suggesting typical brain connectivity[81].

There is also evidence of test-dependent differences between males and females diagnosed with HFA in terms of brain function. Beacher and colleagues observed greater temporal, parietal, middle frontal region activation in HFA males and typical females than in HFA females and typical males during mental rotation tasks, such as visuospatial processing[82]. Similarly, males and females with HFA differ in their neural activity during the processing of social understanding. Whole brain analysis reported that HFA and typical developing females show the same response when processing social information, whereas males with HFA have an atypical temporal lobe activation pattern[83]. Thus, for certain cognitive and social domains, males and females with HFA could be considered as two clinical sub-samples, as they behave differently. Interestingly, the anatomical specificity of the structural and functional studies described above is potentially important due to the involvement of the frontal and temporal lobe in higher-order cognitive functioning that appears to be atypical in ASD.

Although the findings collected to date are not exhaustive, it could be postulated that HFA males and females appear to differ on a neurobiological level. Additional preclinical and clinical research is needed to investigate the substantial etiological gender diversity.

Discussion: implications for clinical settings and everyday life

As described previously, the diagnostic difficulties in identifying females with ASD without intellectual disability are due to supplementary compensatory strategies that are supported by the protective socio-cultural environment. However, it has been documented that the phenotypical representation of the symptoms of females is different to those of males with HFA[84]. Current literature shows that the clinical manifestation in the preschool age is similar for both genders[85,86]. During primary and middle school, the differences between girls and boys are minimal, but they increase in adolescence, when females try to compensate for their deficits with a greater determination to learn social norms[87,14] at the cost of a greater effort and suffering, thereby demonstrating a greater interest in relationship and social cues to males with ASD.

One aspect worthy of consideration are the comorbidity differences between genders, as it is now less clear whether females with ASD have a different comorbidity profile compared to males with ASD. The current opinion is that females, beyond the misdiagnosis bias, tend to present concomitant internalizing disorders earlier, whereas males more often present externalizing problems[46]. Again, considering age is crucial, because the levels of depressive and anxiety symptoms become similar for both genders in late adolescence[88]. For females, adolescence can be a vulnerable period for the development of comorbidities because it is characterized by the challenges of puberty and changes in peer-to-peer relationships, which are based more on introspective and metacognitive styles[89].

A gender and diagnosis interaction has been identified for externalizing problems, especially for the hyperactivity and inattention domains. In a recent study, May and collaborators[90] found that younger males with HFA were more severely impaired than younger females with HFA, but these differences disappeared by the age of 10-12 years. Interestingly, individuals with ASD (regardless of gender) presented more hyperactive and inattention deficits than their typically-developing matched peers.

Gender differences in HFA have been also explored in certain aspects of everyday work life and sexuality. With regard to the workplace, it is not possible to define clear results due to the limited sample sizes and the presence of numerous qualitative studies[91]. One study showed that females experienced more challenges in multitasking and stress management[92] whereas another showed no differences between genders at work[93].

Sexuality is an important aspect that has been seen to vary between genders in individuals with high-functioning autism: females tended to be more exposed to adverse sexual experiences than males and typically developing people, but males reported a greater desire for and engagement in sexual contact[94]. Men with HFA tended to feel greater sexual anxiety, lower sexual arousability, lower dyadic desire, and fewer positive sexual cognitions[95], more hypersexual and paraphilic fantasies[96], but better sexual function[95] and a greater interest in sexuality[97] than women with HFA.

To conclude, diagnostic camouflaging, misdiagnosis or co-morbidities influence the timing and likelihood of autism identification in females, representing a challenge for the diagnosis[54] and for the appropriate selection of the treatment program. Indeed, a misdiagnosis or incorrect diagnosis leads to unspecific intervention (either pharmacological or behavioral) that may not have the desired effect on the targeted competences/impairments and, in the worst-case scenario, could be even detrimental.

Key messages

- Autism spectrum disorder occurs more often in males than in females.
- Importance of considering intelligence quotient, functional adaptation, executive function, socio-cultural expectations, language and pragmatic skills when exploring gender differences in ASD.
- Future research should seek to further explore differences between genders in individuals with a high-functioning autism spectrum condition when considering the core ASD symptoms.
- The neurobiological findings concerning sex differences in high-functioning autism, although not exhaustive, represent a promising starting point for elucidating the role of genetic and environmental factors leading to the gender bias in the prevalence of ASD.
- Implications of gender bias in high-functioning autism in everyday life and clinical settings have to be more widely explored and some factors (e.g. age) may have a crucial impact on it.
- Importance of considering gender differences in individuals with a high-functioning autism spectrum condition in order to program more efficient intervention strategies.

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Correspondence to:
Maria Luisa Scattoni
Italian National Istitute of Health
Research Coordination and Support Service
Viale Regina Elena 299
00161 Rome, Italy
email marialuisa.scattoni@iss.it