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A Review of the Role of Female Gender in Autism Spectrum Disorders

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Abstract This paper reviews the literature exploring gender differences associated with the clinical presentation of autism spectrum disorders (ASD). The potentially mediating effect of comorbid psychopathology, biological and neurodevelopmental implications on these gender differences is also discussed. A vastly heterogeneous condition, while females on the lower-functioning end of the spectrum appear to be more severely affected, an altered clinical manifestation of the disorder among high-functioning females may consequently result in many being un or misdiagnosed. To date, there is strong bias in the literature towards the clinical presentation of ASD in males. It is imperative that future research explores gender differences across the autism spectrum, in order to improve researchers', clinicians' and the publics' understanding of this debilitating disorder.

Keywords Gender · Symptomatology · Diagnosis · Etiology

Introduction

Autistic disorder, Asperger's disorder (AD) and pervasive developmental disorder not otherwise specified (PDD, NOS) (from herein referred to collectively as autism spectrum disorders [ASD] except for when distinction is necessary) are a set of behaviorally defined neurodevelopmental disorders characterized by social and communicative impairments, as well as restricted, repetitive and stereotypical behaviors and interests (RRBI) (American Psychiatric Association [APA] 1994). The clinical presentation of the disorder can be highly heterogeneous. While some affected individuals may present with a high level of intellectual disability (ID) (Charman et al. 2006) and have little to no speech (Wilkinson 1998), others may present with an average or superior level of intelligence (Charman et al. 2006) and have no delay in language development, yet still experience significant difficulty with social interaction and restricted and repetitive behaviors (APA 1994).

ASD affect males at a higher frequency than females (Brugha et al. 2011; Kim et al. 2011), with average estimates across studies suggesting a 4:1 ratio for the spectrum as a whole (Fombonne 2003, 2009). However this gender ratio is not evenly distributed across the spectrum. Multiple epidemiological studies have suggested that towards the lower-functioning end of the autism spectrum, including those with comorbid ID, this ratio becomes approximately 2:1 (see Fombonne 2003, 2009; Mattila et al. 2011) although in a high probability group (recruited from a disability registry), Kim et al. (2011) report an increased ratio of 5.1:1, with the presence of an ID also more common among this group. Towards the high-functioning end of the spectrum, those with a normal level of intellectual function, this gender ratio may increase to approximately 6:1 (see Fombonne 1999). There is, however, recent research to challenge these findings and to indicate lower gender ratios for the autism spectrum than those previously observed. Kim et al. (2011) and Mattila et al. (2011) note male:female gender ratios of 2.5:1 and 1.8:1 in ASD, based on DSM-IV and DSM-IV-TR, respectively. Kim et al. (2011) highlight that for many of these children the condition

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was either not reported by parents, untreated, or misdiagnosed, which may be mediated by cultural confounds with associated stigma, and hence that may have influenced this result. Moreover, Mattila et al. (2011) report a comparable ratio of 1.7:1 in high-functioning autistic individuals using this criteria. Concerns are raised however, that some individuals on the high-functioning end of the spectrum may not be classified by the proposed DSM-V criteria (Mattila et al. (2011)), which may have implications for affected females. Recent evidence suggests that the observed gender ratio may be influenced by greater cognitive impairment among females with ASD. Dworzynski et al. (2012) suggest that individuals with ID may be more likely to meet the diagnostic cut-off for ASD, while those who score comparably on measures of autistic traits (as measured by the Childhood Autism Spectrum Test [CAST]), without this comorbidity, do not meet the cut-off for clinical diagnosis.

Consequently, there is a great deal of literature regarding the varying profile of autism as expressed by affected males; our understanding of the female profile of autism, however, remains largely unclear. This gap in our understanding could lead to misinterpretation and misunderstanding of the disorder and how it affects each individual. As described by Attwood (2007), it appears that females with ASD may develop strategies to cope or adapt to certain situations, subsequently "camouflaging" their symptoms. Alternatively, females may present with an altered phenotype that is more difficult to diagnose, or not adequately captured by current diagnostic instruments.

Though preliminary, there is evidence suggesting an altered neuropathophysiology in females with ASD. The key focus of this paper will be to draw attention to differences that arise in the clinical presentation of the disorder. To begin, we will discuss gender differences with regard to the diagnostic triad of deficits, followed by comorbid psychopathologies commonly affecting females with ASD. Subsequently, prominent theories regarding the etiology of autism will be discussed in terms of their effect on females, and as a possible factor contributing to the altered clinical presentation. Limitations of the literature to date will also be discussed. The importance of gaining a deeper understanding of the female profile of autism will become apparent. Without such knowledge, affected females will, in some cases, remain un- or misdiagnosed, consequently failing to receive appropriate treatment and intervention that could significantly improve their quality of life.

Methods

A literature search of the Medline and Psych-Info databases was conducted concurrently using combinations of the search terms (1) *autism,* or *Asperger's*; (2) *gender, sex,* or *females*; and (3) *symptom presentation, social skills, language, communication, behavior, comorbid, etiology, chromosome, chromosomal mutation, aneuploidy, copy-number variant, X-inactivation, imprinting, genetics, heritability, twin, broad phenotype, brain development, quality of life*. To ensure inclusion of all pertinent information, we also reviewed relevant references from those articles identified in the initial search.

Abstracts of articles of interest were then screened for relevance to this particular paper. Empirical papers and clinical case studies describing either the effects of gender on clinical symptoms or female specific traits associated with ASD were included in this review. Given the limited availability of such literature, there were no restrictions on age range, specific diagnosis or dates of publication.

Results

The results of this search yielded a total of 113 papers, empirical studies, case reports and clinical opinions which describe or assist to inform our understanding of gender differences observed in ASD. For clarity and easy reference, a summary of these reports is provided in Online Resource 1.

A total of 33 reports discuss the clinical presentation of ASD between affected males and females, 26 of which (78.8 %) provide support for an altered phenotypic profile across the triad for affected females. Greater impairment in developing friendships is noted among the female cohort in five studies, though four studies note more appropriate play behavior is seen in the female sub-sample. Similar levels of communicative ability between affected males and females were described by seven empirical reports, while three provide support for greater impairment in this domain for males with ASD. Eight empirical reports note similar levels of RRBI impairment between males and females with ASD, however five support that females are less impaired in this domain. Three empirical reports explore cognitive ability as a factor mediating gender differences in ASD, while five studies investigate cognitive differences between males and females with ASD. Further, three reports highlight differences in areas of restricted and stereotypical interests among affected females compared to males, while a clinical case report of six affected girls and a book based on clinical opinion implicate these (potentially) atypical RRBI to the gender differences observed in the social and communicative domains.

Thirty-one empirical studies, case reports and reviews describe comorbid psychopathological, biological and neurological conditions in ASD. No gender differences are noted in eight of ten (80 %) of the research reports identified investigating gender differences in comorbid mood and behavioral psychopathology in ASD, while the remaining

20 % indicate greater levels of comorbid mood and behavioral psychopathology among affected females. A further eight case reports (two), reviews (two) and empirical studies (four) describe vast overlap between ASD symptomatology and eating disturbances, suggesting under- or misdiagnosis of affected females as a result of these behaviors; these eating patterns are interpreted as atypical manifestations of RRBI.

Further, fifteen empirical reports, four clinical case reports and six reviews propose that genetic factors contribute to sex differences in susceptibility to ASD; providing consensus that females may be genetically protected, or require a higher genetic load, to present with clinical features of ASD to a level required for diagnosis. A further seven empirical reports and two reviews suggest that prenatal androgen exposure may have implications for some characteristics of ASD. Of these, three empirical reports measure sex-hormone serum levels in adults, while four provide indirect support for elevated levels of male sex-hormones; none provide a direct measure of pre-natal androgen levels.

Of the nine empirical reports investigating gender differences in brain development in ASD, eight (88.9 %) reports indicate that while both males and females with ASD experience atypical brain growth, the precise nature of these changes differs between males and females, even taking normal sexual dimorphism into account.

In the rest of this paper we discuss each of these areas in greater detail, with special attention to the potential mediating roles of cognitive ability, age and diagnostic factors, as well as neuro-biological factors that may influence gender differences in ASD.

Discussion

Clinical and Diagnostic Features

While many authors report similar clinical profiles between male and female children with ASD (Amr et al. 2011; Andersson et al. 2012; Mayes and Calhoun 2011), gender differences in the clinical presentation of the condition have been noted, and will be discussed below. Cognitive ability (Lord et al. 1982; Mayes and Calhoun 2011; Sipes et al. 2011; Park et al. 2012; Volkmar et al. 1993), and age (Carter et al. 2007; Mayes and Calhoun 2011; McLennan et al. 1993) are most often suggested to be the greatest mediating factors influencing the symptomotology, and gender differences observed in the clinical presentation of ASD.

Developing Friendships

Of the many forms of social deficits that can be experienced by individuals with ASD, it would appear that for females

the greatest difficulty is in the formation and maintenance of appropriate peer relationships and friendships (McLennan et al. 1993). Holtmann et al. (2007) note trends indicating that affected females may experience greater difficulty in this domain based on the 'group play with peers' sub-scale of the Autism Diagnostic Interview-Revised (ADI-R), despite this not being statistically significant. Furthermore, Carter et al. (2007) report that parents of females with ASD observed greater social deficits and lower competencies with regard to empathetic behaviors compared to parents of affected males. Clinically, this effect of gender was not identified based on the socialization sub-scale of the ADI-R or Autism Diagnostic Observation Schedule (ADOS; Carter et al. 2007). Using alternative measures relying less stringently on diagnostic criteria, however, many researchers have identified significantly greater impairment in social functioning for affected females. For example, studies using the Diagnostic Interview for Social and Communication Disorders (DISCO; Billstedt et al. 2007), the Child Behavior Checklist (CBCL; Holtmann et al. 2007) and the Vineland Social Maturity Scale (Lord et al. 1982) have all noted greater social impairment in affected females.

Together, these results suggest that affected females may present with an altered phenotype against the established diagnostic criteria. Although impairments in these areas do exist, they may be less readily identifiable. Furthermore, some researchers have suggested that older females may experience greater difficulty developing friendships (Holtmann et al. 2007; McLennan et al. 1993). For example, none of the female participants in the McLennan et al. (1993) study had any type of reciprocal friendship after the age of 10, while at earlier time points the results indicated greater difficulty in this domain for males. In terms of the social deficit sub-scale as a whole, however, the authors noted that males overall had greater impairment based on the ADI (McLennan et al. 1993).

An often cited explanation for the described sex differences in social interaction and friendships relates to the notion of increased social expectations being placed on females (Carter et al. 2007; Holtmann et al. 2007; McLennan et al. 1993). Similarly, Cheslack-Postava and Jordan-Young (2012) suggest that adult perception of gender roles may influence their interactions with children and hence may also mediate their perception, or recognition, of ASD symptomatology. Both McLennan et al. (1993) and Holtmann et al. (2007) relate the aforementioned pattern of more severe social deficits in females, particularly regarding the development and maintenance of appropriate peer relationships, to gender roles and differences in upbringing for male and female children. For example, McLennan et al. (1993) highlight that while typical social activities between females tend to rely more heavily on communication and reciprocal sharing of interests, males have social options that require

much less reliance on communication and reciprocity, such as sports, hence the deficits in these domains are highlighted for affected girls. Based on mothers' reports, Bauminger and Kasari (2000) support the notion that individuals with ASD preferred to engage in play with friends that required the least amount of interaction, such as watching movies or playing video games. Furthermore, McLennan et al. (1993) suggest that as females with ASD tended to spend more time in predominantly male filled special needs classrooms, curriculum may have focused primarily on the male gender; thus impeding their ability to develop and interact with female peers. Despite the difficulties in social interaction experienced by affected individuals, Bauminger and Kasari (2000) highlight that they do indeed feel lonely, and may in fact desire friendship. Hence, while there is research to suggest that females may be more severely impaired in terms of developing friendships, implications such as the societal norms surrounding different interactions and activities for males and females, as discussed by McLennan et al. (1993), should be considered. Increased demands for more intense interpersonal interaction for a group with known difficulty in that domain may magnify the impairment in such situations for females with ASD.

Play Behavior

Despite there being evidence to suggest that females with ASD are likely to have been considered a 'tomboy' at some stage in their development (Ingudomnukul et al. 2007), the literature has long suggested more appropriate play behavior among females with ASD in comparison to affected males (Lord et al. 1982; McLennan et al. 1993; Tsai and Beisler 1983). In particular, recent research indicates that affected females display superior imaginative play skills, and suggests that this skill may in fact be preserved among this group (Knickmeyer et al. 2008). Although individuals with ASD were less likely to choose games involving pretense when compared to typically developing (TD) children, this study indicated that affected females were more likely to play or choose to play *female-typical* games requiring pretense. By contrast, affected males did not show a preference for any pretense items. With respect to sex-typical play that does *not* require pretense, males showed preference for male-typical play, while females did not show preference for either male or female typical play (Knickmeyer et al. 2008).

To consider an alternative hypothesis based on clinical observation, some authors describe a phenomenon whereby affected females express a keen interest in social situations and interaction (Attwood 2007; Kopp and Gillberg 1992). For example, a girl with ASD may thoroughly observe and analyze the social and play behavior of others and imitate this through their own play with dolls or imaginary friends,

or even adopt the observed persona in their own interactions with others (Attwood 2007). Kopp and Gillberg (1992) further describe autistic girls as more likely to display patterns of "clinging" behaviors towards others, as well as patterns of echolalia and imitation of other people's actions. As such, it appears that the restricted interests of affected females may actually mask the presentation of their social deficits. As a result, affected females display what *appears* to be socially-appropriate play behavior (Attwood 2007), but lack a deeper understanding of the social value and meaning of their interactions and play (Kopp and Gillberg 1992).

Communicative Deficits

As with many aspects of ASD, the literature concerning the role of gender in communicative ability in ASD is inconsistent. Many studies note equivalent communicative ability between males and females with ASD (Amr et al. 2011; Andersson et al. 2012; Holtmann et al. 2007; Mandy et al. 2012; Mayes and Calhoun 2011; Pilowsky et al. 1998; Solomon et al. 2012). These factors may, however, be mediated by variability in measures and methodology used, or age effects. For example, while Park et al. (2012) identified greater impairment in non-verbal communication among affected boys, others have suggested greater communicative deficits as a whole among affected females based on formal diagnostic classification criteria (Hartley and Sikora 2009), global measures of functioning (Carter et al. 2007), or various behavioral measures (Lord et al. 1982; Tsai and Beisler 1983). Kopp and Gillberg (1992) describe six cases of high-functioning girls with ASD, all of whom displayed excessive patterns of language use such as echolalia or repetitive questioning of others. More recently, an empirical study by Andersson et al. (2012) similarly noted proportionately increased instances of echolalia among affected girls (6/20 girls, 3/20 boys). While echolalia is a common feature of ASD, Kopp and Gillberg (1992) regarded the presentation of this behavior to be atypically excessive.

To the contrary, McLennan et al. (1993) and Lai et al. (2011) both identify superior socio-communicative skills among females with ASD. Among a sample aged 6–36 years, McLennan et al. (1993) describe greater abnormality among affected males prior to 5 years of age, whereas no difference was noted at the time of testing. Among an adult sample, Lai et al. (2011) identified no gender-related differences during childhood, based on information provided by participant's primary caregivers during that period. Assessment of current autistic symptomotology based on ADOS scores, however, suggested greater socio-communicative ability among the female subsample. In support of this superior performance, Attwood

(2007) describes girls with AD as "little philosophers," engaging in conversation regarding their observations and beliefs of social convention and events. Hence, the strong interest in socialization demonstrated by affected females may again serve to mask clinical symptoms as their restricted interests are more socially appropriate than those displayed by affected males.

Restricted and Repetitive Behaviors and Interests

Similar to the literature regarding social deficits in ASD, there are inconsistencies across studies investigating the effect of gender on RRBI. While comparable symptomology in this domain has been noted among affected children and adolescents (Carter et al. 2007; Holtmann et al. 2007; Solomon et al. 2012; Szatmari et al. 2006), and across a child-to-adult sample (McLennan et al. 1993), trend level data across these studies would suggest greater impairment among the male cohorts. Other studies report significant differences, favoring females, in RRBI. Specifically, female toddlers (Hartley and Sikora 2009), children, adolescents (Bölte et al. 2011; Mandy et al. 2012; Park et al. 2012), and adults (Lai et al. 2011) have all been identified as being less impaired with regard to clinically identifiable RRBI. Sipes et al. (2011) provide evidence that this may be mediated by developmental level. Based on parent report, affected females with an average level of development (based on developmental quotient; DQ) exhibited the least RRB compared to affected males with an average DQ, and affected males and females with low DQ (Sipes et al. 2011).

Researchers suggest that this difference is most prominent for higher order cognitive processes, as opposed to sensory level motor behaviors. An early study by Lord et al. (1982), which controlled for IQ, noted more frequent and unusual stereotypical visual interests, and less appropriate and routinized play, in males with ASD. Szatmari et al. (2012) provide further support, reporting the largest gender differences for items measuring "unusual preoccupations," "circumscribed interests," and "repetitive use of objects or interest in parts of objects". This does not necessarily suggest that females with ASD have no impairment in this domain, but instead that symptoms may not be as clinically identifiable as those presented by males (Kopp and Gillberg 1992). For example, there is evidence to suggest that females with ASD may not present with the same behavioral pattern of visual self-stimulation via extreme preoccupation with particular interests or (parts of) objects (Kopp and Gillberg 1992; Lord et al. 1982; Nicholas et al. 2008). This is possibly due to less developed visuospatial skills (Kopp and Gillberg 1992), and as described in the sections above, females may even develop restricted interests in the realm of social interaction

(Attwood 2007; Kopp and Gillberg 1992) which goes unrecognized under this category and serves to mask the symptom presentation in the social and communicative domains. Pertinent to consider, given the forthcoming changes in DSM-5 that include "unusual sensory behaviors" as a core diagnostic criteria, are differences in sensory stimulation that may not have been captured by current standardized measures. As current measures (DSM-IV), do not adequately incorporate this criteria, using items 71–73 of the ADI-R Lai et al. (2011) specifically investigated such behaviors. Interestingly, they identified more life-long unusual sensory responses among affected females, which highlights the importance of further investigation in this domain. Further there have been suggestions of more frequent and unusual stereotypical visual interests for affected females (Lord et al. 1982).

While further supporting the notion that females with ASD present with less RRBI, Szatmari et al. (2012) add that affected males from a family containing at least one female family member with ASD present with the highest level of RRBI, followed by males from families where those affected are all male. As will be discussed in detail later in this review, the authors interpret this finding as support for the hypothesis that biological mechanisms may serve as protective factors for the development of ASD in females (Szatmari et al. 2012). Hence, a greater degree of genetic abnormality must be present in order for ASD to be expressed in a female (Tsai and Beisler 1983; Tsai et al. 1981).

Comorbid Psychopathology

Mood and Behavioral Characteristics

Although depression and anxiety are regarded as the most commonly occurring comorbid psychopathologies among ASD samples (Hofvander et al. 2009; Lugnegard et al. 2011; Matson and Nebel-Schwalm 2007), many studies have failed to identify gender difference in such disorders between affected toddlers, children and adolescents (Park et al. 2012; Simonoff et al. 2008; Solomon et al. 2012) or adults (Hofvander et al. 2009; Lai et al. 2011; Lugnegard et al. 2011). This finding remains relatively stable across the spectrum, with no effects of gender on comorbid psychopathology, those with ID (Horovitz et al. 2011; Tsakanikos et al. 2011; Worley and Matson 2011) or with higher levels of cognitive functioning (Hofvander et al. 2009; Lai et al. 2011; Lugnegard et al. 2011).

Hartley and Sikora (2009), on the other hand, suggest that affected female toddlers may experience increased difficulties with such comorbid conditions. This study, however, did not account for expected sex differences associated with these conditions and their symptoms,

which would be imperative given the greater instance of such conditions among females in the wider population (Angst et al. 2002). Additionally, Holtmann et al. (2007) note increased psychopathology in areas relating to social, thought and attention problems among female children with high-functioning ASD as measured by the CBCL, though this difference was not clinically identified by the ADOS or ADI-R.

An investigation of aggressive behaviors among individuals with ID by Cohen et al. (2010) found that females with ASD and ID exhibited aggressive behaviors, including self-directed verbal and physical abuse, over and above those that were identified among males with ASD or those with ID but no presence of ASD. Imperative to consider alongside this finding however, Kyrkou (2005) highlights that females with ASD and ID may display increased aggressive behaviors such as pushing or pinching people (along with other related symptoms) while experiencing premenstrual symptoms, and as a result of their ASD may not be able to communicate their discomfort, heightening agitation and potentially resulting in misunderstanding and mismanagement of such behaviors. To the contrary, Amr et al. (2011) identify increased instances of delinquent behavior among affected boys in a sample with varying IQ, while Kozlowski et al. (2012) suggest no effect of gender on aggressive behaviors in individuals with ASD. Of note however, is that gender differences in aggressive behaviors were not noted among non-ASD participants in this sample either (Kozlowski et al. 2012). Further, a study exploring challenging behaviors among children with ASD found no effect of gender, although of a sample of 157, five exhibited self-injurious or aggressive behavior (three male and two female) (Murphy et al. 2009). When considering that the sample consisted of 130 males and only 27 females, proportionately, it appears that this type of behavior may have been more common in the female sub-sample. As with core symptoms, researchers have identified age and developmental stage as factors that may influence the presentation of certain forms of psychopathology. Worley and Matson (2011), for example, highlight the potential impact that a wide age range may have on identification of psychopathology. Similarly, research by Horovitz et al. (2011), who focused their study on psychopathology in infants and toddlers, may be limited in that while symptoms of psychopathology are present, measurable gender differences may not manifest until later in life.

Eating Patterns

Eating disturbances or abnormal eating behaviors are commonly noted in individuals with ASD (Råstam 2008).

Moreover, researchers have described an overlap between the behavioral phenotypes observed in the eating patterns of ASD and anorexia nervosa (AN) (Råstam 2008; Zucker et al. 2007), or emphasized the presence of autistic traits or features (namely, weak central coherence) in individuals with AN (Southgate et al. 2008). While the literature on this topic remains scarce, research has indicated high instances of comorbidity of these psychopathologies among females. For example, a study exploring cognitive ability in AN details that a significant proportion of the clinical sample also had a diagnosis of ASD (Gillberg et al. 2007), as did a pilot study of child onset neurological disorders in eating disorders (Wentz et al. 2005). There have also been relevant case reports (Stiver and Dobbins 1980), one in particular suggesting that the eating pattern associated with the AN manifested itself as a form of repetitive behavior noted in ASD (Hackler 1986), a notion further supported by Råstam (2008). The striking over-representation of ASD symptomatology in individuals with AN has led some researchers to the hypothesis that AN may in fact be a female variant of ASD (Odent 2010). This must, however, be considered with caution, as to date it appears that no empirical research has explored this phenomenon directly.

Gender and Identity

There are case reports demonstrating gender dysphoric tendencies, or inconsistency between biological sex and gender identification, in males (Mukaddes 2002; Williams et al. 1996) and females (Kraemer et al. 2005; Landen and Rasmussen 1997) with ASD. Nevertheless, it is controversial as to whether these conditions occur as comorbid disorders, or whether the behaviors associated with gender dysphoria are simply atypical manifestations of RRBI. While in non-clinical samples males are more often referred to clinics for treatment of gender identity disorders than females (Zucker and Lawrence 2009), it has been suggested that prevalence among the general population may in fact be almost equal between males and females (Landén et al. 1996). The only published empirical report investigating this comorbidity, to our knowledge, found that more males with ASD suffered from such complications than affected females (de Vries et al. 2010). This finding appears to contradict the hypothesis that prenatal androgen exposure may increase male-typical tendencies among those with ASD (Baron-Cohen et al. 2005) (further discussion provided below). De Vries et al. (2010) suggest that, based on this hypothesis, females with ASD should be more susceptible to developing gender dysphoric tendencies, and do not provide any indication as to why males with ASD would have such tendencies.

Cognition and Neuropsychological Profiles

IQ

The varying cognitive profiles of individuals with ASD demonstrate the vast heterogeneity of the condition. There is consensus among researchers however, that affected females may be more often represented among those with lower cognitive ability, as discussed earlier in this review (see Fombonne 2003, 2009). An investigation of gender differences in the cognitive profiles of affected children, without cognitive impairment, suggests that the cognitive differences observed in ASD may vary depending on task. While similar cognitive profiles were observed for affected girls and boys overall (which may be expected given that this study specifically recruited individuals with IQ > 70), Koyama et al. (2009) noted gender differences in nonverbal subtests of the Weschler Intelligence Scale for Children-III. Specifically, affected girls demonstrated superior performance on Coding and Symbol Search, while affected boys demonstrated superior performance on Block Design. This finding is further supported by Bölte et al. (2011), among a child sample. The authors however, did not identify a relationship between performance on these tasks and clinical features of ASD. This finding of reduced performance on Block Design tasks highlights the potentially atypical phenotype of ASD among affected girls, as past research indicates greater reliance on processing of details, rather than global processing among individuals with ASD (Bölte et al. 2011). This superior performance on tasks requiring attention to detail however, may not be generalised to all such tasks. Gender differences have not been noted in performance on the Embedded Figure Test among affected children (Bölte et al. 2011), or adults (Lai et al. 2012). Given that females with ASD tend to be proportionately more likely to experience intellectual disability, similar studies including more impaired samples are imperative for our understanding of gender profiles of ASD, as those currently available in the literature focus on those with IQ > 70.

Executive Functioning

Preliminary evidence suggests more severe deficits among females with ASD with regard to executive functioning tasks (Lemon et al. 2011; Nydén et al. 2000). Lemon et al. (2011) note slowed response inhibition in affected female children compared to affected male children and healthy controls on the stop task. This difference in response inhibition performance was not replicated by Nydén et al. (2000), however it is imperative to note that this study investigated neuropsychiatric conditions more generally(pervasive developmental disorders [5 females, 5 males]/attention deficit hyperactivity

disorder [12 females, 12 males] combined) among children, and thus further exploration as to whether this difference in performance is specific to ASD is warranted. Further, age effects should be considered, as Lai et al. (2012) did not replicate this finding among an adult ASD sample. Nydén et al. (2000) however, did note superior perfomance among clinical males in more global measures of executive functioning, with males out performing females on the Tower-of-London task. In an ASD sample Bölte et al. (2011) did not replicate this finding using the Tower-of-Hanoi task, however affected females outperformed males on the Trail-Making-Test; which was correlated with less impairment in the RRBI domain. Bölte et al. (2011) highlight that differences in sampling between these two studies (high functioning ASD/PDD and attention deficit hyperactivity disorder [ADHD]) may influence the results. Thus, further replication is imperative.

Theory of Mind

Difficulty in attributing mental states is a common deficit among individuals with ASD. Lai et al. (2012) did not identify a difference in emotion recognition between men and women with ASD. To this extent however, the authors highlight milder impairment based on ADOS scores among affected women. Thus, further support is provided for affected females being able to superficially mask or camouflage their social deficit. Nydén et al. (2000) further corroborate this theory. Although clinical girls (PDD and ADHD) had greater difficulty in a mentalizing task compared to TD girls overall, a trend indicating greater impairment among the PDD sub-sample was noted.

Etiology

Heritability

ASD are known to be highly heritable, both in terms of a clinical diagnosis (Schwichtenberg et al. 2010) and also in terms of a broader autism phenotype (Bolton et al. 1994; Pickles et al. 2000; Schwichtenberg et al. 2010), and concordance rates among monozygotic (MZ) twins are much higher than that of dizygotic (DZ) twins (see Ronald and Hoekstra 2011, for a review). While not a key focus of the study, Hallmayer et al. (2011) describe concordance rates as seemingly comparable between male and female MZ and DZ twin sets despite large differences in sample size (though statistical comparison of this is not provided). In contrast, Lichtenstein et al. (2010) note concordance among only one female DZ twin set in their study, and none among MZ female twins. While these findings must be considered with caution as they may be a reflection of less female twin sets being included in the described

analysis, they also prompt further investigation into the underlying genetic influences of this heritability. Moreover, lending support to the notion of increased genetic load among families with affected females (as proposed by Tsai and Beisler 1983; Tsai et al. 1981), Hallmayer et al. (2011) note that concordance for female siblings of 76 affected males with ASD was 5.3 %, however this increased to 50 % for male twins of six affected females. Among 54 males with a strict diagnosis of autism, concordance for female twins was 3.7 %, while for twin brothers of two female probands this concordance rate was 50 %. Though intriguing, it must be emphasized that these findings relevant to female probands are among very small samples. Further, while investigating concordance rates of MZ and DZ twins among those clinically diagnosed with ASD, Taniai and colleagues noted a greater influence of additive genetic factors in the heritability of ASD among females (Taniai et al. 2008). Though preliminary, such twin studies of heritability in ASD demonstrate an effect of gender worthy of further investigation.

Familial Aggregation

Early studies suggest that affected females may have a greater threshold for ASD (i.e., they require a greater degree of genetic abnormality for symptoms to be expressed) (Tsai and Beisler 1983; Tsai et al. 1981). This is thought to be reflected in affected females having a greater number of first degree relatives on the spectrum compared to affected males (Tsai et al. 1981), possibly reflecting greater genetic liability in these families. While a number of more recent reports have not demonstrated evidence to support this claim (Goin-Kochel et al. 2007; Pickles et al. 2000; Szatmari et al. 2000), most recently, Robinson et al. (in press) provide evidence to support the "female protective effect" of ASD. Autistic traits in female and male probands scoring in the 90–95th percentile, and their DZ twins, recruited from the Twins Early Developmental Study and the Childhood and Adolescent Twin Study of Sweden were investigated. Independant analysis of each database as well as a combination of the two provide evidence of more autistic traits among siblings of affected females, independent of the sex of the sibling or percentile rank of the proband. Hence these findings suggest greater genetic load among families with an affected female (Robinson et al., in press). More broadly however, Boutin et al. (1997) note cognitive difficulties in more first degree relatives of female probands in comparison to first degree relatives of male probands. Further, Constantino et al. (2010) add that in families with more than one affected child, non-affected males tend to display more sub-threshold autistic characteristics than females, possibly again highlighting the susceptibility threshold among females.

Based on the premise of greater genetic loading among families with more than one affected child, Banach et al. (2009) expected that males would be more severely affected than their female siblings. This study found no difference in cognitive abilities between affected siblings; in families with only one affected child, however, females tended to be more likely to have ID than males (Banach et al. 2009). It is speculated that this may occur as a result of parents' decision to not have any more children after the birth of a disabled child, in order to reduce the likelihood of having affected siblings (Constantino et al. 2010; Volkmar et al. 1993). Given the increased possibility of an autistic female having an ID (Fombonne 2003), this may explain why this effect appears to be more common in families with autistic girls. These discrepant findings may be mediated by cognitive ability (Goin-Kochel et al. 2007) or even symptomatology (Constantino et al. 2010; Szatmari et al. 2012). More research is required before any further conclusions can be drawn.

Autosomal CNV

Genetics are known to have an integral role in the development of many neurodevelopmental disorders, including ASD. While to date no single genetic marker has been identified as being responsible for the condition, genetic mutations have been noted across the autism spectrum (Sebat et al. 2007). Numerous studies have identified many copy number variations (CNV) in individuals with ASD, in the form of duplications and deletions on autosomes and sex chromosomes. While ASD can be sporadic or inherited, there is some consensus that investigating de novo genetic mutations may prove beneficial for our understanding of the genetic nature and development of the disorder (Gilman et al. 2011; Levy et al. 2011; Sanders et al. 2011; Zhao et al. 2007). Of note, however, is that de novo events only occur in 8–10 % of probands (Levy et al. 2011; Sebat et al. 2007; Zhao et al. 2007). Interestingly, recent evidence suggests a link between females affected with ASD in simplex families and older paternal age, hence suggesting a non-familial link. Although indirect, such findings warrant further investigation to gain a clearer understanding of the impact of genetic mechanisms on the development of ASD in females. While recurrent de novo mutations, both in the form of duplications or deletions, have been identified among some probands (Levy et al. 2011; Sanders et al. 2011) and may represent risk variants, they do not provide a conclusive genetic marker directly responsible for ASD. It has also been suggested that ASD may be a result of interactions between several mutations, rather than a single risk variant (Zhao et al. 2007). Nonetheless, several pivotal advances have contributed to our understanding of the gender dimorphisms observed in ASD.

Recent investigation has indicated that female probands often have more, and larger, de novo CNV compared to male probands (Gilman et al. 2011; Levy et al. 2011), suggesting that more genes are implicated in each mutation among the former, and highlighting the heterogeneous nature of the condition. Sebat et al. (2007) note an increased proportion of females with de novo mutations among probands in comparison to those where such mutations were not identified, suggesting that the 4:1 sex ratio observed in the general ASD population cannot be accounted for by sex differences in the penetrance of de novo CNV. The larger CNV observed in affected females could support the long speculated hypothesis that an underlying protective factor may minimize, or at least camouflage, the clinical presentation of ASD among affected females. Accordingly, a greater amount of abnormality may be required for the phenotype to present (Gilman et al. 2011; Robinson et al., in press; Tsai and Beisler 1983; Tsai et al. 1981). Furthermore, while investigating specific networks of genes involved in neuronal processes and synapse development in the brain, Gilman et al. (2011) describe not only a larger amount of genes involved in female probands' CNV, but also that the genes associated with CNV of female probands may be "more important" due to their connections with other genes from relevant networks. This finding lends support to the relatively novel findings of more severely atypical brain development in females with ASD compared to affected males (Bloss and Courchesne 2007; Schumann et al. 2009; Schumann et al. 2010), as will be detailed in following sections. The underlying cause of this sex specific protection, however, is yet to be determined. It has been further suggested that females may act as carriers of genetic mutations influencing the development of ASD, which in turn can be transmitted to their offspring, with increased risk to male children (Zhao et al. 2007). The authors, however, further note that a risk genotype can be present in both males and females in the absence of the associated phenotypic expression (Zhao et al. 2007).

Vast heterogeneity has been identified in the manner in which these mutations manifest, confirming the pertinence of furthering our understanding of all mechanisms underlying the condition. Levy et al. (2011) note that even on a recurrently identified CNV, namely 16p11.2, these events may occur as either duplications or deletions involving the same gene. This study also found that this recurrent CNV was more common among male probands (Levy et al. 2011), indicative of reduced penetrance of this mutation among females. Hence, while males may be more often affected by specific CNV, the way in which the behavioral phenotype manifests could vary depending on the type of mutation. The specific genes affected by CNV can influence phenotypic/behavioral expression (Gilman et al. 2011;

Sanders et al. 2011). For example, Sanders et al. (2011) note a relationship between the number of genes and IQ among male probands; specifically, a decrease in IQ points was found for those with a higher number of genes, a finding that was not present among the female probands despite trends towards more "gene-rich" CNV among this group. While purely speculative, this would suggest that the specific genes involved in this phenotype may not have been affected in the female cohort.

X-Linkage

Autistic-like symptoms have been noted in many conditions known to have a genetic origin, particularly linked to the X-chromosome (Marco and Skuse 2006). Research suggests X-chromosome involvement in the atypical social behaviors and interactions observed in ASD, and indicates that heritability of these traits may be increased for males (Loat et al. 2008). Important to consider, many case studies have identified X-chromosome mutations in girls with ASD, although often these individuals have comorbid conditions known to be of genetic origin, specifically involving the reported genes (Edens et al. 2011; Qiao et al. 2008; Ramocki et al. 2009; Shinawi et al. 2009; Thomas et al. 1999; Vazna et al. 2010; Young et al. 2008). Thus, Young et al. (2008) appropriately draw attention to the importance of minimizing misdiagnosis of an ASD by ruling out the possibility of known genetic conditions. Further, such case reports do not provide enough evidence to evaluate specific gene, or genetic network, involvement in ASD.

X-Inactivation

There is growing agreement among researchers that the X-chromosome is involved in ASD and moreover that this chromosomal involvement may serve as a protective factor for females. As females have two X chromosomes, they hence have double the amount (or dose) of X-chromosome genes compared to males. X-inactivation is a process by which one of the two X-chromosomes in female mammals (including humans) is randomly inactivated to equate the number of active X-genes between males and females (Avner and Heard 2001). An X-chromosome can be inactivated at random, although there is also evidence to suggest that in some cases, preferential inactivation can occur. Matsuo et al. (1999) suggest that in a female, expression of symptoms associated with an abnormal gene may be suppressed due to the preferential inactivation of a mutated or abnormal gene on an X-chromosome. Consequently, when such symptoms are expressed, this may occur as a result of incomplete preferential inactivation, or random inactivation of the affected gene (Matsuo et al. 1999). It has

been suggested that this may also be the case in ASD (Edens et al. 2011), however this is yet to be empirically addressed. The available literature on the role of X-inactivation in ASD is limited and the findings contradictory. Loat et al. (2008) attribute skewed or non-random X-inactivation to autistic-like symptomatology in healthy individuals. Empirical studies (Talebizadeh et al. 2005) and case reports (Edens et al. 2011; Shinawi et al. 2009; Vazna et al. 2010) investigating peripheral blood cells among affected females further support this claim. Talebizadeh et al. (2005) report that affected females displayed a significantly greater percentage of X-inactivation skewness in comparison to healthy siblings. While highly skewed X-inactivation was noted in some of the TD children, of note is that 50 % (5 out of 10) of mothers with autistic daughters with highly skewed X-inactivation also showed skewed X-inactivation, while none of the mothers of non-affected children with highly skewed X-inactivation displayed this trend. Such abnormalities may be genetically passed or occur de novo (Thomas et al. 1999). Furthermore, no identifiable genetic mutation was identified or associated with this skewness (Talebizadeh et al. 2005). Findings to the contrary, however, have been reported in studies assessing blood (Gong et al. 2008) and brain (Nagarajan et al. 2008) cells of females with ASD and mothers of affected children. While some mothers of girls with ASD were found to have highly skewed X-inactivation, Gong et al. (2008) did not find a significant difference between these mothers and healthy controls, nor did they find a significant difference between affected girls and healthy controls. The cause of these inconsistent findings remains unknown, but considering the available literature as a whole it could be speculated that (a) while preferential X-inactivation may protect females from expressing X-linked mutations, mutations on the remaining autosomes do not have the same amount of biological protection, and (b) some genes on the inactive chromosome continue to be expressed (see Baron-Cohen et al. 2011), and, hence, the possibility of mutated genes being expressed on these "inactivated" chromosomes does still exist. Given that X-inactivation is a phenomenon occurring only in females, it would be impossible to compare gender differences to this extent, however the available research on this phenomenon does assist in our understanding of the gender ratio observed in ASD.

Parental Imprinting

Another hypothesis in support of the X-chromosome serving as a protective factor in affected females is that of genetic imprinting. To be clear, as females inherit one X-chromosome from either parent, it is hypothesized that the presence of a paternally inherited X-chromosome

existing only in females may raise their threshold for phenotypic expression of autistic symptomatology (see Skuse 2000). Genomic imprinting involves the silencing, or deletion, of alleles or genes from one parent. With respect to ASD, it has been hypothesized that a paternally imprinted X-gene may increase liability to express the ASD phenotype. As this paternally inherited X-chromosome is not present in males, they are less protected (Skuse 2000). Research investigating the role of maternal versus paternal X-chromosome inheritance in females with Turner's syndrome (a monosomic condition where one X-chromosome is completely or partially deleted) has provided some evidence to suggest that genetic imprinting may play a role in the symptomology and gender ratio observed in ASD (Skuse et al. 1997). This study found that those with a paternal X-chromosome displayed greater social skills (potentially mediated by greater executive functioning) and verbal intelligence, and were less likely to receive educational special needs recommendations in comparison to those with a maternal X-chromosome (Skuse et al. 1997). Further, Creswell and Skuse (1999) present five cases of girls with Turner's syndrome and ASD. All cases analysed displayed a genetically intact maternal X-chromosome and a genetically abnormal or absent paternally derived X-chromosome, further supporting the hypotheses that (a) genetic imprinting influences the gender ratio observed in ASD, and (b) paternal X-chromosomes serve as protective factors in the expression of ASD (Creswell and Skuse 1999). To date, while there is growing discussion regarding the role of genetic imprinting mediating the expression of ASD between males and females (see Badcock 2011; Baron-Cohen et al. 2011; Creswell and Skuse 1999; Skuse 2000; Skuse et al. 1997), there have not been, to our knowledge, any studies directly assessing the impact of X-chromosome imprinting in the observed gender ratio in ASD. Further research directly exploring this hypothesis in an ASD sample is imperative to further our understanding of the genetic nature of the condition.

Evidence from Sex Chromosome Aneuploidies

Individuals with sex chromosome aneuploidies involving an affected X-chromosome, such as Turner's syndrome (XO) (Skuse et al. 1997), or trisomies such as Klinefelter syndrome (XXY), are reported to display some level of autistic traits (Bruining et al. 2009; van Rijn et al. 2008), and in some cases may even have a comorbid diagnosis of ASD (Bishop et al. 2011). Notably, comorbid diagnosis (Bishop et al. 2011), or ASD traits (Ross et al. 2012), have also been noted in individuals with XYY syndrome, a trisomy with an affected Y chromosome. Moreover, these studies note that these characteristics were more prevalent

among XYY boys, in comparison to XXY boys (Bishop et al. 2011; Ross et al. 2012). Though preliminary, these studies lend some support to sex chromosome abnormalities being involved in ASD, with Y-chromosome effects perhaps being particularly pronounced (see Baron-Cohen et al. 2011). Symptomatically, sex chromosome aneuploidies may most affect social, language and communication skills amongst affected individuals (Bishop et al. 2011; Lee et al. 2012). While X and Y aneuploidies have both been associated with ASD symptomatology, there does not appear to be a dosage effect (relative to the number of additional chromosomes) of additional X-chromosomes in social difficulty (Lee et al. 2012). The authors however, describe X-chromosome dosage effects of increased impairments in structural language, while a Y-chromosome dosage effect may be present relative to pragmatic language impairment. Such chromosomal abnormalities account for a very small portion of ASD cases and are associated with a wide variety of comorbid medical conditions as well as intellectual disability that could increase the level of autistic symptomatology independent of direct effects of X or Y chromosome genes. It should also be noted that social and communicative deficits, while cardinal features of ASD, are also found in a number of other psychiatric conditions (Bruining et al. 2009; van Rijn et al. 2008).

Hormonal Influences

The *androgen theory* of autism proposes that exposure to elevated levels of fetal testosterone is associated with the development of ASD and associated symptoms (Auyeung et al. 2009; Baron-Cohen et al. 2005; Chapman et al. 2006; Knickmeyer et al. 2006a; Knickmeyer and Baron-Cohen 2006; Knickmeyer et al. 2008; Milne et al. 2006). Behaviorally, this can be supported by the *extreme male brain theory,* which describes ASD as being extreme variants of the male brain given the superior proficiency in systemizing tasks and difficulty with empathizing (Baron-Cohen et al. 2005).

Researchers have identified a trend suggesting that the ratio of the lengths of the second and fourth digits (2d:4d) is negatively correlated with exposure to elevated levels of prenatal testosterone (Lutchmaya et al. 2004). In TD populations, this ratio is known to be sexually dimorphic, with males having a lower 2d:4d ratio compared to females, for whom this ratio has been reported to be almost equal (Manning et al. 1998). It appears that females with ASD may be more vulnerable to effects of male androgens than their male counterparts as a result of elevated exposure to prenatal testosterone, which seems to balance out this aforementioned sexual dimorphism. While lower 2d:4d ratios have been noted in individuals with ASD (Milne

et al. 2006) and in their immediate family (Manning et al. 2001) compared to TD individuals, there does not appear to be an effect of gender on this ratio in affected children (Bloom et al. 2010; Manning et al. 2001), which would indicate an increased effect of exposure to fetal testosterone among affected females. Among an adult sample however, Bejerot et al. (2012) noted higher 2d:4d ratio among men with ASD compared to TD men. Similar ratios were noted between women with ASD and TD women. Two considerations must be made here - these studies are correlational in nature, and should be interpreted accordingly and moreover, Bejerot et al. (2012) identify that 2d:4d ratio can normalize with age, and hence may explain the lack of support for previous findings.

At a biological level, Ruta et al. (2011) provide evidence to suggest elevated androgen levels among individuals with ASD. Notably, while in TD samples males have higher androgen levels than females, comparable androgen levels between males and females with ASD were noted (Ruta et al. 2011). This therefore suggests that while androgen levels are elevated in males and females with ASD, the effect of this may be increased among affected females. Moreover, females with ASD have been noted to have higher bioactive testosterone compared to TD females (Bejerot et al. 2012), while affected males had comparable testosterone levels to TD males. Moreover, while investigating this theory at a molecular level, Schwarz et al. (2011) note sex-specific biomarkers between those affected with AD and TD controls. Female sex-specific analytes included growth factors such as brain derived neurotropic factor and hormones such as growth hormone, luteinizing hormone and free testosterone, as well as endothelin-1. Male sex-specific analytes included cytokines, fatty-acid binding protein, chromogranin A, thrombopoietin, and erythropoietin. Overlap was seen between sexes for interleukin, tissue factor, IL-1B, and glutamic oxaloacetic transaminase 1. Moreover, the identified analytes in females were shown to predict diagnosis (AD or control) reliably in females, but not males, and vice versa, thus highlighting that the observed gender differences in AD extend beyond the level of the behavioral phenotype (Schwarz et al. 2011). This study provides biological support for the androgen theory of autism, as mentioned above, and the androgen related biomarkers and heightened testosterone identified in affected females may indicate greater exposure to fetal testosterone among this cohort.

These theories have led to speculation regarding the influence of the male hormone testosterone and the development of male offspring, and therefore the greater prevalence of ASD in the male population (see Mouridsen et al. 2010). Moreover, the effects of prenatal androgen exposure have been implicated in some of the hormonal aspects observed in females with ASD (Ingudomnukul

et al. 2007; Knickmeyer et al. 2006b), as will be discussed below. Contrary to this theory however, Bejerot et al. (2012) describe ASD as a gender defiant disorder, rather than an extreme male brain, given the observed androgynous features identified in affected men and women.

Associated Biological Complications

Ingudomnukul et al. (2007) hypothesized that this exposure to abnormally high levels of androgens may increase the risk of hormone related medical complications for females with ASD. Compared to healthy controls (mean age 43.4 years), females with ASD (mean age 38.2 years) reported higher instances of hormone related conditions such as hirsutism and polycystic ovary syndrome, as well as pubertal abnormalities such as delayed onset, severe acne and irregular or delayed menstrual cycle. Knickmeyer et al. (Knickmeyer et al. 2006a, b) also support that females with ASD have a delayed onset of menstruation and note that this could result from abnormally high exposure to fetal testosterone.

Further, women with ASD and mothers of affected individuals (male and female) report increased instances of personal or family history of ovarian, uterine or prostate cancers, growths and tumors (Ingudomnukul et al. 2007). More recently, a study by Kao et al. (2010) notes a relationship between the prevalence of ASD and the occurrence of specific female forms of cancer, with breast cancer of highest prevalence. In contrast, a pilot study by Blatt et al. (2010) including both males and females found no evidence of a different prevalence rate of cancer among children and adolescents with ASD in the general population. The authors note the preliminary nature of this study and the small sample size as limitations to the findings. The age range of this study must also be considered: both the studies by Kao et al. (2010) and Ingudomnukul et al. (2007) note such findings among older individuals with ASD. While it would be impossible to explore gender differences with regard to some of these conditions, such findings do assist in our understanding of the wider implications that females with ASD may experience.

Brain Development

The past decade has seen a dramatic increase in researchers' understanding of ASD at a neurological level. A cross-sectional study of children aged 2–16 years by Courchesne et al. (2001) was among the first to note abnormal neuroanatomical growth in affected individuals, including significantly larger head circumference, total brain volume (TBV) and abnormal gray and white matter volumes compared to TD children. Prenatally (Whitehouse et al. 2011), and even at birth (Courchesne et al. 2001; Whitehouse et al.

2011), these features are comparable between affected and non-affected infants. Retrospective measures of head circumference indicate that accelerated brain growth can begin as early 4–5.9 months for some individuals (Nordahl et al. 2011) and becomes most prominent between the ages of 2–4 years, after which a slowing in this growth is described (Courchesne et al. 2001). Following this period of aberrant brain growth, there appears to be a cessation in this growth pattern, leading to a balancing out, or even a slight decrease in the brain size of those with ASD compared to neuro-typical individuals (Aylward et al. 2002; Courchesne et al. 2001).

Not surprisingly given the heterogeneity of ASD, a great deal of variance has been noted in this abnormal growth in various parts of the brain, between genders (Bloss and Courchesne 2007; Nordahl et al. 2011; Schumann et al. 2009, 2010), and also in relation to symptom onset patterns (Nordahl et al. 2011). While it is well established that sexual dimorphisms exist at a neurological level in healthy individuals (Reiss et al. 1996; Wilke et al. 2007), few studies have explored this phenomenon in those with ASD. From these studies which have included female participants *and* investigated gender differences, it has emerged that affected females may not only display an altered neuropathophysiology (Courchesne et al. 2001; Sparks et al. 2002) compared to the abnormal pattern of brain development observed in affected males, but also that this neuroanatomical growth pattern may be more global and severe in the affected female ASD population (Bloss and Courchesne 2007; Schumann et al. 2009, 2010). Important to note, however, is that to date these studies are limited by sample size, including more than three times the number of affected boys relative to girls.

Bloss and Courchesne (2007) directly explored gender differences at a neurological level in those affected by ASD. They describe a substantial neuroanatomical difference between affected boys and girls, while controlling for expected sexual dimorphisms. The authors note that affected females displayed all of the size-related abnormalities observed in affected boys; however, the extent of this appeared more severe and widespread in the female sub-group. Z-score calculations based on sex-matched controls suggest that affected females experienced greater abnormality than affected males in temporal gray and white matter, and cerebellar gray matter volumes. Furthermore, compared to same-sex controls, girls with ASD showed reduced cerebellar grey matter volume, while no such reduction in structural volume was noted in the boys with ASD (Bloss and Courchesne 2007). Moreover, while noting bilateral enlargement of the hippocampus and amygdala among affected males, this pattern of enlargement was not observed among the female sub-sample (Sparks et al. 2002). In contrast, while amygdala enlargement overall

was noted in the ASD sample recruited by Schumann et al. (2009), the authors note greater enlargement of the amygdala among affected females than in affected males, compared to age and sex-matched healthy controls. Moreover, while investigating structural abnormalities among an ASD sample, Sparks et al. (2002) note that among affected males, cerebellar size was enlarged proportionally to that of the cerebrum, but this pattern was not observed among the female sample. Hence the possibility that females with ASD experience a somewhat different (rather than more severe) pattern of brain abnormality must be considered. Beacher et al. (2012), albeit in an adult sample, provide further evidence to support the notion of different, rather than more severe brain abnormality among affected females. In particular, the authors suggest that the expected sexual dimorphisms observed in TD populations are atypical in those with AD (Beacher et al. 2012). Increased grey matter in the right inferior parietal lobule and rolandic operculum, and increased factional anisotropy (FA) in the corpus collosum, the bilateral cingulum and the corona radiata were noted in TD males versus females, however this difference was not present when comparing the AD sub-groups. Moreover, trend level data indicates lower FA in males with AD compared to TD males.

In terms of the neurodevelopmental growth trajectory among those with ASD, Bloss and Courchesne (2007) suggest that affected boys may reach their peak brain growth earlier than affected girls, for whom growth of certain regions continues (Bloss and Courchesne 2007). Furthermore, the authors note a correlation between age and cerebral, frontal, parietal and occipital white matter volume in females with ASD, while an age related correlation was observed only in frontal and parietal white matter of matched controls. In comparison, there was no age related correlation for any structure or tissue of interest in the male ASD sample, despite significant age related correlations being observed for most structures and tissues of interest in matched controls (Bloss and Courchesne 2007; see also, Giedd et al. 1999). A longitudinal study by Schumann et al. (2010) provides further support for the notion of an altered neurodevelopmental trajectory between affected boys and girls with autism. Specifically, the authors report an age-by-diagnosis interaction for parietal and cingulate gray matter, as well as total cerebral volume, in males. A greater number of regions showed an age-by-diagnosis interaction in females, including frontal, temporal, and parietal gray matter, as well as total white matter volume, total gray matter volume and total cerebral volume. While the aforementioned studies have investigated children, Tepest et al. (2010) found no sex differences in TBV and corpus callosum size while comparing adults with ASD. While undoubtedly an important finding, as

mentioned previously in this review, this pattern of atypical brain growth is most prominent in the early years of childhood, after which a pattern of normalization arises (see Redcay and Courchesne 2005).

While there is now evidence suggesting a possible difference in brain growth patterns between males and females with ASD, the impact of this difference in relation to symptom presentation, expression and severity remains unknown. Schumann et al. (2009) note that while affected females exhibited substantially larger amygdala volumes, there was no significant correlation between structural volume and well-established clinical measures of symptom severity, while a significant correlation between these two variables was found for affected males. Moreover, Nordahl et al. (2011) examined total cerebral volume in relation to symptom onset (early onset or regression), and found that affected males who had experienced regression had increased total cerebral volume in comparison to TD individuals, while those who did not experience regression were comparable to matched controls. In contrast, this pattern was not present in the female sub-sample.

To date, the cause of this atypical brain development is yet to be determined. Factors such as premature myelination, excessive proliferation of axons and dendrites (Courchesne et al. 2003; Courchesne et al. 2001), ineffective synaptic pruning (Schumann et al. 2010), and atypical levels of brain-derived neurotrophic factors (Schumann et al. 2010; Schwarz et al. 2011) have all been implicated in this process, however further research would be required before solid conclusions can be drawn.

Associated Neurological Complications

While ID is often diagnosed comorbidly with ASD (see Fombonne 2003; Matson and Shoemaker 2009), a consistently replicated finding is that females diagnosed with ASD are at increased risk of this comorbidity (Banach et al. 2009; Cohen et al. 2010; Fombonne 2003, 2009; Lord and Schopler 1985; Tsai and Beisler 1983; Volkmar et al. 1993; Wing 1981). This increased prevalence of ID among affected females has been demonstrated to potentially lead to more severe complications for this group. As has been discussed throughout this paper, however, there remains the possibility that many affected females may be un-or misdiagnosed, and consequently excluded from such studies. Thus, it is pertinent that this be considered as a factor possibly leading to bias in results, and such studies considered with caution.

It is well established that epilepsy is common among individuals with ID (Balogh et al. 2010); and moreover, that epilepsy may be more common in females with ASD (Danielsson et al. 2005; Gabis et al. 2005; Turk et al. 2009). Importantly, Gabis et al. (2005) found that this

comorbidity was more common in individuals diagnosed with autistic disorder rather than in those with AD or PDD, NOS. Hence, those on the lower-functioning end of the autism spectrum are more likely to have an additional diagnosis of epilepsy (Gabis et al. 2005). This is consistent with the notion that females are affected by a more severe ASD phenotype compared to males (Nydén et al. 2000) and that females tend to be more represented at the lower-functioning end of the autism spectrum (Chakrabarti and Fombonne 2005; Fombonne 2003).

A meta-analysis of 23 studies exploring comorbid ID, ASD, and epilepsy highlighted that the risk for epilepsy in those with ASD may be related to ID, and also to sex (Amiet et al. 2008). This study noted the male: female gender ratio of those affected with ASD and epilepsy to be 2:1 (Amiet et al. 2008), bearing a striking similarity to the gender ratio noted for individuals with comorbid ASD and ID (Fombonne 2003) and further supporting that females with ASD are more severely affected. Danielsson et al. (2005) noted an even smaller, almost equal gender ratio among individuals with ASD and epilepsy (1.2:1) in a sample of individuals all with ASD and ID. This can further be supported by the finding of Gabis et al. (2005), who noted that epilepsy was more common in those on the lower-functioning end of the autism spectrum compared to those with AD, given that a) intellectual disability is not present in individuals with AD and b) the wider gender ratio seen in AD as compared to ASD (Chakrabarti and Fombonne 2005). This, however, is not supported by a retrospective follow-up study by Hara (2007) exploring epilepsy in individuals with ASD and varying levels of ID (normal/mild [IQ > 50], moderate [IQ 35–49], severe [IQ 20–34] and profound [IQ < 19]). In this study, gender was not identified to be a factor contributing to the rates of epilepsy among these individuals.

Considerations for Future Research

When considering the available literature, three main limitations are evident. Possibly one of the greatest limitations in the literature regarding gender differences in ASD is the statistical and methodological approached often employed. Often, studies do not include enough females to conduct gender comparison, or even recruit entirely male samples. Consequently, there is a heavy reliance on research with a strong male bias. Unfortunately, given the difficulty of recruitment to this extent as a result of increased prevalence of ASD among males, in many cases controlling for this limitation is quite difficult. This limitation has been addressed by recent studies however, with many including equal sample sizes, with enough female participants to perform gender comparison (Beacher et al. 2012; Bejerot et al. 2012; Lai et al. 2011, 2012; Mandy et al. 2012; Ruta et al. 2011; Szatmari et al. 2012).

Second, while interpreting the literature, researchers must consider the methodology and measures used. For example, many of the aforementioned studies used well-established and reputable instruments for the diagnosis and identification of ASD in research settings, some of which relied on parent report while others on clinical observation. Kopp et al. (2010) draw our attention to an important point regarding the use of parent report measures. In an entirely female sample, the authors noted a subset of cases for whom parent report indicated scores well below the cut-off for a pervasive developmental disorder on the ADI-R. In the clinical context, however, the authors state that these girls "were found socially very disabled, odd, and with impaired functioning" (Kopp et al. 2010; p. 173). Pilowsky et al. (1998) further accentuate this concern, explaining that of the 70 participants diagnosed based on the ADI-R and Childhood Autism Rating Scale (a measure based on clinical observation and interaction with the patient), 10 had their diagnosis supported by only one of these measures; 50 % each for the parent report and clinical observation. This observation is by no means intended to suggest or imply the superiority of either form of assessment, simply to recognize the potential confounds of such assessment.

Moreover, considering the possibility of an altered clinical presentation of ASD among females (Attwood 2007), affected females may be undiagnosed or misdiagnosed, and therefore excluded from research due to a poor understanding of the clinical manifestation of this disorder in this group. For example, Lai et al. (2011) note that many of the affected females involved in their study failed to meet the cut-off criteria for the ADOS, however met the criteria for a clinical diagnosis as determined by experienced clinicians and the ADI-R. This is supported by a number of case studies presented by Kopp and Gillberg (1992), which suggest that females with ASD may present with a phenotype that is difficult to categorize/diagnose, calling for more in-depth and detailed clinical assessment. Those females who have been diagnosed with ASD based on current criteria will score accordingly; for those females who present with an atypical phenotype, however, they will be considered "odd" rather than being formally or accurately diagnosed. It has further been suggested that, even when symptom severity is comparable between males and females, the latter are less likely to receive a formal diagnosis (Giarelli et al. 2010; Russell et al. 2011). Begeer et al. (in press) highlight that while in children, affected girls with autistic disorder were diagnosed later than boys with AD, there was no difference in age of diagnosis for autistic disorder or PDD, NOS. Moreover, among an adult sample, females with autistic disorder were diagnosed later than males with autistic disorder, while there was no difference in age of diagnosis for AD or PDD, NOS. These

differences in age at diagnosis may, at least in part, be mediated by associated differences in cognitive profiles (e.g. ID) or comorbidities (e.g. seizures), resulting in autistic behaviors being considered a secondary problem to the other conditions (Giarelli et al. 2010). Research investigating screening for autistic traits in the general population highlights the need to investigate specific response styles (Posserud et al. 2008), or more specifically, to account for known gender differences in behavioral profiles (Williams et al. 2008) rather than relying primarily on cut-off scores (Posserud et al. 2008). A recent study, and one of the first to investigate gender differences between children with a diagnosis of ASD versus those without a clinical diagnosis but scoring highly on the CAST, supports this notion. Dworzynski et al. (2012) note that the difference between diagnosed and non-diagnosed girls' overall CAST score did not differ significantly, while there was a significant CAST score difference between diagnosed and non-diagnosed boys. Moreover, with regard to the clinical triad, diagnosed girls had greater social impairment than high-CAST girls. Communicative and RRBI impairments were comparable between high-CAST girls. Diagnosed boys however, had greater social and communicative impairment compared to high-CAST boys, while RRBI profiles were similar for this cohort. The authors interpret this finding as reflective of either (a) some unknown coping mechanism protecting girls from reaching the threshold for clinical diagnosis, or (b) as being reflective of a strong male bias in the clinical understanding of ASD resulting in females with ASD being un- or misdiagnosed (Dworzynski et al. 2012). Kopp and Gillberg (2011), to our knowledge, present the first published attempt to account for gender specific characteristics. The Autism Spectrum Screening Questionnaire-Revised Extended Version (ASSQ-REV) is based on the original ASSQ, however has been revised to include 18 additional items perceived as being specific to the clinical presentation of females with ASD. While boys and girls with ASD did not differ on this measure (Kopp and Gillberg 2011), and more in-depth clinical research would be required to formulate more reliable female specific items and measures, future research of this type is imperative for our understanding of the female profile of ASD.

Finally, it is important for researchers to consider the impact that additional confounding variables such as age (Carter, et al., 2007; McLennan, et al. 1993) or cognitive ability (Lord et al. 1982; Nydén et al. 2000; Volkmar et al. 1993) may have on perceived gender differences. Lai et al. (2012) note correlations between age and reaction time, as well as IQ and response accuracy. Thus, it is important that these variables are considered and accounted for. For example, females with ASD have been shown to present with more severe, or at least atypical, impairment regarding

clinical expression compared to affected males (particularly social and communicative characteristics, as described previously in this review), however this effect tends to disappear when controlling for cognitive abilities (Lord et al. 1982; Volkmar et al. 1993). Dworzynski et al. (2012) provide preliminary support that cognitive ability may serve as an underlying factor contributing to the gender ratios observed in those diagnosed with ASD. They highlight that odds for girls with ASD who fall 1.5 standard deviations (SD) below the average for overall verbal and non-verbal cognitive abilities were 4–9 times greater than non-ASD (high scoring CAST) girls. In comparison, a similar finding was only noted for males with regard to verbal cognition, and the odds were much lower (only 2.5 times more likely to fall 1.5 SD below the mean; Dworzynski et al. 2012). While many studies commonly recruit individuals with HFA, in several instances researchers fail to include those on the lower-functioning end of the spectrum, or those who have a cognitive impairment. Given ethical and methodological difficulty in recruitment of the latter, this is understandable, albeit concerning given that our knowledge of this debilitating disorder remains extremely biased. On one hand, while the literature describing the presentation of ASD in high-functioning females is growing, there is an entire sub-group (those with cognitive impairment, or who fall just below cut-offs for clinical diagnosis) for whom researchers have an extremely limited knowledge. Importantly, as it currently stands, research indicates that a greater proportion of affected females fit into this category (Fombonne 2003, 2009). Moreover, as is described above, there may be many affected females across the spectrum who are not included in such studies as a result of altered clinical presentation.

Conclusion

Though the literature is scarce, it appears that the implications of female gender in ASD are twofold. On the lower-functioning end of the spectrum, while males are still predominantly represented, the incidence of females with ASD increases dramatically, indicative of a more severe cognitive impairment among affected females who are diagnosed with ASD. Yet the altered presentation of clinical symptoms, as well as cognitive profiles and comorbid conditions experienced by females on the higher-functioning end of the spectrum, may serve to mask or camouflage their clinical symptoms, resulting in under- or misdiagnosis among this cohort. While researchers are yet to determine a mechanism directly accountable for these observed sex differences, our increasing understanding of biological, neurodevelopmental and comorbid mediators brings forth the opportunity for many novel hypotheses to

be explored. Much of the available literature to this extent is preliminary and contradictory, and as yet no solid conclusions can be drawn. Nonetheless, such research is imperative for increasing researchers', clinicians', and the community's knowledge of ASD.

The literature to date is biased toward an understanding of the *male* profile of autism, and an extremely limited knowledge of the female profile is available, potentially leading to inappropriate treatment and management of symptoms for this cohort. It is imperative that future research aims to better understand autism from a female perspective. Gender comparisons should be conducted in prospective studies, exploring behavioral and neurobiological mechanisms underlying the disorder that may affect clinical presentation. Such research is crucial to ensure that the best possible level of care is provided to all individuals affected by this debilitating disorder and that future treatment options are more directed and suitable for all who are affected.

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