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Gender differences in core symptomatology in autism spectrum disorders across the lifespan

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GENDER DIFFERENCES IN CORE SYMPTOMATOLOGY IN AUTISM SPECTRUM DISORDERS ACROSS THE LIFESPAN

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TABLE OF CONTENTS

ABSTRACT

A preponderance of males with autism spectrum disorders (ASD) has been evident since the initial writings on the topic. This male predominance has consistently emerged in all ASD research to date in epidemiological as well as clinical populations. Despite this long recognized gender disparity in ASD, surprisingly there is a paucity of research addressing gender as it relates to core ASD symptom presentation. Gender differences may manifest with regard to symptom domains, severity, breadth, and so forth. The present research examined gender differences in ASD symptomatology in three populations: infants and toddlers at risk for developmental disability, children and adolescents, and adults with intellectual disability (ID). No significant gender differences in ASD symptoms were found in the infant/toddler or child/adolescent populations. In the adult population, in participants with ID alone, females had higher endorsements of social (i.e., participation in social games, sports, and activities; interest in other's side of the conversation; and imitation) and communication (i.e., interest in other's side of the conversation and reading body language) impairments compared to males. This study has considerable implications in both the clinical and research realms regarding identification and intervention issues for females with ASD, as well as stimulating a future research agenda in this area.

INTRODUCTION

A preponderance of males in autism spectrum disorders (ASD) has been evident since the two seminal publications associated with the origin of the disorders (Asperger, 1944; Kanner, 1943). In 1943, Leo Kanner published *Autistic Disturbances of Affective Contact*, describing 11 cases, 8 of whom were boys. In 1944, Hans Asperger published *'Autistic Psychopathy' in Childhood* (translated title) describing 4 "prototypical" cases, all of whom were male. This gender disparity has been consistently reported to date, with current estimates of a male to female ratio of approximately 4:1 (Fombonne, 2003, 2005, 2007). Although there is a long history of a consistently identified gender disparity in ASD, a paucity of research has addressed gender as it relates to core symptom presentation in ASD.

The present review will present background information on ASD, such as the history and current diagnostic criteria. Next, assessment instruments for ASD which have been employed in studies of gender differences will be described. Following will be a brief discussion of findings involving gender differences in typically developing individuals in domains relevant to ASD. Finally, an in depth review of the literature base on the nature and etiology of gender differences in ASD will be presented.

History

Leo Kanner (1943)

In 1943, Leo Kanner described 11 children with common characteristics which "form a unique 'syndrome,' not heretofore reported" (Kanner, 1943, p. 242). He reported that some of these children may have previously been considered as "feebleminded or schizophrenic" (Kanner, 1943, p. 242). However, he provided distinguishing features characteristic of autism.

Kanner acknowledged that this report was preliminary since all of the children were at the time still under the age of 11 (Kanner, 1943).

Kanner designated the core symptom as an "*inability to relate themselves* in the ordinary way to people and situations from the beginning of life," an "*extreme autistic aloneness* that, whenever possible, disregards, ignores, shuts out anything that comes to the child from the outside" (Kanner, 1943, p. 242). The children did not assume an anticipatory posture prior to being picked up. They did not respond when spoken to, and some had been thought to have hearing impairments. They did not attend to others, were indifferent to being separated from parents, and did not interact or play with other children. Kanner noted that three of the children were "mute;" however, two of them had been reported to say some words. Moreover, Kanner declared that there was no "fundamental difference" from the verbal children, as they had excellent rote memory, but did not use language for communication to convey meaning (Kanner, 1943, p. 243). They exhibited echolalia, pronoun reversal, and literal and inflexible interpretation and use of language. In addition, Kanner classified food as an intrusion from the outside, noting that the children exhibited food refusal, vomiting, and feeding difficulties (Kanner, 1943). Also described as an intrusion from the outside were "*loud noises and moving objects*" (e.g., tricycles, elevators, vacuums, egg beaters, stethoscope examination, etc.) which triggered "a major panic" (Kanner, 1943, p. 245).

In addition to aloneness, another main feature described by Kanner included "an *anxiously obsessive desire for the maintenance of sameness*" (Kanner, 1943, p. 245, 1971). The children's actions were as "*monotonously repetitious*" as their speech (Kanner, 1943, p. 245). They were distressed by changes in routine and surroundings, or things being broken or incomplete. Items such as blocks had to be arranged in a certain way. The children engaged in

certain rituals and insisted on activities being completed in the same order or way. There was a "*limitation in the variety of spontaneous activity*" (Kanner, 1943, p. 246). The children had a "good *relation to objects*" and pictures in contrast to people (Kanner, 1943, p. 246). They engaged in spinning objects and rhythmic body movements. In his conclusion, Kanner stated, "All of the children's activities and utterances are governed rigidly and consistently by the powerful desire for aloneness and sameness" (Kanner, 1943, p. 249).

Regarding intelligence, Kanner (1943, p. 247) stated "Even though most of these children were at one time or another looked upon as feebleminded, they are all unquestionably endowed with *good cognitive potentialities*. They all have strikingly intelligent physiognomies." Kanner pointed to strengths in vocabulary and memory, and purported that formal intelligence testing could not be carried out due to "limited accessibility" (1943, p. 248). He also noted that all of the children came from "*highly intelligent families*" (Kanner, 1943, p. 248); though, he did not acknowledge the bias with regard to access to services.

Finally, Kanner acknowledged the similarities between "the combination of extreme autism, obsessiveness, stereotypy, and echolalia" and schizophrenia (Kanner, 1943, p. 248). However, he asserted the conditions were separate for several reasons. In autism, symptoms are present from birth. In addition, relations to objects, although not people, remain intact in autism. Regarding the course, Kanner reported progress and improvement in autism. He noted that in schizophrenia, people withdraw from the world they were previously in touch with. In contrast, in autism, the children "gradually *compromise*" into a world they were never in touch with (Kanner, 1943, p. 249). He reported that speech becomes more spontaneous and functional, eating improves, noises and moving objects are better tolerated, tantrums decrease, and rote reading ability is acquired (Kanner, 1943). Moreover, the need for contact with other people in

some aspects is recognized and the children start playing alongside, although not with, peers (Kanner, 1943).

Hans Asperger (1944)

Kanner and Asperger published their seminal articles on "autistic" conditions in children around relatively the same time. Yet, Kanner's writings were well recognized internationally, in contrast to Asperger's which did not receive much attention for decades (Van Krevelen, 1971; Wing, 1981a). Hans Asperger had first described autism in 1938 (Asperger, 1938), and published *Die „Autistischen Psychopathen" im Kindesalter* in 1944. However, it was not until 1981 when Lorna Wing published *Asperger's Syndrome: A Clinical Account* (Wing, 1981a) that greater interest ensued in the English literature. Moreover, Asperger's 1944 publication was not translated into English for 47 years (translated as *'Autistic Psychopathy' in Childhood* [1] by Uta Frith in 1991). Although Kanner and Asperger spoke the same language, were from the same city, and described similar cases in the same year using the same terminology (autism), it is often acknowledged that they never met and were not aware of each other's work (e.g., Frith, 2004; Van Krevelen, 1971). Conversely, some have recently claimed that although Asperger was not aware of Kanner's 1943 article, Kanner may have been aware of Asperger's 1938 published lecture (Fitzgerald, 2008; Lyons & Fitzgerald, 2007).

Asperger acknowledged Bleuler's contribution in coining the term "autism" to capture symptoms in schizophrenia (Asperger, 1944; Bleuler, 1910, 1911, 1950; Frith, 1991). According to Asperger, the similarity in autism and schizophrenia was in "the shutting-off of relations between self and the outside world" (Asperger, 1944; Frith, 1991, p. 39). Asperger noted that the contrast is that in autism, this disconnection is present from the start, while in schizophrenia it is

[1] Frith (1991, p. 37) noted that the term "autistic psychopathy" could have been translated into "autistic personality disorder" in today's terminology.

progressive (as also noted by Kanner), in addition to the lack of psychosis in autism (Asperger, 1944; Frith, 1991).

Asperger presented 4 prototypical cases, all boys ranging from 6 to 11 years in age (Asperger, 1944; Frith, 1991). Consistent with Kanner, Asperger declared social impairment as the core feature of autism (Asperger, 1944; Frith, 1991). The children he described were not able to understand or apply the unwritten rules of social behavior. Klin, McPartland, and Volkmar (2005) and Wing (1981a) summarized Asperger's observations of the children's characteristics as follows: impairment in nonverbal communication (e.g., facial expressions, gestures, decoding other's cues); idiosyncratic verbal communication (e.g., pedantic "little professor" speech, one-sidedness in conversation, pronoun reversal, repetitive speech, neologisms, lack of understanding of subtle jokes, inappropriate intonation); special interests or egocentric preoccupations with unusual and circumscribed interests that interfere with social/adaptive functioning (e.g., early knowledge of letters and numbers; rote memory strengths; vast knowledge in areas such as astronomy, history, bus routes; mass accumulation of facts; musical ability; all despite specific learning problems in some subjects); intellectualization of affect (e.g., poor empathy); repetitive activities and resistance to change (e.g., spinning objects, distress in unfamiliar places; collecting objects); motor abnormalities (e.g., clumsiness, odd posture and gait, poor coordination, impaired writing, stereotyped body/limb movements); and behavior/conduct problems (e.g., school problems, aggression, noncompliance, bullying by peers, anxiety). Additionally, Asperger reported that autism was not recognized prior to 3 years of age, and that these autistic traits ran in families (Klin, McPartland, et al., 2005; Wing, 1981a).

Of particular importance is that, in contrast to Kanner (1943), Asperger (1944) wrote about the gender disparity in autism. He wrote, "It is fascinating to note that the autistic children

we have seen are almost exclusively boys" (Asperger, 1944; Frith, 1991, p. 84). He noted that some girls had "contact disturbances which were reminiscent of autism," though none had the "fully formed" or "fully fledged" picture as did the four boys presented (Asperger, 1944; Frith, 1991, pp. 84-85).

Upon exploring the current literature and hypotheses for the gender disparity in ASD, Asperger's original writings on gender differences have significant relevance. Asperger admitted that the etiology was not known (Asperger, 1944; Frith, 1991). He noted that some girls had developed these traits after encephalitis. He purported, "There is certainly a strong hint at a sex-linked or at least sex-limited mode of inheritance" (Asperger, 1944; Frith, 1991, p. 84). Further, he noted that it could just be by chance that he had not encountered autism in girls, or that autistic traits in girls are not apparent until post-puberty. Asperger also observed that several mothers of children with autism had autistic features (Asperger, 1944; Frith, 1991). Finally, Asperger related symptoms of autism to a number of purported important gender variables (e.g., cognition, emotions, instincts), writing:

> The autistic personality is an extreme variant of male intelligence, of the male character. Even within the normal variation, we find typical sex differences in intelligence. In general, girls are better learners. They are more gifted for the concrete and the practical, and for tidy, methodical work. Boys, on the other hand, tend to have a gift for logical ability, abstraction, precise thinking and formulating, and for independent scientific investigation. This is the reason, too, why in general boys at older age levels do better than girls in the Binet test. The narrowly logical and abstract items which start at the ten-year level are simply more congenial to boys! In the autistic individual the male pattern is exaggerated to the extreme. In general, abstraction is congenial to male thought processes, while female thought processes draw more strongly on feelings and instincts. In the autistic person abstraction is so highly developed that the relationship to the concrete, to objects and to people has largely been lost, and as a result the instinctual aspects of adaptation are heavily reduced. (Asperger, 1944; Frith, 1991, pp. 84-85)

Beyond Kanner (1943) and Asperger (1944)

A vast amount of literature on ASD has accumulated since Kanner and Asperger's original writings. Historically, early on debates in the literature ensued regarding the etiology of ASD, the distinction between autism and childhood schizophrenia, and whether Asperger's "autistic psychopathy" was a distinct disorder from Kanner's "early infantile autism" (Richdale & Schreck, 2008). These debates will be briefly presented as follows.

Concerning etiology, early psychogenic theories focused on the parent-child relationship, relating ASD to factors such as parental characteristics and cold, unloving "refrigerator mothers" (Bettelheim, 1967; Eveloff, 1960). This claim was unfounded and challenged by families and researchers (Rimland, 1964). Presently, a single causal explanation for ASD has not been identified, and the view is that ASD is likely multifactorial (Matson & Minshawi, 2006). There is strong evidence for a genetic component (for reviews see Freitag, 2007; Gupta & State, 2007; O'Roak & State, 2008; Rutter, 2000), and a host of other theories (e.g., neurochemical, environmental, dietary, pre/postnatal, behavioral) have been proposed (for reviews see Matson & Minshawi, 2006; Newschaffer, et al., 2007; Rutter, 2005). As an important example, theories implicating immunizations (e.g., measles-mumps-rubella [MMR] vaccine; the thimerosal preservative in vaccines) have been proposed, but disproven via empirical research (e.g., Doja & Roberts, 2006; Fombonne, 2008; Schechter & Grether, 2008; B. Taylor, 2006; Uchiyama, Kurosawa, & Inaba, 2007). Of concern is that harmful and ineffective treatments have been derived from various theories lacking empirical evidence (Levy & Hyman, 2005; Metz, Mulick, & Butter, 2005; Wong & Smith, 2006).

Since the inception of autism, distinguishing between ASD and schizophrenia was of noted importance (Asperger, 1944; Frith, 1991; Kanner, 1943). This confusion was evident even

in the naming the condition using the word "autism," which had been coined by Bleuler (1910) to describe a symptom in schizophrenia (Asperger, 1944; Frith, 1991; Kanner, 1943). Early on, Asperger and Kanner (Asperger, 1944; Frith, 1991; Kanner, 1943) asserted that autism could be differentiated based on onset, course, and lack of psychosis (or as Kanner put it, intact relations to objects though not people). With regard to differential diagnosis, research efforts demonstrated that autism was distinguishable from both schizophrenia and ID (Rutter, 1968, 1978, 1999). It was found that autism could be distinguished from schizophrenia based on a number of factors such as the sex ratio, family history and characteristics, cognitive ability, course, onset, presence of hallucinations and delusions, symptomatology, and speech delay (Kolvin, 1971; Rutter, 1972).

As early as 1962, researchers have debated the similarities and differences between Asperger's "autistic psychopathy" and Kanner's "early infantile autism," and whether the two are distinct diagnostic entities (Van Krevelen, 1971; Van Krevelen & Kuipers, 1962). Initially, Van Krevelen (1971) argued the two could be differentiated based on onset, milestones (i.e., walking and talking), communication, eye contact, interaction with the environment, social prognosis, and the notion that autism was a psychotic process and Asperger's was a personality trait. Although Wing (1981a) is credited with introducing Asperger's syndrome, she did not intend to purport that it was distinct from autistic disorder (Klin, Volkmar, & Sparrow, 2000). Wing (1981a) pointed out a number of differences (e.g., severity of impairments, aloof versus passive or odd social behavior, speech ability and communicative use of language, gestures, stereotyped/repetitive behavior versus special interests, IQ, and motor skills), but asserted that the two disorders were more alike than unalike. Research into the relationship between "high functioning autism" and Asperger's disorder has long since continued (Frith, 2004; Schopler,

Mesibov, & Kunce, 1998), and researchers have delineated distinctions in a number of areas (for a review see Matson & Wilkins, 2008). Further, Volkmar and Klin (2005) noted that other issues have involved whether Asperger's is a milder form of autistic disorder (e.g., Leekam, Libby, Wing, Gould, & Gillberg, 2000; Ozonoff, South, & Miller, 2000), or if it is different in the nature of social difficulties, neuropsychological profile, outcome, or comorbidity (e.g., Howlin, 2003; Miller & Ozonoff, 2000; Tantam, 2000). In conclusion, many researchers have asserted that Asperger's disorder is part of the ASD spectrum, yet distinct from autistic disorder; however, the current diagnostic criteria appear inadequate, as will be discussed further in the following section (Matson & Wilkins, 2008).

Diagnostic Criteria

Prior to inclusion as a separate category in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition* (DSM-III; American Psychiatric Association [APA], 1980), a number of diagnostic criteria were used for autism (DeMyer, Churchill, Pontius, & Gilkey, 1971; Ferrari, 1982). Eisenberg and Kanner (1956) put forth the two essential features of autism as extreme self-isolation and obsessive insistence on the preservation of sameness, and noted that the onset was prior to age 2. The British Working Party (Creak, 1961) delineated nine criteria for "schizophrenic syndrome of childhood," some of which were incorporated into later assessment instruments and diagnostic criteria for ASD. Rutter's (1978) definition was highly influential and similar to the definition used when autism was first incorporated into the *DSM-III* (APA, 1980). Rutter (1978) set four necessary criteria: onset before 30 months; impaired social development with special characteristics inconsistent to intellectual level; delayed and deviant language development with defined features inconsistent to intellectual level; and insistence on sameness (i.e., stereotyped play, abnormal preoccupations, resistance to change). Though less influential,

another definition was put forth by the National Society for Autistic Children (NSAC; Ritvo & Freeman, 1977). The NSAC's five criteria included onset before 30 months and disturbances in four areas: developmental rate and/or sequences; responsiveness to sensory stimuli; speech, language, and cognitive capacities; and relating to people, events, and objects (Ritvo & Freeman, 1977). Numerous revisions have ensued since autism's first inclusion in the *DSM* (for a detailed review see Volkmar & Klin, 2005). The current *DSM* criteria for ASD will now be presented.

The current *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR; American Psychiatric Association [APA], 2000) includes five disorders under the diagnostic category of Pervasive Developmental Disorders (PDD): autistic disorder; Asperger's disorder; pervasive developmental disorder not otherwise specified (PDD-NOS); Rett's disorder; and childhood disintegrative disorder (CDD). Corresponding classifications in *the International Classification of Diseases, 10th Edition* (World Health Organization [WHO], 1992) include childhood autism; Asperger's syndrome; atypical autism, other PDD, and PDD unspecified; Rett's syndrome; and other childhood disintegrative disorder, respectively. Rett's disorder and CDD are both rare disorders characterized by the presence of regression in skills (Volkmar, State, & Klin, 2009). Moreover, Rett's and CDD are typically not viewed as included under autism spectrum disorders (ASD) or characteristic of ASD (Volkmar, et al., 2009). Reminiscent of Rutter (1978), the three core symptoms of ASD include qualitative impairments in social interaction and communication, and restricted, repetitive, and stereotyped patterns of behavior, interest, or activities. The five disorders under the *DSM-IV-TR*'s PDDs will now be presented.

Autistic Disorder

For autistic disorder, impairments must be evident in all three core symptom domains including socialization, communication, and restricted, repetitive, and stereotyped patterns of behavior, interest, or activities. Overall, six or more symptoms total must be endorsed, with a minimum of two symptom endorsements in the area of social impairment (APA, 2000). Delays or abnormal functioning before the age of 3 must be evident in either social interaction, social language, or pretend play (APA, 2000). Finally, the clinical presentation cannot be not more representative of Rett's disorder or CDD (APA, 2000).

In the area of qualitative impairment in social interaction, the four criteria involve impairments in: use of nonverbal behavior (e.g., eye contact, body posture, gestures, facial expression) to regulate social interaction; development of peer relationships appropriate to developmental level (e.g., lack of interest in making friends or understanding of how to socially interact); spontaneous seeking to share enjoyment, interests, or achievements (e.g., not showing, bringing, or pointing out objects they find interesting); and social or emotional reciprocity (e.g., not actively participating in social games, preferring solitary activities, involving others as tools, impaired awareness of others, lack of recognition of the needs of others or others' distress; APA, 2000).

Criteria for qualitative communication impairments include: delay in development or total lack of spoken language without attempts to communicate in alternative ways such as gestures (e.g., lack of pointing, nodding, or head shaking, not understanding simple questions or directions); if verbal, impairment in initiating or sustaining conversations; stereotyped and repetitive use of language (e.g., repeating words/phrases regardless of meaning, echolalia, reciting, lack of understanding of idioms, humor, irony, and implied meaning) or idiosyncratic

language (e.g., using words in an odd manner, neologisms); and lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level (APA, 2000).

With regard to restricted repetitive and stereotyped patterns of behavior, interest, or activities, criteria include: encompassing preoccupation with stereotyped, restricted patterns of interests of abnormal intensity or focus (e.g., dates, phone numbers, radio station call letters); inflexible adherence to nonfunctional routines or rituals (e.g., lining things up in the same way repetitively, distress over trivial changes such as rearranged furniture, new dinner utensils, or change in route); stereotyped, repetitive motor mannerisms (e.g., hand flapping, finger movements, rocking, dipping); and persistent preoccupation with parts of objects (e.g., buttons, parts of the body, spinning wheels, opening/closing doors, fans; APA, 2000).

The *DSM-IV-TR* also describes potential associated features of autistic disorder in a number of areas: intelligence (poorer verbal versus nonverbal skills, hyperlexia, calendar calculations); behavior (hyperactivity, inattention, impulsivity, aggression, self-injurious behavior, tantrums); sensory (increased pain tolerance, touch or sound oversensitivity, exaggerated reactions to light or smells, fascination with certain stimuli); eating (food selectivity, pica); sleeping (early waking, rocking); mood/affect (laughing or crying for no apparent reason, lack of emotional reactivity); fear (lack of response to real danger, fear of harmless objects); and depression in individuals with the cognitive capacity to recognize impairments (APA, 2000).

Finally, the *DSM-IV-TR* discusses features related to developmental age. Infants may exhibit failure to cuddle; indifference or aversion to affection or touch; lack of eye contact, response to facial expressions, or social smiling; and failure to respond to voices (APA, 2000). Young children may fail to differentiate between adults, cling mechanically to others, or use the hand of others as a tool without making eye contact (APA, 2000). As they age, children may

engage in verbal rituals (e.g., expecting certain answers to ritualized prompts), lack understanding of personal boundaries, or be inappropriately intrusive in social interaction (APA, 2000). Finally, older individuals may demonstrate exceptional rote memorization skills (e.g., dates, chemical formulas, lyrics), and repeat this data inappropriately in a social context (APA, 2000).

Asperger's Disorder

Asperger's disorder was not incorporated into the *DSM* until the fourth edition in 1994 (American Psychiatric Association [APA], 1994). As with autism, a number of diagnostic frameworks (e.g., ICD-10 draft, 1988; Asperger, 1944; I. C. Gillberg & Gillberg, 1989; Szatmari, Bremner, & Nagy, 1989; Tantam, 1988; Wing, 1981a) were employed prior to its inclusion in the *DSM* (Ghaziuddin, Tsai, & Ghaziuddin, 1992). Moreover, inconsistencies in the application of the current diagnostic criteria for Asperger's disorder have continued to be evident in the field (Klin, McPartland, et al., 2005; Klin, Saulnier, Tsatsanis, & Volkmar, 2005). An overview of the current diagnostic criteria and ongoing issues surrounding these criteria follows.

Regarding the current *DSM-IV-TR* criteria for Asperger's disorder, the criteria in the socialization and behavioral domains are the same as those for autistic disorder. However, the *DSM-IV-TR* does describe some qualitative differences between autistic and Asperger's disorder in those areas. In the area of socialization, autistic disorder may be characterized by social and emotional indifference and self-isolation (APA, 2000). In contrast, with Asperger's, the person may be motivated to seek social interaction, but may do so in an eccentric, one-sided, insensitive way (e.g., continually talking about personal topics of interest without regard for the other people; APA, 2000). In the behavioral domain, autistic disorder may be more typified by stereotypic motor mannerisms, preoccupation with parts of objects, rituals, and distress with

changes (APA, 2000). In contrast, in Asperger's, the person may spend the majority of his/her time gathering lots of facts and information about a circumscribed interest (APA, 2000).

The *DSM-IV-TR* criteria also address communication, cognitive, and adaptive functioning. Regarding communication, the *DSM-IV-TR* criteria indicate that there can be no clinically significant general delay in language (i.e., single words used by 2 years of age and communicative phrases used by 3 years of age; APA, 2000). Yet, abnormalities in communication may be present (e.g., turn-taking in conversation, narrow range of topics, verbose speech; APA, 2000). These abnormalities may stem from social impairments, lack of knowledge and application of conversation principles, deficits in decoding nonverbal cues, and lack of self-monitoring (APA, 2000). With regard to cognitive and adaptive functioning, the *DSM-IV-TR* criteria require that there is no significant delay in the development of cognitive, age appropriate self-help, adaptive behavior (excluding social interaction), and curiosity of the environment in childhood (APA, 2000).

Two additional criteria are listed in the *DSM-IV-TR* for Asperger's disorder. There must be clinically significant impairment in important areas of functioning (e.g., social, occupational; APA, 2000). In addition, criteria cannot be met for another PDD or schizophrenia (APA, 2000).

Finally, as with autistic disorder, the *DSM-IV-TR* presents associated features and developmental considerations for Asperger's disorder. With regard to associated features, ID is typically not present, although mild ID may become evident during the school years (APA, 2000). There may be strengths in verbal ability (e.g., vocabulary, rote auditory memory), but weaknesses in nonverbal ability (e.g., visual motor and visual spatial skills; APA, 2000). Adolescents may learn to use strengths to compensate for weaknesses (APA, 2000). During school age, verbal strengths may mask social impairments, leading teachers and caregivers to

think that behavior problems are due to stubbornness (APA, 2000). Regarding motor skills, clumsiness and awkwardness may impact socialization (e.g., sports participation, teasing; APA, 2000). Additional associated features may include hyperactivity and inattention, and comorbid psychopathology (e.g., depression, anxiety) may emerge in adolescence and adulthood due to teasing, isolation, and increased ability to recognize impairments (APA, 2000). Social relationships may not be developed within the person's age group, but rather, with persons much younger or older in age (APA, 2000). The *DSM-IV-TR* also emphasizes that it is important to differentiate between "normal social awkwardness" and "normal age-appropriate interests and hobbies," in that in Asperger's, social deficits are severe and preoccupations are "all-encompassing" and interfere with skill acquisition (APA, 2000, p. 83).

Volkmar and Klin (2005) pointed out a number of debated issues with the current criteria for Asperger's disorder. These have included the precedence rule (i.e., Asperger's cannot be diagnosed if criteria for autistic disorder is fulfilled); the language delay criteria; and whether the unusual circumscribed interests and motor issues Asperger described are required for diagnosis (Tryon, Mayes, Rhodes, & Waldo, 2006; Volkmar & Klin, 2005). As one intriguing example, Miller and Ozonoff (1997) reported that Asperger's cases would not have met the current criteria for Asperger's disorder, but rather, autistic disorder.

Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)

PDD-NOS is the most prevalent but least researched of all the ASD (Matson & Boisjoli, 2007; Matson & LoVullo, 2009). Volkmar, State, and Klin (2009) noted that the "residual" nature of this diagnostic category has posed a considerable challenge in both research and practice. The *DSM-IV-TR* notes that a diagnosis of PDD-NOS requires severe and pervasive impairment in development of reciprocal social interaction, along with abnormalities in at least

one of the other two symptom domains of ASD (i.e., verbal or nonverbal communication; stereotyped behavior, interests, and activities; APA, 2000). The person cannot meet diagnostic criteria for another PDD, schizophrenia, or personality disorder (i.e., schizotypal, avoidant; APA, 2000). The diagnosis of PDD-NOS includes "atypical autism" as well, when criteria for autistic disorder are not met due to late onset and/or atypical or subthreshold symptom presentation (APA, 2000).

Rett's Disorder

Rett's disorder is unique in that it is the only PDD that occurs almost exclusively in females and has an identified genetic cause (Amir, et al., 1999; Hagberg, Aicardi, Dias, & Ramos, 1983; Rett, 1966). Most individuals (most estimates are approximately 95% ranging from 85 to 100%) with classic Rett's disorder have MECP2 (methyl-CpG binding protein) mutations at Xq28 (Deidrick, Percy, Schanen, Mamounas, & Maria, 2005; Erlandson & Hagberg, 2005). Diagnosis of Rett's disorder must be made clinically, as MECP2 mutations result in a wide variety of phenotypes within and outside of Rett's disorder (Erlandson & Hagberg, 2005; Hagberg, Hanefeld, Percy, & Skjeldal, 2002; Hammer, Dorrani, Dragich, Kudo, & Schanen, 2002; Matson, Dempsey, & Wilkins, 2008; Matson, Fodstad, & Boisjoli, 2008).

Regarding *DSM-IV-TR* criteria for Rett's disorder, there must be apparently normal prenatal and perinatal development and psychomotor development during the first 5 months of life, as well as normal head circumference at birth (APA, 2000). Further, after a period of normal development, there must be a deceleration of head growth (between 5 and 48 months), loss of purposeful hand skills (between 5 and 30 months) and emergence of stereotyped hand movements such as hand wringing, loss of social engagement (however, social interaction often develops later), emergence of poorly coordinated gait or trunk movements, and severe

impairments in the development of expressive and receptive language and severe psychomotor retardation (APA, 2000).

Four clinical stages have been described for the progression of classic Rett's syndrome (Hagberg, 2002). Normal development occurs from 6-18 months, followed by developmental stagnation involving deceleration of head and general overall growth and hypotonia (Chahrour & Zoghbi, 2007). The regression phase begins from 1 to 3-4 years of age and involves autistic features (e.g., expressionless face, "in another world," loss of social interaction), loss of hand skills and emergence of hand stereotypies (e.g., hand wringing, flapping, mouthing), loss of communication skills, loss of motor coordination, mental retardation, respiratory abnormalities (e.g., hyperventilation during wakefulness), and seizures (Chahrour & Zoghbi, 2007; Deidrick, et al., 2005; Hagberg, 2002). Seizures, which occur in as many as 90% of individuals, peak in adolescence to young adulthood, decrease in early middle age, and are a rare and minor concern after age 40 (Hagberg, 2005). The third stage is a pseudostationary or plateau period with onset between 2-3 to 10 years of age and may continue for years (Ben Zeev Ghidoni, 2007; Chahrour & Zoghbi, 2007). Improvement may be noted in areas such as autistic features, communication skills, irritability, and attention span, while other features such as scoliosis, motor problems, and autonomic abnormalities (e.g., constipation, cardiac abnormalities) become worse (Chahrour & Zoghbi, 2007; Deidrick, et al., 2005). It is noted that intense eye contact may continue into adulthood (Hagberg, 2002). The fourth stage involves late motor deterioration resulting in decrease or loss of mobility and Parkinsonian features (Chahrour & Zoghbi, 2007; Hagberg, 2002). Sleep problems also vary with age and mutation type (Young, et al., 2007). Nocturnal laughter has been found to decrease with age, while nocturnal seizures and daytime sleeping increase with age (Young, et al., 2007).

Childhood Disintegrative Disorder (CDD)

In 1908, Theodor Heller described one female and five males with what he termed *dementia infantilis* (Heller, 1908; Hendry, 2000; Matson & Mahan, 2009; Mouridsen, 2003; Volkmar & Rutter, 1995). This disorder has been referred to by a variety of names, and is currently listed under as a PDD in the *DSM-IV-TR* as childhood disintegrative disorder (CDD; APA, 2000). The *DSM-IV-TR* criteria for CDD specify first, seemingly normal development (i.e., age appropriate verbal/nonverbal communication, social relationships, play, and adaptive behavior) for up to at least 2 years of age (APA, 2000). Second, prior to 10 years of age, there is a clinically significant loss of previously acquired skills in at least two of five areas (i.e., expressive or receptive language; social skills or adaptive behavior; bowel or bladder control; play; motor skills; APA, 2000). Third, abnormalities of functioning must be present in at least two of the three domains of ASD (i.e., social, communication, behavior; APA, 2000). Lastly, the clinical presentation cannot be better accounted for by another PDD or schizophrenia (APA, 2000).

Prevalence

Regarding prevalence, in an epidemiological review, Fombonne (2005) estimated the prevalence of ASD as 60 per 10,000 (1 out of 167 people). Specifically, the estimated prevalence for PDD-NOS was 20.8/10,000 (1/481), for autistic disorder 13/10,000 (1/769), for Asperger's disorder 2.6/10,000 (1/3,846), for CDD 1.9/100,000 (1/52,632). Prevalence estimates have ranged from 0.41/10,000 (Boltshauser & Künzle, 1987) to 2.23/10,000 (Skjeldal, von Tetzchner, Aspelund, Herder, & Lofterld, 1997) for Rett's disorder (see Laurvick, et al., 2006). The prevalence of ASD has been rising, likely due to a combination of factors such as changes in diagnostic criteria and methodology, diagnostic substitution, availability of services, policy

changes in special education, and increased professional and public awareness (Fombonne, 2005; Wing & Potter, 2002).

With regard to gender, no epidemiological study of ASD (excluding Rett's disorder) to date has yielded a greater number of females than males (Fombonne, 2003, 2007). The male to female ratio in epidemiological studies has ranged from 1.33:1 (16:12; McCarthy, Fitzgerald, & Smith, 1984) to 16:1 (Wing, Yeates, Brierley, & Gould, 1976) with an average ratio of 4.3:1 (Fombonne, 2003, 2005, 2007). The male to female ratio varies according to cognitive ability, with a median sex ratio of 5.5:1 for intelligence in the normal range, compared to 1.95:1 for moderate to severe intellectual disability (ID) (Fombonne, 2005, 2007). The co-occurrence of ID and ASD in general has been an important topic. It has frequently been reported that the large majority of individuals with autism also have ID; however, current rates may be lower than previous estimates (Bryson, Bradley, Thompson, & Wainwright, 2008; Edelson, 2006; Ritvo & Ritvo, 2006).

Assessment

A number of assessment instruments have been developed to assess autistic symptoms. ASD measures vary in age range, purpose (e.g., population screening, diagnostic), format (e.g., clinician or informant rated, observation, interview), practicality/resources (administration time, cost, clinician training), psychometric properties (reliability and validity), and ability to assess the range of ASD including autistic disorder, PDD-NOS, and Asperger's disorder (S. L. Bishop, Luyster, Richler, & Lord, 2008; Lord & Corsello, 2005; Matson, 2007; Matson, Nebel-Schwalm, & Matson, 2007; Nebel-Schwalm & Matson, 2008; Ozonoff, Goodlin-Jones, & Solomon, 2005). In addition, the performance of ASD assessment instruments have been shown to vary based on individual characteristics, such as cognitive and language ability, ASD symptom severity, age

(due to developmental differences in symptom presentation), and sensory and/or motor impairments. Assessment efforts have largely focused on children compared to adults, particularly in the area of earlier identification (Matson, 2007; Matson & Neal, 2009; Matson, Nebel-Schwalm, et al., 2007; Matson, Wilkins, & González, 2008). Finally, assessment measures have also been developed to assess autistic traits in the general population, based on a dimensional view of ASD as normally distributed traits in the population (see Volkmar, et al., 2009). Though there are a large number of ASD assessment instruments available, including earlier as well as more recently developed tools, this discussion encompasses those which have been used to assess gender differences in ASD symptoms and those used in the present study.

Infants and toddlers

CHecklist for Autism in Toddlers (CHAT; Baron-Cohen, Allen, & Gillberg, 1992). The CHAT is a screener designed to identify children at risk for ASD at 18 month check-ups with the pediatrician. The measure consists of 9 parent report questions and 5 interactive items (scored as pass or fail). It focuses on joint attention and pretend play. At 3.5 years, 10 out of 12 children who failed the CHAT had a diagnosis of autism at follow-up (Baron-Cohen, et al., 1996). However, at 6-year follow-up at age 7, sensitivity was low and many ASD cases were missed (Baird, et al., 2000). The CHAT has also been evaluated for ability to distinguish autism from other developmental disabilities in 2 to 3 year olds (Scambler, Hepburn, & Rogers, 2006; Scambler, Rogers, & Wehner, 2001).

Modified CHecklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001). The M-CHAT is a parent rating scale designed for use at 24 month check-ups, but can be used for ages 16 to 30 months. It has 23 items (including the 9 parent report items from the CHAT) and is expanded for ASD rather than just autism. Items are rated as “yes” or “no.”

Critical items involve interest in other children, proto-declarative pointing, bring objects to show the parent, imitating, responding to name, and following a point. The M-CHAT screen is initially failed if any three items or any two critical items are failed. To reduce false positives and unnecessary referrals for children who fail the M-CHAT, a follow-up interview is employed. Robins and colleagues (2001) evaluated the M-CHAT in a general population sample and an early intervention sample. The M-CHAT had a sensitivity of 87%, specificity of 99%, positive predictive power of 80%, and negative predictive power of 99%. Cronbach's alpha was 0.85 (Robins, et al., 2001). Further research of the psychometric properties of the M-CHAT has been conducted (L. C. Eaves, Wingert, & Ho, 2006; Kleinman, et al., 2008; Kuban, et al., 2009; Pandey, et al., 2008; Robins, 2008; Snow & Lecavalier, 2008).

Quantitative CHecklist for Autism in Toddlers (Q-CHAT; Allison, et al., 2008). The Q-CHAT is a 25-item parent rating scale for ages 18 to 24 months. It is intended for population screening for ASD. Three items from the joint attention and pretend play domains on the CHAT were retained, and additional items from other domains such as language development, repetitive behaviors, and social communication were added. Some items have similar wording to items on the M-CHAT. Items are scored on a 5-point scale from 0 to 4 based on frequency of occurrence. It takes 5 to 10 minutes to complete. Allison and colleagues (2008) evaluated the psychometrics of the Q-CHAT. Cronbach's alpha was 0.67 for the total sample, 0.83 for the ASD group, and 0.81 for participants 36 months of age and younger in the ASD group. Regarding test-retest reliability, the intraclass correlation coefficient was 0.82. Participants with ASD diagnoses who were 36 months of age and younger had higher scores on the Q-CHAT that the control group. Limitations of this preliminary study include that the diagnoses were not verified, IQ data was not available, the ASD group was significantly older (M = 45 months, SD = 10 months; range: 19

to 63 months) than the control group, and parents completed the Q-CHAT post-ASD diagnosis (Allison, et al., 2008).

Baby and Infant Screen for Children with aUtIsm Traits – Part 1 (BISCUIT-Part 1; Matson, Wilkins, Sevin, et al., 2009). The BISCUIT-Part 1 is part of a newly developed battery to assess ASD symptoms, comorbid symptoms, and challenging behaviors in babies and infants. It is a 62-item clinician-rated scale designed to aid in the diagnosis of autism and PDD-NOS. Each item is rated for the extent that it is/was ever a problem in comparison to typically developing children of the same age. Each item is rated as "0 = Not different; no impairment," "1 = Somewhat different; mild impairment," or "2 = Very different; severe impairment." Reliability of the BISCUIT-Part 1 was evaluated in a sample identified as at risk for developmental disabilities ages 17 to 37 months (M = 26.83, SD = 5.27). Internal consistency reliability was 0.97 (Matson, Wilkins, Sevin, et al., 2009). Validity of the BISCUIT-Part 1 has also been established. In differentiating between ASD and non-ASD in an at risk sample, compared to the M-CHAT, the BISCUIT-Part 1 produced higher sensitivity (93.4 versus 74.1), comparable specificity (86.6 versus 87.5), and a higher overall correct classification rate (88.8 versus 83.0). (Matson, Wilkins, Sharp, et al., 2009). Sensitivity, specificity, and overall correct classification for the BISCUIT-Part 1 were 84.7, 86.4, and 86.1 respectively for differentiating no diagnosis from PDD-NOS, and 84.4, 83.3, and 83.9 for differentiating PDD-NOS from autistic disorder (Matson, Wilkins, Sharp, et al., 2009). Additional research to further develop the psychometric properties of the BISCUIT is underway (e.g., factor analysis).

Children, Adolescents, and Adults

Childhood Autism Rating Scale (CARS; Reichler & Schopler, 1971; Schopler, Reichler, DeVellis, & Daly, 1980; Schopler, Reichler, & Renner, 1988). The CARS contains 15 items

which are clinician-rated based on observations and information gathered from other sources (e.g., record review, interviews, etc.). It can be used for individuals over 2 years of age to differentiate autism from other developmental disabilities. Items are rated on a 7-point scale and summed to a total score. Domains include: relating to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste/smell/touch response and use, fear or nervousness, verbal communication, nonverbal communication, activity level, consistency of intellectual response, and general impressions. A total score of 15 to 29.5 is in the "Non-Autistic" range, 30 to 36.5 in the "Mildly-Moderately Autistic" range, and 37 to 60 in the "Severely Autistic" range. Psychometrics included internal consistency of 0.94, inter-rater reliability of 0.71, and test-retest reliability of 0.88 with a kappa of 0.64 for agreement of the autistic and non-autistic categories (Schopler, et al., 1988). Validity correlations were 0.84 with clinical ratings made during diagnostic sessions using the *Psychoeducational Profile* (PEP; Schopler & Reichler, 1979), and 0.80 with independent clinical assessments by a child psychologist and psychiatrist using referral records, parent interviews, and unstructured clinical interviews with the child (Schopler, et al., 1988). Validity was also established under alternate conditions (i.e., parent interview, classroom observation, and chart [case history] review) and with raters as professionals from other fields with little training or experience in ASD (Schopler, et al., 1988). Regarding use at older ages, Mesibov and colleagues (1989) readministered the CARS to adolescents and adults ages 13-18 years (mean age 15.9) first examined prior to age 10. CARS scores had decreased, so the authors recommended lowering the cutoff score for this age group to improve accuracy (Mesibov, et al., 1989). The psychometric properties of the CARS have been extensively researched (DiLalla & Rogers, 1994; R. C. Eaves & Milner, 1993; Garfin, McCallon, & Cox, 1988; Magyar & Pandolfi, 2007; Perry, Condillac, Freeman, Dunn-Geier, &

Belair, 2005; Pilowsky, Yirmiya, Shulman, & Dover, 1998; Rellini, Tortolani, Trillo, Carbone, & Montecchi, 2004; Saemundsen, Magnússon, Smári, & Sigurdardóttir, 2003; Sevin, Matson, Coe, & Fee, 1991; W. L. Stone, et al., 1999; Sturmey, Matson, & Sevin, 1992; Teal & Wiebe, 1986; Van Bourgondien, Marcus, & Schopler, 1992; Ventola, et al., 2006).

Autism Behavior Checklist (ABC; Krug, Akick, & Almond, 1980). The ABC is a 57-item rating scale for ages 3 and older originally designed for use in educational settings. Items are rated dichotomously and weighted with scores from 1 to 4. The ABC has 5 subscales: sensory, relating, body and object use, language, and social and self-help skills. The authors reported good psychometric properties, though methodological issues (e.g., small sample size, non-blind raters, use of percent agreement) have been acknowledged (Volkmar, Cicchetti, Dykens, & Sparrow, 1988). Further research of the psychometric properties of the ABC has yielded questionable reliability and validity, particularly in terms of classification rates and factor structure (R. C. Eaves & Williams, 2006; Miranda-Linne & Melin, 2002; Rellini, et al., 2004; Sevin, et al., 1991; Volkmar, et al., 1988; Wadden, Bryson, & Rodger, 1991). In addition, the content emphasizes areas not in the current diagnostic criteria (e.g., sensory, problem behavior; Lord & Corsello, 2005; Ozonoff, et al., 2005; Sturmey, et al., 1992). In conclusion, the ABC has not been recommended for use as a screening or diagnostic instrument (Lord & Corsello, 2005; Ozonoff, et al., 2005).

Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). The ADI-R is a revision of the original ADI (Le Couteur, Rutter, Lord, & Rios, 1989). It is a semistructured parent interview for diagnosis of autistic disorder. Most items are coded from "0 = no definite behavior of the type specified" to "2 = definite abnormal behavior of the type described in the definition and coding." Some items have a code of "3" for extreme severity.

Items are rated differently based on behavior between 4 to 5 years of age, current behavior (past 3 months), and behavior that has ever occurred at any age. Both diagnostic and current behavior scoring algorithms are available. The ADI-R has two separate scoring algorithms based on verbal ability. For a diagnosis of autistic disorder, cutoffs must be met in all four areas: Communication, Reciprocal Social Interaction, Restricted and Repetitive Behaviors and Interests, and Age of Onset. Regarding psychometrics, Lord and colleagues (1994) reported good inter-rater and internal consistency reliability, adequate test-retest reliability, and good validity with *DSM-IV/ICD-10* diagnoses.

The ADI-R has some limitations. The ADI-R requires extensive clinician training and administration time (Ozonoff, et al., 2005). It provides scoring for autistic disorder only, rather than the range of ASD. The ADI-R can be used for children with a mental age greater than 2 years through adulthood (Lord, et al., 1994). However, validity of the ADI-R has not been established in very young children and those with low mental ages (Chawarska, Klin, Paul, & Volkmar, 2007; Gray, Tonge, & Sweeney, 2008; Ventola, et al., 2006), thus a toddler version in being developed (S. L. Bishop, et al., 2008). In adults, issues have been raised with the use of retrospective parent report, relationship between lifetime and current algorithms, and developmental changes in symptoms (e.g., Bölte & Poustka, 2000; Seltzer, et al., 2003; Shattuck, et al., 2007). Modifications have been made during use with older adolescents and individuals with severe/profound ID and sensory/motor impairments (e.g., Bryson, et al., 2008). Finally, the ADI-R is subject to bias in that it is based on parent report, though a companion observational instrument (Autism Diagnostic Observation Schedule-Generic; ADOS-G) is available also (Matson & Minshawi, 2006).

Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord, et al., 2000). The ADOS-Generic (ADOS-G) is a semistructured, interactive assessment measuring social and communication symptoms of ASD. The ADOS-G does not probe for restricted interests and repetitive behaviors, but they can be coded if observed (Lord, et al., 2000). Most items are scored from "0 = no evidence of abnormality related to autism" to "2 = definite evidence." Some items have a code of "3" for severe abnormalities interfering with the observation. Final scores yield classifications of autism, non-autism ASD/PDD-NOS, or nonspectrum. The examiner chooses one of four 30 minute modules to administer based on the person's language and developmental level. Module 1 is based on the Pre-Linguistic ADOS (PL-ADOS; DiLavore, Lord, & Rutter, 1995) and is for children who are preverbal or use single words or simple phrases (though not spontaneously or consistently). Module 2 is for children who use flexible phrase speech but are not verbally fluent. Module 3 is based on the original ADOS (Lord, Rutter, Goode, & Heemsbergen, 1989) and is used when children are verbally fluent and playing with toys is considered age appropriate. Module 4 is for adolescents and adults with fluent speech and is conducted via a conversational interview instead of toy play. Module 4 contains socioemotional items from the original ADOS, questions about daily living, and additional tasks. Lord and associates (2000) reported excellent inter-rater, test-retest, and internal consistency reliability. Regarding validity, classification for autistic disorder was better than that for PDD-NOS (Lord, et al., 2000).

The ADOS-G has some limitations, and revisions have been ongoing to address some of these issues. As with the ADI-R, the ADOS-G requires extensive clinician training. Difficulties have been found in using the ADOS to assess restricted, repetitive behaviors and interests (Matson & Minshawi, 2006). As with any observational measure, it is limited to current behavior

and context, and may not provide the opportunity to observe less frequent behaviors (Ozonoff, et al., 2005). The scoring algorithms of the ADOS-G have been revised in response to several findings (Gotham, et al., 2008; Gotham, Risi, Pickles, & Lord, 2007). The revised algorithm aimed to improve classification and reduce age and IQ effects (Gotham, et al., 2008; Gotham, et al., 2007). In addition, the Social and Communication domains were combined into a Social Affect domain, and items for Restricted, Repetitive Behavior were included in the scoring algorithm (Gotham, et al., 2008; Gotham, et al., 2007). A toddler version of the ADOS is in development to address issues in assessing very young children (S. L. Bishop, et al., 2008). Efforts have also been made to adapt the ADOS and PL-ADOS for adults with severe to profound ID (Berument, et al., 2005).

Autism Spectrum Disorders – Diagnostic – Child Version (ASD-DC; Matson & González, 2007). The ASD-DC is part of a three scale battery to assess ASD symptoms, comorbid psychopathology, and challenging behaviors in children and adolescents ages 3 to 18 years. It is a 40-item rating scale. Raters (parents, caregivers, teachers, etc.) are instructed to rate each item for the extent that it is/was ever a problem in comparison to other children of the same age. Each item is rated as "0 = Not different; no impairment," "1 = Somewhat different; mild impairment," or "2 = Very different; severe impairment." Psychometric properties of the ASD-DC have been established. Regarding reliability, internal consistency has been found to be excellent at 0.99, inter-rater reliability good at 0.67, and test-retest reliability excellent at 0.77 (Matson, Gonzalez, Wilkins, & Rivet, 2008). Exploratory factor analysis yielded four subscales: Nonverbal Communication/Socialization, Verbal Communication, Social Relationships, and Insistence on Sameness/Restricted Interests (Matson, Boisjoli, & Dempsey, 2009). Regarding validity, the ASD-DC has been found to have good total correct classification rates between

children with: no diagnosis and atypical development (84.3%) and atypical development and ASD (87.8%); Asperger's disorder and PDD-NOS (89.5%) and PDD-NOS and autistic disorder (77.1%); and children meeting *DSM-IV-TR/ICD-10* criteria for an ASD (84.3%) (Matson, González, & Wilkins, 2009). Finally, convergent validity has been established with the CARS (Matson, Mahan, Hess, Fodstad, & Neal, in press) and the ADI-R (Matson, Hess, Mahan, & Fodstad, in press).

Autism Spectrum Disorders – Diagnostic – Adult Version (ASD-DA; Matson, Terlonge, & González, 2006). The ASD-DA is a part of a three scale battery to assess ASD symptoms, comorbid psychopathology, and challenging behaviors in adults with ID. It is a 31-item clinician-rated scale. Each item is rated for the extent that it is/was ever a problem in comparison to other people of the same age who live in the community. Items are rated as "0 = Not different; no impairment" or "1 = Different; some impairment." Psychometric properties of the ASD-DA have been established. Regarding reliability, internal consistency has been found to be excellent at 0.94 (Matson, Wilkins, & González, 2007). Inter-rater reliability (0.30) and test-retest reliability (0.39) have been found to be adequate (Matson, Wilkins, et al., 2007). Exploratory factor analysis yielded three subscales: Social Impairment, Communication Impairment, and Restricted Interests/Bizarre Sensory Responses (Matson, Wilkins, et al., 2007). Validity has been established with the DASH-II, MESSIER, VABS, and *DSM-IV-TR/ICD-10* criteria (Matson, Wilkins, Boisjoli, & Smith, 2008). The ASD-DA has been shown to have diagnostic utility in differentiating adults with ASD from those with ID, and adults with autistic disorder from those with PDD-NOS (Matson, Boisjoli, González, Smith, & Wilkins, 2007).

Autistic Traits in the General Population

A number of measures have been used to examine gender differences in autistic traits in the general population. These include the *Autism Spectrum Screening Questionnaire* (ASSQ; Ehlers & Gillberg, 1993; Ehlers, Gillberg, & Wing, 1999; Posserud, Lundervold, & Gillberg, 2006) and the *Social Responsiveness Scale* (SRS; Constantino, 2005; Constantino & Todd, 2003). The ASSQ was designed to screen for ASD (particularly Asperger's and high-functioning autism) in children ages 6 to 17 years. The ASSQ is a 27-item rating scale completed by parents and/or teachers. Items are scored on a 3-point scale from "0 = not true" to "2 = certainly true." Factor analysis yielded 3 factors: Social difficulties, Motor/Tics/OCD, and Autistic Style (Posserud, et al., 2008). Psychometric properties of the ASSQ have been examined in a variety of settings and samples (Ehlers & Gillberg, 1993; Ehlers, et al., 1999; Posserud, et al., 2006; Posserud, Lundervold, & Gillberg, 2009; Posserud, et al., 2008). The SRS (formerly *Social Reciprocity Scale*) is a 65-item rating scale completed by an informant such as a parent or teacher (Constantino, Przybeck, Friesen, & Todd, 2000; Constantino & Todd, 2000). It can be used for ages 4 to 18 years. Items are scored from "0 = never true" to "3 = almost always true." The SRS assesses areas such as social awareness, social information processing, capacity for reciprocal social responses, social use of language, and stereotypic/repetitive behaviors/preoccupations (Constantino, et al., 2004). Psychometric properties of the SRS have been established (Bölte, Poustka, & Constantino, 2008; Charman, et al., 2007; Constantino, et al., 2009; Constantino, et al., 2003; Constantino, et al., 2007).

Some measures have been used to examine gender differences in autistic traits in the general population while also including a subgroup of participants with ASD. These have included the three versions of the *Autism Spectrum Quotient* (AQ) for children (AQ-Child;

Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008), adolescents (AQ-Adol; Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006), and adults (AQ-Adult; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), the *Childhood Autism Spectrum Test* (CAST; Scott, Baron-Cohen, Bolton, & Brayne, 2002), and the Q-CHAT (Allison, et al., 2008). The Q-CHAT was described above, and the CAST will be described below. Regarding the AQ measures, these were designed to measure autistic traits in the general population without ID. The adult version is a self-report measure, while the child and adolescent versions are parent rating scales. The AQ measures contain 50 items rated on a 4-point scale from "Definitely Agree" to "Definitely Disagree." They cover 5 domains: social skills, attention to detail, attention switching, communication, and imagination. The AQ-Child has 47 retained items and was factor analyzed into 4 subscales: mind reading, attention to detail, social skills, and imagination (Auyeung, et al., 2008).

Childhood Autism Spectrum Test (CAST). The CAST was previously named the *Childhood Asperger Syndrome Test,* and was renamed because it can be used for other ASD and is not solely for Asperger's disorder (Auyeung, et al., 2009). It was originally designed as a screening tool for Asperger's disorder and related social communication difficulties in the general population (Scott, et al., 2002). The CAST is a 37-item parent rating scale for children 4 to 11 years of age (Scott, et al., 2002). Items are rated as "yes" or "no." There are 31 key scored items, and 6 control items on general development which are not scored. Items cover areas such as conversation, language difficulties, social interaction (e.g., eye contact), play activities, rigid/repetitive behaviors, and interests and sharing interests with others (Auyeung, et al., 2009). Regarding psychometrics, test-retest reliability for the CAST total score was 0.83 (Spearman's rho), and the kappa value for agreement for scoring above or below the cutoff value of 15 was

0.70 (J. Williams, et al., 2006). In a high scoring sample, values for test-retest reliability were a Spearman's rho of 0.67 and a kappa of 0.41 (Allison, et al., 2007). For internal consistency reliability, Auyeung and colleagues (2009) found a Cronbach's alpha value of 0.85. Matson and associates (2008) found the CAST was highly correlated with the Krug Asperger's Disorder Index (KADI; Krug & Arick, 2003) and Gilliam Asperger's Disorder Scale (GADS; Gilliam, 2001), but had a lower area-under-the-curve value for classifying Asperger's disorder. The CAST had a sensitivity of 73%, specificity of 46%, positive predictive power of 85%, and negative predictive power of 75% in classifying Asperger's disorder from high functioning autism and typical development (Matson, Dempsey, & Rivet, 2008). Scott and colleagues (2002) found a sensitivity of 88%, specificity of 98%, and positive predictive value of 64% for the CAST. Williams and colleagues (2005) found a sensitivity of 100%, specificity of 97%, and positive predictive value of 50%. Thus, Williams and Brayne (2006) noted that the CAST may yield false positives, resulting in undue use of resources for follow-up assessments and anxiety for families.

Gender Issues in ASD Assessment

A number of considerations are important relative to gender differences in the assessment of ASD. Koenig and Tsatsanis (2005) pointed out that gender differences in presentation have not been sufficiently addressed in studies of key instruments used in the field such as the ADI and ADOS. Standardization samples for ASD instruments consist of predominately males, with a male to female ratio of approximately 3:1 (Koenig & Tsatsanis, 2005). For disorders such as ASD that have such a pronounced gender difference, Rutter, Caspi, and Moffitt (2003) noted that there is a paucity of research addressing the validity of diagnostic criteria for males and females. In addition, symptoms in the criteria or items in assessment instruments may be biased in that

they are more typical of one gender, raising the issue of whether separate criteria based on gender are needed (Bell, Foster, & Mash, 2005; Rutter, Caspi, & Moffitt, 2003). These concerns yield research questions involving assessment and diagnosis (e.g., would it be appropriate to have different norms or cutoff scores on instruments, or different diagnostic criteria content or requirements depending on gender?). Therefore, during assessment, careful consideration should be given according to the individual's gender, age, and cognitive/adaptive level, as opposed to only comparing females to typically developing males or males with ASD (Koenig & Tsatsanis, 2005).

Gender Differences in the General Population

Quite a large literature base exists concerning gender differences in the general population in a multitude of variables (Hyde, 2007). However, this is beyond the scope of the current topic. Hence, this section will encompass a brief review of the research involving gender differences in the general population which have potential implications related to ASD symptoms (i.e., socialization, communication, regulatory behavior), as discussed by Koenig and Tsatsanis (2005). Nonetheless, it is notable that even in typically developing populations, some research has yielded mixed findings, and some differences are slight rather than meaningful (e.g., Charman, Ruffman, & Clements, 2002; Jarrold, Butler, Cottington, & Jimenez, 2000; Koenig & Tsatsanis, 2005; Wallentin, 2009). For the large majority of these variables, gender differences in individuals with ASD have not yet been sufficiently examined (Koenig & Tsatsanis, 2005).

Regarding socialization, Koenig and Tsatsanis (2005) reviewed some evidence to suggest a potential female advantage in decoding facial expressions and nonverbal cues, empathizing, and theory of mind (e.g., Bacon, Fein, Morris, Waterhouse, & Allen, 1998; Brown & Dunn, 1996; McClure, 2000; Nydén, Hjelmquist, & Gillberg, 2000). If females do possess greater skills

in these areas, Koenig and Tsatsanis (2005) hypothesized that females with ASD could either show less socialization impairment compared to males with ASD, or appear more impaired compared to typically developing females. Koenig and Tsatsanis (2005) also pointed out gender differences in the number of peers, types of activities, and social roles in children's peer groups which could pose differing social demands for girls and boys with ASD (e.g., McLennan, Lord, & Schopler, 1993).

With regard to communication, females show a slight advantage in early language development, though this does not persist through childhood, and other purported gender differences have been frequently cited but are not supported according to the research base (Wallentin, 2009). On the other hand, Koenig and Tsatsanis (2005) emphasized some aspects of language which have social implications related to ASD. For example, Koenig and Tsatsanis (2005) reviewed evidence suggesting females build relationships through sharing thoughts and emotions, while males build relationships focusing on object/activity related themes (e.g., sports, hobbies). Thus, girls with ASD may have more trouble developing friendships, due to impairments in social communication skills (Koenig & Tsatsanis, 2005).

Finally, less research has addressed gender differences in restricted interests and repetitive behavior. In typically developing children (8 to 72 months of age), Evans and associates (1997) did not find significant gender differences related to behaviors such as compulsions, routines, and rituals. In typically developing 2-year-olds, Leekam and colleagues (2007) found boys had greater overall repetitive behavior, particularly in the area of preoccupations with restricted patterns of interest. Koenig and Tsatsanis (2005) cited evidence indicating greater difficulties with self-regulation and inhibition control in boys. These authors hypothesized that if repetitive behavior in ASD serves to either reduce arousal or provide sensory

stimulation, girls may have less difficulty decreasing their reliance on these behaviors (Koenig & Tsatsanis, 2005).

Gender Differences in ASD

Intelligence (IQ)

Gender differences in IQ in ASD. Early on in both epidemiological studies and in the literature concerning gender differences in ASD, differences regarding intelligence consistently emerged. In the first epidemiological study of ASD, Lotter (1966) found that 100% of girls (*n* = 9) had an IQ score below 55 compared to 57% of boys (*n* = 13 out of 23), a sex ratio of 1.4:1. In a review of epidemiological studies, Fombonne (2005) found a median sex ratio of 5.5:1 when intelligence was in the normal range, compared to 1.95:1 in those with moderate to severe ID. Numerous researchers have found lower IQ scores in females with ASD compared to males (Banach, et al., 2009; Lord, Schopler, & Revicki, 1982; Pilowsky, et al., 1998; Tsai & Beisler, 1983; Tsai, Stewart, & August, 1981; Volkmar, Szatmari, & Sparrow, 1993; Wing, 1981b). Regarding male to female ratios, Wing (1981b) found 1 girl compared to 16 boys with an autism diagnosis. In a separate group with the triad of language and social impairments, male to female ratios were 9.5:1 in those with IQ above 50, compared to 2.2:1 for IQ between 20 and 49, and 0.9:1 for IQ between 0 and 19 (Wing, 1981b). Tsai, Stewart, and August (1981) found a male to female ratio of 4.7:1 when IQ was greater than 70 compared to 2.9:1 when IQ was below 50. Lord, Schopler, and Revicki (1982) found a male to female ratio of 5.2:1 when IQ was 80 or greater versus 3.3:1 when IQ was below 40. Tsai and Beisler (1983) found a male to female ratio of 4.43:1 when IQ was greater than 50 compared to 1.31:1 when IQ was below 50. Significantly more females had IQ scores below 50 (Tsai & Beisler, 1983). Lord and Schopler (1985) found that females with ASD were more prevalent when IQ was less than 34. Volkmar, Szatmari, and

Sparrow (1993) found higher sex ratios when IQ was greater than 70. Males with autism were 8.8 times (and males with PDD-NOS were 1.5 times) more likely to have an IQ over 70 than females (Volkmar, et al., 1993).

Findings of lower cognitive ability in females with ASD and greater male to female ratios in the absence of ID have continued to be replicated in more recent studies. In a study of 8-year-olds with ASD in South Carolina, Nicholas and colleagues (2008) found that 72.7% of girls had an IQ below 70 compared to 56.4% of boys. The sex ratio was 4.9:1 when IQ was above 70 compared to 2.4:1 when IQ was less than 70. Finally, the proportion of males to females with ASD was similar when IQ was below 34 (Nicholas, et al., 2008). Bhasin and Schendel (2007) found a higher male to female ratio in children with ASD and an IQ above 70 (4.6:1) compared to those with ASD and an IQ below 70 (3.5:1). In simplex (single incidence) families, Banach and colleagues (2009) found that 54.8% of females compared to 20.3% of males had an IQ below 50. The sex ratios were similar when IQ was below 50, compared to 8.3:1 when IQ was above 70 (Banach, et al., 2009). In contrast in multiplex families, where more than one child has ASD, gender differences in IQ have not been found (Banach, et al., 2009; Spiker, et al., 2001).

In contrast to the previously mentioned studies which used an ASD population, Bryson and associates (2008) used an epidemiological study of ID in Ontario to examine the prevalence of autism in adolescents with mild (IQ = 50 to 75) or severe (IQ < 50) ID. Consistent with previous research, the overall male to female ratio for autism was 2.3:1, with higher ratios in mild ID (2.8:1) compared to severe ID (2:1; Bryson, et al., 2008). These authors further analyzed the frequency data. Regardless of ID, overall, males were more likely to have autism. Regardless of autism, females were more likely to have severe ID versus mild ID. However, males with severe ID were significantly more likely to have autism than males with mild ID or females.

These authors highlighted the increased risk of autism in males with severe ID (Bryson, et al., 2008).

In conclusion, findings related to ID are one of the earliest and most consistent findings in the literature concerning gender differences in ASD. Females with ASD have lower average intellectual ability than males, and the male to female sex ratio in ASD is highest when ID is not present. Given the evidence for significant gender differences in ASD associated with ID, it follows that factors related to ID must be considered in evaluating the research that has been conducted in this area.

Relationships between gender differences, IQ, and ASD. Researchers have pointed out methodological issues associated with IQ in studies of gender differences in ASD. The relationships between gender differences, IQ, and autism symptoms have not yet been determined (Lord & Schopler, 1985; Volkmar, et al., 1993). Previous research has not distinguished between severity of autism and severity of ID (Lord & Schopler, 1985; Volkmar, et al., 1993). Furthermore, Volkmar, Sparrow, and Szatmari (1993) noted that the appropriateness of controlling for IQ depends on whether low IQ is a cause or consequence of gender differences in ASD. If low IQ is a separate associated feature, controlling for it may result in overmatching (i.e., controlling for factors that are not confounding variables) and inhibit understanding of true differences (Volkmar, et al., 1993). Research and hypotheses have since been put forth concerning these issues.

Nishiyama and associates (2009) evaluated gender differences in genetic and environmental factors underlying the relationship between IQ and autistic traits via twins with ASD. Genetic factors impacting autistic traits were highly similar to those impacting IQ for boys (-0.94) and girls (-0.95). Regarding individual specific environmental factors influencing autistic

traits, there was a moderate association to those influencing IQ for boys (-0.29) and girls (-0.59). Thus, no significant gender differences were found in the genetic and environmental factors influencing autistic traits and IQ, and genetic factors underlying both ASD and IQ were highly similar (Nishiyama, et al., 2009). This is consistent with evidence suggesting overlap in genes contributing to ID and ASD (Gupta & State, 2007; Laumonnier, et al., 2004; Marshall, et al., 2008). In a review of the genetic research in ASD, Gupta and State (2007) noted that the majority of findings have implicated mutations that could result in cognitive impairment or social impairment, or impairments in both areas. It is important to note that Nishiyama and colleagues (2009) measured autistic traits as a whole via the CARS. However, based on previous research with different assessment instruments and populations, these authors purported that autistic traits in the area of socialization appear orthogonal to IQ, while communication impairments and repetitive behaviors appear to be moderately related to IQ. Hence, further research into gender differences in IQ and ASD is needed, particularly in light of recent research highlighting the dimensional and fractionable nature of autistic traits (see Happé & Ronald, 2008; Happé, Ronald, & Plomin, 2006; Mandy & Skuse, 2008; Skuse, 2007; Volkmar, et al., 2009; Waterhouse, 2008; Yirmiya, 2008).

Skuse (2007) put forth a hypothesis about the relationship between gender, IQ, and autistic traits. Skuse (2007) discussed research indicating that ASD and autistic traits frequently present in individuals with both idiopathic ID or ID associated with a variety of genetic conditions (e.g., Fragile X, tuberous sclerosis; Zafeiriou, Ververi, & Vargiami, 2007). In addition, particularly in genetic studies, strict diagnostic criteria have been employed in an attempt to reduce heterogeneity, yielding samples with mostly moderate to severe ID (Skuse, 2007). Furthermore, Skuse (2007) cited evidence from general population studies that autistic

traits are continuously distributed (i.e., dimensional as opposed to categorical) and, in contrast to studies of samples with ASD, uncorrelated with verbal or nonverbal IQ. Skuse (2007) concluded that despite their association, ASD and ID do not typically have common causes. Rather, the genes that have been implicated in ASD are instead important for developing aspects of cognitive ability needed to compensate for vulnerability to underlying autistic traits (i.e., social-cognitive processing; Skuse, 2007). These autistic traits lead to a clinically identifiable disorder in individuals with low IQ, males, or those with "independent neurodevelopmental vulnerability owing to a wide range of gene mutations, chromosomal anomalies or environmental insults" (Skuse, 2007, p. 387). With reference to gender differences in ASD, it may be that "females are equally at risk, in terms of genetic predisposition, but a factor relating to genetic or hormonal sex differences enables them to compensate for that risk. They are, therefore, less likely to manifest the full range of autistic symptoms, as conventionally measured" (Skuse, 2007, p. 393).

In summary, there is a multitude of evidence to suggest overlap in genetic factors related to ASD and IQ; however, Nishiyama and associates (2009) did not identify gender differences in this relationship. Further research is needed as symptom areas in ASD (e.g., social, communication, behavior) may be differentially associated with IQ. Autistic traits frequently present in ID and have been found to be associated with IQ. Conversely, in the general population, autistic traits have been found to be continually distributed and not related to IQ. Skuse (2007) purported that ASD and ID do not have common causes. Rather, females may be similar in genetic predisposition to ASD, but more able to compensate for that risk than males. Thus, the causal relationships between ID, ASD, and gender differences remain unclear and complicate investigation of the nature and etiology of gender differences in ASD.

ASD symptoms

Despite the long recognized predominance of males with ASD, few researchers have examined gender differences in ASD symptoms. There is a dearth of research (fewer than 10 studies) on gender differences in ASD symptoms in an ASD population. Regarding IQ, methodology has differed, with researchers either not controlling for IQ (Hus, Pickles, Cook, Risi, & Lord, 2007; Nicholas, et al., 2008; Tsai & Beisler, 1983; Tsai, et al., 1981), limiting inclusion to participants within the average IQ range (Holtmann, Bölte, & Poustka, 2007; McLennan, et al., 1993), using IQ as a covariate or matching participants based on IQ (A. S. Carter, et al., 2007; Pilowsky, et al., 1998), or conducting the analyses both with and without IQ as a covariate (Banach, et al., 2009; Lord, et al., 1982; Volkmar, et al., 1993). Regarding age, the large majority of the research involved children, with one researcher focusing on toddlers (A. S. Carter, et al., 2007) and three researchers including adult participants, up to mid-thirties (McLennan, et al., 1993; Pilowsky, et al., 1998) or early-fifties (Hus, et al., 2007) in age. Researchers have also examined gender differences in ASD symptoms in the general population (Auyeung, et al., 2008; Baron-Cohen, et al., 2006; Baron-Cohen, et al., 2001; Constantino & Todd, 2003; Loat, Haworth, Plomin, & Craig, 2008; Posserud, et al., 2006), sometimes including a subgroup of participants with ASD (Allison, et al., 2008; Ronald, et al., 2006; J. G. Williams, et al., 2008). As with the literature in the ASD population, most of this research involved children, with one study focusing on an adult population (Baron-Cohen, et al., 2001) and one on a toddler population (Allison, et al., 2008). Following is a review of the literature on gender differences in ASD based on the core symptom areas (i.e., socialization, communication, restricted interests/repetitive behavior), as well as the literature in the general population on gender differences in ASD symptoms.

Socialization. Lord, Schopler, and Revicki (1982) found lower *Vineland Adaptive Behavior Scales* (VABS; Sparrow, Balla, & Cicchetti, 1984) Social Quotients in females ages 3 to 8 years with ASD, though this difference disappeared when IQ was included as a covariate. No significant differences were found on *Psychoeducational Profile* (PEP) scales involving inappropriate affect and relating/human interest (Lord, et al., 1982). Tsai and Beisler (1983) found that boys had greater social (as measured by the *Developmental Profile* Social Subscale) and play (as measured by the *Symbolic Play Test*) abilities than girls with ASD. In a population-based study, Nicholas and colleagues (2008) found no significant gender differences in 8-year-olds with ASD on the *DSM-IV-TR* social impairment criteria. In children with ASD (age: $M = 9$, $SD = 6$), Banach and colleagues (2009) found no significant gender differences on the ADI-R or VABS social domains in simplex or multiplex families, and this finding held both with and without IQ used as a covariate. In toddlers ages 18 to 33 months, Carter and colleagues (2007) examined gender differences with age and nonverbal ability (as measured by the *Mullen Scales of Early Learning* Visual Reception Scale) as covariates. Girls showed more Social Interaction impairment on the ADI-R, poorer socialization skills as measured by the VABS, and poorer Competence in the areas of Mastery Motivation (e.g., claps for self, curious, persists on difficult tasks, wants to do things independently, likes figuring things out like stacking blocks) and Empathy on the *Infant-Toddler Social and Emotional Assessment* (ITSEA). No significant gender differences were found in Reciprocal Social Interaction on the ADOS or Social Relatedness on the ITSEA (A. S. Carter, et al., 2007).

Several researchers have examined gender differences in samples with higher cognitive abilities and ASD. McLennan, Lord, and Schopler (1993) examined gender differences on the ADI for participants with ASD matched on non-verbal IQ (all above 60) and age (range: 6 to 36

years). Females had greater impairments in current friendships and reciprocal social interaction, while males had greater separation anxiety and impairments in reciprocal social interaction and communication prior to the age of 5. No significant gender differences were found for nonverbal social behaviors or sharing enjoyment/modifying behavior to context (McLennan, et al., 1993). Holtmann, Bölte, and Poustka (2007) examined gender differences on the ADI-R, ADOS, and *Child Behavior Checklist* (CBCL) for participants with ASD matched on IQ (all above 70) and age (range: 2 to 20 years). Females had greater impairments in ADI-R current group play with peers and CBCL Social Withdrawal and Social Problems, while males had greater endorsements on inappropriate facial expression at 4 to 5 years of age and current showing/directing attention. No significant gender differences were found on the overall social domains of the ADI-R or ADOS (Holtmann, et al., 2007).

Communication. Tsai and Beisler (1983) found that boys had greater receptive and expressive language abilities (as measured by the *Sequenced Inventory of Communication Development*) than girls with ASD. Nicholas and colleagues (2008) found no gender differences in *DSM-IV-TR* communication criteria. Banach and colleagues (2009) found no significant gender differences in children with ASD on the ADI-R or VABS communication domains in multiplex families, and this finding held both with and without IQ used as a covariate. In contrast, in simplex families, girls exhibited less communication impairment on the ADI-R and lower adaptive communication skills on the VABS; however, these differences were no longer significant when IQ was used as a covariate. Knickmeyer and colleagues (2008) found that females with ASD ages 4 to 14 years engaged in more pretend play (as measured by the *Children's Play Questionnaire*). In toddlers, Carter and colleagues (2007) found girls with ASD to have greater impairments in the area of communication as measured by the ADOS, and

expressive and receptive communication as measured by the VABS. No significant gender differences were found on nonverbal communication as measured by the ADI-R or in receptive and expressive language as measured by the *Mullen Scales of Early Learning* (A. S. Carter, et al., 2007).

In studies of samples with higher cognitive abilities and ASD, McLennan and colleagues (1993) found that females with ASD demonstrated less impairment in social play at 4 to 5 years of age on the ADI, while no significant gender differences were found in the areas of gesture, conversation, language abnormalities, prosody/intonation, or communication (current and ever). Holtmann and colleagues (2007) found no significant gender differences in the area of communication on the ADI-R or ADOS.

Restricted Interests and Repetitive Behavior. In perhaps the earliest study focusing on gender differences in ASD, Tsai, Stewart, and August (1981, p. 168) described greater abnormal motor movements in females with ASD, which they described as "dystonia, abnormal posture and gait, dystonic posturing of hands and fingers, hand flapping, tremor, tic-like movement, ankle clonus, and emotional facial paralysis (i.e., asymmetry of the lower portion of the face when children smiled or spoke spontaneously)." This finding of increased abnormal motor movements in girls with ASD has not been supported in further studies. Lord, Schopler, and Revicki (1982) found that boys with ASD had more peculiar visual interests on the CARS and inappropriate, routinized, and stereotypic play on the PEP, with IQ covaried out. Banach and colleagues (2009) found no significant gender differences in children with ASD on the ADI-R restricted, repetitive, and stereotyped behavior domain in simplex or multiplex families, and this finding held both with and without IQ used as a covariate. Nicholas and colleagues (2008) found that boys with ASD had more preoccupation with parts of objects, routines and rituals, and

stereotyped mannerisms based on *DSM-IV-TR* criteria; however, no significant gender differences were found regarding restricted interests. In toddlers with ASD, Carter and colleagues (2007) found no significant gender differences on restricted, repetitive, and stereotyped behaviors on the ADI-R or ADOS. Finally, in studies of samples with higher cognitive abilities and ASD, no significant gender differences were found on restricted, repetitive, stereotyped behaviors on the ADI (McLennan, et al., 1993) or ADI-R (Holtmann, et al., 2007).

All ASD Symptoms. Several studies have included a range of intellectual ability levels and failed to find any gender differences in ASD symptoms. Volkmar, Szatmari, and Sparrow (1993) used IQ as a covariate and found no significant gender differences on the *Autism Behavior Checklist* (ABC), *ICD-10* criteria, or VABS. In participants ages 20 months to 34 years, Pilowsky and colleagues (1998) matched groups on mental age and found no significant gender differences on the ADI-R or CARS. Finally, in participants ages 4 to 52 years (M = 7.75, SD = 4.58), Hus and associates (2007) found no significant gender differences in groups based on ADI-R items involving: word or phrase acquisition, repetitive sensory motor actions (i.e., hand and finger or other complex mannerisms, repetitive use of objects, unusual sensory interests, and rocking), insistence on sameness (i.e., resistance to trivial change in environment, compulsions/rituals, difficulties with change in routine or environment), or savant skills (i.e., visuospatial, memory, musical, and computational ability).

Conclusion. In summary, overall relatively few differences in ASD symptoms have been found between males and females. Three studies found no significant gender differences in any ASD symptom areas. Some findings of greater socialization and communication impairments and abnormal motor movements in girls appear to have been related to lower IQ. Some studies

found greater impairments in females via interview but not observation, or in current but not early functioning. Regarding specific findings, in socialization, one toddler study found girls had greater impairments (e.g., social interaction, adaptive social skills, empathy). In the average IQ range, females have been found to have greater impairments in some areas (e.g., friendships, reciprocal interaction, group play), but fewer impairments in others (e.g., social anxiety, showing/directing, and early reciprocal interaction, communication, and inappropriate facial expressions). Regarding communication, in toddlers, one study found girls to have greater communication abnormalities (via interview but not observation) and adaptive communication impairments (on the VABS but not the *Mullen*). In the average IQ range, no significant gender differences have been found in communication with the exception of females having less impairment in social play at 4-5 years. Regarding restricted, repetitive, and stereotyped behaviors, some research has found that boys had greater peculiar visual interests, inappropriate/stereotypic play, preoccupation with parts of objects, routines/rituals, and stereotyped mannerisms. In studies of toddlers or individuals in the average IQ range, no significant gender differences in this behavioral domain have been found.

In the General Population. A number of studies have examined gender differences in ASD symptoms in the general population, some with a subgroup of participants with ASD. In the general population, boys ages 7 to 9 have been found to score significantly higher on the ASSQ (Posserud, et al., 2006), and males ages 7 to 15 have been found to score significantly higher on the SRS (Constantino & Todd, 2003), with higher scores indicating the presence of more autistic traits. In a population study of the CAST on children ages 4 to 10 years, boys scored higher than girls, and these results held when ASD and a mixed special needs group were removed from the sample (J. G. Williams, et al., 2008). In a study of twins at 8 years of age (90 with ASD), Ronald

and colleagues (2006) also found that boys scored higher on the CAST. In a study of 8-year-old twins, Loat and colleagues (2008) found greater social impairments as measured by the CAST in boys; however, boys and girls did not differ significantly on other CAST domains or relationship problems as measured by the Relationships Problems Questionnaire. On the Autism Spectrum Quotient (AQ), males in the control group scored significantly higher than females, while there were no significant gender differences in participants with high functioning autism or Asperger's on the child (Auyeung, et al., 2008), adolescent (Baron-Cohen, et al., 2006), and adult (Baron-Cohen, et al., 2001) versions. This same pattern held in a sample aged 19 to 63 months on the Q-CHAT (Allison, et al., 2008). Males in the control group scored higher on the Q-CHAT than females; however, there were no significant gender differences in the ASD sample (Allison, et al., 2008). To summarize, in general population studies, males have been found to have more autistic traits; however, in subgroups of participants with ASD, no gender differences have been found.

Age

Much of the literature in ASD has involved children and adolescents rather than adults (Matson & Neal, 2009). Regarding epidemiology, in Fombonne's (2003, 2005, 2007) reviews, all studies reviewed included children and adolescents, with only one study including participants up to age 27 years (Ritvo, et al., 1989). In studies of gender differences in ASD symptoms, most research has been on children, with some emphasis on toddlers (Allison, et al., 2008; A. S. Carter, et al., 2007) and adults (Baron-Cohen, et al., 2001; Hus, et al., 2007; McLennan, et al., 1993; Pilowsky, et al., 1998). Several studies of gender differences in ASD either matched groups on age or entered age as a covariate. Studies of gender differences in ASD concerning onset, course, and adult outcome are examined below.

Onset. Few studies have addressed gender differences in onset of ASD, and this issue has not been examined systematically as the focus in any studies. In participants with ASD and an IQ above 60, McLennan and colleagues (1993) reported that males were more likely to have an overall onset and play deficits before age 3 as measured by the ADI, while no gender differences were found in the frequency of onset of language and social deficits before age 3. Volkmar, Szatmari, and Sparrow (1993) noted no significant gender differences on age of onset. Thus, further research is needed regarding gender differences in onset of ASD.

Course. Only one study directly addressed gender differences in the course of ASD. In a sample with ASD and an IQ above 60, McLennan and colleagues (1993) found different patterns of gender differences based on time period of ADI items (i.e., early items prior to age 5, current items, and "ever" items). Females showed less impairment in early social and communicative behavior (e.g., social imitative play, seeking and offering comfort). However, this pattern was reversed in older children, adolescents, and adults, where females showed greater social impairments in friendships. McLennan and colleagues (1993) posed several possible explanations for these differences. For older females, peer activities are heavily dependent on social interests and communication, whereas males may have social options (e.g., spectator sports) which are less verbal and interactive. In addition, females in the study had often been in special education settings predominately with males, thus limiting opportunities to meet females with common interests. Finally, items on the ADI are different across time period. For example, early items focus on brief, responsive interactions with caregivers such as imitation and social play, while later items focus on friendships and initiation of social behavior such as greeting and sharing activities (McLennan, et al., 1993).

Lord, Schopler, and Revicki (1982) examined their findings according to age groups and found significant differences; however, no significant interaction effects emerged between age and gender. Regarding age, both with and without IQ as a covariate, children ages 5 to 8 years showed greater eye-hand coordination and perceptual skills than 3 to 4 year olds, while children ages 3 to 6 years showed greater adaptive social skills than 7 to 8 year olds. With IQ as a covariate, 5 to 6 year olds showed fewer peculiar visual interests than the other age groups (Lord, et al., 1982).

Studies of ASD traits in the general population with a subgroup with ASD have yielded comparable results across the lifespan. These studies have all revealed greater ASD traits in males in the general population; however, no gender differences were found in the subgroups with ASD. This trend was found for children, adolescents, and adults without ID (Auyeung, et al., 2008; Baron-Cohen, et al., 2006; Baron-Cohen, et al., 2001), as well as for toddlers (Allison, et al., 2008).

Outcome. Howlin, Goode, Hutton, and Rutter (2004) conducted a follow-up study of outcome in 68 adults with ASD and a performance IQ score above 50. The average age when first seen was 7 years (range 3 to 15 years) and the average follow-up age was 29 years (range 21 to 48 years). Only 7 women were included in the sample, and they were similar in age, IQ, language, reading, and spelling ability (Howlin, Goode, Hutton, & Rutter, 2004). No significant gender differences were found on measures of language level, abnormal use of language, repetitive, stereotyped behaviors, or overall social outcome. However, no females were rated as having a "Good" outcome, and five were rated as having "Poor" or "Very Poor" outcomes in areas of educational, vocational, residential, and social status (Howlin, et al., 2004).

Billstedt, Gillberg, and Gillberg (2007) conducted a follow-up study of 75 males and 30 females using the *Diagnostic Interview for Social and Communication DisOrders* (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002), a semistructured interview to aid in the diagnosis of ASD and related disorders. The follow-up period ranged from 13 to 22 years and the average follow-up age was 26 years (range 17 to 40 years). Female gender was predictive of greater abnormalities in social interaction, but not associated with impairments in reciprocal communication and limitation in self-chosen activities (Billstedt, Gillberg, & Gillberg, 2007). It is notable that more females than males in this study had epilepsy, which has been associated with intellectual disability/greater brain dysfunction and, hence, risk for poorer outcomes (Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005).

Diagnosis

Compared to males with ASD, females have been found to experience a lack of diagnosis, delay in diagnosis, and misdiagnosis with regard to ASD. In an early epidemiological study, Wing and Gould (1979) found that even when male to female ratios were the same for severity of social impairment, males were 15 times more likely to be diagnosed with ASD compared to females. In a follow-up report of the 11 children seen in 1943, Kanner reported that the girls were referred to the clinic at later ages (6 to 8 years) compared to boys (2 to 6 years; Kanner, 1971). Kopp and Gillberg (1992) reported case histories of 6 females between the ages of 6 and 10 years with ASD and an IQ above 60. None of the girls were diagnosed with ASD prior to the age of 6 years (4 were over 8 years), even though abnormal development and social, communicative, and imaginative deficits had been identified before the age of 2. Previous impressions had included ADHD, minimal brain dysfunction, developmental delay, and speech and motor concerns (Kopp & Gillberg, 1992). Finally, researchers have found undiagnosed ASD

in females with anxiety disorders (Kopp & Gillberg, 1997) and anorexia nervosa (Nilsson, Gillberg, Gillberg, & Råstam, 1999).

Two more recent studies have examined gender differences in diagnostic experiences in ASD. Goin-Kochel, Abbacchi, and Constantino (2006) found that girls were diagnosed at significantly later ages for Asperger's disorder (average age of 8.9 versus 7.0 years) and PDD-NOS (5.1 versus 3.9 years), but not autistic disorder (3.7 versus 3.3 years). No significant gender differences were found for number of professionals seen, though this was positively correlated with age at diagnosis. Earlier age at diagnosis was associated with greater parental education, income, and satisfaction with the diagnostic process (Goin-Kochel, et al., 2006). Siklos and Kerns (2007) found that parents of a female child with ASD experienced significantly more difficulty during the diagnostic process. The time frame from the first visit to a health care professional to a final diagnosis was significantly longer for females with ASD (average of 4 years 2 months) compared to that for males (average 2 years 2 months). Age at diagnosis was later for females (average of 6 years 1 month) compared to males (average of 4 years 8 months). Despite these differences, there were no significant gender differences in the number of professionals seen during the diagnostic process or reports of satisfaction and stress levels (Siklos & Kerns, 2007).

Psychopathology

Rutter, Caspi, and Moffitt (2003) reviewed the literature on gender differences in psychopathology in general, grouping these differences into two main categories. First are neuropsychiatric disorders (e.g., autism, ADHD, reading disorder), characterized by onset during childhood and greater prevalence in males (Rutter, et al., 2003). The second category encompasses emotional disorders (e.g., depression, eating disorders), characterized by onset

during adolescence and greater prevalence in females (Rutter, et al., 2003). Although antisocial behavior has adolescent onset and male preponderance, the male to female ratio is much higher when onset is during childhood (Moffitt & Caspi, 2001; Moffitt, Caspi, Rutter, & Silva, 2001).

Few studies have examined gender differences in psychopathology in ASD. In participants with ASD and an IQ above 70, Holtmann and colleagues (2007) found females had higher thought problems and attention problems as measured by the CBCL, but no significant gender differences on the CBCL Somatic, Anxious/Depressed, Delinquent Behavior, or Aggressive Behavior subscales. Bölte, Dickhut, and Poustka (1999) found no significant sex differences in individuals with ASD ages 4 to 18 on the CBCL with age and IQ included as covariates. Matson and Love (1990) examined parent-reported fears in 2.5 to 17 year olds with and without ASD. Overall, average fear scores on the *Revised Fear Survey Schedule for Children* were higher for females compared to males (Matson & Love, 1990). In toddlers with ASD, Carter and colleagues (2007) found a trend towards more Atypical Depression/Withdrawal on the ITSEA in females with ASD, but no significant differences on the Externalizing, Internalizing, Dysregulation, or Maladaptive subscales.

Developmental, Self-help, and Motor Skills

Some researchers have examined gender differences in developmental, self-help, and motor skills in ASD. Tsai and Beisler (1983) found that boys had greater perceptual-motor abilities (as measured by the Developmental Profile Physical and Self-Help Subscales) than girls with ASD; however, these differences disappeared when groups were matched on age and receptive language ability. Wing (1981b) found that boys were more likely to be ambulatory than girls, though ID was not accounted for. In participants who were ambulatory, the male to female ratio was similar (Wing, 1981b). Volkmar, Szatmari, and Sparrow (1993) used IQ as a covariate

and found no significant gender differences on the VABS. In toddlers with ASD, Carter and colleagues (2007) found no significant gender differences in daily living skills on the VABS. Boys did, however, have better gross motor skills as measured by the VABS and both gross and fine motor skills as measured by the Mullen (A. S. Carter, et al., 2007). In individuals with ASD and intelligence scores above 70, Holtmann and colleagues (2007) found no statistically significant gender differences in developmental milestones, though females did achieve them earlier than boys.

Neuropsychological/Cognitive

Two studies have examined gender differences in ASD from a neuropsychological perspective using the *Wechsler Intelligence Scales for Children-III* (WISC-III). These studies included children with ASD and average intellectual ability. The authors discussed cognitive theories related to ASD (e.g., executive functioning, theory of mind, weak central coherence) (for a review see Tsatsanis, 2005).

Nydén, Hjelmquist, and Gillberg (2000) examined neuropsychological performance in 8- to 12-year-old children with average IQ. Participants included clinic referred boys and girls with either ASD or ADHD, and a typically developing comparison girl group, with each group comprised of 17 participants. Clinic girls performed worse on tests of global executive functions (*Tower of London*) and theory of mind (*Cartoon Explanation Tasks - Mental*). No statistically significant differences were found on other tests of executive functions (i.e., inhibiting prepotent response [*Becker Go-No-Go and Conflict* paradigms], stopping an ongoing response [*Trail Making Tests*], and interference control [*Stroop Test*]) and cognitive ability (i.e., WISC-III Freedom from Distractibility, WISC-III Processing Speed, and a visuospatial ability task derived

from the Block Design subtest). However, clinic boys did demonstrate better performance on the measures (with the exception of Processing Speed) than did clinic girls (Nydén, et al., 2000).

Koyama and colleagues (2009) examined sex differences on the WISC-III Japanese version in 26 girls (mean age 8.2 years) and 116 boys (mean age 9 years) with ASD and average IQ. Girls performed significantly better than boys on the Processing Speed Index, which consists of the Coding and Symbol Search subtests. Poor performance on Processing Speed subtests may be reflective of the distractibility, extreme slowness, circumstantiality, and drive for perfection in children with high functioning autism (Ehlers, Nydén, Gillberg, & Dahlgren Sandberg, 1997). Boys' performance on the Block Design subtest was significantly better than girls, supportive of a detail focused cognitive style and the weak central coherence hypothesis in ASD (Happé, 1999; Happé & Frith, 2006; Shah & Frith, 1993). Boys scored higher on the Block Design subtest compared to other performance subtests, while girls demonstrated a more even profile across performance subtests. No significant sex differences were found on Full Scale IQ, Verbal IQ, Performance IQ, or on the verbal subtests. Both boys and girls performed worse on the Comprehension subtest relative to other verbal subtests, reflective of difficulty understanding social contexts and solving social problems (Koyama, Kamio, Inada, & Kurita, 2009).

Family Size and Birth Order

Researchers have examined gender differences in individuals with ASD in family characteristics such as birth order, family size, and so forth. However, Volkmar, Sparrow, and Szatmari (1993) cautioned that in familial studies, stoppage (i.e., not having more children after the birth of a child with a disability) may operate differently by gender. Stoppage may be increased in females due to greater ID, resulting in fewer siblings and underestimation of risk in siblings of females (Volkmar, et al., 1993). Tsai, Stewart, and August (1981) found females with

ASD were more often first-born, only child, and were from smaller families. Pilowsky and colleagues (1998) found no significant gender differences in parental age at the time of the individual's birth, birth order of individual, or number of siblings. In individuals with ASD and nonverbal intelligence scores above 60, Lord, Mulloy, Wendelboe, and Schopler (1991) found that females with ASD were from smaller families, and were more likely to be first-born whereas males with ASD were more likely to be first- or fourth-born or later. In a more recent larger sample familial aggregation study, Goin-Kochel and colleagues (2007) found no gender differences in family size of individuals with ASD.

Neurological, Genetic, and Medical Comorbidity

Researchers have examined gender differences in ASD as related to pre-, peri-, and post-natal complications, birth defects, dysmorphic features, identified syndromes, and epilepsy. In one of the earliest studies of gender differences in ASD, Tsai, Stewart, and August (1981) found greater evidence of neurological impairment in females with ASD, such as abnormal EEGs, history of epilepsy, evidence of brain damage according to Rutter and Lockyer's (1967) criteria, and enuresis. However, these authors did not account for the gender disparity in ID. Research in the area of gender differences in comorbid neurological, genetic, and medical factors in ASD has since continued. Some researchers have since proposed subgroups of ASD based on these factors. Following is a review of the literature base related to gender differences in ASD in pregnancy and birth complications, birth defects, dysmorphic features, identified syndromes, and epilepsy.

Gender differences in pre-, peri-, and post-natal complications in individuals with ASD have been examined. Several researchers have found no significant gender differences in pre-, peri-, and post-natal complications in individuals with ASD (C. Gillberg & Gillberg, 1983;

Mason-Brothers, Ritvo, Guze, & Mo, 1987; Zwaigenbaum, et al., 2002). However, results of these studies are complicated by the small number of females in samples and the presence of ID (Lord, et al., 1991). In individuals with ASD and nonverbal intelligence scores above 60, Lord, Mulloy, Wendelboe, and Schopler (1991) obtained similar results (no significant gender differences). In contrast, in a sample of 23 males and 23 females with intelligence scores above 70, Holtmann and colleagues (2007) found that females had more pre-, peri-, and post-natal complications than males, though no gender differences in neurological soft signs (specifics not reported by the authors) were found. Finally, Schendel and Bhasin (2008) found that girls with low birth weight had a significant fourfold increased risk for ASD and ID, while boys with low birth weight did not have an increased risk for ASD alone.

Miles and associates (2005) have classified cases of "complex autism" versus "essential autism" and examined gender differences. Complex cases were classified by having more dysmorphic features and/or microcephaly, and comprised all 11 cases in this study with an identified syndrome (i.e., chromosomal; single gene disorders such as tuberous sclerosis and Sotos; fetal valproate exposure) (Miles, et al., 2005). Miles and associates (2005) found a higher male to female ratio in essential autism compared to complex autism (6.5:1 versus 3.2:1). In addition, more individuals with essential autism had a family history of ASD, siblings with ASD, higher IQ, and regression at onset (Miles, et al., 2005). Conversely, more individuals with complex autism had seizures and an abnormal EEG and brain MRI (Miles, et al., 2005). In an earlier study, Miles and Hillman (2000) found comparable results in that the male to female ratio decreased with physical anomalies (i.e., minor anomalies, measurement abnormalities, descriptive traits, malformations) and abnormal brain MRI results. Specifically, compared to an overall sex ratio of 4.2:1, the sex ratio was significantly lower for those who had both abnormal

morphology and abnormal brain MRI (2.1:1 compared to 23:1), as well as for those with abnormal morphology alone (1.7:1 compared to 7.5:1) (Miles & Hillman, 2000). Six cases (5 male, 1 female) in this study had genetic syndromes (i.e., ring chromosome 8, del 8q22, der 15, Sotos, tuberous sclerosis) (Miles & Hillman, 2000).

In a population-based study in Atlanta, Georgia, Schendel, Autry, Wines, and Moore (2009) examined major birth defects (e.g., central nervous system/eye, cardiovascular, genitourinary, musculoskeletal, chromosomal syndromes, etc.) in ASD in relation to gender differences. Inconsistent with Miles's (2000, 2005) findings, sex ratios were higher in children with ASD and major birth defects (6.8:1) compared to the overall ASD male to female ratio of 3.8:1. However, of the sample with major birth defects, the male to female ratio was lower in those with a developmental disability (i.e., ID, cerebral palsy, vision loss) in addition to ASD compared to ASD only (6.3:1 versus 8:1), though it is notable that few participants had birth defects and ASD without another developmental disability (Schendel, et al., 2009).

Amiet and colleagues (2008) conducted a meta-analysis of epilepsy in ASD as related to ID and gender. Females had an increased relative risk of epilepsy, and the male to female ratio of ASD was higher in individuals without epilepsy (3.5:1) compared to those with epilepsy (close to 2:1). In addition, as expected, the prevalence of epilepsy was higher for individuals with ID (Amiet, et al., 2008). Follow-up studies of adults diagnosed with ASD in childhood have shown higher rates of epilepsy in females (Billstedt, et al., 2007; Danielsson, et al., 2005), and epilepsy has been shown to be associated with the presence of greater intellectual and adaptive impairments (Danielsson, et al., 2005).

Genetic Models and Linkage

Twin studies have been employed to evaluate gender differences in models examining the contribution of genetic and both shared and unique environmental factors to ASD. In a general population study using the SRS, Constantino and Todd (2003) found no significant gender differences in the model. Similarly, Mazefsky, Goin-Kochel, Riley, and Maes (2008) did not find model differences by gender in an ASD only sample using the ADI-R. In contrast, in a primarily general population sample, Ronald and colleagues (2006) found gender differences in the model using the CAST. Using multiple measures of social, behavioral, and cognitive measures as well as the CAST in the general population, Loat and colleagues (Loat, Asbury, Galsworthy, Plomin, & Craig, 2004; Loat, et al., 2008) found higher heritability estimates in males, but hypothesized this was more indicative of X-linked quantitative trait loci. In summary, results have been inconsistent in the few studies which have been conducted, and these studies have varied widely in methodology, namely the population and instruments employed. Finally, as mentioned previously, Nishiyama and associates (2009) did not find significant gender differences in genetic and environmental factors in the relationship between autistic traits and IQ.

Several researchers have found differential results of linkage studies based on gender. Sex-specific linkages have been found on chromosomes 17 (Cantor, et al., 2005; Duvall, et al., 2007; J. L. Stone, et al., 2004; Strom, et al., 2009), 7 (Lamb, et al., 2005; Schellenberg, et al., 2006), 11 (Autism Risk Genome Project Consortium, et al., 2007; Duvall, et al., 2007; Schellenberg, et al., 2006), and 15 (Autism Risk Genome Project Consortium, et al., 2007; Lamb, et al., 2005), as well as on chromosome 16 (Lamb, et al., 2005), 4, 8, and 10 (Duvall, et al., 2007), and 5 and 9 (Autism Risk Genome Project Consortium, et al., 2007). In addition, Lamb and colleagues (2005) found parent of origin effects on chromosomes 7 and 9. Therefore,

stratifying genetic linkage analyses based on gender and whether genes were inherited from the mother or father has yielded differential results on a number of chromosomes.

Etiology of Gender Differences in ASD

A wide range of hypotheses on the etiology of gender differences in ASD have been proposed, implicating a number of different mechanisms. Given the evidence for high heritability of ASD, the large majority of researchers turned to genetic hypotheses to account for the significant gender differences, and this is evident even in the initial early hypotheses put forth. This focus on genetics is consistent with the ASD literature base in general (Matson & LoVullo, 2009). Miles and Hillman (2000, p. 251) declared "It is commonly acknowledged that in order to understand the genetic basis of autism, we will have to understand the male predominance." Hence, gender differences have been an important variable in the area of genetics and ASD. Other hypotheses have implicated gender differences in typically developing populations, brain lateralization, and hormonal influences. Finally, while most hypotheses have focused on biological etiologies, a few have noted environmental factors such as diagnostic issues and potential gender biases.

Multifactorial Liability/Threshold Model

Tsai and colleagues (Tsai & Beisler, 1983; Tsai, et al., 1981) applied the multifactorial genetic transmission hypothesis to account for gender differences in ASD. According to Tsai and colleagues, in this model, "liability" is a normally distributed underlying variable comprising all genetic and environmental factors relevant to the etiology. All people have some liability, but they do not become affected unless the liability exceeds a certain critical value called the threshold. Males have a lower threshold for brain dysfunction and less significant genetic "liabilities" are required for a male to end up with ASD than a female. Females have a higher

threshold, and require a higher "dose" of genes to be impacted. Therefore, as the less frequently affected sex, females with ASD would have more severe deficits, more affected relatives with any form of the disorder, and a greater proportion of relatives with more severe deficits (Tsai & Beisler, 1983; Tsai, et al., 1981). Tsai and colleagues (Tsai & Beisler, 1983; Tsai, et al., 1981) found support for this model in that females with ASD had more first-degree relatives with cognitive/language impairments or ASD.

Further research has not yielded any support for this liability/threshold model. Risk for the broader autism phenotype has not been found to be higher in relatives of females compared to males with ASD (Bolton, et al., 1994; Pickles, et al., 2000; Szatmari, et al., 2000). Boutin and associates (1997) did find more first degree relatives with cognitive disabilities (i.e., language delay, ID, learning disabilities) in those with ASD who were female and had an IQ less than 50; however, in their sample, there were no gender differences in IQ. Pickles and colleagues (2000) did not find significant differences in severity or type of phenotypic expression in relatives by sex of the proband, nor were there elevated rates on the mother's side for male probands. In a recent large sample study, Goin-Kochel and colleagues (2007) did not find an increased risk of ASD in relatives of females with ASD, even when controlling for IQ. Goin-Kochel and colleagues (2007) concluded that there is a lack of support for increased genetic liability for ASD in families of females with ASD, and that earlier findings (Tsai & Beisler, 1983; Tsai, et al., 1981) may be better accounted for by lower IQ in females. Consistent with Goin-Kochel and colleagues' (2007) conclusion, in multiplex families, Banach and colleagues (2009) did not find a significant difference in IQ, severity of autistic symptoms, or adaptive social and communication functioning in male siblings with ASD based on whether they had a brother versus a sister with ASD (with the exception of slightly greater socialization impairment in males

with ASD with a brother with ASD, which is in the opposite direction predicted by the liability/threshold model).

Genetic Variability

Wing (1981b) applied Taylor and Ounsted's (1972) hypotheses about gender differences in developmental disabilities to ASD. Taylor and Ounsted (1972) reported that a wide variety of disabilities (e.g., Down's syndrome, cerebral palsy) have a higher prevalence in males, and those with the lower prevalence tend to be more severely impaired. Taylor and Ounsted (1972) also hypothesized that higher prevalence and less severity in males may be due to their greater genetic variation in the majority of measurable characteristics. Wing (1981b) noted that, therefore, more males may show mild ASD features as a direct result of this genetic variability, while females may show these features only as a result of some type of pathology.

This model would predict higher rates of identifiable organic conditions in females compared to males with ASD. In support of this, Wing (1981b) found that identifiable organic conditions were more frequently associated with profound ID in girls versus severe and moderate ID in boys. However, Tsai and Beisler (1983) examined the percentages and rates of organic conditions based on Wing's (1981b) data, and found them similar overall in boys and girls (56% and 65%, respectively). When IQ was below 50, rates for boys and girls (67% and 68%, respectively) were similar (Tsai & Beisler, 1983; Wing, 1981b). In participants with an IQ above 50, boys had more identifiable organic conditions (27% compared to 0%); however, only one girl was included in this IQ range (Tsai & Beisler, 1983; Wing, 1981b). Finally, inconsistent with Wing's (1981b) prediction, Schendel and colleagues (2009) found higher male to female ratios in children with ASD and major birth defects; however, the ratio was lower in those with a ASD and ID compared to ASD only.

Wing's (1981b) genetic variability hypothesis has not been further researched directly. However, researchers have expanded upon the notion of greater genetic variability in males in relation to epigenetic hypotheses (see X-inactivation/X-linkage and X-linked male extremes hypotheses described below). Rutter, Caspi, and Moffitt (2003) pointed out that genetic variability has been posed as an explanation for a number of disorders, though there has not been substantial systematic research to provide evidence for the hypothesis. Regarding Wing's (1981b) hypotheses about gender differences in pathology and ID in ASD, some related data, albeit limited, has emerged. This area of research is impacted by the type of pathology and related ID, rare conditions resulting in small sample sizes, and sex linked genetics. In children without physical anomalies and/or an identified syndrome or etiology (essential versus complex autism), Miles and colleagues (2005) found more males compared to females, higher IQ, and more ASD relatives. Based on this data, Beaudet (2007) noted that the gender ratio in cases with identified genetic mutations is likely equal. In contrast, Schendel and associates (2009) found a higher male to female ratio in children with ASD and major birth defects.

Language and Visuospatial Skills

Wing (1981b) described another hypothesis of gender differences in ASD based on available research at that time concerning gender differences in typically developing populations. She quoted Asperger (1944) describing the syndrome as "an extreme variant of male intelligence and male character" (Wing, 1981b, p. 135). Wing (1981b) reported that in the general population, females have been found to have better language skills, and poorer visuospatial and math skills. Males may be more susceptible to language and communication deficits such as those in ASD, but more likely to have useful visuospatial abilities (Wing 1981b). Females may be less vulnerable to language and communication deficits, but those with ASD may have fewer

compensating visuospatial skills and be more likely to have profound ID (Wing, 1981b). Wing (1981b) further noted that visuospatial skills may be implicated in developing repetitive routines involving manipulating objects.

Wing (1981b) did point out data available at the time which were inconsistent with this hypothesis. First, differences in visuospatial and language skills are seen in adolescence in comparison to ASD symptoms which emerge in infancy/early childhood. Second, although speech and language disorders are more frequent in boys, developmental receptive language disorder, which has overlap with ASD, is low in frequency for both boys and girls. Finally, higher functioning individuals with ASD score higher on verbal versus performance subtests on the Wechsler intelligence scales (though this may reflect rote memory ability and not understanding), and have poor coordination. Wing (1981b) also noted that it has not been fully established that typically developing girls have superior social interaction skills.

Gillberg, Winnergård, and Wahlström (1984) expanded upon Wing's (1981b) hypothesis, suggesting a link between autism and the sex chromosomes based on a case with XYY syndrome. These authors (1984, p. 353) cited Wing (1981b) as hypothesizing that autism "might result from the pathological exaggeration of typically male behavioral traits." Visuospatial skills and some ASD symptoms (e.g., insistence on sameness, restricted interests, preoccupation with objects) could be characterized as exaggerations of male characteristics (Kopp & Gillberg, 1992). Conversely, communication impairments in ASD could be characterized as an exaggeration of male language development (i.e., slower and more vulnerable than that of females), and social communication impairments as an area typically less well-developed in males (Kopp & Gillberg, 1992). In line with Wing's (1981b) association of autism with too much male or insufficient female influence, Gillberg and colleagues (1984) cited possible links

between autism and an excess of male chromosome material (as in XYY syndrome and findings of long Y chromosomes) or a deficiency in female chromosome material (as in fragile X and Lesch-Nyhan syndrome) (C. Gillberg, et al., 1984).

In evaluating gender differences in language and visuospatial skills in children with ASD, Lord, Schopler, and Revicki's (1982) results varied depending on whether IQ was accounted for. Boys did perform better than girls on eye-hand integration and perceptual tasks, though these differences did not remain when IQ was covaried. These skills may reflect developmental differences for both genders, as older children's performance on these tasks exceeded that of younger children (Lord, et al., 1982). Regardless of IQ, boys exhibited more unusual visual responses than girls. When IQ was covaried, boys also demonstrated more routinized and stereotypic play and less appropriate play compared to girls. Finally, no gender differences emerged in the areas of affect and relating to people, nor in receptive language when IQ was covaried (Lord, et al., 1982).

To further evaluate Wing's (1981b) hypothesis, McLennan, Lord, and Schopler (1993) examined gender differences in individuals with ASD and an IQ greater than 60. They predicted that females would show less impairment in social and communication domains based on Wing's (1981b) premise, and fewer unusual visual interests and stereotyped behaviors based on Lord and colleagues' (1982) findings (McLennan, et al., 1993). McLennan and colleagues (1993) did find males had greater deficits in early social and communicative behavior than females, though this trend was reversed in older age groups. In addition, no gender differences were found in restricted, repetitive, or stereotyped behaviors (McLennan, et al., 1993).

Lateralization of Brain Function

Lord, Schopler, and Revicki (1982) derived hypotheses about gender differences in ASD based on available research at the time relating to gender differences in brain functioning in the general population. As reported by Lord and colleagues (1982), language deficits have been attributed to left hemisphere damage, while perceptual skills suggest intact right hemispheric functioning. In addition, females have been shown to have less lateralization (i.e., smaller differences in left-right hemisphere functioning). If this is true, Lord and colleagues (1982) suggest how this could be applied to gender differences in ASD. In females, because specific skills are not linked to a specific hemisphere, more extensive bilateral brain damage would be needed to produce specific deficits such as those present in ASD. In contrast, for males more limited dysfunction or smaller lesions in a specific area may be sufficient to result in ASD. Lord and colleagues' (1982) reported that their findings of lower performance across cognitive measures in females could be interpreted as evidence for more extensive brain dysfunction in females with ASD compared to males.

Extreme Male Brain (EMB) Theory

Baron-Cohen and Hammer (1997) argued that autism is an extreme form of the male pattern of neurodevelopment. They linked this idea back to Hans Asperger's (1944) writings describing how "the autistic personality is an extreme variant of male intelligence" (Frith, 1991, p. 84). The EMB theory proposes that ASD is an extreme form of the male brain, where empathizing is hypo-developed and systemizing is hyper-developed (Baron-Cohen, 2002). Empathizing refers to a drive or capacity to identify others' emotions (e.g., theory of mind) and thoughts and respond with an appropriate emotion, while systemizing refers to a drive or capacity to analyze variables in a system, derive underlying rules governing a system, and

construct systems in order to predict lawful events (Baron-Cohen, 2002). These terms were originally described as folk psychology (everyday understanding of people's mental states or theory of mind) and folk physics (everyday understanding of objects related to physical causality and spatial relations), respectively (Baron-Cohen & Hammer, 1997). Baron-Cohen (2002) asserted that systemizing predicts weak central coherence (i.e., focus on details as opposed to global processing of information) in ASD. Baron-Cohen (2008) asserted that hypersystemizing can explain preference for and success in predictable/lawful systems (e.g., math, spinning objects, calendar dates, engines) in ASD, as well as difficulties (e.g., resistance to change, need for sameness) in the unlawful social world of human behavior.

Baron-Cohen and colleagues (Baron-Cohen, 2002, 2008; Baron-Cohen & Hammer, 1997; Baron-Cohen, Knickmeyer, & Belmonte, 2005) reported evidence suggesting that in the general population, females demonstrate strengths in empathizing and males in systemizing, while individuals with ASD have impairments in empathizing and strengths in systemizing. In the general population, Baron-Cohen (2008) cited research finding females show more turn-taking, are better at decoding nonverbal communication, have more cooperative, reciprocal, collaborative speech, talk more about feelings (as opposed to objects or activities), and from birth, gaze longer at faces, especially eyes (compared to inanimate objects). Regarding males in the general population, Baron-Cohen (2008) cited research findings that males show more interest in systemizable toys, have occupations related to systemizing, and perform better on tests of math, assembly, mental rotation, locating objects in patterns, and map reading. In individuals with ASD, Baron-Cohen (2008) cited research finding impairments in false belief tasks and emotion recognition, and strengths in specific skills (e.g., calculation, memorization), attention to detail, and picture-sequencing. Though these differences have been found, there was still

considerable overlap between male and female distributions, effect sizes were variable, and these were population differences not to be extrapolated to individuals (Baron-Cohen, 2008).

Baron-Cohen has further proposed that exposure to fetal androgens are involved in the masculinization of the brain (Baron-Cohen, 2002; Baron-Cohen & Hammer, 1997; Baron-Cohen, et al., 2005). This is related to earlier writings (e.g., Geschwind & Behan, 1982; Geschwind & Galaburda, 1985; Hines & Shipley, 1984; Leboyer, Osherson, Nosten, & Roubertoux, 1988) concerning lateralization of brain function and fetal androgen exposure. In support of this, Baron-Cohen and colleagues (Baron-Cohen & Hammer, 1997; Baron-Cohen, et al., 2005) cited additional research linking male gender and ASD with left-handedness, brain differences (e.g., amygdala growth, cortex enlargement with a skewed balance between local and long-distance tracts), and lower 2D:4D (i.e., ratio between the length of the 2^{nd} and 4^{th} digit which has been used as a proxy for fetal testosterone in the first trimester). They also cited research concerning masculine traits and ASD traits in individuals with congenital adrenal hyperplasia (CAH; causes excess adrenal androgen production) (e.g., Knickmeyer, et al., 2006). Baron-Cohen (2002) purported that fetal testosterone level impacts developmental precursors for empathy such as early social (e.g., eye contact, attention to faces) and language (i.e., vocabulary) development, as well as for systemizing (e.g., attention to detail, narrow interests). Baron-Cohen (2008) cited research showing negative relationships between fetal testosterone and eye contact at 1 year of age, social skills at 4 years, and empathizing at 8 years, and positive relationships with narrow interests, systemizing, and locating objects in patterns. Much debate has ensued surrounding this theory and how to evaluate it (Auyeung, et al., 2009; Barbeau, Mendrek, & Mottron, 2009; Baron-Cohen, Auyeung, Ashwin, & Knickmeyer, 2009; Falter, Plaisted, & Davis, 2008a, 2008b; Klin, 2009; Knickmeyer, Baron-Cohen, Auyeung, & Ashwin, 2008).

Further hypotheses about the involvement in hormones in gender differences in ASD have been proposed by other researchers. For example, Carter (2007) proposed that excess or abnormal activity in systems that rely on arginine vasopressin (which is androgen-dependent) could impact development of ASD traits in males. She further proposed that oxytocin (estrogen-dependent) may be protective to females, and females may be less sensitive to vasopressin than males (C. S. Carter, 2007). In addition, Yamasue and colleagues (2009) implicated oxytocin, hypothesizing a role in social reciprocity and brain regions implicated in social behaviors. These hypotheses have not yet been empirically validated. Finally, gender differences have long been attributed primarily to hormonal masculinization of the male brain. However, researchers have recently emphasized additional mechanisms as well (i.e., epigenetics), which may be impacted by a multitude of environmental and biological factors, but also occur independent of hormonal influences (Craig, Harper, & Loat, 2004; Davies & Wilkinson, 2006; Gabory, Attig, & Junien, 2009; Skuse, 2000). These epigenetic mechanisms will be reviewed in the following section as it pertains to the etiology of gender differences in ASD.

X-Chromosome Epigenetics

Given the pronounced sex ratio found in ASD, traditional explanations have been explored (e.g., X-linked recessive inheritance, expression being sex limited or sex influenced, multifactorial inheritance, death in females, genetic heterogeneity; Miles & Hillman, 2000), though few have been sufficiently investigated and none have fully panned out (Schanen, 2006). While some findings have suggested X-chromosome involvement (Jacquemont, et al., 2006; Jamain, et al., 2003; Klauck, et al., 2006; Laumonnier, et al., 2004; Liu, et al., 2001; Marshall, et al., 2008; Shao, et al., 2002; Thomas, et al., 1999; Vincent, et al., 2005), no consistent X-chromosome cause has been identified excluding Rett's disorder (O'Roak & State, 2008).

Recognizing that the etiology of gender differences in ASD was increasingly complex, researchers have implicated epigenetic theories, which have been expanded on to encompass evolutionary components (Marco & Skuse, 2006). Epigenetic processes can impact gene expression without changing DNA sequence (Delcuve, Rastegar, & Davie, 2009). Skuse (2006) described a number of epigenetic ways X-linked genes could be implicated in gender differences, including X-inactivation, differential expression of X-linked genes based on chromosomal and gonadal sex (sex chromosome composition and whether *Sry*, the sex-determining gene for testis development, is present), and genomic imprinting.

Imprinting. In imprinting, alleles are differentially marked for expression or silencing. Whether or not genes are expressed or silenced depends on which parent they are inherited from. As an example, Prader-Willi syndrome and Angelman syndrome were the first identified disorders in humans involving imprinted genes (Horsthemke & Buiting, 2008). In addition, Rett's disorder is caused by a mutation in MeCP2 (Amir, et al., 1999), a gene involved in imprinting regulation (LaSalle, 2007). Several researchers have implicated imprinting in the etiology of gender differences in ASD, with some incorporating evolutionary theories.

Skuse (1999, 2000; 1997) proposed the imprinted-X liability threshold model based on findings in females with Turner's syndrome (monosomy X). In Turner's syndrome, Skuse and colleagues (1997) found that females who had inherited the X-chromosome from the father had superior social-communicative skills compared to those who had inherited the X-chromosome from the mother. The imprinted-X liability threshold model holds that the threshold for expression of ASD symptoms is influenced by the presence of an imprinted genetic locus on the X-chromosome, which influences the development of skills needed for normal fluent social communication. This locus is silent in the one X-chromosome males get from the mother. In

males, having a single X-chromosome reduces the threshold at which phenotypic expression of ASD symptoms occur. Females have a higher threshold because they have a second X-chromosome from the father in which the locus is expressed. The model proposes that genetic vulnerability is primarily due to effects from autosomal loci, and ASD symptoms largely result from genetic or environmental influences independent of the sex chromosomes (Skuse, 1999, 2000; Skuse, et al., 1997).

Skuse's model has not yet been subject to extensive further evaluation, particularly in relation to ASD. Donnelly and associates (2000) presented an additional case of a female with autistic disorder, Turner's syndrome, and a maternally inherited X-chromosome. Thomas and colleagues (1999) presented eight females with deletions on the short arm of the X-chromosome, three of whom had autistic disorder. In contrast, in female probands, Pickles and colleagues (2000) did not find higher rates of the broader autism phenotype in paternal grandmothers or daughters of paternal uncles as would be consistent with Skuse's model. With regard to Turner's syndrome, researchers have investigated Skuse's imprinting hypothesis related to memory (D. V. M. Bishop, et al., 2000), ADHD (Russell, et al., 2006), physical/medical variables and academic achievement (Sagi, et al., 2007), and mouse models (see Lynn & Davies, 2007).

Shaner, Miller, and Mintz (2008) proposed an explanation as to why this counterintuitive mechanism (i.e., a maternal imprint that impairs social communication skills in sons, as Skuse has suggested) may have evolved. Parents have to identify offspring most likely to survive and reproduce in order to successfully allocate their resources, whereas offspring have to advertise health to attract parental resources. Infants and toddlers who are more articulate, expressive, playful, and socially engaged are more successful at attracting parental attention, protection, resources, and so forth (Shaner, Miller, & Mintz, 2008). Skills in language, facial expression,

creative play, and coordinated social interaction may have been selected by parents as an indicator of fitness to aid them in determining investment (Shaner, et al., 2008). Shaner and colleagues (2008) purported that offspring vary significantly in these skills, these skills correlate with underlying fitness, and autism may be the low-fitness extreme of this variation. Regarding sex differences, mothers must be more selective in resource allocation to sons, as sons require more resources, increase the time frame until the mother can have another child, and have variable reproductive success compared to females (Shaner, et al., 2008). Therefore, in males, the development of fitness indicator skills (i.e., early social/communicative behaviors) must be even more complex, demanding, and sensitive to genetic quality and environmental hazards to ensure they are reliable and valid indicators. These skills are less sensitive in females, so they are impacted less frequently but when impacted, reflect more severe genetic/environmental insults (Shaner, et al., 2008). In reference to imprinting, it is of maternal benefit to silence genes that nonselectively increase offspring's ability to extract resources, while the contrary is true for fathers. Further, maternal imprints have a greater impact on sons because sons only have one X-chromosome (Shaner, et al., 2008). This results in greater variance in the trait and increases in occurrence at the extremes. The unique proposal of this imprinting hypothesis is that imprinting serves to alter the fitness sensitivity of a parent-selected fitness indicator (Shaner, et al., 2008).

Similarly, Badcock and Crespi (Badcock & Crespi, 2006; Badcock & Crespi, 2008; Crespi & Badcock, 2008) hypothesized that there is an evolutionary struggle between the mother and father to turn gene expression up or down (i.e., via imprinting) based on cost/benefit to the parent during early and later development. In addition, these authors asserted that ASD is the diametric opposite of psychotic spectrum conditions (schizophrenia, bipolar, major depression), which are of more paternal versus maternal benefit, respectively. Regarding the diametric

opposite component of this theory, Badcock and Crespi (2008) cited evidence of characteristics in ASD (e.g., higher birth weight, lower 2:4 digit ratio, high levels of growth factors, larger brain size, thicker cortex, lack of gray matter loss, larger more reactive amygdala, smaller corpus callosum, greater lateralization, right-hemisphere dysfunction, underdeveloped mirror neuron system) in which the opposite is found in the psychotic spectrum. Cognitively, Badcock and Crespi (2008) cited evidence contrasting ASD characteristics (e.g., deficits in eye contact, interpreting intention, joint attention, theory of mind, abstract thinking, imagination, inner speech, verbal skills, and global processing) to those in the psychotic spectrum (e.g., paranoia, delusions, enhanced theory of mind, magical ideation, hallucinations, increased global processing). These authors purported that ASD and psychotic spectrum disorders are on opposite extremes of a continuum between mechanistic (male brain) and mentalistic cognition (female brain), respectively (Crespi & Badcock, 2008). Regarding cost/benefit to parents, Crespi and Badcock (2008) cited evidence of maternal benefits for offspring with schizophrenia (e.g., smaller infants, slower growth, later onset, less demanding behaviorally, ability to have more offspring, increased fertility in offspring) compared to ASD.

In terms of sex differences, Crespi and Badcock (2008) asserted that the interaction between paternal versus maternal imprinting effects and male and female sex differences account for the resulting phenotypes. The most severe impairments occur in females with ASD (classic autism, ID, Rett's, equal M:F) and males with schizophrenia (psychosis with negative symptoms, severe poor prognosis, mildly higher M:F), where the imprinting effects are biased towards the parent of the opposite sex (Crespi & Badcock, 2008). Conversely, disorders are more common and less severe when sex and parental gene bias are compatible. For example, greater paternal imprinting effects in males yields the extreme male or paternal brain (Asperger's/HFA,

decreased ID, high M:F), while greater maternal imprinting effects in females yields the extreme female or maternal brain (psychosis with positive symptoms, relatively good outcome, high F:M) (Crespi & Badcock, 2008). Much debate has ensued surrounding this theory (see multiple commentaries and the author replies in Crespi & Badcock, 2008).

X-Inactivation/X-Linkage Hypothesis. Loat and colleagues (Loat, et al., 2004; Loat, et al., 2008) proposed the presence of quantitative trait loci (QTL) on the X-chromosome for social, behavioral, and cognitive traits such as those found in ASD. In addition, they proposed that gender differences in ASD arose due to X-inactivation (Loat, et al., 2008). Females have two X-chromosomes while males have only one. To keep females from having a double dose of X-linked genes, either the maternal or paternal X-chromosome in each cell is randomly inactivated (Craig, et al., 2004). In males, genes subject to random X-inactivation will be fully expressed because they have a single X-chromosome, but expression in females is dependent on a mosaic pattern (Skuse, 2006). However, a number of genes escape inactivation and some of these do not have Y-chromosome homologues, resulting in two active copies in females versus one in males (Craig, et al., 2004). Males may lack a functional copy on the Y chromosome for X-linked genes that escaped inactivation (Skuse, 2006). In addition, although random X-inactivation should result in roughly 50% maternal and 50% paternal active X-chromosomes, inactivation may be skewed either by chance or as a result of mutations on the X-chromosome (Craig, et al., 2004). Loat and colleagues (2004, 2008) hypothesized that in monozygotic twins, female twins would be less similar than male twins on these X-linked traits due to random X-inactivation. Conversely in dizygotic twins, female twins would be more similar on these traits than male twins, due to the presence of an active paternal X-chromosome in half of the cells, compared to

males having either the mother's maternal or paternal X-chromosome (Loat, et al., 2004; Loat, et al., 2008).

Some evidence has been found in support of the X-inactivation/X-linkage hypothesis. Loat and colleagues (2004) found stronger correlations in monozygotic male compared to female twins for prosocial behavior at 2 years, verbal ability at 3 years, and peer problems at 4 years of age. Regarding dizygotic twins, female twins were more similar in the areas of prosocial behavior and verbal ability at 3 years of age (Loat, et al., 2004). In further examination of this hypothesis, Loat and colleagues (2008) found evidence for the same pattern for teacher reported prosocial and problem behavior at 7 years, and parent reported social impairments as measured by the CAST at 8 years. Female monozygotic twins were less similar in hyperactivity and problem behavior, while female dizygotic twins were more similar on the CAST composite and communication and non-social domains (Loat, et al., 2008). Trends of less similarity in monozygotic female twins were found in the areas of peer problems, academic achievement, language achievement, and non-verbal cognitive ability (Loat, et al., 2008). As measured by the CAST in a primarily general population sample, Ronald and colleagues (2006) found significantly higher monozygotic twin correlations for social impairments and overall ASD symptoms in males, while female monozygotic twin correlations were significantly higher in the area of restricted, repetitive behaviors and interests. There was also a trend towards higher dizygotic twin correlations in females compared to males in all areas of the CAST, especially when scores were above 95% (Ronald, et al., 2006). In an ASD only population, Mazefsky and colleagues (2008) found a trend towards higher correlations for both monozygotic and dizygotic twins in males compared to females on nonverbal communication and social dysfunction as measured by the ADI-R.

X-Linked Male Extremes. In the general population, males exhibit greater variance than females for many traits (e.g., intelligence) and thus are overrepresented at the extremes of distributions (e.g., Hedges & Nowell, 1995; Johnson, Carothers, & Deary, 2008; Lehre, Lehre, Laake, & Danbolt, 2009). The X-chromosome contains a high density of genes important for brain development and reproduction, and ID is approximately three times more often related to genes on the X-chromosome versus the autosomes (Zechner, et al., 2001). These genes for cognitive ability on the X-chromosome may have evolved due to selection in males by females (Zechner, et al., 2001). Regarding extremes, in females, X-linked gene expression is averaged out across cells via X-inactivation (Craig, et al., 2004; Lehre, et al., 2009). In contrast, males exhibit extreme X-linked phenotypes, as they are impacted by X-linked genes without a Y homologue (Craig, et al., 2004; Skuse, 2005, 2006; Zechner, et al., 2001). Skuse (2005, 2006) described how males are more impacted by these X-linked traits (e.g., intelligence, social cognition, emotion regulation) than females, resulting in more exceptional abilities in some areas, but also in more mental impairments due to mutations.

Some researchers have examined gender differences in variability in ASD traits. Across the lifespan in the general population, males have been found to exhibit a greater number of autistic traits compared to females (Allison, et al., 2008; Auyeung, et al., 2008; Baron-Cohen, et al., 2006; Baron-Cohen, et al., 2001; Constantino & Todd, 2003; Posserud, et al., 2006; J. G. Williams, et al., 2008). In addition, these studies have found distinct distributions between males and females, as well as larger standard deviations in males (Auyeung, et al., 2008; Baron-Cohen, et al., 2001; Constantino & Todd, 2003; Posserud, et al., 2006; J. G. Williams, et al., 2008). In contrast, in twins ages 2-4 years, Loat and colleagues (2004) found similar variances in males and females for a number of traits (i.e., anxiety, prosocial behavior, hyperactivity, conduct

problems, peer problems, and cognitive ability). In conclusion, the X-linked male extremes hypothesis of gender differences in ASD has not been fully evaluated.

Skewed X-Chromosome Inactivation. Some researchers have investigated non-random, or skewed, X-chromosome inactivation as an explanation for gender differences in ASD. In an initial investigation using peripheral blood cells, Talebizadeh and colleagues (2005) found that skewed X-inactivation was more common in females with autism compared to females without autism, and was more heritable in females with autism compared to rates in the general population. In contrast, Gong and colleagues (2008) did not replicate these findings. In addition, using samples from the frontal cortex and blood, Nagarajan and associates (2008) did not find more frequent X-inactivation skew in females with autism or mothers of males with autism. However, further research is needed using a variety of samples and methodologies (Nagarajan, et al., 2008). Finally, the role of X-linked genes which escape inactivation in the etiology of gender differences in ASD has yet to be explored (Gong, et al., 2008).

Mosaic X-Chromosome Aneuploidy. Iourov and associates (2006; 2008) hypothesized that the male to female ratio in ASD was the result of an abnormal number (aneuploidy) of X-chromosomes in some cells (mosaicism) in the brain. One study has found that unexplained autism in males was associated with low-level mosaic aneuploidy in peripheral blood cells (Yurov, et al., 2007). This hypothesis has not yet been empirically evaluated.

Sporatic and Inherited Genetic Models

Researchers have discussed gender differences in ASD as related to two types of genetic models: sporadic (simplex) versus inherited or familial (multiplex). These two models have been examined in relation to essential (idiopathic) versus complex (syndromic) autism (Miles et al., 2005), and inherited versus *de novo* copy number variations (non-inherited sequence changes in

sections of DNA; Jacquemont, et al., 2006; Marshall, et al., 2008; Sebat, et al., 2007; Zhao, et al., 2007). Beaudet (2007) discussed Miles and colleagues' (2000, 2005) findings along with recent findings of *de novo* copy number variations in relation to gender differences in ASD (Jacquemont, et al., 2006; Sebat, et al., 2007). Beaudet (2007) estimated that only half of these *de novo* mutations have been identified to date. Furthermore, the gender ratio in cases with identified mutations is likely equal, excluding X-linked disorders (Beaudet, 2007). This leaves a large number of people with ASD without identified DNA sequence changes, a group which is predominately male, and has higher IQ and normal features in appearance (Beaudet, 2007). Thus, overall, Beaudet (2007) proposed a mixed etiology model for autism, where each case could have genetic or epigenetic mutations which could be *de novo* or inherited. Similarly, Zhao and associates (2007) proposed "a unified genetic theory for sporadic and inherited autism," comprised of two groups. The vast majority of ASD occurs in simplex (low-risk or sporadic) families resulting from *de novo* mutations which have poor penetrance in females (i.e., they have the mutation but do not express the clinical phenotype) and high penetrance in males (Zhao et al., 2007). A small minority of ASD occurs in multiplex (high-risk or inherited) families, where female carriers transmit the mutation dominantly, and the risk to male offspring is 50/50 (Zhao et al., 2007). Lastly, Banach and colleagues (2009) found lower IQ in females with ASD from simplex but not multiplex families. These authors pointed out that *de novo* copy number variants have been found to be more common in simplex versus multiplex families and may be more common in females with ASD (Marshall, et al., 2008; Sebat, et al., 2007). Banach and colleagues (2009) purported that there may be a greater frequency of genomic risk factors in simplex families, particularly in females, associated with both ASD and lower non-verbal intelligence, versus males having a more familial form of ASD and higher intelligence. This line of research

points to impact of stratification of ASD samples in genetic research based variables such as gender, simplex or multiplex families, presence of other conditions (e.g., genetic syndromes, birth defects, dysmorphic features, ID, medical conditions, language impairment), and ASD symptom areas (Folstein, 2006; Happé & Ronald, 2008; Happé, et al., 2006; Skuse, 2007; Waterhouse, 2008).

Diagnostic Issues with Gender

Kopp and Gillberg (1992) hypothesized that ASD is underdiagnosed in females because the diagnostic criteria and behavioral phenotype have been derived from typical male cases. Thus, the phenotype may differ in girls. Kopp and Gillberg (1992) contrasted the behavioral presentation of six girls with autism to that typical of males with autism. Socially, in contrast to "extreme autistic aloneness," these girls "tended more towards 'clinging' to other people, imitating their speech and movements without a deeper understanding of the silent laws of ordinary social interaction, inability to understand the emotional content of facial expressions as they show in real-life interaction, treating people as objects and only brief periods of aloofness" (Kopp & Gillberg, 1992, p. 96). All three of the girls who were presented with a theory of mind test failed it. Some of the girls presented similar to Wing's (1989) "active but odd" classification. In the area of communication, the girls exhibited extreme echolalia and repetitive questioning. Regarding behavior, in contrast to preoccupation with objects and circumscribed interests as seen in boys with autism, these girls demonstrated an "overall lack of initiative" (Kopp & Gillberg, 1992, p. 97). Typically developing girls are less hyperactive and aggressive, behaviors which are associated with ASD and reason for referral (C. Gillberg, 2007). Kopp and Gillberg (1992, p. 97) purported that difficulties in boys may be difficult to ignore or dismiss, as boys "may be both aggressive and domineering and show strong initiative in their insistence on sameness."

Typically developing girls speak sooner and more frequently than boys (C. Gillberg, 2007). Thus, greater language and social imitation skills may mask a core deficit (e.g., empathy) in girls (Kopp & Gillberg, 1992). Finally, girls may not exhibit visual self-stimulation behaviors typical of autism because they lack exceptional visuospatial skills (Kopp & Gillberg, 1992).

A number of diagnostic barriers may ensue for girls with ASD. Only the most severe cases may be referred for evaluation (C. Gillberg, 2007). Girls with ASD may instead receive vague diagnoses (e.g., learning disorder) or other diagnoses such as obsessive-compulsive, conduct, paranoid, depressive, personality, or eating disorders (C. Gillberg, 2007; Kopp & Gillberg, 1992). As described previously, females with significant ASD impairments have experienced misdiagnosis (Kopp & Gillberg, 1992, 1997; Nilsson, et al., 1999), delayed diagnosis (Goin-Kochel, et al., 2006; Kanner, 1971; Kopp & Gillberg, 1992; Siklos & Kerns, 2007), greater difficulty in the diagnostic process (Siklos & Kerns, 2007), and lack of diagnosis (Wing & Gould, 1979).

Gender Biases

In the literature on gender differences in ASD, few researchers have discussed the possibility of environmental/social gender biases in ASD (A. S. Carter, et al., 2007; Holtmann, et al., 2007; McLennan, et al., 1993). Gender biases may exist in areas such as parent report, parent expectations, upbringing, sex role models, and socialization. With daughters, parents may expect more social and communicative behavior (A. S. Carter, et al., 2007; McLennan, et al., 1993). This expectation may impact both their behavior towards the child and interpretation of the child's actions (McLennan, et al., 1993). For example, parents may provide more prompts to daughters to behave in an affectionate and social manner (McLennan, et al., 1993). In addition, as informants during assessment, parents may interpret behavior of daughters to suggest more

social interest and motivation (McLennan, et al., 1993). Similarly, because parents expect more socially desirable behavior from their daughters, they may perceive them as having greater impairments resulting in a larger discrepancy between expectations and actual behavior (Holtmann, et al., 2007). In their toddler study, Carter and associates (2007) noted that parents rated girls as having lower competence in areas such as empathy compared to boys, though this was not evident upon observation with the ADOS. Finally, as mentioned previously, the social and communicative nature of peer relationships in females may be more demanding compared to males (McLennan, et al., 1993). These issues have not yet been examined empirically.

Purpose

For disorders such as ASD that have such a pronounced gender difference, Rutter, Caspi, and Moffitt (2003) pointed out that there is a dearth of research addressing a variety of key issues (e.g., the validity of diagnostic criteria for males and females). In addition, gender differences have not been sufficiently addressed with regard to assessment instruments (Koenig & Tsatsanis, 2005; Rutter, et al., 2003). The large body of research literature concerning the assessment, treatment, and etiology of ASD has been conducted with predominantly male samples (Bell, et al., 2005). Hence, extrapolating this body of knowledge to females with ASD poses concerns (Koenig & Tsatsanis, 2005). Rutter and associates (2003) also pointed out the need for evaluation of gender differences with regard to developmental variables, chronicity and recurrence, and comorbidity and severity.

Despite the long observed male predominance in ASD, there is a paucity of research examining gender differences in ASD. A host of methodological issues have plagued research in this area and contributed to the inconsistent findings which have emerged. Given the large male to female ratio, ascertainment of female participants has been an obstacle. In the studies that

have been conducted in this area, small female sample sizes have posed difficulties (Koenig & Tsatsanis, 2005). Additionally, one of the major issues has been how to handle the IQ disparity (Volkmar, et al., 1993). Widely varying results have been found based on how IQ is addressed (e.g., Lord, et al., 1982; Volkmar, et al., 1993). Volkmar, Szatmari, and Sparrow (1993) emphasized that it is unclear whether it is appropriate to control for IQ, as the relationships between IQ, ASD, and gender have not been fully fleshed out. Additional methodological issues, which apply to research in ASD in general as well, have been acknowledged. These include changes over time in the diagnostic criteria and categories, heterogeneity in presentation, age ranges and developmental changes in symptom presentation, differences in samples (ascertainment bias, stringency of definitions, epidemiological versus clinical), and so forth (A. S. Carter, et al., 2007; Lord & Schopler, 1985; Volkmar, et al., 1993).

Hence, the current knowledge base related to gender differences in ASD is scant, and additional research in this area is warranted. It remains unclear how much of the gender disparity is an actual difference in prevalence and/or presentation or reflective of problems in the current diagnostic system (Koenig & Tsatsanis, 2005). Furthermore, gender differences in severity of impairment related to autistic symptoms, cognitive ability, and adaptive skills in ASD have not been determined (Koenig & Tsatsanis, 2005).

The present study examined gender differences in ASD symptoms in three populations covering the lifespan, employing instruments developed for their respective age ranges. The first study examined gender differences in ASD symptoms in infants and toddlers in an "at risk" sample who have developmental delays or a medical condition likely to result in a developmental delay. The second study examined gender differences in ASD symptoms in children and adolescents. Finally, the third study examined gender differences in ASD symptoms in adults

with ID. These data provide insight into gender differences in ASD symptom presentation across a wide span of development. All studies included comparison groups of both males and females without ASD, which is important given increasing evidence for the presence of autistic traits in the general population. A fine-grained analysis of ASD symptoms was conducted, considering emerging data of the fractionability of the triad of impairments.

These data have significant implications informing assessment and intervention for females with ASD. Gender differences may manifest with regard to symptom domains, breadth of symptoms, symptom severity, and so forth. This information is important clinically to improve identification and knowledge, and work towards addressing diagnostic pitfalls with females with ASD. In addition, gender differences related to intervention needs, prioritized areas, and potential targets for intervention may become evident. This information is important in both the clinical and research realms regarding diagnosis and treatment. As there is a paucity of research, these data serve to stimulate future research priorities in the area of gender differences in ASD symptoms.

STUDY 1

Method

Participants

Participants included children ages 17 to 36 months enrolled in the EarlySteps program. EarlySteps is Louisiana's Early Intervention System under the Individuals with Disabilities Education Act, Part C, which provides services to infants and toddlers and their families from birth to 36 months. Children qualify for services if they have a medical condition likely to result in a developmental delay, or have developmental delays. These include diagnoses such as cerebral palsy, epilepsy, allergies, ear infections, asthma, heart or lung diseases, meningitis, prematurity, hearing or visual impairments, hypotonia, reflux, and so forth. Participants with identified sex chromosome disorders (i.e., Klinefelter's syndrome [n = 1]) were excluded. Six participants (3 females and 2 males with ASD and 1 male without ASD) prescribed psychotropic medications (i.e., antipsychotics, antidepressants, anticonvulsants, stimulants, sleep medications) were excluded. Participant groups were formed on the basis of gender and the presence of an ASD diagnosis (Female ASD, Female Control, Male ASD, and Male Control).

Table 1 provides initial participant characteristics by diagnostic group. Chi-square analyses revealed no significant group differences based on ethnicity or epilepsy. Regarding age, participants ranged from 17 to 36 months (M = 26, SD = 5). An analysis of variance (ANOVA) revealed no significant group differences based on age, F (3, 941) = 0.68, p = .566. However, significant group differences were revealed based on Developmental Quotients (DQ) from the *Battelle Developmental Inventory-Second Edition* (BDI-2; Newborg, 2005), F (3, 941) = 24.24, p < .001. Regardless of gender, participants without ASD had higher BDI-2 DQ scores than those with ASD.

Table 1

Participant Characteristics (N = 945) by Diagnostic Group

	Female		Male	
	ASD	Control	ASD	Control
	(*n* = 66)	(*n* = 202)	(*n* = 212)	(*n* = 465)
Ethnicity, Frequency (%)				
Caucasian	33 (52)	105 (54)	95 (47)	242 (56)
African American	26 (41)	81 (42)	89 (44)	168 (39)
Hispanic	1 (2)	3 (2)	2 (1)	9 (2)
Other	3 (5)	5 (3)	15 (8)	16 (4)
Epilepsy, F (%)	1 (2)	3 (2)	12 (6)	12 (3)
Age in months, *M* (*SD*)	26.52 (4.69)	25.80 (5.21)	26.24 (4.67)	25.85 (4.80)
BDI-2 DQ, *M* (*SD*)	74.83 (14.43)	90.22 (13.82)	74.49 (14.20)	89.05 (31.71)

Groups were matched to the best extent possible on relevant demographic variables (e.g., developmental level, age, epilepsy, ethnicity) and by randomly deleting cases achieving equal sample sizes. Table 2 provides participant characteristics by diagnostic group following matching. Chi-square analyses again revealed no significant group differences based on ethnicity or epilepsy. Participants ranged in age from 17 to 35 months (M = 26, SD = 5). An ANOVA revealed no significant group differences based on age, F (3, 260) = 0.12, p = .951. BDI-2 DQs ranged from 46 to 117 (M = 76, SD = 13). An ANOVA revealed no significant group differences based on DQs from the BDI-2, F (3, 260) = 1.36, p = .257.

Table 2

Participant Characteristics (N = 264) by Diagnostic Group Following Matching

	Female		Male	
	ASD	Control	ASD	Control
	(*n* = 66)	(*n* = 66)	(*n* = 66)	(*n* = 66)
Ethnicity, F (%)				
Caucasian	33 (52)	38 (58)	30 (46)	40 (61)
African American	26 (41)	25 (38)	31 (47)	24 (36)
Hispanic	1 (2)	0 (0)	1 (2)	0 (0)
Other	3 (5)	3 (5)	4 (6)	2 (3)
Epilepsy, F (%)	1 (2)	2 (3)	2 (3)	2 (3)
Age in months, *M* (*SD*)	26.52 (4.69)	26.17 (5.65)	26.67 (4.88)	26.38 (5.06)
BDI-2 DQ, *M* (*SD*)	74.83 (14.43)	77.97 (10.27)	74.15 (14.50)	77.29 (12.04)

Measures

Baby and Infant Screen for Children with aUtism Traits (BISCUIT; Matson, Wilkins, Sevin, et al., 2009). The BISCUIT-Part 1 is part of a newly developed battery to assess ASD symptoms, comorbid symptoms, and challenging behaviors in infants and toddlers. It is a 62-item clinician-rated scale designed to aid in the diagnosis of autism and PDD-NOS. Each item is rated for the extent that it is/was ever a problem in comparison to typically developing children of the same age. Each item is rated as "0 = Not different; no impairment," "1 = Somewhat different; mild impairment," or "2 = Very different; severe impairment." Reliability of the BISCUIT-Part 1 was evaluated in a sample identified as at risk for developmental disabilities

ages 17 to 37 months (*M* = 26.83, *SD* = 5.27). Internal consistency reliability was 0.97 (Matson, Wilkins, Sevin, et al., 2009). Validity of the BISCUIT-Part 1 has also been established. In differentiating between ASD and non-ASD in an at risk sample, compared to the M-CHAT (Robins, et al., 2001), the BISCUIT-Part 1 produced higher sensitivity (93.4 versus 74.1), comparable specificity (86.6 versus 87.5), and a higher overall correct classification rate (88.8 versus 83.0) (Matson, Wilkins, Sharp, et al., 2009). Sensitivity, specificity, and overall correct classification for the BISCUIT-Part 1 were 84.7, 86.4, and 86.1 respectively for differentiating no diagnosis from PDD-NOS, and 84.4, 83.3, and 83.9 for differentiating PDD-NOS from autistic disorder (Matson, Wilkins, Sharp, et al., 2009).

Diagnostic classifications were made by a licensed doctoral level clinical psychologist with over 30 years of experience in the developmental disabilities field who was blind to BISCUIT scores. Diagnostic classifications were based on clinical judgment using algorithms based on *DSM-IV-TR* criteria for Autistic Disorder and PDD-NOS (APA, 2000), M-CHAT scores, and developmental profile scores from the *Battelle Developmental Inventory-Second Edition* (BDI-2; Newborg, 2005). Inter-rater reliability data for diagnostic classifications on a subset of participants (*n* = 203) was calculated. A second doctoral level clinical psychologist with experience in the assessment and treatment of children with developmental disabilities made diagnostic classifications based on the same information available to the first psychologist. This psychologist was blind to diagnostic classifications provided by the first psychologist. Inter-rater reliability (Kappa = 0.93; Percent agreement = 97.6%) was excellent. Variations of this diagnostic methodology have been previously employed in studies (e.g., Fombonne, et al., 2004; Yeargin-Allsopp, et al., 2003).

Procedures

Assessments were conducted individually in the child's home or daycare setting. Assessment included a one-to-one primary caregiver interview and observations of the child. Each assessment measure was conducted according to the instructions provided for the instruments. Assessors held at minimum a bachelor's degree and were certified or licensed in a field qualifying them to provide services for the EarlySteps program. Academic credentials ranged from bachelor's degrees in early childhood education to doctoral degrees in psychology. Certifications/licensures were in the disciplines/areas of education, occupational therapy, physical therapy, special instruction, social work, speech-language pathology, and psychology. These assessors all held a caseload and were experienced in assessment and intervention procedures for young children. Assessors participated in a full day workshop by the authors of the BISCUIT. The workshop provided background information on ASD and the assessment measures employed in the study, as well as practice administrations with a question and answer session. This study was approved by the Louisiana State University and State of Louisiana Department of Health and Hospitals review boards, and appropriate ethical guidelines and procedures were followed.

Analyses

An ANOVA was conducted with group (Female ASD, Female Control, Male ASD, and Male Control) as the independent variable and the BISCUIT-Part 1 total score (sum of all items) as the dependent variable. Post hoc comparisons using a Bonferroni correction were conducted to determine which groups were significantly different from each other. In order to determine the sample size needed, an *a priori* power analysis was conducted using G*Power 3 software (Faul, Erdfelder, Lang, & Buchner, 2007). For an ANOVA, the specified parameters included: a

medium effect size of 0.25, a Type 1 error probability of $\alpha = .05$, power of 0.80, and 4 groups. Based on these parameters, a sample size of 180 was required.

Hypothesized Results

In the literature, only two studies have evaluated gender differences in toddlers. In an ASD group, girls had greater impairments in reciprocal social interaction (via parent interview) and communication (via observation), and no other significant gender differences in ASD symptoms were found (Carter et al., 2007). In the general population, boys had more ASD symptoms, though no significant gender differences were found in a subgroup with ASD (Allison et al., 2008). In the typically developing population, girls may have strengths in underlying social/communication skills, and exhibit less repetitive behaviors (e.g., preoccupations, interests; (Koenig & Tsatsanis, 2005). However, no studies have examined gender differences in ASD symptoms in an at-risk toddler population. For the current study, it was hypothesized that regardless of gender, those in the ASD group would have more ASD symptoms as measured by the BISCUIT Part 1 than those in the control group. Regarding gender differences, it was hypothesized that in the non-ASD group, boys would have more ASD symptoms compared to girls, whereas no significant gender differences would be found in those with ASD.

Results

Prior to the analyses, data were examined for missing values, outliers, and consistency with the assumptions of ANOVA. Twelve cases were deleted due to multiple missing values. For all possible item values (58,590), 3 missing values (< 1%) were identified and replaced with the mean (Tabachnick & Fidell, 2007). The remainder of data screening procedures were conducted by examining the dependent variables separately according to group (Female ASD, Female

Control, Male ASD, and Male Control). Using a criterion of *z* scores greater than 3.29 (Tabachnick & Fidell, 2007), 5 participants in the Male Control group had scores identified as univariate outliers. These participants were removed from the analysis.

The ANOVA results revealed significant group differences in ASD symptoms as measured by the BISCUIT Part 1, F (3, 260) = 70.60, $p < .001$, partial $\eta^2 = .449$. Females with ASD (M = 41.13, SD = 24.10) and males with ASD (M = 44.20, SD = 22.17) had significantly higher ASD symptom endorsements ($p < .001$) than female controls (M = 11.47, SD = 7.06) and male controls (M = 12.64, SD = 7.22). No significant gender differences were found between participants with ASD or participants in the control group ($p = 1.00$).

Secondary Analyses

To further elucidate the relationship between cognitive ability and gender differences in ASD symptoms and to allow for further comparison across all three studies, secondary analyses were conducted using only participants with BDI-2 scores of 70 and above. An ANOVA was conducted with group (Female ASD, Female Control, Male ASD, and Male Control) as the independent variable and the BISCUIT-Part 1 total score as the dependent variable. Post hoc comparisons using a Bonferroni correction were conducted to determine which groups were significantly different from each other. The ANOVA results revealed significant group differences in ASD symptoms as measured by the BISCUIT Part 1, F (3, 172) = 47.23, $p < .001$, partial $\eta^2 = .452$. Females with ASD (M = 34.62, SD = 21.55) and males with ASD (M = 39.43, SD = 17.18) had significantly higher ASD symptom endorsements ($p < .001$) than female controls (M = 10.34, SD = 6.52) and male controls (M = 11.86, SD = 6.97). No significant gender differences were found between participants with ASD or participants in the control group ($p > .05$).

Discussion

Gender differences in ASD symptoms were examined in an at-risk toddler population matched on developmental level. As hypothesized, ASD symptoms were not significantly different between males and females with ASD. However, in those without ASD, the hypothesis that symptomatology would be higher in males compared to females was not supported. That is, males and females without ASD did not differ significantly in overall ASD symptoms.

Thus far, gender differences in ASD symptoms in toddlers have been examined in only two previous studies. In toddlers with ASD aged 18 to 33 months, Carter and colleagues (2007) used age and nonverbal ability as covariates. Carter and associates (2007) did not find significant gender differences in reciprocal social interaction (ADOS), social relatedness (ITSEA), nonverbal communication (ADI-R), receptive/expressive language (Mullen), or restricted, repetitive, and stereotyped behaviors (ADI-R and ADOS). However, girls showed greater impairments the area of socialization (ADI-R and VABS), empathy (ITSEA), and communication (ADOS and VABS; A. S. Carter, et al., 2007). Allison and colleagues (2008) used parent report via the Q-CHAT in a sample aged 19 to 63 months from the general population with a subgroup with ASD. These researchers found greater ASD symptoms in boys in the general population, but no significant gender differences in the subgroup diagnosed with ASD (Allison et al., 2008).

The present study was the first evaluation of gender and ASD symptoms in an at-risk population. This study extended upon Carter and colleagues' (2007) research by including both participants with and without ASD in a larger scale sample, and upon Allison and colleagues' (2008) research by measuring developmental level, a critical factor to examine with regard to

gender and ASD. Furthermore, the present study included a clinician-rated measure designed specifically for this population, which incorporated a direct observational component.

Consistent with previous research, no significant gender differences were found in toddlers with ASD. Based on findings in the general population, it was hypothesized that male toddlers who were at-risk for a developmental delay but not diagnosed with ASD would have greater ASD symptomatology. However, this hypothesis was not supported. It is notable that the present study focused on an at-risk population and did not focus on the typically developing toddler population as examined by Allison and associates (2008). However, secondary analyses were conducted with participants with a developmental quotient of 70 or above and comparable results were obtained.

A number of implications for future research directions in this area are evident. First, the current study examined overall ASD symptoms, but did not examine symptom domains separately. Future research should examine gender differences in toddlers with regard to specific symptom domains (i.e., socialization, communication, and restricted, repetitive, and stereotyped behaviors). In addition, future studies should examine gender differences in ASD symptoms with an additional comparison group of typically developing toddlers. Finally, future studies should examine gender differences in toddlers longitudinally, given evidence for developmental changes in symptom presentation as well as follow-up regarding diagnosis.

STUDY 2

Method

Participants

Participants included parents or caregivers of children and adolescents ages 3 to 17 years. Both typically developing children and children with developmental disorders were recruited from various sites and settings such as schools, outpatient clinics, parent advocacy and support groups, and so forth. Participant groups were formed on the basis of the presence of an ASD diagnosis and gender. The control group consisted of participants with no Axis I diagnoses, who also did not meet research criteria for ASD (see *Measures* section below). Participants with identified sex chromosome disorders (i.e., Fragile X syndrome [$n = 2$], Turner's syndrome [$n = 1$]) were excluded.

Table 3 provides initial participant characteristics by diagnostic group. Chi-square analyses were employed to evaluate group differences on relevant demographic variables. No participants had deafness and all participants were ambulatory. No significant group differences were revealed based on ethnicity, epilepsy, or blindness. Chi-square analyses indicated significant group differences in terms of the level of intellectual disability, χ^2 (3, $N = 309$) = 17.48, $p < .001$, and verbal ability, χ^2 (3, $N = 241$) = 8.41, $p = .038$. Specifically, regardless of gender, more participants with ASD had ID and more males with ASD were non-verbal. Regarding age, participants ranged from 3 to 17 years ($M = 8.46$, $SD = 3.46$). An ANOVA revealed significant group differences based on age, F (3, 305) = 3.34, $p = .020$. Males with ASD were significantly older than males with ID alone ($p = .017$).

Table 3

Participant Characteristics (N = 309) by Diagnostic Group

	Female		Male	
	ASD	Control	ASD	Control
	(*n* = 45)	(*n* = 71)	(*n* = 111)	(*n* = 82)
Intellectual Disability, F (%)	8 (18)	2 (3)	20 (18)	3 (4)
Ethnicity, F (%)				
Caucasian	22 (76)	62 (91)	66 (77)	62 (80)
African American	4 (14)	2 (3)	10 (12)	11 (14)
Hispanic	1 (3)	3 (4)	3 (4)	1 (1)
Other	2 (7)	1 (2)	7 (8)	4 (5)
Blindness, F (%)	0 (0)	1 (2)	0 (0)	0 (0)
Epilepsy, F (%)	1 (4)	0 (0)	3 (5)	0 (0)
Non-Verbal, F (%)	1 (4)	1 (1)	5 (8)	0 (0)
Age in years, *M* (*SD*)	8.11 (3.48)	8.30 (3.33)	9.24 (3.78)	7.74 (2.92)

Groups were matched to the best extent possible on relevant demographic variables (e.g., age, ID, sensory impairments, epilepsy) and by randomly deleting cases achieving equal sample sizes. The thirty-three participants with ID were excluded. Eight participants in the Male Control group who had previously reported ASD diagnoses were excluded. Nine female and 18 male participants without ASD who had Axis I diagnoses (e.g., ADHD, anxiety disorders, etc.) were excluded, as well as two male participants prescribed psychotropic medications. Table 4 provides

participant characteristics by diagnostic group following matching. No participants had deafness or blindness, and all participants were ambulatory and verbal. Chi-square analyses were employed to evaluate group differences on relevant demographic variables. No significant group differences were revealed based on ethnicity or epilepsy. Regarding age, participants ranged from 3 to 17 years (M = 7.75, SD = 3.42). An ANOVA revealed no significant group differences based on age, F (3, 144) = 0.004, p = 1.000. Of participants with ASD, 10 females and 15 males were prescribed psychotropic medications. Seventy-three percent of females and 87% of males had previous ASD diagnoses (i.e., autistic disorder, PDDNOS). Autism Spectrum Disorder diagnoses made previous to this study for females and males respectively included autistic disorder (5%; 24%), Asperger's disorder (3%; 19%), PDD-NOS (24%; 27%), and ASD unspecified (41%; 16%). ASD unspecified included children whose parents reported an ASD diagnosis without specifying a diagnosis of autistic disorder, Asperger's disorder, or PDD-NOS.

Measures

Autism Spectrum Disorders – Diagnostic – Child Version (ASD-DC; Matson & González, 2007). The ASD-DC is part of a three scale battery to assess ASD symptoms, comorbid psychopathology, and challenging behaviors in children and adolescents ages 3 to 18 years. It is a 40-item rating scale. Raters (parents, caregivers, teachers, etc.) are instructed to rate each item for the extent that it is/was ever a problem in comparison to other children of the same age. Each item is rated as "0 = Not different; no impairment," "1 = Somewhat different; mild impairment," or "2 = Very different; severe impairment." Psychometric properties of the ASD-DC have been established. Regarding reliability, internal consistency has been found to be excellent at 0.99, inter-rater reliability good at 0.67, and test-retest reliability excellent at 0.77 (Matson, Gonzalez, et al., 2008). Exploratory factor analysis yielded four subscales: Nonverbal

Table 4

Participant Characteristics (N = 148) by Diagnostic Group Following Matching

	Female		Male	
	ASD (n = 37)	Control (n = 37)	ASD (n = 37)	Control (n = 37)
Ethnicity, F (%)				
Caucasian	18 (78)	34 (94)	28 (85)	31 (89)
African American	4 (17)	1 (3)	1 (3)	3 (9)
Hispanic	0 (0)	1 (3)	3 (9)	0 (0)
Other	1 (4)	0 (0)	1 (3)	1 (3)
Epilepsy, F (%)	1 (5)	0 (0)	1 (3)	0 (0)
Age in years, *M* (*SD*)	7.77 (3.57)	7.78 (3.43)	7.76 (3.66)	7.70 (3.15)

Communication/Socialization, Verbal Communication, Social Relationships, and Insistence on Sameness/Restricted Interests (Matson, Boisjoli, et al., 2009). Regarding validity, the ASD-DC has been found to have good total correct classification rates between children with: no diagnosis and atypical development (84.3%) and atypical development and ASD (87.8%); Asperger's disorder and PDD-NOS (89.5%) and PDD-NOS and autistic disorder (77.1%); and children meeting *DSM-IV-TR/ICD-10* criteria for an ASD (84.3%) (Matson, González, et al., 2009). Convergent validity has been established with the CARS (Matson, Mahan, et al., in press) and the ADI-R (Matson, Hess, et al., in press).

Diagnostic and Statistical Manual – Fourth Edition – Text Revision (DSM-IV-TR)/International Classification of Diseases, Tenth Edition (ICD-10) Checklist (DSM-IV-TR/ICD-10 Checklist). The *DSM-IV-TR/ICD-10 Checklist* (APA, 2000, WHO, 1992) is an 18-item composite symptoms checklist for ASD. Raters (parents, caregivers, teachers, etc.) are instructed to rate each item as "yes" or "no" as it applies to the child. The checklist contains items encompassing the three core areas of impairments in ASD including impairments in Socialization (5 items), impairments in Communication (7 items), and Restricted, repetitive, and stereotyped patterns of behavior, interests, or activities (6 items). In addition, raters endorse whether the delays or abnormal functioning were present prior to the age of 3 years in at least one of the three areas. Regarding reliability, robust results have been found for internal consistency (.95), inter-rater (.89), and test-retest (.96) reliability (Matson, Gonzalez, et al., 2008).

Research criteria for the *DSM-IV-TR/ICD-10 Checklist* were developed in order to standardize designation of an ASD diagnosis and determine inclusion criteria. Corresponding to the minimal criteria needed for an ASD diagnosis, two items in the area of socialization and one item on the communication or restricted interests/repetitive behaviors domains must be endorsed. The classification system was used under the supervision of a licensed doctoral level clinical psychologist.

Procedures

Parents or caregivers of the child or adolescent completed the measures by rating each item according to the directions printed at the top of the form. Clinical psychology doctoral students who had been trained in the scale administration and research procedures were available to resolve any questions or issues the raters may have encountered in completing the measures.

This study was approved by the Louisiana State University Institutional Review Board, and appropriate ethical guidelines and procedures were followed.

Analyses

An ANCOVA was conducted with group (Female ASD, Female Control, Male ASD, and Male Control) as the independent variable, the ASD-DC total score as the dependent variable, and age as the covariate. Post hoc comparisons using a Bonferroni correction were conducted to determine which groups were significantly different from each other.

A multivariate analysis of variance (MANOVA) was conducted with group (Female ASD, Female Control, Male ASD, and Male Control) as the independent variable and the ASD-DC subscales (Nonverbal Communication/Socialization, Verbal Communication, Social Relationships, and Insistence on Sameness/Restricted Interests) as the dependent variables. First, the multivariate test was examined to determine if there were significant group differences in terms of ASD symptoms as measured by the ASD-DC. Next, between-subject effects were examined to determine if there were significant group differences in each of the ASD symptom domains. Finally, post hoc analyses using a Bonferroni correction were conducted to determine which groups were significantly different from each other in the ASD symptom domains.

In order to determine the sample size needed, an *a priori* power analysis was conducted using G*Power 3 software (Faul, et al., 2007). For the MANOVA global effects analyses, the specified parameters included: a medium effect size of f^2 (V) = 0.25, a Type 1 error probability of $\alpha = .05$, power of 0.80, 4 groups, and 4 response variables. Based on these parameters, a sample size of 28 is required. For the MANOVA special effects and interactions analyses, the specified parameters included: a medium effect size of f^2 (V) = 0.25, a Type 1 error probability

of $\alpha = .05$, power of 0.80, 4 groups, 1 predictor, and 4 response variables. Based on these parameters, a sample size of 53 was required.

Hypothesized Results

It was hypothesized that regardless of gender, those in the ASD group would have more ASD symptoms as measured by the ASD-DC than those in the control group. Concerning gender differences, it was hypothesized that males would exhibit more overall ASD symptoms than females in participants both with and without ASD. In participants with ASD, it was hypothesized that in comparison to males, females would show greater impairments in social relationships, but less impairment in insistence on sameness/restricted interests. In the control groups, it was hypothesized that males would have greater endorsements of ASD symptoms in all four areas (i.e., Nonverbal Communication/Socialization, Verbal Communication, Social Relationships, and Insistence on Sameness/Restricted Interests).

Results

Prior to the analyses, data were examined for missing values, outliers, and consistency with the assumptions of MANOVA. Data screening procedures were conducted by examining the dependent variables separately according to group (Female ASD, Female Control, Male ASD, and Male Control). Using a criterion of *z* scores greater than 3.29 (Tabachnick & Fidell, 2007), 2 participants in the Female Control and 2 participants in the Male Control groups had at least one subscale score identified as a univariate outlier. These participants ($n = 4$) were removed from the analysis. Finally, 2 participants in the Female Control and 2 participants in the Male Control groups were identified as multivariate outliers using Mahalanobis distance with a significance value of $p < .001$ (Tabachnick & Fidell, 2007). These participants ($n = 4$) were removed from the analysis.

The ANCOVA results revealed significant group differences in ASD symptoms as measured by the ASD-DC, F (3, 143) = 104.28, $p < .001$, partial $\eta^2 = .686$. Age as a covariate did not provide significant adjustment to ASD symptoms, F (1, 143) = 0.36, $p = .550$, partial $\eta^2 = .003$. Females with ASD ($M = 45.46$, $SE = 2.34$) and males with ASD ($M = 44.65$, $SE = 2.34$) had significantly higher ASD symptom endorsements ($p < .001$) than females without ASD ($M = 4.68$, $SE = 2.34$) and males without ASD ($M = 2.64$, $SE = 2.34$). No significant gender difference was found between participants with or without ASD ($p = 1.00$).

The MANOVA results indicated significant differences on ASD symptomatology between groups, Wilks' Lambda = .240, F (12, 373) = 22.26, $p < .001$, partial $\eta^2 = .379$. Significant differences were found between groups for all ASD symptom domains – Nonverbal Communication/Socialization: F (3, 144) = 92.06, $p < .001$, partial $\eta^2 = .657$; Verbal Communication: F (3, 144) = 45.90, $p < .001$, partial $\eta^2 = .489$; Social Relationships: F (3, 144) = 116.46, $p < .001$, partial $\eta^2 = .708$; and Insistence on Sameness/Restricted Interests: F (3, 144) = 78.75, $p < .001$, partial $\eta^2 = .621$. Females with ASD and males with ASD had significantly higher ASD symptom endorsements ($p < .001$) than females without ASD and males without ASD on all subdomains of the ASD-DC. No significant gender difference was found between participants with or without ASD ($p = 1.00$). Table 5 provides mean and standard deviation values on ASD-DC subscales for participant groups (i.e., Female ASD, Female Control, Male ASD, Male Control).

Discussion

Gender differences in ASD symptoms were examined in a child and adolescent population without ID. Total ASD symptoms overall as well as four ASD symptom domains

Table 5

Mean (M) and Standard Deviation (SD) Values on Autism Spectrum Disorders – Diagnostic – Child Version (ASD-DC) Subscales for Participant Groups (Female ASD, Female Control, Male ASD, Male Control)

	Female		Male	
	ASD	Control	ASD	Control
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Nonverbal Communication/ Socialization	17.65 (6.54)[a]	1.68 (5.19)[b]	17.35 (8.63)[a]	0.46 (0.99)[b]
Verbal Communication	10.35 (4.93)[a]	1.57 (3.81)[b]	9.54 (5.70)[a]	1.30 (2.63)[b]
Social Relationships	9.41 (3.48)[a]	0.73 (2.31)[b]	9.00 (3.70)[a]	0.32 (0.88)[b]
Insistence on Sameness/ Restricted Interests	8.05 (3.96)[a]	0.70 (1.54)[b]	8.76 (4.30)[a]	0.57 (1.19)[b]

Note. Means in a row sharing superscripts (a, b) are not significantly different.

(i.e., Nonverbal Communication/Socialization, Verbal Communication, Social Relationships, and Insistence on Sameness/Restricted Interests) were examined. No significant gender differences in ASD symptoms were found as hypothesized.

Thus far, gender differences in ASD samples without lower cognitive abilities have been examined in two studies. McLennan, Lord, and Schopler (1993) matched male and female participants with ASD aged 6 to 36 years on non-verbal IQ (above 60). On the ADI, females had greater impairments in current friendships and reciprocal social interaction, while males had greater separation anxiety and impairments in reciprocal social interaction, communication, and social play prior to the age of 5 (McLennan, et al., 1993). No significant gender differences were

found in the areas of nonverbal social behaviors, sharing enjoyment/modifying behavior to context, gesture, conversation, language abnormalities, prosody/intonation, communication, or restricted, repetitive, stereotyped behaviors (McLennan, et al., 1993). Holtmann, Bölte, and Poustka (2007) examined gender differences on the ADI-R, ADOS, and CBCL for participants aged 2 to 20 years with ASD matched on IQ (above 70). Females had greater impairments in current group play with peers on the ADI-R and social withdrawal/problems on the CBCL, while males had greater endorsements on inappropriate facial expression at 4 to 5 years of age and current showing/directing attention on the ADI-R. No significant gender differences were found on the overall social domains or in the area of communication on the ADI-R or ADOS, or in restricted, repetitive, stereotyped behaviors on the ADI-R (Holtmann, et al., 2007). Thus, in these two studies, females showed greater current impairments in some aspects of socialization, (e.g., friendships, reciprocal interaction, group play), and fewer impairments in some aspects of socialization and communication (e.g., showing/directing attention; early separation anxiety, reciprocal interaction, communication, inappropriate facial expressions, and social play). In both studies, most areas examined revealed few significant differences and none were found in the area of restricted, repetitive, stereotyped behaviors.

Other studies of gender differences in ASD symptoms in children and adolescents have found varying results depending on if and how IQ was accounted for in the study. With IQ accounted for, Lord and colleagues (1982) found males to have greater peculiar visual interests and stereotypic play, while several researchers found no significant gender differences in ASD symptoms (Banach, et al., 2009; Hus, et al., 2007; Pilowsky, et al., 1998; Volkmar, et al., 1993). Without accounting for IQ, researchers have found more preoccupation with parts of objects, routines and rituals, and stereotyped mannerisms in males with ASD (Nicholas, et al., 2008) and

more pretend play in females with ASD (Knickmeyer, et al., 2008). In studies conducted in the general population, greater autistic traits have been found in males (Constantino & Todd, 2003; Loat, et al., 2008; Posserud, et al., 2006; Ronald, et al., 2006; J. G. Williams, et al., 2008); however, in subgroups of participants with ASD without ID, no significant gender differences have been found (Auyeung, et al., 2008; Baron-Cohen, et al., 2006).

In the current study, gender differences in ASD symptoms were examined in a child and adolescent population. This investigation extends the work of McLennan and colleagues (1993) and Holtmann and associates (2007) in that the sample size was much larger and included comparison groups without ASD. It was hypothesized that females with ASD would show greater impairments in social relationships, but less impairment in insistence on sameness/restricted interests compared to males with ASD, and that males without ASD would have greater endorsements in all four ASD symptom domains compared to females without ASD. These hypotheses were not supported: that is, no significant gender differences were found in the present study. However, the findings in the present study are relatively consistent with the general body of literature in that the majority of researchers have found few to no gender differences in ASD, although differences in some symptoms on some measures have been found.

There are several pertinent aspects of the present study relevant in comparing the current results to previous research. First, this study was limited to participants without ID, similar to work by McLennan and associates (1993) and Holtmann and colleagues (2007). Thus, an examination across a range of cognitive abilities was not conducted. This has implications for generalizability given the comorbidity of ASD and ID. Second, in contrast to studies in the general population with participants without ID, a measure designed for ASD symptoms was employed rather than a general population measure designed to assess the broad range of ASD

traits. This may account for the lack of gender differences in ASD symptoms in the control group as hypothesized. Third, the control group was a narrower and pure group, as participants with a previous ASD diagnosis, an Axis 1 diagnosis, or those prescribed psychotropic medication were excluded. A strength of the current study is the use of objective criteria in order to standardize ASD classifications. However, as with any research comparing groups using diagnostic classifications, issues brought up by previous researchers regarding gender differences in ASD symptoms (i.e., lack of diagnosis, delay in diagnosis, and misdiagnosis in females; diagnostic criteria and research on the disorder based primarily on males; biases in parent report, expectations, and socialization) are not addressed (A. S. Carter, et al., 2007; C. Gillberg, 2007; Holtmann, et al., 2007; McLennan, et al., 1993). Finally, for the present study, a parent report measure was utilized; however, an observational measure was not included. Carter and associates (2007) found varying results on a parent interview versus an observational measure, and discussed potential biases based on parental expectation of greater social competence in girls.

There are several implications for future research from the current study. Foremost is the need for further research into the relationship between IQ, ASD symptoms, and gender. A challenge to this line of research is identifying an adequate size of females with ASD, as well as a comparison group of children with ID without ASD, with the increasing prevalence of ASD that has occurred due to a number of factors (e.g., diagnostic criteria and methodology, diagnostic substitution, service availability, special education policy changes, increased awareness; Fombonne, 2005; Wing & Potter, 2002). Therefore, multiple informants and multiple measures (e.g., observational) need to be employed. Next, longitudinal examinations of gender differences in ASD is warranted given the evidence for developmental changes in symptom presentation and gender differences in the course of ASD. In addition, an examination of

comorbidity and diagnostic issues (i.e., delay, lack of, and misdiagnosis in females; diagnostic criteria as it applies to females; biases in parental report, expectations, and socialization) is warranted.

STUDY 3

Method

Participants

Participants included adults with ID residing at one of two developmental centers in the United States, each with approximately 300 and 600 residents. Level of ID was previously determined through evaluations conducted by a licensed psychologist using the criteria outlined in the *DSM-IV-TR* (APA, 2000); a standardized measure of cognitive ability (e.g., *Stanford Binet Intelligence Scales* or *Leiter International Performance Scale*), behavioral observations, and the *Vineland Adaptive Behavior Scales* (VABS; Sparrow, et al., 1984; Sparrow, Cicchetti, & Balla, 2005). Participant groups were formed on the basis of the presence of an ASD diagnosis and gender (Female ASD, Female Control, Male ASD, and Male Control). The control group participants were a randomly chosen sample of residents without an Axis 1 diagnosis or psychotropic medication prescription, who also did not meet research criteria for ASD (see *Measures* section below). Participants with diagnoses of Rett's disorder (n = 6), CDD (n = 2), or identified sex chromosome disorders (Fragile X Syndrome; n = 1) were excluded. Fourteen participants with a severity of ID that was unspecified were excluded.

Table 6 provides initial participant characteristics by diagnostic group. Chi-square analyses were employed to evaluate group differences on relevant demographic variables. No significant group differences were revealed based on ethnicity, deafness, epilepsy, or ambulatory status. Chi-square analyses indicated significant group differences in terms of level of intellectual disability, χ^2 (9, N = 303) = 51.54, p < .001, verbal ability, χ^2 (3, N = 303) = 17.47, p = .001, and blindness, χ^2 (3, N = 303) = 17.37, p = .002. Specifically, regardless of gender, more participants with ASD had profound ID and were non-verbal. More female participants with

Table 6

Participant Characteristics (N = 303) by Diagnostic Group

	Female		Male	
	ASD	Control	ASD	Control
	(*n* = 65)	(*n* = 71)	(*n* = 89)	(*n* = 78)
Intellectual Disability, F (%)				
Profound	59 (91)	46 (65)	83 (93)	50 (64)
Severe	5 (8)	18 (25)	3 (3)	19 (24)
Moderate	1 (2)	5 (7)	3 (3)	9 (12)
Mild	0 (0)	2 (3)	0 (0)	0 (0)
Ethnicity, F (%)				
Caucasian	47 (72)	59 (83)	74 (83)	54 (69)
African American	18 (28)	12 (17)	15 (17)	24 (31)
Deafness, F (%)	4 (6)	3 (4)	6 (7)	5 (6)
Blindness, F (%)	14 (22)	2 (3)	8 (9)	6 (8)
Epilepsy, F (%)	17 (26)	13 (18)	29 (33)	18 (23)
Verbal, F (%)	19 (29)	41 (58)	29 (33)	40 (51)
Ambulatory, F (%)	42 (65)	51 (72)	69 (78)	54 (69)
Age in years, *M* (*SD*)	48.17 (12.99)	57.31 (13.96)	48.76 (10.30)	52.58 (13.92)

ASD had blindness. Regarding age, participants ranged from 18 to 88 years (*M* = 52, *SD* = 13). An analysis of variance (ANOVA) revealed significant group differences based on age, *F* (3,

299) = 7.92, $p < .001$. Females with ID alone were significantly older than females with ASD and males with ASD, but not males with ID alone.

Groups were matched to the best extent possible on relevant demographic variables (e.g., age, level of ID, sensory impairments, epilepsy) and by randomly deleting cases achieving equal sample sizes. Table 7 provides participant characteristics by diagnostic group following matching. Chi-square analyses were employed to evaluate group differences on relevant demographic variables. No significant group differences were revealed based on level of intellectual disability, verbal ability, blindness, ethnicity, deafness, epilepsy, or ambulatory status. Regarding age, participants ranged from 18 to 87 years (M = 52, SD = 12). An analysis of variance (ANOVA) revealed no significant group differences based on age, F (3, 228) = 1.52, p = .206. Of participants with ASD, 22% of females and 33% of males were prescribed psychotropic medications for comorbid Axis I disorders. Fifty-two percent of females and 69% of males had previous ASD diagnoses (autistic disorder and PDDNOS).

Measures

Autism Spectrum Disorders – Diagnostic – Adult Version (ASD-DA; Matson, et al., 2006) The ASD-DA is a part of a three scale battery to assess ASD symptoms, comorbid psychopathology, and challenging behaviors in adults with ID. It is a 31-item clinician-rated scale. Each item is rated for the extent that it is/was ever a problem in comparison to other people of the same age who live in the community. Items are rated as "0 = Not different; no impairment" or "1 = Different; some impairment." Psychometric properties of the ASD-DA have been established. Regarding reliability, internal consistency has been found to be excellent at 0.94 (Matson, Wilkins, et al., 2007). Inter-rater reliability (0.30) and test-retest reliability (0.39) have been found to be adequate (Matson, Wilkins, et al., 2007). Exploratory factor analysis

Table 7

Participant Characteristics (N = 232) by Diagnostic Group Following Matching

	Female		Male	
	ASD (n = 58)	Control (n = 58)	ASD (n = 58)	Control (n = 58)
Intellectual Disability, F (%)				
Profound	52 (90)	46 (79)	53 (91)	47 (81)
Severe	5 (9)	9 (16)	2 (3)	8 (14)
Moderate	1 (2)	3 (5)	3 (5)	3 (5)
Ethnicity, F (%)				
Caucasian	43 (74)	47 (81)	49 (85)	39 (67)
African American	15 (26)	11 (19)	9 (16)	19 (33)
Deafness, F (%)	4 (7)	2 (3)	4 (7)	4 (7)
Blindness, F (%)	8 (14)	2 (3)	7 (12)	6 (10)
Epilepsy, F (%)	14 (24)	13 (22)	19 (33)	12 (21)
Verbal, F (%)	19 (33)	28 (48)	19 (33)	25 (43)
Ambulatory, F (%)	39 (67)	41 (71)	47 (81)	38 (66)
Age in years, *M* (*SD*)	49.53 (12.57)	54.26 (12.22)	51.00 (9.94)	52.17 (13.97)

yielded three subscales: Social Impairment, Communication Impairment, and Restricted Interests/Bizarre Sensory Responses (Matson, Wilkins, et al., 2007). Validity has been established with the DASH-II, MESSIER, VABS, and *DSM-IV-TR/ICD-10* criteria (Matson,

Wilkins, Boisjoli, et al., 2008). The ASD-DA has been shown to have diagnostic utility in differentiating adults with ASD from those with ID, and adults with autistic disorder from those with PDD-NOS (Matson, Boisjoli, et al., 2007).

Diagnostic and Statistical Manual – Fourth Edition – Text Revision (DSM-IV-TR)/International Classification of Diseases, Tenth Edition (ICD-10) Checklist (DSM-IV-TR/ICD-10 Checklist). The *DSM-IV-TR/ICD-10 Checklist* (APA, 2000, WHO, 1992) is an 11-item composite symptoms checklist for ASD. Each item is endorsed as "yes" or "no" as it applies to the person. The checklist contains items encompassing the three core areas of impairments in ASD including impairments in Socialization (2 items), impairments in Communication (6 items), and Restricted, repetitive, and stereotyped patterns of behavior, interests, or activities (3 items). Regarding reliability, internal consistency has been found to be good at 0.73 and inter-rater reliability adequate at 0.41 (Matson, Wilkins, et al., 2007).

Research criteria for the *DSM-IV-TR/ICD-10 Checklist* were developed in order to standardize designation of an ASD diagnosis. Two independent raters (clinical psychology doctoral students) completed the *DSM-IV-TR/ICD-10 Checklist* via interviews with two independent staff. For assignment into the ASD group, both raters had to endorse three or more symptoms. All participants who had previously established ASD diagnoses given by licensed psychologists met the checklist criteria. Group assignment was made independent of previous ASD diagnoses.

Procedures

The ASD-DA and *DSM-IV-TR Checklist* were administered by clinical psychology doctoral students to residential support staff who had known the participant for at least 6 months. Interviews took place at the developmental center in a private setting free from

distraction, either at the participants' home or day program. The administrator explained the response options to the informant and asked whether each item is/was ever a problem for the participant in question. Questions were encouraged and clarification was provided for the informant when necessary. The university and state research review boards approved this study, and appropriate ethical guidelines and procedures were followed.

Analyses

An ANCOVA was conducted with group (Female ASD, Female Control, Male ASD, and Male Control) as the independent variable, the ASD-DA total score as the dependent variable, and age as the covariate. Post hoc comparisons using a Bonferroni correction were conducted to determine which groups were significantly different from each other.

A MANOVA was conducted with group (Female ASD, Female Controls, Male ASD, and Male Controls) as the independent variable and the ASD-DA subscales (Social Impairment, Communication Impairment, and Restricted Interests/Bizarre Sensory Responses) as the dependent variables. First, the multivariate test was examined to determine if there were significant group differences in terms of ASD symptoms as measured by the ASD-DA. Next, between-subject effects were examined to determine if there were significant group differences in each of the ASD symptom domains. Finally, post hoc analyses using a Bonferroni correction were conducted to determine which groups were significantly different from each other in the ASD symptom domains.

In order to determine the sample size needed, an *a priori* power analysis was conducted using G*Power 3 software (Faul, et al., 2007). For the MANOVA global effects analyses, the specified parameters included: a medium effect size of f^2 (V) = 0.25, a Type 1 error probability of $\alpha = .05$, power of 0.80, 4 groups, and 3 response variables. Based on these parameters, a

sample size of 24 was required. For the MANOVA special effects and interactions analyses, the specified parameters included: a medium effect size of f^2 (V) = 0.25, a Type 1 error probability of $\alpha = .05$, power of 0.80, 4 groups, 1 predictor, and 3 response variables. Based on these parameters, a sample size of 48 was required.

Hypothesized Results

For the current study, it was hypothesized that regardless of gender, those in the ASD group would have more ASD symptoms as measured by the ASD-DA than those in the control group. Regarding gender differences, it was hypothesized that males would exhibit more overall ASD symptoms than females. In particular, it was hypothesized males might exhibit more restricted interests/bizarre sensory responses. There is scant literature available on gender differences in adults with ASD and ID; therefore, further detailed hypotheses based on group were limited.

Results

Prior to the analyses, data were examined for missing values, outliers, and consistency with the assumptions of MANOVA. For all possible item values (10,106), 4 missing values (0.04%) were identified and replaced with the mean (Tabachnick & Fidell, 2007). The remainder of data screening procedures were conducted by examining the dependent variables separately according to group (Female ASD, Female Control, Male ASD, and Male Control). Using a criterion of *z* scores greater than 3.29 (Tabachnick & Fidell, 2007), 2 participants in the Female ASD and 1 participant in the Male ASD group had at least one subscale score identified as a univariate outlier. These participants ($n = 3$) were removed from the analysis. Finally, there were no multivariate outliers identified using Mahalanobis distance with a significance value of $p < .001$ (Tabachnick & Fidell, 2007).

The ANCOVA results revealed significant group differences in ASD symptoms as measured by the ASD-DA, F (3, 227) = 36.32, $p < .001$, partial $\eta^2 = .324$. Age as a covariate did not provide significant adjustment to ASD symptoms, F (1, 227) = 0.17, $p = .677$, partial $\eta^2 = .001$. Females with ASD ($M = 25.28$, $SE = 0.91$) and males with ASD ($M = 24.89$, $SE = 0.91$) had significantly higher ASD symptom endorsements ($p < .001$) than females with ID alone ($M = 17.58$, $SE = 0.91$) and males with ID alone ($M = 14.22$, $SE = 0.90$). No significant gender difference was found between participants with ASD ($p = 1.00$), though for participants with ID alone, there was a trend ($p = .055$) towards higher ASD symptom endorsements for females compared to males.

The MANOVA results indicated significant differences on ASD symptomatology between groups, Wilks' Lambda = .622, F (9, 550) = 13.15, $p < .001$, partial $\eta^2 = .146$. Significant differences were found between groups for all ASD symptom domains – Social Impairment: F (3, 228) = 31.58, $p < .001$, partial $\eta^2 = .294$; Communication Impairment: F (3, 228) = 20.95, $p < .001$, partial $\eta^2 = .216$; and Restricted Interests/Bizarre Sensory Responses: F (3, 228) = 34.89, $p < .001$, partial $\eta^2 = .315$. Regarding socialization and communication symptoms, pairwise comparisons revealed no significant gender differences for participants with ASD ($p > .05$); however, for participants with ID alone, compared to males, females had higher endorsements of social ($p = .041$) and communication ($p = .028$) impairments. Regarding restricted interests and bizarre sensory responses, no significant gender differences were found for participants with ASD or ID alone ($p > .05$). Table 8 provides mean and standard deviation values on ASD-DA subscales for participant groups (Female ASD, Female Control, Male ASD, Male Control).

Table 8

Mean (M) and Standard Deviation (SD) Values on Autism Spectrum Disorders – Diagnostic – Adult Version (ASD-DA) Subscales for Participant Groups (Female ASD, Female Control, Male ASD, Male Control)

	Female		Male	
	ASD	Control	ASD	Control
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Social Impairment	13.59 (2.62)[a]	9.31 (5.40)	13.42 (3.11)[a]	7.12 (5.35)
Communication Impairment	8.36 (0.97)[a]	6.74 (2.49)	7.84 (1.32)[a]	5.69 (2.61)
Restricted Interests/ Bizarre Sensory Responses	6.21 (2.27)[a]	3.59 (2.62)[b]	6.83 (2.06)[a]	3.09 (2.62)[b]

Note. Means in a row sharing superscripts (a, b) are not significantly different.

Chi-square analyses were conducted for item endorsements on the Social Impairment and Communication Impairment subscales of the ASD-DA for males and females with ID alone. Regarding social impairments, gender differences were found for the following items: "Interest in participating in social games, sports, and activities," χ^2 (1, N = 116) = 5.19, p = .023; "Interest in another person's side of the conversation (e.g., talks to people with intention of hearing what others have to say," χ^2 (1, N = 116) = 5.12, p = .024; "Imitation of an adult or child model (e.g., caregiver waves "bye" then the child waves "bye")," χ^2 (1, N = 116) = 7.76, p = .005; "Participation in games or other social activities," χ^2 (1, N = 116) = 7.76, p = .005. Concerning communication impairments, gender differences were found for the following items: "Interest in

another person's side of the conversation (e.g., talks to people with intention of hearing what others have to say)," χ^2 (1, N = 116) = 5.12, p = .024, and "Reads nonverbal cues (body language) of other people," χ^2 (1, N = 116) = 6.83, p = .009.

Secondary Analyses

To further elucidate the relationship between cognitive ability and gender differences in ASD symptoms and to allow for further comparison across all three studies, secondary analyses were conducted with participants without ASD or ID. Participants included 26 females (age: M = 43, SD = 16) and 25 males (age: M = 40, SD = 18) residing in the community. An ANOVA was conducted with group (Female Non-ID Control and Male Non-ID Control) as the independent variable and the ASD-DA total score as the dependent variable. No significant differences were found in ASD symptoms between males (M = 0.68, SD = 2.08) and females (M = 0.15, SD = 0.46) without ASD or ID, F (1, 49) = 1.59, p = .213.

Discussion

The present study investigated gender differences in ASD symptoms in adults with ID. No significant gender differences were found for participants with ASD. However, for participants with ID alone, females had higher endorsements of social (i.e., participation in social games, sports, and activities; interest in other person's side of the conversation; and imitation) and communication (i.e., interest in other person's side of the conversation; and reading nonverbal cues) impairments compared to males.

ASD research has focused more on children and adolescents rather than adults (Matson & Neal, 2009). That trend persists in the study of gender differences in ASD symptoms, with only four studies having included adults. Pilowsky and colleagues (1998) found no significant gender differences on the ADI-R or CARS in participants ages 20 months to 34 years matched on

mental age. In addition, Hus and associates (2007) found no significant gender differences in participants ages 4 to 52 years on ADI-R items involving word or phrase acquisition, repetitive sensory motor actions, insistence on sameness, and savant skills. McLennan, Lord, and Schopler (1993) examined gender differences on the ADI for participants with ASD 6 to 36 years matched on non-verbal IQ (above 60). No significant gender differences were found in subdomains of socialization, communication, or restricted, repetitive, stereotyped behaviors on the ADI; however, females had greater impairments in current friendships and reciprocal social interaction, but less separation anxiety and impairments in reciprocal social interaction, communication, and social play prior to the age of 5. (McLennan, et al., 1993). Finally, in the general population, Baron-Cohen and colleagues (2001) found higher symptom endorsements in males without ASD on the AQ, but no significant gender differences in participants with high functioning autism or Asperger's (Baron-Cohen, et al., 2001).

Due to the scant literature available on gender differences in adults with ASD and ID, specific hypotheses for the present study were limited. It was hypothesized that males would exhibit more overall ASD symptoms, potentially in the area of restricted interests/bizarre sensory responses, than females. This hypothesis was not supported in that no significant gender differences were found for participants with ASD. In contrast, for participants with ID alone, females had higher endorsements of social (i.e., participation in social games, sports, and activities; interest in other person's side of the conversation; and imitation) and communication (i.e., interest in other person's side of the conversation; and reading body language) communication impairments compared to males. This finding warrants further investigation, particularly in more varied degrees of ID. There is a dearth of research on ASD in adults, gender differences in ASD, as well as gender differences in ID (see Hodapp & Dykens, 2005), making

the present study in an even narrower research area (i.e., gender differences in adults with ASD and ID) and thus, limiting comparisons with previous literature. Finally, in adults without ID or ASD, no significant gender differences in ASD symptoms were found. As with the findings in Study 2 with children and adolescents, the present study used a measure designed for ASD symptoms rather than a general population measure designed to assess the broad range of ASD traits, which may account for the lack of gender differences in ASD symptoms in those without ASD or ID as previous research has found (i.e., Baron-Cohen, et al., 2001).

The present study provides only a preliminary investigation of gender differences in ASD symptoms in adults, and much further research is warranted in this area. Several strengths are notable, including the large sample size, inclusion of a comparison group without ASD, use of objective criteria to standardize ASD diagnoses, and use of a measure designed specifically for the adult ASD and ID population. As pointed out with Study 2, the most significant need is for further research into the relationship between IQ, ASD symptoms, and gender. The full range of ID as well as participants without ID should be represented. The current study represented primarily the profound range of ID and individuals residing in institutional settings. This level of ID encompasses a broad range of functioning which measures of cognitive and adaptive ability are not able to capture. Thus, in the present study, even though level of ID and other characteristics (e.g., physical and sensory impairments) were accounted for, specific level of functioning for males and females was not examined. Future research should aim to examine more specific levels of cognitive and adaptive functioning. Again, similar to Study 2, a challenge is identifying an adequate sample size of females with ASD, as well as a comparison group with ID without ASD, with the increasing prevalence of ASD. Additional future directions include

using multiple measures (e.g., observational), examining gender differences in ASD longitudinally, and addressing comorbidity and diagnostic issues.

GENERAL DISCUSSION

The predominance of males with ASD has long been recognized; however, gender differences in ASD symptoms have been examined by few researchers. Fewer than 10 studies have examined gender differences in ASD symptomatology in participants with ASD. Thus, the literature base in this area is scant. Overall, previous research has shown relatively few differences in ASD symptoms based on gender. Findings have varied widely as a function of how intellectual ability was addressed, based on current or early functioning, and assessment methodology (i.e., observation or parent interview). In studies of the general population, greater autistic traits have been found in males.

The present study examined gender differences in ASD symptoms in three populations (i.e., toddler, child/adolescent, and adult), using assessments specifically developed for the ASD population and age range. The first study included infants and toddlers in an "at risk" sample (i.e., have developmental delays or a medical condition likely to result in a developmental delay). The second study examined gender differences in ASD symptomatology in children and adolescents. Finally, the third study involved adults with ID. These data are valuable as they span a wide range of development, include comparison groups without ASD (important given research findings of autistic traits in the general population), and examine symptom domains separately, given emerging data concerning fractionability of the triad of ASD symptomatology.

In the present study, no significant gender differences in ASD symptoms were found in the toddler or child/adolescent populations. Thus, based on groups with a categorical diagnosis, significant gender differences in ASD symptoms were not found. It is important to note that diagnostic groups are determined based on the current criteria, for which the research base has largely been founded based on males. Furthermore, measures used in the present study and

previous studies of gender differences in ASD have demonstrated that there may not be significant gender differences in the number of certain impairments and criteria possessed. However, these measures may not be detecting qualitative or more subtle aspects in which males and females may differ. In the adult population, in participants with ID alone, females had higher endorsements of social and communication impairments compared to males. Specifically, social impairments included participation in social games, sports, and activities, interest in other's side of the conversation, and imitation, while communication impairments included interest in other's side of the conversation and reading body language. This finding warrants further investigation, as the literature in adults with ASD and gender differences in ASD and ID are scant. This is particularly important given the broad range of functioning encompassed within the various levels of ID.

The present study aimed to stimulate future research into disparities in ASD symptom domains, breadth, and severity considering age and developmental/cognitive level. Identification of implications for assessment and intervention for females with ASD are paramount. With this line of research, a host of additional issues are relevant and deserve future attention. These include validity of the diagnostic criteria, assessment instruments, heterogeneity in presentation, developmental changes in symptom presentation, course, comorbidity biases, informant biases in report and expectations, and socialization (Koenig & Tsatsanis, 2005; Rutter, et al., 2003).

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