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Parental Age at Conception: An Examination of Risk Factors Related to Autism Severity and Comorbid Psychopathology

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PARENTAL AGE AT CONCEPTION: AN EXAMINATION OF RISK FACTORS RELATED
TO AUTISM SEVERITY AND COMORBID PSYCHOPATHOLOGY

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TABLE OF CONTENTS

LIST OF TABLES

ABSTRACT

Many researchers have cited the continuing increase in the prevalence of autism worldwide and have speculated on the potential causes of that increase. One theory that suggests at least a contributory effect is the general trend for parents to have children at later ages. Previous research has begun to examine the relationship between advanced parental age at conception and the incidence of autism and have noted strong relationships between advanced parental age and other developmental disabilities. The purpose of this study was to not only confirm the relationship between advanced parental age and autism risk but to extend that knowledge to the association between parental age and severity of autism symptoms as well as comorbid psychopathology. The current study included 252 participants between the ages of 2-17 years of age and their parents. It was found that paternal age and child's gender were both significant predictors of an autism diagnosis in this clinical sample. Males were found to have an odds ratio of 4.17 (95% Confidence Interval, 2.06-8.44) when compared to females. While the effect was not as large for paternal age, the predictive power was found to be statistically significant (odds ratio = 1.06; 95% Confidence Interval, 1.00-1.12). Child's gender and paternal age were also found to be significant predictors of autism severity; however, paternal age was not found to be a significant predictor of comorbid symptoms. Interestingly, maternal age was not found to be a significant predictor of autism risk, severity, or comorbid psychopathology in this sample. Possible explanations for this finding and other findings are discussed, as well as future directions for research in this area.

CHAPTER 1: INTRODUCTION

Autism Spectrum Disorder is a complex neurodevelopmental disorder that is typically diagnosed within the first few years of life (Matson, 2007; Nebel-Schwalm & Matson, 2009; Tidmarsh & Volkmar, 2003). The history of autism is relatively short but has gone through many different changes in its conceptualization, diagnostic criteria, and overall prevalence since it was originally described by Leo Kanner (1943). The core features of autism include deficits in social communication skills and the presence of restricted interests and repetitive behaviors (Brereton, Tonge, & Einfeld, 2006; Leekam, Prior, & Uljarevic, 2011; Tidmarsh & Volkmar, 2003). The prevalence of autism continues to rise with recent estimates suggesting that 1 in 68 meet criteria for autism (CDC, 2014). The rise in autism prevalence has been described by many but researchers have not agreed on a cause for the increase in rates. Increased awareness, improved identification and assessment, and changing diagnostic criteria have been cited as likely causes (Matson & Kozlowski, 2011); however, others have found that this can account for only some of the increase (Hansen, Schendel, & Parner, 2015).

While the core features of autism have persisted, the diagnostic criteria and names of autism have changed throughout its history including recent changes in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (*DSM-5*). These changes will have impacts on research and prevalence rates just as previous changes have in the past. Of more pressing concern is the negative effect that these changes will have on families and those that will no longer meet criteria for an Autism Spectrum Disorder (Tsai, 2014). In addition to changes in the conceptualization and diagnostic criteria of autism, researchers continue to search for etiological clues to determine the root causes of autism

Numerous theories of autism have been posited by researchers throughout the decades. While autism appears to have a strong hereditary component, genetics alone cannot explain or predict who develops the disorder. Additional theories have investigated environmental factors including theories regarding socialization, environmental toxins, and prenatal health. One recent theory that has been associated with an increased risk of autism is related to parental age at conception. As the age of first time mothers increases (Matthews & Hamilton, 2009) and the use of assisted reproductive technologies increases (Hediger, Bell, Druschel, & Buck Louis, 2013) children are at higher risk of developing chromosomal and genetic disorders (Hook, Cross, & Schreinemachers, 1983). The same appears to be true for autism and researchers have begun to see associations between parental age at conception and autism risk. Only one study to date, however, has examined this risk in relation to autism severity (Itzchak, Lahat, & Zachor, 2011) and is the focus of this study.

Additionally, children and adults with autism have been shown to have higher rates of comorbid disorders. This includes comorbid genetic conditions (e.g., Fragile X, Down Syndrome), medical conditions (e.g., asthma, allergies, gastrointestinal problems), and psychopathology (e.g., anxiety, depression, attention-deficit/hyperactivity disorder). This study also aimed to examine the relationship between autism comorbid psychopathology symptoms and parental age at conception. Discussion of these points and research regarding the causes of autism and support for this study are provided.

CHAPTER 2: AUTISM HISTORY

What we now refer to as Autism Spectrum Disorder (ASD) has a relatively short history in terms of human existence. It was a relatively unknown disorder until the middle of the 20th century. Even then, autism was not well defined or understood and was unknown to the average individual. It was not until the 1980's and 90's that autism research began to find support among the general public and government. ASD continues to be a disorder that, to this day, is not well understood or defined. Many individuals today know someone with an ASD, but the history of autism is still only known by few outside the world of academics and research. The term "Autism Spectrum Disorder" has come to be known by several different names throughout its short history as discussed later in the chapter. While great advances in research and assessment have been made in defining and diagnosing ASD, much work is still needed to better understand this disorder.

The term "autism" or "autistic thinking" was originally used to describe a trait of schizophrenia. Eugen Bleuler (1913) used the term to describe a fairy tale or fantasy state of thinking that is commonly found in those with schizophrenia. This type of thinking is also seen in those without schizophrenia in the form of daydreaming and pretend/imaginative play; however, the schizophrenic becomes lost in the fantasy and the lines begin to blur between fantasy and reality. The more the schizophrenic lives in this fantasy the more the fantasy becomes his/her reality. Bleuler noted that as long as the "autistic thinking" is not interfered, the schizophrenic individual continues to think rationally and reasonably; however, if one attempts to disrupt or challenge his thinking, it is then that the irrational and illogical manifestations of the disease are apparent (Bleuler, 1913).

In 1943, Leo Kanner published the seminal article on autism entitled "Autistic Disturbances of Affective Contact." Kanner used the term from schizophrenia to help describe the avoidance of social contact with the outside world. This phenomenon is something that was common in the schizophrenic and appeared to be a key feature in those with autism as well. The use of the term also led to confusion between the two disorders throughout its history. As Kanner and others began to examine these individuals more closely it was apparent that these were two very different disorders; however, the separation from schizophrenia took several decades and is a distinction that continues to be debated (Cohen, Paul, & Volkmar, 1986; de Bruin, de Nijs, Verheij, Hartman, & Ferdinand, 2006; Towbin, Dykens, Pearson, & Cohen, 1993).

Core Symptoms

Many of the symptoms that we consider "core-features" of autism today were observed by Kanner (1944, 1954) in his initial observations of these children. These children with "early infantile autism," as Kanner initially labeled them, exhibited difficulties with making and sustaining appropriate eye contact, a strong desire and insistence of sameness, an excellent rote memory in those with language, and overall speech and language deficits among other similarities (Kanner, 1943, 1944). Kanner observed and documented these similarities initially in 11 children under the age of 12. He suspected that at least some of the symptoms of autism were maintained or cultivated through a common pattern of parental indifference toward the child with little attention paid to the emotional needs of the child (Kanner, 1949).

One of the first core symptoms that Kanner (1943, 1944) recognized was their inability to form appropriate social relationships with the people around them or an "extreme autistic aloneness." Parents described their children as "self-sufficient" or appeared to be "in a shell" and "oblivious

to things around them." The observations that Kanner made continue to be a part of the core symptoms of autism with deficits in making and keeping social relationships and difficulties in understanding social norms. The problems are also apparent in Kanner's observations of a lack of eye contact and general difficulties in social reciprocity. He noted that these children had a good "relation with objects" but treated individuals as if they were just another piece of furniture in the room.

Another core symptom recognized by Kanner (1943) was the odd use of language and general speech/language deficits. Of Kanner's initial 11 cases, eight cases had acquired speech with varying levels of delays/deficits. Of those that had acquired speech, Kanner noted that they had unusually strong vocabularies and an excellent rote memory for repeating previously learned nursery rhymes, prayers, and other phrases. However, Kanner noted that these children rarely used their language skills for communicative purposes. They exhibited peculiarities in their use of language including delayed and immediate echolalia, pronoun reversals, general speech delays or abnormal patterns of speech development (e.g., speaking full sentences after years with no speech), and strict literal use of language. These children really struggled with using language in a practical and pragmatic way. Because of their advanced vocabularies and rule-driven use of language, along with a stoic affect and general aloofness, some of these children gave an impression to others that they also had advanced cognitive abilities.

A third core symptom recognized by Kanner (1943) was an extreme desire for the "preservation of sameness." The children that Kanner observed exhibited struggles with changes in their routines and often used their time to place objects in order or patterns. Some of these children would be aware of minute changes in their environment which led to distress, anxiety, and tantrums. Kanner believed that many of the children engaged in repetitive behaviors and had

5

a restricted range of interests and activities due to this insistence on sameness. Other problems believed to be related to this included early feeding problems and excessive tantrums.

Kanner noted symptoms of autism even within the first two years of life and theorized that all deficits were present at birth but became more pronounced with age. For example, he cited work by Gesell in his original article (Kanner, 1943) stating that the many children begin to exhibit anticipatory movements before being picked up by the age of 4 months. Kanner noted that this anticipatory reaction to being picked up was lacking in many of the children at a very young age (Kanner, 1954). In addition to this, Kanner believed that all of the core symptoms noted above were present from birth but remained unrecognized until the children were placed in environments where these skills were necessary (e.g. school, church, social interactions, etc.). Parents of autistic children often described their children as being relatively quiet and happiest when left alone and that these characteristics were present in early infancy (Kanner, 1943). Additionally, feeding problems were noted early on including problems with nursing from birth.

Early Observations

Even early in his observations of children with autism, Kanner noted a significant imbalance in gender ratios with a higher prevalence of the syndrome in males. Kanner noted a gender ratio of approximately four-to-one by the time he had diagnosed over 100 cases with autism (Kanner, 1951; Kanner & Eisenberg, 1957) and is a ratio that holds generally true today. This observation was important in beginning to differentiate autism from childhood Schizophrenia and in determining etiological factors involved in autism (Kanner, 1971b; Rutter, 1968). Kanner suggested a differing trajectory and severity of symptoms between genders noting that males were generally referred for evaluation between 2 and 6 years of age, whereas females were generally referred between 6 and 8 years of age. Many key observations have been

made by Kanner and others in the early history of autism that are still important in our understanding and search for etiological factors involved in the development of autism.

Spurring one of the more controversial theories of autism development, Kanner noted that of the original 11 cases, all fathers were fairly successful and intelligent holding advanced degrees and most of the mothers were college graduates holding a wide range of prestigious careers (Kanner, 1943). This theory of autistic children only coming from affluent and intelligent families was perpetuated for decades. Kanner reported in 1954 that "we have not encountered any one autistic child who came of unintelligent parents" and other researchers noted the correlations between successful and intelligent parents and autistic children (Rutter, 1968). Although some researchers at the time reported many cases of autism in families with average or below average intelligence (Bender, 1959) researchers continued to cite the correlation decades later (Dor-Shav & Horowitz, 1984; McAdoo & DeMyer, 1977).

Kanner's belief that autistic children were the product of highly successful and intelligent parents eventually spurred another theory of the development of autism. Kanner, and others since, noted that many mothers of autistic children tended to be affluent and intelligent but also less emotionally engaged with their children. Researchers at the time believed that this lack of affection toward the autistic child could maintain or even foster many of the symptoms noted above. Kanner believed that the environment, and therefore the parent-child relationship, was an important part of the development of autism. He noted that there were no generalizations that could be made regarding the child's physical condition, circumstances of birth, or a general pattern of heredity (noting that almost none of the family members had a history of Schizophrenia) (Kanner, 1954). He also noted that many parents, especially mothers, tended to exhibit obsessiveness regarding the development of their child and a general lack of affection

toward their children. He mentioned that many parents also exhibited significant struggles with social functioning and referred to some of these parents as "successfully autistic adults" (Kanner, 1954).

The importance of parent-child relationships and expressing affection toward children was something that was also being researched close to the time that Kanner began to write about these autistic children and affected his view regarding the development of autism. For example, Goldfarb (1945) wrote about the effects of psychological deprivation and the consequences of emotional deprivation in infants. The symptoms of this emotional deprivation appeared to closely mimic symptoms of autism that were being described by Kanner. Goldfarb noted that emotional deprivation can cause isolation, aggression, "affective impoverishment," anxiety, and language deficiencies. Additionally, Bakwin (1949) reported that many cases of "hospitalism," which was a failure to thrive in infants placed in hospitals before the age of one, were due to emotional deprivation. These children also exhibited traits similar to those of autistic children, including a lack interest in the environment, lack of social smiling, feeding problems, and were relatively quiet with little crying. The symptoms of "hospitalism" were first thought to be due to malnutrition or infection and so nutrition was increased and boxes were built to decrease the amount of human contact that each child had. It was later determined that more handling, attention, affection, and presence of mothers decreased the rate of "hospitalism" without increasing the rate of infections. This research undoubtedly affected the view of Kanner in describing autistic children and the relationship with their parents.

Much of the early history of autism is attributed to the discoveries of Kanner; however, similar observations and articles were written by an Austrian doctoral student around the same time as Kanner's observations. Hans Asperger's article "Autistic Psychopathy in Childhood,"

8

which was published in German, went relatively unnoticed until it was translated into English in 1991 by Uta Frith (Asperger & Frith, 1991). Asperger's work did not go completely unnoticed prior to 1991. Van Krevelen (1971) published a paper discussing the differences between Autistic Disorder and Autistic Psychopathy, claiming that they were erroneously thought to be the same disorder but were in fact two separate disorders and he described the essential characteristics and differences of each disorder. Asperger's work on Autistic Psychopathy naturally led to the diagnostic category of Asperger's Disorder found in the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*; APA, 2000). Asperger's descriptions were similar to those of Kanner in 1943 including special interests, odd eye gaze, behavioral problems, language abnormalities, and other symptoms. Probably the most striking similarity was both Kanner's and Asperger's choice to describe these children as "autistic." Although many have argued that these two disorders are separate syndromes, due to their similarities and conceptualization on a continuum these are now viewed as disorders falling within the scope of Autism Spectrum Disorder according to the current DSM (*DSM-5*; APA, 2013).

Historical Nosology and Diagnostic Criteria

Kanner continued to examine and document cases of autism and attempted to develop a classification of early infantile autism as a diagnosis separate from any other. He attempted to separate autism from the schizophrenias and provided compelling evidence for doing so but eventually supported autism as a form of early onset childhood schizophrenia (Kanner, 1949). Kanner also provided evidence to discriminate autism from other similar disorders such as Heller's disease (Childhood Disintegrative Disorder), congenital word deafness, and other disorders. The criteria for autism were further narrowed to include two core symptoms including

extreme self-isolation (autistic aloneness) and insistence on sameness that often results in restricted interests and activities (Kanner, 1954, 1958; Kanner & Eisenberg, 1957).

As other researchers became aware of infantile autism, debate grew regarding autism as either an early onset form of schizophrenia or a disorder that was completely separate from the schizophrenias (Kanner, 1958). Yet, other researchers and clinicians continued to diagnose many of these children with childhood schizophrenia (Bender & Grugett, 1956). As time passed, increased awareness of infantile autism began to spread and was diagnosed in individuals across the globe. However, without a clear conceptualization and understanding of the disorder and the lack of clear diagnostic criteria, many individuals were misdiagnosed. The sensitivity and specificity of the diagnostic criteria became a growing problem and early infantile autism became the automatic and substitute diagnosis for cases of hospitalism (discussed above), separation anxiety, depression, true cases of childhood schizophrenia, and organic disorders (Eveloff, 1960; Kanner, 1958). On the reverse side, many children with autism were being labeled as deaf, mentally defective, or diagnosed with childhood schizophrenia (Ritvo & Provence, 1954).

In a debate similar to the diagnostic substitution debate that continues today (see diagnostic substitution in following chapters), Mosse (1958) noted the large increase in misdiagnosed individuals. He discussed the dangers of such behavior by clinicians and researchers. Mosse noted that many treatments for adults were being generalized for these children including electroconvulsive therapy. Mosse attempted to delineate schizophrenia and how it contrasts from autism and other similar disorders citing cases in which children with behavior problems or juvenile delinquents were labeled as schizophrenics. Mosse proposed that childhood schizophrenia, and therefore early infantile autism, was actually a disorder very

different from later onset adult schizophrenia and was a label that was misused and overly

diagnosed in the United States. Kanner (1971a) later described childhood schizophrenia as a

"pseudo diagnostic wastebasket" citing the need to better differentiate between infantile autism,

childhood schizophrenia, and other disorders of childhood.

As the debate of autism and childhood schizophrenia continued, researchers attempted to

further differentiate disorders with similar characteristics. Other researchers, however, felt that

the distinction between certain disorders was unnecessary. For example, Bender (1959) stated

that there was no need to differentiate autism from forms of mental deficiency while others still

attempted to make such distinctions. Eveloff (1960) noted common confusion between the

autistic child and those with other problems such as hospitalism, analytic depression, "mental

defectiveness", and childhood schizophrenia. In an attempt to better distinguish between the

disorders, Eveloff cited several studies that suggested that autism and schizophrenia were two

very different disorders. Such evidence included abnormal EEG's in schizophrenic children and

relatively normal reading in autistic children. He also cited studies which displayed a differing

level of family inheritance including a low incidence of schizophrenia in family members of

autistic children (Bender & Grugett, 1956; Kanner & Eisenber, 1957). Further evidence was

provided to better distinguish between the two disorders including differing sex ratios and

intellectual profiles and a lack of delusions or hallucinations in autistic individuals (Rutter 1968).

Early Classification Systems

As the distinction between autism and schizophrenia began to gain traction and increased

support and evidence, Rutter (1968) proposed a different classification system for these disorders

of childhood. The first classification included children with schizophrenia symptoms with onset

in early adolescents. He noted that these children generally have symptoms that mimic adult

11

schizophrenia and that the two are indistinguishable when they reach adulthood; this also included many cases of childhood schizophrenia. The second classification was for children that experienced autistic-like features after a period of normal development with an onset between the ages of 3-5 years of age. This group included cases of Heller's disease (Childhood Disintegrative Disorder). The last classification was for children with autism symptoms with onset from birth to 3 years of age, including the typical case of autism as described by Kanner.

As the classification system was put into place, many clinicians struggled with distinguishing between those with Autistic Disorder and those with an intellectual disability (ID). Researchers and clinicians noted that these two disorders commonly co-occurred and struggled with choosing the best diagnoses. This led to the development of a tri-axial model of classification, where an individual's intellectual abilities were separate. A second category was clinical psychiatric problems with a third axis focusing on etiological factors (Rutter et al., 1969). Under this classification system, children with infantile autism were now categorized under the broader term of infantile psychosis, although many researchers, by this point (including Rutter), had noted a lack of hallucinations, delusions, or other psychotic features in these children. Other categories developed included disintegrative psychosis (e.g., Childhood Disintegrative Disorder), schizophrenia (e.g., childhood schizophrenia), and other psychoses.

As the axial model of classification began to gain favor and support, another axis was added. This multi-axial model (Rutter, 1972) included psychiatric and intellectual functioning axes as before but split etiological factors into "associated or etiological biological factors" (Axis III) and "associated or etiological psychosocial factors" (Axis IV). For autism, this classification system also involved a few minor revisions including the cutoff ages for onset of autism symptoms noting that about 20% of children exhibit a period of normal development followed by

a period now referred to as autistic regression (Tidmarsh & Volkmar, 2003). To further distinguish autism from schizophrenia, Rutter also proposed that childhood schizophrenia instead be included under the category for adult schizophrenia.

Diagnostic and Statistical Manual of Mental Disorders (DSM)

DSM-III. Although these classification systems had been proposed, many individuals with autism were still diagnosed with childhood schizophrenia. The main barrier to appropriate diagnosis was the fact that an autism diagnosis did not appear in the first or second edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders* (DSM & *DSM-II*; APA 1952, 1968). Infantile autism was finally introduced in the third edition of the DSM and was listed under the newly created category of Pervasive Development Disorders (*DSM-III*; APA, 1980). The criteria for infantile autism included a pervasive lack of response to others, deficits in language development, odd use of language or pronoun reversals (if speech was present), insistence on sameness, odd interests or attachments to objects, onset prior to 30 months of age, and the absence of schizophrenic features such as delusions and hallucinations.

DSM-III-R. Infantile autism was renamed to Autistic Disorder in the revised version of *DSM-III* (*DSM-III-R*; APA, 1987). The diagnostic criteria were also altered to reflect several dimensions of deficits and the broadening of criteria to include more individuals with similar symptomatology. The *DSM-III-R* required 8 of 16 items with an algorithm that included at least two impairments in reciprocal social interaction, one communication impairment, and one restricted interest or activity. The age of onset was removed and included a specifier if age of onset was after 36 months of age to include those children with Childhood Disintegrative Disorder or other late onset autism symptoms. Additional categories were also added including Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS).

13

Since *DSM-III-R*, the DSM has been through several other editions including the *DSM-IV*, *DSM-IV-TR* (which included very little changes with respect to autism), and the recent *DSM-5*. While only minor changes were made between the *DSM-III-R* and *DSM-IV-TR*, significant changes were made to the autism diagnostic criteria in the new *DSM-5*. These changes, and the impacts that they have on research and prevalence will be discussed in the following chapter.

CHAPTER 3: PREVALENCE AND DIAGNOSTIC CRITERIA

Prevalence

The Centers for Disease Control and Prevention (CDC), through their Autism and Developmental Disabilities Monitoring Network, recently released an updated estimate of the prevalence of ASD in the United States from data collected in 2010. The CDC currently estimates that about 1 in 68 children in the United States have been identified with ASD (CDC, 2014). Over the past decade, this rate has been found to increase dramatically with an estimated rate of 1 in 150 in 2000 (CDC, 2007) and 1 in 110 in the year 2006 (CDC, 2009). That means that the rate of ASD in the United States has more than doubled between 2000 (6.7 per 1,000 children) and 2010 (14.7 per 1000 children).

While the CDC's estimates of prevalence are the most well-known and used statistics in describing the rise in autism, several researchers have debated the value and methods used to obtain these numbers. For example, Mandell and Lecavalier (2014) noted several methodological issues within these studies including ascertaining diagnoses through clinical or educational records which are often unclear or inaccurate. Educational classifications of autism tend to rely on parent interviews and brief observations and rating forms (Waite & Woods, 1999) and less often involve social/play based assessments or structured interviews. Although Mandell and Levacalier (2014) noted the many great uses of the CDC studies, they also strongly advised against the continued use of these studies as "true" prevalence studies as no in-person assessment or sufficient standardization of diagnosis is employed across sites. These problems are apparent in the discrepancies between sites with 1 in 46 children diagnosed with ASD in New Jersey compared to 1 in 175 in Alabama (CDC, 2014). The disparities are also apparent in differences

between racial/ethnic proportions and likely reflect differences in the diagnostic procedure and access to care rather than a true difference in the prevalence between areas.

The current estimate of ASD, including the recently reported estimate from the CDC, appears to be between approximately 1 in 150 and 1 in 68 children in the United States (CDC, 2014; Fombonne, Quirke, & Hagen, 2009; Lord & Bishop, 2010; Matson & Shoemaker, 2009; Nicholas et al., 2008). These data make ASD the second most frequent developmental disorder preceded by intellectual disability and followed by cerebral palsy (Nicholas et al., 2008). ASD occurs in all racial, ethnic, and socioeconomic groups (CDC, 2014; Durkin et al., 2010) and is 4-5 times more common in males versus females (CDC, 2014; Fombonne, 2003).

Racial/Ethnic Differences

While some disparities in the diagnosis of ASD are apparent across different race/ethnic groups (CDC, 2014), researchers, in general, report no significant differences between race and prevalence of ASD (Horovitz, Matson, Rieske, Kozlowski, & Sipes, 2011; Yeargin-Allsopp et al., 2003). Many of the differences in the large CDC studies and some other studies are believed to be attributable to methodological problems and differences in many cultural factors including access to care, age at diagnosis, and several other cultural factors. For example, Mandell, Listerud, Levy, and Pinto-Martin (2002) found significant differences in the age of diagnosis of ASD between white and black children. They found that black children received the diagnosis later than their white peers and cite differences in help-seeking behavior, access to care and support, and clinician behaviors and potential causes of the disparity. In another study, researchers found that children of ethnic minorities were less likely to receive a diagnosis of ASD when compared to white peers and that the difference increased in the presence of comorbid intellectual disability (Mandell et al., 2009). They also suggest that these differences

were likely due to differences in assessment by professionals based on race/ethnic minority status.

Although there is a general consensus among researchers that autism affects all race/ethnic groups equally, several researchers have begun to further investigate differences between these groups and to also consider immigration status. In one such study from the UK, Keen, Reid, and Arnone (2010) found that black children were at higher risk than white peers for a diagnosis of ASD. They also found that children of mothers born outside of Europe who then immigrated to the UK had higher rates of ASD when compared to European born mothers and that this accounted for much of the difference between black and white children. They also noted that immigrants from specific regions of the world (e.g., Caribbean) had much higher risks than other immigrants. Similar results were found of Europeans immigrating to Australia in a 1976 study that spurred interest in the immigration status variable of autism (Harper & Williams, 1976; Wing, 1980). Other studies also cite immigration status as a risk factor for autism, especially for certain ethnic groups such as Somali immigrants in Sweeden (Barnevik-Olsson, Gillberg, & Fernell, 2010) as well as in Minneapolis, Minnesota (Hewitt et al., 2013).

Socioeconomic Status. Higher intelligence, income, and overall socioeconomic status have all been associated with an increased risk for autism. Kanner and others noted throughout the early history of autism the observation that most of their clients came from higher-functioning families. Although this has been refuted by many researchers since that time, researchers continue to measure socioeconomic status and its association with risk of autism spectrum disorders. Most researchers to date, such as Daniels and Mandell (2014), have found that families with higher socioeconomic statuses were more likely to seek assessment and

services for their child with ASD than lower socioeconomic families. This finding is likely what has led to disparities between different geographical, ethnic, and income groups.

Some studies have continued to examine socioeconomic status and the possible relation with increased risk for autism spectrum disorders. In a Swedish population-based study (Rai et al., 2012), researchers found that those with a lower socioeconomic status were at higher risk of having a child with ASD. More specifically, they found that parents with lower incomes and occupations that included more manual labor were more likely to have a child with autism (OR = 1.4, 95% CI = 1.3-1.6) and that these associations were present even after controlling for parental ages and several other health and pregnancy related factors. The importance of this study is the large sample size (nearly 600,000 children) in a country that has free universal healthcare and routine screening for developmental disabilities. The effects that are commonly seen in the United States due to health disparities are hypothetically minimized in a country that offers such wide spread healthcare equally.

Sex Ratio

Early in the history of autism, Kanner and others noted the higher prevalence of autism in males. Children diagnosed with early infantile autism exhibited a clear sex ratio of about 4:1 (Kanner, 1951; Kanner & Eisenberg, 1957). This sex ratio appeared to be a good estimate of the actual ratio and is found in large prevalence studies today (CDC, 2014; Fombonne, 2003). Although the sex ratio has remained fairly constant, some researchers have examined differences in the ratio based on different factors. For example, when examining autistic individuals with IQs below 50, the ratio between males and females is much lower than individuals with IQs above 50 (Tsai, Stewart, & August, 1981; Tsai & Beisler, 1983; Wing, 1981). The higher prevalence in males lends support to the idea that autism is a predominately X-linked disorder

and more severe cases in females lends support to the idea that inheritance in multifactorial (Lord & Schopler, 1985; Reich, Cloninger, & Guze, 1975).

Autism Epidemic

Regardless of the methodological implications of the CDC prevalence studies noted above, researchers agree that there has been a significant increase in the number of diagnosed cases of autism with a rate that appears to have grown almost exponentially over the last two decades. The cause of this increase, however, is something that is strongly debated throughout the literature (Fombonne, Quirke, & Hagen, 2009; Matson & Kozlowski, 2011). Matson and Kozlowski (2011) provided an examination and review of other causes of the increase in prevalence rates discussed throughout the literature. Variables discussed in the research base include inaccurate diagnoses, differences in research methodology, environmental factors, cultural differences, and increased awareness. They also noted increased awareness among researchers, clinicians, primary care physicians, and parents as a likely source of the increase in prevalence rates over time as well as advancements in the diagnosis of ASDs at progressively earlier ages (CDC, 2009). Some of the most researched and supported theories of the increase in autism prevalence are discussed below.

Increased Awareness. One of the most cited causes to the increase in autism prevalence over the decades has been increased awareness of the disorder (Matson & Kozlowski, 2011). Autism was relatively unheard of in the public eye until the 1980's and 90's. Only recently have parents become more aware of the signs and symptoms of autism and are now more likely to seek treatment and assessment of developmental delays related to autism. Increased awareness amongst pediatricians and mental health care workers are also believed to contribute to the increased prevalence in recent decades (Wing & Potter, 2002). Additionally, increased

19

awareness at a governmental level also has affected laws and programs that help families receive assessment and treatment which has increased the number of children assessed for autism and developmental delays (Gurney et al., 2003).

Improved Identification. One recent study examined the prevalence of autism in Stockholm, Sweden in 2011 (Idring et al., 2014). They found that the increased prevalence among children (2-17 years of age) was approximately 3.5 times that recorded in 2001. The dramatic increase, however, was disproportionately found in those with ASD without an intellectual disability which increased in the same time period eightfold. The authors suggest that the huge increase was due to increased awareness but also improved diagnostic tools and identification abilities. The increase amongst those with an intellectual disability was relatively unchanged over the 10 year span which suggests that autism has not been increasing, but rather that we have become more proficient in identifying autism in those that traditionally would have been overlooked due to an average IQ.

Changing Diagnostic Criteria. Changing diagnostic criteria is another common factor cited by researchers as affecting the large increase in the autism prevalence. Changes within the DSM, for example, have directly affected the rates of ASD between editions (Fombonne et al., 2009; Matson & Kozlowski, 2011; Shattuck, 2006). Autistic Disorder was not included in the DSM until 1980 with *DSM-III*, therefore prevalence rates prior to this date are hard to calculate and were based on different criteria. Changes in criteria over the revisions and versions of the DSM have become broader and included a wider range of symptoms. The move to include a broader symptom presentation over time has therefore increased the number of individuals that meet criteria for the disorders. Recent changes to the *DSM-5* will also likely affect prevalence rates for autism and, due to the change in the criteria and classification of this spectrum of

disorders, direct comparisons using the new *DSM-5* criteria will not be possible. Further discussion on the impact of the new *DSM-5* criteria on prevalence rates and future research are discussed at the end of this chapter.

Diagnostic Substitution. Another theorized cause to the increase in autism prevalence rates is the idea of diagnostic substitution. Diagnostic substitution occurs when diagnostic criteria or general diagnostic practices change, even slightly, and individuals are moved from one diagnostic category to another leading to apparent increases and decreases in respective prevalence rates (Newschaffer, 2006; Shattuck, 2006).   An example of this is evinced by the increase in rates of ASD and corresponding decrease in ID rates over the same time period. Even Kanner noted that many children with autism were diagnosed as being either deaf or intellectually disabled (Kanner, 1944). As the diagnostic criteria change, the specificity and sensitivity of the diagnostic categories become more exclusive or inclusive. While some researchers have opposed this explanation of increasing prevalence (Blaxill, 2004) or found no evidence in support of the theory (Newschaffer, Falb, & Gurney, 2005), others suggest that it could, at the very least, be contributing to the increase.

In a study examining school classification of ASD, Shattuck (2006) noted a significant rise in educational classifications of ASD between 1994 and 2003; however, this increase corresponded to a similar decrease in other diagnostic categories such as mental retardation and learning disabilities. In a similar study in Canada, researchers found that about 52% of the increase in British Columbia schools between 1996 and 2004 was due to diagnostic substitution (Coo et al., 2008). With further examination, however, they found that when also taking into account individuals who previously had autism classification who were then switched to another educational category, diagnostic substitution accounted for a little over 30% of the total increase.

21

Other Hypothesized Causes of the Increase. In a recent Danish study, researchers found that changes in diagnostic criteria, awareness, and reporting practices, such as those instances discussed above, accounted for 60% of the increase in autism rates (Hansen, Schendel, & Parner, 2015). While almost two-thirds of the increase was attributable to factors noted above, there is still quite a bit of variability that has not been accounted for. This leads us to consider other variables which may account for the increase or to consider that a true increase in the incidence of autism has occurred. Many other causes of the increase in autism have been speculated and studied ranging from modern environmental causes (discussed in Chapter 4) and assortative mating (Baron-Cohen, 2006) to Wi-Fi use (Mariea & Carlo, 2007) and alien abductions (Menkin, 2013). Further research in this area will be important to determine the cause of the autism increase which in turn may also provide important clues into the etiology of autism.

<center>**Autism Diagnostic Criteria**</center>

The diagnostic criteria of autism have changed multiple times through its relatively short history. One of the most widely used set of criteria is from the American Psychiatric Associations *Diagnostic and Statistical Manual of Mental Disorders* (DSM) which has included Autistic Disorder or Autism Spectrum Disorder since the 3rd edition of the manual (*DSM-III*; APA, 1980). While the history of the diagnostic criteria was discussed in earlier chapters, recent changes in diagnostic criteria have created debate regarding the effects of these changes on prevalence rates and research. While the criteria still hold many of the same signs and symptoms that were apparent even in Kanner's first observations of autism (Kanner, 1943), even small diagnostic changes can have large effects on prevalence rates. Much of the data for this research study, as well as research reviewed here, was completed using criteria from the *DSM-IV-TR*

<center>22</center>

(APA, 2000) or similar criteria from the 10th edition of the World Health Organization's

International Classification of Diseases (ICD-10; WHO, 1993). Therefore the criteria for *DSM-*

IV-TR will be reviewed followed by the subsequent criteria from the *DSM-5*.

DSM-IV-TR

Diagnostic criteria are of great importance for researchers, as the reliability of such

diagnoses, whether they be medical or mental disorders, is vital to the ability to collaborate and

compare research across the globe. If one child in the United States is diagnosed using

significantly different criteria than a child in the United Kingdom, then comparisons between the

two children are hard to make. The same is true when making comparisons across time for

groups, even within the same geographical area, when criteria are changed. In terms of autism,

diagnostic criteria have continued to be developed and changed over time. The DSM and ICD

manuals have different criteria for mental disorders but have grown closer overtime (Tidmarsh &

Volkmar, 2003). The criteria between the two manuals are very similar in relation to pervasive

developmental disabilities; therefore the following sections will focus on the criteria of the *DSM-*

IV-TR. The category of Pervasive Developmental Disabilities includes five different diagnoses

including Autistic Disorder, Asperger's Disorder, Rett's Disorder, Childhood Disintegrative

Disorder, and Pervasive Developmental Disorder- Not Otherwise Specified. The diagnostic

criteria for each disorder and guides for differential diagnoses will be discussed.

Autistic Disorder. The diagnostic criteria for autism in the *DSM-IV-TR* (APA, 2000)

maintain many of the core features that Kanner (1943) observed in his initial cases of early

infantile autism. To meet a diagnosis of autism, an individual must exhibit deficits in social

interaction, communication, and restricted/repetitive interests/activities. An algorithm is used

and individuals must meet at least six of the 12 criteria to warrant the diagnosis including two

impairments in socialization, one in communication, and one repetitive/restricted behavior/interest. Examples of impairments within the social domain include poor eye contact, impaired use of gestures, lack of appropriate peer relationships, impaired social/emotional reciprocity, and lack of spontaneous sharing/showing. Within the communication domain, impairments may include a lack or delay in verbal language development, impairments in initiating and sustaining conversations with others, lack of imitation or make-believe play, and stereotyped or idiosyncratic use of language. Within the restricted/repetitive behaviors/interests, examples of impairments include overly restrictive interests or preoccupations, stereotyped and repetitive motor mannerisms, preoccupations with parts of an object or playing with objects in a repetitive fashion (e.g. spinning, lining up), and over-adherence to routines or rituals. In order to meet criteria for Autistic Disorder, the child must also exhibit these delays/abnormalities prior to 3 years of age and not better accounted for by another mental disorder such as Rett's Disorder or Childhood Disintegrative Disorder.

When clinicians are considering Autistic Disorder as a possible diagnosis, it is important to also consider and "rule-out" other potential possibilities that may better account for the pattern of deficits. This is important not only in research but also in providing individuals with appropriate treatments and intervention services developed for that disorder. The most obvious disorders to consider in the differential diagnosis of Autistic Disorder are other Pervasive Developmental Disorders such as Rett's and Childhood Disintegrative Disorder. Other diagnoses that should also be considered that have overlapping symptomatology may include Schizophrenia, Selective Mutism, Receptive-Expressive Language Disorders, and Intellectual Disability (Mental Retardation in *DSM-IV-TR*).

As seen through the historical association between Schizophrenia and Autistic Disorder, the two disorders can have overlapping symptoms; however, there are several features that differentiate the two disorders. The first feature to consider is age of onset. One of the criteria for autism is onset before 3 years of age. Schizophrenia rarely occurs before 7 or 8 years of age, whereas autism symptoms can appear as early as birth (Green et al., 1984). Other markers for autism include the presence of intellectual disability (although not conclusive evidence either way) and the absence of hallucination and delusions which are common in Schizophrenia (Green et al., 1984; Mash & Barkley, 2003). The co-occurrence of Autistic Disorder and Schizophrenia is very rare with rates similar to the general population (Volkmar & Cohen, 1991).

Another important disorder to consider in the differential diagnosis of Autistic Disorder is Selective Mutism. Selective Mutism is a disorder in which a child refuses or fails to speak in everyday social situations (especially structured settings like school) with no deficits in speech and communication development and appropriate use of language in other situations or with family members (Scott & Beidel, 2011). The age of onset is usually before the age of 5 and becomes apparent when such communication is required and refusal begins to interfere with daily functioning (Reuther, Davis, Moree, & Matson, 2011). The differentiation between Autistic Disorder and Selective Mutism is the presence of normal speech and communication skills and the absence of repetitive/restricted behaviors/interests. Social impairment may be present in Selective Mutism but are qualitatively different and generally do not occur at home or other less structured settings. The reason that many children with Selective Mutism are evaluated for an ASD is their refusal to speak at school which may mimic social and communication deficits seen in autistic children. Finally, the communication deficits in children with Autistic Disorder tend to be more severe and may include immediate or delay echolalia,

pronoun reversals, and other language impairments (Bartak, Rutter, & Cox, 1975; Mash & Barkley, 2003).

Due to the high incidence of intellectual disabilities in those with Autistic Disorder, it is also important to distinguish between those with Autistic Disorder and comorbid Intellectual Disability and those with Intellectual Disability alone. The identification of Autistic Disorder in those with severe and profound mental retardation can be difficult to assess but is present in almost half of all those diagnosed with Autistic Disorder (Fombonne, 1999). Although individuals with intellectual disabilities may have social and communication deficits, the presence of deficits above and beyond what would be expected given their level of intellectual functioning may be an indicator of comorbid Autistic Disorder.

There are several other disorders that share commonalities with Autistic Disorder and that also commonly co-occur. The differential diagnostic process should also include assessment of Attention-Deficit/Hyperactivity Disorder, Obsessive Compulsive Disorder, and Anxiety Disorders, although this comorbidity can be difficult to assess in young children or those with comorbid intellectual disabilities.

Asperger's Disorder. Asperger's Disorder is considered to be an ASD and viewed by many as a high-functioning form of Autistic Disorder (Howlin, 2003), although research suggests these are two separate entities (Matson & Wilkins, 2008a; Ozonoff, South, & Miller, 2000; Szatmari, 1992). Asperger's is similar to Autistic Disorder in that they have impairments in social interaction and restricted interests but are characterized by normal language development, although they may have abnormalities in their use of language (Tidmarsh & Volkmar, 2003). The diagnostic criteria for Asperger's Disorder in the *DSM-IV-TR* (APA, 2000) requires six criteria be met to warrant the diagnosis including at least two social impairments and

one restricted/repetitive interest/behavior. Much like Autistic Disorder, examples of impairments in socialization may include poor eye contact, impaired use of gestures, odd body postures, failure to develop and keep appropriate peer relationships, lack of social and emotional reciprocity, and a lack of spontaneous sharing of enjoyment, interests, or achievements. Within the domain of restricted/repetitive behaviors/interests, impairments include extreme preoccupations or restricted interests, over-adherence to rituals or routines, stereotyped/repetitive motor mannerisms, and preoccupation with parts of objects. There is no age of onset stated as in Autistic Disorder and is generally believed to have an onset (or at least begins to interfere) around school age. These symptoms must also cause significant impairment in areas of functioning with no delays in language development, cognitive development, self-help skills, or adaptive behavior.

In terms of differential diagnosis, it is important to first rule-out any other Pervasive Developmental Disorders. The differentiation between Asperger's Disorder and high-functioning autism can be very difficult. Matson and Wilkins (2008a) provide evidence from numerous studies to help differentiate Asperger's Disorder from high functioning autism. Important markers noted to help in differentiating Asperger's from Autistic Disorder include the age of onset (earlier onset in Autistic Disorder), less severe early symptoms, advanced language comprehension, higher adaptive skills and cognitive functioning, and fewer overall symptoms of autism. Individuals with Asperger's have been found to have a milder developmental course and overall better prognosis (Ozonoff, South, & Miller, 2000). Those with Asperger's also tend to exhibit differences in the type of repetitive/restricted interest/behaviors. They are less likely to exhibit abnormal motor mannerism and more likely to exhibit restricted interests and preoccupations when compared to peers with Autistic Disorder.

Rett's Disorder. Rett's Disorder is a rare genetic disorder that, under the *DSM-IV-TR* (APA, 2000) is considered a Pervasive Developmental Disorder. The disorder is named after Andreas Rett who described 22 females that exhibited repetitive hand-wringing, developmental regression, and other symptoms similar to Autistic Disorder. Rett's discovery went relatively unnoticed until 1983 when Hagberg, Aicardi, Dias, and Ramos described 35 females with similar traits and cited Rett's original work. Rett's Disorder is one of the rarest Pervasive Developmental Disorders but is also cited as one of the common causes of intellectual disability in females (Amir et al., 1999). The disorder generally manifests between 6-18 months of age after a period of general normal development. Rett's Disorder is the only ASD listed under Pervasive Developmental Disorders that has a single known genetic cause. The disorder is an X-linked disorder that causes a mutation of the MECP2 gene which then fails to encode for the MeCP2 binding protein. Although the disorder was originally believed to only occur in females, it was later discovered that it commonly occurs in males (given the X-linked nature of the gene involved); however, most males with the disorder are either profoundly disabled or the mutation is fatal.

Criteria for Rett's Disorder requires that individuals exhibit a period of normal development including normal pre/perinatal development, psychomotor development (prior to 5 months of age), and average head circumference at birth. These children then experience a slowing of head growth (between 5 and 48 months of age), regression in previously acquired hand movements (between 5 and 30 months of age), loss of social engagement, poor gross motor coordination, impaired language, and repetitive/stereotyped hand mannerisms (generally hand-wringing).

The differential diagnosis of Rett's Disorder from other Pervasive Developmental Disorders involves observations of head growth deceleration, loss of purposeful hand movements, and midline hand-wringing behaviors. Rett's Disorder generally has an earlier onset than Asperger's or Childhood Disintegrative Disorder and occurs almost exclusively in females. Poorly coordinated trunk movements and abnormal gait are also common in children with Rett's Disorder.

Childhood Disintegrative Disorder. Childhood Disintegrative Disorder was first recognized by Theodore Heller in 1908. Originally termed "dementia infantilis," the disorder was commonly referred to as Heller's disease and was often compared to infantile autism in the days of Kanner. Childhood Disintegrative Disorder involves a severe and pronounced regression after a period of relatively normal development during the first 3-4 years of life. This regression often leads to profound intellectual disability and has a poor prognosis for recovery (Kurita, 2011; Volkmar, Koenig, & State, 2005). Criteria for the disorder under the *DSM-IV-TR* (APA, 2000) state that the individual must have relatively normal development during the first two years of life with normal verbal and non-verbal communication, social interactions, and adaptive behavior. This is then followed by a significant and marked loss of skills in at least two of the following areas: expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. This loss of skills must occur before the age of 10 years and have abnormal functioning in two of the following areas similar to those with other Pervasive Developmental Disorders: social interaction, communication, or restricted, repetitive, and stereotyped patterns of behavior, interests, or activities.

The differential diagnosis of Childhood Disintegrative Disorder from other Pervasive Developmental Disorders relies heavily on developmental history. Although many children with

Autistic Disorder exhibits regression in skills, the regression in Childhood Disintegrative

Disorder generally happens later in development (e.g., 3-4 years or older) and is a dramatic loss

of previously acquired skills. Differential diagnosis between the two disorders can be difficult

and researchers note that further research is needed to differentiate between the two disorders

(Kurita, 2011). Due to the current criteria, children could meet for either disorder if their

regression occurs between the ages of 2 and 3 years of age. Other factors can help to

differentiate between the two disorders (Hendry, 2000) but is generally diagnosed based on age

of onset and premorbid cognitive abilities. Research in this area, however, is very sparse due to

the low incidence with only about 100 identified cases reported (Klin & Volkmar, 1997). Due to

the inability to differentiate between the two disorders, some have called into question the

validity of the separate disorder (Hendry, 2000) while others still support its clinical value

(Malhotra & Gupta, 2002; Mouridsen, 2003; Volkmar, 1992; Volkmar & Rutter, 1995).

Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). PDD-NOS

is a disorder with unclear lines and boundaries and has been characterized as an extremely

heterogeneous diagnostic category (Tidmarsh & Volkmar, 2003) used to diagnose subthreshold

symptoms or atypical presentations of autism (Mesibov, 1997). Under the *DSM-IV-TR* (APA,

2000) a diagnosis for PDD-NOS is given when there are significant impairments in the core

features related to Autistic Disorder (i.e., social interactions, verbal/nonverbal communication,

and restricted/repetitive behaviors/interests). A diagnosis of PDD-NOS should only be

considered after first ruling out all other Pervasive Developmental Disorders as well as other

disorders that may share common symptoms including Schizophrenia, Schizotypal Personality

Disorder, and Avoidant Personality Disorder.

Many researchers have noted that the criteria for PDD-NOS are too broad and inclusive and have contributed to the rise in overall ASD diagnoses. Minor changes in the wording were included in the text-revision of the *DSM-IV-TR* to make the criteria stricter. Researchers have also recommended changes in the criteria for PDD-NOS to exclude those individuals that do not have impairments in social interactions, which is believed to be the core hallmark of ASD (Volkmar, Shaffer, & First, 2000).

DSM-5

Diagnostic criteria for the current edition of the DSM (*DSM-5*; APA, 2013) are very different from previous versions of the DSM and have moved away from the classification used previously and by the IDC-10. Many of the disorders present in the *DSM-IV-TR* are now removed from the *DSM-5* and included in the broader category of Autism Spectrum Disorder. Autism Spectrum Disorder appears under the heading of Neurodevelopmental Disorders alongside disorders such Intellectual Disabilities, ADHD, Learning Disorders, and Speech/Language Disorders. There is no reference to Pervasive Developmental Disorders and no appearance of previous disorders like Asperger's Disorder or Childhood Disintegrative Disorder. Instead, all of these disorders are categorized by the larger idea of an Autism Spectrum Disorder. Several things have changed in regards to diagnostic criteria, communicating severity of symptoms, and specifiers in this edition of the DSM.

Diagnostic Criteria. The diagnostic criteria in the *DSM-5* (APA, 2013) place a heavier and more exclusive emphasis on deficits in the core areas associated with autism. In order to meet criteria for Autism Spectrum Disorder, individuals must exhibit deficits in two main areas: social communication and restricted/repetitive behaviors/interests.

Within the social communication domain, individuals must exhibit impairments in three areas. First, individuals must exhibit significant impairments in social and emotional reciprocity such as struggles with reciprocal social communication, impairment in showing and sharing of interests or emotions, or failure to engage in other social interactions. Second, individuals must also exhibit impairments in nonverbal social communication such as poor eye contact, impaired use and understanding of gestures, and impaired use of facial expressions or other forms of nonverbal communication. Lastly, individuals must also exhibit deficits in developing and maintaining social relationships.

In addition to the impairments in social communication, individuals must also exhibit impairments in at least two of the following four restricted/repetitive behaviors/interests. The first criteria is stereotyped/repetitive motor movements, use of objects (e.g., lining up toys), or speech (e.g., echolalia). Second is an insistence on sameness or over-adherence to routines and rituals. Third, individuals may exhibit restricted interests such as an excessive preoccupation or a strong attachment to certain objects. Lastly, individual may also exhibit sensory abnormalities such as over- or under-reactivity to different sensory input (e.g., loud noises, certain textures, lights).

In addition to the above criteria, individuals must also exhibit symptoms sometime during the developmental period and they must cause significant impairment in areas of functioning. Other disorders should also be ruled-out (as discussed below) but a specific criterion is that these symptoms are not better accounted for by an intellectual disability. The *DSM-5* does clearly state that the two disorders do commonly co-occur and therefore social communication deficits should be significantly lower than what would be expected for the individuals general developmental level.

Severity Levels. The *DSM-5* also brings new severity levels along with the newly revised autism criteria. When diagnosing an individual with Autism Spectrum Disorder, a severity rating is also provided for each of the two main symptom areas (i.e. social communication and restricted, repetitive behaviors). The severity ratings are on a 3-point scale that describes the level of support needed within each symptom area ranging from Level 1 (requiring support) to Level 3 (requiring very substantial support). For example, a severity rating of Level 3 within the social communication domain characterizes an individual with severe deficits in social communication that would require a very substantial support to function within that domain. This criteria may include a child that is non-verbal or avoids social interactions and requires a lot of support to function in this area.

Specifiers. In addition to the severity levels noted above, the *DSM-5* also uses specifiers to describe impairments that commonly co-occur in individual with Autism. The first two specifiers are used to describe impairments in intellectual or language impairment. As many individual with autism also exhibit significant intellectual disabilities, the first specifier is used to describe whether such impairments are present and the degree to which they are present. This may include an intellectual disability with its severity or may refer to a global developmental delay in younger children. The second specifier is used to describe language impairments that co-occur with autism including receptive, expressive, or pragmatic language impairments. Additional specifiers are used to describe the co-occurrence of other neurodevelopmental, mental, or behavioral disorders or catatonia. A final specifier is used when Autism Spectrum Disorder is diagnosed in association with a known medical or genetic condition. The specifier would be used in cases such as those with Fragile-X syndrome which is a common cause of ASD.

Differential Diagnosis. Due to the changes in the structure of Autism Spectrum

Disorder in the *DSM-5*, considerations for differential diagnoses have changed. Because most of

the Pervasive Developmental Disorders of *DSM-IV-TR* have been subsumed by the Autism

Spectrum Disorder diagnosis, there is no need to provide differential diagnosis between the

differing, yet similar, disorders. Differential diagnosis of Selective Mutism is still an important

point and is not different from that described above. The addition of a new disorder within the

Neurodevelopmental Disorders category does share many symptoms with Autism Spectrum

Disorder. Social (pragmatic) communication disorder involves deficits in the use of social and

nonverbal communication including the use of overly formal language, deficits in adapting

language to different situations, and difficulties with understanding sarcasm, humor, or non-

literal language. It is believed that many children that previously met criteria for Asperger's

syndrome may fit into this category.

Effects of *DSM-5* Criteria

As history has shown, the effects of changing diagnostic criteria, even minor changes,

can have tremendous effects in clinical assessment, treatment, and also for researchers. The new

DSM-5 autism criteria and the conceptualization of this heterogeneous group of individuals will

have many effects in several different areas. Researchers have discussed the negative effects of

these changes on prevalence and incidence rate tracking, research, and treatment interventions.

The negative effects on families of children with current diagnoses, and those who have yet to be

assessed, have also been addressed.   Several of these problems are discussed below.

Numerous studies have already begun to investigate the effects of *DSM-5* changes on the

prevalence of autism. While some believe that *DSM-5* criteria "will lead to negligible changes in

prevalence estimates" (Lord & Gotham, 2014), researchers have already begun to research the

impact that these changes will have on prevalence rates. In a review of such research studies,

Tsai (2014) notes that somewhere between 9% and 54% (median of 30%) of those diagnosed

under *DSM-IV-TR* criteria would no longer qualify for a diagnosis under *DSM-5*. In an attempt

to address this problem, the *DSM-5* included the following statement in the *DSM-5* diagnostic

criteria:

> Note: Individuals with a well-established DSM-IV-TR diagnosis of autistic disorder,
> Asperger's disorder, or pervasive developmental disorder not otherwise specified should
> be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits
> in social communication, but whose symptoms do not otherwise meet criteria for autism
> spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Although this statement was added to relieve the negative impact on those who had

already received the diagnosis, and likely to appease those asking for a change, this does not

appropriately address those individuals who have not been assessed who would meet criteria

under *DSM-IV-TR* but not under *DSM-5*. This "grandfathering" clause only delays the negative

impacts that *DSM-5* criteria will have on individuals and families. For example, researchers

have found that those children who would have met criteria under *DSM-IV*, but not in *DSM-5*,

exhibit similar impairments in expressive communication (Beighley, Matson, Rieske, Konst, &

Tureck, 2014), personal-social development (Rieske, Matson, Beighley, Williams, & Turygin,

2014), as well as common comorbid symptoms (Williams, Matson, Beighley, Rieske, & Adams,

2014) and would benefit from treatments and interventions developed for this population.

However, under the new criteria, unless the child has already been assessed and received a

diagnosis, they will no longer meet criteria for this disorder and will likely be undiagnosed and

therefore likely will not be able to receive appropriate intervention. The development of Social

Communication Disorder, which is new to the *DSM-5*, was thought to capture many of those

who would no longer meet criteria for ASD. Social Communication Disorder appears to include

those who exhibit ASD without restricted or repetitive behaviors; however, this leaves a gap in those who exhibit ASD symptoms with one repetitive/restricted behavior (Volkmar & Reichow, 2014) rather than two symptoms in that category. This gap includes a large subset of individuals who continue to exhibit significant impairments without needed services.

The changes made to these criteria will not only affect those who will no longer meet criteria but will also greatly disrupt prevalence studies that have been completed using the old criteria (Tsai, 2014). Most researchers have cited the exclusionary nature of the revised criteria and estimate that about 30% of children who met criteria under *DSM-IV-TR* would not meet criteria under *DSM-5* (Tasi, 2014). It would then be likely that a large amount of children who will not meet criteria under *DSM-5* will go undiagnosed which will greatly affect prevalence rates in future studies. Volkmar and Reichow (2014) noted that the change in diagnostic criteria combinations was reduced from more than 2,000 possible combinations in *DSM-IV-TR* to 11 possible combinations in *DSM-5*. Additionally, they noted that increasing the requirement for restricted interests and repetitive behaviors from one of four criteria in *DSM-IV-TR* to two of four criteria in *DSM-5* will likely capture more individuals with ID or other cognitive impairments while excluding those with higher cognitive abilities but who still exhibit significant social and communication impairments thought to be the core symptom presentation of autism spectrum disorders and fewer repetitive behaviors. While Lord and Gotham (2014) note that certain criteria were eliminated as they were found to not be specific to autism (e.g., deficits in expressive language development) the increased focus of repetitive and restricted behaviors contradicts this thought as these are commonly found in individual with ID as well. Because the criteria are so different between editions of the *DSM*, comparisons between studies using the two different editions do not make sense, and any conclusions drawn from those comparisons may be

erroneous. Many researchers, therefore, continue to use the *ICD-10* criteria which more closely

mirror those of the *DSM-IV-TR* in their research.

Another challenge that is presented by the changes in the categorization of ASD is the

absence of Asperger's Disorder from the *DSM-5* in spite of research supporting the

differentiation of Asperger's Disorder and high-functioning autism (Ghaziuddin, 2010). Many

researchers have documented the differences between the disorders (see review from Matson &

Wilkins, 2008a), and those demonstrating the symptoms of Asperger's Disorder will likely be

the most affected by the new criteria. Although those with a long standing Asperger's Disorder

will meet criteria for Autistic Disorder given the provisional statement above, in the future, many

individuals with the disorder will go undiagnosed as the new criteria place greater emphasis on

communication impairments which are less common (or less pronounced) in children and adults

with Asperger's Disorder. The negative impacts that these changes have on families and

individuals with the disorder have been researched (Galligan, Feinstein, Sulkes, Bisagno, &

Stein, 2013; Linton, Krcek, Sensui, & Spillers, 2014) and while some researchers view the

change as a potential evolutionary step in the diagnostic conceptualization of autism (Volkmar &

McPartland, 2014), others view this as a major step backwards (Tsai, 2013; Tsai & Ghaziuddin,

2014). The new criteria were developed in hopes of eliminating the problem of the same child

being diagnosed with PDD-NOS, Autism, and Asperger's by different clinicians (Lord &

Gotham, 2014). The DSM-5 sought to move from the multi-categorical model of *DSM-IV-TR* to

a more dimensional model (Lord & Gotham, 2014); however, others feel that this was a move

toward a more monothetic approach as utilized in *DSM-III* (Volkmar & Reichow, 2014).

Ultimately, the changes in *DSM-5* appear to marginalize those with higher IQs who exhibit

significant social and communication impairments and restricted interests but who do not

demonstrate other repetitive behavior. The *DSM-5* criteria have also been shown to be less

sensitive for young toddlers, although this was also cited as one of the main reasons for changing

some of the criteria in *DSM-5* (Volmar & Reichow, 2014).

CHAPTER 4: CAUSES OF AUTISM

Little is currently known regarding the cause of autism and most researchers today posit that there are likely several causes of autism. Most theories regarding autism etiology currently involve a combination of genetic, environmental, and even epigenetic factors. While autism has been found to be largely hereditary in nature, there are no known bio markers (Ecker et al, 2010; Posey, Stigler, Erickson, & McDougle, 2008) to consistently or accurately diagnose autism; although researchers continue to work on this problem and develop methods for discovering biomarkers and using these as a diagnostic tool (Ratajczak, 2011). Evidence from family and twin studies show a strong genetic component to autism but does not account for all of the variance and does not sufficiently predict those at greatest risk for developing the disorder. Other researchers have noted the importance of brain development prenatally and the importance of the gestational period in the development of ASD. Others, note changes in the environment and the increased contact we have with environmental toxins. The purpose of this chapter is to review many of the theorized causes of autism in the peer-reviewed literature and the research support (or lack thereof) for each of these theories. While this chapter is not exhaustive regarding all the theories of autism, many of the more popular theories will be presented.

Genetic

Few researchers will debate the fact that autism is a largely hereditary disorder. Research studies have repeatedly shown that autism has a strong genetic base that may further interact with other environmental or epigenetic factors. Of the genetic studies investigating autism, twin studies reveal the strongest evidence for the role of genetics. Understanding the concordance rates between twins can help us to understand the genetic variables involved in autism etiology. Monozygotic twin share identical genomes whereas dizygotic twins share approximately 50% of

the genome. Since most other factors are held constant during pregnancy (parental age, environmental factors inside the womb, etc.) these studies help to control for extraneous variables. Early studies on concordance rates between mono- and dizygotic twins reported that monozygotic twins had a 91% concordance rate whereas dizygotic twins had a concordance rate of 0% (Steffenburg et al., 1989). While more recent studies have not found such disparate results, the general trend has been mirrored in numerous studies. One paper examined the difference in rates between males and females and found higher concordance rates for males than females (Hallmayer et al., 2011). Male monozygotic twins had estimated concordance rates of 77% for autism whereas female monozygotic twin concordance rates were about 50% , with greater variability.   For dizygotic twins, the concordance rates were similar to each other with reported rates of 31% for males and 36% for females.

The same study investigating the concordance rates between twin pairs with autism found that genetic heritability accounted for about 38% of the variance in autism between mono- and dizygotic twins (Hallmayer et al., 2011). The study also suggests that almost 60% of the variance could be explained by shared environmental factors, specifically pre- and peri-natal factors. Therefore, although evidence shows that autism has a strong genetic component, other environmental factors also contribute a significant proportion of the risk for autism. The greatest environmental risk factors, as shown by evidence below, appear to occur during early developmental pre- and peri-natal periods.

Environmental

While genetics play a large role in the etiology of autism, researchers have shown that our environment plays a large role in the development of autism. Many different theories regarding the cause of autism when it comes to our environment have been posited. Early

theories focused on parental characteristics such as intelligence, success, and lack of emotional closeness with their offspring. More recent theories have focused on the effects of environmental toxins and related risk factors. Research findings have highlighted the importance of the prenatal environment as well as risk factors after birth. Finally, researchers have also begun to investigate the importance of maternal and paternal age at conception as a specific risk factor for autism in offspring. Many of these theories will be discussed below.

Socialization Theories

    Refrigerator Mothers. One of the oldest theories regarding the cause of autism stems from Kanner's early observations of parents (specifically mothers) as being inattentive to the emotional needs of their autistic child and describing many of these parents as "successfully autistic adults" (Kanner 1949, 1954). A few accounts in the early history of autism led to the growing concern for the emotionally cold mothers including a description of such a case by Despert in 1951. Despert described a mother who had a son with infantile autism. The mother was encouraged by doctors and psychiatrists to give up her care of the child due to her inability to provide for his emotional needs. The mother gave her child up to get the care he needed and after a time the mother returned to report that she was pregnant with another child. She was worried that her and her husband would not be able to provide for the needs of the second child and that it would develop infantile autism as well. After the child was born he exhibited normal development for several years but then began to show some similar signs of infantile autism. The parents were instructed to hire help in the home to provide for the emotional needs of the child. The second child never met criteria for infantile autism but Despert attributed this to the effectiveness of the intervention and supported the theory of the "refrigerator mother." This theory continued to be perpetuated by numerous authors (Eveloff, 1960; Kanner, 1958; Kanner

41

& Eisenberg, 1957) and was further popularized by Bruno Bettelheim (1967) who presented and discussed the theory in his book *The Empty Fortress*.

The theory of "refrigerator mothers" was not really challenged until almost 1970 when researchers began to present opposing views to the well-established idea that parental emotional deprivation was the cause of autism (DeMyer, Hingtgen, & Jackson, 1981; McAdoo & DeMyer, 1977; Rutter, 1968; Rutter & Bartak, 1971). Kanner eventually clarified (or recanted) his position by citing his original work in 1943 in which he states that symptoms of autism can be observed in many children shortly after birth but that he could not exclude the parent-child relationship as a potential variable in the further development of the disorder (Kanner, 1971b).

Toxin Theories

Environmental Teratogens. Researchers have begun to investigate many different environmental teratogens and their association with autism. Theories of autism risk due to environmental toxins have included theories of lead and mercury poisoning (Yassa, 2014), automotive exhaust, and even specific types of vegetable oil. Many studies have recently investigated the effects of "persistent organic pollutants" such as polychlorinated biphenyls (PCBs) and their association with autism risk. Cheslack-Postava and colleagues (2013) found that mothers with high levels of PCBs and similar pollutants in blood serums during pregnancy were at an increased risk for having a child with autism. A similar study of post-mortem brain tissue found increased levels of polychlorinated biphenyls in individuals with 15q11-q13 duplications syndrome which is believed to be a specific genetic cause of autism (Mitchell et al., 2012). Similar levels were not found in neurotypical controls or those with other neurodevelopmental disorders including autism without a known genetic etiology. The

researchers suggest that PCB exposure may have been a risk factor for developing the genetic anomaly leading to a specific type of ASD.

Several other environmental toxins have also been implicated in the etiology of autism. For example, mercury has been the center of several theories including vaccination theories. A recent study investigating mercury levels in the blood of newborns and their mothers found no association between mercury levels and autism (Yau et al., 2014). A meta-analytic study was completed that separated ethylmercury exposure (from vaccines containing thimerosal) and environmental mercury exposure (Yoshimasu, Kiyohara, Takemura, & Nakai, 2014). They found that exposure to mercury from vaccinations did not increase the risk for autism (odds ratio = 0.99) but that environmental exposure did (odds ratio = 1.66).

Pesticides. Our modern world involves the broad distribution of fruits, vegetables, and various plant based materials. Due to the large rise in agricultural exports and imports in modernized cultures we have also seen a large rise in the use of pesticides. Another theory of autism involves the dramatic increase in pesticide use and cites that the increase closely parallels the dramatic increase in autism prevalence. Many pesticides have been found to have neurotoxic effects and have been implicated in neurodevelopmental delays (Grandjean, Harari, Barr, & Debes, 2005).

In a study exploring numerous pesticides and their potential association with ASD, researchers examined the use of these pesticides, the proximity of pregnant mothers, and subsequent rates of autism (Roberts et al., 2007). The study examined 465 children with ASD and almost 7,000 controls and researchers were able to determine proximity of residence to large scale pesticide use. The researchers showed that mothers that lived within 500 meters of a field that dispersed organochlorine pesticides were at a significantly higher risk of having a child with

autism than a mother that did not live near these field sites (odd ratio = 6.1; 95% confidence interval, 2.4-15.3). They also found that this risk increased dependent on the poundage of organochlorine used and decreased as a function of distance from these field sites. The effects were strongest for mothers that were exposed during the first 8 weeks of gestation, a period which involves development of the central nervous system in the fetus. In a similar study, Shelton et al. (2014) found that residential proximity to varying pesticides (e.g., organophosphates, pyrethroids, and carbamates) during pregnancy increased risk of the child developing ASD, developmental delays, or both. In fact, they found that proximity to organophosphates any time during gestation was associated with a 60% increased risk for ASD and higher for other exposures during different trimesters.

Opioid Excess Theory. Although not a true environmental toxin theory of autism, the endogenous opiate precursor theory is related to our diet and the consumption of opiate precursors that lead to an opioid excess. This theory was originally proposed by Panksepp (1979) after observing that opiate use tends to mimic symptoms of autism during use (although only briefly). The theory states that the brain opioid system is overactive and causes the social (and related) deficits seen in autism. This theory has led to research investigating opiate antagonists (Gillberg, 1995) and special diets for the treatment of autism. For example, gluten and casein are precursors to opiate production and therefore gluten-free/casein-free (GFCF) diets have been recommended by some professionals to treat symptoms of autism. Although many parents of children on GFCF diets report significant improvements after starting the diet (Pennesi & Klein, 2012), clinical investigations of such diets have shown no significant improvements (Elder et al., 2006).

Prenatal Theories

Prenatal Viral Infections. Human and animal models of autism have implicated prenatal viral infections in the cause of ASD. Although the exact etiological mechanism in autism development due to prenatal infection is not well understood, researchers have found evidence suggesting that abnormal myelination of genes found in animal models of autism may be the mechanism involved (Fatemi et al., 2009). In one study, researchers found no significant association between maternal infection during pregnancy and autism risk; however, when researchers began to investigate the timing and type of infection a pattern began to emerge (Atladottir et al., 2010). They found that mothers with a viral infection during the first trimester had a significantly increased risk for having a child with autism and mothers with a bacterial infection during the second trimester were also at increased risk, although not to the same extent.

Congenital rubella has previously been found to be associated with high rates of autism (Chase, 1971). Several other viral infections have since been linked to autism that can occur during the prenatal or early perinatal period of development. Maternal infections that have been shown to be associated with higher rates of autism include influenza, toxoplasmosis, genital/reproductive infections and other related pathogens (Brown, 2012) as well as congenital cytomegalovirus infections (Sakamoto, Moriuchi, Matsuzaki, Motoyama, & Moriuchi, 2015). In addition to prenatal viral infections, infections after birth and during infancy have also been found to be associated with autism (see below) and theories regarding the etiology of autism involve the inflammatory process in the brain caused by these infections (Onore, Schwartzer, Careaga, Berman, & Ashwood, 2014).

Prenatal Vitamin Deficiency. Vitamin deficiency that has also been implicated in autism with one study citing a lack of iodine in the diet of a pregnant or nursing mother.

Researchers have noted a decrease in the amount of iodine in the diets of many individuals in the United States and internationally (Hollowell et al., 1998; Caldwell, Jones, & Hollowell, 2005). Sullivan (2009) noted that this decrease coincides with the increased incidence of autism and suggests that an iodine deficiency in pregnant and nursing mothers may also be a potential cause of autism. Researchers have long known the negative effects that iodine deficiencies can have on the population ranging from mild IQ loss to severe intellectual disability and cretinism (Delange, 2001). Sullivan posits that a mild deficiency of a pregnant mother could lead to hypothyroxinemia (see maternal thyroid deficiency below) and cause neurodevelopmental problems in the fetus. This has also been linked to the increase in attention-deficit hyperactivity disorder (Vermiglio et al., 2004) which is also considered a neurodevelopmental disorder. There are several other theories regarding vitamin deficiencies which have cited associations with lack of folic acid, B-vitamins, and many others.

Maternal Pharmaceuticals. Many studies have investigated the effects of different drugs taken during pregnancy on the developing fetus. Several of these studies have implicated certain pharmaceuticals in the development of autism or an autism-like syndrome. For example, Thalidomide use during early pregnancy has previously been associated with an increased risk for autism (Miyazaki, Narita, & Narita, 2005; Stromland, Nordin, Miller, Askerstrom, & Gillberg, 1994). Although the drug is no longer used in pregnant women, it was readily available in Germany in the 1950's and was used to treat morning sickness in pregnant women until it was found to cause severe physical deformities and death in developing fetuses.

In addition to Thalidomide, the use of anticonvulsants such as valproic acid or sodium valproate have also been associated with increased risk of autism, especially when used during the early stages of fetal development (Miyazaki et al., 2005; Rasalam et al., 2005). One study

46

suggests that maternal use of anticonvulsant drugs during pregnancy led to an increase in autism that was between 8 and 18 times higher than that of the general population (Rasalam et al., 2005). Evidence for the mechanisms involved in the development of autism symptoms after valproic acid exposure have been investigated in animal models and humans (Kim et al., 2013) and parental valproic acid exposure in rodents has been proposed as a strong animal model of autism for research (Roullet, Lai, & Foster, 2013).

Antidepressant and anxiolytic medication use during pregnancy has also been associated with autism risk and are commonly prescribed medications, even during pregnancy (El Marroun, White, Verhulst, & Tiemeier, 2014). A recent meta-analytic study examined the association between autism and use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy (Man et al., 2015). Their study found that a strong association is present between SSRI use during pregnancy and autism risk. Many studies noted that early use of SSRIs during pregnancy could have negative effects on the developing fetus; additionally, due to the long half-life of many SSRIs, many studies also investigated SSRI use at 3 months prior to conception and suggest that use before pregnancy could still pose a risk for offspring.

Maternal Substance Use. Similar to the theories of maternal pharmaceuticals noted above, several studies have investigated the association between drug and alcohol use during pregnancy and autism. It is well known that alcohol consumption by a pregnant mother could lead to developmental abnormalities in the fetus classified as fetal alcohol syndrome (Jones & Smith, 1973). Developmental effects of alcohol consumption during pregnancy on the fetus include facial abnormalities, growth deficiencies, and intellectual disabilities in addition to a host of other developmental problems. Although research in this area is sparse, some case and small sample reports have suggested an association between fetal alcohol syndrome and autism

spectrum disorder (Nanson, 1992). Autism-related behaviors have been reported in several

studies of alcohol exposure in utero and the two disorders do co-occur (Aronson, Hagberg, &

Gillberg, 1997; Harris, MacKay, & Osborn, 1995). Larger studies, however, have found no

association between alcohol consumption and autism (Eliasen et al., 2010). Other studies have

cited high rates of autism in offspring of mothers who abused cocaine (Davis et al., 1992).

Maternal Thyroid Deficiency. Several studies have investigated the link between

autism and a deficiency or abnormality in the release of thyroid hormones of pregnant and

nursing mothers.   Proper levels of thyroid hormones are an important part of human functioning

and development. The fetus is unable to produce its own thyroid hormones until about 4-5

months of gestation and therefore is dependent on receiving the hormone from its mother

(Morreale de Escobar, Obregon, & Escobar del Rey, 2004). Maternal thyroid hormones cross

the blood-brain barrier to the fetus during gestation and play a crucial role in neurodevelopment

(Bernal, Guadano-Ferraz, & Morte, 2003). Lack of sufficient thyroid hormone, or

hypothyroxinemia, during pregnancy can lead to the fetus developing significant cognitive

impairments or even cretinism in the case of iodine deficiency (Delange, 2001). Researchers

have found that there is a critical window in relation to the effects of thyroid hormones on the

developing brain starting at about 8-9 weeks gestation (Iskaros et al., 2000) through about 32

weeks gestation (Haddow et al., 1999), although the fetus becomes less reliant on maternal

thyroid hormones by this point.

Román (2007) postulated that hypothyroxinemia during key developmental periods of

gestation (about 8-12 weeks), in conjunction with other thyroid disrupting processes, may lead to

neurodevelopmental abnormalities and deficits that can cause autism. He stated that low thyroid

hormones can be caused by an iodine deficiency and eating foods or coming in contact with

48

chemicals with antithyroid effects (e.g., certain foods, PCB's, mercury, cigarette smoke). Many environmental toxin theories of autism (see above) are believed to act through decreasing thyroid function. Although little research has been done in this area, some researchers have found links between thyroid function and autism spectrum disorders. For example, Molloy et al. (2006) found an increased risk of autism in families with a history of autoimmune thyroiditis. In a large nationwide Danish study, researchers examined the effects of maternal thyroid dysfunction in over 30,000 births on the rates of ADHD and ASD in their offspring (Andersen, Laurberg, Wu, & Olsen, 2014). Results of this study lend strong support for this theory of autism. They found that maternal hyperthyroidism increased the risk of ADHD by about 1.2 times (adjusted hazard ratio (HR) 1.23; 95% CI 1.05-1.44) and that maternal hypothyroidism increased risk of ASD by about 1.3 times (adjusted HR 1.34; 95% CI 1.14-1.59) during the study period (1991-2004). This increased risk, however, was not found in mothers with thyroid dysfunction that was treated prior to birth of the child. In another national birth cohort study, Brown et al. (2015) examined over 900 matched birth pairs in Finland to further examine the link between ASD and thyroid dysfunction. They did not find any significant association between maternal thyroid hormone levels at birth and risk of ASD in their sample; however, they did find a significant association between a thyroid autoantibody involved in autoimmune thyroiditis and autism in the offspring. In fact, they noted a nearly 80% increased risk of autism in offspring of mothers that were found to have significant levels of the autoantibody during pregnancy.

Fetal Testosterone Theory. Researchers have known the effects of testosterone in uetero on sexual development and differentiation for a long time. More recently, researchers have also investigated the sex differences in both animals and humans and the effects that differing levels of testosterone can have on other areas of development and functioning.

Knickmeyer and Baron-Cohen (2006) provided a review of research that shows the effects of testosterone on cognitive and social functioning. Females have been found to perform better than males in tasks of theory of mind, language-skills, and reading non-verbal signals in addition to overall social and communication abilities. Researchers have not only found sex differences on these types of tasks but differences based on increased/decreased testosterone in females/males, respectively. Females introduced to high levels of testosterone have been found to show impairments in many of the tasks noted above. Researchers have also found associations between amniotic testosterone levels and autism spectrum symptoms in both males and females. Because of the role of testosterone in sexual development, this theory of autism is closely related to the extreme male brain theory of autism discussed later in this chapter.

In a study investigating the effects of fetal testosterone on social functioning and restricted interests in young children, Knickmeyer, Baron-Cohen, Raggat, and Taylor (2005) collected and measured fetal testosterone during gestation via amniotic fluid samples. Parents then completed rating forms for their child at the age of 4 years to assess for social or communication problems and restricted interests. They found that higher levels of fetal testosterone during gestation were highly correlated with social difficulties (after adjusting for sex differences) and restricted interests in boys. This study supports the testosterone theory of autism in some areas (overall social difficulties, restricted interests) but found no association between testosterone levels and other deficits common in autistic individuals (e.g. pragmatic language use).

Researchers in another study investigated this theory utilizing a different methodology in collecting and measuring testosterone levels and measuring pragmatic language abilities. Whitehouse and colleagues (2010) used collected samples of umbilical cord blood at birth and

measured levels of total testosterone as well as biologically active 'free' testosterone in female newborns. They then measured pragmatic language 10 years later through parent report on a measure of pragmatic language use difficulties. They found that although total testosterone levels were not associated with pragmatic language difficulties, as observed in previous studies (Knickmeyer et al., 2005), higher levels of free testosterone at birth were associated with greater difficulties in pragmatic language use at the age of 10 years in their sample of females. Additional studies have also implicated fetal testosterone in overall autism risk (Auyeung et al., 2009).

Postnatal Neurodevelopment Theories

       Viral Infections. In addition to the maternal infections noted above, several viral infections after birth, during infancy, and beyond have been implicated in autism risk. Many of these theories involve the effects of viral encephalitis which can cause damage to the temporal lobe and other areas of the brain that have been implicated in autism (DeLong, Bean, & Brown, 1981; Gillberg, 1986; Greer, Lyons-Crews, Mauldin, & Brown, 1989). Such viral encephalitis cases that have led to autism have been shown in cases of enterovirus infections (Marques, Brito, Conde, Pinto, & Moreira, 2014), herpes simplex, varicella, and measles (Stigler, Sweeten, Posey, & McDougle, 2009). Some rare cases have even described the development of autism symptoms after viral encephalitis in older children. For example, DeLong, Bean, and Brown (1981) described an 11-year-old girl that developed autism symptoms after suffering from herpes simplex virus encephalitis but resolved overtime. Similarly, Gillberg (1986) described a 14-year-old female that also developed symptoms of autism after encephalitis caused by the herpes simplex virus; however, this child continued to exhibit symptoms even 10 years later.

Amygdala theory. The amygdala and related structures are believed to be involved in drive-related behaviors and emotions. The amygdala begins to develop very early in gestation (about 4-6 weeks) and continues to develop after birth. One of the core impairments in individuals with ASD is deficits in social functioning and understanding the emotions and intentions of others. Through his work with primates, Brothers (1990) posited that social intelligence could be linked with specific parts of the brain and proposed the first neural basis of social intelligence. Researchers have noted that social and cognitive intelligence are indeed two separate functions that are controlled by different parts of the brain. For example, some highly intelligent individuals that excel in areas of mathematics, engineering, and other non-social domains of science have marked deficits in social functioning (Baron-Cohen, Wheelwright, Stone, & Rutherford, 1999). Others struggle with non-social domains of cognitive intelligence and are very social in both typically developing and developmentally delayed individuals (Karmiloff-Smith, Grant, Bellugi, & Baron-Cohen, S., 1995). While several areas of the brain have been theorized to be part of this "social brain," the amygdala theory of autism has been researched independently to assess possible contributions to our knowledge of ASD.

In an fMRI study examining amygdala activation during a theory of mind task, Baron-Cohen and colleagues (2000) had participants determine gender and then emotional states when presented with a picture of someone's eyes. They found that individuals with ASD did not exhibit amygdala activation during these tasks when compared to matched neurotypical controls. Individuals with ASD also performed poorly on these tasks, as expected given deficits in such theory of mind tasks and understanding the emotions of others. Similar studies using other types of neuroimaging have produced support for this theory of autism (Critchley et al., 2000; Ohnishi et al., 2000; Otsuka, Harada, Mori, Hisaoka, & Nishitani, 1999). Several postmortem studies

have also found abnormalities in the amygdala and related brain areas in those with ASD (Sweeten, Posey, Shekhar, & McDougle, 2002). Additionally, studies have also noted ASD-type behaviors and social deficits in those with specific types of brain damage that have affected the amygdala and related structures while still having intact cognitive functioning (Damasio, Tranel, & Damasio, 1990). These studies lend support to the idea that the amygdala plays an important role in our social functioning and that abnormal development or functioning of the amygdala may be an important component of ASD. Further research and knowledge surrounding this theory could open new lines of thinking regarding assessment and diagnosis of ASD (through neuroimaging) and our conceptualization of what causes autism and how it develops. Future research in this area could focus on environmental, genetic, and epigenetic factors that affect amygdala development and function early in the developmental or even prenatal period. Related structures of the brain have also been implicated in ASD (Baron-Cohen & Ring, 1994; Baron-Cohen, Ring, Moriarty, et al., 1994; Sweeten et al., 2002) and researchers have begun to evaluate their role in the etiology of ASD.

      Extreme male brain theory. Another theory of autism is the extreme male brain theory that originally stems from the work of Hans Asperger's but popularized by the work of Simon Baron-Cohen. This theory has close ties to both the fetal testosterone theory and the amygdala and related structures theories of autism. In 1944, when Hans Asperger's wrote about the autistic children that he observed, he stated that "the autistic personality is an extreme variant of male intelligence" and that "in the autistic individual, the male pattern is exaggerated to the extreme" (Asperger & Frith, 1991). Baron-Cohen revived the theory and provided a review of current research in support of this theory (Baron-Cohen, 2002; Baron-Cohen & Hammer, 1997). In the theory, Baron-Coehn (2002) suggests that the male and female brain have specific

strengths in "systemising" and "empathizing," respectively. Evidence to support these generalized brain types include observations that females appear to be better equipped to engage in social, nurturing, and empathetic interactions when compared to males. Further evidence exists in laboratory experiments that show superior performance by females in tasks of pragmatic language use, eye contact, judging and discriminating others emotions, and several other related tasks. Males, on the other hand, have been shown to exhibit superior performance on tasks of attention to detail, mental rotation and map reading, mechanics, mathematics, physics, and engineering.

Through these observations of differences in the general male and female brain, Baron-Cohen (2002) suggests that the autistic individual is just an example of an extreme male brain. He notes that not all females are good "empathisers" and not all males are good "systemisers" but that each is a generalization of the typical male/female brain. He notes that the autistic individual exhibits extremes in many of the tasks above; whereas the differences between the typical male and female individual would be small. For example, the typical male would use less eye contact than the typical female; however, the autistic individual may exhibit extreme deficits in eye contact. Baron-Cohen points out that most individuals with autism would exhibit significant impairments in the tasks related to the female/empathizing brain (e.g., deficits in pragmatic language, eye contact) but are more likely to exhibit significant strengths in male/systemizing tasks (e.g., attention to detail, non-verbal cognitive tasks). Additionally, there is a tendency of family members of autistic individuals to be over-represented in fields such as engineering and related fields that require strong "systemizing" abilities but do not require strong "empathizing" abilities. Baron-Cohen also cites evidence regarding functional differences in the

54

brain (e.g., abnormal amygdala size) and other theories that lend support to this extreme male brain theory of autism (e.g., fetal testosterone theory).

Parental Age at Conception

A more recent theory of autism etiology, and the target of this study, is that advanced parental age at the time of conception may contribute to the risk of a child developing ASD. This theory of autism ties in to many other theories of autism and coincides with social trends and increased prevalence rates of autism across time. For example, the average age of first time mothers has increased by 3.6 years in the United States between the years of 1970 to 2006, with similar increases in all developed nations (Mathews & Hamilton, 2009). With advancements in reproductive technologies, mothers are able to have children at more advanced ages than previously possible; however, the risk of neurodevelopmental disabilities is increased in association with advanced maternal age, use of assisted reproductive technology, and higher incidence of plural births when using these technologies (Hediger, Bell, Druschel, & Buck Louis, 2013).

Researchers have found that advanced maternal age is proportionately related to risk of chromosomal abnormalities in offspring leading to genetic disorders such as Down or Klinefelter syndromes (Hook, Cross, & Schreinemachers, 1983). Although the evidence linking maternal age and autism risk is not as conclusive, researchers have begun to examine such associations as well as the effects of advanced paternal age at conception. For example, McGrath et al. (2014) found that offspring of older fathers were at increased risk for schizophrenia, mental retardation, and autism spectrum disorders. While it is unclear how maternal and paternal ages at conception affect autism risk, several studies and theories have been developed to help improve our knowledge about the complex genetic and environmental interactions at play in autism risk.

55

Parental Age and Down Syndrome

Down syndrome is a developmental disorder that has been shown to have increased risk proportionately related to maternal age. Penrose (1933) was the first to demonstrate the effects of advanced maternal age and risk for Down syndrome (then referred to as mongolism). While Penrose found no effect of paternal age on the risk for Down syndrome, other studies since have noted that the high correlation between maternal and paternal age have masked the effects of paternal age (Mantel & Stark, 1967). Although paternal age appears to have less of an effect and is believed to affect risk differently, studies have shown that advanced paternal age does increase the risk of Down syndrome. For example, Fisch et al. (2003) found that advanced paternal age increased the risk of a Down syndrome offspring only with mothers greater than 35 years of age. Additionally, couples older than 40 years of age were more than 6 times more likely to have a child with Down syndrome than couples under the age of 45.

It is unclear why maternal age has a higher influence on Down syndrome risk than paternal age; however, several theories provide strong explanations for such an effect. In a review of the current evidence regarding advanced parental ages in Down syndrome research, Girirajan (2009) discussed the possible mechanisms involved in the increased risk of older parents, particularly mothers. The majority of Down syndrome cases come from errors during maternal meiotic events. Female germ cells go through a short mitotic proliferation during the prenatal period and then the first stage of meiosis (MI) begins and is only completed after first ovulation (menarche) at the onset of puberty. The second stage of meiosis (MII) begins shortly after but is again not completed until fertilization is complete. Researchers have found that the majority of errors resulting in Down syndrome occur during MI (Girirajan, 2009; Vranekovic et al., 2012) with only about 10% occurring during MII. The process of mitosis and meiosis of

56

germ cells in males is very different. Girirajan (2009) summarized the process of meiosis in

males (MI and MII) as occurring only after puberty and is an ongoing event that follows an

extended period of mitotic proliferation. The key difference that Girirajan points out is the

prolonged period of MI and MII in females for each individual germ cell. The extended period

of MI and MII leads cells to be more likely to be affected by a host of different environmental

factors before completing each stage and is at increased risk as mothers become older.

Although the effects of paternal age are not as clear in the etiology of Down syndrome,

researchers have been able to trace paternal origins of trisomy 21 in a small percentage of cases.

For example, Vranekovic et al. (2012) found that the genetic abnormality of trisomy 21 in Down

syndrome were primarily of maternal origin (93%); however, 5% were of paternal origin with

the remaining 2% from mitotic origins.

Paternal Age and Autism

In a large national birth cohort study completed in Finland, Lampi and colleagues (2013)

found that advanced parental age was associated with an increased risk of having an autistic

child. The study compared more than 4,700 children with ASD to controls without ASD and

found an increased risk for ASD in children of mothers aged 35 years or more. They also found

an increased risk for autism in children born of fathers between the ages of 35-49 years.

Additionally, the study also found evidence for an increased risk of PDD-NOS in children born

to teenage mothers younger than 19 years of age.

In an even larger study completed in California, researchers examined the effects of

parental age on autism risk over a 10-year period (1990-1999) with over 12,000 cases (Shelton,

Tancredi, & Hertz-Picciotto, 2010). In terms of maternal age, they found that mothers under the

age of 25 years had the lowest risk of having a child with autism with the highest risk amongst

mothers greater than 40 years of age regardless of paternal age (adjusted odds ratio 1.51; 95%

confidence interval = 1.35-1.70) when compared to mothers between 25-29 years of age. In

regard to paternal age, however, the effects are not as linear. The effect of advanced paternal age

(greater than 40 years) had the greatest effect amongst mothers less than 30 years of age but had

almost no additional effect on mothers greater than 30 years of age. Other studies yet have

implicated paternal age as a risk factor regardless of maternal age (Gabis, Raz, & Kesner-

Baruch, 2010), and maternal/paternal age at conception appears to have a complex interaction

that cannot be explained by basic genetic or environmental factors (Parner et al., 2012).

In a large meta-analytic study that examined results of 16 epidemiological studies, Sandin

et al. (2012) found that mothers of advanced maternal age (defined as greater than 35 years of

age in this study) were significantly more likely to have a child with autism when compared to

mothers between the ages of 25-29 years of age (adjusted relative risk 1.31; 95% confidence

interval = 1.19-1.45). Additionally, unlike the study completed by Lampi et al. (2013), Sandin

and colleagues (2012) found that risk of autism significantly decreased for mothers under the age

of 20 years when compared to mothers between the ages of 25-29 years (relative risk = 0.76;

95% confidence interval = 0.60 – 0.97).

Other Related Factors

Menarche. The age of puberty in children has decreased dramatically since the 19th and

20th centuries with most researchers noting changes in diet, nutrition, and overall health as main

contributing factors to the decrease (Walvoord, 2010). The age of menarche has been measured

in several different studies with the recent mean age ranging from 12.1 to 12.9 with most studies

reporting an earlier onset of menarche in black females. Whether the age of menarche continues

to decrease is currently debated with some researchers noting a slight increase in age when

examining historical trends (Nichols et al., 2006). Age of menarche is influenced by nutrition beginning from gestation and throughout childhood (Krieger et al., 2015). Early puberty has also been linked with increased risk for breast cancer, diabetes, obesity, and other cardiovascular diseases.

It is unclear how earlier menarche could affect risk for having offspring with developmental disabilities or autism spectrum disorder based on our current understanding. In relation to the theorized causes of genetic mutations such as those seen in Down syndrome as discussed by Girirajan (2009), a decrease in age of menarche would lead to a decrease in the amount of time germ cells spend in the MI phase and an increase in the time in MII phase. This would likely lead to a decrease in cases of Down syndrome due to MI errors and a possible increase in MII errors; however, comparative evidence is not available to make such conclusions. In relation to autism, it does not appear that the general trend in the increase of autism over the last decade is reflected by a continuing decrease in the age of menarche as many researchers have noted either an increase or static trend in age of menarche. Ultimately, the possible relations between these are unclear given our current level of understanding.

Assisted Reproductive Technology. Advances in reproductive technology to overcome problems with infertility have helped countless families bear children which in the past would not have been possible. These technologies have also helped mothers become pregnant at later and later ages than previously possible. Several researchers have noted, however, that with the use of assisted reproductive technologies and the higher incidence of plural births, there is increased risk of a host of neurodevelopmental disabilities (Hediger, Bell, Druschel, & Buck Louis, 2013).

Some researchers have examined the use of assisted reproductive technologies in relation to autism spectrum disorders. For example, Zachor and Itzchak (2011) found that assisted reproductive technology was much more common in children with ASD than in typically developing children in a large Israeli sample. The study suggests that assisted reproductive technologies may be a significant risk factor for autism spectrum disorders. Dolinska (2009), however, posits that the risk for developmental disabilities in parents who use in vitro fertilization are more closely linked with the age and health of the mother (and to some degree the father) than any risks posed by in vitro fertilization itself. Zachor and Itzchak (2011) found that parental ages of those with ASD who were born with or without the use of assisted reproductive technology were not significantly different; however, these results do not support or reject the effects of these technologies in ASD risk.

Oral Contraceptives. Some researchers have suggested that the rise in oral contraceptive use may be related to the increased incidence of autism spectrum disorders (Strifert, 2014). Strifert posits that hormones in oral contraceptives may have effects that increase the risk for autism spectrum disorders. He also suggests that the increases in oral contraceptive use have mirrored increases in autism incidence.

The use of contraceptives, the increase in assisted reproductive technologies, the increase in age at first pregnancy, and the decrease in age at menarche may all play a role in the increased incidence in autism. In line with the description of maternal meiotic events and the increased risk for environmental insults, the result of these factors may lengthen that period and further increase risk from environmental factors.

Overall, research trends support the theory of increasing parental age at conception as a risk factor for having a child with autism; however, the biological, environmental, and epigenetic

factors at play are not well understood. It is known that the average age of a mother's first

pregnancy has increased in recent decades, and parental age appears to be, at the very least, a

contributing factor to the rising prevalence of autism. For example, Shelton et al. (2010)

estimated that this trend in older first time mothers can account for approximately a 4.6%

increase in the autism incidence in California over the period from 1990-1999. The mechanisms

involved in the etiology of autism associated with parental age at conception are not well

understood, and evidence suggests that different mechanisms are at play in older fathers than in

older mothers (Lee & McGrath, 2015). In fathers, it appears that there is an increased risk for de

novo insertions and deletions as age increases that are related to autism risk (Dong et al., 2014);

however, further research in this area is needed to understand the mechanisms involved.

Environmental and epigenetic factors are an ever growing focus in autism research and

are believed to be closely tied to parental age and overall nutrition and health. One point of

focus within this area of research is the role that the difference in methylation of neurons plays in

the genesis of autism spectrum disorders. In a recent study at Johns Hopkins, Ladd-Acosta and

colleagues (2014) found four specific brain regions of individuals with autism that were

differentially methylated when compared to neurotypical brains postmortem. These results were

then replicated in three of the four same brain regions in another postmortem sample. Results

suggest differences in methylation between ASD and neurotypical brains; however, the cause of

those differences is yet to be determined. For example, the differences may provide clues as to

the neurogenesis of autism spectrum disorders; however, it is also likely that the differences are

caused by the progress of the disorder itself. More recently, researchers have noted methylation

differences in certain genes taken from placental samples in children with ASD (Behnia et al.,

2015) which limit the effects that could have been caused by the course of autism, as the methylation differences were present at birth.

CHAPTER 5: COMORBID CONDITIONS

Researchers continue to study and investigate the causes of autism and develop treatments and interventions. While many researchers and clinicians focus on the core features of autism, others have realized that there are several other problems that are common in children and adults with autism. Researchers have not only focused on those factors above but have begun to recognize that other comorbid conditions are also very common within the autism spectrum. In fact, several genetic, medical, and psychological disorders have been found to occur at higher rates in individuals with ASD than in the typically developing population. The views and conceptualization of this co-occurrence has changed overtime as many of these disorders were not though to occur in children/adults with ASD. The presence of these disorders in those with ASD poses additional challenges related to assessment and diagnostic practices as well as treatment and intervention options. Many of the common comorbid conditions that co-occur with autism will be discussed and the implications involved.

Comorbid Genetic Conditions

There are many genetic conditions that co-occur in children and adults with ASD. Researchers have shown that autism has a strong genetic component but there still is no clear etiological evidence to pinpoint any single cause. Researchers have investigated the rates of genetic syndromes within those with autism and several disorders have a disproportionately high prevalence rate amongst those with autism when compared to the rest of the population. Some of the more common genetic conditions and their linkage to autism are discussed.

Fragile X Syndrome

Fragile X is an inherited genetic disorder that affects males more often and to a higher degree than females, given its X-linked nature. The prominent physical characteristics of Fragile

X include an elongated face and large or protruding ears; these characteristics vary depending on gender and the severity of the mutation. It is considered to be one of the leading causes of intellectual disabilities in males and one of the known genetic causes of autism. The prevalence of autism in those with Fragile X is high; however, the rates have ranged widely from 25-33% (Bailey et al., 1998; Rogers, Wehner, & Hagerman, 2001) to upwards of 60% (Lozano, Hare, & Hagerman, 2015). Although Fragile X is a known genetic cause for autism, it only accounts for about 2% of autism cases (Kielinen, Rantala, Timonen, Linna, & Moilanen, 2004). Although the exact linkage between autism and Fragile X is still unknown, researchers continue to investigate possible associations and genetic etiologies (Zafeiriou, Ververi, & Vargiami, 2007).

Tuberous Sclerosis

Tuberous sclerosis is a genetic disorder that affects many different parts of the body including the skin, heart, kidneys, and the brain. It involves the growth of benign tumors (tubers) with effects than can vary widely, ranging from benign skin lesions to vision impairments, seizures, and intellectual disabilities (Islam & Roach, 2015). In fact, it is estimated that approximately 90% suffer from seizures and about 60% from varying levels of intellectual disability (Winterkorn, Pulsifer, & Thiele, 2007). Children with tuberous sclerosis have increased rates of ASD (Gillberg, Gillberg, & Ahslen, 1994). The rates of autism within those with tuberous sclerosis have varied widely, ranging from 16% to upwards of 86% (Harrison & Bolton, 1997; Zafeiriou, Ververi, & Vargiami, 2007). Even with the lowest estimated rate, autism is present in a large subset of those with tuberous sclerosis. In those with autism, the rates of tuberous sclerosis are much lower with estimates ranging from 0-4%; however, researchers suggest that autistic individuals with co-occurring seizures are much more likely to have tuberous sclerosis with rates ranging from 8-14% (Smalley, 1998; Wong, 2006). Several

64

theories have investigated the etiological associations with autism including specific mutations

of known tuberous sclerosis complex genes, specifically *TSC2* gene mutations (Lewis, Thomas,

Murphy, & Sampson, 2004), as well as developmental effects of tubers in the brain related to

social, cognitive, and language development with evidence suggesting a strong relationship

between autism risk and tubers primarily in the temporal lobe (Bolton & Griffiths, 1997).

Down Syndrome

Down syndrome is a chromosomal syndrome that is caused by an extra copy of the 21st

chromosome (trisomy 21) and is a disorder which typically involves distinct facial characteristics

and delays in physical and cognitive development. Down syndrome is one of the most common

causes of intellectual disability with average intellectual functioning in the mild to moderate

range of intellectual disability (Caban-Holt, Head, & Schmitt, 2015). While it was long believed

that an individual with Down syndrome could not have autism, recent research suggests that

approximately 10% of individuals with Down syndrome also have an ASD (Zafeiriou, Ververi,

& Vargiami, 2007). The etiological associations between autism and Down syndrome are not

well understood but researchers have found that early seizure activity (infantile spasms) appears

to be a major risk factor for autism in those with Down syndrome (Eisermann et al., 2003)

amongst other theories (see Zafeiriou, Ververi, & Vargiami, 2007).

Other Genetic Disorders

There are many genetic disorders which researchers are investigating in relation to autism

and may produce clues in regards to the etiological basis of ASD. Autism appears at much

higher rates in many of these genetic disorders and therefore are also more common in children

with autism. Researchers have investigated the association of autism with defects in

chromosome 15 (e.g., Angelmann, Prader-Willi, 15q duplications/deletions) and chromosome 17

(e.g., neurofibromatosis) amongst other genetic disorders such as untreated PKU, Di George syndrome (22q11 deletion), and Sotos syndrome (Zafeiriou, Ververi, & Vargiami, 2007). Research of autism within these disorders may help to rule out other hypothesized causes of autism or identify risk factors that may lead to a better etiological understanding of ASD.

Comorbid Medical Conditions

Children and adults with autism have been found to have higher rates of certain medical conditions than typically developing populations. The causes of such medical conditions are not well understood and could be related to many of the genetic disorders discussed above. Researchers have begun to investigate the rates of certain medical comorbidities and the causes for the higher prevalence in this population. Several of the more common comorbid medical conditions will be discussed.

Asthma and Allergies

Although the research is limited, some researchers have examined the rates of asthma amongst individuals with ASD. In a recent report from the California CHARGE study (CHildhood Autism Risks from Genetics and the Environment study), Lyall, Van de Water, Ashwood, and Hertz-Picciotto (2015) found that the prevalence of asthma and overall allergies in children with autism was not significantly different from typically developing children. However, they noted that children with more pronounced stereotypies were more likely to have allergies and food allergies, specifically, were endorsed more often in children with ASD than in typically developing children. Although Lyall and colleagues did not find higher rates of asthma in autistic children other researchers have reported significant findings. For example, in a large national survey, Kotey, Ertel, and Whitcomb (2014) found that asthma was 35% more common in autistic children than in typically developing children. In another large study, researcher

found that children with autism were more susceptible to allergies and autoimmune diseases but less likely to be diagnosed with asthma (Zerbo et al., 2015). While some research suggests higher rates overall, further research in this area is needed to confirm the preliminary results.

Gastrointestinal Problems

Many researchers have noted the higher rate of gastrointestinal problems in children and adults with autism spectrum disorder. Several theories, in fact, suggest that these gastrointestinal problems may play an etiological role in autism (see chapter 4). The rates of gastrointestinal problems have varied widely, ranging from 9% to 91% of the autistic population (Mannion & Leader, 2013b). However, most researchers agree that gastrointestinal problems occur at much higher rates in children with autism than in typically developing peers. In one study, researchers examined gastrointestinal symptoms in children with autism compared to their typically developing siblings and found that children with ASD had gastrointestinal problems at a rate almost four times higher than their siblings (Wang, Trancredit, & Thomas, 2011). In another study, Mannion and Leader (2013a) found that 79.3% of children with autism in their sample exhibited significant gastrointestinal problems including abdominal pains, constipation, diarrhea, nausea, and bloating. They also reported that gastrointestinal problems co-occurred at a high rate (67.8%) with sleep problems and was more common in those without comorbid intellectual disability. While research has shown a high concordance between autism and gastrointestinal problems, research is lacking regarding the causes of these problems and why they are so much higher in the ASD population in comparison to the typically developing population.

Epilepsy

The presence of epilepsy is common in children and adults with ASD; however, rates reported by research studies have also varied widely and little is known regarding the cause of

such problems. The rate of epilepsy in individuals with autism has ranged from 2.4% to 46% with large population studies estimating between 6.6% to 22.5% (El Achkar & Spence, 2015). In addition to the risk already posed by having autism, several other factors can also increase risk for epilepsy including intellectual disability and being female (El Achkar & Spence, 2015). Conversely, children with ASD and epilepsy are more likely to have intellectual deficits and to exhibit more severe symptoms of autism and challenging/maladaptive behaviors (Viscidi et al., 2014).

Comorbid Psychopathology

Several psychological disorders have been found to commonly co-occur in children and adults with ASD. In fact, many of these disorders have been found to occur at higher rates in individuals with ASD than in typically developing children (Williams, Matson, Beighley, Rieske, & Adams, 2014). Many of these problems are considered to be attributable to core autism symptoms (feeding problems, sleep problems, challenging behaviors); however, several distinct disorders that commonly co-occur in this population are discussed.

Anxiety

Anxiety disorders have found to occur at much higher rates in individual with autism than in typically developing children and adults and many consider anxiety to be another common feature of ASD (Bellini, 2004). Some studies have reported rates of anxiety as high as 84%, though most studies estimate between 40-50% of individual with autism also exhibit significant anxiety (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Gjevik, Eldevik, Fjaeran-Granum, & Sponheim, 2011; Morgan, Roy, & Chance, 2003; Simonoff et al., 2008; White, Oswald, Ollendick, & Scahill, 2009). Although some have suggested that intellectual functioning may mediate this relationship, current research suggests that high rates of comorbid

anxiety is present regardless of intellectual functioning (Mayes, Calhoun, Murray, Ahuja, &

Smith, 2011). However, other studies have noted that verbal IQ (along with autsim seveirty and

age) is a strong predicotr of anxiety symptoms (Mayes, Calhoun, Murray, & Zahid, 2011;

Sukhodolsky et al., 2008). Although many children with autism meet criteria for an anxiety

disorder and exhibit a significant level of anxiety symptoms (White et al., 2009), many

researchers believe that anxiety symptoms exhibited in these children are part of the ASD

symptomatology and not a separate anxiety disorder (Caron & Rutter, 1991; White, Bray, &

Ollendick, 2012; White et al., 2009).

Due to overlapping symptomatology, differentiating between anxiety and ASD symptoms

can be hard in many cases. For example, Social Anxiety Disorder is very common in typically

developing individuals and has symptoms with overlapping impairments commonly found in

those with ASD. Both involve deficits in socialization and social communication and

distinguishing between the two can be difficult in young children. Although not necessarily

considered an anxiety disorder, Obsessive-Compulsive Disorder also has several overlapping

symptoms in regards to repetitive behaviors and can also be hard to differentiate at times (Lewin,

Wood, Gunderson, Murphy, & Storch, 2011; Wood & Gadow, 2010).

Several researchers have cited the higher rate of anxiety disorders in families of children

with ASD and research which shows that core symptoms of ASD are highly correlated with high

anxiety levels and more social maladjustment (Chang, Quan, & Wood, 2012; Wood & Gadow,

2010). Additionally, anxiety symptoms have been shown to increase in relation to the severity of

ASD symptoms (Kanne, Abbacchi, & Constantino, 2009; Sukhodolsky et al., 2008); although

not all studies have reported this association (Simonoff et al., 2008). A recent study by

Williams, Leader, Mannion & Chen (2015) suggests that anxiety symptoms in children with

autism are positively correlated with increased gastrointestinal problems and sleep problems as well.

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a disorder that commonly co-occurs in children with autism. Under the *DSM-IV-TR*, the presence of ASD and ADHD could not co-occur. This has changed under the recent *DSM-5*; however, the exclusionary criteria of *DSM-IV-TR* have stunted research in this area of comorbidity. Regardless, several researchers have recognized the overlap between the two disorders and research studies examining the prevalence of the co-occurrence have been completed. Prevalence estimates of ADHD have ranged from 20% to 70% with most researchers agreeing that about half of all children with ASD also meet criteria for ADHD (Matson, Rieske, & Williams, 2013). As with anxiety, the symptoms of ASD and ADHD commonly overlap and can be difficult to differentiate; however, Mayes, Calhoun, Mayes, & Molitoris (2012) demonstrated that the two disorders have several discriminating symptoms as well. Their study found that although ADHD symptoms are common in a large majority of individuals with autism, the reverse is not true and that ADHD symptoms and ASD symptoms can be delineated in both populations.

Depression

Although depression may be harder to assess in children and adolescents with ASD due to social communication deficits, depression has been found to occur at high rates in individuals with autism. Matson and Williams (2014) provided a review of current evidence regarding these comorbid conditions and many studies suggest that depression is present in approximately 50% of individuals with ASD. In a study of suicidal behavior, researchers also found high rates of suicidal ideation (14%) that was many times higher than typically developing peers (Mayes,

Gorman, Hillwig-Garcia, & Syed, 2013). Symptoms of depression are apparent across the

spectrum of ASD and are of special concern to those that work with adolescents with high-

functioning autism who exhibit greater depressive and anxiety symptoms than typically

developing peers (Hammond & Hoffman, 2014).

CHAPTER 6: STUDY

Purpose

Many researchers have cited the continuing increase in the prevalence of autism worldwide and have speculated on the potential causes of that increase. One researched theory that suggests at least a contributory effect is the general trend for parents to have children at later ages. Previous research has begun to examine the relationship between advanced parental age at conception and the incidence of autism. Most have found support for this theory of autism and continue to examine the additional risk factors that might be at play. The purpose of this research study is to not only confirm the relationship between advanced parental age and autism risk but to also examine the relationship of parental age with the severity of autism symptoms. Only one study to date has examined this relationship and found no evidence for an association between advanced parental age and autism severity (Itzchak, Lahat, & Zachor, 2011) but was limited in its age distributions of mothers and fathers. Additionally, the methodology of measuring autism severity was unclear.

Other studies of the effects of parental age on ASD have viewed ASD as a dichotomous or categorical variable without reference to severity of symptoms. Individuals with ASD make up a very heterogeneous group of individuals with varying levels of impairment. These impairments are not only along a single continuum, but rather occur across multiple domains of impairment including social, communication, cognitive, adaptive, and other areas of functioning. In addition to autism severity, this study also aimed to measure severity of comorbid symptoms and their association with parental age. This study sought to elucidate these relationships related to advanced parental age and the severity of autism symptomatology and comorbid psychopathology.

Method

Participants

The participants for this study were taken from a pre-existing database which included 756 children ranging from 2 to 17 years of age who were recruited through a university outpatient child clinic. Participants in the clinic were referred for a variety of presenting problems including developmental delays, Autism Spectrum Disorder, ADHD, anxiety, learning problems, and/or challenging behaviors. Participants and their families completed several assessments as part of a larger battery including demographic information, family and developmental history, diagnostic interviews, and parent/teacher rating forms. The current study utilized participants with completed data from the *Autism Spectrum Disorders- Assessment Battery for Children* (Matson & Gonzalez, 2007) including the demographic information and parental ratings on the *ASD-DC* and *ASD-CC*. Of the 756 children in the database, 254 had valid parent data available from at least one parent. Two additional participants were excluded due to missing data on the ASD-DC. The final sample included 252 participants and demographics are presented in Table 1.

Table 1
Participant Demographics

	(n = 252)
Age in years	
Range	2-17
Mean	8.49
SD	3.61
Gender	
Male	65.2%
Female	34.8%
Race	
Caucasian	81.4%
African-American	11.1%
Hispanic	3.6%
Other/Unspecified	4.0%

Note: SD = Standard Deviation.

Measures

Autism Spectrum Disorder-Diagnostic for Children (*ASD-DC*; Matson & González, 2007a). The *ASD-DC* is one part of a larger, comprehensive battery designed to assess for ASDs, screen for comorbid psychopathology, and identify challenging behaviors in children ages 2 through 18 years (Matson & González, 2007a). The measure contains items related to each of the three core symptom domains that individuals with ASDs are often characterized by: socialization impairments, communication deficits, and marked presence of restricted/repetitive behaviors and/or interests. It is completed by parents/caregivers, and each of the 40 items is rated as "0" (not different; no impairment), "1" (somewhat different; mild impairment), or "2" (very different; severe impairment). When rating each item, informants are asked to compare their child to same-aged typically developing peers.

The *ASD-DC* has been shown to be a reliable and valid measure for diagnosing ASDs. Internal consistency of the measure is excellent ($\alpha = .99$), and it has good test-retest reliability ($\kappa_\omega = .77$) and inter-rater reliability ($\kappa_\omega = .67$; Matson, González, Wilkins, & Rivet, 2007). The convergent validity of the *ASD-DC* has been established by comparing the measure to other already validated ASD diagnostic tools, including the *Childhood Autism Rating Scale* (Schopler, Reichler, DeVellis, & Daly, 1980) and the *Autism Diagnostic Interview-Revised* (Lord & Rutter, 1994) (Matson, Mahan, Hess, Fodstad, & Neal, 2010). A total score can be calculated and used to assist in the ASD diagnostic process. A total score cutoff of 33 suggests significant autism-related symptoms. With this cutoff, the *ASD-DC* has a sensitivity of 84.3%, specificity of 98.2%, and overall correct classification rate of 91.3% (Matson, González, & Wilkins, 2009).

Autism Spectrum Disorders- Comorbidity for Children (ASD-CC). The *ASD-CC* (Matson & Gonzales, 2007b) is a 39-item, informant-based rating scale designed to assess

children 2-16 years of age for symptoms of psychopathology which have been found to commonly co-occur with ASD. Commonly co-occurring psychopathology include depression, conduct disorder, attention-deficit/hyperactivity disorder, tic disorder, obsessive-compulsive disorder, phobias, and eating disorders (Matson & Gonzales, 2007b). Using a 3-point Likert type scale, items are rated according to severity of 0 (not a problem or impairment), 1 (mild problem or impairment) or 2 (severe problem or impairment). The *ASD-CC* has been found to have acceptable psychometric properties with moderately good test–retest reliability ($\kappa = .51$) and inter-rater reliability ($\kappa = .46$), as well as good internal consistency ($\alpha = .91$; Matson & Wilkins, 2008b). Additionally, convergent validity has been established with the clinical subscales of the *BASC-2 (*Matson, LoVullo, Rivet, & Boisjoli, 2009). Subscales of the *ASD-CC* include tantrum, repetitive, avoidant, conduct, over-eating, under-eating, and worry/depressed behaviors. Higher scores within each domain represent greater severity of symptoms. A total score can also be calculated which represents overall problems related to comorbid psychopathology.

Procedure

Prior to assessment administration, this study was approved by the university's Institutional Review Board. Parents who agreed to their child's participation gave informed consent, and efforts were made to also obtain child assent when possible. All participants received a comprehensive battery of assessments and packets containing the *ASD-DC* and *ASD-CC*, among other measures, and were either administered by trained graduate students in the outpatient clinic or were completed independently by the parents with a trained administrator available to answer any further questions. Although only portions of the *ASD-DC* and *ASD-CC* were used during this study, all measures were administered in their entirety with other assessments that are a part of the comprehensive battery. Participants were excluded if they were

outside the given age range, missing key demographic information, or were missing more than

two items on the described scales (i.e., two participants were excluded due to incomplete *ASD-*

DC). Regression imputation and expectation-maximizations techniques have been recommended

when missing more than 5% of data points; however, due to the low number of participants

missing items (i.e., less than 1%), listwise deletion is considered an acceptable technique that

will have little effect on analyses (Rubin, Witkiewitz, St. Andre, & Reilly, 2007).

Statistical Analyses

Prior to computing statistical analyses, the demographic and assessment data was

reviewed in order to ensure that item values were present and valid (i.e., within the constraints of

the measure's scoring criteria). Participants missing more than two data points for any given

measure were excluded from that individual analysis. Descriptive statistics were conducted in

order to determine the means of all included variables including scores on the *ASD-DC* and *ASD-*

CC (see Table 2 below). Demographics were also calculated for the total sample including the

child's age, gender, ethnicity (see Table 1 above). Estimated parental ages at conception were

also determined by adjusting parental age at assessment by child's age at assessment (as

calculated by date of birth) plus 9 months (i.e., Parental Age – Childs Age – 9 months = Parental

Age at Conception). Although this is not an exact measurement of parental age at conception, it

is considered to be a good estimate given the age range in the given sample (see Table 3 below).

Additionally, this estimate is similar to age at birth estimates used in other studies of parental

age.

All analyses were conducted using SPSS 22.0. An a-priori power analysis was

completed to determine the desired sample size for this study using G*Power (Faul, Erdfelder,

Lang, & Buchner, 2007). Given a desired power level of 0.80, an anticipated effect size of at

least 0.10 (f^2), and error probability set at $\alpha=0.015$ (to adjust for family-wise error due to multiple tests), the minimum sample size required for this study to complete the multiple regression was at least 149 participants.

Table 2
Sample Means

	N	Mean	SD	Minimum	Maximum
ASD-DC Total	252	27.32	25.55	0.00	77.00
ASD-CC Total	246	17.00	14.92	0.00	71.00

Table 3
Parental Age at Conception

	N	Mean	SD	Minimum	Maximum
Maternal Age (years)	248	27.71	5.67	14	49
Paternal Age (years)	203	31.06	7.31	15	59

Preliminary Statistics

Preliminary statistics were completed to assess for significant covariates within the sample. Child's age, gender, and ethnicity were assessed to see if these variables were significantly correlated with predictor (maternal and paternal age at conception) or outcome (ASD severity and comorbid symptom severity) variables. Variables found to significantly correlate with predictor or outcome variables were included as covariates in the following statistical analyses. Pearson's correlations were used to assess the child's age with parental age, ASD severity ratings, and comorbid symptom severity ratings. Spearman's correlations were then used to assess gender and ethnicity in regards to the same variables.

The remaining statistical analyses are described in three parts. Part 1 included statistical analyses to confirm previous findings regarding parental age and increased rates of autism spectrum disorder in offspring. Part 2 focused on parental age at conception as a predictor of autism severity. Part 3 investigated the relationship between parental age at conception and comorbid psychopathology.

Part 1

Statistical analyses were first completed to confirm previous research regarding parental age at conception as a predictor of an autism diagnosis in offspring. Maternal and paternal ages at conception were used as predictors and the presence or absence of an ASD diagnosis served as the outcome variable. The presence of ASD diagnosis was based on all available testing data including the *ASD Child Battery* and other available data from the diagnostic assessment and made by a licensed clinical psychologist using *DSM-IV-TR* criteria for an ASD diagnosis. Binomial logistic regressions were utilized to examine significant predictors in the models. Significant covariates, as identified in preliminary statistics, were also included in the analyses to account for any variability provided by these variables.

Part 2

Statistical analyses were then completed to examine the value of parental age at conception in predicting autism severity and were the main focus of this study. This part of the study focused on autism severity as a continuous variable as measured by the *ASD-DC*. The total severity score from the *ASD-DC* for each child was used as the outcome variable in a hierarchical multiple regression which included maternal and paternal age at conception as predictors. This analysis also included identified covariates to control for the effects of these

variables as the first step in the hierarchical multiple regression. The regressions were completed

based on the assumptions and steps as outlined by Field (2009).

Part 3

Lastly, statistical analyses were completed to examine parental age at conception as a

separate predictor of comorbid psychopathology symptoms in children with ASD. Parental age

at conception continued to be used as the predictor in a hierarchical multiple regression with the

total score from the ASD-CC, as a measure of overall comorbid psychopathology severity,

serving as the outcome variable. As with other analyses, identified covariates were included to

control for their effects. The regressions were completed based on the assumptions and steps as

outlined by Field (2009).

<div align="center">Results</div>

Preliminary analyses testing the relationship between child's age, gender, and ethnicity

with predictor variables (maternal and paternal age at conception) and outcome variables (ASD

severity and comorbid symptom severity) were completed to assess for significant covariates to

be used in subsequent analyses. Pearson's correlations between child's ages were calculated

against predictor and outcome variables. Results of Pearson's correlations revealed significant

correlations between child's age and paternal age at conception ($r = -.149$, $p = .034$) as well as

child's age and *ASD-CC* total score ($r = .132$, $p = .039$).

Spearman's correlations were then completed to assess gender and ethnicity with other

predictor and outcome variables. Child's gender was found to significantly correlate with *ASD-

DC* total scores ($r_s = .165$, $p = .009$) and *ASD-CC* total scores ($r_s = .170$, $p = .007$). Child's

ethnicity was not found to be significantly correlated with any of the included variables.

Because of the results of these preliminary statistics, child's age and gender were used as covariates in subsequent analyses.

A binomial logistic regression was then completed based on the assumptions and steps as outlined by Field (2009). The presence of ASD was based on the diagnosis given by the licensed clinical psychologist from the full developmental assessment and participants were categorized as "ASD" or "No ASD." The logistic regressions included child's age and gender as covariates in the model. The full logistic regression model based on the diagnostic category (ASD/ No ASD) was statistically significant, $\chi2(4) = 23.865$, $p < .001$. The model explained 15.5% (Nagelkerke R^2) of the variance and correctly classified 62.8% of cases. Of the four predictor variables, two were found to be statistically significant: child's gender and father's age at conception. Child's gender was found to be a significant predictor and males had 2.4 times higher odds of exhibiting an autism spectrum disorder than females in this sample. Paternal age was also found to be a significant predictor in the model; however, maternal age was not (see Table 4).

Table 4
Logistic Regression Predicting Diagnosis of ASD

(n=199)	B	SE	Wald	p	Odds Ratio	95% CI
Age	-0.03	0.04	0.38	.539	0.97	0.89-1.06
Gender	1.43	0.36	15.73	.000	4.17	2.06-8.44
Mother's Age	-0.06	0.04	2.17	.141	0.95	0.88-1.02
Father's Age	0.06	0.03	4.20	.040	1.06	1.00-1.12
Constant	-1.58	1.02	2.41	.121	0.21	

Note: Gender is for males compared to females

A hierarchical multiple regression was then conducted to examine the predictive value of parental ages at conception in regard to autism severity as measured by the *ASD-DC* total score. The child's age and gender were entered into the first step of the regression model to control for these covariates in the analyses. Maternal and paternal ages were entered into step two of the regression. The final model accounted for a significant proportion of the variance in autism severity scores (*ASD-DC* total score) [R^2 = .053, $F(4, 197)$ = 2.722, p = .031]; however, the final model was not significantly different from the previous model which included just child's age and gender [ΔR^2 = .022, $\Delta F(2, 193)$ = 2.22, p = .111]. Further investigation of individual variables shows that maternal age was not a significant predictor of autism severity, however, paternal age was found to be a significant predictor, even after controlling for the child's age and gender (see Table 5).

Table 5
Hierarchical Regression Analysis of ASD-DC Total Score

(n = 199)	ΔR^2	Cohen's f^2	b	$SE\ b$	β
Step 1					
Constant			32.94	4.84	
Age			-0.29	0.51	-0.04
Gender			-9.22	3.77	-0.17*
Step 2	0.022	0.02			
Constant			23.08	10.95	
Age			-0.18	0.52	-0.02
Gender			-8.55	3.76	-0.16*
Maternal Age			-0.44	0.41	-0.10
Paternal Age			0.67	0.32	0.19*

Note. R^2 =.032 for Step 1. *p<.05

Finally, a hierarchical multiple regression was then conducted to examine the predictive value of parental ages at conception in regards to autism comorbid severity as measured by the *ASD-CC* total score. The child's age and gender were entered into the first step of the regression model to control for these covariates in the analyses. Maternal and paternal ages were entered into step two of the regression. The final model accounted for a significant proportion of the

variance in autism comorbid severity scores (*ASD-CC* total score) [$R^2 = .052$, F (4, 192) = 2.655,

$p = .034$]; however, the final model was not significantly different from the previous model

which assessed covariates of child's age and gender [$\Delta R^2 = .014$, ΔF (2, 192) = 1.45, $p = .237$].

Further investigation of individual variables shows that neither maternal age nor paternal age

were found to be a significant predictor after controlling for the child's age and gender (see

Table 6).

Table 6
Hierarchical Regression Analysis of ASD-CC Total Score

(n = 199)	ΔR^2	Cohen's f^2	b	$SE\ b$	β
Step 1					
Constant			14.61	2.81	
Age			0.48	0.30	0.11
Gender			-5.02	2.19	-0.16*
Step 2	0.014	0.01			
Constant			17.36	6.38	
Age			0.48	0.30	0.11
Gender			-4.77	2.19	-0.15*
Maternal Age			-0.40	0.24	-0.15
Paternal Age			0.26	0.19	0.13

Note. $R^2 = .038$ for Step 1. *$p<.05$,

Discussion

Several hypotheses were formed prior to completing the current study based on previous

research findings in the area of autism and parental age. Previous research has shown a strong

association between advanced parental age at conception and risk for autism in their offspring

(Hook, Cross, & Schreinemachers, 1983; Lampi et al., 2013, McGrath et al., 2014; Shelton,

Tancredi, & Hertz-Picciotto, 2010). Few studies have investigated how parental age contributes

to the overall severity of autism symptoms, given that ASD is such a heterogeneous disorder.

Preliminary statistic of our sample showed that the child's age and gender were significantly

correlated with several predictor and outcome variables. For examples, child's age was

significantly correlated with paternal age at conception and *ASD-CC* total scores. While it was unclear why child's age was significantly correlated with paternal age (and not maternal age), it was not surprising to find the correlation between child's age and *ASD-CC* scores as children typically begin to exhibit more comorbid problems (e.g., anxiety, withdrawn behavior, phobias, feeding problems) as they get older and symptoms are easier to observe by parents and clinicians. Child's gender was also found to be significantly correlated with both *ASD-DC* and *ASD-CC* total scores with males exhibiting higher scores on both measures. This correlation is likely related to the higher prevalence of ASD and comorbid psychopathology in males. Child's race was not found to be significantly correlated with any predictor or outcome variables; therefore, child's age and gender were included in all subsequent analyses as covariates.

First, it was hypothesized that maternal and paternal age at conception would serve as significant predictors of autism risk in offspring. It was believed that maternal and paternal age would each have independent effects on autism risk such that as parental age increased, risk for autism also increased. A binomial logistic regressions was completed to assess for this relationship. The regression utilized the diagnosis made by a licensed clinical psychologist using all information from the assessment including the *ASD-Child Battery,* developmental history, and any developmental and cognitive testing that was completed as part of the assessment. Results of the analysis were statistically significant and correctly classified 62.8% of cases based on predictors and covariates. Child's gender and paternal age were found to be significant predictors in the model; however, maternal age was not a significant predictor. Child's gender was found to pose a significant increased risk for an autism diagnosis, similar to numerous studies, with an Odds Ratio of 4.17 (95% Confidence Interval, 2.06-8.44). While father's age was found to be statistically significant, the Odds Ratio for an autism diagnosis was relatively

small at 1.06 (95% Confidence Interval, 1.00-1.12). Results of these analyses were not consistent with the majority of epidemiological studies completed regarding maternal and paternal age and autism risk. The differences in this study are believed to be related to the type of sample utilized in the study. While most studies to date have used large population-based samples, the current study utilized a clinical sample that included children who were referred for a host of neurodevelopmental problems including autism, intellectual and developmental disabilities, attention-deficit/hyperactivity disorder, and anxiety. As previous studies have found that advanced maternal age poses increased risk for several different developmental disorders, the effect of maternal age may be masked in a sample that includes only children with some type of developmental concerns. The statistically significant finding of paternal age in this sample may be associated with the incongruent effects paternal age seen in several other studies (Gabis, Raz, & Kesner-Baruch, 2010; Lampi et al., 2013).

Although maternal and paternal age were not found to affect autism rates as expected, additional analyses were conducted to determine if parental age was related to the severity of autism symptoms as conceptualized using a continuous variable. It was hypothesized that maternal and paternal age at conception would serve as significant predictors of autism severity. Previous research has viewed autism as a dichotomous or nominal variable with only one study to date viewing autism as a dimensional variable based on severity ratings. It was believed that as maternal and paternal age increased, their offspring would have higher severity ratings of autism symptoms overall and that these effects would continue to be present after controlling for covariates such as age and gender of the child. A hierarchical multiple regression was completed with covariates entered into the first step and paternal ages entered into the second step. While the final model was found to be statistically significant, the increased predictive power of

parental ages after accounting for the effects of the child's age and gender was not statistically significant. However, as seen in the last analysis, the child's gender and paternal age were found to be significant predictors in the final model.

Lastly, it was hypothesized that parental ages at conception would also serve as significant predictors of comorbid psychopathology in children with ASD. It was believed that as maternal and paternal age at conception increased, there would be higher severity ratings of comorbid psychopathology reported in their offspring. As with autism severity ratings, the final model was found to be statistically significant and accounted for a significant proportion of the variance in comorbid severity scores. Unlike analyses of autism severity ratings, child's gender was found to be the only significant predictor of comorbid severity ratings; maternal and paternal ages were not found to be significant predictors.

Few studies have examined the relationship between parental ages and autism severity. The current study found disparate support for this theory. Itzchak, Lahat, and Zachor (2011), reported in their study that no association was found between advanced parental age and autism severity in their sample. The current study found no significant effects of maternal age at any level of the study; however, several statistically significant results were found in relation to paternal age. Father's age was found to be a significant predictor of an autism diagnosis after controlling for other covariates (e.g., child's age and gender). Father's age was also found to be a significant predictor of autism severity scores in the final model which included child's age, gender, and maternal age. Only child's gender was found to be a significant predictor of comorbid severity ratings. While it is unclear based on the results of the current study, it is possible that maternal age connotes the risk for neurodevelopmental problems broadly based on previous research findings and may be the cause for no significant findings in this clinical

sample. Additionally, it is unclear how paternal age may affect developmental risks and severity of symptoms. It is possible that paternal age connotes additional risks that could increase severity of symptoms when combined with maternal and other present risk factors. Results of the current study, however, are not sufficient to make such assumptions, but further research in this area may help to elucidate those factors and risks involved in advanced paternal age at conception.

Another possible contributing factor related to the lack of a significant finding in maternal age at conception is the distribution in ages between mothers and fathers. In our current sample, 85.1% of mothers were between the ages of 19-34 as compared to 72.9% of fathers. While the percentages of mothers and fathers under the age of 19 were similar (3.2% and 2.0%, respectively), the age of mother and fathers over the age of 35 were quite disparate (11.7% and 25.1%, respectively) and even more so for mothers and fathers over the age of 40 (2.8% and 11.8%, respectively). This might have, at least, a contributing effect to the lack of maternal age effects on the current sample and should be considered in future research.

As noted, the current study was not without limitations. Due to the clinical nature of the sample, all participants were referred for neurodevelopmental and affective problems ranging from intellectual and developmental disabilities to anxiety and depression. The sample is not representative of the total population and therefore may not assess the full effects of maternal and paternal age on autism risk. Future studies may look to examine autism severity in a larger sample of just children with ASD or a broader population-based sample. However, the current study is representative of the typical clinical sample that presents for assessments across the country and results of this study are pertinent to clinicians in several different assessment settings who work with children with neurodevelopmental disabilities.

Another limitation is the measurement on parental age at conception. Although most studies use parental age at birth as their variable, research suggesting the importance of the prenatal period should take age at conception into consideration. The current study was not able to determine exact age at conception as parental date of birth was not available. Future studies should seek to obtain more accurate data in regards to parental age at conception and further information regarding the length of the gestational period.

Additionally, it is unclear how different parental characteristics may affect behavior ratings and ratings of autism symptoms. These are inherent problems in using parent-report rating scales for assessment of behavior and autism symptoms. For example, Schroeder, Hood, and Hughes (2010) found that mothers consistently rated their child's behaviors as more severe than fathers on the Child Behavior Checklist. It is also unclear how parental ages may affect behavior ratings or parenting strategies that may lead to more behavior problems. Further research is needed in this area but these possible effects should be taken into consideration when interpreting these results.

Much is still unknown regarding the etiology of autism spectrum disorders and the factors which predict risk, severity, and comorbid psychopathology. Further research is needed in this area to better understand the complex nature of the heterogeneous disorder. The current study did lend support to the idea that paternal ages are a factor in risk and severity of autism in a clinical sample, and further research is needed to explore that relationship. Future research may also help us to understand the complex relationship between maternal and paternal age and risk for developmental disabilities in general and the biological mechanism that may be affecting such risk. Several hypotheses have been postulated to help elucidate this complex disorder which appears to be affected by genetic, environmental, and epigenetic factors. Much has been

learned regarding autism and related developmental disabilities over the last several decades;

however, much work is needed to better understand this disorder and to better serve those

individual and families affected.

REFERENCES

American Psychiatric Association. (1952). *Diagnostic and statistical manual of mental disorders* Washington, DC: Author.

American Psychiatric Association. (1968). *Diagnostic and statistical manual of mental disorders (2nd ed.).* Washington, DC: Author.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders (3rd ed.).* Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders (3rd ed., revised).* Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (4th ed. - text revision).* Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnsotic and statistical manual of mental disorders (5th ed.).* Washington, DC: Author.

Amir, R. E., Van den Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics, 23*, 185.

Andersen, S. L., Laurberg, P., Wu, C. S., & Olsen, J. (2014). Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study. [Article]. *BJOG: An International Journal of Obstetrics & Gynaecology, 121*(11), 1365-1374. doi: 10.1111/1471-0528.12681

Aronson, M., Hagberg, B., & Gillberg, C. (1997). Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: A follow-up study. *Developmental Medicine & Child Neurology, 39,* 583-587.

Asperger, H., & Frith, U. (1991). 'Autistic psychopathy' in childhood. In U. Frith (Ed.), *Autism and Asperger syndrome.* (pp. 37-92). New York, NY US: Cambridge University Press.

Atladóttir, H. Ó., Thorsen, P., Østergaard, L., Schendel, D. E., Lemcke, S., Abdallah, M., & Parner, E. T. (2010). Maternal Infection Requiring Hospitalization During Pregnancy and Autism Spectrum Disorders. [Article]. *Journal of Autism & Developmental Disorders, 40*(12), 1423-1430. doi: 10.1007/s10803-010-1006-y

Auyeung, B., Baron-Cohen, S., Ashwin, E., Knickmeyer, R., Taylor, K., & Hackett, G. (2009). Fetal testosterone and autistic traits. [Article]. *British Journal of Psychology, 100*(1), 1-22. doi: 10.1348/000712608x311731

Bailey, D. B., Jr., Mesibov, G. B., Hatton, D. D., Clark, R. D., Roberts, J. E., & Mayhew, L. (1998). Autistic behavior in young boys with fragile X syndrome. *Journal of Autism and Developmental Disorders, 28,* 499-508.

Bakwin, H. (1949). Emotional deprivation in infants. *The Journal of Pediatrics, 35*, 512-521.

Barnevik-Olsson, M., Gillberg, C., & Fernell, E. (2010). Prevalence of autism in children of Somali origin living in Stockholm: A brief report of an at-risk population. *Developmental Medicine & Child Neurology, 52,* 1167-1168.

Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Sciences, 6*(6), 248-254. doi: http://dx.doi.org/10.1016/S1364-6613(02)01904-6

Baron-Cohen, S. (2006). Two new theories of autism: hyper-systemising and assortative mating. *Archives of Disease in Childhood, 91,* 2-5.

Baron-Cohen, S., & Hammer, J. (1997). Is autism an extremem form of the male brain? *Advances in Infancy Research, 11,* 193-217.

Baron-Cohen, S. & Ring, H. (1994). A model of the mindreading system: neuropsychological and neurobiological perspectives. In P. Mitchell & C. Lewis (Eds.), *Origins of an understanding mind.* Hillsdale, NJ: Lawrence Erlbaum.

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. R. (2000). The amygdala theory of autism. *Neuroscience & Biobehavioral Reviews, 24*(3), 355-364. doi: http://dx.doi.org/10.1016/S0149-7634(00)00011-7

Baron-Cohen, S., Ring, H., Moriarty, J., Shmitz, P., Costa, D., & Ell, P. (1994). Recognition of mental state terms: A clinical study of autism, and a functional neuroimaging study of normal adults. *British Journal of Psychiatry, 165,* 640-649.

Baron-Cohen, S., Wheelwright, S., Stone, V., & Rutherfor, M. (1999). A mathematician, a physicist, and a computer scientist with Aspergre Syndrome: Performance on folk psychology and folk physics tests. *Neurocase, 5,* 475-483.

Bartak, L., Rutter, M., & Cox, A. (1975). A comparative study of infantile autism and specific developmental receptive language disorder: I. The children. *British Journal of Psychiatry, 126*, 127-145.

Behnia, F., Parets, S. E., Kechichian, T., Yin H., Dutta, E. H., Saade, G. R., Smith, A. K., & Menon, R. (2015). Fetal DNA methylation of autism spectrum disorders candidate genes: Association with spontaneous preterm birth. *American Jounral of Obstetrics and Gynecology, 212,* 533.e1-9.

Beighley, J. S., Matson J. L., Rieske, R. D., Konst, M J., & Tureck, K. (2014). Differences in communication skills in toddlers diagnosed with autism spectrum disorder according to the *DSM-IV-TR* and the *DSM-5*. *Research in Autism Spectrum Disorders, 8,* 74-81.

Bellini, S. (2004). Social skill deficits and anxiety in high-functioning adolescents with autism spectrum disorders. *Focus on Autism & Other Developmental Disabilities, 19*, 78-86.

Bender, L. (1959). Autism in children with mental deficiency. *American Journal of Mental Deficiency, 64*, 81-86.

Bender, L., & Grugett, A. E., Jr. (1956). A study of certain epidemiological factors in a group of children with childhood schizophrenia. *The American Journal Of Orthopsychiatry, 26*, 131-145.

Bernal, J., Guadano-Ferraz, A., & Morte, B. (2003). Perspectives in the study of thyroid hormone action on brain development and function. *Thyroid, 13,* 1005-1012.

Bettelheim, B. (1967). *The empty fortress: Infanile autism and the birth of the self.* Oxford England: Free Press of Glencoe.

Blaxill, M. F. (2004). What's going on? The question of time trends in autism. *Public Health Reports, 119,* 536-551.

Bleuler, E. (1913). Autistic thinking. *American Journal of Insanity, 69*, 873-886.

Bolton, P. F., & Griffiths, P. D. (1997). Association of tuberous sclerosis of temporal lobes with autism and atypical autism. *Lancet, 349,* 392-395.

Brereton, A. V., Tonge, B. J., & Einfeld, S. L. (2006). Psychopathology in children and adolescents with autism compared to young people with intellectual disability. *Journal of Autism & Developmental Disorders, 36*, 863-870.

Brothers, L. (1990). The social brain: A project for integrating primate behaviour and neurophysiology in a new domain. *Concepts in Neuroscience, 1,* 27-51.

Brown, A. S. (2012). Epidemiologic studies of exposure to prenatal infeciton and risk of schizophrenia and autism. *Developmental Neurobiology, 72,* 1272-1276.

Brown, A. S., Surcel, H.-M., Hinkka-Yli-Salomäki, S., Cheslack-Postava, K., Bao, Y., & Sourander, A. (2015). Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 57*(0), 86-92. doi: http://dx.doi.org/10.1016/j.pnpbp.2014.10.010

Caban-Holt, A., Head, E., & Schmitt, F. (2015). Down syndrome. In R. N. Rosenberg & J. M. Pascual (Eds.), *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Diseases* (5th ed.) (pp. 163-170).

Caldwell, K. L., Jones, R., & Hollowell, J. G. (2005). Urinary iodine concentrations: United States national health and nutrition examination survey 2001-2002. *Thyroid, 15,* 692-699.

Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry, 32,* 1063-1080.

Centers for Disease Control and Prevention. (2007). Prevalence of autism spectrum disorders: Autism and developmental disabilities monitoring network, six sites, United States, 2000. *Morbidity and Mortality Weekly Report, Surveillance Summaries, 56*(1), 1-11.

Centers for Disease Control and Prevention. (2009). Prevalence of autism spectrum disorders: Autism and developmental disabilities monitoring network, United States, 2006. *Morbidity and Mortality Weekly Report, Surveillance Summaries, 58*(10), 1-20.

Centers for Disease Control and Prevention. (2014). Prevalence of autism spectrum disorder among children aged 8 years: Autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *Morbidity and Mortality Weekly Report, Surveillance Summaries, 63* (2), 1-21.

Chang, Y., Quan, J., & Wood, J. (2012). Effects of Anxiety Disorder Severity on Social
    Functioning in Children with Autism Spectrum Disorders. *Journal Of Developmental &
    Physical Disabilities*, *24*(3), 235-245.

Chase, S. (1971). Autism in children with congenital rubella. *Journal of Autism and Childhood
    Schizophrenia, 1,* 33-47.

Cheslack-Postava, K., Rantakokko, P. V., Hinkka-Yli-Salomäki, S., Surcel, H.-M., McKeague, I.
    W., Kiviranta, H. A., . . . Brown, A. S. (2013). Maternal serum persistent organic
    pollutants in the Finnish Prenatal Study of Autism: A pilot study. *Neurotoxicology and
    Teratology, 38*(0), 1-5. doi: http://dx.doi.org/10.1016/j.ntt.2013.04.001

Cohen, D. J., Paul, R., & Volkmar, F. R. (1986). Issues in the classification of pervasive
    developmental disorders: Toward *DSM-IV*. *Journal of the American Academy of Child
    and Adolescent Psychiatry, 25,* 213-220.

Coo, H., Oullette-Kuntz, H., Lloyd, J. E. V., Kasmara, L., Holden, J. J. A., & Lewis, M. E. S.
    (2008). Trends in autism prevalence: Diagnostic substitution revisited. *Journal of Autism
    and Developmental Disorders, 38,* 1036-1046.

Critchley, H. D., Daly, E. M., Bullmore, E.T., Willaims, S. C. R., Amelsvoort, T. V., Robertson,
    D. M., … Murphy, D. G. M. (2000). The functional neuroanatomy of social behaviour:
    Changes in cerebral blood flow when people with autistic disorder process facial
    expressions. *Brain, 123,* 2203-2212.

Damasio, A., Tranel, D., Damasio, H. (1990). Individuals with sociopathic behaviour caused by
    frontal lobe damage fail to respond autonomically to socially charged stimuli.
    Behavioural Brain Research, 14, 81-94.

Daniels, A. M., & Mandell, D. S. (2014). Explaining differences in age at autism spectrum
    disorder diagnosis: A critical review. *Autism*,*18*(5), 583-597.
    doi:10.1177/1362361313480277

Davis, E., Fennoy, I., Laraque, D., Kanem, N., Brown, G., & Mitchell, J. (1992). Autism and
    developmental abnormalities in children with perinatal cocaine exposure. *Journal of the
    National Medical Association, 84,* 315-319.

de Bruin, E. I., de Nijs, P. F. A., Verheij, F., Hartman, C. A., & Ferdinand, R. F. (2006). Multiple
    complex developmental disorder delineated from PDD-NOS. *Journal of Autism and
    Developmental Disorders, 37,* 1181-1191.

de Bruin, E. I., Ferdinand, R. F., Meester, S., de Nijs, P. F. A., & Verheij, F. (2007). High rates
    of psychiatric co-morbidity in PDD-NOS. *Journal of Autism & Developmental
    Disorders, 37*, 877-886.

Delange, F. (2001). Iodine deficiency as a cause of brain damage. *Postgraduate Medical
    Journal, 77,* 217-220.

DeLong, G.R., Bean, S. C., Brown, F. R. (1981). Acquired reversible autistic syndrome in acute
    encephalopathic illness in children. *Archives of Neurology, 38,* 191-194.

DeMyer, M. K., Hingtgen, J. N., & Jackson, R. K. (1981). Infantile autism reviewed: a decade of research. *Schizophrenia Bulletin, 7*, 388-451.

Despert, J. L. (1951). Some considerations relating to the genesis of autistic behavior in children. *The American Journal Of Orthopsychiatry, 21*, 335-350.

Dolinska, B. (2009). In vitro fertilization (IVF) and the risk of birth and developmental defects—facts and fictions. *Polish Psychological Bulletin*, *40*(3), 145-155. doi:10.2478/s10059-009-0027-x

Dong, S., Walker, M. F., Carriero, N. J., DiCola, M., Wilsey, J., Ye, A. A., … Sanders, S. J. (2014). De novo inerstions and deletions of predominantly paternal origin are associated with autism spectrum disorder. *Cell Reports, 9,* 16-23.

Dor-Shav, N. K., & Horowitz, Z. (1984). Intelligence and personality variables of parents of autistic children. *Journal of Genetic Psychology, 144*, 39.

Durkin, M. S., Maenner, M. J., Meaney, F. J., Levy, S. E., DiGuiseppi, C., Nicholas, J. S., … Schieve, L. A. (2010). *PLoS One, 5*, e11551. doi: 10.1371/journal.pone.0011551

Ecker, C., Marquand, A., Mourao-Miranda, J., Johnston, P., Daly, E. M., Brammer, M. J.,…Murphy, D. G. (2010). Describing the brain in autism in five dimensions-magnetic resonance imaging-assisted diagnosis of autism spectrum disorder uising a multiparameter classification approach. *Journal of Neuroscience, 30,* 10612-10623.

Eisermann, M. M., DeLaRaillere, A., Dellatolas, G., Tozzi, E., Nabbout, R., Dulac, O., & Chiron, C. Infantile spasms in Down syndrome: Effects of delayed anticonvulsive treatment. *Epilepsy Research, 55,* 21-27.

El Achkar, C. M., & Spence, S. J. (2015). Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. *Epilepsy and Behavior,in press.* Advnaced publication. doi: 10.1016/j.yebeh.2014.12.002

El Marroun, H., White, T., Verhulst, F. C., & Tiemeier, H. (2014). Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. *European Child & Adolescent Psychiatry, 23*(10), 973-992. doi: 10.1007/s00787-014-0558-3

Elder, J. H., Shankar, M., Shuster, J., Theriaque, D., Burns, S., & Sherrill, L. (2006). The gluten-free, casein-free diet in autism: Results of a preliminary double blind clinical trial. *Journal of Autism and Developmental Disorders, 36,* 413-420.

Eliasen, M. Tolstrup, J. S., Nybo Andersen, A. M., Gronaek, M., Olsen, J., & Strandberg-Larsen, K. (2010). Prenatal alcohol exposure and autistic spectrum disorders: A population-based prospective study of 80,552 children and their mothers. *International Journal of Epidemiology, 39,* 1074-1081.

Eveloff, H. H. (1960). The autistic child. *Archives Of General Psychiatry, 3*, 66-81.

Fatemi, S. H., Folsom, T. D., Reutiman, T. J., Abu-Odeh, D., Mori, S., Huang, H., & Oishi, K. (2009). Abnormal expression of myelination genes and alterations in white matter fractional anisotropy following prenatal viral influenza infection at E16 in mice.

Schizophrenia Research, 112(1–3), 46-53. doi: http://dx.doi.org/10.1016/j.schres.2009.04.014

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175-191.

Field, A. P. (2009). *Discovering statistics using SPSS* (3rd ed.). Los Angeles: SAGE Publications.

Fisch H., Hyun G., Golden R., Hensle T. W., Olsson C. A., & Liberson, G. L. (2003). The influence of paternal age on Down syndrome. *Journal of Urology, 169*, 2275–2278.

Fombonne, E. (1999). The epidemiology of autism: A review. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences, 29*, 769-786.

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: An update. *Journal of Autism and Developmental Disabilities, 33,* 365-382.

Fombonne, E., Quirke, S., & Hagen, A. (2009). Prevalence and interpretation of recent trends in rates of pervasive developmental disorders. *Mcgill Journal Of Medicine: MJM: An International Forum For The Advancement Of Medical Sciences By Students, 12*, 73-73.

Gabis, L., Raz, R., & Kesner-Baruch, Y. (2010). Paternal age in autism spectrum disorders and ADHD. *Pediatric Neurology, 2010, 43,* 300-302.

Galligan, M. G., Feinstein, C., Sulkes, S. S., Bisagno, J. M., & Stein, M. T. (2013). Asperger syndrome and *DSM-5*: A dilemma for a college freshman. *Journal of Developmental and Behavioral Pediatrics, 34,* 529-532.

Ghaziuddin, M. (2010). Brief report: Should the DSM V drop asperger syndrome? *Journal of Autism & Developmental Disorders, 40*, 1146-1148.

Gillberg, C. (1986). Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. *Journal of Autism and Developmental Disorders, 16,* 369-375.

Gillberg, C. (1995). Endogenous opioids and opiate antagonists in autism: Brief review of empirical findings and implications for clinicians. *Developmental Medicine & Child Neurology, 37,* 239-245.

Gillberg, C., Gillberg, I. C., & Ahlsen, G. (1994). Autistic behavior and attention deficits in tuberous sclerosis: A population-based study. *Developmental Medicine and Child Neurology, 36,* 50-56.

Girirajan, S. (2009). Parental-age effects in Down syndrome. *Journal of Genetics*, *88*(1), 1-7.

Gjevik, E., Eldevik, S., Fjaeran-Granum, T., & Sponheim, E. (2011). Kiddie-SADS reveals high rates of *DSM-IV-TR* disorders in children and adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 41*, 761-769.

Goldfarb, W. (1945). Effects of psychological deprivation in infancy and subsequent stimulation. *The American Journal Of Psychiatry, 102*, 18-33.

Grandjean, P., Harari, R., Barr, D., & Debes, F. (2005). Pesticide exposure and stunting as independent predictors of neurobehavioral deficits in Ecuadorian school children. *Pediatrics, 117,* 546-556.

Green, W. H., Campbell, M., Hardesty, A. S., Grega, D. M., Padron-Gayol, M., Shell, J., & Erlenmeyer-Kimling, L. (1984). A Comparison of schizophrenic and autistic children. *Journal of the American Academy of Child Psychiatry, 23*, 399-409.

Greer, M. K., Lyons-Crews, M., Mauldin, L. B., Brown, F. R. (1989). A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. *Journal of Autism and Developmental Disorders, 19,* 317-326.

Gurney, J. G., Fritz, M. S., Ness, K. K., Sievers, P., Newschaffer, C. J., & Shapiro, E. G. (2003). Analysis of prevalence trens of autism spectrum disorder in Minnesota. *Achrives of Pediatrics and Adolescent Medicine, 157,* 622-627.

Haddow, J. E., Palomaki, G. E., Allan, W. C., Willaims, J. R., Knight, G. J., Gagnon, J.,…Klein, R. Z. (1999). Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine, 341,* 549-555.

Hagberg, B., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Annals Of Neurology, 14*, 471-479.

Hallmayer, J., Cleveland, S., Torres, A., Phillips, J. Cohen, B., Torigoe, T., … Risch, N. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry, 68,* 1095-1102.

Hammond, R. K., & Hoffman, J. M. (2014). Adolescent with high-functioning autism: An investigation of comorbid anxiety and depression. *Journal of Mental Health Research in Intellectual Disabilities, 7,* 246-263.

Hansen, S. N., Schendel, D. E., & Parner, E. T. (2015). Explaining the increase in the prevalence of autism spectrum disorders: The proportion attirubutable to change in reporting practices. *JAMA Pediatrics, 169,* 56-62.

Harper, J., & Williams, S. (1976). Infantile autism: The incidence of national groups in a New South Wales survey. *The Medical Journal of Australia, 10,* 299-301.

Harris, S. R., MacKay, L. L., & Osborn, J. A. (1995). Autistic behaviors in offspring of mothers abusing alcohol and other drugs: A series of case reports. *Alcohol: Clinical and Experimental Research, 19,* 660-665.

Harrison, J. E. & Bolton, P. F. (1997). Annotation: Tuberous sclerosis. *Journal of Child Psychology and Psychiatry, 38,* 603-614.

Hediger, M. L., Bell, E. M., Druschel, C. M., & Buck Louis, Germaine M. (2013). Assisted reproductive technologies and children's neurodevelopmental outcomes. *Fertility and Sterility, 99,* 311-317.

Hendry, C. N. (2000). Childhood disintegrative disorder: should it be considered a distinct diagnosis? *Clinical Psychology Review, 20*, 77-90.

Hewitt, A., Gulaid, A., Hamre, K., Esler, A., Punyko, J., Reichle, J. & Reiff, M. (2013). *Minneapolis Somali autism spectrum disorder prevalence project: Community report 2013*. Minneapolis, MN: University of Minnesota, Institute on Community Integration, Research and Training Center on Community Living.

Hollowell, J. G., Staehling, N. W., Hannon, W. H., Flanders, D. W., Gunter, E. W., Maberly, G. F.,…Jackson, R. J. (1998). Iodine nutrition in the United States. Trends and public health implications: Iodine excretion data from national health and nurtition examination surveys I and III (1971-1974 and 1988-1994). *Journal of Clinical Endocrinology and Metabolism, 83,* 3401-3408.

Hook, E. B., Cross, P. K., & Schreinemachers, D. M. (1983). Chromosomal abmormality rates at amniocentesis and in live-born infants. *Journal of the American Medical Association, 249,* 2034-2038.

Horovitz, M., Matson, J. L., Rieske, R. D., Kozlowski, A. M., & Sipes, M. (2011). The relationship between race and challenging behaviours in infants and toddlers with autistic disorder and pervasive developmental disorder-not otherwise specified. *Developmental Neurorehabilitation, 14,* 208-214.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and asperger syndrome. *Journal of Autism & Developmental Disorders, 33*, 3-3.

Idring, S., Lundberg, M., Sturm, H., Dalman, C., Gumpert, C., Rai, D., …Magnusson, C. (2014). Changes in prevalence of autism spectrum disorders in 2001-2011: Findings from the stockholm youth cohort. *Journal of Autism and Developmental Disorders,* doi:10.1007/s10803-014-2336-y

Iskaros, J., Pickard, M., Evans, I., Sinha, A., Hardiman, P., & Ekins, R. (2008). Thyroid hormone receptor gene expression in first trimester human fetal brain. *Journal of Clinical Endocrinology and Metabolism, 85,* 2620-2623.

Islam, M. P. & Roach, E. S. (2015). Tuberous Sclerosis Complex. In R. N. Rosenberg & J. M. Pascual (Eds.), *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Diseases* (5th ed.) (pp. 935-943).

Itzchak, E. B., Lahat, E., & Zachor, D. A. (2011). Advanced parental ages and low birth weight in autism spectrum disorders: Rates and effect on functioning. *Research in Developmental Disabilities, 32,* 1776-1781.

Jones, K. L., & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet, 302,* 999-1001.

Karmilloff-Smith, A., Grant, J., Bellugi, U., Baron-Cohen, S. (1995). Is there a social module? Language, face-processing and thoery of mind in William's Syndrome and autism. *Journal of Cognitive Neuroscience, 7,* 196-208.

Kanne, S. M., Abbacchi, A. M., & Constantino, J. N. (2009). Multi-informant ratings of psychiatric symptom severity in children with autism spectrum disorders: the importance of environment context. *Journal of Autism and Developmental Disorders, 39,* 856-864.

Kanner, L. (1943). Autistic distubances of affective contact. *The Nervous Child, 2*, 217-250.

Kanner, L. (1944). Early infantile autism. *The Journal of Pediatrics, 25*, 211-217.

Kanner, L. (1949). Problems of nosology and psychodynamics of early infantile autism. *American Journal of Orthopsychiatry, 19*, 416-426.

Kanner, L. (1951). The conception of wholes and parts in early infantile autism. *The American Journal Of Psychiatry, 108*, 23-26.

Kanner, L. (1954). To what extent is early infantile autism determined by constitutional inadequacies? *Research publications - Association for Research in Nervous and Mental Disease, 33*, 378-385.

Kanner, L. (1958). The specificity of early infantile autism. *Zeitschrift für Kinderpsychiatrie, 25*, 108-113.

Kanner, L. (1971a). Childhood psychosis: A historical overview. *Journal of Autism & Childhood Schizophrenia, 1*, 14-19.

Kanner, L. (1971b). Follow-up study of eleven autistic children originally reported in 1943. *Journal Of Autism And Childhood Schizophrenia, 1*, 119-145.

Kanner, L., & Eisenberg, L. (1957). Early infantile autism, 1943-1955. *Psychiatric Research Reports, 7*, 55-65.

Keen, D. V., Reid, F. D., & Arnone, D. (2010). Autism, ethnicity and maternal immigration. *The British Journal of Psychiatry, 196,* 274-281.

Kielinen, M., Rantala, H., Tomonen, E., Linna, S. L., & Moilanen, I. (2004). Associated medical disorders and disabilities in children with autistic disorder: A population-based study. *Autism, 8,* 49-60.

Kim, K. C., Kim, P., Go, H. S., Choi, C. S., Park, J. H., Kim, H. J., . . . Shin, C. Y. (2013). Male-specific alteration in excitatory post-synaptic development and social interaction in pre-natal valproic acid exposure model of autism spectrum disorder. [Article]. *Journal of Neurochemistry, 124*(6), 832-843. doi: 10.1111/jnc.12147

Klin, A., & Volkmar, F. R. (1997). The pervasive developmental disorders: Nosology and profiles of development. In S. S. Luthar, J. A. Burack, D. Cicchetti & J. R. Weisz (Eds.), *Developmental psychopathology: Perspectives on adjustment, risk, and disorder.* (pp. 208-226). New York, NY US: Cambridge University Press.

Knickmeyer, R. C., & Baron-Cohen, S. (2006). Fetal Testosterone and Sex Differences in Typical Social Development and in Autism. [Article]. *Journal of Child Neurology, 21*(10), 825-845. doi: 10.2310/7010.2006.00213

Knickmeyer, R., Baron-Cohen, S., Raggatt, P., Taylor, K. (2005). Foetal testosterone, social relationships, and restricted interests in children. *Journal of Child Psychology and Psychiatry, 46,* 198-210.

Kotey, S., Ertel, K., & Whitcomb, B. (2014). Co-occurrence of autism and asthma in a nationally-representative sample of children in the United States. *Journal of Autism and Developmental Disorders, 44,* 3083-3088.

Krieger, N., Kiang, M. V., Kosheleva, A., Waterman, P. D., Chen, J. T., & Beckfield, J. (2015). Age at menarche: 50-year socioeconomic trends among US-born black and white women. *American Journal of Public Health*, *105*(2), 388-397. doi:10.2105/AJPH.2014.301936

Kurita, H. (2011). Childhood disintegrative disorder. In E. Hollander, A. Kolevzon & J. T. Coyle (Eds.), *Textbook of autism spectrum disorders.* (pp. 99-105). Arlington, VA US: American Psychiatric Publishing, Inc.

Ladd-Acosta, C., Hansen, K. D., Briem, E., Fallin, M. D., Kaufmann, W. E., & Feinberg, A. P. (2014). Common DNA methylation alterations in multiple brain regions in autism. *Molecular Psychiatry*,*19*(8), 862-871. doi:10.1038/mp.2013.114

Lampi, K. M., Hinkka-Yli-Salomaki, S., Lehti, V., Helenius, H., Gissler, M., Brown, A. S., & Sourander, A. (2013). Parental age and risk of autism spectrum disorders in a Finnish naitonal birth cohort. *Journal of Autism and Developmental Disorders, 43,* 2526-2535.

Lee, B. K. & McGrath, J. J. (2015). Advancing parental age and autism: Multifactorial pathways. *Trends in Mollecular Medicine, 21,* 118-125.

Leekam, S. R., Prior, M. R., & Uljarevic, M. (2011). Restricted and repetitive behaviors in autism spectrum disorders: A review of research in the last decade. *Psychological Bulletin, 137*, 562-593.

Lewin, A., Wood, J., Gunderson, S., Murphy, T., & Storch, E. (2011). Phenomenology of Comorbid Autism Spectrum and Obsessive-Compulsive Disorders Among Children. *Journal Of Developmental & Physical Disabilities*, *23*(6), 543-553.

Lewis, J. C., Thomas, H. V., Murphy, K. C., & Sampson, J. R. (2004). Genotype and psychological phenotype in tuberous sclerosis. *Journal of Medical Genetics, 41,* 203-207.

Linton, K. F., Krcek, T. E., Sensui, L. M., Spillers, J. L. H. (2014). Opinions of people who self-identify with autsim and Asperger's on *DSM-5* criteria. *Research on Social Work Practice, 24,* 67-77.

Lord, C., & Bishop, S. L. (2010). Autism spectrum disorders: Diagnosis, prevalence, and services for children and families. *Social Policy Report*. Volume 24, Number 2: Society for Research in Child Development.

Lord, C. & Gotham, K. (2014). DSM-5 and ASD: Reflection and commentary. In T. E. Davis III, S. W. White, & T. H. Ollendick (Eds.), *Handbook of Autism and Anxiety* (pp. 247-261). Autism and Child Psychopathology Series (Series Editor: Johnny L. Matson). Switzerland: Springer International Publishing.

Lord, C., & Rutter, M. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism & Developmental Disorders, 24*, 659-685.

Lord, C., & Schopler, E. (1985). Differences in sex ratios in autism as a function of measured intelligence. *Journal of Autism and Developmental Disorders, 15,* 185-193.

Lozano, R., Hare, E. B., & Hagerman, R. J. (2015). Fragile X-associated disorders. In R. N. Rosenberg & J. M. Pascual (Eds.), *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Diseases* (5th ed.) (pp. 183-195).

Lyall, K., Van de Water, J., Ashwood, P., Hertz-Picciotto, I. (2015). Asthma and allergies in children with autism spectrum disorders: Results from the CHARGE study. *Autism Research,* in press. Epub ahead of print. doi: 10.1002/aur.1471

Malhotra, S., & Gupta, N. (2002). Childhood disintegrative disorder. Re-examination of the current concept. *European Child & Adolescent Psychiatry, 11*, 108-114.

Man, K. K. C., Tong, H. H. Y., Wong, L. Y. L., Chan, E. W., Simonoff, E., & Wong, I. C. K. (2015). Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorders in children: A systematic review and meta-analysis of observaitonal studies. *Neuroscience and Biobehavioral Reviews, 49,* 82-89.

Mandell, D., & Lecavalier, L. (2014). Should we believe the centers for disease control and prevention's autism spectrum disorder prevalance estimates? *Autism, 18,* 482-484.

Mandell, D. S., Listerud, J., Levy, S. E., & Pinto-Martin, J. A. (2002). Race differences in the age at diagnosis among Medicaid-eligible children with autism. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*, 1447-1453. doi:10.1097/00004583-200212000-00016

Mandell, D. S., Wiggins, L. D., Yeargin-Allsopp, M., Carpenter, L. A., Daniels, J., Thomas, K. C., … Kirby, R. S. (2009). Racial/ethnic disparities in the identificaiton of children with autism spectrum disorders. *American Journal of Public Health, 99,* 493-498.

Mannion, A., & Leader, G. (2013a). An analysis of the predictors of comorbid psychopathology, gastrointestinal symptoms and epilepsy in children and adolescents with autism spectrum disorder. *Research in Autism Spectrum Disorders, 7,* 1663-1671.

Mannion, A., & Leader, G. (2013b). Comorbidity in autism spectrum disorder: A literature review. *Research in Autism Spectrum Disorders, 7,* 1595-1616.

Mantel, N. & Stark, C. R.(1967). Paternal age in Down's syndrome. *American Journal of Mental Deficiency, 71,* 1025-1027.

Mariea, T. J., & Carlo, G. L. (2007). Wireless radiation in the etiology and treatment of autism: Clinical observations and mechanisms. *Journal of the Autralasian College of Nutritional & Environmental Medicine, 26,* 3-7.

Marques, F., Brito, M. J., Conde, M., Pinto, M., & Moreira, A. (2014). Autism spectrum disorder secondary to enterovirus encephalitis. *Journal of Child Neurology, 29,* 708-714.

Mash, E. J., & Barkley, R. A. (2003). *Child Psychopathology, Second Edition*. New York: Guilford Press.

Mathews, T. J., & Hamilton, B. E. (2009). Delayed child bearing: More women are having their first child later in life. *NCHS data brief, 2,* 1-8. Hyattsville, MD: National Center for Health Statistics.

Matson, J. L. (2007). Current status of differential diagnosis for children with autism spectrum disorders. *Research in Developmental Disabilities, 28*, 109-118.

Matson, J. L. & Gonzalez, M. L. (2007a). Autism Spectrum Disoders- Diagnosis- Child Version. Baton Rouge, LA: Disability Consultants, LLC.

Matson, J. L. & Gonzalez, M. L. (2007b). Autism Spectrum Disorders- Comorbidity- Child Version. Baton Rouge, LA: Disability Consultants, LLC.

Matson, J. L., Gonzalez, M. L., & Wilkins, J. (2009). Validity study of the Autism Specturm Disorders- Diagnostic for Children (ASD-DC). *Research in Autism Spectrum Disorders, 3,* 196-206.

Matson, J. L., Gonzalez, M. L., Wilkins, J., & Rivet, T. T. (2007). Reliability of the Autism Spectrum Disoder-Diagnosis for Children (ASD-DC). *Resesarch in Autism Spectrum Disorders, 2,* 533-545.

Matson, J. L., & Kozlowski, A. M. (2011). The increasing prevalence of autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*, 418-425.

Matson, J. L., LoVullo, S. V., Rivet, T. T., & Boisjoli, J. A. (2009). Validity of the Autism Spectrum Disorder-Comorbid for Children (ASD-CC). *Research in Autism Spectrum Disorders, 3,* 345-357.

Matson, J. L., Mahan, S., Hess, J. A., Fodstad, J. C., & Neal, D. (2010). Convergent validity of the Autism Spectrum Disorder-Diagnostic for Children (ASD-DC) and Childhood Autism Rating Scales (SCARS). *Research in Autism Spectrum Disorders, 4*, 633-638.

Matson, J. L., Rieske, R. D., & Williams, L. W. (2013). The relationship between autism spetrum disorders and attention-deficit/hyperactivity disorder: An overview. *Research in Developmental Disabilities, 34,* 2475-2484.

Matson, J. L., & Shoemaker, M. (2009). Intellectual disability and its relationship to autism spectrum disorders. *Research in Developmental Disabilities, 30*, 1107-1114.

Matson, J. L., & Wilkins, J. (2008a). Nosology and diagnosis of asperger's syndrome. *Research in Autism Spectrum Disorders, 2*, 288-300.

Matson, J. L., & Wilkins, J. (2008b). Reliability of the Autism Spectrun Disorders-Comorbidity for Children (ASD-CC). *Journal of Developmental and Physical Disabilities, 20,* 327-336.

Matson, J. L. & Williams, L. W. (2014). Depression and mood disordes among persons with autism spectrum disorders. *Research in Developmental Disabilities, 35,* 2003-2007.

Mayes, S. D., Calhoun, S. L., Mayes, R. D., & Molitoris, S. (2012). Autism and ADHD: Overlapping and discriminating symptoms. *Research in Autism Spectrum Disorders, 6,* 277-285.

Mayes, S. D., Calhoun, S. L., Murray, M. J., Ahuja, M., & Smith, L. A. (2011). Anxiety, depression, and irritability in children with autism relative to other neuropsychiatric disorders and typical development. *Research in Autism Spectrum Disorders, 5*, 474-485.

Mayes, S.D., Calhoun, S. L., Murray, M. J., & Zahid, J. (2011). Variables associated with anxiety and depression in children with autism. *Journal of Developmental and Physical Disabilities, 23,* 325-337.

Mayes, S. D., Gorman, A. A., Hillwig-Garcia, J. & Syed, E. (2013). Suicide ideation and attempts in children with autism. *Research in Autism Spectrum Disorders, 7,* 109-119.

McAdoo, W. G., & DeMyer, M. K. (1977). Research related to family factors in autism. *Journal of Pediatric Psychology, 2,* 162-166.

McGrath, J. J., Petersen, L., Agerbo, E., Mors, O., Mortensen, P. B., & Pedersen, C. B. (2014). A comprehensive assessment of parental age and psychiatric disorders. *JAMA Psychiatry, 71*(3), 301-309. doi:10.1001/jamapsychiatry.2013.4081

Menkin, M. (2013). Causes of Autism Epidemic. *Aliens and Children.* Retrieved from http://aliensandchildren.org/Cause_of_Autism_Epidemic.htm

Mesibov, G. B. (1997). What is PDD-NOS and how is it diagnosed? *Journal of Autism and Developmental Disorders, 27*, 497-498.

Mitchell, M. M., Woods, R., Chi, L-H., Schmidt, R. J., Pessah, I. N., Kostyniak, P. J., & LaSalle, J. M. (2012). Leves of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorders. *Environmental and Molecular Mutagenesis, 53,* 589-598.

Miyazaki, K.., Narita, N., & Narita, M. (2005). Maternal administration of thalidomide or valproic acid causes abnormal seotonergic neurons in the offspring: Implication for pathogenesis of autism. *International Journal of Developmental Neuroscience, 23,* 287-297.

Molloy, C. A., Morrow, A. L., Meinzen-Derr, J., Dawson, G., Bernier, R., Dunn, M.,…Lord, C. (2006). Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disoder: A CPEA study. *Journal of Autism and Developmental Disorders, 36,* 317-324.

Morgan, C. N., Roy, M., & Chance, P. (2003). Psychiatric comorbidity and medication use in autism: A community survey. *Psychiatric Bulletin, 27*, 378-381.

Morreale de Escobar, G., Obergon, M. J., Escobar del Rey, F. (2004). Role of thyroid hormone during early brain development. *European Journal of Endocrinology, 151,* 1-14.

Mosse, H. L. (1958). The misuse of the diagnosis childhood schizophrenia. *The American Journal Of Psychiatry, 114*, 791-794.

Mouridsen, S. E. (2003). Childhood disintegrative disorder. *Brain & Development, 25*, 225-228.

Nanson, J. L. (1992). Autism in fetal alcohol syndrome: A report of six cases. *Alcoholism: Clinical and Experimental Research, 16,* 558-565.

Nebel-Schwalm, M. S., & Matson, J. L. (2008). Differential Diagnosis. In L. M. Johnny (Ed.), *Clinical Assessment and Intervention for Autism Spectrum Disorders* (pp. 91-129). San Diego: Academic Press.

Newschaffer, C. J. (2006). Investigating diagnostic substitution and autism prevalence trends. *Pediatrics, 117,* 1436-1437.

Newschaffer, C. J., Falb, M. D., & Gurney, J. G. (2005). National autism prevalence trends from United States special education data. *Pediatrics, 115,* e277-e282.

Nichols, H. B., Trentham-Dietz, A., Hampton, J. M., Titus-Ernstoff, L., Egan, K. M., Willett, W. C., & Newcomb, P. A. (2006). From menarch to menopause: Trends among US women born from 1912 to 1969. *American Jounral of Epidemiology, 164,* 1003-1011.

Nicholas, J. S., Charles, J. M., Carpenter, L. A., King, L. B., Jenner, W., & Spratt, E. G. (2008). Prevalence and characteristics of children with autism-spectrum disorders. *Annals of Epidemiology, 18*, 130-136.

Ohnishi, T., Matsuda, H., Hashimoto, T., Kunihiro, T., Nishikawa, M., Uema, T., & Sasaki, M. (2000). Abnormal regional cerebral blood flow in childhood autism. *Brain, 123,* 1838-1844.

Onore, C. E., Schwartzer, J. J., Careaga, M., Berman, R. F., & Ashwood, P. (2014). Maternal immune activation leads to activated inflammatory macrophages in offspring. *Brain, Behavior, and Immunity, 38*(0), 220-226. doi: http://dx.doi.org/10.1016/j.bbi.2014.02.007

Otsuka, H., Harada, M., Mori, K., Hisaoka, S., & Nishitani, H. (1999). Brain metabolites in the hippocampus-amygdala region and cerebellum in autism: An [1]H-MR spectroscopy study. *Neuroradiology, 41,* 517-519.

Ozonoff, S., South, M., & Miller, J. N. (2000). *DSM-IV*-defined asperger syndrome: Cognitive, behavioral and early history differentiation from high-functioning autism. *Autism: The International Journal of Research and Practice, 4*, 29-46.

Panksepp, J. (1979). A neurochemical theory of autism. *Trends in Neurosciences, 2,* 174-177.

Parner, E. T., Baron-Cohen, S., Lauritsen, M. B. Jorgensen, M., Schieve, L. A., Yeargin-Allsopp, M., & Obel, C. (2012). Parental age and autism spectrum disorders. *Annals of Epidemiology, 22,* 143-150.

Pennesi, C. M. & Klein, L. C. (2012). Effectiveness of the gluten-free, casein-free diet for children diagnosed with autsim spectrum disorder: Based on parental report. *Nutritional Neuroscience, 15,* 85-91.

Penrose, L. S. (1933). The relative effects of paternal and maternal age in mongolism. *Journal of Genetics, 27*, 219–224.

Posey, D. J., Stigler, K. A., Erickson, C. A., & McDougle, C. J. (2008). Antipsychotics in the treatment of autism. *Journal of Clinical Investigation, 118,* 6-14.

Rai, D., Lewis, G., Lundberg, M., Araya, R., Svensson, A., Dalman, C., & ... Magnusson, C. (2012). Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. *Journal of The American Academy Of Child & Adolescent Psychiatry*, *51*(5), 467-476.e6.

Rasalam, A. D., Hailey, H., Williams, J. H., Moore, S. J. Turnpenny, P. D., Lloyd, D. J., & Dean J. C. (2005). Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Developmental Medicine & Child Neurology, 47,* 551-555.

Ratajczak, H. V. (2011). Theoretical aspects of autism: Causes--A review. [Article]. *Journal of Immunotoxicology, 8*(1), 68-79. doi: 10.3109/1547691x.2010.545086

Reich, T., Cloninger, C. R., & Guze, S. B. (1975). The multifactorial model of disease transmission: 1. Description of the model and its use in psychiatry. *British Journal of Psychiatry, 127,* 1-10.

Reuther, E. T., Davis, T. E., III, Moree, B. N., & Matson, J. L. (2011). Treating selective mutism using modular CBT for child anxiety: A case study. *Journal of Clinical Child and Adolescent Psychology, 40*, 156-163.

Rieske, R. D., Matson, J. L., Beighley, J. S., Williams, L. W., & Turygin, N. (2014). Personal-social development differences in toddlers diagnosed with autsim spectrum disorder: *DSM-IV-TR* versus *DSM-5*. *Research in Autsim Spectrum Disorders, 8,* 1307-1315.

Ritvo, S., & Provence, S. (1954). Form perception and imitation in some autistic children: diagnostic findings and their contextual interpretation. *The Psychoanalytic Study of the Child, 8*, 155-161.

Roberts, E. M., English, P. B., Grether, J. K., Windham, G. C., Somberg, L., & Wolff, C. (2007). Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley. [Article]. *Environmental Health Perspectives, 115*(10), 1482-1489.

Rogers, S. J., Wehner, D. E., & Hagerman, R. (2001). The behavioral phenotype in fragile X: Symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioral Pediatrics, 22,* 409-417.

Román, G. C. (2007). Autism: Transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *Journal of the Neurological Sciences, 262*(1–2), 15-26. doi: http://dx.doi.org/10.1016/j.jns.2007.06.023

Roullet, F. I., Lai, J. K. Y., & Foster, J. A. (2013). In utero exposure to valproic acid and autism — A current review of clinical and animal studies. *Neurotoxicology and Teratology, 36*(0), 47-56. doi: http://dx.doi.org/10.1016/j.ntt.2013.01.004

Rubin, L. H., Witkiewitz, K., St. Andre, J., & Reilly, S. (2007). Methods for handling missing data in the behavioral nuerosciences: Don't throw the baby rat out with the bath water. *The Journal of Undergraduate Neuroscience Education, 5,* A71-A77.

Rutter, M. (1968). Concepts of autism: A review of research. *Journal of Child Psychology and Psychiatry, 9*, 1-25.

Rutter, M. (1972). Childhood schizophrenia reconsidered. *Journal Of Autism And Childhood Schizophrenia, 2*, 315-337.

Rutter, M., & Bartak, L. (1971). Causes of infantile autism: Some considerations from recent research. *Journal of Autism & Childhood Schizophrenia, 1*, 20-32.

Rutter, M., Lebovici, S., Eisenberg, L., Sneznevskij, A. V., Sadoun, R., Brooke, E., & Lin, T. Y. (1969). A tri-axial classification of mental disorders in childhood. An international study. *Journal Of Child Psychology And Psychiatry, And Allied Disciplines, 10*, 41-61.

Sandin, S., Hultman, C. M., Kolevzon, A., Gross, R., MacCabe, J. H., & Reichenberg, A. (2012). Advancing maternal age is associated with increasing risk for autism: A review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry, 51,* 477-486.

Sakamoto, A., Moriuchi, H., Matsuzaki, J., Motoyama, K., & Moriuchi, M. (2015). Retrospective diagnosis of congenital cytomegalovirus infection in children with autism spectrum disorder but no other major neurologic deficit. *Brain and Development, 37*(2), 200-205. doi: http://dx.doi.org/10.1016/j.braindev.2014.03.016

Schopler, E., Reichler, R. J., DeVellis, R. F., & Daly, K. (1980). Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *Journal of Autism and Developmental Disorders, 10*, 91-103.

Schroeder, J. H. (2010). Inter-Parent Agreement on the Syndrome Scales of the Child Behavior Checklist (CBCL): Correspondence and Discrepancies. *Journal of Child & Family Studies, 19*(5), 646-653.

Scott, S., & Beidel, D. C. (2011). Selective mutism: an update and suggestions for future research. *Current Psychiatry Reports, 13*, 251-257.

Shattuck, P. T. (2006). The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education [corrected] [published erratum appears in PEDIATRICS 2006 Aug;118(2):852]. *Pediatrics, 117*, 1028-1037.

Shelton, J. F., Geraghty, E. M., Tancredi, D. J., Delwiche, L. D., Schmidt, R. J., Ritz, B., . . . Hertz-Picciotto, I. (2014). Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. [Article]. *Environmental Health Perspectives, 122*(10), 1103-1109. doi: 10.1289/ehp.1307044

Shelton, J. F., Tancredi, D. J., & Hertz-Picciotto, I. (2010). Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Research, 3,* 30-39.

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry, 47*, 921-929.

Smalley, S. L. (1998). Autism and tuberous sclerosis. *Journal of Autism and Developmental Disorders, 28,* 407-414.

Steffenburg, S., Gillberg, C, Hellgren, L., Andersson, L, Gillberg, I. C., Jakobsson, G., & Bohman, M. (1989). A twin study of autism in denmark, finland, iceland, norway, and sweden. *Journal of Child Psychology and Psychiatry, 30,* 405-416.

Stigler, K. A., Sweeten, T. L., Posey, D. J., & McDougle, C. J. (2009). Autism and immune factors: A comprehensive review. *Research in Autism Spectrum Disorders, 3,* 840-860.

Strifert, K. (2014). The link between oral contraceptive use and prevalence in autism spectrum disorder. *Medical Hypotheses*, *83*(6), 718-725. doi:10.1016/j.mehy.2014.09.026

Stromland, K., Nordin, V., Miller, M., Akerstrom, B., & Gillberg, C. (1994). Autism in thalidomide embryopathy: A population study. *Developmental medicine & Child Neurology, 36,* 351-356.

Sukhodolsky, D. G., Scahill, L., Gadow, K. D., Arnold, L. E., Aman, M. G., McDougle, C. J., . . . Vitiello, B. (2008). Parent-rated anxiety symptoms in children with pervasive developmental disorders: Frequency and association with core autism symptoms and cognitive functioning. *Journal of Abnormal Child Psychology, 36*, 117-128.

Sullivan, K. M. (2009). Iodine deficiency as a cause of autism. *Journal of the Neurological Sciences, 276*(1–2), 202. doi: http://dx.doi.org/10.1016/j.jns.2008.09.016

Sweeten, T. L., Posey, D. J., Shekhar, A., & McDougle, C. J. (2002). The amygdala and related structures in the pathophysiology of autism. *Pharmacology, Biochemistry, and Behavior, 71,* 449-455.

Szatmari, P. (1992). The validity of autistic spectrum disorders: A literature review. *Journal of Autism and Developmental Disorders, 22*, 583-600.

Tidmarsh, L., & Volkmar, F. R. (2003). Diagnosis and epidemiology of autism spectrum disorders. *Canadian Journal of Psychiatry, 48*, 517.

Towbin, K. E., Dykens, E. M., Pearson, G. S., & Cohen, D. J. (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. *Journal of the American Academcy of Child and Adolescent Psychiatry, 32,* 775-782.

Tsai, L. (2013). Asperger's Disorder will be back. *Journal of Autism and Developmental Disorders, 43,* 2914-2942.

Tsai, L. (2014). Impact of *DSM-5* on epidemiology of Autsim Specturm Disorder. *Research in Autism Spetrum Disorders, 8,* 1454-1470.

Tsai, L., & Beisler, J. M. (1983). The development of sex differences in infantile autism. *British Journal of Psychiatry, 142*, 373-378.

Tsai, L., & Ghaziuddin, M. (2014). *DSM-5* ASD moves forward into the past. *Journal of Autism and Developmental Disorders, 44,* 321-330.
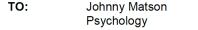
Tsai, L., Stewart, M. A., & August, G. (1981). Implication of sex differences in the familial transmission of infantile autism. *Journal of Autism and Developmental Disorders, 11*, 165-174.

Van Krevelen, D. A. (1971). Early infantile autism and autistic psychopathy. *Journal of Autism & Childhood Schizophrenia, 1*, 82-86.

Vermiglio, F., LoPresti, V. P., Moleti, M., Sidoti, M., Tortorella, G., Scaffidi, G.,…Trimarchi, F. (2004). Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iddoine deficiency: A possible novel iodine deficiency disorder in developed countries. *Jounral of Clinical Endocrinology and Metabolism, 89,* 6054-6060.

Viscidi, E. W., Johnson, A. L., Spence, S. J. Buka, S. L., Morrow, E. M., & Triche, E. W. (2014). The association between epilepsy and autism symptoms and maladaptive behaviors in children with autism spectrum disorder. *Autism, 18, 996-1006.*

Volkmar, F. R. (1992). Childhood disintegrative disorder: issues for *DSM-IV*. *Journal of Autism and Developmental Disorders, 22*, 625-642.

Volkmar, F. R., & Cohen, D. J. (1991). Comorbid association of autism and schizophrenia. *The American Journal Of Psychiatry, 148*, 1705-1707.

Volkmar, F. R., Koenig, K., & State, M. (2005). Childhood disintegrative disorder. In F. R. Volkmar, R. Paul, A. Klin & D. Cohen (Eds.), *Handbook of autism and pervasive developmental disorders, Vol. 1: Diagnosis, development, neurobiology, and behavior (3rd ed.).* (pp. 70-87). Hoboken, NJ US: John Wiley & Sons Inc.

Volkmar, F. R. & McPartland, J. C. (2014). From Kanner to *DSM-5*: Autism as an evolving diagnostic concept. *Annual Review of Clinical Psychology, 10,* 193-212.

Volkmar, F. R. & Reichow, B. (2014). The evolution of autism as a diagnostic concept: From Kanner to DSM-5: A commentary. In T. E. Davis III, S. W. White, & T. H. Ollendick (Eds.), *Handbook of Autism and Anxiety* (pp. 217-230). Autism and Child Psychopathology Series (Series Editor: Johnny L. Matson). Switzerland: Springer International Publishing.

Volkmar, F. R., & Rutter, M. (1995). Childhood disintegrative disorder: results of the *DSM-IV-TR* autism field trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*, 1092-1095.

Volkmar, F. R., Shaffer, D., & First, M. (2000). PDDNOS in *DSM-IV*. *Journal of Autism and Developmental Disorders, 30*, 74-75.

Vranekovic, J., Bozovic, I. B., Grubic, Z., Wagner, J., Pavlinic, D., Dahoun, S., & ... Brajenovic-Milic, B. (2012). Down Syndrome: Parental origin, recombination, and maternal age. *Genetic Testing and Molecular Biomarkers*, *16*(1), 70-73.

Waite,V., & Woods, K. (1999). Educaitonal psychologists' assessments of autism. *Educational Psychology in Practice, 15,* 167-173.

Walvoord, E. C. (2010). The timing of puberty: Is it changing? Does it matter?. *The Journal of Adolescent Health: Official Publication Of The Society For Adolescent Medicine*, *47*(5), 433-439. doi:10.1016/j.jadohealth.2010.05.018

Wang, L. W., Tancredi D. J., & Thomas, D. W. (2011). The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. *Journal of Developmental and Behavioral Pediatrics, 32,* 351-360.

White, S., Bray, B., & Ollendick, T. (2012). Examining Shared and Unique Aspects of Social Anxiety Disorder and Autism Spectrum Disorder Using Factor Analysis. *Journal Of Autism & Developmental Disorders*, *42*(5), 874-884.

White, S. W., Oswald, D., Ollendick, T., & Scahill, L. (2009). Anxiety in children and adolescents with autism spectrum disorders. *Clinical Psychology Review, 29*, 216-229.

Whitehouse, A. J. O., Maybery, M. T., Hart, R., Mattes, E., Newnham, J. P., Sloboda, D. M., . . . Hickey, M. (2010). Fetal androgen exposure and pragmatic language ability of girls in middle childhood: Implications for the extreme male-brain theory of autism. *Psychoneuroendocrinology, 35*(8), 1259-1264. doi: http://dx.doi.org/10.1016/j.psyneuen.2010.02.007

Williams, L. W., Matson, J. L., Beighley, J. S., Rieske, R. D., & Adams, H. L. (2014). Comorbid symptoms in toddlers diagnosed with autism spectrum disorder with the *DSM-IV-TR* and the *DSM-5* criteria. *Research in Autism Spectrum Disorders, 8,* 186-192.

Willliams, S., Leader, G., Mannion A., & Chen, J. (2015). An investigation of anxiety in children and adolescents with autism spectrum disorders. *Research in Autism Spectrum Disorders, 10,* 30-40.

Wing, L. (1980). Childhood autism and social class: A question of selection? *The British Journal of Psychiatry, 137,* 410-417.

Wing, L. (1981). Sex ratios in early childhood autism and related conditions. *Psychiatry Research, 5,* 129-137.

Wing, L., & Potter, D. (2002). The epidemiology of autistic spectrum disorders: Is the prevalence rising? *Mental Retardation and Developmental Disabilities Research Reviews, 8,* 151-161.

Winterkorn, E. B., Pulsifer, M. B., & Thiele, E. A. (2007). Cognitive prognosis of patients with tuberous sclerosis complex. *Neurology, 68,* 62-64.

Wong, V. (2006). Study of the relationship between tuberous sclerosis complex and autistic disorder. *Journal of Child Neurology, 21,* 199-204.

Wood, J. J., & Gadow, K. D. (2010). Exploring the Nature and Function of Anxiety in Youth with Autism Spectrum Disorders. Clinical Psychology: Science & Practice, 17(4), 281-292.

World Health Organization. (1993). *The ICD-10 classification of mental and behavioural disorders : diagnostic criteria for research*. Geneva :: World Health Organization.

Yassa, H. A. (2014). Autism: A form of lead and mercury toxicity. *Environmental Toxicology and Pharmacology, 38*(3), 1016-1024. doi: http://dx.doi.org/10.1016/j.etap.2014.10.005

Yau, V. M., Green, P. G., Alaimo, C. P., Yoshida, C. K., Lutsky, M., Windham, G. C., . . . Croen, L. A. (2014). Prenatal and neonatal peripheral blood mercury levels and autism spectrum disorders. *Environmental Research, 133*(0), 294-303. doi: http://dx.doi.org/10.1016/j.envres.2014.04.034

Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C., & Murphy, C. (2003). Prevalence of autism in a US metropolitan area. *Journal of the American Medical Association, 289,* 49-55.

Yoshimasu, K., Kiyohara, C., Takemura, S., & Nakai, K. (2014). A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/hyperactivity disorder in the childhood. *NeuroToxicology, 44*(0), 121-131. doi: http://dx.doi.org/10.1016/j.neuro.2014.06.007

Zachor, D. A., & Itzchak, E. B. (2011). Assisted reproductive technology and risk for autism spectrum disorder. *Research in Developmental Disabilities: A Multidisciplinary Journal*, *32*, 2950-2956.

Zafeiriou, D. I., Ververi, A., & Vargiami, E. (2007). Childhood autism and associated comorbidities. *Brain and Development, 29,* 257-272.

Zerbo, O., Leong, A., Barcellos, L., Bernal, P., Fireman, B., & Croen, L. A. (2015). Immune mediated conditions in autism spectrum disorders. *Brain, Behavior, and Immunity,in press.* Advanced publication. doi: 10.1016/j.bbi.2015.02.001

APPENDIX

ACTION ON PROTOCOL CONTINUATION REQUEST

Institutional Review Board
Dr. Dennis Landin, Chair
130 David Boyd Hall
Baton Rouge, LA 70803
P: 225.578.8692
F: 225.578.5983
irb@lsu.edu | lsu.edu/irb

TO: Johnny Matson
Psychology

FROM: Dennis Landin
Chair, Institutional Review Board

DATE: April 14, 2015

RE: **IRB#** 2609

TITLE: Developing the Autism Spectrum Disorder (ASD)

New Protocol/Modification/Continuation: _Continuation_

Review type: Full ___ Expedited _X_   **Review date:** _4/14/2015_

Risk Factor: Minimal ____X____   Uncertain _____   Greater Than Minimal_____

Approved_____X_____ Disapproved_____

Approval Date: _4/14/2015_   **Approval Expiration Date:** _4/13/2016_

Re-review frequency: (annual unless otherwise stated)

Number of subjects approved: _2,000_

LSU Proposal Number (if applicable)**:**

Protocol Matches Scope of Work in Grant proposal: (if applicable) ___

By: Dennis Landin, Chairman _____

PRINCIPAL INVESTIGATOR: PLEASE READ THE FOLLOWING –
Continuing approval is CONDITIONAL on:
1. Adherence to the approved protocol, familiarity with, and adherence to the ethical standards of the Belmont Report, and LSU's Assurance of Compliance with DHHS regulations for the protection of human subjects*
2. Prior approval of a change in protocol, including revision of the consent documents or an increase in the number of subjects over that approved.
3. Obtaining renewed approval (or submittal of a termination report), prior to the approval expiration date, upon   request by the IRB office (irrespective of when the project actually begins); notification of project termination.
4. Retention of documentation of informed consent and study records for at least 3 years after the study ends.
5. Continuing attention to the physical and psychological well-being and informed consent of the individual participants, including notification of new information that might affect consent.
6. A prompt report to the IRB of any adverse event affecting a participant potentially arising from the study.
7. Notification of the IRB of a serious compliance failure.
8. SPECIAL NOTE:
All investigators and support staff have access to copies of the Belmont Report, LSU's Assurance with DHHS, DHHS (45 CFR 46) and FDA regulations governing use of human subjects, and other relevant documents in print in this office or on our World Wide Web site at http://www.lsu.edu/irb

VITA

Robert D. Rieske was born in Utah in 1981. He is married with four children and currently resides in Idaho and is an Assistant Professor at Idaho State University in the Clinical Psychology program. His research has focused on assessment and treatment of children and adults with intellectual and developmental disabilities with an emphasis in Autism Spectrum Disorders. He has worked with individuals a broad range of developmental disabilities as well as adolescents with severe mental illness in residential treatment settings. He received his Bachelor of Science degree in Behavioral Science from Utah Valley University in 2008. He received his Master's Degree in Clinical Psychology from Louisiana State University and is expected to graduate with his Ph.D. in Clinical Psychology from Louisiana State University in 2015. His current clinical and research interests are the assessment and treatment of individuals with Autism Spectrum Disorders and other developmental disabilities, with a particular emphasis in comorbid anxiety.