Social Communication and Interactions Symptoms in Fragile X Syndrome: The Underlying Comorbidities of Autism Spectrum Disorder and Anxiety

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Abstract

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability. The genetic syndrome is often accompanied by high rates of comorbid autism spectrum disorder (ASD) and anxiety. Many symptoms of FXS and ASD overlap, and symptoms of anxiety may appear to be symptoms of ASD. Further, changes in DSM-5 ASD criteria may affect the prevalence of ASD in FXS. The present study examined the prevalence of individuals with FXS who met diagnostic criteria for ASD, especially social communication impairments within the context of DSM-5 changes, and examined parent-reported anxiety as a predictor of ASD diagnosis. A total of 74 participants between the ages of 12 and 40 were administered the Stanford-Binet, 5th Edition, Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2), Social Communication Questionnaire (SCQ), and Anxiety Depression and Mood Scale. ASD symptoms were examined across 4 methods: 1) Met based on ADOS-2; 2) met cut-off on the SCQ; 3) met ASD criteria for both ADOS-2 and SCQ; and 4) met based on DSM-5 criteria. The percentage of individuals meeting study diagnostic determination (ADOS-2 + SCQ) for ASD (28%) was similar to previous reports, and was slightly lower than the percentage meeting for the DSM-5 (37%). More individuals met SCI criteria than RRBI criteria. More males met criteria for all ASD variables than females. Multiple regression analyses indicated that parent-reported anxiety did not predict any ASD variables; rather age and nonverbal intelligence were predictive of most ASD variables. Cognitive functioning and variable RRBI symptoms may predict ASD in FXS more strongly than anxiety.

Social Communication and Interactions Symptoms in Fragile X Syndrome: The Underlying Comorbidities of Autism Spectrum Disorder and Anxiety

Fragile X syndrome (FXS) is characterized by cognitive deficits and a diverse set of behavioral outcomes (Boyle & Kaufmann, 2010). There is great variability in the phenotypes presented; yet virtually all phenotypes include impairments in social communication and interactions. In the past, many of the social impairments observed in FXS were attributed to comorbid autism spectrum disorder (ASD). With the recent changes in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5) however, it is becoming evident that not all social impairments are a result of ASD. Some researchers have suggested that autism symptoms observed in FXS may be a result of severe cognitive deficits (Rogers, Wehner, & Hagerman, 2001). Other researchers suggest that social communication symptoms of ASD are actually a result of anxiety (Wheeler et al., 2014). At this time, it is unclear the extent to which anxiety affects the social communication symptoms observed in individuals with FXS. Thus, research on the relationship and impact of anxiety on individuals with FXS is needed.

Fragile X Syndrome

FXS is the most common inherited cause of intellectual disability and one of the leading known genetic causes of ASD (Crawford, Acuña, & Sherman, 2001). FXS is a genetic condition that is estimated to affect approximately 1 in 4000 males and 1 in 8000 females (Hagerman, 2008). Individuals with FXS often exhibit physical abnormalities that include an elongated face, large ears, a prominent jaw, increased head circumference, and mitral valve prolapse (Hagerman 2002). The physical characteristics tend to differ between individuals, and the phenotype that is presented is dependent upon numerous genetic factors.

The biological mechanisms underlying FXS are caused by a mutation of the fragile X mental retardation 1 gene (*FMR1),* which is located on the X-chromosome (Pieretti et al., 1991). The mutation is a product of a repeat of the Cytosine-Guanine-Guanine (CGG) trinucleotide sequence. Typically, individuals have a CGG trinucleotide sequence of less than 55 repeats (Tsiouris & Brown, 2004). However, individuals with full mutation FXS have a CGG expansion, which repeats 200 or more times (Oostra & Willmsen, 2003).

Expansion of the CGG sequence of *FMR1* results in methylation of the *FMR1* gene, which halts the production of the fragile X mental retardation protein (FMRP; Coffee et al., 2009). FMRP is essential in typical brain formation and has been associated with synaptic development, including synaptic maturity and plasticity, as well as experience-dependent learning (Hagerman, Ono, & Hagerman, 2005). With such implications, the reduction or absence of FMRP can have negative consequences for individuals in terms of cognitive functioning and contributes to intellectual disability. Reduced FMRP production can cause a variety of cognitive deficiencies including learning and memory deficits (Crum-Bailey, Dennison, Weiner, & Hawley, 2013). Indeed, individuals with FXS are characterized as having weak spatial short-term memory, difficulty processing sequential information, and trouble directing and sustaining attention (Freund & Reiss, 1991).

Intellectual Ability in Individuals with Fragile X Syndrome

Although reduced or absence of FMRP is almost certainly implicated in cognitive deficits, the variability in functioning can also be attributed, in part, to several factors. For example, the IQ of individuals with FXS ranges from the severe intellectual disability range to normal intelligence (Farzin & Koldewyn, 2014). In adult males with FXS, 95% have an IQ below 70 and the average IQ score for males with FXS is between 40-49 (Farzin & Koldewyn, 2014). In

contrast, only 25-33% of females with FXS have an IQ at 70 or below. The average IQ for females is between 70-90. The higher IQ observed in females is due to the genetic characteristics of FXS. Because FXS is an X-link disorder, females are less severely affected due to the presence of a second X-chromosome (Center for Disease Control and Prevention [CDC], 2013).

Although there is variability in overall IQ scores, the profile of specific strengths and weakness appear to be consistent. Findings from Van der Molen et al. (2010) support this notion. In the study, researchers divided 43 adult males, 18-48 years of age, across three subgroups - high, intermediate, and low functioning. Subgroups were assigned based on the participant's performance on neuropsychological and intelligence testing. Results indicated that although the extent of the strengths and weakness varied depending on level of functioning, all groups displayed similar cognitive characteristics such as strengths in visuo-perceptual recognition and weaknesses in verbal reasoning.

Although there is great variability in the presentation of symptoms, there are many characteristics that are present in a majority of the FXS population. Some of the most common behaviors observed in individuals with FXS include shyness, social avoidance, social anxiety, hyperactivity, impulsivity, inattention, tantrums, aggressiveness towards others, self-injurious behavior and destructiveness during explosive outbursts (Tsiouris & Brown, 2004). It is likely that the behavioral problems observed in individuals with FXS are a result of low cognitive abilities and limited communication abilities.

Communication in Individuals with Fragile X Syndrome

Although there is variability in impact, the majority of males with FXS have intellectual disability, which contributes to significant challenges in communication. While individuals with

FXS have been characterized to have a relative strength in receptive language – the ability to understand spoken words, they often have difficulty in the realm of expressive language – which is defined by Abbeduto, Brady, and Kover (2007) as the number of different words spoken by an individual Deficits in expressive language contribute to difficulties in social situations for individuals with FXS. Because individuals with FXS experience difficulty expressing themselves, communication with others is impaired. The expressive language impairment is largely displayed in the domain of pragmatic (i.e., social) language impairment.

Pragmatic language - a type of expressive language – is defined by the American Speech-Language-Hearing Association(2014) as involving three major communication skills: using language, changing language, and following rules. Pragmatic language involves the use of language in social context to express oneself or convey needs, interest, or intentions (Abbeduto et al., 2007). Proficiency of pragmatic language largely relies on one's ability to use verbal and nonverbal signals, give background information that is relevant to the conversation, and understand societal conventions for communication. With deficits in expressive language, individuals with FXS experience challenges in communicating verbally and nonverbally. In addition, individuals with FXS have difficulty with topic maintenance, selection of appropriate words, and modifying language to match the expectations of the communicative partner (Klusek, Martin, Losh, 2014). Similar to expressive language impairments, pragmatic language skills are not fully acquired by individuals with FXS due to deficits in cognitive functioning.

Comorbidities

In addition to cognitive characteristics of FXS, the manifestation of comorbid and co-occurring conditions largely influence pragmatic language skills and the social ability of individuals with FXS. ASD and anxiety are among the most common comorbid conditions

associated with FXS. Bailey, Raspa, Olmsted, and Holiday (2008) conducted a survey on comorbid conditions associated with FXS and found that 70% of males and 56% of females with FXS had co-occurring anxiety. The same study found that comorbid autism occurred at a rate of 46% in males and 16% in females. These comorbidities greatly influence the characteristics and capabilities of individuals with FXS. Anxiety and ASD are both commonly linked with social communication deficiencies and when combined with the cognitive impairments of FXS, the effects on social communication ability are exacerbated.

Autism Spectrum Disorder

ASD is one of the most severe behavioral abnormalities observed in FXS. ASD is a common neurodevelopmental disorder and is marked by persistent deficits in social communication and social interactions as well as repetitive or restricted behaviors and interest (American Psychiatric Association [APA], 2013). The hallmark of autistic-like features is social impairment (National Institute of Neurological Disorders and Stroke [NINDS], 2014). Some common social abnormalities observed in ASD are gaze aversion, inability to interpret social cues, lack of empathy, repeating or echoing words, and difficulty expressing needs (NINDS, 2014; CDC, 2014). Individuals with ASD have a relative weakness in pragmatic language and as a result are often unable to engage in typical conversations. In addition to social deficits, individuals with ASD often engage in repetitive movements. Some common repetitive movements observed in ASD are rocking, biting, head banging, repetitive actions, hypo- and hyper-reactivity to sensory input, and fascination with a narrow range of topics (NINDS, 2014; CDC, 2014).

The CDC (2014) estimates ASD to affect approximately 1 in 68 children. In the FXS population, the ASD prevalence is greater. In a survey of 401 males (ages 3-11) with FXS, ASD

was reported in 48.9% (Talisa, Boyle, Crafa, & Kaufmann, 2013). The same study found the prevalence of ASD in adolescent and adults males with FXS to occur at a rate of 41.2%. Studies have even shown that individuals with FXS who do not meet full diagnostic criteria for ASD will often display some of the milder symptoms implicated with the disorder. Up to 90% of males with FXS display autistic-like features such as perseveration, repetitive speech, and poor eye contact (Hagerman, 2002). Research also suggests that cognitive deficits may amplify autism symptoms (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010).

However, ASD, unlike the more objective FXS genetic diagnosis, is behaviorally defined. In order to be diagnosed with ASD, an individual must display a specified number of autistic-related symptoms across multiple contexts. The DSM-5 (2013) defines the behavioral criteria for ASD as:

1. Criterion A: "Persistent deficits in social communication and social interaction, … as manifested by:"
    a. Deficits in social emotional reciprocity
    b. Deficits in nonverbal communicative behavior
    c. Deficits in developing, maintaining, and understanding relationships
2. Criterion B: "Restricted, repetitive patterns of behavior, interest, or activities, as manifested by at least two of the following:"
    a. Stereotyped or repetitive motor movements
    b. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
    c. Highly restricted, fixated interests that are abnormal in intensity or focus
    d. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of

the environment

These criteria have recently changed. With the publication of DSM-5 in 2013, the APA tightened the diagnostic criteria for ASD. The most notable change was the converging of the two, previously separate, DSM-IV-TR categories, impairments in social interactions and impairments in communication, into Criteria A (APA, 2013). The new singular category, as described above, includes deficits in social-emotional reciprocity, nonverbal communication, and developing relationships. With the changes, individuals must display symptoms in each of the three SCI criteria to meet criteria for ASD.

Changes made to the DSM-5 have the potential to significantly impact the diagnosis of ASD in individuals with FXS. A survey on autistic behaviors was conducted with 751 caregivers of individuals with full-mutation FXS (Wheeler et al., 2014). The researchers found that of the males who met overall DSM-IV-TR diagnostic criteria for Autistic Disorder, just under half also met for ASD based on DSM-5 criteria. The same study found that of the females who met Autistic Disorder criteria from DSM-IV-TR, only 37.5% also met ASD criteria for DSM-5. Results from Wheeler et al., (2014) suggest that fewer individuals with FXS will meet diagnostic criteria for ASD based on DSM-5. This is a major change because prior to the publication of DSM-5, nearly half of individuals with FXS were also diagnosed with comorbid ASD.

Due to the high rate of comorbidity between FXS and ASD while using DSM-IV-TR criteria, there have been a number of studies investigating the phenotypic overlap between the two disorders (Losh et al., 2012). Research has revealed that individuals with FXS and ASD display a distinct neurobehavioral profile compared to individuals with FXS only. Both males

and females with FXS and comorbid ASD exhibit weaker communication and social skills, greater behavioral problems, and greater cognitive impairments than males with FXS only or males with idiopathic autism (Bailey, Hatton, Mesibov, Ament, & Skinner, 2002; Kaufmann et al., 2004; Rogers et al., 2001). Research on the cognitive, language, and social-cognitive skills of individuals with FXS suggest that children with comorbid FXS and ASD (FXS+ASD) were more likely to achieve the lowest possible standard score on the Stanford-Binet, 4th Edition (Thordike, Hagen, & Sattler, 1986) than were children with FXS only (Lewis et al., 2006). Lewis et al. (2006) described cognitive impairments as more substantial in individuals with FXS+ASD as opposed to individuals only diagnosed with FXS. Results also indicated that individuals with FXS+ASD were more impaired than individuals with FXS only in the realms of receptive language and theory of mind. Losh et al. (2012) found similar results: Deficits in pragmatic language and theory of mind were restricted to individuals with FXS+ASD. In individuals with FXS only, receptive language is typically described as a relative strength. The results from both studies support the notion that FXS+ASD represents a distinct behavioral profile within FXS: a profile that places individuals at a high risk for problems with nonverbal cognition, language comprehension, and theory of mind (Lewis et al., 2006).

Although there is evidence to suggest a distinct neurobehavioral profile of FXS and comorbid ASD, there is also research to suggest that ASD in FXS is not true ASD (Abbeduto, McDuffie & Thurman, 2014). Abbeduto et al., (2014) found important differences in behavioral manifestations and behavioral correlates of ASD in FXS relative to idiopathic ASD. Individuals with FXS and comorbid ASD tend to have less severe impairments in social and communication symptoms than individuals with idiopathic ASD; indicating a difference in presentation of symptoms. In addition, boys with FXS and comorbid ASD had higher generalized anxiety

scores on the ADAMS compared to boys with idiopathic ASD (Thurman, McDuffie, Hagerman, & Abbeduto, 2014). These results indicate that symptoms of ASD in FXS are distinguishable from symptoms of idiopathic ASD, thus suggesting that ASD in FXS may not be true ASD.

In addition, there has been debate concerning the etiology of symptoms observed in individuals with FXS and comorbid ASD. It has been suggested that ASD symptoms observed in FXS are a result of more severe impairments and intellectual disability overall (Rogers et al., 2001). Reduction in the ASD prevalence in FXS potentially provides support for this theory. With the publication of DSM-5 and the tighter ASD criteria, the prevalence of ASD in FXS has the potential to be reduced. This possibility is evident in data of Wheeler et al. (2014) who found more individuals with FXS met criteria for Autistic Disorder based on DSM-IV-TR, than met for ASD based on DSM-5. Based on DSM-5 ASD criteria, many individuals in the Wheeler et al., (2014) sample were sub-threshold for ASD criteria regardless of their level of cognitive impairment, which has led researchers to hypothesize that another comorbidity, such as anxiety, is increasing the rates of ASD.

With the etiology of ASD symptoms in FXS in question, the possibility of ASD symptoms in FXS being a result of a different psychopathology should be considered. ASD symptoms such as gaze aversion, difficulty communicating, failing to make desires known, and overall social deficits are also common symptoms observed in anxiety (CDC, 2014; NINDS, 2014). Given the high rates of anxiety in individuals with FXS, it is possible that symptoms of anxiety have been mistaken for ASD symptoms. Few investigations of anxiety in individuals with FXS have used standardized definition and measures (Talisa, et al., 2014). Therefore, there is a paucity of research on anxiety in FXS, resulting in insufficient data on characteristics, frequency, and severity of anxiety disorder in FXS.

Anxiety and FXS

The rate of anxiety in individuals with FXS is three times greater than the rate in the general population. In individuals with FXS, anxiety is observed in 70% of males 56% of females (Bailey et al., 2008). More than half of FXS individuals affected by anxiety disorders have been diagnosed with multiple conditions (Cordeiro, Ballinger, Hagerman, & Hessl, 2011). Cordeiro et al., (2011) examined the rates of anxiety disorders in FXS and found the most common anxiety disorders associated with FXS to be specific phobia, which occurs at a rate of 64.9% in males and 51.4% in females, social phobia which occurs at the rate of 34.5% in males and 39.5% in females, and selective mutism occurring at a rate of 28.1% in males and 25.3% in females.

Co-occurring anxiety in FXS creates great difficulty in the realms of communication and social interaction. Due to the cognitive impairments and communication challenges that are present in individuals with FXS, anxiety diagnoses are challenging to make (Boyle & Kaufmann, 2010). Therefore, many of the findings about anxiety in FXS have come from parent-report data. Many parent-report questionnaires have indicated high rates of social withdrawal in children with FXS (Cordeiro et al., 2011). Social withdrawal and social avoidance have a negative impact on communication ability and therefore hinders language and social development (Klusek et al., 2014). Due to impairments in communication, social interactions are problematic for individuals with FXS and ultimately lead to the avoidance of social encounters. The combination of low verbal capabilities and social withdrawal creates the social anxiety experienced by many individuals with FXS (Tonnsen, Malone, Hatton, & Roberts, 2013). Social anxiety can be observed during conversational speech and often results in deficiencies in pragmatic language.

Anxiety can impair the social skills of individuals to a point where they are uncomfortable, and in some cases, unable to communicate with others.

Study Rationale

The comorbid and co-occurring conditions, ASD and anxiety, often accompany FXS and largely contribute to the social communication deficits observed in the genetic syndrome. In the past, social communication symptoms observed in FXS were attributed to comorbid ASD. With the changes made to ASD criteria, however, it is becoming increasingly evident that social communication symptoms in FXS may be a result of a condition other than ASD. In regards to the debate concerning the etiology of ASD symptoms in FXS, it has been hypothesized that the social-communication symptoms used in diagnosing ASD in FXS may be more of a result of anxiety, as opposed to core deficits in social communication and interaction (Lewis et al., 2006).

With the overlap of symptoms between ASD and anxiety it is often difficult to distinguish etiology: without careful consideration of the differential diagnosis, anxiety symptoms could easily be viewed as a reflection of autism (Wheeler et al., 2014). Due to the limited knowledge of the relationship between anxiety and FXS, the role anxiety plays on social communication symptoms within FXS is unclear. It is also unclear how and if the interaction between anxiety and ASD impacts social communication outcomes within the FXS population. Thus, research on the relationship and impact of anxiety in FXS is important in understanding the overlap of social communication symptoms within the FXS population.

Present Study

In the present study, social communication symptoms in individuals with full mutation FXS are investigated. The primary aims of the study were:

Aim 1: Examine the variability in the frequency of ASD diagnoses based on multiple

diagnostic assessments and criteria.

Question 1. What is the frequency of individuals who met ASD criteria based on multiple diagnostic assessments and criteria?

Question 2. What is the frequency of individuals who met criteria across the two broad ASD criteria (Social Communication and Interaction – SCI and Repetitive or Restricted Behaviors or Interest – RRBI) and each of the three SCI criteria (A1 – Social emotional reciprocity; A2 – Communicative Behavior; A3 – Relationships with Others)?

Question 3. Are there differences in the frequency of those who meet criteria based on the two broad ASD criteria and each of the three SCI criteria based on age or gender?

Question 4. Are there differences by age or gender in the severity of each of the three SCI criteria?

Aim 2: Examine the relationships among parent-reported anxiety scores, age, nonverbal IQ, the three SCI criteria, and the diagnosis of ASD as determined by different diagnostic criteria.

Question 5. Which DSM-5 criteria are most strongly correlated with anxiety symptoms?

Question 6. After controlling for age and nonverbal IQ to what extent do parent-reported anxiety scores predict scores on the three SCI criteria and an ASD diagnosis as defined by diagnostic criteria?

In order to further understand how symptoms of autism align with various ASD diagnostic methods, I also examined the frequency of individuals with FXS who met criteria based on multiple variables of ASD. The frequency of individuals who met ASD criteria based on the diagnostic methods were examined for variability and analyzed for differences in symptom severity. The two broad ASD criteria (SCI and RRBI) and three SCI criteria were

examined for frequency and to see which has most strongly correlated with parent-reported anxiety scores. I hypothesized that the frequency of individuals meeting criteria based on SCI would be lower than the percentage of individuals meeting criteria based on RRBI. Based on the changes made in DSM-5, this study also examined the extent to which parent-reported anxiety scores predict SCI symptoms on the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2; Lord et al., 2012) as well as an ASD diagnosis as defined by different diagnostic criteria. I hypothesized that parent-reported anxiety would significantly predict SCI scores and a diagnosis of ASD as defined by either diagnostic criteria. Further, I hypothesized that all SCI criteria would be correlated with anxiety scores. Age, nonverbal IQ and parent-reported anxiety scores were used to predict scores on the SCI criteria and an ASD diagnoses as determined by different diagnostic criteria.

Methods

Participants

A total of 75 participants were included in the initial analysis. One participant had a nonverbal IQ score that was identified as an outlier and excluded from the analysis. After removing one outlier, the sample size was reduced to 74 participants, 47 (64%) males and 27 (36%) females. A number of the participants had incomplete demographic information. For example, information on race/ ethnicity was only obtained from 68 individuals. The majority of the participants were Caucasian (78%). The sample included few African American individuals (4%) and few Asian, Pacific Islander, Hispanic, or individuals who identified as "Other" (e.g., biracial), each representing 1% of the sample. Information on income was collected from 44 individuals. This sample is relatively wealthy, the majority of the sample (89%) had an income above 65,000. Due to the lack of variability in race and family income, these variables were not

included in the analysis. As seen in Table 1, the average age of the participants was 22.00 (*SD* = 7.20). The average age for males was 22.17 (*SD* = 7.45) and the average age for females was 21.70 (*SD* = 6.88; see Table 2). There was no significant difference in the age of the participants based on gender, $t(72) = 0.27$, $p = 0.79$ (See Table 2).

Data were collected from an NICHD funded RO1, Decisional Capacity for Informed Consent in Fragile X Syndrome. The decisional capacity study is a collaboration between Research Triangle Institute (RTI) and the University of North Carolina at Chapel Hill (UNC). Participants for the decisional capacity study were recruited using a variety of sources, including recruiting families who had participated in previous longitudinal studies the FX research registry maintained by UNC, and announcements on the National Fragile X Foundation web site.

The decisional capacity study assented and consented both minors and adults, some of whom have legal guardians, to participate in the study. Individuals who were nonverbal were excluded from the study due to the likelihood that they would experience difficulty completing the assessment battery. Data for the current study were collected between July 2013 and December 2014.

Measures

The decisional capacity study includes a large battery of neurocognitive assessments designed to examine factors associated with decisional capacity in individuals with FXS. These included measures of intellectual ability, executive functioning, autism, adaptive behavior, memory, and communication. From the larger battery, this study used measures to assess intellectual ability, autism, and anxiety. All assessments were administered by trained research assistants supervised by Dr. Anne Wheeler, a licensed psychologist with >15 years assessment

experience with individuals with FXS and other disabilities. The measures in the present study were standardized and have strong psychometric properties.

Demographics. Caregivers completed a demographic questionnaire used to collect family information (e.g., who lives in the home), caregiver education level, race/ ethnicity, income, and parental marital status. For the current study, only questions related to race/ethnicity, income, gender, and age were examined.

Intellectual ability. The *Stanford Binet Intelligence Scales-5th edition* (SB5; Roid, 2003) is a norm-referenced measure of intelligence and cognitive ability. The SB5 includes ten subtests which consist of verbal and nonverbal scores on each of the five neurocognitive factors; Fluid Reasoning, Knowledge, Quantitative Reasoning, Visual-Spatial Reasoning, and Working Memory. The five factors have been revised to provide more accurate assessment of low-functioning children as well as adults with intellectual disabilities. All examiners were trained to administer the SB5. Due to the limited verbal abilities of individuals with FXS, the current study only examined nonverbal IQ. Visual inspection of nonverbal IQ revealed a negatively skewed distribution with a larger cluster of IQ scores near the floor (Standard Score = 40; see Figure 1). Due to the cognitive deficits in individuals with FXS, a floor effect for nonverbal IQ, as measured by the SB-5, was observed. In order to address the floor effect, nonverbal IQ scores were transformed based on the algorithm described in Sansone et al., (2014). Each participant's nonverbal IQ subtest scores were rescaled based on an age-dependent z-score transformation. The formula used for the individual *i* falling into the *j*th age band was:

$$z_{ij} = \frac{r_{ij} - \mu}{\sigma_j}$$

where r_{ij} is the subtest raw score, μ_j and σ_j represent the mean and standard deviation from the corresponding age band and subtest from the standardized sample. Once all 5 subtest scores were transformed, the subtest scores were averaged to obtain one overall transformed nonverbal IQ score. The transformed nonverbal IQ score was then rescaled using a mean of 100 (*SD* = 15) in order to compare the transformed nonverbal IQ scores to the normative sample.

After all nonverbal IQ scores were transformed; the data was reassessed for normality and outliers. One outlier with a transformed NVIQ score of 3 was identified and removed from the data set. Distribution of the transformed NVIQ scores appeared normal (see Figure 2).

Autism spectrum disorder symptoms. Due to discrepancies in the field about the most effective way to evaluate ASD, the complex nature of the disorder, and the exacerbated ASD symptoms due to FXS, this study examined ASD symptoms in multiple ways using different diagnostic assessments and criteria. The four methods used to assess ASD symptomology were 1) based on scores on the Social Communication Questionnaire, 2) based on scores on the Autism Diagnostic Observation Schedule, 2nd Edition, 3) based on the study definition of diagnostic determination, and 4) based on DSM-5 criteria (See Table 3). Each diagnostic method is detailed below.

Social Communication Questionnaire. *The Social Communication Questionnaire* is a parent-report measure used to assess autism symptomology (SCQ; Rutter, Bailey, & Lord, 2003). The SCQ is a 40-item screening measure that asks parents *yes/no* questions about their child's behavior. The SCQ was designed as a companion for the *Autism Diagnostic Interview-Revised (*ADI-R) and evaluates communication skills and social functioning in children who may have autism or ASD. The decisional capacity study used the lifetime form of the SCQ, which evaluates an individual's entire developmental history. The questionnaire provides a total score

that is interpreted in relation to specific cutoffs. Parent responses are converted to a score of 1 or 0, corresponding to "yes" or "no" depending on the question. A score of 1 indicates the presence of autism and a 0 reflects the lack of autism. Individuals with SCQ scores above fifteen are recommended for further diagnostic assessment.

Autism Diagnostic Observation Schedule- 2nd Edition. The *Autism Diagnostic Observation Schedule- 2nd Edition* (ADOS-2; Lord et al., 2012) is a revision of the original ADOS. Revisions include updated protocols, revised algorithms, a new Comparison Score, and an additional Toddler Module.

Similar to the original ADOS, the ADOS-2 is a semi-structured standardized assessment of communication, social interaction, play, and restricted and repetitive behaviors. The ADOS-2 uses semi-structured activities and questions to provide opportunities to observe social communication and other symptoms of ASD. The ADOS-2 provides cutoff scores for autism and autism spectrum classification as well as Comparison Scores. Individuals receiving a score of 6 or lower on the ADOS-2 are not considered to be on the autism spectrum. An individual who receives a score of 7 or 8 on the ADOS-2 is considered to be on the autism spectrum and individuals receiving a score of 9 or above are considered to have autism.

Each of the five ADOS-2 modules was created to provide an accurate picture of autism symptomology that is unaffected by communication ability. The modules assess communication abilities ranging from toddlers who do not consistently use phrased speech to verbally fluent adolescents and adults. In the decisional capacity study, modules 2-4 were used depending on the participant's communication level. Trained administers of the ADOS-2 decided which module was appropriate for each participant. All assessors were certified and trained on the assessment including which module to administer.

Diagnostic Determination. The gold standard for an ASD diagnosis includes identifications of the behavioral symptoms (e.g., social communication deficits) as can be observed using the ADOS-2, and parent-reported symptoms and developmental history such as the SCQ. For the present study, a diagnostic determination of ASD was made if participants had scores above the autism cut-off for ASD on both the ADOS-2 (assessing the current observable symptoms of autism) and the SCQ (assessing symptoms of autism that happened in the past). Thus "diagnostic determination" is the term used to indicate the most conservative diagnostic method, and the one used by the larger decisional capacity study to determine autism status in the sample. However, because of the focus in this study on the different ways autism is presented, the ADOS-2, SCQ, and DSM-5 were all used to examine ASD status.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Items from the ADOS-2 were mapped onto DSM-5 ASD criteria to create an algorithm to determine whether individuals met ASD criteria based on DSM-5 (See Table 4). The algorithms used by ADOS-2 provide a Comparison Score that does not match directly with DSM-5 criteria (See Table 5). Item mapping was necessary in order for algorithms to represent the current ASD criteria. Item mapping was adapted from Huerta, Bishop Duncan, Hus, and Lord (2012) who had mapped the original ADOS onto proposed DSM-5 criteria. Revisions to item mapping included checking the proposed criteria by Huerta et al., (2012) with published DSM-5 criteria, comparing items on the first edition of the ADOS to items on the ADOS-2, and having an expert diagnostician review and confirm the validity of the item mapping (see Table 4).

Anxiety symptoms. The *Anxiety, Depression, and Mood Scale* (ADAMS, Esbensen, Rojahn, Aman, & Ruedrick, 2003) is a parent-report measure developed to assess anxiety, depression, and mania in individuals with intellectual disability. Empirical research was used to

demonstrate the psychometric properties of the ADAMS (Esbensen, 2003). The ADAMS is a 28-item measure that asks questions regarding manic/ hyperactive behavior, depressed mood, social avoidance, general anxiety, and obsessive/ compulsive behaviors. Each item is rated on a 0 (*not a problem)* to 3 (*severe problem)* scale, with scores indicating the frequency and severity with which a symptom or behavior occurs. For the present study only questions assessing social avoidance and generalized anxiety were examined. Social avoidance was assessed by 7 of the 28 items. Scores were calculated by summing the totals of each of the 7 items. Generalized anxiety was assessed by 7 of the 28 items. Scores were calculated by summing the totals of each of the 7 items (see Appendix 1 for specifics regarding social avoidance and generalized anxiety measures).

Procedures

Participants were scheduled for a data collection visit in the participant's home or school determined by the family's preference. Two weeks prior to the visit, the participant and/or their primary caregiver were sent a packet with consent and assent forms and self-report/parent report rating scales and questionnaires. On the day of the evaluation, participants completed all measures in the neurocognitive battery. For those whose parents did not have legal guardianship, their consent was requested to have their parents/caregivers answer questions about their history. Individuals with FXS received $60 and their parents/caregivers received $60 for study participation.

Statistical Analysis

The present study examined ASD and anxiety in individuals with FXS. The two research aims were designed to investigate the overlap of ASD and anxiety symptoms in individuals with

FXS and to examine social communication and interactions symptoms. Analysis and reasoning for each aim are detailed below.

Aim 1: Examine the variability in the frequency of ASD diagnoses based on multiple diagnostic assessments and criteria.

Question 1. What is the frequency of individuals who met ASD criteria based on multiple diagnostic assessments and criteria?

Descriptive statistics (i.e., frequencies) were calculated to identify the number of individuals who met ASD criteria based on each diagnostic method.

Question 2. What is the frequency of individuals who met criteria across the two broad ASD criteria (SCI and RRBI) and each of the three SCI criteria (A1 – Social Emotional reciprocity; A2 – Communicative Behavior; A3 – Relationships with Others)?

Descriptive statistics (i.e., frequencies) were calculated to identify the number of individuals who met criteria across the two broad ASD criteria and each of the three SCI criteria.

Question 3. Are there differences in the frequency of those who meet criteria based on the two broad ASD criteria and each of the three SCI criteria based on age or gender?

Separate chi-squared test for independence were calculated to examine differences between those who met criteria based on the two broad ASD criteria and each of the three SCI criteria based on age and gender.

Question 4. Are there differences by age or gender in the severity of each of the three SCI criteria?

Descriptive statistics (i.e., range, mean, and variance) were calculated and multiple independent samples t-tests were run to examine differences in total symptom count on each of the three SCI criteria.

Aim 2: Examine the relationships among parent-reported anxiety scores, age, nonverbal IQ, the three SCI criteria, and the diagnosis of ASD as determined by different diagnostic criteria.

Question 5. Which DSM-5 criteria are most strongly correlated with anxiety symptoms?

Correlations were run to examine the relationship between each DSM-5 criteria and anxiety symptoms.

Question 6. After controlling for age and nonverbal IQ to what extent do parent-reported anxiety scores predict scores on the three SCI criteria and an ASD diagnosis as defined by diagnostic criteria?

Regression analyses were conducted to examine predictors of scores on the three SCI criteria of DSM-5 and an ASD diagnosis in individuals with FXS. An ordinary least squares regression was conducted to examine predictors of scores on each the three SCI criteria. Separate logistic regressions were conducted to examine predictors of ASD diagnosis as determined by diagnostic determination and DSM-5 criteria.

Results

Data was analyzed using IBM SPSS Software (version 22.0). Scatterplots and histograms were examined for normality and outliers. Analysis revealed that the ages of the participants were not distributed evenly amongst adolescents and adults (see Figure 3). Due to the large cluster of older adolescents (M = 14.65, SD = 1.74) and younger adults (M = 25.69, SD = 5.96), age was examined as a continuous variable.

Initial analysis revealed a positive correlation between ADAMS social avoidance scores and ADAMS generalized anxiety scores. In order to reduce the number of variables and maintain an accurate assessment of anxiety symptoms, scores on the ADAMS social avoidance

subscale and ADAMS generalized anxiety subscale were averaged to obtain one singular anxiety score. Both anxiety subscales had 7 items from the ADAMS and were on the same 0-3 scale, allowing them to be combined. Combining the two anxiety subscales allowed for including symptoms of social avoidance and generalized anxiety, both of which are hypothesized to be related to impairments in social communication.

Nonverbal Intellectual Ability

The average nonverbal IQ was moderately impaired or delayed (M = 55.15, SD = 20.20) for the sample, yet the range was covered a wide margin (range = 16-102; see Table 1). An independent samples t-test revealed that, on average, males had a lower nonverbal intelligence score (M = 44.34) than females (M = 74.69), $t(72) = -8.85$, $p < 0.001$ (see Table 2).

Aim 1: Examine variability in the frequency of autism spectrum disorder (ASD) diagnoses based on multiple diagnostic assessments and criteria.

Question 1. What is the frequency of individuals who met ASD criteria based on multiple diagnostic assessments and criteria?

Autism Diagnostic Observation Schedule, 2nd Edition. Based on the algorithms used to identify symptoms suggestive of an autism spectrum disorder, 33 (46%) individuals met criteria based on the ADOS-2. Chi-squared test revealed that more males (94%) met criteria based on the ADOS-2 than females (6%), $\chi^2 (1, N = 74) = 23.79$, $p < 0.001$. The average age of the individuals who met ADOS-2 criteria was 21.49 (SD = 7.40; see Table 6). There was no significant difference in the ages of the individuals who met criteria and the ages of the individuals who did not meet criteria. On average, the nonverbal IQ was lower for individuals who met ADOS-2 criteria (M = 42.59) than for individuals who did not meet ADOS-2 criteria (M = 65.51), $t(72) = 5.82$, $p < 0.001$.

Social Communication Questionnaire. Based on the parent-reported SCQ scores, 30 individuals (41%) had a score higher than 15, indicating possible ASD. The average SCQ score for the entire sample was 12.95 (*SD* = 7.02; Range = 0-28; see Table 7). There were more males who met SCQ criteria (77%) than females (23%), which approached significance, $\chi^2(1, N = 74) = 3.77$, $p = 0.052$. The average age of individuals who met SCQ criteria was 20.20 (*SD* = 3.76). Age did not differ significantly between individuals who met SCQ criteria and individuals who did not. Nonverbal IQ scores were significantly lower for individuals who met SCQ criteria (*M* = 45.13) than for individuals who did not meet SCQ criteria (*M* = 62.14, $t(72) = -3.87$, $p = 0.001$).

Diagnostic Determination. Based on the decisional capacity project's definition of diagnostic determination (a score higher than 15 on the SCQ and autism classification based on the ADOS-2), 20 individuals (27%) met criteria. More males met diagnostic determination criteria (90%) than females (10%), $\chi^2(1, N = 74) = 8.297$, $p = 0.004$. The average age for individuals who met diagnostic determination was 19.10 (*SD* = 5.55; see Table 8). Individuals who met diagnostic determination criteria were younger (19.10) than individuals who did not meet criteria (*M* = 23.06), $t(72) = -2.16$, $p = 0.034$. On average, the individuals who met criteria for diagnostic determination had a lower nonverbal IQ (*M* = 42.87) than individuals who did not meet criteria (*M* = 59.78, $t(72) = -3.42$, $p = 0.003$. Table 9 displays descriptive statists for the measures used to determine diagnostic determination (SCQ and ADOS-2). There were 10 individuals who met SCQ criteria but not ADOS-2 and 13 individuals who met ADOS-2 but not SCQ. There were 31 individuals who did not meet criteria based on either assessment.

DSM-5 ASD Status. Based on the item mapping of the ADOS-2 onto DSM-5, 27 individuals (36%) had symptoms that were consistent with DSM-5 ASD criteria. Chi-squared test revealed that more males met DSM-5 ASD criteria (93%) than females (7%), $\chi^2(1, N = 74)$

= 15.51, $p < 0.001$. The average age of individuals who met DSM-5 ASD criteria was 21.30 (*SD* = 6.88; see Table 10). Age did not differ significantly between individuals who met criteria and individuals who did not meet criteria. On average, the nonverbal IQ was lower (*M* = 43.69) for individuals who met criteria than the nonverbal IQ of individuals who did not meet criteria (*M* = 61.88), $t(72) = -4.10$ $p = 0.001$.

***Overlap between diagnostic methods*.** Table 11 displays descriptive statics of each classification system used to assess autism status (SCQ, ADOS-2, Diagnostic Determination, and DSM-5). There were 16 (22%) individuals who met criteria based on all autism diagnostic methods and 30 (41%) individuals who did not meet criteria for any of the autism diagnostic methods. Examinations of the individuals who met criteria based on some, but not all autism diagnostic methods, are detailed below.

Of the 20 individuals who met ASD criteria based on diagnostic determination, 16 (80%) also met ASD criteria based on DSM-5 (see Figure 4). DSM-5 ASD status was determined based on the item mapping of the ADOS-2 onto DSM-5 (see Table 4). Table 12 displays case studies for the 4 (20%) individuals who met ASD criteria based on diagnostic determination, but did not meet ASD criteria based on DSM-5. Of these 4 individuals, 3 were male. Visual inspection of their item mapping on the DSM-5, revealed that all 4 individuals met the social communication and interaction (SCI) criteria of DSM-5, but did not meet the repetitive and restricted behavior or interest (RRBI) criteria of DSM-5. All 4 individuals had RRBI symptoms consistent with the stereotyped behaviors criterion (B1) of DSM-5 ASD criteria, but did not meet one of the remaining RRBI criteria on the DSM-5 (B2; insistence on sameness, B3; restricted interests, or B4; reactivity to sensory input; See Appendix 2). The 4 individuals needed one additional RRBI symptom in order to meet DSM-5 ASD criteria.

Of the 27 individuals who met DSM-5 ASD criteria, 16 (59%) also met ASD criteria based on diagnostic determination (see Figure 4). Table 12 displays case studies for the 11 (41%) individuals who met DSM-5 ASD criteria, but did not meet based on diagnostic determination. Of these 11 individuals, 10 were male. Visual inspection of their data revealed that the majority (9; 82%) failed to meet diagnostic determination due to scores below the autism cutoff on the SCQ, the 1 female failed to meet diagnostic determination because of a score below the autism cutoff on the ADOS-2, and 1 individual failed to meet diagnostic determination because of a score below the autism cutoff on the SCQ and scores below the autism cutoff on the ADOS-2 (see Figure 5).

Question 2. What is the frequency of individuals who met criteria across the two broad ASD criteria (SCI and RRBI) and each of the three SCI criteria (A1 – Social Emotional reciprocity; A2 – Communicative Behavior; A3 – Relationships with Others)?

Based on the item mapping of the ADOS-2 onto the DSM-5, 40 individuals (54%) displayed symptoms on the ADOS-2 that were consistent with the SCI criteria of the DSM-5. Fewer individuals (n = 30; 41%) displayed symptoms on the ADOS-2 that were consistent with the RRBI criteria of the DSM-5 (see Table 14).

SCI Criteria. There were 61 individuals (82%) who displayed at least one symptom on the ADOS-2 that was consistent with the 'social-emotional reciprocity' criterion (A1) of the DSM-5; 55 individuals (74%) who displayed at least one symptom on the ADOS-2 that was consistent the 'communicative behaviors' criterion (A2) of the DSM-5; and 47 individuals (64%) who displayed at least one symptom on the ADOS-2 that was consistent with the 'relationships with others' criterion (A3) of the DSM-5 (see Table 15 for descriptive statistics; see Appendix 2 for detailed information on DSM-5 ASD criteria).

RRBI Criteria. Based on the item mapping of the ADOS-2 onto DSM-5, 46 individuals (62%) displayed at least one symptom that was consistent with the 'stereotyped behaviors' criterion (B1) of DSM-5; 6 individuals (8%) displayed at least one symptom that was consistent with the 'insistence on sameness' criterion (B2) of DSM-5; 23 individuals (31%) displayed at least one symptom that was consistent with the 'restricted interest' criterion (B3); and 20 individuals (27%) displayed at least one symptom that was consistent with the 'reactivity to sensory input' criterion (B4) of DSM-5 (see Table 16 for descriptive statistics; see Appendix 2 for detailed information on DSM-5 ASD criteria).

Question 3. Are there differences in the frequency of those who meet criteria based on the two broad ASD criteria and each of the three SCI criteria based on age or gender?

SCI Criteria. Based on the item mapping of the ADOS-2 onto DSM-5, 40 individuals (35 males, 75%; 5 females, 19%) displayed symptoms on the ADOS-2 that were consistent with the SCI criteria of the DSM-5 (see Table 14). As expected, a chi-square test revealed that more males (88%) met SCI criteria than females (12%), $\chi^2(1, N = 74) = 21.62$, $p < 0.001$. There was no significant difference between the age of individuals who met SCI criteria and the age of the individuals who did not meet criteria (see Table 15). The nonverbal IQ was lower ($M = 44.29$) for individuals who met SCI criteria than for individuals who did not meet SCI criteria ($M = 67.61$), $t(72) = -6.00$, $p < 0.001$.

***Social Emotional Reciprocity (A1) Criterion*.** There were 61 individuals (41 males, 88%; 20 females, 74%) who displayed at least one symptom on the ADOS-2 that was consistent with criterion A1 of DSM-5 (see Table 14). There was no significant difference in gender between the individuals who met criterion A1 and individuals who did not meet criterion A1. The average age of the individuals who met criteria on A1 was 21.82 ($SD = 7.09$). There was no

significant difference in the age of individuals who met criterion A1 and the age of individuals who did not meet criterion A1 (see Table 15). On average, individual who met criterion A1 had lower nonverbal IQ scores (M = 52.51) than individuals who did not meet criterion A1 (M = 67.34), $t(72) = -2.49$, $p = 0.015$.

***Communicative Behaviors (A2) Criterion*.** Based on the item mapping of the ADOS-2 onto DSM-5, 55 individuals (40 males, 85%; 15 females, 56%) displayed at least one symptom on the ADOS-2 that was consistent with criterion A2 of DSM-5 (see Table 14). A chi-squared test revealed that more males met criterion A2 (73%) than females (27%), $\chi^2(1, N = 74) = 7.85$, $p = 0.012$. The individuals who met criterion A2 were about 22.16 years old (SD = 7.28). The age of individuals did not differ significantly between individuals who met criterion A2 and individuals who did not. Nonverbal IQ scores were significantly lower for individuals who met criterion A2 (M = 50.57) than individuals who did not meet criterion A2 (M = 68.16), $t(72) = -3.51$, $p = 0.001$ (see Table 15).

***Relationships with Others (A3) Criterion*.** There were 47 individuals (39 males, 83%; 8 females, 30%) who displayed at least one symptom on the ADOS-2 that was consistent with criterion A3 of DSM-5 (see Table 14). A chi-squared test revealed that more males met criterion A3 (83%) than females (17%), $\chi^2(1, N = 74) = 21.06$, $p < 0.001$. The average age of the individuals who met criterion A3 was 20.85 (SD = 6.83). There was no significant difference between the age of individuals who met criterion A3 and those who did not. The average nonverbal IQ was lower for individuals who met criterion A3 (M = 45.51) than individuals who did not meet criterion A3 ((M = 71.57), $t(72) = 6.79$, $p < 0.001$ (see Table 15).

RRBI Criteria. Based on the item mapping of the ADOS-2 onto DSM-5, 30 individuals (26 males, 55%; 4 females, 15%) displayed symptoms on the ADOS-2 that were consistent with

RRBI criteria of DSM-5 (see Table 14). More males met RRBI criteria (87%) than females (13%), $\chi^2(1, N = 74) = 11.76$, $p = 0.001$. Individuals who met RRBI criteria were about 21.23 years old ($SD = 6.65$). The age of individuals who met RRBI criteria did not differ significantly from the age of the individuals who did not meet criteria. Nonverbal IQ scores were significantly lower for individuals who met RRBI criteria ($M = 46.02$) than the nonverbal IQ scores of individuals who did not meet RRBI criteria ($M = 61.52$), $t(72) = -3.46$, $p < 0.001$ (see Table 16).

Stereotyped Behaviors (B1) Criterion. There were 46 individuals (39 male, 83%; 7 female, 26%) who displayed at least one symptom on the ADOS-2 that was consistent with criterion B1. A chi-squared test reveled that more males (85%) met criterion B1 than females (15%), $\chi 2(1, N = 74) = 23.732$, $p < 0.001$ (see Table 14). The mean age for individuals meeting criterion B1 was 20.98 ($SD = 6.46$; see Table 16). There was not a significant difference in the age of individuals meeting criterion B1 and individuals not meeting criterion B1. On average, nonverbal IQ scores were lower for individuals meeting criterion B1 ($M = 47.74$) than individuals not meeting criterion B1 ($M = 67.76$), $t(72) = -4.63$, $p < 0.001$.

Insistence on Sameness (B2) Criterion. A small number of individuals displayed symptoms on the ADOS-2 that were consistent with criterion B2 (n = 6; 5 males, 11%; 1 female, <1%). Because of the limited number of individuals meeting criterion B2 no further analyses were completed.

Restricted Interest (B3) Criterion. Based on the item mapping of the ADOS-2 onto the DSM-5, 23 (19 males, 40%; 4 females, 15%) individuals displayed at least one symptom on the ADOS-2 that was consistent with criterion B3. More males met criterion B3 (83%) than females (17%), $\chi 2 (1, N = 74) = 5.251$, $p = 0.022$ (see Table 14). The average age of individuals

meeting criterion B3 was 22.70 (*SD* = 7.78). The age of the individuals did not differ significantly between individuals who met criterion B3 and individuals who did not. The nonverbal IQ scores did not differ significantly between individuals who meet criterion B3 and individuals who did not meet criterion B3 (see Table 16).

Reactivity to Sensory Input (B4) Criterion. There were 20 individuals (15 males, 32%; 5 females, 19%) who displayed at least one symptom on the ADOS-2 that was consistent with criterion B4. There was no significant gender difference between individuals who met criterion B4 and individuals who did not (see Table 14). Individuals who meet criterion B4 were, on average, 22.55 years old (*SD* = 7.29). Age did not differ significantly between individuals who meet criterion B4 and individuals who did not. There was no significant difference in nonverbal IQ scores between individuals who met criterion B4 and individuals who did not meet criterion B4 (see Table 16).

Question 4. Are there differences by age or gender in the severity of each of the three SCI criteria?

To examine severity, the number of symptoms each participant displayed in each of the three SCI criteria was calculated (see Table 17). An independent samples t-test revealed that males displayed more symptoms consistent with SCI criteria (*M* = 6.83) than females (*M* = 3.41), t (72) = 3.82, $p < .001$ (see Table 18). There was not a correlation between the age of the participant and the number of displayed that are encompassed under SCI criteria, *r* (72) = -0.181, $p = 0.122$ (see Table 18). The age of the participant did not correlate with the number of SCI symptoms for males, *r* (72) = -0.24, $p = 0.110$ or females, *r* (72) = -0.17, $p = 0.407$ (see Tables 20-21).

Social Emotional Reciprocity (A1). Males displayed more A1 symptoms (M = 3.19) than females (M = 1.56), t (72) = 3.29, p = .002 (see Table 18). There was a weak negative correlation between the age of the participant and the number of symptoms displayed that are encompassed under criterion A1 $r(72) = -0.238$, $p = 0.041$(see Table 19); indicating that as the age of the participant increases the number of symptoms displayed that are encompassed under criterion A1 decreases. There was a weak negative correlation between the age of male participants and the number of symptoms displayed that are encompassed under criterion A1, $r(72) = -0.30$, $p = 0.042$; indicating that as the older males had fewer symptoms that met criterion A1 (see table 20). The age of female participants did not correlate with the number of symptoms encompassed under criterion A1, r (72) = -0.20, p = 0.319 (See Table 21).

Communicative Behavior (A2). As can be seen in Table 18, males displayed more A2 symptoms (M = 2.23) than females (M = 1.41), t (72) = 2.32, p = .023. There was not a significant correlation between the age of the participant and the number of symptoms displayed that are encompassed under criterion A2, $r(72) = 0.005$, $p = 0.966$ (see Table 19). This was true for males $r(72) = 0.04$, $p = 0.792$ and females, $r(72) = -0.07$, $p = 0.734$ (see Tables 20-21).

Relationships with Others (A3). Males displayed more symptoms encompassed under criterion A3 (M = 1.40) than females (M = 0.44), t (72) = 5.21, $p < .001$ (see Table 18). There was a weak negative correlation between the age of the participant and the number of symptoms displayed that are encompassed under criterion A3, $r(72) = -0.244$, $p = 0.036$; indicating that as the age of the participant increases the number of symptoms displayed that are encompassed under criterion A3 decreases (see Table 19). The same is true for male participants, $r(72) = -0.38$, $p = 0.008$; indicating that older males had fewer symptoms that are consistent with criterion A3 (see Table 20). There was no significant correlation between the age of the female

participants and the number of symptoms displayed that are encompassed under criterion A3, $r(72) = -0.16$, $p = 0.426$ (see Table 21).

Aim 2: Examine the relationships among parent-reported anxiety scores, age, nonverbal IQ, the three SCI criteria, and the diagnosis of ASD as determined by different diagnostic criteria.

Question 5. Which DSM-5 criteria are most strongly correlated with anxiety symptoms?

Based on the item mapping of the ADOS-2 onto DSM-5, the number of symptoms displayed that were encompassed under SCI criteria did not correlate with the ADAMS combined anxiety scores, $r(72) = 0.027$, $p = 0.821$, the same was true for the social emotional reciprocity criterion (A1), $r(72) = 0.092$, $p = 0.436$, the communicative behavior criterion (A2), $r(72) = -0.046$, $p = 0.697$, and the relationships with others criterion (A3), $r(72) = -0.027$, $p = 0.822$ (see Table 19).

Question 6. After controlling for age and nonverbal IQ to what extent do parent-reported anxiety scores predict scores on the three SCI criteria and an ASD diagnosis as defined by diagnostic criteria?

Social Emotional Reciprocity (A1). As can be seen in Table 22, an Ordinary Least Squares Regression Analysis revealed that anxiety did not significantly predict scores on criterion A1 (B = 0.025, $t(70) = 0.228$, $p = 0.820$) when controlling for age and nonverbal IQ. Both age (B = -0.250, $t(70) = -2.291$, $p = 0.025$) and nonverbal IQ scores (B = -0.558, $t(70) = -3.272$, $p = 0.002$) were significant predictors of social emotional reciprocity scores.

Communicative Behaviors (A2). Anxiety did not significantly predict scores on criterion A2 (B = -0.092, $t(70) = -0.798$, $p = 0.427$) when controlling for age and nonverbal IQ. The same was true for age, B = 0.012, $t(70) = 0.12$, $p = 0.107$. Nonverbal IQ scores were

significant predictors of communicative behavior scores, B = -0.297, $t(70) = -2.578$, $p = 0.012$ (See Table 23).

Relationships with Others (A3). As can be seen in Table 24, an Ordinary Least Squares Regression Analysis revealed anxiety did not significantly predict scores on criterion A3 (B = -0.002, $t(70) = -0.024$, $p = 0.981$) when controlling for age and nonverbal IQ. Both age (B = -0.331, $t(70) = -3.568$, $p = 0.001$) and nonverbal IQ (B = -0.571, $t(70) = -6.139$, $p < 0.001$) did significantly predict scores on the relationships with others criterion.

Diagnostic Determination ASD Criteria. A logistic regression revealed anxiety was not a significant predictor of ASD as determined by diagnostic determination (a score higher than 15 on the SCQ and autism classification based on the ADOS-2). Age and nonverbal IQ did significantly predict an ASD diagnosis as determined by diagnostic determination (See Table 25).

DSM-5 ASD Criteria. As can be seen in Table 26, a logistic regression revealed that anxiety did not significantly predict an ASD diagnosis as determined by DSM-5 criteria. The same was true for age. Nonverbal IQ did significantly predict a diagnosis of ASD based on DSM-5 criteria.

Discussion

The purpose of this study was to describe variability in the frequency of autism spectrum disorder (ASD) diagnoses based on multiple diagnostic assessments and criteria in individuals with fragile X syndrome (FXS). Further, this study sought to examine the extent to which anxiety may contribute to the likelihood of an individual with FXS meeting ASD criteria based on multiple diagnostic methods. Because ASD is a behaviorally diagnosed disorder, and due to the significant cognitive deficits and comorbid anxiety often observed in individuals with FXS,

ASD is difficult to diagnosis. Previous research has suggested that ASD symptoms may be a result of the cognitive impairments in individuals with FXS (Rogers et al., 2001). In addition, there are many overlapping symptoms between ASD and anxiety (e.g., gaze aversion, difficulty in social situations), which make it difficult to distinguish between the two psychopathologies (Wheeler et al., 2014). Thus, this study sought to examine the prevalence of ASD through multiple diagnostic methods in attempt to gain a better understanding of the nature of ASD in FXS. The use of multiple diagnostic methods allowed for the examination of ASD symptomology through parent-reported and observational measures.

Variability based on Diagnostic Methods

The first aim of this study was to examine the variability in the frequency of ASD diagnosis. Results of this study show that 22% of individuals met ASD criteria based on all diagnostic methods used to assess autism in the present study and 40% of individuals did not meet ASD based on any of the diagnostic methods (e.g., SCQ, ADOS-2, Diagnostic Determination, and DSM-5). Based on the stringent study diagnostic determination criteria, 27% of the sample met ASD criteria. More individuals (36%) met based on DSM-5 diagnostic criteria. Interestingly, there were many individuals (38%) who met ASD criteria on some diagnostic measures, but not all. These are the borderline participants who may get and ASD diagnosis depending on the severity of other variables. For example, 9 (12%) individuals meet ASD criteria based on SCQ scores only. One reason individuals may have met criteria on the SCQ while not meeting on other measures is that the SCQ is a measure of developmental history. The SCQ is a parent-report measure and asks questions about the history of symptoms. Thus, parents were drawing on the early history of symptoms in addition to assessing present symptoms. Another possibility is that parents have difficulty accurately reporting symptoms

because they are untrained and may be unaware of how ASD symptoms are actually displayed (Wheeler et al., 2014). Thus, symptoms reported may have been due to a comorbid disorder or due to a skewed parental reference point as to what autism symptoms look like.

There were 4 (5%) individuals who meet ASD criteria based on the ADOS-2 only. The nature of the ADOS-2 administration may explain this occurrence. The ADOS-2 is an observational test and was conducted by a trained clinician. The semi-structured administration of the ADOS-2, with an unfamiliar adult, may have caused stress to the participant and caused anxiety symptoms that are similar to symptoms of ASD (e.g., unusual facial expressions, difficulty communicating). Such symptoms have been described in previous studies and are thought to occur because of the combination of low verbal capabilities and social withdrawal (Tonnsen et al., 2013). These symptoms may not surface at home because individuals with FXS are more comfortable with their families and will use a wider range of social skills while at home (Wheeler et al., 2014). Thus, during the ADOS-2 administration, the participant may have appeared more socially impaired than he or she typically would.

A small percentage of individuals (5%) met ASD criteria based on diagnostic determination, but not based on DSM-5. Interestingly, these individuals failed to meet ASD criteria based on DSM-5 due to the RRBI criteria. Each participant displayed only one of the four RRBI symptoms where two symptoms are required to meet criteria. Examination of the entire sample was in line with these results and reveled that more individuals met SCI criteria than RRBI criteria. These findings may be a result of the way DSM-5 criteria was determined (i.e., item mapping of ADOS-2 onto DSM-5). The item mapping allowed more opportunity for the observation of SCI symptoms (12-15 items) on the ADOS-2 than RRBI symptoms (5-6

items). Thus, individuals had a higher chance of displaying a symptom consistent with SCI criteria then RRBI criteria.

Results from the present study do not support the hypothesis that fewer individuals would meet criteria for SCI than RRBI criteria, due to the changes in DSM-5 (Wheeler et al., 2014). Previous literature suggests that the combination of the two previously separate DSM-IV-TR criteria social interaction and communication caused a reduction in the number of individuals who meet SCI criteria (Wheeler et al., 2014). A diagnosis of ASD as defined by the DSM-5 requires that individuals have symptoms in each of the three SCI criteria (i.e., social emotional reciprocity, communicative behaviors, and relationships with others) as well as the two symptoms in the RRBI criteria (i.e., stereotyped behaviors, insistence on sameness, restricted interests, and reactivity to sensory input). As a result, it was hypothesized that fewer individuals would meet for SCI criteria than would meet for RRBI criteria. Because DSM-5 RRBI criteria only requires individuals to have two symptoms out of the four possible RRBI criteria it was expected that fewer individuals would meet for more stringent SCI criteria than RRBI criteria. Additionally, previous research showed that a higher percentage of individuals failed to meet DSM-5 criteria due to SCI criteria, not RRBI (Huerta et al., 2012). Results from Wheeler et al., (2014) found similar results in that more individuals met RRBI criteria than SCI. Based on parent-reported symptoms of ASD in FXS based on the DSM-5, Wheeler et al., (2014) found that the majority of males (86.4%) and over half of females (61.7%) met DSM-5 RRBI criteria, whereas less than one third of males (29.4%) and females (13.0%) met DSM-5 SCI criteria. When SCI criteria were relaxed (only requiring 2 SCI symptoms as opposed to 3) the rate of ASD nearly tripled (Wheeler et al., 2014). One possible explanation for this discrepancy between the current study and previous studies is that data from Huerta et al., (2012) used a non-

FXS sample of individuals aged 2-17 years 11 months and Wheeler et al., (2014) used different ASD diagnostic methods. Huerta et al., (2012) did not identify individuals with FXS for the study and only included individuals who had been previously diagnosed with ASD. Thus, the results from Huerta et al., (2012) did not encompass core deficits observed in individuals with FXS and may not be generalizable to the FXS population. Additionally, since only individuals previously diagnosed with ASD were included in the analysis, the sample likely did not include individuals with moderate ASD symptoms (e.g., the individuals in this study who met ASD criteria for some diagnostic methods but not all). Thus, the individuals of interest for the current study were likely not included in the Huerta et al., (2012) sample. Contrastingly, the Wheeler et al., (2014) sample included individuals with FXS, but this study was limited to parent-report. Because parents are not trained to recognize and know ASD symptoms, their report may not have been as accurate. Data for the current study were based on observable behavior (e.g., ADOS-2) and parent-reports on the SCQ. Thus, the combination of observation and parent-report may have given a more accurate picture of ASD status in the current study.

Additionally, the difference between previous research and results of the current study could be because DSM-5 ASD status was based on the item mapping of the ADOS-2. Because the ADOS-2 is a structured assessment with a stranger, individuals with FXS may have displayed more SCI symptoms during the ADOS-2 administration than they typical. The ADOS-2 also allowed more opportunity for the observation of SCI symptoms than RRBI symptoms. The combination of the assessment environment and increased opportunity to display SCI symptoms may be the reason results from the current study are not in line with previous research.

There were 11 (15%) individuals who met ASD criteria for DSM-5 but not diagnostic determination. Similarly, results from the entire sample showed that more individuals met ASD

criteria for DSM-5 (37%) than diagnostic determination (28%). The percentage of individuals who meet ASD criteria based on diagnostic determination was in line with previous reports (Bailey et al., 2008). It was expected more individuals would meet DSM-5 criteria than diagnostic determination criteria because diagnostic determination was designed to be a more stringent ASD criteria than DSM-5 criteria. Because individuals had to meet ASD cutoff scores on both the SCQ and ADOS-2 to be considered to have ASD based on diagnostic determination, it was expected that fewer individuals would meet for diagnostic determination than DSM-5.

In addition, the nature of the two diagnostic methods may have caused fewer individuals to meet for diagnostic determination than DSM-5. The SCQ portion of diagnostic determination was parent-reported and drew on current symptomology as well as developmental history. DSM-5 diagnoses were determined based on the item mapping of the ADOS-2 onto DSM-5 criteria. Therefore, DSM-5 diagnoses were based on observation during the ADOS-2 and did not take into account parent-report or developmental history. Parent-reports may have provided information that was unavailable for the DSM-5 diagnostic criteria. Without parent-reports, autism-like symptoms are attributed to ASD. Thus, the number of individuals meeting criteria for DSM-5 may have been higher because there were no parent-reports to give additional information or developmental history.

Variability by Gender

More males met criteria based on all ASD diagnostic methods (ADOS-2, SCQ, Diagnostic Determination, and DSM-5) than females. These findings are in line with previous prevalence estimates of ASD (Bailey et al., 2008) and were expected as FXS affects males more severely than females (Tsiouris & Brown, 2004).

Variability by Age

Previous research suggests that autism status and symptoms are more severe and prominent in younger individuals because younger individuals with FXS and ASD are at higher risk for attention problems, hyperactivity/impulsivity, and aggression (Talisa et al., 2013). Additionally, research has shown that social ability improves with age, thus the social deficits characteristic in FXS would also decrease with age (Lewis et al., 2006). In the current study, the impact that age had on ASD status varied by how ASD was measured (e.g., ADOS-2, SCQ) and defined (e.g., DSM-5 criteria and diagnostic determination). The age of individuals who met criteria based on the ADOS-2, SCQ, DSM-5, SCI criteria, and the communicative behavior criterion (A2), did not differ significantly by age from individuals who did not meet criteria; indicating that younger and older participants were equally as likely to meet criteria. Regression analyses supported these results, in that DSM-5 ASD status was not significantly predicted by age. Interestingly, there was a negative correlation between age and the number of symptoms displayed that were encompassed by the social emotional reciprocity (A1) criterion and the relationships with other (A3) criterion, suggesting that younger individuals displayed more A1 and A3 symptoms. Regression analyses supported these results, such that age significantly predicted higher scores on criterion A1 and A3. Intellectual ability may have played a role in the relationship between age and symptoms of ASD. Research has found that young individuals with FXS are more likely to achieve the lowest possible standard score on intelligence test (Lewis et al., 2006). IQ is often associated with deficits in language and communication abilities and may exacerbate ASD symptoms. Thus, young individuals, who also have a low IQ, are more likely to display ASD symptoms related to language and communication. In addition, research has found that language in FXS improves with age. Studies have associated improvements in expressive language with age, finding that once children begin to talk, even if its delayed,

expressive language will continue to develop (Abbeduto et al., 2007). Thus, older individuals may have less impaired language skills thus may have fewer social communication symptoms.

The second aim of this study was to examine relationships between parent-reported anxiety scores, nonverbal IQ, each of the three SCI criteria and age. Contrary to expectations, results suggest that parent-reported anxiety did not predict ASD as determined by any of the possible ASD diagnostic strategies available for this analysis. Further there were no significant relationships between parent-reported anxiety and any of the three SCI criteria. The data did not support the hypothesis that parent-reported anxiety would predict SCI scores or a diagnosis of ASD. Based on previous research that autism may have its origin in anxiety (Lewis et al., 2006), it was hypothesized that parent-reported anxiety scores would predict ASD diagnoses. Instead, results revealed that nonverbal IQ scores and age were more strongly predictive of SCI scores and ASD diagnosis. It is likely that the low nonverbal abilities of the participants coincided with lower receptive and expressive language skills (Boyle & Kaufmann, 2010). Thus, the deficits in language abilities may have exacerbated symptoms of ASD. Further, previous research has found that impairment in IQ may amplify autism symptomology (Hall et al., 2010). It could be the case that the low nonverbal IQ of individuals in this sample was the driving force behind ASD symptoms. Alternatively, a "third" variable may affect both nonverbal IQ and ASD symptomology. Although it was hypothesized that anxiety could be the "third" variable, results did not support that hypothesis. The lack of support for anxiety affecting ASD symptoms could be due to the way anxiety was measured for the current study. Anxiety was only examined by one, parent-reported, measure. Because caregivers are uneducated in terms of anxiety symptoms, reports may have been inaccurate. Additionally, genetics factors could be influencing ASD symptoms in individuals with FXS. The genetics of ASD is not entirely

understood and secondary mutations resulting from FXS could be the cause of ASD symptoms (Losh et al., 2012).

Further research is needed to help identify additional factors associated with increased ASD symptoms in FXS. Additional predictors could include cognitive and behavioral correlates as well as genetic mutations. Additionally, why some individuals with FXS clearly meet ASD criteria, some clearly do not, and others meet criteria based on some, but not all, diagnostic methods is an important area for future research. Because a diagnosis of ASD is an important factor in qualification for specific school/ community based services measurement issues, as well as learning more about the nature of ASD in FXS, may impact services.

Limitation and Future Direction

For the current study, anxiety was assessed using the ADAMS. The ADAMS has been established as a valid measure for assessing anxiety in individuals with intellectual disability (Esbensen et al., 2003). Although the ADAMS is valid, it is parent-reported and may not have accurately measured anxiety symptoms for the current study. Caregivers are often untrained and lack knowledge about how to accurately report anxiety symptoms. Additionally, caregivers typically only observe the anxiety symptoms of their child. Thus, without others to compare symptoms to, caregivers may exaggerate or underreport the anxiety symptoms of their child. Relying solely on a parent-reported measure for anxiety does not give the opportunity for trained clinicians to make judgments about the true nature of anxiety-like symptoms.

Other study limitations include not having a clinical evaluation of ASD symptoms. All diagnostic methods used for evaluating ASD were based on the presence of absences of autism-like symptoms and did not allow a clinician to judge whether the symptoms was caused by ASD.

Even for the ADOS-2, where a clinician observed behaviors and gave a score based on his or her judgment, no clinical evaluation was collected for this study. Only the algorithm based on the presence or absence of symptoms was examined. However, this study did examine ASD from multiple diagnostic assessments and criteria. By using parent-reported data (SCQ), observational data (ADOS-2), stringent ASD criteria (diagnostic determination), and diagnostic criteria (item mapping of ADOS-2 onto DSM-5) this study was able examine multiple dimensions of ASD.

Despite these limitations, this study contributed to the understanding of ASD in FXS. The finding that anxiety did not predict any ASD variables, but rather nonverbal IQ and age were more predictive of ASD variables, provides a better understanding of the relationship between FXS and ASD. Future studies with larger sample size will allow for further examination of the variability in individuals who meet criteria for some ASD diagnostic methods but not all methods. These studies should focus on differences between individuals who meet criteria for some ASD diagnostic methods but not all, individuals who meet criteria for all ASD diagnostic methods, and who meet criteria for no ASD diagnostic methods. Future studies should expand upon the ASD diagnostic methods used in this study (e.g., clinical evaluation of ASD) as well as examine anxiety from additional methods in order to see if anxiety is a differential predictor for individuals who meet criteria for some ASD diagnostic methods but not all ASD diagnostic methods.

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Table 1
Descriptive for Entire Sample (N = 74)

Variables	*M*	*SD*	Range
Age	22.00	7.20	12-40
ADAMS Combined Anxiety Scores	10.73	6.91	0-27
Nonverbal IQ	55.15	20.20	16-102

Table 2
Descriptive Statistics for Entire Sample by Gender (N = 74)

	Male n = 47			Female n = 27			
Variable	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	22.17	7.45	12-40	21.70	6.88	12-39	0.27
ADAMS Combined Anxiety Score	11.09	6.58	2-27	10.11	7.55	0-24	0.58
Nonverbal IQ	44.34	11.91	16-68	74.69	17.24	31-102	-8.85***

*** $p < 0.001$

Table 3
Comparison of Diagnostic Methods

	SCQ	ADOS-2	Diagnostic Determination	DSM-5
Method	Assessment	Assessment	Criteria	Criteria
Measurement	Parent-reported	Direct assessment	Combined parent-report and direct assessment	Select items from direct assessment
Primary Skills and Behaviors Assessed	• Communication • Social functioning • Developmental Milestones	• Communication • Social interaction • Play • Restricted and repetitive behaviors	See SCQ and ADOS-2	• Deficits in social communication and interaction • Repetitive and restricted behaviors or interests
Pros	• Includes developmental history	• Allows for clinical assessment of symptoms	• Uses parent-report and direct assessment measure • Common method of measurement in research	• Drawn from DSM-5, which is used to diagnose ASD
Cons	• Based on parent-report only	• Testing environment may create anxiety or amplify ASD symptoms	• Stringent ASD Criteria	• Does not incorporate clinical impression
Example	Parents answer a number of "yes/no" questions • Do you have to and fro "conversations" with her/him that involve taking turns or building on what you have said?	Clinicians rate a specific behavior on a 0-3 scale • Quality of Social Overtures - Summary of the quality of the child's attempts to initiate social interactions with the examiner, not on the frequency of such attempts.	• See SCQ and ADOS	Items from them the ADOS-2 were mapped onto DSM-5 criteria • The *conversation* item (To-and-fro use of words and phrases in social conversations) was mapped onto the social emotional reciprocity criterion (A1) of DSM-5

Table 4

Item Mapping of the ADOS-2 onto DSM-5

Criteria	Module 2	Module 3	Module 4
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:			
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interest, emotions, or affect; to failure to initiate or respond to social interactions.	A5, B3, B4, B5, B6, B8, B9a, B11	A5, A6, A8, B4, B7, B10	A5, A6, A8, B4, B9, B11, B12
2. Deficits in nonverbal communicative behaviors used for social interactions, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body-language, or deficits in understanding and use of gestures; to a lack of facial expression or nonverbal communication	A6, A7, B1, B2, B7	A9, B1, B2, B3	A9, A10, B1, B2, B3, B5
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.	B10, B12	B9, B11	B11, B12
B. Restricted, repetitive patters of behavior, or activities, as manifested by at least two of the following, currently or by history:			
1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).	A3, A4, D2, D4	A3, A4, D2	A3, A4, D2
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food everyday).	N/A	D5	D5
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).	N/A	D4	D4
4. Hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/ temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).	D1	D1	D1

Table 5
Items in ADOS-2 Algorithm vs. Items in DSM-5 Algorithm

	Items in ADOS-2 Algorithm	Items in DSM-5	
		Included in ADOS-2 Algorithm	Excluded from ADOS-2 Algorithm
Module 2	A4, A6, A7, B1, B2, B3, B5, B8, B11, B12, D1, D2, D4	A4, A6, A7, B1, B2, B3, B5, B8, B10, B11, B12, D1, D2, D4	A3, A5, B4, B6, B7, B9a, B10,
Module 3	A4, A7, A8, A9, B1, B2, B4, B7, B9, B10, B11, D1, D2, D4	A4, A6, A8, A9, B1, B2, B4, B7, B9, B10, B11, D1, D2, D4,	A3, A5, A6, B3, D5
Module 4	A4, A8, A9, A10, B1, B2, B6, B8, B9, B11, B12, C1, D1, D2, D4, D5	A4, A8, A9, A10, B1, B2, B9, B11, B12, D1, D2, D4, D5	A3, A5, A6, B3, B4, B5

Table 6
Descriptive Statistics for ASD Criteria based on the ADOS-2 (N = 74)

	Met Criteria n = 33			Did Not Meet Criteria n = 41			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	21.49	7.40	12-40	22.42	7.10	12-39	-0.55
ADAMS Combined Anxiety Scores	10.73	6.52	2-27	10.73	7.30	0-25	0.003
Non-Verbal IQ	42.59	11.61	34-68	65.51	19.98	16-102	-5.82***

*** $p < 0.001$

Table 7

Descriptive Statistics for ASD Criteria based on SCQ Scores (N = 74)

	Met Criteria n = 30			Did Not Meet Criteria n = 44			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
SCQ Score	19.60	3.76	15-28	8.41	4.71	0-15	-10.86***
Age	20.20	6.83	12-36	23.23	7.26	12-40	-1.80
ADAMS Combined Anxiety Score	12.50	6.65	3-25	9.52	6.91	0-27	1.85
Nonverbal IQ	45.13	15.40	16-86	62.14	20.24	25-102	-3.87***

*** $p < 0.001$

Table 8
Descriptive Statistics for ASD Criteria Based on Diagnostic Determination (N = 74)

	Met for Diagnostic Determination n = 20			Did Not Met for Diagnostic Determination n = 54			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	19.10	5.55	12-36	23.06	7.47	12-40	-2.16*
ADAMS Combined Anxiety Score	11.85	6.04	3-25	10.32	7.22	0-27	0.85
Nonverbal IQ	42.87	12.14	24-68	59.78	20.76	16-102	-3.42***
SCI Symptom Count	9.95	2.50	6-13	3.91	3.24	0-12	7.50***

* $p < 0.05$
*** $p < 0.001$

Table 9
Descriptive Statistics Broken Down by Diagnostic Determination Criteria (N = 74)

	Met SCQ Only n = 10		Met ADOS-2 Only n =13		Met Both SCQ and ADOS-2 (ASD Status) n =20		Met Neither SCQ and ADOS-2 n = 31	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	22.40	8.78	25.15	8.54	19.10	5.55	22.4	6.64
ADAMS Combined Anxiety Score	13.80	7.91	7.08	42.18	11.85	6.02	9.74	6.94
Nonverbal IQ	49.65	20.47	42.18	11.21	40.99	14.63	70.79	17.06

Table 10
Descriptive Statistics Based on DSM-5 ASD Criteria (N = 74)

	Met Criteria n = 27			Did not Meet Criteria n = 47			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	21.30	6.88	12-40	22.40	7.42	12-39	-0.64
ADAMS Combined Anxiety Score	10.52	5.76	3-25	10.85	7.56	0-27	0.20
Nonverbal IQ	43.69	12.13	24-68	61.88	21.04	16-102	-4.10***
SCI Symptoms Count	9.00	2.66	5-13	3.62	3.33	0-12	7.17**

** $p < 0.01$
*** $p < 0.001$

Table 11
Descriptive statistics by Measures of ASD

	Met SCQ		Met ADOS-2		Met Diagnostic Determination		Met DSM-5		Met All ASD Measures		Met No ASD Measures	
	f	%	*f*	%	*f*	%	*f*	%	*f*	%	*f*	%
	30	41	33	45	20	27	27	37	16	22	30	41
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	20.20	6.83	21.49	7.39	19.10	5.55	21.30	6.88	19.625	5.90	22.40	6.75
ADAMS Combined Anxiety Score	12.50	6.65	10.73	6.52	11.85	6.04	10.52	5.76	12.188	5.84	9.70	7.05
Nonverbal IQ	45.13	15.40	42.59	11.61	42.87	12.14	43.69	12.13	43. 09	11.78	70.93	17.35

Table 12

Case Studies for Individuals *Who Met ASD Criteria Based on Diagnostic Determination, but Did Not Meet ASD Criteria for the DSM-5 (n = 4)*

	Gender	Age	ADAMS Combined Anxiety Scores	Nonverbal Intelligence
Participant 1	M	22	3	44
Participant 2	M	13	9	31
Participant 3	M	17	21	42
Participant 4	F	16	9	67

Table 13

Case Studies for Individuals *Who Met DSM-5 ASD Criteria, but Did Not ASD Criteria Based on Diagnostic Determination (n = 11)*

	Gender	Age	ADAMS Combined Anxiety Scores	Non-Verbal Intelligence	SCQ Score
Participant 1	M	28	9	37	13
Participant 2	M	28	19	36	12
Participant 3	M	20	5	29	10
Participant 4	M	40	3	49	13
Participant 5	M	23	11	28	6
Participant 6	M	16	5	62	13
Participant 7	M	13	3	42	9
Participant 8	M	26	12	47	12
Participant 9	M	23	11	67	11
Participant 10	M	15	7	50	3
Participant 11	F	29	4	58	16
Mean		23.73	8.09	46	10.72

Table 14

Frequencies for those who met for DSM-5 ASD Criteria (N = 74)

			Males		Females		
Variables	*f*	%	*f*	%	*f*	%	χ^2
SCI	40	54	35	75	5	19	21.62***
(A1)Social Emotional Reciprocity	61	82	41	88	20	74	2.05
(A2) Communicative Behaviors	55	74	40	85	15	56	7.85**
(A3)Relationships with Others	47	64	39	83	8	30	21.06***
RRBI	30	41	26	55	4	15	11.76***
(B1) Stereotyped Behaviors	46	62	39	83	7	26	23.73***
(B2) Insistence on Sameness	6	8	5	11	1	4	1.11
(B3) Restricted Interests	23	31	19	40	4	15	5.25*
(B4) Reactivity to Sensory Input	20	27	15	32	5	19	1.56

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 15
Descriptive Statistics for DSM-5 SCI Criteria (N = 74)

Social Communication and Interaction Criteria of DSM-5 (SCI)

	Met Criteria n = 40			Did not Meet Criteria n = 34			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	21.48	6.96	12-40	22.62	7.53	12-39	-0.68
ADAMS Combined Anxiety Score	10.63	6.57	2-27	10.85	7.40	0-25	-0.14
Nonverbal IQ	44.29	12.97	16-72	67.61	19.93	26-102	-6.00***

The Social Emotional Reciprocity Criterion of DSM-5 (A1)

	Met Criteria n = 61			Did not Meet Criteria n = 13			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	21.82	7.09	12-40	22.85	7.96	12-34	-0.46
ADAMS Combined Anxiety Score	11.15	6.90	1-27	8.77	6.89	0-25	1.13
Nonverbal IQ	52.52	19.93	16-99	67.34	17.29	43-102	-2.49*

The Communicative Behaviors Criterion of DSM-5 (A2)

	Met Criteria n = 55			Did not Meet Criteria n = 19			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	22.16	7.28	12-40	21.53	7.12	12-39	0.33
ADAMS Combined Anxiety Score	11.31	6.72	2-27	9.05	7.37	0-22	1.23
Nonverbal IQ	50.57	17.92	16-93	68.16	21.10	28-102	-3.51***

The Relationships with Others Criterion of DSM-5 (A3)

	Met Criteria n = 47			Did not Meet Criteria n = 27			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-value
Age	20.85	6.83	12-40	24.00	7.51	12-39	-1.84
ADAMS Combined Anxiety Score	10.77	6.59	1-27	10.67	7.57	0-25	-0.59
Nonverbal IQ	45.51	13.37	16-74	71.57	19.39	26-102	-6.79***

* $p < 0.05$
*** $p < 0.001$

Table 16

Descriptive Statistics for DSM-5 RRBI Criteria (N = 74)

Repetitive and Restricted Behaviors or Interests Criteria of DSM-5

	Met Criteria n = 30			Did not Meet Criteria n = 44			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-test
Age	21.23	6.65	12-40	22.52	7.58	12-39	-0.75
ADAMS Combined Anxiety Score	10.43	5.56	3-25	10.93	7.76	0-27	-0.30
Nonverbal IQ	46.02	14.05	24-77	61.52	21.50	16-102	-3.46***

The Stereotyped Behaviors Criterion of DSM-5 (B1)

	Met Criteria n = 46			Did not Meet Criteria n = 28			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-test
Age	20.98	6.46	12-40	23.68	8.12	12-39	-1.58
ADAMS Combined Anxiety Score	10.41	6.34	1-27	11.25	7.87	0-25	-0.502
Nonverbal IQ	47.75	15.48	16-98	67.76	21.28	26-102	-4.632***

The Insistence on Sameness Criterion of DSM-5 (B2)

	Met Criteria n = 6			Did not Meet Criteria n = 68			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-test
Age	21.00	9.96	12-40	22.09	7.00	12-39	-0.353
ADAMS Combined Anxiety Score	10.83	6.65	3-19	10.72	6.99	0-27	-0.038
Nonverbal IQ	59.01	7.39	49-68	54.80	20.96	16-102	0.486

The Restricted Interest Criterion of DSM-5 (B3)

	Met Criteria n = 23			Did not Meet Criteria n = 51			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-test
Age	22.70	7.78	12-40	21.69	6.98	12-39	0.556
ADAMS Combined Anxiety Score	9.52	5.15	1-19	11.28	7.56	0-27	-1.009
Nonverbal IQ	49.29	13.96	24-77	57.88	22.09	16-102	-1.727

The Reactivity to Sensory Input Criterion of DSM-5 (B4)

	Met Criteria n = 20			Did not Meet Criteria n = 54			
Variables	*M*	*SD*	Range	*M*	*SD*	Range	t-test
Age	22.55	7.29	12-40	21.80	7.23	12-39	0.398
ADAMS Combined Anxiety Score	10.20	6.04	3-25	10.93	7.26	0-27	-0.399
Nonverbal IQ	48.02	17.29	24-92	57.84	20.71	16-102	-1.886

*** $p < 0.001$

Table 17
Descriptive Statistics for Number of SCI Symptoms (N = 74)

Total			
Variables	*M*	*SD*	Range
SCI	5.58	4.04	0-13
A1. Social Emotional Reciprocity	2.60	2.20	0-8
A2. Communicative Behaviors	1.93	1.52	0-5
A3. Relationships with Others	1.05	0.89	0-2

Table 18
Descriptive Statistics for Number of SCI Symptoms by Gender (N = 74)

	Males			Females			
Variables	M	SD	Range	M	SD	Range	t-value
SCI	6.83	3.80	0-13	3.41	3.55	0-13	3.82***
A1. Social Emotional Reciprocity	3.19	2.20	0-8	1.56	1.78	0-7	3.29***
A2. Communicative Behaviors	2.23	1.34	0-5	1.41	1.69	0-5	2.34*
A3. Relationships with Others	1.40	0.77	0-2	0.44	0.75	0-2	5.21***

* $p < 0.05$
*** $p < 0.001$

Table 19
Correlation Matrix

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1) Age	1.00									
(2) Anxiety	-0.007	1.00								
(3) Nonverbal IQ	-0.042	-0.26	1.00							
(4) SCQ	-0.001	0.333**	-0.597***	1.00						
(5) Number of A1 Symptoms	-0.238*	0.092	-0.422***	0.379***	1.00					
(6) Number of A2 Symptoms	0.005	-0.046	-0.345**	0.286**	0.624***	1.00				
(7) Number of A3 Symptoms	-0.244*	-0.027	-0.575***	0.463***	0.762***	0.469***	1.00			
(8) Number of SCI Symptoms	-0.181	0.027	-0.486***	0.415***	0.946***	0.818***	0.810***	1.00		
(9) Race	0.111	0.110	0.169	-0.274*	-0.222	-0.022	-0.182	-0.168	1.00	
(10) Income	0.204	0.890	0.150	-0.162	-0.093	-0.026	-0.235	-0.091	-0.150	1.00

* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level
*** Correlation is significant at the .0001 level

Table 20
Correlation Matrix for Males

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) Age	1.00							
(2) Anxiety	0.18	1.00						
(3) Nonverbal IQ	-0.12	-0.02	1.00					
(4) SCQ	0.02	0.33*	-0.31*	1.00				
(5) Number of A1 Symptoms	-0.30*	0.04	-0.12	0.21	1.00			
(6) Number of A2 Symptoms	0.04	-0.08	-0.13	0.08	0.68***	1.00		
(7) Number of A3 Symptoms	-0.38**	-0.05	-0.20	0.21	0.71***	0.37**	1.00	
(8) Number of SCI Symptoms	-0.24	-0.12	-0.15	0.19	0.96***	0.82***	0.75***	1.00

* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level
*** Correlation is significant at the .0001 level

Table 21
Correlation Matrix for Females

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
(1) Age	1.00							
(2) Anxiety	0.33	1.00						
(3) Nonverbal IQ	0.04	-0.35	1.00					
(4) SCQ	0.09	0.36	-0.66***	1.00				
(5) Number of A1 Symptoms	-0.20	0.14	-0.54**	0.36	1.00			
(6) Number of A2 Symptoms	-0.07	-0.05	-0.38	0.35	0.47*	1.00		
(7) Number of A3 Symptoms	-0.16	-0.11	-0.63***	0.44	0.76***	0.46*	1.00	
(8) Number of SCI Symptoms	-0.17	0.02	-0.58**	0.44	0.89***	0.81***	0.81***	1.00

* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level
*** Correlation is significant at the .0001 level

Table 22
Summary of Ordinary Least Squares Regression Analysis for Variables Predicting Scores on the Social Emotional Reciprocity (A1) Criterion of the DSM-5 ASD Criteria

	B	*Std. Error*	β	*t*	*p*
Age	-0.138	0.060	-0.250	-2.291	0.025*
ADAMS Combined Anxiety Scores	0.014	0.063	0.025	0.228	0.820
Nonverbal IQ	-0.071	0.022	-0.358	-3.272	0.002**

* $p < 0.05$
** $p < 0.01$

Table 23
Summary of Ordinary Least Squares Regression Analysis for Variables Predicting Scores on the Communicative Behavior (A2) Criterion of the DSM-5 ASD Criteria

	B	*Std. Error*	β	*t*	*p*
Age	0.005	0.044	0.012	0.12	0.107
ADAMS Combined Anxiety Scores	-0.036	0.046	-0.092	-0.798	0.427
Nonverbal IQ	-0.040	0.016	-0.297	-2.578	0.012*

* $p < 0.05$

Table 24
Summary of Ordinary Least Squares Regression Analysis for Variables predicting Scores on the Relationships with Others (A3) Criterion of the DSM-5 ASD Criteria

	B	*Std. Error*	β	*t*	*p*
Age	-0.072	0.020	-0.331	-3.568	0.001**
ADAMS Combined Anxiety Scores	-0.001	0.021	-0.002	-0.024	0.981
Nonverbal IQ	-0.044	0.007	-0.571	-6.139	0.000***

** $p < 0.01$
*** $p < 0.001$

Table 25
Summary of Logistic Regression Analysis for Variables predicting an ASD Diagnosis based on Diagnostic Determination

	B	Std. Error	df	*p*
Age	-0.124	0.051	1	0.016*
ADAMS Generalized Anxiety	0.037	0.046	1	0.421
Nonverbal IQ	-0.063	0.21	1	0.002**

* $p < 0.05$
** $p < 0.01$

Table 26
Summary of Logistic Regression Analysis for Variables predicting an ASD Diagnosis based on DSM-5 Criteria

	B	*Std. Error*	df	*p*
Age	-0.040	0.039	1	0.307
ADAMS Combined Anxiety Scores	-0.026	0.041	1	0.525
Nonverbal IQ	-0.063	0.019	1	0.001***

*** $p < 0.001$

Figure Captions

Figure 1. Nonverbal IQ Scores Prior to Score Transformation

Figure 2. Nonverbal IQ Scores After Score Transformation

Figure 3. Distribution of Participant Age

Figure 4: Frequency of Individuals Meeting Autism Criteria Based on Diagnostic Criteria

Figure 5: Frequency of Individuals Meeting Autism Criteria Based on Diagnostic Assessment

Figure 1

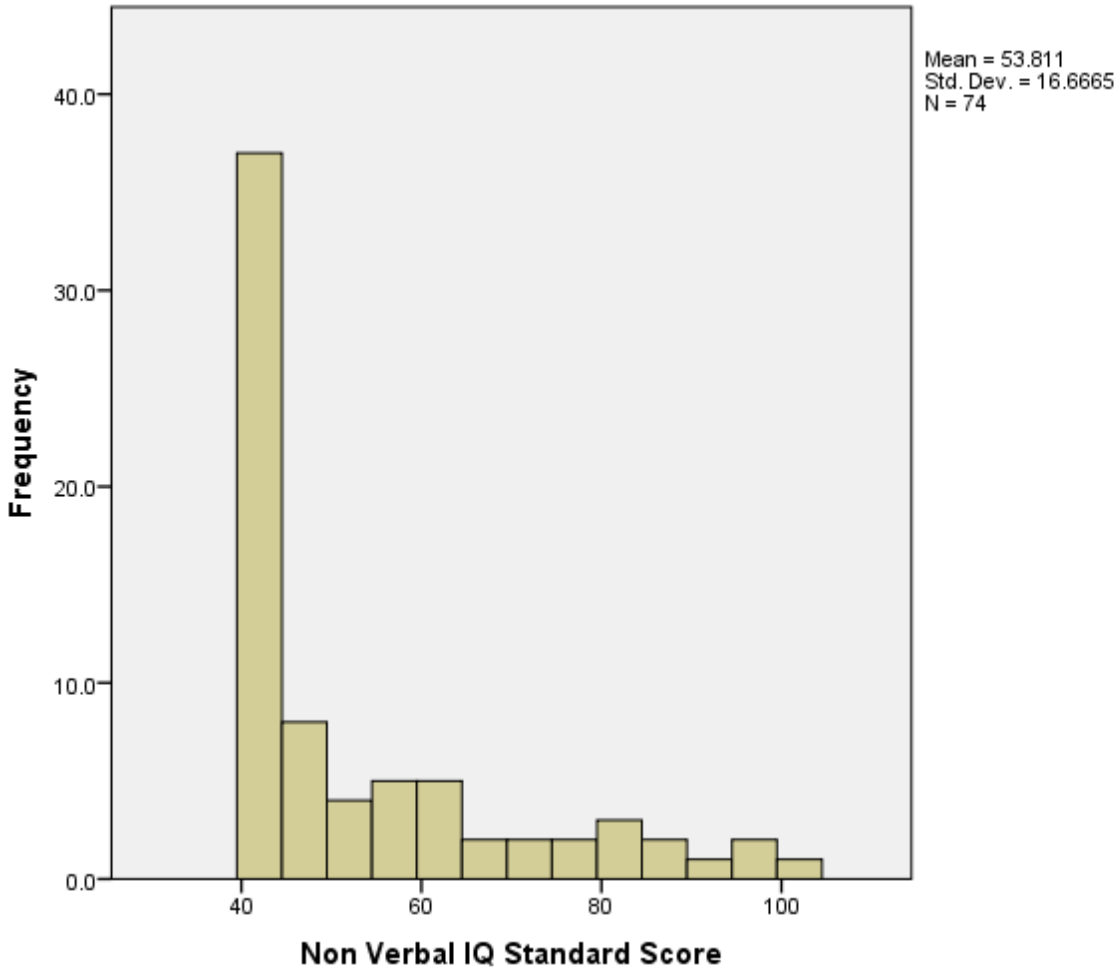

Mean = 53.811
Std. Dev. = 16.6665
N = 74
Frequency
40.0
30.0
20.0
10.0
0.0
40
60
80
100
Non Verbal IQ Standard Score

Figure 2

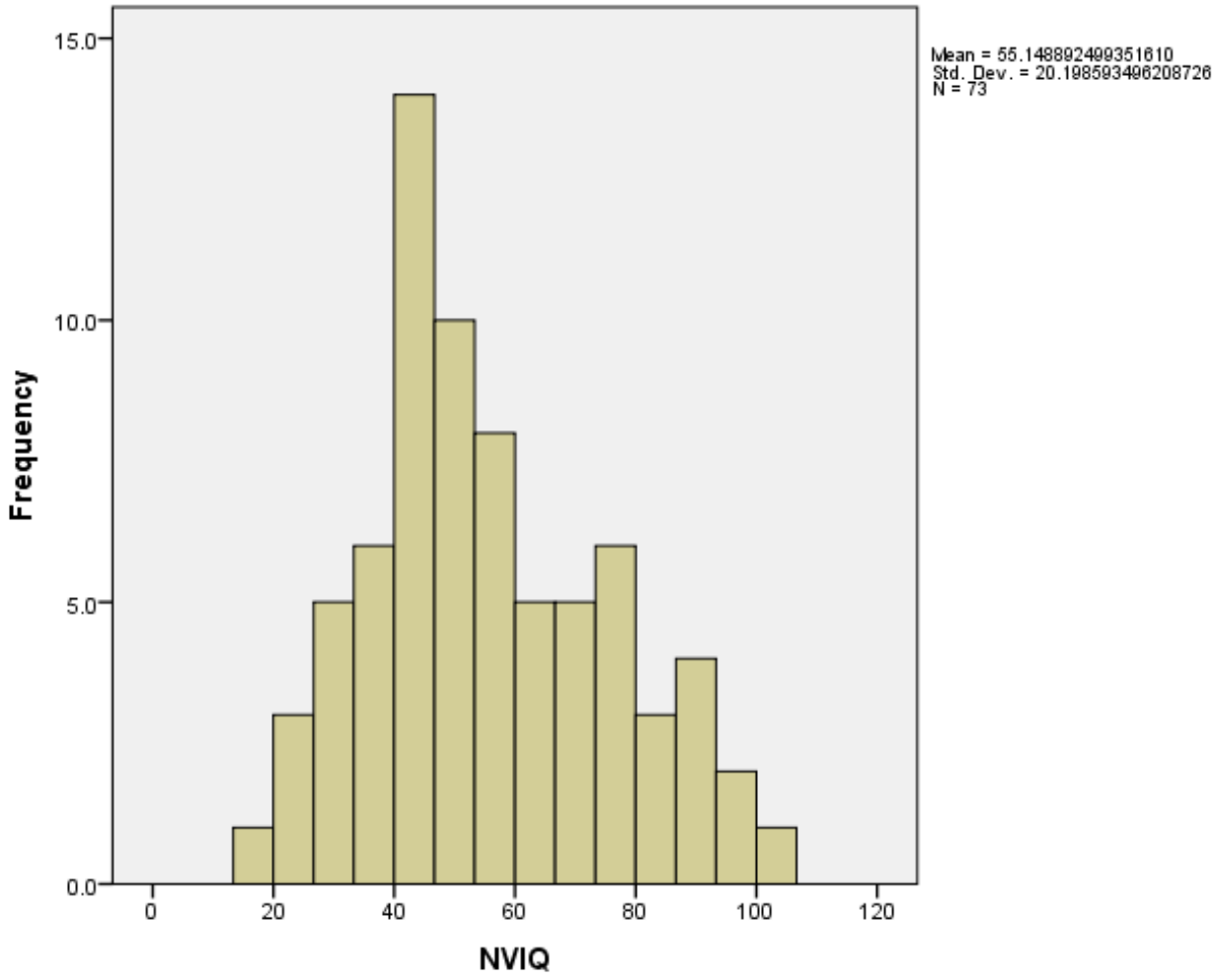

Mean = 55.148892499351610
Std. Dev. = 20.198593496208726
N = 73
Frequency
15.0
10.0
5.0
0.0
0
20
40
60
80
100
120
NVIQ

Figure 3

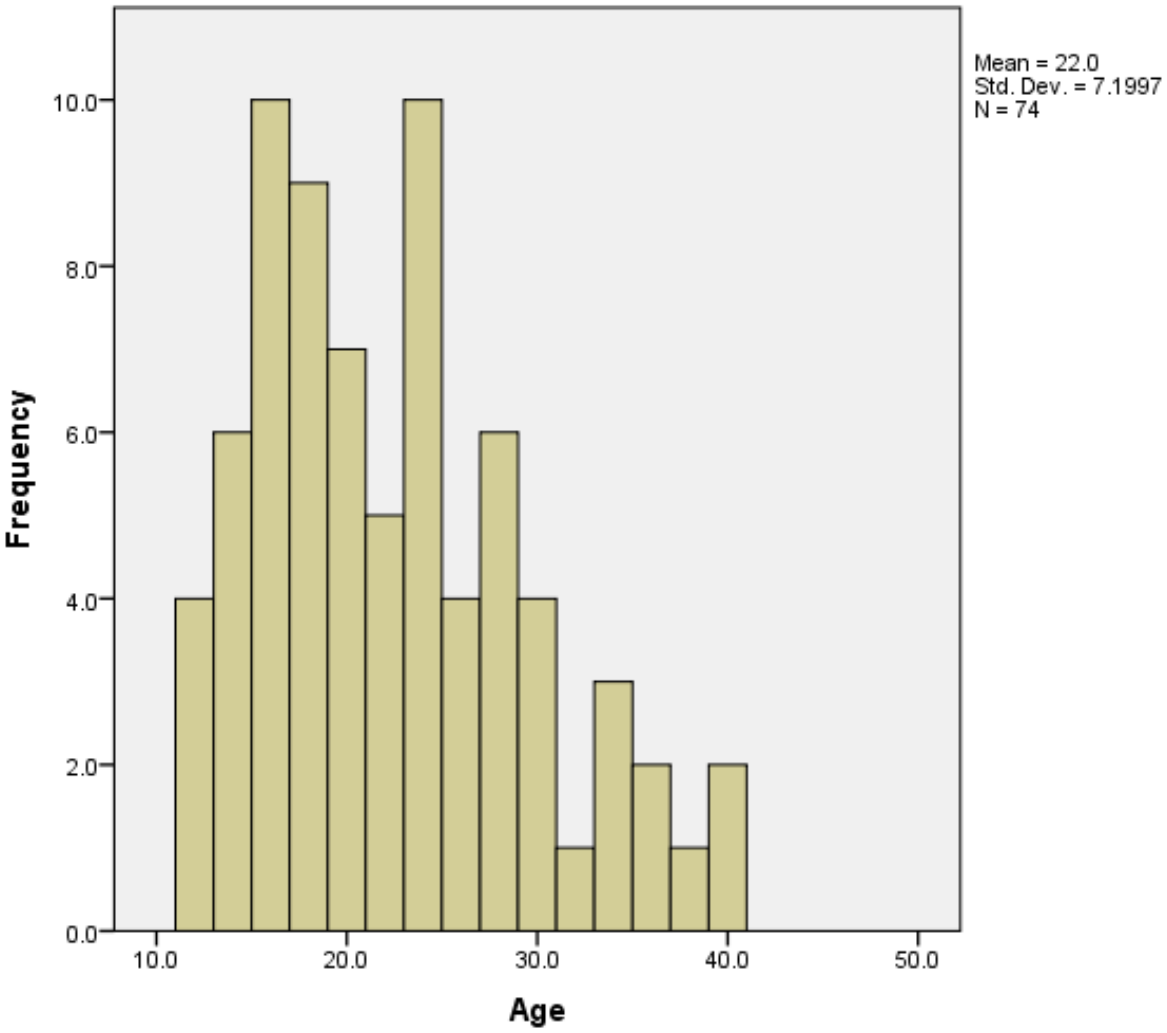

Mean = 22.0
Std. Dev. = 7.1997
N = 74
Frequency
10.0
8.0
6.0
4.0
2.0
0.0
10.0
20.0
30.0
40.0
50.0
Age

Figure 4

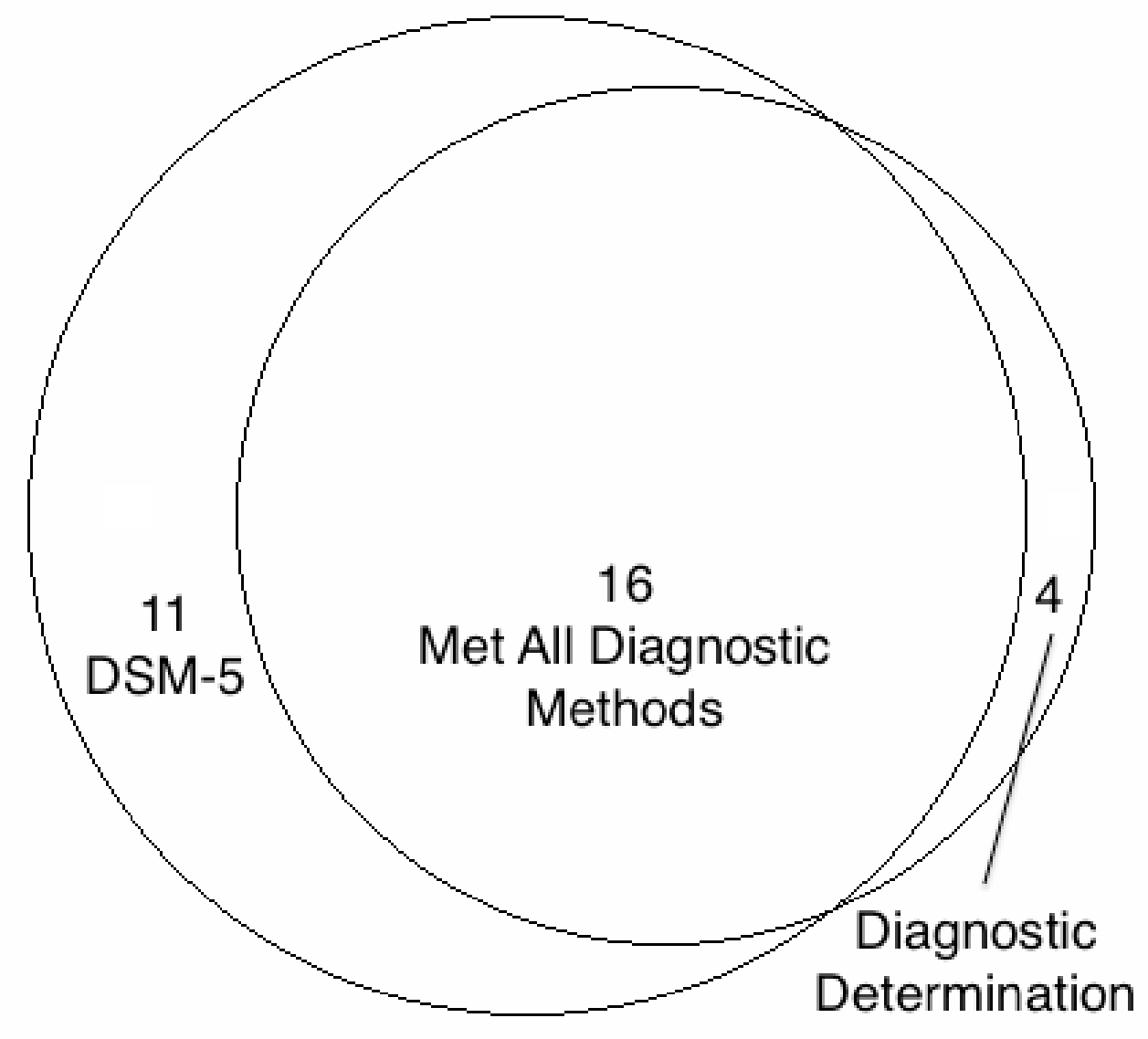
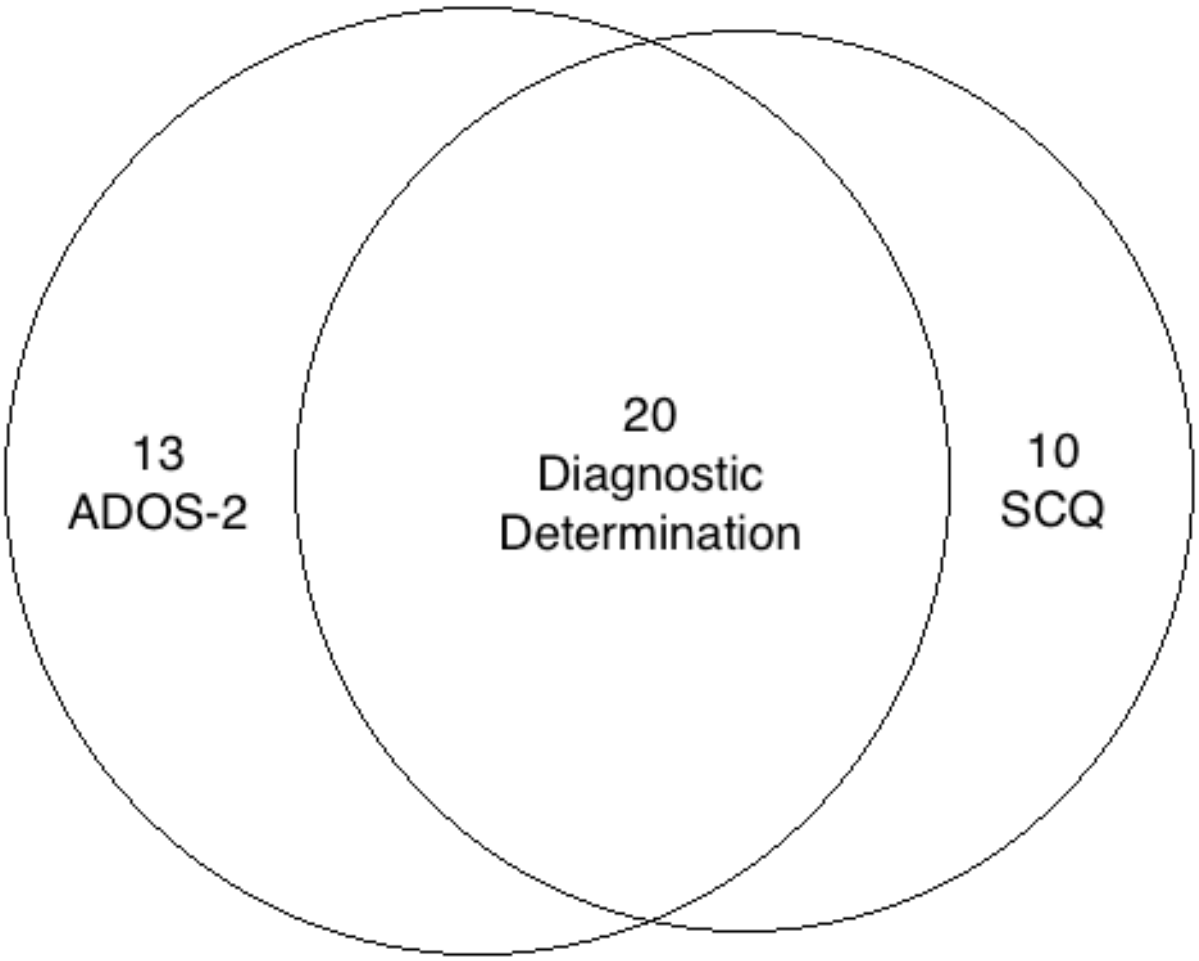

11
DSM-5
16
Met All Diagnostic
Methods
4
Diagnostic
Determination

Figure 5



Appendix 1
ADAMS Social Avoidance and Generalized Anxiety Questions

Social Avoidance				
Problems initiating communication ……...……...	0	1	2	3
Withdraws from other people ……...	0	1	2	3
Shy …….....	0	1	2	3
Avoids others, spends much of time alone ……...	0	1	2	3
Lacks emotional facial expressions …….....	0	1	2	3
Avoids eye contact ……	0	1	2	3
Avoids peers …….....	0	1	2	3
Generalized Anxiety				
Nervous ……	0	1	2	3
Does not relax or settle down ……	0	1	2	3
Tense …….	0	1	2	3
Worried …….	0	1	2	3
Anxious …….	0	1	2	3
Experiences panic attacks …….	0	1	2	3
Trembles when frightening situations are not present ……..	0	1	2	3

Appendix 2
DSM-5 ASD Criteria

A. ***SCI:*** Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):

A1. *Social Emotional Reciprocity*: Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

A2. *Communicative Behaviors*: Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

A3. *Relationships with Others:* Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers

B. ***RRBI*:** Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

B1. *Stereotyped Behaviors*: Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

B2. *Insistence on sameness:* Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

B3. *Restricted Interest*: Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

B4. *Reactivity to Sensory Input:* Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).