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Prevalence And Predictors Of Attention Deficit Hyperactivity Disorder In Adolescent And Adult Males With Fragile X Syndrome And Autism Spectrum Disorder

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PREVALENCE AND PREDICTORS OF ATTENTION DEFICIT HYPERACTIVITY
DISORDER IN ADOLESCENT AND ADULT MALES WITH FRAGILE X SYNDROME
AND AUTISM SPECTRUM DISORDER

by

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ABSTRACT

Individuals with fragile X syndrome (FXS) experience disproportionate rates of diagnoses of attention-deficit/hyperactivity disorder (ADHD) when compared to the general population. Exact prevalence rates and outcomes for individuals with a diagnosis of FXS and ADHD is not well known.   The current study assesses rates of ADHD diagnosis in individuals with FXS as well as tests the prediction of a diagnosis of ADHD from levels of autism spectrum disorder (ASD) symptom presentation. The present study included 30 individuals with FXS aged 13-25 and were assessed using a structured diagnostic interview. Interviews were conducted with individual's parents' due to low cognitive ability found in individuals with FXS. ASD symptoms were not found to be a significant predictor of ADHD in our sample. Diagnostic prevalence rates of ADHD were found to be 45% for the FXS sample. Individuals with FXS experience diagnostic rates of ADHD significantly higher than those found in the general population. The presence of ASD does not appear to account for the differences found in these rates.

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CHAPTER 1

INTRODUCTION

1.1 ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Attention Deficit/Hyperactivity Disorder (ADHD), is a neurodevelopmental disorder marked by symptoms of hyperactivity, inattention, and executive functioning deficits (Akinbami, Liu, Pastor, & Reuben, 1998; Nikolas, Klump, & Burt, 2015). It is the most commonly diagnosed behavioral disorder in typically developing children with rates of ADHD in the general population ranging from 9-11% during childhood to about 4% in adults (APA, 2013; Kessler et al., 2006). The DSM 5th Edition (DSM-5) breaks ADHD into two subgroups: inattentive (ADHD-I) and hyperactive/impulsive (ADHD-H; APA, 2013). Additionally, a diagnosis of ADHD combined (ADHD-C) type can be received when diagnostic criteria is met for both inattentive and hyperactive types. In children with ADHD, symptoms present through a spectrum of deficits that can impact academic, social and cognitive functioning (De Boo & Prins, 2007; Solanto, Pope-Boyd, Tryon, & Stepak, 2009).

Children with a diagnosis of ADHD are prone to a number of negative developmental risk factors that can have cascading impacts on their functioning. For example, children with ADHD are often more socially rejected by their peers and are also viewed more negatively by their peers (De Boo & Prins, 2007). In many cases, this is due to the fact that children with ADHD have difficulty staying on topic in conversations,

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often initiate or engage in conversations at inappropriate times, and engage in frequent off-task and rule breaking behaviors (De Boo & Prins, 2007; Erhardt & Hinshaw, 1994). Cumulatively, these behaviors in childhood lead to maladaptive social functioning in adults who continue to experience symptoms and consequences of ADHD later in life. In fact, adults with ADHD are more likely to be incarcerated, engage in drug use, be unemployed, miss more days of work and have less education than adults without ADHD (Secnik, Swensen, & Lage, 2005). In addition, adults with ADHD are found to change occupations more frequently, and have a higher number of failed relationships (Barkley, Fischer, & Smallish, 2002; Biederman, 2004).

As can be seen, the impacts of ADHD in the general population can have severe consequences. In addition to the general population, the symptoms of ADHD have been found to be pervasive and impairing in specific neurodevelopmental disorders including fragile X syndrome (FXS) and non-syndromic autism spectrum disorder (ASD). Studying the presentation of ADHD in high risk neurodevelopmental groups such as FXS and ASD is important because of the significant impact that a comorbid diagnosis of ADHD can have on the functioning and long-term outcomes for persons with these disorders. Additionally, studying ADHD in the presence of two disorders that also have elevated features of ASD will advance the field to a greater understanding of the unique and shared dimensions of the behavioral phenotypes found in non-syndromic ASD and autism associated with FXS. As such, studying ADHD in these high risk neurodevelopmental groups is ideal for furthering our understanding of the underpinnings and phenotypic expression of ASD, FXS and ADHD independently and collectively.

1.2 FRAGILE X SYNDROME

Fragile X syndrome is a monogenetic disorder that is the primary known genetic cause of ASD and intellectual disability (ID; Scerif, et al., 2012). The full mutation is identified by a cytosine-guanine-guanine (CGG) repeat >200 on the FMR1 gene found on the X chromosome. The CGG repeat expansion is associated with reduced fragile X mental retardation protein (FMRP), which is involved in typical brain maturation. Fragile X syndrome affects 1: 5,000 live births in males (Centers for Disease Control, 2015). The behavioral phenotype of FXS is marked by high levels of challenging behaviors and symptoms such as inattention, hyperactivity, and hyperarousal; these symptoms are all related to ADHD (Hatton et al., 2002; Thurman, McDuffie, Hagerman, & Abbeduto, 2014).

FXS is associated with a number of comorbidities, however, ADHD has been found to be the most common and diagnosable condition in individuals with FXS (Backes et al., 2000; Baumgardner, Reiss, Freund, & Abrams, 1995). Even though ADHD is the most commonly diagnosed behavioral disorder in FXS, reported rates of ADHD in individuals with FXS vary depending on age and type of measure utilized (Sullivan, 2006). Per some reports, approximately 22% to 74% of males with FXS display features of at least one of the three sub-types of ADHD (Backes, Genc, Schreck, et al., 2000; Lo-Castro, D'Agati, & Curatolo, 2011; Reilly, Senior, & Murtagh, 2015). Hyperactivity and inattention are hallmark behavioral features of both ADHD and FXS; however, direct investigation of overlaps in these symptom profiles and diagnostic rates in the presence of FXS has only been investigated to a limited degree (Reilly, Senior, & Murtagh, 2015). This points to the need of identifying which of these behavioral features

results from either FXS or ADHD. Further, this information will allow for the understanding of the behavioral underpinnings of ADHD symptom presentations to aid in the development of targeted treatments and interventions within each of these individual clinical groups.

Multiple studies have investigated symptom prevalence rates in children and adolescents with FXS using symptom based behavioral measurement. (Backes et al., 2000; Bailey, Raspa, Olmsted, & Holiday, 2008; Hartley et al., 2011; Newman, Leader, Chen, & Mannion, 2015; Smith, Barker, Seltzer, Abbeduto, & Greenberg, 2012; Sullivan et al., 2006). Most often behavioral rating scales are filled out by parents, rating their child's behavior. Symptom based behavioral measures are continuous in their measurement system and allow for researchers to examine features of a disorder and change in behavior over time, independent of whether the symptoms are sufficient to warrant a formal diagnosis. Across studies utilizing rating scales to examine ADHD in FXS, symptom rates (either meeting borderline or clinically significant rates) varied greatly depending on composition of sample and types of measures used with symptom rates ranging from 36% to 78% (Lachiewicz, 1992; Lachiewicz and Dawson, 1994; Baumgardner et al., 1995; Backes et al., 2000; Hatton et al., 2002, as cited in Sullivan et al., 2006). Specifically, the highest rates of symptom presentation appear evident when the Child Behavior Checklist (CBCL) Attention Scale is utilized with 78% to 80% scoring above clinical significance on this scale across multiple samples (Bailey et al., 2008; Newman et al., 2015).

In contrast, relatively few studies have examined diagnostic prevalence rates of ADHD in children with FXS utilizing a diagnostic measure as opposed to symptom based

measures (Backes et al., 2000; Sullivan et al., 2006). In the diagnostic based literature, rates of ADHD in males with FXS are reported to range from 54% to 74% (Backes et al., 2000; Sullivan et al., 2006) which is significantly higher than the rates of both ~10% for children and 4% for adults in the general population. The diagnostic rates for ADHD in FXS are somewhat lower than symptom-based rates as they fall in the lower end of what has been found in the symptom based literature. This is to be expected when using screening measures that are aimed at over identifying individuals for a range of different disorders to allow for more careful, targeted examination of an individual's behavior. When examining the methodology of both symptom and diagnostic based studies more closely, there is a lack of utilization of ADHD specifc measures (i.e. Conner's-3). Utilizing ADHD specific measures in individuals with FXS may give a clearer and more accurate picture of what true comorbid rates of ADHD are.

Further concerns related to the lack of ADHD specific diagnostic literature for individuals with FXS relates to the ability to interpret the findings from the literature that does exist. Of the two diagnostic studies found in the literature, each only used a sample of children and adolescents, and do not extend into the adult population. Additionally, the genetic composition of the samples in these studies not being homogeneous; with one including both males and females with the full mutation in their sample (Sullivan et al., 2006) and the other including males with the full and pre-mutation (Backes et al., 2000). Backes (2000) also excluded individuals who could not understand the instructions of the cognitive assessment thus possibly introducing a skew with more cognitively capable individuals being included in their sample. This is not standard practice in studies indcluding individuals with FXS given intellectual disability (ID) is a hallmark feature of

FXS. This wide prevalence range and lack of structure in the genetic makeup of previous samples calls for the need for more research to help us understand in what symptom domains and at what ages the impact of ADHD is on individuals with FXS.

Given what we know about the impacts of the symptoms of ADHD in the general population and the poor life course trajectory for individuals with FXS, outcomes for adults with FXS who also have a comorbid diagnosis of ADHD are expectedly poor (Hartley et al., 2011). In a longitudinal study aimed at looking at the impact of ADHD in childhood on social functioning in adults with FXS, found that elevated ADHD symptoms were a significant predictor of impaired social functioning for males with FXS 15-25 years old (Chromik et al., 2015). Thus, the impacts of ADHD symptomatology in FXS early in life has significant implications for life course trajectory and independence later in life for these individuals. However, in a national, one-time, survey study of functioning in adults with FXS, did not find inattention and hyperactivity to be directly related to poor outcomes in adulthood (Hartley et al., 2011). However, regardless of other diagnoses or conditions, inattention and hyperactivity have been shown to significantly impact an individual's ability to build friendships and engage in appropriate social interactions. In the same study, the two strongest predictors of positive adult outcomes for individuals with FXS were functional skills and appropriate social interactions (Hartley et al., 2011). Thus, the well-documented negative impacts that ADHD has on social skills is a likely contributor to impairments for individuals with FXS across early childhood with important implications for functioning later in life.

In summary, ADHD is highly prevalent and significantly impairing in individuals with FXS. However, significant limitations are present across many studies, yielding

caution when interpreting their results. Three of the primary limitations include failure to control for large variability in the age and genetic status in samples, a lack of study in the adolescent and young adult developmental stage, and an over-reliance on rating scales rather than diagnostic measures. As such, the present study will contribute to the literature by targeting a genetically homogenous sample of adolescents and adults with FXS and using a diagnostic interview.

1.3 AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a social communication and restricted and repetitive behavior disorder that affects 1: 68 children (CDC, 2015). ASD is a highly heritable disorder, with a largely heterogeneous etiology. Research shows that 22% to 83% of children with ASD are also diagnosed with ADHD (see review by Leitner, 2014). Prior to the most current version of the DSM, ADHD could not be diagnosed in the presence of ASD. However, now that these two disorders may be co-diagnosed, the need to study and understand each of them in isolation, as well as in the presence of one another, is imperative. Consistent with the literature on FXS and ADHD, the type of sample, age of participants, and types of measures used are important factors that contribute to the variance in reported prevalence rates for individuals with non-syndromic ASD (Visser, Rommelse, Greven, & Buitelaar, 2016).

Many of the negative social implications of ASD are also experienced by children who receive a diagnosis of ADHD demonstrating significant symptom overlap. Peer rejection and difficulty entering and maintaining appropriate conversations impact children with ASD and those with ADHD without ASD (Ashwood et al., 2015). Further, a review aimed at summarizing what the field currently knows about the comorbidity of

ASD and ADHD points to a number of studies find that children with comorbid ASD and ADHD have lower cognitive ability, lower adaptive skills, and greater impairments in social, emotional and school functioning (Leitner, 2014). Thus, the deficits presented by ASD alone, coupled with additional deficits created by ADHD, place children with these co-diagnoses at risk for poorer outcomes across multiple domains throughout their lifetime (Sikora, Vora, Coury, & Rosenberg, 2012). However, because little research has focused on the impacts of comorbid ASD and ADHD in adolescence or adulthood, little is known about how these co-diagnoses affect individuals later in life. Likewise, little research has been conducted on the presence and impact of individuals with non-syndromic ASD who also have ID and ADHD. In one of the few existing studies, 17% of six to 17-year-old children with ASD+ID had ADHD (Stevens et al., 2016). The present study will expand upon this work by investigating rates of ADHD in a sample of adolescents and adults with non-syndromic ASD and comorbid ID contrasted to FXS.

Within the context of FXS, about 60% of children with a diagnosis of FXS also receive a diagnosis of ASD (Harris et al., 2008). Previous research has shown that the presence of ASD does not consistently predict ADHD behaviors in individuals with FXS (Newman et al., 2015; Sullivan et al., 2006). The relationship of ASD severity and ADHD in FXS remains unclear, with some reports showing a relationship with autism severity features (Sullivan, 2006) and others not showing a relationship when autism is used as a grouping variable (Newman, 2015; Hatton, 2002). The present study aims to investigate the relationship of non-syndromic ASD (i.e., ASD without FXS or another genetic disorder) and ADHD symptoms in the presence of FXS.

1.4 SUMMARY

Rates of ADHD within individuals with FXS ranges from 40% to 80%. Rates of ADHD in individuals with ASD ranges from 14% to 78%. However, these rates are based upon a majority of samples comprised of children. Thus, little is known about the diagnostic rates of ADHD in FXS and ASD in a genetically and sex homogenous sample. Previous literature has shown that presence ADHD in either ASD or FXS is associated with overall greater impairment in functioning. Thus, the need to understand rates of ADHD in clinical adult populations is imperative to understand gaps in treatment and developmental trajectories of these comorbid disorders.

1.5 THE CURRENT STUDY

Presently, more is known about the genetics of FXS than about the behavioral phenotype (Tranfaglia, 2010). Despite the high prevalence and impairment associated with ADHD in specific neurodevelopmental disorders, little research has been conducted comparing adolescents and adults with non-syndromic ASD to FXS when looking at ADHD. In addition, no study has ever compared FXS to non-syndromic ASD with the goal of identifying ADHD within each of these high-risk populations with an older adolescent and adult sample.

The present study aims to characterize the prevalence and predictors of ADHD using a DSM-based diagnostic interview employing a strict diagnostic criteria model requiring the presence of impairment complemented by consideration of the presence of features independent of impairment. The focus of this study is on adolescent and adult males with FXS contrasted to males with non-syndromic ASD given the high prevalence of ADHD in each of these populations. By taking a differential diagnostic approach to

known genetic and behaviorally similar neurodevelopmental disorders, we will contribute information to the field regarding diagnostic rates across these two disorders which will allow for more targeted interventions.

1.6 RESEARCH QUESTIONS

The following three primary research questions were addressed in this study, and the relevant hypotheses are included.

1. *What is the diagnostic prevalence of the three sub-types of ADHD (Inattentive, Hyperactive, and Combined) in an adolescent and young adult sample of males with FXS?* It is hypothesized that 75% of our FXS sample will meet for a diagnosis of ADHD, with more individuals meeting for ADHD inattentive type, over the other two subtypes.

2. *Is autism symptom severity associated with a diagnosis of ADHD in adolescent and adult males with FXS?* We hypothesize that higher levels of ASD symptomology will be found in individuals with FXS who also meet for a diagnosis of ADHD.

3. *Is the diagnostic prevalence of the three sub-types of ADHD (Inattentive, Hyperactive, Combined) different in adolescent and young adult males with FXS contrasted to males with non-syndromic ASD?* It is hypothesized that overall ADHD diagnostic rates will be higher in the FXS sample than in the non-syndromic ASD sample. Further, it is hypothesized that all the ADHD diagnostic subtypes will be found to have higher rates in the FXS sample than in the non-syndromic ASD sample.

CHAPTER 2

METHODS

2.1 PARTICIPANTS

Participants with FXS were drawn from a larger longitudinal, multiple site study focused on language development during the transition into adulthood (R01 PI: Abbeduto). Only individuals who participated at the University of South Carolina (USC) site were included in this study given a more focused interest on ADHD and the presence of sufficient resources at the USC site. The FXS group was recruited nationally through parent listservs, social media, postings by the National Fragile X Foundation, and with the help of the Research Participant Registry Core of the Carolina Institute for Developmental Disabilities at the University of North Carolina at Chapel Hill. Participants with non-syndromic ASD were recruited locally to each research site through local advertisements, social media, parent support groups, the South Carolina Department of Disabilities and Special Needs (n = 13) and participation in a complementary study (n = 7) at USC aimed at examining social communication profiles within families of children with ASD (F32 PI: Klusek).

Participants included 31 males with FXS and 20 males with ASD. Ages ranged from 16-24 years old for the FXS group (M = 18.73, SD = 2.13) and 13-22 years old for the ASD group (M = 18.86, SD = 2.18). Average participant characteristics can be found for each group in Tables 2.1 and 2.2. Participants with FXS had the full mutation of the

FMR1 gene (> 200 CGG repeats) confirmed through genetic testing. Clinical diagnoses of autism within the non-syndromic ASD group were confirmed through study participation and the presence of FXS was ruled out based on a review of genetic records.

All participants were verbally communicative (minimum combination of at least three words), spoke English as their primary language, and lived with their biological parents at least during the first year of enrollment in the study.

2.2 PROCEDURES

Data collection occurred based on established procedures of the larger language R01, which was designed with four annual assessments (Times 1-4), and the F32 which represented a single assessment. The current study focused on ADHD as an extension of both the larger R01 and F32 studies; thus, we accessed existing data that were part of each ongoing study along with the newly added ADHD diagnostic measure integrated into the existing protocols. Per the standard protocol for the R01, the ADOS and cognitive scores were completed at Time 1 and the ADHD diagnostic measure was added in Year 2 (T2). Study visits lasted two-days, and included a team of trained staff members who administered all behavioral assessments, and completed interviews with the participants' mothers.

2.3 MEASURES

2.3.1 ADHD DIAGNOSIS The Children's Interview for Psychiatric Syndromes – Parent version (PChIPS; (Fristad, Teare, Weller, Weller, & Salmon, 1998), was administered to determine the presence of ADHD symptoms and diagnosis in the non-syndromic ASD and FXS samples. The PChIPS is a structured parent interview used to assess presence of psychiatric disorders in children and adolescents aged 6-17 years old.

Table 2.1
ASD Participant Characteristics

	Whole Group
n	20
Age	17 years 6 months (23.28 months)
Leiter Growth Score	489.85 (19.00)
ADOS Severity Score	7.2 (1.86)
Race	
African American	10%
Asian	5%
American Indian or Alaskan Native	0%
Hispanic Latino	5%
Caucasian	75%
Bi-racial	5%

Table 2.2
FXS Participant Characteristics

	Whole Group	With ASD	Without ASD
n	31	23	8
Age	17 years 6 months (34.87 months)	17 years 4 months (35.14 months)	17 years 9 months (33.83 months)
Leiter Growth Score	459.9 (14.04)	456 (15.33)	466.5 (5.41)
ADOS Severity Score	5.677 (2.28)	5 (1.30)	2.375 (0.70)
Race/Ethnicity	African American 9.6% Asian 3.2% American Indian or Alaskan Native 3.2% Hispanic Latino 6.4% Caucasian 77.4%	African American 0% Asian 0% American Indian or Alaskan Native 0% Hispanic Latino 12.5% Caucasian 87.5%	African American 13% Asian 4.3% American Indian or Alaskan Native 4.3% Hispanic Latino 4.3% Caucasian 73.9%

It uses a DSM based diagnostic model to assess symptom count, duration, and impairment consistent with DSM criteria. Questions pertaining to symptomology are presented and scored in a yes/no format. The full version of the PChIPS assesses for 20 DSM-IV disorders; however, only 10 of these disorders were administered to parents' due to the nature of the behavioral phenotype of FXS and ASD. Only the ADHD section was included in analyses for the present study. The current version of the PChIPS assesses diagnostic criteria per the DSM-IV, however we considered the two major changes that DSM-5 made to the diagnostic criteria for ADHD. These are allowing the concurrent diagnosis of ADHD and ASD and for a retrospective ADHD diagnosis to be made if 5 symptoms were endorsed to be present before age 12. Since no changes were made to the symptoms listed for ADHD from DSM-IV to DSM-5, no structural changes were made to the PChIPS scoring form. Although all the participants in this study were above the age of 12, the number of symptoms needed to meet for a diagnosis of ADHD was still held at six, due to the average developmental age of individuals with FXS and those with low IQ. However, we also calculated the rates using the adult criteria of five symptoms to complement the child rates given no established procedure for applying DSM ADHD criteria to adolescent and adult samples with low mental ages (see Figure 2.1 and 2.2).

The PChIPS was first examined on a sample of 36 typically developing children aged six to 13 years of age (Fristad, et al, 1998). Of the 36 participants included in the study, 78% were boys. The study aimed at determining the convergent validity of the PChIPS with the original interview, the Children's Interview for Psychiatric Syndromes (Weller, Weller, Fristad, Rooney, & Schecter, 2000). For ADHD, a kappa coefficient of

0.122 was found between the ChIPS and the PChIPS, with 50% agreement between the two measures. (Fristad, et. Al, 1998).

The PChIPS has also been investigated with a sample of ASD children using the Child and Adolescent Symptom Inventory (CASI; Witwer, 2012), where strong intraclass correlation coefficients (ICC's) were found (Hyperactive = .92, Inattentive = .97, and Combined = .93) but fair to moderate kappa agreements (Hyperactive = 0.43, Inattentive = 0.60, and Combined = 0.27). Although the PChIPS has not yet been used in a FXS sample, it was designed for individuals with the same mental age as the participants included in this study. Inter-rater reliability was calculated based upon percent agreement for type of ADHD sub-type diagnosis. Twenty percent of the FXS sample had reliability calculated ad 25% of the ASD group had reliability calculated. Percent agreement was 100% for both groups. The categorical distinction of presence/absence of an ADHD disorder based on DSM-5 criteria was the primary dependent variable in the analyses.

2.3.2 ASD SYMPTOM SEVERITY The Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012) was administered to confirm autism diagnostic status in the ASD group, determine ASD status in the FXS group, and document severity of ASD features across groups. The ADOS-2 consists of a series of semi-structured interviews and play opportunities between an examiner and a participant, allowing for the observation of developmentally appropriate and inappropriate responses to these social exchanges. The ADOS-2 also used a continuous index of ASD symptoms by utilizing severity scores for overall behaviors. These overall symptom severity scores were used in analysis as a predictor for ADHD in the FXS group. The ADOS-2 was administered and scored live by graduate-level professionals who completed standard
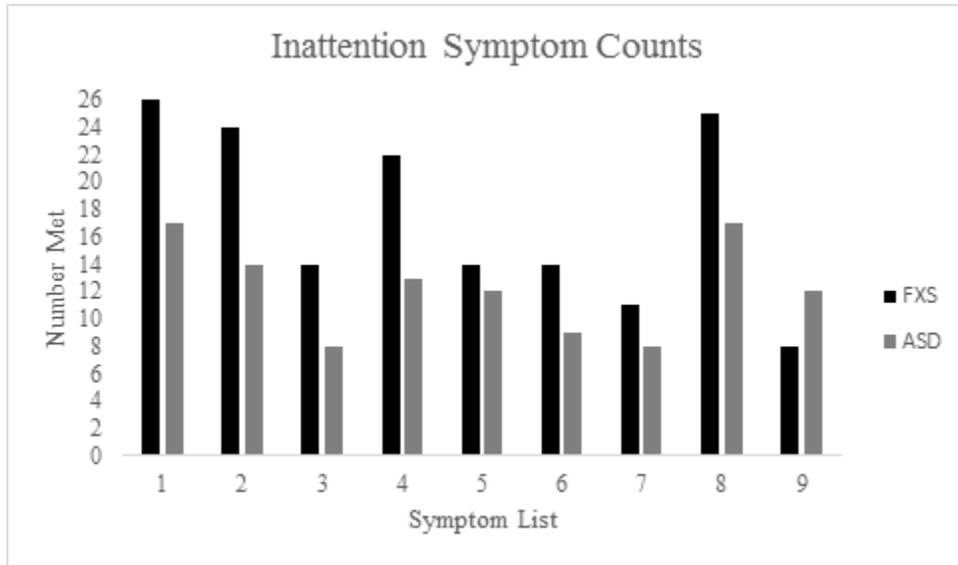
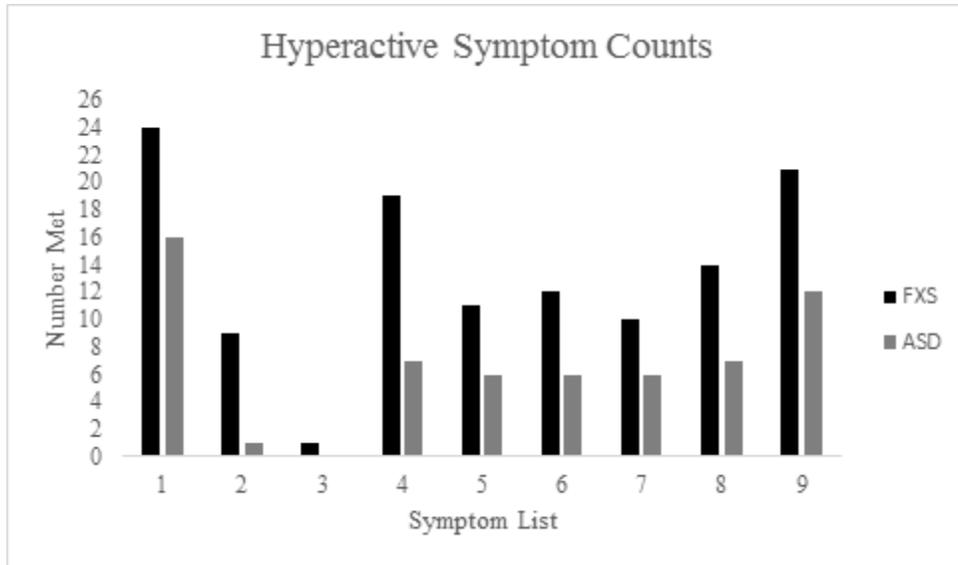*Figure 2.1.* Bar graph showing inattentive symptom level endorsement.

Figure 2.2 Bar graph showing hyperactive/impulsive symptom level endorsement.

research reliability training. Ten percent of the administrations were randomly selected and second-scored by video for inter-reliability across both groups which was yielded to be above 80% across all items and algorithm scoring for the ADOS-2. The severity score was used as a continuous variable indicating degree of ASD symptom severity.

2.3.3 COGNITIVE ABILITY The Leiter-R is a non-verbal intelligence measure intended for use in subjects who have limited receptive and expressive language capabilities. Growth scores obtained from the Leiter-R were used in analysis to control for floor effects. Due to low cognitive abilities in these populations floor effects can significantly affect standard scores, thus impacting analyses (Roid & Miller, 1997). The growth score was used as a continuous variable to indicate cognitive level.

2.4 STATISTICAL ANALYSES

Data were analyzed using IBM SPSS Statistics 24. To examine our first and third research questions, diagnostic prevalence rates for each of the two groups were determined by calculating proportion of participants that met criteria for a DSM-5 diagnosis of ADHD. Proportions were also calculated based on symptom count criteria for each of three sub-types of ADHD. To answer our second research, question a logistic regression model was built including autism symptom severity as a predictor of ADHD diagnosis. Correlations were run to determine appropriateness of predictors included in the model. To answer our third research question, chi-squared analyses were calculated to examine any significant differences in prevalence rates between the FXS group and the non-syndromic ASD group for a DSM-5 diagnosis of ADHD as well as for symptom count criteria for each of the three sub-types of ADHD. In addition to answering the previous research questions, a number of descriptive statistics are included for review to

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help further characterize and understand the behavioral makeup of adolescents and adults with FXS and ASD in the present sample due to the lack of knowledge that is present in the current literature for these clinical groups. This includes looking at medication treatments in both of this study's samples to help understand the impact of medication on the rating and presentation of symptoms at this age.

CHAPTER 3

RESULTS

3.1 PREVALENCE OF ADHD IN FXS

To analyze our first research question, prevalence rates for each of the ADHD subtypes were obtained for the FXS group. For ADHD-I 29% of individuals met criteria ($n = 9$); for ADHD-H 6.5% ($n = 2$); and for ADHD-C 12% ($n = 4$). Thus, 48.3% of the FXS sample met diagnostic criteria for ADHD as defined by the DSM-5 ($n = 15$).

3.2 AUTISM SYMPTOM SEVERITY AS A PREDICTOR OF ADHD IN ADOLSCENT AND ADULT MALES WITH FXS

To analyze our second research question, a logistic regression model was run to determine if autism symptom severity was predictive of a diagnosis of ADHD in the FXS sample. No significant results were found F(1,1) = -.098, $p = .545$.

3.3 DIFFERENCES BETWEEN RATES OF ADHD IN ADOLESCENTS AND ADULTS WITH FXS AND NON-SYNDROMIC ASD

To analyze our third research, question chi-squared tests were run. No significant differences were found between the FXS and ASD groups for any of the ADHD subtypes; ADHD-I: X^2 (1) = 1.375, $p = .244$; ADHD-H: X^2 (1) = .212, $p = .645$; ADHD-C: X^2 (1) = .099, $p = .753$; nor for a collective DSM-5 diagnosis of ADHD X^2 (1) = .833, $p = .361$.

3.4 PREVALENCE OF ADHD IN NON-SYNDROMIC ASD

Prevalence of ADHD in the ASD group was as follows: 40% met for ADHD-I (n = 8), 5% met for ADHD-H (n = 1), and 10% met for ADHD-C (n = 2).

3.5 DIFFERENCES IN ADHD PREVALENCE BASED ON CLINICAL FACTORS

In the present study 60% of the non-syndromic ASD sample were categorized as having ID (the remaining eight range from low average to above average IQ). Of these, 66% yielded a diagnosis of ADHD. This rate is much higher than what has been found in previous ID research. In the FXS group 23 participants had FXS+ASD based on ADOS severity scores. Of these, 47.8% met for a diagnosis of ADHD. Similar rates were found in the FXS only group. See Table 3 for a summary of these findings.

3.6 MEDICATION USE IN THE PRESENT SAMPLE

We also descriptively looked at stimulant medication use in each of our samples. In the FXS group 48.3% of the sample indicated that they were receiving medication to target attention and/or hyperactivity. Of these 60% were taking a stimulant medication. In the ASD group only 15% of the sample indicated they were receiving medication to target attention and/or hyperactivity. All of these individuals were receiving stimulant medicants. One participant in this group was taking two stimulant medications.

Table 3.1

Breakdown of ADHD subtype prevalence by clinical group

	n	Any ADHD	ADHD-I	ADHD-H	ADHD-C
Whole FXS Group	31	45%	29%	5%	11%
FXS+ASD	23	47.8%	21.7%	8.6%	17.4%
FXS only	8	50%	50%	0	0
Whole ASD Group	20	55%	40%	5%	10%
ASD+ID	12	75%	50%	8.3%	8.3%
ASD w/o ID	8	62.5%	37.5%	12.5%	12.5%

CHAPTER 4

DISCUSSION

Attention Deficit/Hyperactivity Disorder is the most commonly diagnosed comorbid disorder within FXS, with rates ranging between 40% to 80% (Backes et al., 2000; Lo-Castro, D'Agati, & Curatolo, 2011; Reilly et al., 2015). In the general population symptoms of ADHD cause significant impairment in social functioning and peer relationships in childhood (De Boo & Prins, 2007; Erhardt & Hinshaw, 1994). Further, many of these symptoms last into adulthood and cause impairments that impact many facets of everyday living that can impede high quality and successful independent living in the general adult population. The symptoms of ADHD that are maintained in adults in the general population, are also maintained in populations of adults with developmental and genetic disorders. The present study investigated the presence of ADHD in FXS and if autism severity is a significant predictor of ADHD in FXS, using a homogenous genetic sample. The present study also directly compared ADHD in FXS to another neurodevelopmental disorder that is also highly associated with ADHD.

4.1 FXS FINDINGS

The overall prevalence of a diagnosis of ADHD in the present sample of adolescents and adults with FXS was 48.3%. This number falls in the lower range of rates that have been found in previous diagnostic samples for children with FXS (Backes et al., 2000; Sullivan et al., 2006), which ranges from 46% to 54%. These findings did not support our hypothesis which was that 75% of the FXS would meet for a diagnosis of ADHD.

However, there are two ways to interpret these findings. The current finding of 48.3% is consistent with what has been found in other studies indicating that the use of the PChIPS, as a diagnostic measure in FXS, is likely a valid measurement tool.

However, with little research on the diagnostic rates that extend into the adult FXS population, more research needs to be conducted in order to discern whether or not diagnostic rates found in adolescence and childhood are indeed maintained into early adulthood. Second, the symptom count of six was used in order to meet for a diagnosis of ADHD in the present study. This decision was based on the mental age and general functioning of individuals with FXS. However, in exploratory, descriptive analyses, we looked at rates of ADHD when using the diagnostic cut-off of five symptoms, which the current DSM allows for individuals over the age of 12. When using the chronological cut-off for symptom criteria instead of the mental age cut-off, rates of ADHD diagnosis on the PChIPS tripled. These exploratory findings suggest that measurement criteria under the DSM-5 for ADHD need to be studied further in individuals with FXS and within other samples of individuals with ID when considering diagnoses for older individuals. These differences in rates could significantly impact how we view trajectories of ADHD over the life course in FXS as well as impact how and when we provide intervention to these individuals.

4.2 PREDICTIVE MODEL RESULTS

In a logistic regression model looking at the predictive ability of autism symptom severity on a diagnosis of ADHD within our FXS sample, no significance was found. These results are similar to those found in previous literature that examine a younger

sample that includes both males and females (Newman et al., 2015). This finding does not support our hypothesis that individuals with FXS+ASD would show higher rates of ADHD than those with FXS only. However, when looking at a descriptive breakdown between the FXS+ASD and FXS only group, interesting differences are observed. When looking at diagnostic rate differences between these two groups, in the FXS only group, these individuals only met for a diagnosis of ADHD-I, whereas individuals in the FXS+ASD group met for diagnoses in all three categories. Thus, maybe the question is not about whether or not individuals meet for a diagnosis of ADHD but what type of diagnosis they meet for as this can also guide and information how we treat individuals who meet for different subtypes of ADHD.

4.3 ASD FINDINGS

Diagnostic rates of ADHD in individuals with non-syndromic ASD in the present study was 55%. This rate is in line with rates of ADHD in ASD found in previous literature (Goldstein and Schwebach, 2004, 59%; Ponde et al., 2010, 53%; Ghanizadeh 2012, 54%; and Stevens, 2016, 54%). However, these listed studies utilized samples of children ranging in ages from six to 18 years old; thus, not tapping into the adult age population. This finding suggests that rates of ADHD in non-syndromic ASD found in childhood are maintained into adolescence and early adulthood. However, similar to rates within the FXS sample, when looking at diagnostic symptom criteria of five instead of six rates in the ASD sample also increased.

4.4 DIFFERENCES BETWEEN FXS AND NON-SYNDROMIC ASD GROUP

No significant differences were found between the diagnostic rates of each of the three subtypes of ADHD between the ASD and FXS groups. These findings did not

support our hypothesis that rates for ADHD would be higher in the FXS than in the ASD group. However, when considering the measurement questions related to deciding on which symptom count DSM-5 criteria to use with adolescents and adults with ID, calls into question the validity of these findings. Much more research is needed to help explain valid measurement criteria, and accurate rates of ADHD in clinical populations such as FXS and ASD. Regardless the high rates of diagnostic prevalence in comparison to what is found in the general population indicate not only that we are insufficiently mitigating these behaviors earlier in development, but that treatment and intervention are still needed for older individuals with a comorbid diagnosis of FXS and ADHD or ASD and ADHD.

Further, these findings point to a shared phenotype of ADHD within the presence of FXS and non-syndromic ASD due to lack of significant differences found between these groups. These shared phenotypes could mean that interventions found successful for challenging behaviors in one of these clinical groups could also be successful in the other.

4.5 SUMMARY

Findings from the current study suggest that diagnostic prevalence rates in adolescents and young adults with FXS are lower than what has been found in childhood for this population. This could be due to several factors. It is likely that many parents are unable to recognize the behavioral characteristics of ADHD as uniquely different from the behaviors commonly found in FXS. It could also be that many of the behavioral challenges seen in individuals with FXS are not identified as impairing to some families; especially later in development when behaviors have stabilized, medication intervention

is working (Roberts et al., 2011) or families have had almost two decades to understand

and adjust to behaviors. However, given the reduced rates of ADHD in adults versus

children observed in the general community, it is not unanticipated that we observed

lower rates in our samples. Despite the lower rates in these older aged individuals, the

prevalence is still quite high and higher than community samples indicating the need for

sustained treatment at these older ages. The fact that rates in the present study are not

significantly lower than those found in childhood again highlights the need for more

behavioral interventions earlier in development to help lower the symptoms and

diagnostic rates seen in adolescence and adulthood. However, the higher rates found in

the present study make sense as children who are more impaired tend to have a higher

percentage of comorbid diagnoses and present with more severe phenotypic behaviors.

4.6 LIMITATIONS

The present study is not without limitations. The number of participants within

each group was limited particularly in the ASD group. Future research should aim to

increase sample sizes within these groups. Additionally, the use of parent report can be

viewed as a limitation as parent perceptions of impairment can be skewed due to the

significance and level of impairment in children with ID and particularly children with

FXS. However, parent report is also a vital aspect of behavioral research and using parent

report along with clinical judgement should be used together to help further disentangle

the presence of ADHD from FXS specific behaviors. Although the PChIPS was validated

in a sample of individuals with ASD it has not yet been studied in individuals with FXS.

4.7 IMPLICATIONS

The present study has identified the diagnostic rates of ADHD in two adolescent

and adult male neurodevelopmental disorders. The implications of diagnostic rates of

ADHD at ~50% in adolescents and adults with FXS and ASD indicates an increased need

for behavioral interventions at younger ages in these clinical populations. In literature

looking at intervention effectiveness for ADHD in the general population, effectiveness

for behavioral interventions for ADHD have high efficacy rates (Fabiano et al., 2009;

Sonuga-Barke et al., 2013). These rates tend to increase when medication intervention is

used in tandem with behavioral interventions (MTA Cooperative Group, 2004; Pelham

Jr. et al., 2000). Although, it can be speculated that the same behavioral interventions

used with individuals in the general population may not be effective for individuals with

FXS or those with low functioning ASD due to low IQ. However, no behavioral

intervention studies have been conducted with individuals with FXS with a comorbid

diagnosis of ADHD, as current intervention tends to solely focus on the use of

medication. Although medication use for the treatment of ADHD has been proven

effective in individuals with FXS, future research should look at the utility of

implementing behavioral interventions with individuals with FXS who show symptoms

of ADHD, as stated that current evidenced-based literature shows that the combination of

using medication to lessen the symptom presentation of ADHD in cohesion with

behavioral interventions for ADHD symptoms could have significant impact on long-

term functioning and life time health care costs for this population. Since medications

allow for individuals to access the benefits of intervention, setting individuals up to be

more successful in behavioral interventions, combining these two strategies and younger ages in individuals with FXS and ADHD could be critical.

Additionally, this study shows the need for job and life support interventions to include ADHD in order for individuals attempting to obtain some levels of independence to be more successful in these endeavors. Not only will the combination of medication and intervention improve behavioral functioning for individuals with FXS and ADHD, it will also improve their social functioning which opens doors to access a variety of positive benefits in the future and increasing life skills functioning. Thus, future research should look at behavioral interventions that may be effective in helping to decrease the impact of ADHD behaviors in FXS with ASD. Future research should also focus on the early identification of comorbidities and symptom presence within FXS through both behavioral research and bio-behavioral methods. Through the utilization of bio-behavioral methods such as eye-tracking and heart rate variability, earlier identification of children with impairing symptoms can be identified as well as appropriate treatment interventions. With earlier identification of these impairing behaviors with proven effective interventions we can aim to decrease the rates of ADHD and medication use that we see in these adolescent and adults with FXS syndrome and ultimately improve long-term outcomes and later in life functioning.

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