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ADHD in Adolescent and Young Adult Males with Fragile X Syndrome

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Abstract

This study characterized the rates of rates of attention-deficit/hyperactivity disorder (ADHD) in adolescent and young adult males with fragile X syndrome (FXS) using a multi-method approach integrating a DSM-based parent interview (Children's Interview for Psychiatric Syndromes) and a parent rating scale (Child Behavior Checklist; CBCL). Thirty-one males with FXS, aged 16-24 years, participated. Forty-two percent met DSM-5 criteria for ADHD and 35% exceeded the CBCL cut-offs. Agreement between the two classification methods was fair (κ=0.38). Autism symptom severity and nonverbal cognitive ability did not predict ADHD diagnoses/symptoms. Results show high rates of ADHD in males with FXS during late adolescence and young adulthood, which are not accounted for by impaired nonverbal cognitive skills or autism symptom severity. DSM-based ADHD-specific scales are recommended over broadband symptom scales to improve accurate identification.

ADHD in Adolescent and Young Adult Males with Fragile X Syndrome

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder marked by symptoms of hyperactivity, inattention, impulsivity and executive functioning weaknesses (American Psychiatric Association, 2013). ADHD is the most commonly diagnosed behavioral disorder in children, with rates in the general population ranging from 9-11% during childhood to about 4% in adulthood (Danielson et al., 2018; Kessler et al., 2006). Diagnoses of ADHD are nearly three times more common in males than females and are associated with a high degree of cooccurrence with other mental, emotional, and behavioral disorders (Danielson et al., 2018; Reale et al., 2017). The burden of ADHD is significant and there is great value in research aimed at understanding the nature and course of ADHD. Adverse outcomes associated with ADHD include higher rates of injury, social difficulties, and reduced educational and vocational achievement (Harpin et al., 2016; Hinshaw et al., 2012; Kuriyan et al., 2013; Loe & Feldman, 2007). For the majority of affected individuals, ADHD symptoms persist into adulthood and are associated with psychiatric comorbidity, substance abuse, criminal activity, failed relationships and underemployment (Barkley et al., 2004; Biederman et al., 2010; Margherio et al., 2020; Molina et al., 2018).

Although the precise causal mechanism of ADHD is not clear, the evidence supports a strong genetic component (Li et al., 2014; Stergiakouli et al., 2012). Recent discoveries have identified clear genetic overlaps of ADHD to both autism spectrum disorder (ASD) and intellectual disability, and thus, investigations into the interface between ADHD, ASD, and intellectual disability can advance the field (Faraone et al., 2017; Ghirardi et al., 2018; May et al., 2018; Pinto et al., 2016; Stergiakouli et al., 2017). Fragile X syndrome (FXS) may represent a useful genetic model in this regard; FXS is a monogenetic disorder that is the most common known single-gene cause of ASD and the leading inherited cause of intellectual disability (Vissers et al., 2016; Waye & Cheng, 2018). FXS is found in about 1:7,000 males and 1:10,000 females (Hunter et al., 2014) and involves a trinucleotide repeat expansion on the *FMR1* gene. FXS is associated with reduced Fragile X Mental Retardation Protein (FMRP), which is involved in typical brain maturation (Siegel et al., 2017; Zhang et al., 2017). The phenotype of males with FXS is

marked by nearly universal intellectual disability and about cooccurring ASD observed in approximately 60% of males (García-Nonell et al., 2008; Harris et al., 2008; Klusek, Martin, & Losh, 2014).

ADHD is also a common cooccurring condition associated with FXS, with reported rates in children with FXS ranging from 35-93%, as reflected in Table 1 (Backes et al., 2000; Bailey et al., 2008; Bregman et al., 1988; Freund et al., 1993; Hatton et al., 2002; Sullivan et al., 2006; Thurman et al., 2014). Consistent with the profile of ADHD in the general community, ADHD in FXS emerges during childhood (Grefer et al., 2016) and is more likely to affect males than females (Newman et al., 2015; Wheeler et al., 2014). Across studies, the rates of ADHD symptoms and diagnoses in males with FXS are consistently higher than in the general population without FXS and also higher than those with non-specific intellectual disability or other known genetic syndromes (Baumgardner et al., 1995; Reilly et al., 2015). Severity of intellectual impairment does not appear to be associated with the presence or severity of ADHD (Newman et al., 2015); however, this has not been studied extensively. In studies that have examined the relationship of ASD to ADHD in FXS, findings are inconsistent with some reports suggesting that elevated ASD severity is linked with ADHD features (Sullivan et al., 2006), whereas others suggest that ADHD symptoms are similar across individuals with FXS with or without comorbid ASD (Hatton et al., 2002; Newman et al., 2015). In a study that included a group of male children with FXS contrasted to a chronological age, IQ and ASD-severity matched group with non-syndromic ASD, ADHD symptoms were significantly higher in the group with FXS (Thurman et al., 2014). Inattention, rather than hyperactivity, appears to be the most prominent feature of ADHD in FXS, with one investigation of 63 7-13 year-old children with FXS suggesting that 32% exhibited a predominately inattentive ADHD presentation (ADHD-I), 7% exhibited a hyperactive/impulsive presentation (ADHD-H), and 15% exhibited a combined presentation (ADHD-C) (Sullivan et al., 2006). Overall, the evidence supports FXS as a saturated model for ADHD risk that integrates elevated risk for ADHD within the context of intellectual disability and ASD.

The presence of ADHD in males with FXS is associated with significant impairment including reduced prosocial behavior and social functioning (Chromik et al., 2019; Scerif et al., 2012) as well as

increased family burden (Wheeler et al., 2014). The presence of multiple cooccurring conditions within FXS is associated with more significant impairment, with intellectual disability, attention problems, hyperactivity, and anxiety constituting the most common cluster of comorbid disorders in males with FXS (Bailey et al., 2008). Treatment for ADHD in males with FXS primarily involves medication, with stimulant medication reported as moderately to highly effective (Berry-Kravis et al., 2012; Hagerman et al., 1988; Roberts et al., 2011b), and results of a national survey suggest ~45% of people with FXS use stimulants/simulants (Valdovinos et al., 2009). However, evidence suggests that the attention and thought problems associated with ADHD do not differ between children with FXS taking medication and those not being treated, thereby raising questions about medication efficacy (Hatton et al., 2002). Obtaining a better understanding of the targets and benefits of medication is important because pharmaceutical treatment for ADHD is a common approach in FXS. These efforts also have implications for clinical trials in which ADHD-related manifestations of FXS represent common behavioral targets (Berry-Kravis et al., 2013; Budimirovic et al., 2017).

Although there is an emerging body of research that provides insights into ADHD in FXS, there are a number of limitations of this work. First, several studies used samples that were highly heterogeneous including a very broad age range (Gabis et al., 2011; Haessler et al., 2016), inclusion of participants with the *FMR1* premutation (i.e., "carriers" of fragile X) together with those having the full mutation (Newman et al., 2015), and failure to account for ASD (Frolli et al., 2015; Pegoraro et al., 2014). In addition, the focus of research to date has largely been on young children with little work specifically targeting adolescents and young adults. It is unclear from prior research whether individuals with FXS continue to experience high rates of ADHD symptoms into late adolescence and young adulthood. Although some studies suggest a general reduction of symptoms across age (Gabis et al., 2011; Haessler et al., 2016; Wheeler et al., 2014), other reports suggest that the symptoms of ADHD do not abate from early childhood into adolescence (Newman et al., 2015; Thurman et al., 2014).

A final limitation of the extant literature is that studies to date have not used the revised DSM-5 criteria, and there is a clear over-reliance on broad-based measurement tools that detect a wide range of

different symptoms and are not specifically targeted at measuring ADHD (Bailey et al., 2008; Grefer et al., 2016). Although there is value in broad-based measures because they allow for easy detection and screen for a wide variety of disorders, they often lack specificity for individuals who have comorbid disabilities such as ASD (Pandolfi et al., 2012). Utilizing ADHD-specific scales and the most recent DSM-based measures to characterize ADHD in a carefully selected sample is necessary to advance our understanding of the prevalence of ADHD in males with FXS. This work is critical because ADHD in FXS is clearly pervasive and interferes with optimal functioning, and documentation of comorbidities within FXS is essential to directing effective treatment. However, this research is complex given the presence of co-occurring conditions such as intellectual disability and ASD that challenge differential diagnostic efforts. Therefore, using homogeneous genetic samples and implementing clearly defined DSM-based measures will allow for better understanding of true prevalence rates of ADHD in individuals with FXS. A differential diagnostic approach to known genetic and behaviorally similar neurodevelopmental disorders, specifically FXS and ADHD, can contribute to the field regarding diagnostic rates within FXS to allow for more targeted interventions that lead to increased independent living in this population.

The overall aims of the present study, therefore, were to (1) characterize the rate and presentation of ADHD diagnoses in youth with FXS using DSM-5 criteria, (2) determine the proportion of youth with FXS who were reported to have clinical ADHD symptoms on a widely-used parent rating scale, the Child Behavior Checklist (CBCL), as well as the concordance between CBCL symptom cut-offs and DSM-5 ADHD diagnoses; (3) determine the relationship between ASD symptom severity, nonverbal cognitive ability, and ADHD diagnoses and symptoms; and (4) describe the use of medication in relation to ADHD diagnostic status in youth with FXS. We hypothesized that >50% of the youth with FXS would meet criteria for a diagnosis of ADHD, with more individuals meeting for ADHD-I over the other two presentations. We expected moderate concordance between the CBCL ADHD scale and DSM-5 ADHD diagnoses given the concern that broad-based symptoms scales may lack specificity for individuals with intellectual disability and other comorbidities. We hypothesized that higher levels of ASD symptoms

would be associated with ADHD diagnoses and symptoms given evidence for shared genetic mechanisms across ADHD and ASD (Ghirardi et al., 2019; Pinto et al., 2016; Ronald et al., 2008), but that lower nonverbal cognitive ability would not relate to ADHD, consistent with Newman et al. (2015). We expected that about half of participants would be using medications targeting ADHD symptoms, with stimulants being the most common medication type. We expected only moderate alignment between use of ADHD-targeted medications and ADHD diagnoses, considering prior evidence suggesting a high rate of stimulant medication use among individuals with FXS without an ADHD diagnosis (Valdovinos et al., 2009).

Method

Participants

Participants were 31 males with FXS ranging from 16-24 years of age (M = 18.73, SD = 2.13). Genetic testing was conducted on all participants to confirm the full mutation (>200 CGG repeats on 5'UTR of *FMR1*). Females were not included in the present study due to the heterogeneous phenotypic presentation of females with the FXS and the increased clinical involvement in males, which makes understanding of the extent, nature, and course of cooccurring challenges especially pressing for them (Bailey et al., 2008). Participants were drawn from a larger longitudinal multi-site study at the [anonymized for review] and [anonymized for review] which focused on language development during the transition into adulthood [anonymized for review]. Inclusionary criteria for the larger study required that English was the primary language, that the participants consistently used spontaneous two- to three-word utterances, and that they lived at home with their biological mother at study entry. Only individuals who participated at the [anonymized for review] site were included in this study given a more focused interest on ADHD and the presence of sufficient resources at that site. Recruitment was conducted nationally through parent listservs, social media, postings by the National Fragile X Foundation, and with the help of the [anonymized for review]. The annual family incomes of the participants ranged from <$20,000 to >$150,000, with the median income reported at $80,000. Ninety percent of participants were white, 7% were Black or African American, and 3% were Asian.

Procedures

The assessments included in the full protocol were conducted in a university laboratory setting and lasted two days. The measures for the present study are a subset of those administered. Data collection occurred based on established procedures of a larger study, including standardized order of test administration. Administration of the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012) was conducted on the morning of the second day of assessment to allow time for the participant to establish rapport with the examiner. Parent/caregiver report measures were completed by the participant's mother. All measures were completed at the second annual time point of the larger longitudinal study, except the ADOS-2, which was drawn from the first-year time point. ASD symptoms were only measured at study entry in the larger study given the relative stability of ASD symptoms in adolescents with FXS over time (Hernandez et al., 2009). Procedures were approved by the Institutional Review Board of the [anonymized for review] and conform to the ethical standards laid out in the Declaration of Helsinki. All participants assented to participation, and informed consent was obtained from the participants' guardians.

Measures

Children's Interview for Psychiatric Syndromes–Parent version (PChIPS; Fristad, Teare, Weller, Weller, & Salmon, 1998). The PChIPS is a DSM-based diagnostic interview that uses a strict diagnostic criteria model requiring the presence of impairment to assess for the presence of ADHD symptoms and diagnosis. The PChIPS is a structured parent interview to assess presence of psychiatric disorders in children and adolescents aged 6-17 years old, which is consistent with the mental age of the participants enrolled in the present study. It queries symptom count, duration, and impairment consistent with DSM criteria. Questions pertaining to symptomology are presented and scored in a yes/no format. The current version of the PChIPS aligns with the DSM-IV; thus, we adapted the assessment to reflect the updated DSM-5 diagnostic criteria for ADHD, which required two modifications: (1) allowing for the concurrent diagnosis of ADHD and ASD, and (2) allowing a retrospective diagnosis to be made if five symptoms were present before age 12 years. Examiners were trained to administer the PChIPS by a

licensed clinical psychologist. Inter-rater reliability for ADHD presentation classification was calculated on 20% of randomly selected samples. Percent agreement was 100% between the licensed psychologist and trained research staff. The categorical distinction of presence/absence of an ADHD disorder based on DSM-5 criteria served as the primary dependent variable in the analyses. The PChIPS has been applied to conditions associated with intellectual disability, including Phelan-McDermid syndrome (Shaw et al., 2011), FXS (Ezell et al., 2018), and ASD (Witwer & Lecavalier, 2010). High item-level agreement (intra-class correlation coefficients of 0.92 for Hyperactive, 0.97 for Inattentive, and 0.93 for Combined) and fair-to-moderate for diagnostic classification agreement (Hyperactive $\kappa = 0.43$, Inattentive $\kappa = 0.60$, and Combined $\kappa = 0.27$) has been reported between the PChIPS and the Child and Adolescent Symptom Inventory (CASI; Gadow & Sprafkin, 2002) in children with ASD (Witwer et al., 2012).

Attention Deficit/Hyperactivity Problems Scale, Child Behavior Checklist (ADHD Scale, CBCL; Achenbach, 2001) was administered and is a widely used broad-based measure of child emotional and behavioral problems that provides an index of ADHD symptoms. The CBCL is a well-established 118-item parent-report tool that has good reliability and validity and has been widely used in neurodevelopmental disabilities research including FXS. The Attention Deficit/Hyperactivity Problems DSM-oriented subscale consists of 7-items and was designed to align with the symptoms of ADHD as outlined in the DSM. T-scores were computed and used to determine whether individual participants exceeded cut-offs for clinically significant ADHD symptoms; scores of 65-69 are considered “borderline clinical” and scores of 70+ are considered clinically significant. The 6-18 year old CBCL form for was used for all participants and 18-year norms were used to calculate standard scores for participants older than 18, consistent with prior work (Chromik et al., 2019; Roberts et al., 2019; Roberts et al., 2018). The 6-18 form was used for all participants because the items were thought to be more appropriate for the developmental level of young adults with FXS than is the adult form.

Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012). The ADOS-2 was administered to determine ASD status and the severity of ASD symptoms. 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. A continuous index of ASD symptoms, as reflected by the ADOS-2 calibrated severity score, was also computed per the test instructions (Lord et al., 2012). Participants were administered the ADOS-2 module appropriate for their expressive language level and chronological age as specified by the administration manual, with modules 1, 2, and 3 represented in the present sample. The ADOS-2 was administered and scored live by graduate-level professionals who completed standard research reliability training. Ten percent of the administrations were randomly selected and second-scored by video for inter-reliability, with percent agreement above 80% across all items and algorithm items. Twenty-three participants (74.2%) exceeded the threshold for ASD.

Brief IQ, Leiter-R (Roid & Miller, 1997). The Brief IQ of the Leiter-R is a nonverbal intelligence measure that has strong psychometric properties and is appropriate for use with individuals who have limited receptive and expressive language capabilities. Growth scale value scores, which a transformation of raw scores into an equal-interval Rasch scale, were used in analysis to mitigate problems associated with floor effects in the standard scores.

Medications Targeting ADHD Symptoms. Information on medication use was gathered as part of a standard demographic form for the larger study. The use of medications targeting ADHD symptoms was characterized as a bivariate present/absent variable. For the current study, any medication indicated by caregivers as targeting ADHD, attention, or hyperactivity was included (all such medications fell into the drug classes of stimulants or alpha-2 adrenergic agonists, such as guanfacine).

Statistical Analyses

Descriptive statistics were computed and are presented in Table 2. Variables were examined for normal distribution with no need for corrections indicated. A correlation matrix was computed to understand the relationship among variables to inform model specification (Table 3). Chronological age was not associated with the ADHD variables and, therefore, was not covaried in statistical models. To address the first research question regarding the rate and presentation of ADHD, the proportion of individuals who met DSM-5 diagnostic criteria for ADHD on the PChIPS was computed, as was the

percentage of individuals meeting criteria for each ADHD presentation. The second research question was addressed by computing the percentage of individuals who obtained borderline or clinical scores on the CBCL ADHD scale. Cohen's kappa (κ; Cohen, 1960), a measure of nominal scale agreement between two categorization of responses commonly used as a measure of classification accuracy (Kwiecien et al., 2011), was obtained to evaluate the concordance between DSM-5 ADHD diagnoses and the CBCL ADHD scale cut-offs. Concordance between the two measures was also examined descriptively by computing the percent of individuals who did/did not obtain borderline/clinical scores on the ADHD CBCL scale to those who did/did not meet diagnostic criteria for ADHD. Our third research question regarding the relationship between ASD symptom severity, nonverbal cognitive ability, and ADHD diagnoses and symptoms was tested by fitting two logistic regression models that included the ADOS-2 calibrated severity score and the Leiter-R growth scale value scores as predictors of either DSM-5 ADHD diagnoses or the CBCL ADHD subscale cut-off classification. Additionally, to test relationships with continuous ADHD symptoms, a general linear model with fit to test the ADOS-2 calibrated severity score and the Leiter-R growth scale value as predictors of the CBCL ADHD subscale T-score. To address the final research question about medication use, the proportion of participants taking medications targeting ADHD symptoms was computed. All analyses were conducted using SAS software, version 9.4, (SAS Institute Inc., Cary, NC).

Results

Rate of DSM-5 ADHD Diagnoses and Presentations. Thirteen of 31, or 41.9%, of the youth with FXS met DSM-5 diagnostic criteria for ADHD on the PChIPS. Of those who met criteria for ADHD, 69.2% (9/13) exhibited an ADHD-I presentation, 15.4% (2/13) exhibited an ADHD-H, and 15.4% (2/13) exhibited ADHD-C. See Figure 1.

Percent of Individuals Exceeding the CBCL ADHD Scale Cut-offs. Ten of 31, or 32.3%, of the youth with FXS exceeded the CBCL ADHD cut-offs. Of these 10, 5 (16% of the total sample) obtained borderline scores and 5 (16% of the total sample) obtained scores in the clinical range.

Concordance between DSM-5 ADHD Diagnosis and CBCL ADHD Cut-offs. Cohen's kappa was calculated at $\kappa = 0.38$ (95% CI 0.06, 0.71), which is consistent with "fair" levels of agreement (Cohen, 1960). DSM-5 diagnoses and the CBCL ADHD scale cut-offs were concordant for 70.8% of the sample (22/31), see Table 4. Of those who met DSM-5 criteria for ADHD per the PChIPS clinical interview, 53.8% (7/13) also scored within the borderline or clinical range on the CBCL ADHD scale. The majority of individuals who did not meet diagnostic criteria for ADHD also obtained CBCL scores that were below cut-offs, 83.3% (15/18). DSM-5 diagnoses and the CBCL ADHD scale cut-offs were disconcordant for 29.0% of the sample: 19.4% met DSM-5 criteria for ADHD but did not score in the borderline/clinical range for ADHD on the CBCL, and 9.6% scored above CBCL cut-offs but did not meet DSM-5 criteria for ADHD.

ASD Symptom Severity and Nonverbal Cognitive Ability as Predictors of ADHD Diagnoses and Symptoms. The results of the logistic regression model indicated that neither ASD symptom severity ($\chi 2$ [1] = 0.02, p = .878, OR = 1.36) nor nonverbal cognitive ability ($\chi 2$ [1] = 1.74, p = .187, OR = 1.14) were significant predictors of DSM-5 diagnostic criteria for ADHD on the PChIPS. Similarly, neither ASD symptom severity ($\chi 2$ [1] = 0.43, p = .510, OR = 1.26) nor nonverbal cognitive ability ($\chi 2$ [1] = 0.72, p = .396, OR = 1.10) were associated with increased odds of scoring above the cut-off for ADHD on the CBCL. Regression analyses also indicated that the combined influence of ASD symptom severity and nonverbal cognitive ability did not account for significant variance in continuous ADHD subscale T-scores on the CBCL, F (2,28) = 0.05, p = 0.952, $R^2 < 0.01$.

Frequency of Medication Use Targeting ADHD Symptoms. Of the 31 individuals with FXS, 15 (48.4%) were taking medications that target ADHD symptoms. Nine of the 15 were taking stimulant medications. Of the 15 individuals using medications targeting ADHD symptoms, roughly half (53.3%, n = 7) met criteria for DSM-5 ADHD.

Discussion

FXS may serve as a saturated genetic model for ADHD, based on evidence of genetic overlap between intellectual disability, ASD, and ADHD, with prior research focused on children with FXS

suggesting that ADHD is a highly prevalent and impairing cooccurring condition. Extending prior work focused on children, the present study investigated the rates, presentation, and correlates of ADHD in FXS during late adolescence and young adulthood, applying both DSM-5 diagnostic criteria as well as broadband parent rating scales. Forty-two percent of the adolescent and young-adult males with FXS in this study met DSM-5 criteria for ADHD, with neither intellectual disability nor ASD symptom severity predicting ADHD diagnostic outcome or symptoms. Concordance between DSM-5 diagnoses and cut-offs on the ADHD subscale of the CBCL was fair, yielding a concordant ADHD classification for 71% of the sample. Nearly half of the participants were using medications that target ADHD symptoms, although only half of those using ADHD medications met DSM-5 criteria for ADHD. Through inclusion of a relatively homogeneous sample of 16- to 24-year-old males with FXS, the majority of whom exhibited IQ scores consistent with moderate intellectual disability, this report describes for practitioners the expected rates of ADHD co-occurrence in this subpopulation and informs methods for evaluating ADHD for improved identification and access to interventions.

Elevated Rate and Presentation of ADHD in Adolescent/Young Adult Males with FXS

Prevalence rates of ADHD can vary greatly across diagnostic methods, necessitating focused study to clarify baseline rates of ADHD in individuals with FXS. The present study is the first to apply DSM-5 diagnostic criteria to determine ADHD diagnoses in adolescent and young adult males with FXS. Focused investigations of the adolescent/young adult period in FXS are critical as this developmental period tends to be marked by heightened psychopathological risk in the general population (Rutter, 2007).

Forty-two percent of the sample met criteria for ADHD, which is in line with previous diagnostic studies of children with FXS that have reported rates between 35-74% using earlier versions of the DSM (Backes et al., 2000; Sullivan et al., 2006). Therefore, our data support the notion that ADHD continues to represent a significant comorbidity in FXS into early adulthood, at rates that significantly exceed that of the general population. Although some previous research has suggested abatement of ADHD symptoms in FXS with age (Gabis et al., 2011; Wheeler et al., 2014), the results of the current study indicate that ADHD symptoms in adolescents and young adults exceed diagnostic thresholds at at rates comparable to

the rates that have been reported in children. It is possible that symptoms improve with age but continue to exceed diagnostic thresholds—a question that remains to be addressed in future longitudinal work tracking intraindividual change in symptoms and diagnoses across time.

ADHD-I was the most prevalent ADHD presentation, with 29% of the sample exhibiting ADHD-I, 6% ADHD-H, and 6% ADHD-C. Rates of the ADHD presentations align with previous research employing DSM-IV criteria in younger and/or more heterogeneous samples. Sullivan et al. (2006) also observed ADHD-I as the dominant presentation in a sample of 7-13 year-old boys and girls with FXS (*n* = 57); ADHD-I was observed in 32% the sample, ADHD-I in 7%, and ADHD-C in 15%. Similarly, Gabis et al. (2011) detected ADHD-I in 27%, ADHD-H in 13%, and ADHD-C in 7% of an older but smaller sample of 15 males and females with FXS, aged 12-29 years. Corroborating and building these earlier reports using DSM-5 criteria in a more homogeneous sample of males aged 16-24 years, we found that ADHD in adolescent and young adult males with FXS is overwhelmingly characterized by the inattentive symptoms (69% of those who met criteria for ADHD exhibited ADHD-I, and an additional 15% met criteria for ADHD-C). Characterizing ADHD presentation within FXS is of relevance because those presentations are associated with different clinical needs. Relative to ADHD-H, children with ADHD-I are more likely to show social isolation, experience comorbid anxiety and depression, and experience learning and reading difficulties (Baeyens et al., 2006; Paloyelis et al., 2010; Willcutt et al., 2001; Willcutt et al., 2007). In clinical samples, hyperactivity/impulsivity symptoms also tend to improve with age, whereas inattention symptoms are more likely to persist across development (Hurtig et al., 2007).

No Association with Nonverbal Cognitive Ability or ASD Symptoms

We did not detect an association between ASD symptom severity and ADHD diagnoses or symptoms. Findings on the relations between ASD symptoms/comorbidity and attention problems in children with FXS have been conflicting, with differences in the samples and methodologies making it difficult to tease apart the source of discrepancies across reports. Some cross-sectional reports have not detected a relationship between ADHD and ASD symptoms in FXS (Hatton et al., 2002; Newman et al., 2015) and emerging longitudinal evidence suggests that clinical ADHD symptoms in school-aged boys

with FXS remain high and stable across time regardless of whether cooccurring ASD features are also present (Cornish et al., 2013). In contrast, other studies have reported association between ADHD and ASD symptoms in individuals with FXS (Doherty et al., 2020; Smith et al., 2012). In this report, we did not find evidence that ASD symptoms translated to heightened ADHD symptoms or higher likelihood of an ADHD diagnosis in adolescents and young adults with FXS.

Nonverbal cognitive ability was not associated with ADHD symptoms or diagnoses, which aligns with the findings of Newman et al. (2015). Understanding the relationship between ADHD and intellectual disability within the context of FXS, or the lack thereof, has implications for diagnostic practices with regard to the phenomenon of diagnostic overshadowing (e.g., when intellectual disability "overshadows" the presence of comorbid conditions such as ADHD, leading to reduced clinical recognition and treatment of concomitant disorders; Mason & Scior, 2004; White et al., 1995). In the present study, ADHD symptoms and diagnoses were not related to differences in IQ, which lends validity to the ADHD diagnosis in FXS and highlights the need for caution when conceptualizing ADHD symptoms in this group as features that are inherent to the presence of intellectual disability. The identification of ADHD in individuals with FXS is critical to facilitating access to interventions that have the potential to improve quality of life.

Implications for the Assessment of ADHD within Individuals with FXS

This report provides broad support for the utility of the PChIPS for use in FXS, while also underscoring the need for further formal psychometric investigation to validate the PChIPS for use in intellectual and developmental disabilities. Several investigations have now successfully applied the PChIPS to characterize mental health disorders in children with various forms of intellectual and developmental disabilities (Ezell et al., 2018; Shaw et al., 2011; Witwer & Lecavalier, 2010), including a psychometric study by Witwer et al. (2012) that found good reliability and support for concurrent validity when applying the PChIPS to a sample of children with ASD. Interestingly, the PChIPS showed excellent agreement with the CASI for item-level ADHD symptoms, while concordance between the two measures for ADHD diagnostic outcome was only fair. Witwer et al. (2012) speculated that diagnostic

discrepancies may have been related to the challenges of capturing impairment associated with ADHD within a population that also experiences concomitant behavioral difficulties related to ASD (i.e., caregivers may be less reliable in recognizing and endorsing ADHD-related impairment when their child experiences pervasive impairment related to other cooccurring conditions). Notably, however, the PChIPS and CASI were not more discordant in subgroups of children with ASD with IQs above or below 70, suggesting that the PChIPS performed equivocally in children with and without cooccurring intellectual disability (Witwer et al., 2012). While more psychometric work is needed, the present report builds on evidence that the PChIPS can be successfully applied to populations with intellectual disability.

The present study also has implications for the use of the CBCL to characterize ADHD in FXS. The CBCL is a widely-used broadband symptom scale that shows moderate sensitivity and specificity for identifying ADHD in clinical and community settings (Chang et al., 2016). However, the CBCL has also been suggested to lack specificity for individuals with co-occurring disorders (Pandolfi et al., 2012) and, therefore, may result in overestimation of ADHD rates in FXS relative. We found that the Kappa classification agreement between the CBCL ADHD cut-offs and DSM-5 diagnoses determined via the PChIPS were only fair in this sample of adolescents and young adults with FXS. The CBCL missed 19% of those who met DSM-5 criteria for ADHD. Compared to the 42% rate of ADHD determined via the DSM-5, 32% of the sample exceeded the CBCL cut-off scores for ADHD when considering both borderline and clinical scores as elevated. When only clinical CBCL scores were considered, just 16% of the sample exceeded cut-offs. These findings closely mirror the results of Sullivan et al.'s (2006) study of children with FXS in which only 6% of the sample exceeded CBCL ADHD clinical cut-offs, compared to 53% when parents completed a DSM-IV-based ADHD symptom inventory. Together, these findings suggest under-identification of ADHD in FXS via the CBCL, rather than over-identification. Therefore, caution should be exercised when relying on the CBCL to characterize ADHD in individuals with FXS; the use of a DSM-based ADHD-specific interview/symptom inventory appears to improve identification accuracy. When employing the CBCL, both borderline and clinical scores should be considered, as

reliance on only the clinical scores resulted in gross underestimation of ADHD rates in both the present study and in the Sullivan et al. (2006) report.

Medication Use

Nearly half of the adolescents and young adults in this study were using ADHD-targeted medications, which is similar to rates of medication usage found in previous research (Roberts et al., 2011a). Stimulants were the most commonly used drug class to target ADHD, which is notable given that stimulants are poorly tolerated in FXS—they represent the psychotropic medication that is most likely to be discontinued, with common side effects of anxiety, irritability, and mood lability (Berry-Kravis & Potanos, 2004; Valdovinos et al., 2009). Interestingly, about half of the participants who were using ADHD-targeted medications did not meet diagnostic criteria for ADHD. The reason for this is unclear, although it could reflect use of stimulant medications in individuals with FXS who display some subthreshold symptoms of ADHD. It is also possible that ADHD-targeted medications were prescribed to treat symptoms other than ADHD; for example, a nation-wide survey by Valdovinos et al. (2009) found surprisingly high rates of stimulant use in individuals with FXS who had difficulty with anxiety. Although medication is typically the first course of intervention for individuals with FXS who exhibit ADHD, future research should examine the utility of a combined pharmaceutical and behavioral approach, as this approach is typically most effective in the management of ADHD outside of the context of FXS (Parens & Johnston, 2009; Pelham et al., 2000).

Strengths, Limitations, and Directions

Strengths of the present study include the narrow, well-defined sample of individuals with FXS, who were all males with intellectual disability falling between the ages of 16- to 21 years. Although a trade-off to the inclusion of such a homogenous sample was a more limited sample size of 31 individuals, the focused sample clarifies the expected ADHD profile in males with FXS during adolescence and young adulthood, specifically. The use of a DSM-based diagnostic interview to evaluate the presences of ADHD is also a strength, and this is the first report to apply the new DSM-5 criteria to a FXS sample.

There are a number of measurement considerations. First, our multimethod approach incorporating both the PChIPS and the CBCL is a strength. However, it should be acknowledged that differential diagnosis of ADHD in a clinical setting would involve multiple sources of information (parent and teacher report data, behavioral measures, etc) paired with professional clinical judgement. Therefore, our determination of ADHD status is still limited relative to a thorough clinical evaluation. Additionally, our use of parent report can be viewed as a limitation as parent perceptions of impairment can be skewed due to the significant level of impairment in children with intellectual disability and particularly individuals with FXS. However, self-reported behaviors were not an option in this FXS sample due to intellectual disability and low language skills. Future studies pairing parent-report data with clinical observation or teacher-report data may help mitigate rater biases. Another limitation was our use of the CBCL 6-18 form for all participants; 13 participants were above the age range of the norming sample. Although this approach is consistent with prior work (Chromik et al., 2019; Roberts et al., 2019; Roberts et al., 2018) and appropriate given the developmental level of the participants, it should be acknowledged that the standard scores for the older participants may have decreased validity.

Conclusions

ADHD continues to represent a significant comorbidity in FXS through the adolescent and young adult years, with 42% of 16- to 21-year-old males in the present study meeting DSM-5 criteria for ADHD. Evaluation of ADHD via the CBCL yielded lower rates of ADHD and classification agreement between the DSM-5 and CBCL ADHD subscale was only fair, suggesting that overreliance on the CBCL may result in under-characterization of ADHD symptoms in FXS. ADHD diagnoses and symptoms were not predicted by low IQ or the presence of ASD symptoms in this sample of males with FXS, which has implications for the phenomenon of "diagnostic overshadowing," or the clinical tendency to overlook comorbid conditions in the presence of intellectual disability. This report describes for practitioners the expected rates of ADHD in adolescent and young adult males with FXS and ADHD measurement in this group, in efforts to facilitating access to interventions and improve quality of life.

Table 1
Reported Rates of ADHD in Individuals with FXS

Authors (Year)	*n*	Age	Sex (M:F)	Measure	Rate of ADHD
Studies Utilizing Diagnostic Indices of ADHD					
Backes , Genç, Schreck, Doerfler, Lehmkuhl, & Von Gontard (2000)	49	5 – 16 years (*M* = 9 years)	49:0	Kinder-DIPS[a]	74%
Baumgardner, Reiss, Freund, & Abrams (1995)	31	3 – 18 years (*M* = 8 years)	31:0	DSM -III[b]	73%
Freund, Reiss, & Abrams (1993)	17	4 – 27 years	0:17	Diagnostic Interview for Children and Adolescents (DICA)-Parent Version[c]	35%
Pegoraro, Steiner., Celeri, Banzato & Dalgalarrondo (2014)	13	6 – 16 years (*M* = 12 years)	12:1	DSM-IV-TR[d]	77%
Sullivan, Hatton, Hammer, Sideris, Hooper, Ornstein, & Bailey (2006)	59	7 – 13 years (*M* =10 years)	54:5	Childhood Symptom Inventory–4 (CSI-4), Parent Checklist[e] or Adolescent Symptom Inventory -4 (ASI-4), Parent Checklist[f]	54%
				Childhood Symptom Inventory–4 (CSI-4), Teacher Checklist[e] or Adolescent Symptom Inventory -4 (ASI-4), Teacher Checklist[f]	59%
Studies Utilizing Screening/Symptom Rating Scale Indices of ADHD					
Baumgardner, Reiss, Freund, & Abrams (1995)	31	3 – 18 years (*M* = 8 years)	31:0	Aberrant Behavior Checklist (ABC) Hyperactivity Scale, Parent Report[g]	40%
				Aberrant Behavior Checklist (ABC) Hyperactivity Scale, Teacher Report[g]	50%
Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif (2013)	46	58 – 133 months (*M* = 9 years)	46:0	Conner's Teacher Rating Scale – Revised: Short Form[h]	43%
Grefer, Flory, Cornish, Hatton, & Roberts (2016)	33	36 – 55 months (*M* = 41 months)	33:0	CBCL Attention/Hyperactivity DSM-oriented Subscale, Parent Report Form[i] (reported rate does not include borderline scores)	9%
Hatton, Hooper, Bailey, Skinner, Sullivan, & Wheeler (2002)	59	48 - 152 months (*M* = 87 months)	59:0	CBCL Attention Problems Subscale, Parent Report Form[i] (reported rate includes borderline scores)	56%
Newman, Leader, Chen, & Mannion (2015)	47	2 – 17 years (*M* = 8 years)	35:12	Conners-3 Inattention and Hyperactivity/Impulsivity Subscales, Parent Short Version[j] & Conners Early Childhood, Parent Short Version[j]	83%

Note. [a]Schneider et al. (1995); [b]American Psychiatric Association (1980); [c]Reich (2000); [d]American Psychiatric Association (2000); [e]Gadow and Sprafkin (1997); [f]Gadow et al. (1997); [g]Aman et al. (1985); [h]Conners (1997); [i]Achenbach (2001); [j]Conners (2008); [j]Conners (2009)

Table 2
Descriptive Statistics

Variable	*M* (*SD*) Range
Brief IQ Standard Score, Leiter-R	38.97 (5.39) 36.00-56.00
Brief IQ Growth Scale Value, Leiter-R	459.90 (14.27) 420.00-488.00
ASD Severity Score, ADOS-2	5.68 (2.31) 1.00-10.00
ADHD Scale T Score, CBCL	58.87 (2.13) 50.0-73.0

Table 3
Correlation Matrix

	DSM-5 ADHD Diagnosis	ADHD Scale T Score, CBCL	ASD Severity Score, ADOS-2	Brief IQ Growth Scale Value, Leiter-R	Chronological Age
DSM-5 ADHD Diagnosis	---	.40*	-.11	.27	.07
ADHD Scale T Score, CBCL		---	-.01	.06	.12
ASD Severity Score, ADOS-2			---	-.31	-.16
Brief IQ Growth Scale Value Score, Leiter-R				---	.43*
Chronological Age					---

*p< .050

Table 4
Number of Individuals Meeting Criteria for a DSM-5 ADHD Diagnosis in Comparison to CBCL ADHD Cut-offs

	DSM-5 ADHD Diagnosis	
Range of CBCL ADHD Scale T-Score	*Positive (n)*	*Negative (n)*
Clinical	4	1
Borderline	3	2
Normal	6	15
Total	13	18

Figure 1
Percent of Youth with FXS Meeting Criteria for ADHD

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Figure 1