Title

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Journal

Journal of Autism and Developmental Disorders, 49(3)

ISSN

0162-3257

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Publication Date

2019-03-01

DOI

10.1007/s10803-018-3804-6

Peer reviewed

HHS Public Access

Author manuscript

J Autism Dev Disord. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

J Autism Dev Disord. 2019 March ; 49(3): 1131–1141. doi:10.1007/s10803-018-3804-6.

Prevalence and Predictors of Anxiety Disorders in Adolescent and Adult Males with Autism Spectrum Disorder and Fragile X Syndrome

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Abstract

Anxiety disorders affect ~15–20% of youths without neurodevelopmental disorders, with persons having autism spectrum disorder (ASD) and fragile X syndrome (FXS) at elevated risk for anxiety disorders. Few studies have compared rates and predictors of anxiety disorders in adolescents with FXS or ASD. This study directly compares rates, predictors, and medication of anxiety disorders between age-matched, male adolescents with FXS (n = 31) or ASD (n = 20). Results indicate that 51.6% of FXS and 50.0% of ASD adolescents met criteria for an anxiety disorder. Cognitive scores and ASD severity did not predict anxiety. Of those with anxiety, ~40% of the FXS and 20% of the ASD participants were prescribed medications for anxiety.

Keywords

autism spectrum disorder; fragile x syndrome; anxiety; intellectual disability

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Conflict of Interest: Jordan Ezell declares that she has no conflict of interest. Abigail Hogan declares that she has no conflict of interest. Amanda Fairchild declares that she has no conflict of interest. Kimberly Hills declares that she has no conflict of interest. Jessica Klusek declares that she has no conflict of interest. Leonard Abbeduto declares that he has no conflict of interest. Jane Roberts declares that she has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Anxiety disorders are among the most prevalent and debilitating disorders in children and adolescents, affecting approximately 15–20% of individuals under the age of 18 (Beesdo, Knappe, & Pine, 2011; Salum, De Sousa, do Rosário, Pine, & Manfro, 2013). Clinical subgroups, such as autism spectrum disorder (ASD) and fragile X syndrome (FXS), are often at higher risk for developing a comorbid anxiety disorder, which can reduce functioning across multiple domains (Simonoff et al. 2008; Kim et al, 2000). However, a range of prevalence rates is reported in ASD with studies often excluding individuals with an intellectual disability (ID). Further, only one diagnostic study of anxiety has been conducted in FXS (Cordeiro, Ballinger, Hagerman, & Hessl, 2011). Additionally, there is considerable overlap between ASD features and anxiety symptoms in FXS and non-syndromic ASD (Kaufmann et al. 2004; Hall et al. 2008; Kerns et al, 2014; Roberts et al, 2018). Thus, disentangling the presentation and prevalence of anxiety in those with FXS or ASD is critical for the accurate diagnosis of anxiety disorders and the subsequent development of targeted treatments.

Anxiety in Autism Spectrum Disorder

ASD occurs in 1 in 59 children and is characterized by social-communication impairments and repetitive, restricted interests and behaviors (American Psychiatric Association, 2013; Baio et al., 2018). Anxiety is one of the most prevalent comorbid disorders in youth with ASD (van Steensel, Bögels, & Perrin, 2011; White et al., 2014; White, Oswald, Ollendick, & Scahill, 2009). Population-based studies utilizing gold standard diagnostic measures report that 40–50% of individuals with ASD meet diagnostic criteria for an anxiety disorder (White, Oswald, Ollendick, & Scahill, 2009), but other studies using a range of measures report prevalence rates ranging from 11–84% (van Steensel, Bögels, & Perrin, 2011; Simonoff et al., 2008). Previous studies also show a range of rates for specific anxiety disorders in persons with ASD. For instance, rates range from 8–63% for Specific Phobia, 2–35% for Generalized Anxiety Disorder (GAD), and 6–37% for Social Anxiety Disorder (Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998; Simonoff et al., 2008; Bellini, 2006; Green, Gilchrist, Burton, & Cox, 2000; Leyfer et al., 2006; de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Kerns et al., 2014).

This wide variability in diagnostic rates reflects the challenges inherent in diagnosing anxiety disorders in ASD. Difficulties with insight and self-report may contribute to the complexity of accurately measuring anxiety disorders in individuals with ASD (Kerns et al., 2014; van Steensel et al., 2011). Additionally, evidence suggests that anxiety in ASD can present in both typical and atypical profiles in ASD, further complicating the task of diagnosis. For example, a child with ASD and anxiety may display prototypical anxiety symptoms, such as fear of dogs, but may also show more idiosyncratic features of anxiety, such as a fear of beards or toilets (Kerns et al., 2014). Another challenge is the overlap in symptomatology between ASD and anxiety, which can make it difficult to determine whether the presenting behaviors are caused by anxiety or ASD. For instance, social avoidance, restricted interests, repetitive behaviors, fear of change, and hyper- or hypo-reactivity to sensory stimuli can be observed in either ASD or anxiety (Kerns, Kendall, Wood, & Storch, 2017; Van Steensel, Bögels, & Wood, 2013; American Psychiatric

Association, 2013). This overlap can lead to “diagnostic overshadowing” in which anxiety features are attributed to ASD or overlooked because of dominating ASD behaviors (Kerns et al., 2015).

Other potential sources of the wide ranges of prevalence rates include varying sample characteristics (e.g., ASD symptom severity, age) and forms of anxiety measurement. The majority of previous studies exclude individuals with ASD with an IQ below 70, because, in part, measuring anxiety accurately can be difficult in individuals with ID (van Steensel et al., 2011). At least half of individuals with ASD have an IQ below 85, with approximately one third being classified as ID (IQ < 70) (Baio et al., 2018). Therefore, results from previous studies that included only average or above-average IQ (i.e., “high-functioning”) individuals with ASD might not be generalizable to over half of the ASD population. Studies that have examined anxiety in ASD across a wide IQ range have found similar rates of anxiety between ID and normal IQ subgroups (van Steensel et al., 2011; Kuusikko et al, 2008; Sukhodolsky et al., 2008). Additionally, studies that have compared individuals with ASD and ID to individuals with ID only (i.e., non-ASD ID) have reported elevated rates of both typical and atypical features of anxiety in the ASD with ID group (Bakken et al., 2010; Helverschou & Martinsen, 2011). Thus, from the little research that has been done, it appears that individuals with ASD are at an elevated risk for anxiety regardless of intellectual ability.

The impact of ASD severity has also varied across studies, with some studies finding no associations between ASD symptom severity and anxiety (Renno & Wood, 2013; Sukhodolsky et al., 2008), but others reporting a relationship between greater ASD severity and more anxiety symptoms (Gadow, Sprafkin, & Nolan, 2001; Wood & Gadow, 2010). Given that ASD severity and intellectual ability are often correlated (Gotham, Pickles, & Lord, 2012; Venker, Ray- Subramanian, Bolt, & Weismer, 2014), it is important to disentangle the effects of these potential risk factors. Thus, more studies are needed that include lower IQ individuals with ASD to further clarify both the prevalence and predictors of anxiety in this portion of the ASD population (Baio et al., 2018; Cordeiro et al., 2011).

Anxiety in Fragile X Syndrome

FXS is a single-gene disorder caused by a CGG expansion mutation in the *Fragile X Mental Retardation-1* (*FMR1*) gene. An expansion of more than 200 CGG repeats on the *FMR1* gene causes methylation and reduced production of the fragile X mental retardation protein (FMRP), a protein that is essential for typical brain development (Hagerman, Lauterborn, Au, & Berry-Kravis, 2012; Schwarte, 2008). The FXS behavioral phenotype is characterized by shyness, avoidance of eye contact, elevated physiological arousal, social-communication deficits, and ID (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Hessl et al., 2001; Klusek, Roberts, & Losh, 2015; Rogers, Wehner, & Hagerman, 2001). Many of the core features of FXS are qualitatively similar to those of ASD, and approximately 60% of males with FXS also meet diagnostic criteria for ASD (Klusek et al., 2014; Lee et al., 2016).

Anxiety is frequently reported by parents of children with FXS (e.g., Thurman et al., 2014; Bailey et al., 2012; Laxman et al., 2017); however, only one study to date has assessed rates

of anxiety disorders in FXS using a DSM-based diagnostic measure (Cordeiro et al., 2011). This study included 58 males and 39 females with the full-mutation (5–27 years old) and used the Anxiety Disorders Interview Schedule (ADIS-IV) (Grisham, Brown, & Campbell, 2004), a clinical parent interview based on the DSM-IV. Approximately 86% of the sample met diagnostic criteria for any anxiety disorder, 65% met criteria for Specific Phobia, and 35% met criteria for Social Phobia.

Cordeiro and colleagues (2011) also examined the potential effects of ID and ASD comorbidity on anxiety disorder diagnosis. In FXS, social anxiety and specific phobia were both more common in individuals with FXS and ID than in those with FXS only (Cordeiro et al., 2011). Furthermore, an ASD diagnosis was associated with social anxiety and specific phobia, but not other anxiety disorders (Cordeiro et al., 2011). Thus, from that study, it appears that ID and ASD both confer additional risk for certain anxiety subtypes (i.e., specific phobia, social anxiety) in individuals with FXS. Though this study has provided important insight into anxiety risk in FXS, questions remain because of the heterogeneity of this particular sample (e.g., wide age range, inclusion of both males and females). Given that FXS presents differently across sex, developmental level, and chronological age (Garber, Visootsak, & Warren, 2008), more focused samples are needed in order to elucidate the prevalence of anxiety disorders in certain subgroups of FXS.

The Present Study

Although elevated rates of anxiety symptomatology have been reported in ASD and FXS, no study has directly compared anxiety prevalence in these clinical subgroups from a cross-syndrome perspective using a DSM-based measure. Furthermore, the contributions of specific risk factors, such as low IQ and/or high ASD severity, have not been clearly characterized in ASD or FXS. Clarifying the prevalence of, and risk factors for, anxiety in individuals with neurodevelopmental disabilities using a DSM-based anxiety measure will contribute to improved diagnostic accuracy in individuals who have historically been difficult to assess and diagnose.

The first aim was to compare the rates of overall anxiety disorders between adolescents with non-syndromic ASD or FXS and report the rates of specific anxiety disorders. The second aim was to investigate whether NVIQ and ASD symptom severity serve as risk factors an anxiety disorder across the sample of adolescents with ASD or FXS. Additionally, a post hoc exploratory aim was developed to compare the rates of medications prescribed to treat anxiety and compare the alignment of medication for anxiety with an anxiety diagnosis in the non- syndromic ASD group and the FXS group.

Method

Participants

Participants were males with non-syndromic ASD (i.e., ASD with no identified genetic disorder) (n = 20) or FXS (n = 31). The samples were matched on chronological age (p = . 70) ranging from 13 to 24 years of age (M = 18.8, SD = 2.1). Participants were recruited through two complementary studies. The entire FXS sample (n = 31) and a portion of the

ASD sample (n = 12) were recruited as a part of a longitudinal, multi-site study focused on the development of language during adolescence (xrefXX). To expand the sample with ASD, we recruited eight additional participants who were part of a study of social-communication profiles within families of children with FXS and non-syndromic ASD (xrefXX). Inclusion criteria: Age 13 – 24, verbal ability using at least three words, English primary language. Diagnoses of FXS were confirmed in the FXS sample. Exclusion criteria: a known secondary genetic syndrome (e.g., Tuberous Sclerosis) for FXS or any known genetic syndrome for ASD. Females were excluded from the study because of significant cognitive and clinical sex differences present in both ASD and FXS (Rinehart, Cornish, & Tonge, 2011). The diagnosis of ASD was reported by parents then confirmed through the present study as described in detail later. Despite recruitment efforts to match the FXS and ASD groups on low cognitive ability, eight participants with ASD had a NVIQ composite above 70 (see Table 1).

Procedure

Participants were assessed at the xrefXX over two days. Trained research staff members administered all behavioral assessments and parent interviews. Participant families were compensated for travel expenses and provided $50 for study participation. The Institutional Review Board at the xrefXX approved all study protocols. Assent was obtained from the participant and informed consent was obtained from the participant's parent prior to beginning the assessment.

Measures

Anxiety Diagnosis.—The Children's Interview for Psychiatric Symptoms-Parent Version (P-ChIPS) is a DSM-IV based, structured psychiatric interview designed to assess the presence of psychiatric disorders in children and adolescents (Weller, Weller, Fristad, Rooney, & Schecter, 2000). The P-ChIPS was conducted with the parents of participants to measure the presence of Specific Phobia, Social Anxiety Disorder, and Generalized Anxiety Disorder (GAD). The P-ChIPS follows the DSM-IV structure of symptom count, duration, and impairment but was adapted to reflect the DSM-5 criteria for the current study. Specifically, for GAD, frequency of worries had to be endorsed as often as "every day or every other day", and if only one fear or worry was present, then the specific fear or worry was instead addressed in Specific Phobia. We also omitted the requirement that adults need to recognize their fear or anxiety as irrational or excessive in order to be diagnosed with Specific Phobia and Social Anxiety given the nature of the limitations of our samples. Finally, Specific or Social Anxiety symptoms were required to be present for at least six months.

Published kappa coefficients on the PChIPS in a sample with ASD with and without ID range from good to excellent for each anxiety disorder (GAD: .86, Specific Phobia: .76, and Social Phobia: .72), and inter-rater reliabilities for all three anxiety subtypes were in the excellent range (.91–.99) (Witwer & Lecavalier, 2010; Witwer, Lecavalier, & Norris, 2012). For the present study, a licensed clinical psychologist assessed reliability on 20% of the sample. Interrater agreement across all anxiety disorders was 100% for the ASD group and 92% for the FXS group.

Autism Spectrum Disorder (ASD) Symptom Severity.—The Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) is a semi-structured, standardized assessment of communication, social interaction, play, and restricted and repetitive behaviors (Lord, Rutter, DiLavore, Risi, & Gotham, 2012). The ADOS-2 was administered to all participants by graduate-level professionals who had completed research reliability training. The ADOS-2 calibrated severity scores were used to reflect the overall severity of ASD symptoms as well as severity of symptoms in the social-communication domains and restricted/repetitive behavior domains.

Nonverbal Intellectual Ability.—The Leiter-R Brief Nonverbal Intelligence Test was used to assess nonverbal intelligence. The Leiter-R Brief consists of the Figure Ground, Form Completion, Sequential Order, and Repeated Patterns subtests (Roid & Miller, 1997). The overall standard score for the Leiter-R, the Brief IQ, is reported for descriptive purposes in Table 1. Due to low cognitive abilities in these populations, floor effects can significantly truncate standard scores, thus impacting analyses (Hooper, Hatton, Baranek, Roberts, & Bailey, 2000). Therefore, a growth score was used in the analyses to limit floor effects. In contrast to a standard score, which is referenced relative to age peers, a growth score reflects absolute ability level on an equal-interval scale with appropriate psychometric properties, and thus, is often used in populations with ID. The Leiter-R growth score was calculated by mapping the total raw score to the corresponding growth score using the item response theory model (Roid & Miller, 1997; Hooper et al., 2000; Matherly et al., 2018).

Current Anxiety Medication (Family Background Questionnaire).—The Family Background Questionnaire (FBQ) is a parent-report demographics questionnaire developed for use in the project on adolescent language development. Parents report current medication use and the prescribed purpose of the medication. For the current study, any medication indicated by parents as prescribed for anxiety was included.

Quantitative Analyses

Analyses were conducted using RStudio Version 1.0.136 (2015). Data were analyzed for violations of assumptions including homogeneity of variance, normality of residuals, and multicollinearity. The analytic strategy was completed in multiple steps. First, descriptive statistics were run to calculate the rates of overall and specific anxiety disorder diagnoses (i.e., GAD, Specific, Social) in the ASD and FXS groups. Chi-square analysis was used to compare the overall rate of anxiety in the ASD and FXS groups. Then, follow-up independent sample *t*- tests were conducted to compare age, Leiter-R growth scores, and ASD symptom severity across participants with and without anxiety. Next, to test model assumptions, bi-serial correlations were performed to assess associations between the predictors (Leiter-R growth scores and ASD severity) and anxiety, and between the predictors and diagnosis group (FXS or ASD). A logistic regression model was then conducted to analyze ASD severity and Leiter-R growth scores as predictors of anxiety disorders in ASD and FXS. Exploratory descriptive analyses were also conducted to investigate the rates of prescribed anxiety medications across the ASD and FXS groups. Logistic regression models were run to determine whether anxiety medication was a predictor of an anxiety disorder or group (FXS or ASD).

Results

Prevalence of Anxiety Disorders

Overall, 51.6% of the FXS adolescents met criteria for any anxiety disorder, with 12.9% meeting criteria for multiple anxiety disorders. Similarly, 50.0% of adolescents with ASD met criteria for any anxiety disorder, and 30.0% met criteria for multiple anxiety disorders. No significant differences in the rates of overall anxiety diagnoses between the ASD and the FXS group were observed ($X^2(1) = 0.01$, $p > .05$). Rates of specific anxiety diagnoses for each group can be found in Table 2.

Predictors of Anxiety

When comparing individuals with and without an anxiety disorder, no differences emerged between Leiter-R growth scores ($t(49) = 1.00$, $p = .32$) or ASD symptom severity ($t(49) = 0.02$, $p = .99$). Further analyses showed no significant differences between those meeting criteria for anxiety and those who did not meet criteria within the ASD and the FXS groups in terms of Leiter-R growth scores and ASD symptom severity (ps > .05) (see Table 1).

Bi-serial correlations indicated that multicollinearity was not violated for Leiter-R growth scores or ASD severity (rs < .70, ps > .05). Results of the logistic regression analyses indicated that neither Leiter-R growth scores nor ASD symptom severity was a significant predictor of any anxiety disorder for the combined FXS and ASD samples (ps > .05) (Table 3). Given the limited sample size, further inferential statistical tests were not conducted to examine predictors for anxiety disorder subtypes across FXS and ASD.

Post Hoc Exploratory Analysis of Medication in Relation to Anxiety

Descriptive analysis showed that 48.4% of participants with FXS and 20.0% of participants with ASD were currently taking prescribed medications for anxiety. The logistic regression model showed that taking anxiety medications was not significantly predictive of meeting criteria for an anxiety diagnosis ($\chi^2(1) = 0.03$, $p = .86$); however, anxiety medication use was predictive of diagnostic group (FXS or ASD) ($\chi^2(1) = 4.39$, $p = .04$), with anxiety medication use more likely in FXS. Further, across groups, only 38.5% of those meeting criteria for a current anxiety disorder were prescribed an anxiety medication and 36.0% of those who did not meet criteria for a current anxiety disorder, were prescribed an anxiety medication.

Discussion

This is the first cross-syndrome study to investigate the prevalence rates and predictors of DSM-5 anxiety disorders in individuals with ASD or FXS, the majority of whom had ID. Overall, these findings support prior evidence of elevated rates of anxiety in ASD and FXS, but also point to nuanced anxiety subtype profiles between ASD and FXS that could influence the assessment and treatment of anxiety in these populations. For example, the study found that approximately half of the sample for both ASD and FXS met DSM-5 criteria for an anxiety disorder, which is higher than the rate of 15–20% in neurotypical individuals. However, descriptive analyses suggested that the most prevalent disorder in

ASD is GAD, whereas the most prevalent in the FXS group is specific phobia. Interestingly, Leiter-R growth scores and ASD symptom severity were not significant predictors of an anxiety disorder in these clinical subgroups. Further, exploratory analyses found that medication use for anxiety was predictive of FXS, rather than anxiety, suggesting a need for additional exploration of medication as anxiety treatment in ASD and FXS.

Prevalence of Anxiety Disorders

Half of the ASD sample met criteria for at least one anxiety disorder, which is generally consistent with previous population-based studies of ASD (White et al., 2014). The most common diagnosis in ASD was GAD (40% of the sample), while previously reported prevalence rates for GAD in ASD range from 2–35% (Bellini, 2006; Green, Gilchrist, Burton, & Cox, 2000; Leyfer et al., 2006). The high rate of GAD might indicate that some features of ASD, such as atypical fears, restricted interests, and sensory aversions, are being captured under GAD. Thus, measures designed to assess for typical features of GAD, such as excessive worry, might also capture overlapping features of ASD causing the rates of GAD to be further inflated in ASD. On the other hand, atypical signs of GAD may not be distinguishable in measures normed on typical populations. For instance, excessive worry over a special interest, like shiny objects, is often attributed to ASD symptomology and not a co-occurring GAD diagnosis (Kerns et al., 2017; Kerns et al., 2014).

The rates of Social Anxiety Disorder (30%) and Specific Phobia (15%) both fell within the previously reported ranges of 6–37% and 8–63%, respectively (Muris et al., 1998; Simonoff et al., 2008; de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Kerns et al., 2014; Leyfer et al., 2006). In the present study, the most common specific phobia reported was flying insects, which is considered a typical phobia. Previous studies indicate that specific phobias can present atypically in ASD, (e.g., special interests, sensory fears). However, the current measure and previously-reported anxiety measures do not capture atypical phobias (Kerns et al., 2014). Thus, the rates of specific phobia in ASD may not be accurately characterized to date, which may contribute to the wide range of previously reported prevalence rates. Future work, with larger samples, should be conducted to better define typical and atypical symptom profiles of specific phobia in ASD.

In individuals with FXS, Specific Phobia was the highest reported anxiety disorder in both the current study (35.5%) and in the only previous study to examine anxiety subtypes in FXS (Cordeiro et al. 2011: 59.6%), suggesting that specific phobia is a significant concern for this population. The most common Specific Phobias in the FXS sample were needles, crowds, and dogs, although similar to ASD, atypical phobias might not be captured in typical anxiety measures. While rates of GAD were similar between the Cordeiro study and the present study, differences were seen in the rates of Social Anxiety Disorder, (37% in the Cordeiro study;13% in the current study). In order to meet criteria for Social Anxiety Disorder, an individual needs to feel evaluation or scrutiny by others, which requires social awareness. Deficits in social awareness are often seen in individuals with ASD and low cognitive skills. The Cordeiro et al. study had a larger sample that included higher functioning individuals without ID or ASD, and thus, could account for the higher rate of Social Anxiety Disorder. Further, anxiety can present differently across age (Cordeiro et al,

2011), cognitive ability, and sex in FXS (Bailey, Raspa, Olmsted, & Holiday, 2008; Lachiewicz & Dawson, 1994). Thus, the more restricted sample in the present study contributes clarity and precision for the rates of anxiety in adolescent males with FXS, rather than a mixed FXS sample with varying ages, genders, and cognitive abilities.

Predictors of Anxiety

Previous research has suggested that lower cognitive ability and higher ASD severity are associated with anxiety disorders in ASD and FXS, yet the current study did not find a significant relationship between these factors and the presence of an anxiety disorder. Along these lines, significant differences were not seen across the anxious and non-anxious groups for Leiter-R growth scores or ASD severity. However, the lack of variability of Leiter-R growth scores and ASD severity across the anxious and non-anxious groups may have limited the predictive power of these variables in this study. This finding is particularly relevant to our understanding of how to best characterize core features, correlates, and predictors of anxiety in low-functioning or nonverbal samples, as ASD severity and cognitive ability might not be effective predictors of anxiety for low-functioning individuals. Additionally, a larger sample would allow the assessment of predictors for each specific anxiety disorder, as the present study found varying rates between the ASD and FXS groups. Overall, further investigation into potential predictors of anxiety disorders in low functioning samples can aid in the identification of anxiety in individuals with FXS and ASD.

Medication Use in Relation to Anxiety

Based on the high rates of anxiety found in the primary analyses, exploratory analyses were conducted to investigate the rate of anxiety-targeting medication use in our sample. In the present study, over one-third of the FXS and ASD participants who met criteria for a current anxiety disorder were receiving medication for anxiety. These rates are similar to previous research in FXS that indicated that approximately 50% of males with FXS are prescribed medication for anxiety (Berry-Kravis & Potanos, 2004; Berry-Kravis, Knox, & Hervey, 2011). However, over half of the FXS sample that met criteria for an anxiety disorder were not receiving any anxiety specific pharmacological treatment at the time of the study, which indicates a potential disconnect between diagnosis and treatment in these clinical subgroups with anxiety. One reason for this gap may be the perceived efficacy of anxiety medications by parents of children or adolescents with FXS, with one study finding that the majority of parents found anxiety medications “somewhat” effective to “not at all” effective (Bailey et al., 2012). Additionally, anxiety is often considered a part of the core phenotype of FXS, and therefore, additional treatment may not be sought. While studies have shown that anxiety medications can be effective in treating anxiety in around half of individuals with FXS, there are no medications completely effective in treating anxiety alone and no behavioral interventions developed for anxiety in FXS (Erickson et al., 2017; Hagerman et al., 2012). Further, medication is important for the reduction of problematic symptoms, but does not teach new skills to help individuals cope with anxiety. In typically developing and ASD populations the most effective treatment of anxiety is through combination therapy of medication and behavioral treatment, and thus, further investigation into both pharmacological and behavioral interventions are necessary to provide the more effective

options for individuals with FXS (Vasa, Mazurek, Mahajan, & Bennett, 2017; Wehry, Beesdo-baum, Hennelly, Connolly, & Strawn, 2015).

In ASD, previous studies have shown that 77–80% of those diagnosed with comorbid anxiety are prescribed psychotropic medications (Coury et al., 2012; Rosenberg et al., 2010), which is much higher than the reported rate of medication use for anxiety in the present study. In a recent study, it was found that individuals with ASD and ID were significantly less likely to receive a community diagnosis of anxiety than individuals with ASD alone, despite parent reported symptoms (Buck et al., 2014). Because lower functioning individuals with ASD are less likely to receive an anxiety diagnosis, they may also be less likely to receive a pharmacological intervention for treatment. Further, although an increasing number of behavioral interventions for anxiety in ASD exist, anxiety interventions for low-functioning individuals with ASD are limited (Rodgers & Ofield, 2018). In summary, there is substantial, yet inconsistent evidence for co-occurring anxiety in ASD and FXS; we lack, however, targeted pharmacological and behavioral interventions for low functioning clinical populations with co-occurring anxiety.

Limitations and Future Directions

Despite being the first study to examine DSM-5 anxiety diagnoses in adolescent males with non-syndromic ASD and FXS, our study had several limitations. First, our analysis was restricted by the small sample size of low-IQ males with ASD and males with FXS. Further, though the mean NVIQ of the ASD group was below 70 (i.e., in the ID range), the NVIQ of the FXS group was still significantly lower, suggesting that meaningful differences in cognitive ability may exist between these two groups that might have impacted results. An additional limitation to measuring anxiety in a sample with neurodevelopmental disabilities is that the diagnoses were made on parent report and not self-reported by participants. Reliance solely on parental ratings can be problematic given that parents of children with moderate ID have been shown to misattribute signs of anxiety to other causes (Matson et al., 1997). Thus, there were may have been instances where parents misattributed the underlying source of their child's behavior (e.g., anxiety v. inattention) and/or were unsure if their child was experiencing anxiety symptoms at all if they were not verbalized or observed. Another potential limitation is that parent-reported medication use does not take into account parental resistance to medication or clinician recommendations. Also, anxiety alone may not be enough to warrant medication use in these subjects, but other comorbid disorders like ADHD, aggression, or sleep problems, may motivate doctors and parents to pursue medication use. In addition, the P-ChIPS measures current anxiety and thus past history of anxiety symptoms is not assessed. Thus, if medications are effectively treating anxiety, present symptoms may not exceed diagnostic criteria, which could account for the mismatch between diagnosis and medication use. Future research is needed to fully understand the effectiveness and potential resistance to medication use in low functioning individuals.

Future research should include larger samples of low functioning individuals to allow for better detection of varied anxiety profiles. Additionally, future research should include multidimensional measures of anxiety such as physiological (heart rate, cortisol), experimental (temperament, anxiety), and behavioral (gaze aversion, startle response).

Measures developed specifically for individuals with neurodevelopmental disorders are also needed to strengthen diagnostic accuracy of anxiety in FXS and ASD. Previous research has indicated that gaze aversion is frequent in individuals with FXS and ASD, but presents differently between the two disorders (Hall & Venema, 2017; Hessl, Glaser, Dyer-Friedman, & Reiss, 2006; Cohen et al., 1988) and is evident within the first few years of life (Roberts et al., 2009). Further, evidence for differences in physiological arousal in response to social gaze might suggest differences in arousal and emotion regulation between ASD and FXS (Cohen, 1995). Examining the relationship between gaze avoidance, physiological arousal, and social anxiety disorder within and across neurodevelopmental disorders is one example of future research given existing work suggesting potentially nuanced relationships between anxiety, ASD, and eye gaze in both FXS and ASD.

Conclusions

This study supports the growing literature that anxiety is highly prevalent in both ASD and FXS and contributes to refining the ASD and FXS anxiety phenotypes. Research on anxiety prevalence and predictors within these two groups is an important dimension to consider in understanding outcomes in these clinical groups, since approximately half of each group met DSM-5 criteria for an anxiety disorder. There are significant diagnostic and treatment implications of this work. The results of the study suggest that FXS and ASD might have different profiles for specific anxiety disorders. Further, dependence on parent-reported measures alone can limit diagnostic accuracy and power in individuals with low cognitive or verbal abilities, particularly if anxiety presents atypically in these populations. Findings from this study also support that anxiety should be monitored in individuals with FXS with treatment initiated upon confirmation of need. In terms of intervention, behavioral treatment studies for anxiety in individuals with low functioning ASD or FXS have not been conducted. Although evidence- based treatments for anxiety are effective in high functioning individuals with ASD, the majority of these interventions have not been studied and are not appropriate for low-functioning individuals with neurodevelopmental disorders (Sukhodolsky et al., 2013). It is essential that we understand the factors that affect the diagnosis of anxiety disorders in the high-risk populations of ASD and FXS because comorbid anxiety is associated with increased risk for problems such as inattention, hyperactivity, impulsivity, and self-injurious and aggressive behaviors (Talisa, Boyle, Crafa, & Kaufmann, 2014). Thus, further research is necessary to understand effective treatments for anxiety in these lower functioning clinical populations.

Acknowledgements:

National Institute of Child Health and Human Development (5R01HD024356–20)

Acknowledgements: The authors are grateful to the families who participated in this research. This research was funded by the National Institute of Child Health and Human Development (5R01HD024356–20, PI: Abbeduto).

Funding: This study was funded by National Institute of Child Health and Human Development (5R01HD024356–20).

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Table 1

Participant Descriptive Statistics

	FXS ***n* = 31**			**ASD** ***n* = 20**		
	M (SD) ***Range***			***M (SD)*** ***Range***		***t*-test**
Leiter-R Growth Scores	459.90 (14.27) 453–488			489.80 (19.46) 486–532		$t(32.04) = 5.92^{***}$
Brief IQ	38.97 (5.39) 36–56			68.15 (26.2) 40–126		$t(50) = 4.91^{***}$
ASD Severity	5.68 (2.32) 1–10			7.20 (1.91) 4–10		$t(50) = 2.56^{*}$
Age (years)	18.70 (2.03) 16.04–24.09			18.94 (2.20) 13.88–22.59		$t(50) = -0.393$
	FXS+Anxiety ***n* = 16**	**FXS** ***n* = 15**		**ASD+Anxiety** ***n* = 10**	**ASD** ***n* = 10**	
	M (SD)	***M (SD)***	***t*-test**	***M (SD)***	***M (SD)***	***t*-test**
NVIQ Growth Scores	461.38 (11.20)	458.33(17.23)	$t(29) = -0.59$	495.90(15.55)	483.70(21.79)	$t(18) = -1.44$
ASD Severity	5.50 (2.37)	5.87(2.33)	$t(29) = 0.44$	7.50(1.65)	6.90(2.18)	$t(18) = -0.69$
Age (years)	18.55(2.24)	18.87(1.85)	$t(29) = 0.44$	18.28(1.95)	19.61(2.33)	$t(18) = 1.39$

* <.05,

** <.01,

*** <.001

Table 2

Number of Anxiety Disorders By Clinical Group

	FXS ***n*** **= 31**	**ASD** ***n*** **= 20**
No Anxiety Disorder	48.4% (*n* = 15)	50% (*n* = 10)
One Anxiety Disorder	38.7% (*n* = 12)	20% (*n* = 4)
Multiple Anxiety Disorders	12.9% (*n* = 4)	30% (*n* = 6)
Generalized Anxiety Disorder (GAD)	19.4% (*n* = 6)	40% (*n* = 8)
Specific Phobia	35.5% (*n* = 11)	15% (*n* = 3)
Social Phobia	12.9% (*n* = 4)	30% (*n* = 6)

Table 3

Logistic Regression for NVIQ Growth Scores, ASD Severity, and Age Predicting Anxiety By ASD/FXS Group

	Any Anxiety			
Predictor	***B***	***SE B***	e^B	***P***
NVIQ Growth Scores	0.03	0.02	0.97	0.15
ASD Severity	0.01	0.13	1.03	0.95
Group	0.87	0.84	0.38	0.30
Constant	−13.12	9.22	0.00	0.16

Note: e^B = exponentiated *B*.