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Prevalence And Predictors Of Anxiety Disorders In Adolescent And Adult Males With Autism Spectrum Disorder And Fragile X Syndrome

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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 are the most prevalent disorders in children and adolescents, affecting approximately 15-20% of individuals under the age of 18 (Salum et al, 2013). Clinical subgroups, like autism spectrum disorder (ASD) and fragile X syndrome (FXS), have an elevated risk of a co-occurring anxiety disorder. Despite the elevated risk of anxiety in these groups, few research studies have investigated the rates and predictors of anxiety disorders in adolescents with these ASD and FXS. In the current study, participants included males with FXS (n=31) or ASD (n=20) aged 16 to 24. Measures included the Children's Interview for Psychiatric Symptoms-Parent Version (P-ChIPS), the Autism Diagnostic Observation Schedule-2 (ADOS-2), and the Leiter International Performance Scale-Revised (Leiter-R). Descriptive statistics indicated that 48% of the FXS adolescents met criteria for an anxiety disorder compared with 50% in ASD. Additionally, 13% of the FXS and 30% of the ASD sample met for multiple anxiety disorders. Across the FXS and ASD groups 35% versus 15% met for Specific Phobia, 12% versus 30% met for Social Phobia and 33% versus 40% met for GAD, respectively. T-tests showed no significant differences within and across groups for those meeting criteria for an anxiety disorder verses those not meeting criteria for age, NVIQ growth scores, and ASD severity. Results of the binary logistic regression did not show age, NVIQ growth scores, or ASD severity as significant predictors of any anxiety disorder across FXS and ASD. Lastly, approximately 40% of participants with FXS who met criteria for an anxiety disorder were prescribed medications for anxiety, as compared iv

to 20% of the participants with ASD who met criteria for an anxiety disorder. Logistic regression results showed that taking anxiety medications were not significantly predictive of meeting criteria for an anxiety diagnosis however anxiety medication use was predictive of group diagnosis. Our primary finding is that approximately half of the FXS and ASD sample met for an anxiety disorder based on DSM-V criteria. Further, This study is the first that directly compares rates of anxiety disorders across adolescents and adults with FXS and idiopathic ASD within a small range of ages, intellectual ability, and autism severity. Reduced rates of anxiety disorders may be indicative of adolescent or young adult males with lower intellectual functioning who have FXS or ASD.

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CHAPTER 1

INTRODUCTION

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 are often at a higher risk for developing a comorbid anxiety disorder, which has been shown to reduce functioning across multiple domains (Simonoff et al. 2008; Kim et al, 2000). Autism spectrum disorder (ASD) and fragile X syndrome (FXS) are two clinical subgroups with an elevated risk of a co-occurring anxiety disorder. Nearly 60% of males with FXS meet criteria for ASD, and there is considerable overlap between ASD features and anxiety symptoms; thus, disentangling the presentation and prevalence of anxiety in FXS and those with ASD is critical for the accurate diagnosis of anxiety disorders and the subsequent development of targeted treatments. Despite the elevated risk of anxiety in both ASD and FXS, few research studies have investigated the prevalence of anxiety disorders in adolescents with these disorders and comorbid intellectual disability (ID).

1.1 ANXIETY IN AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder that occurs in 1 in 68 children and is characterized by social-communication impairments and repetitive, restricted behaviors (American Psychiatric Association,

2013; Christensen et al., 2016). Anxiety is one of the most prevalent comorbid disorders in ASD youth (Magiati et al., 2015; van Steensel, Bögels, & Perrin, 2011; White, Mazefsky, & Dichter, 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 anxiety, but other studies report prevalence rates ranging from 11-84% (White, Oswald, Ollendick, & Scahill, 2009; van Steensel, Bögels, & Perrin, 2011; Simonoff et al., 2008). Previous studies also show a range of rates for specific anxiety disorders. For instance, reported rates in ASD 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). The wide variability in diagnostic rates highlights the challenges inherent in diagnosing anxiety disorders in ASD and reflects a heterogeneous research population with a range of ages and functioning levels, factors that likely impact anxiety presentation in ASD. Further, adults with ASD and comorbid ID were less likely to receive a community diagnosis of anxiety, despite parent-reported symptoms (Buck et al., 2014).

Several factors contribute to the challenges of accurately diagnosing anxiety disorders in individuals with ASD. One barrier is the overlap in symptomatology between ASD and anxiety. For instance, social avoidance, obsessions and preoccupations, repetitive behaviors, fear of change, and atypical phobias are features of both ASD and anxiety (Kerns, Kendall, Wood, & Storch, 2017; Van Steensel, Bögels, & Wood, 2013). Additionally, evidence suggests that anxiety in ASD presents both prototypically and

atypically relative to the DSM-5 diagnostic characterization of anxiety (Kerns et al., 2014). Thus, the present DSM-5 based measures of anxiety may not accurately reflect the atypical presentations of anxiety in ASD (Kerns et al., 2014). Furthermore, confounding individual differences such as ID, and difficulties with insight and self-report also contribute to the difficulty in accurately diagnosing anxiety disorders in individuals with ASD (Kerns et al., 2014; van Steensel et al., 2011).

Examining potential risk factors for anxiety disorders can provide insight into the development of these disorders and can improve diagnostic accuracy in ASD. Although a number of studies have investigated risk factors for anxiety in ASD, the heterogeneity across studies has reported that age, intellectual ability, and ASD symptom severity have variable impacts on the presence of anxiety in ASD (Kerns et al., 2014; Sukhodolsky et al., 2008; Renno & Wood, 2014). Some studies suggest that individuals with ID are at higher risk of certain anxiety disorders (Sukhodolsky et al., 2008), while other studies have found similar rates of anxiety across both ID and normal IQ in ASD (van Steensel et al., 2011; Kuusikko et al, 2008). The impacts of ASD severity have also varied across studies with some studies finding no associations between ASD severity and anxiety (Sukhodolsky et al., 2008; Renno & Wood, 2014), while others report a relationship between greater ASD severity and fewer anxiety symptoms (Gadow, Sprafkin, & Nolan, 2001; Wood & Gadow, 2010). Overall, these studies highlight that there are several individual factors that may increase the risk for anxiety in children and adolescents with ASD, but similar to the range of diagnostic rates, results vary across a diverse ASD population.

Most existing studies of anxiety in ASD have included heterogeneous samples in regards to ASD severity, age, and anxiety measurement, leading to the wide range of reported prevalence rates (11-84%). However, the majority of previous studies have not included individuals with ASD with an IQ below 70, because, in part, measuring anxiety accurately can be difficult in these individuals (van Steensel et al., 2011). An estimated 56% of individuals with ASD have an IQ below 85, with 31.6% having an ID, thus we lack research on anxiety in around one-third of the ASD population (Christensen et al., 2016; Cordeiro, Ballinger, Hagerman, & Hessl, 2011). There is some evidence that individuals with an ID are four times more likely to present with anxiety symptoms than their neurotypical peers, yet anxiety disorders are not well understood in ASD subgroups of ID (Green, Berkovits, & Baker, 2014; Matson & Matson, 2015). Although characterizing anxiety in ASD is complex because of the heterogeneity within the disorder and the phenotypic overlap, this is an important effort given that co-occurring anxiety is clearly associated with poorer social functioning and increased difficulties in individual and family functioning in individuals with ASD (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Simonoff et al., 2008; White et al., 2009). Thus, research on the prevalence and predictors of anxiety in more homogeneous and lower functioning ASD samples is essential for accurate identification and treatment of comorbid anxiety.

1.2 ANXIETY IN FRAGILE X SYNDROME

Fragile X syndrome (FXS) is a single-gene disorder caused by a CGG expansion mutation on the Fragile X Mental Retardation-1 (*FMR1*) gene. Expansion of more than 200 CGG repeats in the *FMR1* gene causes 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). Reduced FMRP results in the FXS behavioral phenotype, which is characterized by shyness, avoidant eye contact, elevated states of 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; García-Nonell et al., 2008).

Few studies have examined prevalence and severity of anxiety disorders in FXS. In fact, only one study to date has used a DSM-based diagnostic measure to assess rates of anxiety disorders in FXS (Cordeiro et al., 2011). The study included 58 males and 39 females with FXS (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. In this study, 86% of the sample met diagnostic criteria for any anxiety disorder, 65% met criteria for Specific Phobia, and 35% met criteria for Social Phobia. This study also examined the potential effects of age, ID, and ASD comorbidity on anxiety disorder diagnosis. Results indicated that older age, the presence of an ID, and the presence of ASD were associated with increased prevalence in certain anxiety disorders. Though the use of a DSM-based measure is a strength of this study, the heterogeneity of the sample (e.g., wide age range, inclusion of both males and females) makes it difficult to draw firm conclusions about the prevalence of anxiety disorders in FXS. Because FXS presents differently across sex, developmental level, and chronological age, more focused samples are needed in order to clarify the prevalence of anxiety disorders in certain subgroups of FXS.

1.3 THE PRESENT STUDY

Overall, research on anxiety disorders in both ASD and FXS is limited and highlights the challenges associated with accurately measuring anxiety symptoms in neurodevelopmental disorders characterized by ID and social-communicative deficits. Though elevated rates of anxiety symptomatology have been reported in ASD and FXS, no studies to date have directly compared anxiety prevalence in these clinical subgroups from a cross-syndrome perspective using a DSM-based measure to determine anxiety diagnoses, so the application of diagnostic criteria across studies is unclear. Finally, it remains unclear how anxiety presents in individuals with ASD or FXS who have comorbid ID (IQ < 70). Individuals with a comorbid ID are at elevated risk for psychopathology like anxiety, but are understudied, as there are additional challenges to accurately measuring anxiety in lower functioning populations (van Steensel et al., 2011; White et al., 2009). 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), it is essential that we understand how to diagnose these disorders in high-risk populations like ASD and FXS.

This study examined the prevalence and predictors of anxiety disorders to determine the diagnostic rates of anxiety disorders in adolescents with non-syndromic ASD compared to adolescents with FXS. It was hypothesized that the genetic mechanisms of FXS confer elevated risk for anxiety resulting in higher rates of anxiety disorders in the FXS group compared to the ASD group. The second objective was to investigate ASD severity, nonverbal IQ (NVIQ), and age as predictors of anxiety disorders within ASD and FXS. Based on previous studies, it was hypothesized that older

age, lower NVIQ, and elevated ASD severity will contribute to increased anxiety risk, and that these factors would predict a diagnosis of anxiety in ASD and FXS. The third objective was to evaluate the rate of prescribed anxiety medications in these groups and to determine the relationship between anxiety medication use and anxiety disorders. It was expected that anxiety medication rates would be higher in the FXS group than the ASD group because FXS is often viewed as a medical diagnosis versus ASD which is viewed as a behavioral diagnosis (Hernandez et al., 2009). Further, it is hypothesized that individuals prescribed anxiety medications will be more likely to meet criteria for an anxiety disorder across groups.

CHAPTER 2

METHODS

2.1 PARTICIPANTS

Participants included males with non-syndromic ASD (n = 20) or FXS (n = 31) ranging from 16 to 24 years of age (M = 18.8, SD = 2.1). Females were excluded from the study because of the cognitive and clinical heterogeneity across sexes for both ASD and FXS (Rinehart, Cornish, & Tonge, 2011). Diagnosis of FXS was confirmed through genetic testing (> 200 CGG repeats on the *FMR1* gene). In participants with non-syndromic ASD previous diagnosis was confirmed for the present study using gold standard diagnostic measures. Additionally, all participants were required to be able to communicate verbally (minimum combination of at least three words) and speak English as their primary language. Participants were recruited through two complementary studies. The entire FXS sample (n = 31) and a portion of the ASD sample (n = 8) were recruited as a part of a longitudinal, multi-site study focused on the development of language during adolescence in ID (i.e., Matherly et al., in press). The remaining 12 participants with non-syndromic ASD were recruited through a study of social-communication profiles within families of children with FXS and non-syndromic ASD (i.e., Klusek et al., 2017). Despite recruitment efforts to match the FXS and ASD groups on NVIQ, 9 of the participants with ASD had a NVIQ above 70 (see Table 1.1).

2.2 PROCEDURES

Participants were assessed at the Neurodevelopmental Disorders Lab at the University of South Carolina 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 University of South Carolina approved all study protocols. Assent was obtained from the participants and informed consent was obtained from the participant's parent prior to beginning the assessment.

2.3 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 anxiety disorders, including 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. The GAD DSM-5 criteria specify that symptoms of excessive worrying need to occur the majority of days and on multiple topics, and thus, frequency of worries had to be endorsed as often as "every day or every other day" to meet criteria for the DSM-5. Further, if only one fear or worry is present then GAD criteria are not met and the specific fear or worry is instead addressed in Specific Phobia. The DSM-5 P-ChIPS adaptations also included the deletion of the criteria that individuals over the age of 18 need to recognize their fear or anxiety as

irrational or excessive for Specific Phobia and Social Phobia. Further, Specific or Social Phobia symptoms must be present for at least a 6-month duration for the DSM-5.

Published kappa coefficients on the PChIPS ranged from good to excellent for each anxiety disorder (GAD .86, Specific Phobia .76, and Social Phobia .72). Previous studies found the intra-class correlations for all three subtype groups in the excellent range (0.91-0.99), as well as overall agreement for each of the subtypes (GAD: 95.4%, Specific Phobia: 90.7%, Social Phobia: 90.7%) (Witwer & Lecavalier, 2010; Witwer, Lecavalier, & Norris, 2012). For the present study, a licensed clinical psychologist assessed reliability on 20% of the ASD and FXS sample. Overall 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 and scored live 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. Table 1 presents descriptive statistics for overall severity scores for overall behaviors across both ASD and FXS groups.

Nonverbal Intellectual Ability (NVIQ). The Leiter-R is a test of nonverbal intelligence and cognitive abilities (Roid & Miller, 1997). The brief measure contains

four subtests consisting of Figure Ground, Form Completion, Sequential Order, and Repeated Patterns. Due to low cognitive abilities in these populations floor effects can significantly truncate standard scores, thus impacting analyses. Therefore, growth scale value scores, which are a true interval scale unlike standard scores, were used in analysis to limit floor effects.

2.4 STATISTICAL ANALYSIS

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. Next, bi-serial correlations were performed to assess associations between anxiety and age, NVIQ growth scores, and ASD severity. A logistic regression model was then conducted to analyze age, ASD severity, and NVIQ 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. Finally, a logistic regression model was run to assess if anxiety medication was a predictor of anxiety disorders within both the ASD and the FXS group.

Table 2.1 *Participant Demographics for Each Diagnostic Group*

	FXS *n* = 31	ASD *n* = 20	
NVIQ Growth Scores[1] *M*(SD)	459.90(14.27)	490.11(19.94)	*t*(29.3) = 5.76, *p* < 0.001
ASD Severity *M*(SD)	5.68(2.31)	6.81(1.94)	*t*(35.6) = 1.78, *p* = 0.084
Age *M*(SD)	18.70(2.03)	18.18(4.77)	*t*(22.1) = -0.45, *p* = 0.656

Note. [1]Leiter International Performance Scale- Revised.

CHAPTER 3

RESULTS

3.1 PREVALENCE OF ANXIETY DISORDERS IN ASD AND FXS

Descriptive statistics were used to compute the rates of anxiety disorders in FXS and ASD. Findings indicate that 48% of the FXS adolescents met criteria for an anxiety disorder, with 13% meeting for multiple anxiety disorders. Similarly, 50% of adolescents with ASD met criteria for an anxiety disorder, and 30% met criteria for multiple anxiety disorders. Rates of specific anxiety diagnoses for each group can be found in Table 2. Further analysis showed no within- or between-group differences in age, NVIQ growth scores, or ASD severity for those meeting criteria for an anxiety disorder versus those not meeting criteria. (Tables 3.1 and 3.2).

3.2 PREDICTORS OF ANXIETY IN ASD AND FXS

Biserial correlations were run to examine the relationship between anxiety and age, NVIQ growth scores, and ASD severity within FXS and ASD groups. Multicollinearity was not violated for any predictors ($r > .70$, $p > 0.05$), although NVIQ growth scores were moderately correlated with clinical diagnosis (FXS or ASD) ($r = .664$). A logistic regression model was then used to determine if age, NVIQ growth scores, and ASD severity predicted anxiety by group. Results of the binary logistic regression did not show that age, NVIQ growth scores, or ASD severity were significant predictors of any anxiety disorder across FXS and ASD (Table 5). Given the limited

sample size, further inferential statistical tests were not conducted to examine predictors for anxiety disorder subtypes across FXS and ASD.

3.3 MEDICATION USE IN ASD AND FXS

Descriptive statistics were run to assess the rate of prescription anxiety medication use for both the FXS and ASD group. The analysis showed that approximately 40% of participants with FXS and ASD who met criteria for an anxiety disorder were currently taking prescribed medications for anxiety. Biserial correlations did not show a relationship between anxiety medications and an anxiety diagnosis (r = 0.137) but did show a relationship between anxiety medications and group, FXS or ASD (r = 0.394). Logistic regression was then used to assess the relation between anxiety medication and anxiety diagnosis by group. Results showed that taking anxiety medications was not significantly predictive of meeting criteria for an anxiety diagnosis (b = -0.047, $F(1, 50)$ = -0.074, p = .941), however anxiety medication use was more likely in FXS (b = 2.133, $F(1, 50)$ = 2.577, p = .0099 . Further, across groups, only 36% of those meeting criteria for current anxiety were prescribed an anxiety medication and 46% of the sample were prescribed an anxiety medication but did not meet criteria for current anxiety.

Table 3.1 *Number of Anxiety Disorders By Clinical Group*

	FXS	ASD
Overall Anxiety	*n* = 31	*n* = 20
No Anxiety Disorder	51.6% (*n* = 16)	50% (*n* = 10)
One Anxiety Disorder	48.4% (*n* = 11)	50% (*n* = 7)
Multiple Anxiety Disorders	12.9% (*n* = 4)	30% (*n* = 3)

Table 3.2 *Rates of Specific Anxiety Disorders By Clinical Group*

	FXS	ASD
Anxiety Subtype	*n* = 31	*n* = 20
GAD	32.3% (n = 10)	40% (n = 8)
Specific Phobia	35.5% (n = 11)	15% (n = 3)
Social Phobia	12.9% (n = 4)	30% (n = 6)

Table 3.3 *Descriptive Statistics Between Anxiety and Non-Anxiety Within FXS and ASD*

	FXS+Anxiety n = 16		FXS n = 16		
	M	SD	M	SD	*t*-test
NVIQ Growth Scores	460.67	(11.22)	459.31	(16.88)	-0.29
					$p = 0.78$
ASD Severity	6.48	(3.69)	5.62	(2.45)	-0.77
					$p = 0.45$
Age	18.71	(2.21)	18.70	(1.92)	-0.02
					$p = 0.98$

	ASD+Anxiety n = 10		ASD n = 10		
	M	SD	M	SD	*t*-test
NVIQ Growth Scores	495.90	(15.55)	483.70	(21.79)	-1.44
					$p = 0.17$
ASD Severity	7.50	(1.65)	6.90	(2.18)	-0.69
					$p = 0.50$
Age	18.28	(1.95)	19.60	(2.33)	1.38
					$p = 0.19$

Note. M = Mean. SD = Standard Deviation. No significant differences were detected at $p<.05$.

Table 3.4 *Descriptive Statistics Between Anxiety and Non-Anxiety Across FXS and ASD*

	Anxiety n = 25		Non-Anxiety n = 26		
	M	SD	M	SD	*t*-test
NVIQ Growth Scores	474.38	(22.16)	467.92	(22.35)	-1.02 *p* = 0.32
ASD Severity	6.26	(2.18)	5.70	(2.20)	-0.87 *p* = 0.39
Age	17.99	(4.15)	19.02	(2.13)	1.11 *p* = 0.27

Note. M = Mean. SD = Standard Deviation. No significant differences were detected at $p<.05$.

Table 3.5 *Logistic Regression for NVIQ Growth Scores, ASD Severity, and Age Predicting Anxiety By ASD/FXS Group*

	Any Anxiety
	B(SE)
NVIQ Growth Scores	0.03(0.02) *p* = 0.08
ASD Severity	0.13(0.15) *p* = 0.37
Age	-0.01(0.01) *p* = 0.43
Group	0.92(0.91) *p* = 0.32

CHAPTER 4

DISCUSSION

Anxiety is highly prevalent in both ASD and FXS with estimated rates significantly elevated above neurotypical populations. This is the first study to contrast rates of anxiety using a DSM-V based measure across adolescent males with ASD or FXS, most of whom have ID. We found that approximately half of the sample for both ASD and FXS met DSM-V criteria for an anxiety disorder. The study did not find significant differences across age, NVIQ, or ASD severity for those meeting criteria for an anxiety disorder versus those who did not meet criteria for an anxiety disorder within the sample. Additionally, results did not show age, NVIQ, or ASD severity as significant predictors of an anxiety disorder across FXS or ASD. Thus, in a somewhat homogeneous sample, age, NVIQ, and ASD severity are not associated with anxiety in low functioning clinical subgroups.

4.1 RATES OF ANXIETY DISORDERS IN ASD AND FXS

Half of the ASD sample met criteria for at least one anxiety disorder, which is generally consistent with previous population based studies (White et al., 2014). The ASD group showed the highest rate of GAD at 40% of the sample, which is higher than the previously reported range of 2-35% (Bellini, 2006; Green, Gilchrist, Burton, & Cox, 2000; Leyfer et al., 2006) and might indicate that in general, adolescents with lower functioning ASD maybe at a higher risk for GAD. Another potential hypothesis is that features of ASD, such as atypical fears and sensory aversions, are captured under GAD

(Kerns et al., 2017; Kerns et al., 2014). 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), suggesting that these specific anxiety disorders are elevated in ASD regardless of intellectual level.

Overall, both similarities and differences were noted between the current study and the Cordeiro et al. (2011) study of anxiety in FXS. Specific Phobia was the highest reported anxiety disorder in both the current study (40%) and in the Cordeiro et al. (2011) anxiety study (59.6%). Differences were seen in both rates of GAD, 24% compared to 33% in the current study, and Social Phobia, 37% compared to 13% in the current study. It is possible that the differences in the rates of GAD and Social Phobia are related to the heterogeneity between the two samples. The previous study included a wider range of ages and both sexes, whereas our study was more homogeneous in both age and sex. Overall the anxiety disorders in this study and in previous literature are elevated above male neurotypical adolescents' lifetime prevalence of anxiety disorders; approximately 30% for an anxiety disorder, 1.5% for GAD, 7% for Social Phobia, and 17% for Specific Phobia (Merikangas, et al, 2010). While the specific anxiety disorder rates differed between the ASD and FXS groups, approximately half of each group met DSM-5 criteria for an anxiety disorder. The high rate of anxiety disorders in both samples might be indicative of additional phenotypic overlap.

4.2 RELATIONSHIP BETWEEN PREDICTORS AND ANXIETY DISORDERS IN ASD AND FXS

Previous research has shown that cognitive ability, ASD severity, and age can predict anxiety disorders in ASD and FXS, yet the current study did not find a significant relationship between these factors and meeting criteria for an anxiety disorder. One explanation is that the current study sample was focused on a low-functioning sample within a small age range, and further, significant differences were not seen across the anxious and non-anxious groups for age, NVIQ, or ASD severity. Correlations also showed a moderate relationship between FXS or ASD diagnosis and NVIQ, and the regression model showed NVIQ trending towards significance in predicting anxiety. This trend suggests that even in an overall low-functioning sample, NVIQ plays a significant role in our ability to measure and detect anxiety. This finding is particularly important in developing measures and understanding how to best capture features of anxiety in low-functioning or nonverbal samples. Overall, a larger sample would allow for further analysis into potential predictors of specific anxiety disorders, as the prevalence of each specific anxiety disorder varied between the ASD and FXS groups.

This study also contributes to refining the ASD and FXS anxiety phenotypes. Anxiety is clearly 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. Further, 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). Thus, further research is necessary to understand effective treatments for anxiety in these lower functioning clinical populations.

4.3 MEDICATION USE IN RELATION TO ANXIETY DISORDERS IN ASD AND FXS

Medication is a primary form of treatment for anxiety with 40% of the FXS and ASD participants who met criteria for a current anxiety disorder receiving medication for anxiety in this study. 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). Studies have shown anxiety medications like SSRIs are effective in treating anxiety in around 50% of individuals with FXS yet there are no behavioral interventions developed for anxiety in FXS (Erickson et al., 2017; Hagerman et al., 2012). In ASD, however, previous studies show that approximately 30% of individuals are prescribed psychotropic medications but that rate climbs to 77-80% when diagnosed with comorbid anxiety (Coury et al., 2012; Rosenberg et al., 2010). This might suggest that individuals with ASD and ID are less likely to receive an anxiety diagnosis, and therefore, less likely to receive a pharmacological intervention for treatment.

In the present study, of those taking an anxiety medication, approximately 53% met for an anxiety disorder. Additionally, 64% of individuals meeting for an anxiety disorder were not medicated for anxiety. One possible explanation is that the P-ChIPS measures current anxiety (occurring for at least 6 months) and not past anxiety. Thus, the potential mismatch of prescribed anxiety medications and the anxiety diagnosis on the P-

ChIPS might indicate that the medications are effective in suppressing current anxiety symptomology, and thus, causing them not to meet criteria for present anxiety. However close to two-thirds of the 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 gap between diagnosis and treatment in low functioning individuals with anxiety. One reason for this gap maybe 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 phenotype of FXS, and therefore, additional treatment may not be sought.

4.4 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 the population of males with low functioning ASD and males with FXS. Further, the mean NVIQ of the ASD group was below 70, yet there was still a significant difference between the groups NVIQ. An additional limitation to measuring anxiety in a low functioning population is that the diagnoses were made on parent report and not self-reported by participants. Thus, there were likely instances where parents were unsure if their son was experiencing anxiety symptoms that were not verbalized or observed. Our future research will include multi-dimensional measures of anxiety such as physiological (heart rate, cortisol) and experimental observation (LAB-TAB, Anx-DOS) and use of measures developed specifically for individuals with neurodevelopmental disorders (ADIS/ASDD).

4.5 CONCLUSIONS

This study supports the growing literature that anxiety is highly prevalent and pervasive in both ASD and FXS. The majority of the literature in ASD, however, has spanned a wide range of ages and functioning levels, and does not typically include individuals with ASD and ID. The research on anxiety in FXS is more limited and primarily consists of broadband screening measures of anxiety across a wide age range. Prior to this study, research had yet to compare anxiety presentation and moderating factors in adolescents of these two neurodevelopmental disorder subgroups. Research into anxiety disorders and predictors within these two groups is important because there are clear negative impacts of anxiety, like increased aggression and self-injurious behaviors and lower adaptive skills, when comorbid with neurodevelopmental disorders such as ASD and FXS (Talisa et al., 2014; White et al., 2009). This study delves deeper into the DSM-5 anxiety presentations in a homogeneous sample of male adolescents with low functioning ASD and adolescent males with FXS. As a result, there are clear clinical implications for diagnosing anxiety comorbid to neurodevelopmental disorders and ID and treatment implications for the development of appropriate cognitive, behavioral treatments and pharmacological treatments.

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