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Empathy and Anxiety in Young Girls with Fragile X Syndrome

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Abstract

We tested whether empathy is impaired and associated with anxiety in girls with fragile X syndrome (FXS). We measured parent-reported empathy and self-reported anxiety in young girls with FXS and in a developmentally-matched comparison group. Girls with FXS received higher parent-reported scores on cognitive and affective empathy but also self-reported more severe anxiety symptoms, particularly separation anxiety and phobia symptoms, than girls in the comparison group. Girls with FXS who received higher cognitive empathy scores, however, appeared buffered against risk for separation anxiety and phobia symptoms. Girls with FXS experience elevated empathy and anxiety relative to their developmentally-matched peers. Higher cognitive empathy in girls with FXS may indicate resilience against specific forms of anxiety that are commonly observed in FXS.

Keywords

adolescence; anxiety; childhood; empathy; females; Fragile X Syndrome

Fragile X syndrome (FXS) is a genetic condition characterized by interpersonal and emotional difficulties, including face and gaze aversion, social avoidance and withdrawal, and a wide range of other anxiety symptoms and phobias (Bruno et al. 2014; Cordeiro et al. 2011; Freund et al. 1993; Hall et al. 2009). Although FXS is associated with elevated levels of anxiety across various contexts and social situations, it does not appear to be characterized by deficient social motivation (Crawford et al. 2020). In addition, there are

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None

complex and inconsistent findings regarding the nature and development of social-cognitive impairments in FXS (Cornish et al. 2005; Losh et al. 2012; M. M. Mazzocco et al. 1994). For example, Cornish and colleagues (2005) found that children with FXS have impairments in social cognition that are comparable to those observed in children with other learning disorders. In contrast, Losh and colleagues (2012) found that only a subset of children with FXS performed worse than typically developing children on social cognitive tasks. Currently, it is unclear whether FXS is associated with deficits in specific social-emotional and social-cognitive skills, such as perceiving, sharing, and comprehending others' internal states.

Empathy, a multifaceted construct that encompasses these skills (Miller et al. 2016; Zaki et al. 2012), is comprised of both affective and cognitive processes. Affective empathy is the vicarious sharing of the emotions of others, whereas cognitive empathy is the ability to infer others' mental states (Hastings et al. 2014; Shamay-Tsoory 2010). Atypical empathy has been observed in a number of neurodevelopmental disorders (Demurie et al. 2011; Maoz et al. 2019), but autism spectrum disorders (ASD) have likely received the most attention from investigators interested in empathy (Harmsen, 2019). The nature of the relation between ASD and empathy, however, is complicated, perhaps related to the fact that ASD consists of a range of neurodevelopmental disorders with etiological heterogeneity. For example, some recent work found that individuals with ASD and alexithymia demonstrate less affective and cognitive empathy than individuals in a control group, but ASD without alexithymia was only associated with decreased cognitive empathy (Mul et al., 2018). Nevertheless, research pointing to altered empathy in ASD may have implications for empathy in FXS given that children with FXS often present with ASD symptoms, although more often in boys than in girls (Bailey et al. 2008). Furthermore, studies of FXS often use assessments such as the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1989) to measure social behaviors that are closely related to empathy. Unlike idiopathic ASD, however, FXS has a well-defined genetic basis and thus provides a unique model for exploring gene-behavior associations underlying affective and cognitive empathy. Despite the advantages of FXS as a disease model, the considerable interest in empathy in ASD, and overlap between ASD and FXS symptoms, relatively little FXS research has targeted and differentiated affective and cognitive empathy. Wishart and colleagues (2007) did not find evidence for deficient emotion recognition in children with FXS, and there are inconsistent findings regarding whether theory of mind – the ability to attribute mental states to other people – is impaired in FXS (Cornish et al. 2005; Losh et al. 2012). Although prior studies of FXS have documented atypical functioning in other psychological and physiological processes that are implicated in affective empathy (Klusek et al. 2015; Wall et al. 2019), few studies have directly considered whether affective empathy (e.g., sharing others' emotions) is affected in FXS in young girls.

To assess empathy in developmental studies, researchers commonly use parent-report measures of children's behaviors reflecting dispositional affective and cognitive empathy (Dadds et al. 2009; Decety et al. 2018; Deschamps et al. 2014). For example, the Griffith Empathy Measure (GEM; Dadds et al. 2008) asks parents to report on their perceptions of children's tendency to be affected by and to understand the emotions of others (affective and cognitive empathy, respectively). The GEM has been widely used to assess individual differences in empathy in typically developing children (Decety et al. 2018; Gevaux et al. 2020; Nagar et al. 2020) and children with neurodevelopmental disorders such as ASD (Alkire et al. 2020; Deschamps et al. 2014; Soorya et al. 2015) and ADHD (Deschamps et al. 2015; Gumustas et al. 2017; Kohls et al. 2014). To our knowledge, however, this measure has not been used to study individual differences in empathy specifically in females with FXS.

FXS presents a variable clinical phenotype, particularly in females who may be partially protected from the mutation via X-inactivation (Garber et al. 2008). However, the factors that moderate symptom severity in girls with FXS are unclear. Research with populations who do not have FXS suggests that individual differences in empathy and mental health may be related. For example, one body of research suggests that increased affective empathy can serve as a risk factor for increased internalizing symptoms in individuals who are prone to physiological states of hyperarousal (Tone and Tully 2014). Physiological hyperarousal has been observed in FXS (Hall et al. 2009; Klusek et al. 2015), but prior studies have not considered whether increased empathy in FXS may indicate risk for increased anxiety. Conversely, social anxiety has been associated with decreased affective empathy for positive emotions (Morrison et al. 2016) and decreased cognitive empathy (Hezel and McNally 2014), suggesting that some forms of empathy may be protective against anxiety. To date, studies have not considered whether empathy represents risk or resilience in FXS.

Much of the research on social functioning and anxiety in FXS has focused on males, likely because FXS occurs more frequently and presents more severe cognitive and behavioral problems in males than in females (Bartholomay et al. 2019). Nevertheless, females with FXS are at increased risk for anxiety, avoidance, depression, and social difficulties (Bailey et al. 2008; Cordeiro et al. 2011; Freund et al., 1993). Females in the general population also tend to be at greater risk for developing internalizing symptoms (McLaughlin and King 2015), and tend to have higher levels of empathy (Zahn-Waxler and Van Hulle 2012), than males. Sex differences in empathy and psychopathology may be linked, leading investigators to posit that empathy may hold particular clinical significance for anxiety in young girls (Zahn-Waxler and Van Hulle 2012). Studying young girls with FXS, who have a specific genetic risk factor associated with increased anxiety and social dysfunction, offers an important model for advancing our understanding of the relations among gene function, risk for anxiety, and empathy.

Previous studies of FXS have assessed anxiety using clinical interviews or questionnaires with parents and teachers as informants due to concerns about the accuracy of self-report in affected individuals (Wadell et al. 2013). Girls with FXS, however, present milder cognitive deficits relative to males and thus may be more capable of providing meaningful insight into their own symptoms. Indeed, a small but growing number of studies have administered self-report measures in samples of children with neurodevelopmental disorders, including ASD and Turner Syndrome (Kaat and Lecavalier 2015; McCauley et al. 1995; Schiltz et al. 2017). The Multidimensional Anxiety Scale for Children (MASC; March et al., 1997) is a widely used self-report measure that assesses different types of anxiety symptoms in children and adolescents, and is an example of a self-report measure that has shown promise in research on neurodevelopmental disorders (Kaat and Lecavalier 2015; Schiltz et al. 2017).

The MASC and other self-report measures, however, remain underutilized in FXS research (Lesniak-Karpiak et al. 2003).

Here, we examined whether girls with FXS and their developmentally matched peers differed in their parent-reported empathy and self-reported anxiety symptoms. Our first analysis tested whether girls with FXS received different cognitive and affective empathy scores than girls in an age- and IQ-matched comparison group. Our second analysis tested whether girls with FXS differed from our comparison group on self-reported anxiety. Consistent with prior studies using parent-report assessments and clinical interviews (Bailey et al. 2008; Cordeiro et al. 2011; Freund et al. 1993), we expected girls with FXS to self-report more severe anxiety symptoms. Given that ASD is associated with altered empathy and heightened risk for anxiety, and that ASD behaviors and diagnoses are common in children with FXS (although more common in males than in females), our analytic plan included testing whether there were group differences in ASD that could account for potential group differences in empathy and anxiety. Our final set of analyses explored whether cognitive and affective empathy moderated the associations between FXS group status and different types of anxiety symptoms.

Methods

Participants and Procedure

Participants were part of an ongoing longitudinal study of the mechanisms underlying anxiety, avoidance, and arousal in girls with FXS. The current analyses included a sample of child and adolescent girls (ages 6.03-16.31 years; 69% White, 13% Asian, 12% more than one race, 3% Black, 3% unknown/not reported; 19% Hispanic/Latino) with FXS (n=43) and a comparison group of girls without FXS (n=32). The groups were matched for age ($t(73)=0.24$, $p=.809$), verbal IQ (Differential Abilities Scale, verbal abilities; Elliott et al. 2018; $t(73)=1.41$, $p=.163$), and adaptive behavior and functional skills (Communication, Daily Living Skills, and Socialization as assessed by the Vineland-3 Adaptive Behavior Scales; Sparrow et al. 2016; all $t(73)<1.31$, all $p>.197$) (see Table 1 for descriptive statistics). Group-matching of age, verbal IQ, and adaptive behaviors are presented visually in Figure 1.

Participants in the FXS group were recruited from North America through FXS communities such as the National Fragile X Foundation, the Fragile X Clinical and Research Consortium, and the Fragile X Online Registry With Accessible Research Database. All participants in the FXS group were diagnosed by a genetic test as having more than 200 CGG repeats in the fragile X mental retardation 1 (FMR1) gene. Participants in the comparison group were recruited to (group) match girls in the FXS group for sex, age, verbal IQ, and adaptive behavior. These participants were recruited from local school districts, regional centers, parent organizations, academic and clinical centers, a website announcement at our university, and social media sites targeting northern and southern California. Participants in the comparison group exhibited a range of idiopathic developmental delays, intellectual disabilities, and learning disabilities. For both the FXS and comparison group, individuals were excluded from the study if they were born very preterm (<30 weeks), had contraindications for magnetic resonance imaging, had a significant visual or hearing impairment, or current or past diagnosis of a major neurological disorder or major psychiatric disorder (e.g., seizure disorder, psychosis, bipolar disorder, head trauma with loss of consciousness). We did not exclude participants in either group if they received a diagnosis of ADHD, anxiety disorder, specific learning disorder, or ASD (severity level 1) given that these characteristics are commonly observed in FXS and can also be present in children without FXS who experience anxiety symptoms. Consent was obtained from parents of all participants. Assent was also obtained from participants depending on child age and level of functioning. The study protocol was approved by the institutional review board of our university.

Empathy

Parents reported on child empathy using the Griffith Empathy Measure (GEM; Dadds et al., 2008). The GEM is a 23-item measure that includes subscales for assessing affective and cognitive aspects of empathy. The affective empathy subscale includes 9 items assessing children's tendency to share the feelings of others (e.g., "my child becomes sad when other children are sad"; "my child cries or gets upset when another seeing another child cry"; "my child acts happy when another person is acting happy"). The cognitive empathy subscale includes 6 items assessing children's ability to engage in perspective-taking (e.g., "my child can't understand why other people get upset"; "my child rarely understands why other people cry"; "my child doesn't understand why other people cry out of happiness"). Parents rated items on a 9-point scale ranging from 1 (strongly disagree) to 9 (strongly agree). To make scores comparable to previous research with typically developing children (Dadds et al. 2008), we recoded items to range from −4 to 4 and summed items within each subscale to form indices of affective (α = .71) and cognitive empathy (α = .75). Parental reports on the affective and cognitive empathy subscales were not significantly correlated (r=.15, p=.196); this is consistent with prior studies using the GEM (Dadds et al., 2008; Gevaux et al. 2020) and suggests that the two subscales should be treated as separate outcomes.

Anxiety

Participants self-reported on their anxiety symptoms using the Multidimensional Anxiety Scale for Children (MASC; March et al. 1997) The MASC includes subscales to assess different kinds of anxiety symptoms, including separation anxiety/phobias (e.g., "I get scared when my parents go away", α=.63), social anxiety (e.g., "I'm afraid that other kids will make fun of me", α=.80), obsessions and compulsions (e.g., "I have to check things several times or more", α=.81), physical symptoms (e.g., "I get shaky or jittery", α=. 76), harm avoidance (e.g., "I usually ask permission to do things" , α = .58), and generalized anxiety disorder (e.g., "I feel restless and on edge", α=.69). The MASC is designed as a self-report measure, but an administrator was always present to facilitate understanding of the questions for younger and lower functioning children as needed. For all participants, the administrator read the first few questions aloud before evaluating whether the individual child could complete the rest of the items by themselves. Participants rated items on a 4-point scale ranging from 0 (never true about me) to 3 (often true about me). Items were summed within each subscale.

Of the 75 participants who provided data on empathy, MASC data were missing for 15 participants either due to children's age (i.e., younger than 7 years old) or failing to provide useable data during the interview (e.g., child did not understand questions or was unable to provide responses). Thus, analyses including MASC data were based on a sample of 60 participants (n=35 for FXS group and n=25 for comparison group). Within these analyses, both groups were still matched on age ($t(58)=0.80$, $p=.425$), verbal IQ ($t(58)=1.78$, $p=.080$), and Vineland-3 Adaptive Behavior Scales (all $t(58)<1.18$, all ps>.243). Participants who were missing MASC data were younger (mean difference=2.49 years, $t(73)=3.50$, $p=.001$) and had lower daily living skills scores (mean difference=8.25, $t(73)=2.27$, $p=.026$) than participants with complete data. Participants who did and did not provide MASC data did not significantly differ on other study variables (all ps>.080).

Autism

We used the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al. 2012) to assess autistic behaviors. The ADOS-2 is a semi-structured interview in which a trained researcher or clinician engages children in activities meant to elicit symptoms of autism (social, communicative, play and ritualistic/receptive behaviors). We used the ADOS-2 algorithm to compute behavioral scores on social affect, restricted and repetitive behaviors, and an overall total score. The total score was used to determine whether participants were “non-spectrum” or if they reached diagnostic cut-offs for a classification of either “autism” or “autism spectrum”.

Vineland Adaptive Behaviors

We used the Vineland Adaptive Behavior Scale, Third Edition (Vineland-3; Sparrow et al. 2016) to assess participants’ functional skills and quality of life. Parents completed the interview version of the measure to report on their child’s day to day skills in the domains of communication (e.g., listening, understanding, and expressing self through speech and writing), daily living (e.g., self-care, meeting expectations at school), and socialization (e.g., interpersonal relationships, play and leisure, and coping skills). We used Vineland-3 standard scores (mean=100, SD=15) to represent functioning in each domain. Higher scores reflect more developed adaptive skills.

Verbal IQ

We used the Differential Ability Scales, 2nd edition to assess verbal IQ (DAS-2; Elliott et al. 2018). We used standard scores (mean=100, SD=15) on the verbal cluster of the measure to represent verbal IQ.

Statistical Analyses

First, we conducted one-way multiple analysis of variance (MANOVA) tests to examine whether there were group differences in overall empathy and anxiety scores across subscales. We conducted one-way ANOVAs as planned follow-up tests to examine whether girls with FXS and girls in the comparison group differed in specific aspects of empathy and/or anxiety as assessed by individual subscales. Second, we conducted a multiple analysis of covariance (MANCOVA) test to examine whether empathy moderated the association between group status and anxiety scores across MASC subscales (Baron and Kenny 1986). This analysis included group status, affective empathy, cognitive empathy, the interaction between affective empathy and group status, and the interaction between cognitive empathy and group status, as predictors of anxiety symptoms. We conducted planned follow-up regression analyses to test empathy by group status interaction effects on specific types of anxiety. Significant interactions were probed by examining the association between group status and anxiety separately at 1 SD above and below the mean of empathy (affective or cognitive) .

Results

Group comparisons on verbal IQ, adaptive behaviors, and autism behaviors are presented in Table 1. In the total sample, 26 girls met ADOS-2 based criteria for autism (12 girls in the comparison group and 14 girls in the FXS group) and 6 met criteria for autism spectrum (2 girls in the comparison group and 4 girls in the FXS group). Girls with and without FXS did not differ in ADOS-2 based autism diagnoses ($\chi^2[2]=0.35$, $p=.838$).

Group differences in empathy and anxiety are presented in Table 2 and visually in Figure 2. The MANOVA test of empathy showed a statistically significant main effect of group status, $F(2, 72)=6.55$, $p=.002$, partial $\eta^2 = .15$. Follow-up tests showed that girls with FXS received higher scores on affective empathy, $F(1, 72)=7.65$, $p=.007$, partial $\eta^2 = .10$, and cognitive empathy, $F(1, 72)=6.54$, $p=.013$, partial $\eta^2 = .08$, compared to girls in the comparison group (see Figure 2). Prior research using the Griffith Empathy Measure with typically developing girls found that age was positively associated with cognitive empathy scores (Dadd et al. 2008). We did not find that age was associated with empathy scores in the total sample (both $p>.273$) or in the separate testing groups (all ps>.291).

The MANOVA test of anxiety also showed a statistically significant main effect of group status, $F(6, 53)=2.39$, $p=.041$, partial $\eta^2 = .21$. That is, there was a pattern of results differentiating girls with FXS and girls in the comparison group on the MASC anxiety subscales. Follow-up tests showed that girls with FXS reported more severe separation anxiety/phobia symptoms than girls in the comparison group, $F(1, 58)=4.29$, $p=.043$, partial $\eta^2 = .07$. The observed differences between girls with FXS and girls in the comparison group on the other anxiety subscales did not reach statistical significance (all ps>.109).

The interactions between empathy and group status on overall anxiety were not significant (both $p>.155$). We conducted planned follow-up regression analyses to determine whether group status was differentially associated with specific kinds of anxiety symptoms at high and low levels of empathy. The interaction between group status and cognitive empathy in predicting separation anxiety/phobia symptoms was statistically significant ($\beta=-.33$, $p=.011$). At low levels of cognitive empathy, girls with FXS reported more severe separation anxiety/phobia symptoms than girls in the comparison group ($\beta=.65$, $p<.001$). Conversely, at high levels of cognitive empathy, group status was not associated with separation anxiety/phobia symptoms ($\beta=-.02$, $p=.929$). Figure 2 presents the interaction effect and shows that group differences in separation anxiety/phobia symptoms widen at low levels of cognitive empathy and narrow at high levels of cognitive empathy. Figure 2 also shows that cognitive empathy is negatively associated with separation anxiety/phobia symptoms in girls with FXS

(β=−.40, p=.026), but is not associated with symptoms in girls in the comparison group (β=.37, p=.075).

The full regression model is presented in Table 3. The interaction between group status and affective empathy in predicting separation anxiety/phobia symptoms was in the opposite direction of the cognitive empathy by group status interaction effect, but did not reach statistical significance (β=.23, p=.080).

Interaction effects between empathy and group status were not significant in regression models predicting other MASC subscales (all ps>.147)

Discussion

This study examined whether girls with FXS differed from a group of developmentally-matched girls on parent-reported cognitive and affective empathy and self-reported anxiety. Our results suggest that girls with FXS may experience elevated empathy and anxiety, particularly separation anxiety and phobias, relative to their developmentally-matched peers. Furthermore, our findings provide novel evidence that high cognitive empathy may indicate resilience against separation anxiety and phobia symptoms in girls with FXS.

Prior studies have used the GEM to gather information from parents on children’s dispositional cognitive and affective empathy in both typically developing children and in children with neurodevelopmental disorders (Decety et al. 2018; Deschamps et al., 2014, 2015). Our study, however, is the first to administer the GEM in a sample of young girls with FXS. Our finding that girls with FXS received higher cognitive empathy scores is consistent with previous task-based studies suggesting that FXS is not characterized by emotion recognition and theory of mind deficits comparable to those observed in other learning disorders (Losh et al. 2012; Wishart et al. 2007). In addition, this study is the first to suggest that affective empathy is intact in girls with FXS relative to developmentally-matched peers. Given that our study groups were matched on adaptive behaviors, autism behaviors, and autism diagnoses, higher empathy scores in girls with FXS were not likely due to group differences in general communication, social functioning, or autism. Taken together, empathy appears to be a relative strength rather than disability in girls with FXS compared to their developmentally-matched peers. One implication of these findings is that although difficulties associated with FXS in girls are partially attributed to impaired social skills (Mazzocco et al. 1997), these difficulties may not be rooted specifically in understanding and resonating with other people’s emotions. Overall, our use of parent reports of everyday behaviors hypothesized to reflect children’s dispositional empathy complements prior studies that assessed empathy and closely-related constructs in laboratory settings. Nevertheless, further research is needed to replicate our findings, particularly regarding affective empathy given the lack of prior FXS studies on this topic. Future studies of girls with FXS should assess whether parent-report measures of empathy like the GEM correlate with other kinds of lab-based assessments of empathy and related-constructs.

The MASC is a widely used self-report measure of anxiety symptoms in children and adolescents. Consistent with prior studies of anxiety in FXS using parent-report measures and clinical interviews (Cordeiro et al. 2011; Lachiewicz 1992), we found that girls with FXS self-reported higher overall levels of anxiety compared to the comparison group on the MASC. However, when examining each anxiety dimension separately, only the separation anxiety/phobias dimension was statistically significantly higher in girls with FXS. Specific phobia and, to a lesser extent, separation anxiety, are common anxiety symptoms in females with FXS (Cordeiro et al. 2011). In this context, our results suggest that under certain conditions, some girls with FXS may be capable of providing meaningful information about their own experiences of anxiety. Our study adds to a small but growing literature that utilizes self-report measures in an attempt to better understand mental health symptoms in neurodevelopmental disorders (Kaat and Lecavalier 2015; McCauley et al. 1995; Schiltz et al. 2017). It is worth noting, however, that we excluded some participants from these analyses due to their age or them not demonstrating an understanding of, or not providing answers to, MASC questions; the participants who were excluded were younger and had lower scores on daily living skills than those who provided MASC data. Further research is necessary to validate and determine the longitudinal stability of self-report measures of anxiety like the MASC for young girls with FXS.

Elevated affective empathy may indicate risk for anxiety problems in certain developmental contexts (Gambin and Sharp 2016; Tone and Tully 2014; Zahn-Waxler and Van Hulle 2012). In our study, the interaction between affective empathy and group status predicting separation anxiety and phobia symptoms did not reach statistical significance. On the other hand, the direction of the interaction effect suggested that at high, but not low, levels of affective empathy, FXS was associated with more severe separation anxiety and phobia symptoms. Heightened affective empathy may indicate risk in girls with FXS, but this finding should be interpreted with caution given that the interaction effect was a statistical trend. A larger sample, or consideration of parent-report measures of anxiety symptoms, may be needed to detect the moderating effect of affective empathy on risk for anxiety. In contrast, increased cognitive empathy in girls with FXS appeared to be a protective factor. We found that at higher levels of cognitive empathy, girls with FXS were not at increased risk for separation anxiety/phobia symptoms. Conversely, the FXS-related risk for reporting elevated separation anxiety/phobia symptoms was amplified in girls who received lower cognitive empathy scores. Our interaction effect between cognitive empathy and group status fits with the perspective that there are meaningful individual differences and moderators of the clinical phenotype in girls with FXS. Cognitive empathy processes such as perspective-taking may involve adopting a distanced, evaluative approach to understanding other people’s emotions (de Vignemont and Singer 2006; Decety and Lamm 2009). Thus, cognitive empathy processes may inherently regulate affective processes (Buffone et al. 2017; Miller et al. 2020), potentially including those implicated in anxiety problems. One interpretation of our findings is that cognitive empathy could be a useful target for interventions aimed at attenuating anxiety in girls with FXS. Existing social cognition training programs for children with autism (Didehbani et al. 2016) could be considered as possible anxiety interventions for girls with FXS. It is unclear, however, why we found dispositional cognitive empathy to have implications specifically for separation anxiety/phobia symptoms in girls with FXS. One possible explanation is that increased cognitive empathy is a developmental adaptation that buffers against forms of anxiety that girls with FXS are most at risk for experiencing. From a gene-behavior association perspective, diminished fragile x mental retardation protein (FMRP) in girls with FXS leads to disruptions in synaptic plasticity that likely contribute to anxiety (Spencer et al. 2005), but cognitive empathy in girls with FXS may indicate processes that counter this genetic risk. Further research that considers gene function, risk for anxiety, and empathy with other resilience factors could be a promising avenue for future FXS research.

This study had several limitations. First, empathy scores could have been biased by parental factors that differed across our FXS and comparison groups. As a related point, although the Griffith Empathy Measure is widely used, there has been recent debate over whether it provides valid differentiation of cognitive and affective empathy (Dadds 2019; Murphy 2017). Future research using experimental, observational, physiological, and multi-informant measures (Michalska et al. 2013; Miller 2018; Zhou et al. 2003) could complement our study findings and help further illuminate the nature of empathy in girls with FXS. Second, it is unclear whether our findings apply to young boys with FXS, who typically present a more severe clinical phenotype than girls. Thus, it remains possible that boys with FXS present deficits in cognitive and affective empathy, potentially as a result of reduced levels of FMRP. Third, future research should consider cognitive and affective empathy in girls with FXS compared to a typically developing control group. Fourth, given our cross-sectional and correlational study design, we cannot infer whether cognitive empathy plays a causal role in attenuating separation anxiety/phobia symptoms in girls with FXS. Finally, our sample size may have limited our ability to detect statistically significant differences between our FXS and comparison groups, particularly for interaction effects. Future studies with greater statistical power should be conducted to replicate our significant and null findings.

Despite these limitations, our study is important in providing the first evidence that girls with FXS may experience elevated empathy relative to girls with other developmental disorders. We administered a parent-report measure of empathy that is widely used in developmental psychology but had not previously been utilized in FXS research. We also administered a self-report measure of anxiety, and found that girls with FXS reported elevated anxiety, particularly separation anxiety/phobia symptoms. However, higher cognitive empathy in girls with FXS may be related to resilience against this specific form of anxiety.

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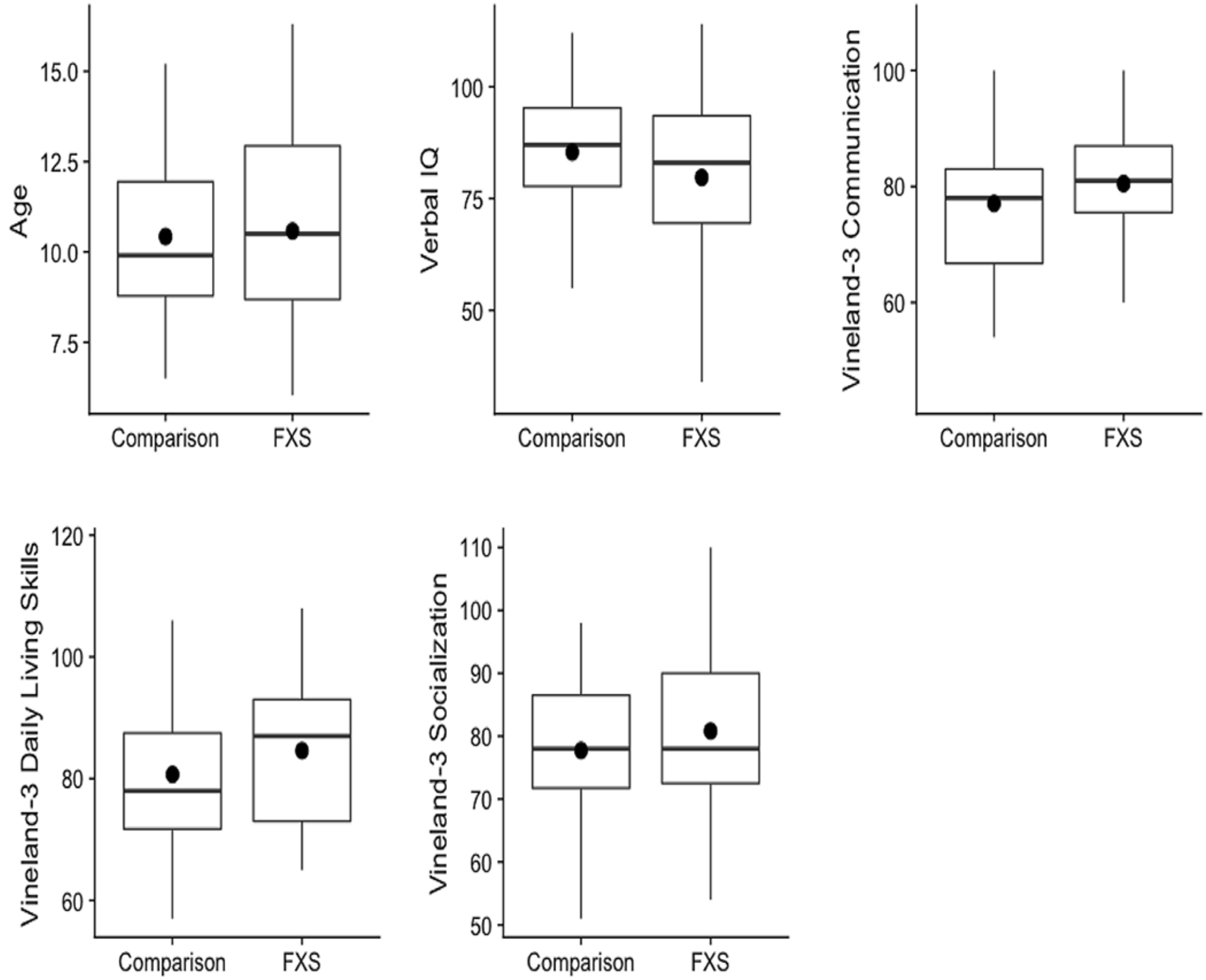

Figure 1.

Groups matched on age, verbal IQ. and adaptive behaviors.

Note. FXS = Fragile-X Syndrome. The black horizontal line inside of the box represents the median. The red dot represents the mean. Higher values reflect higher scores.

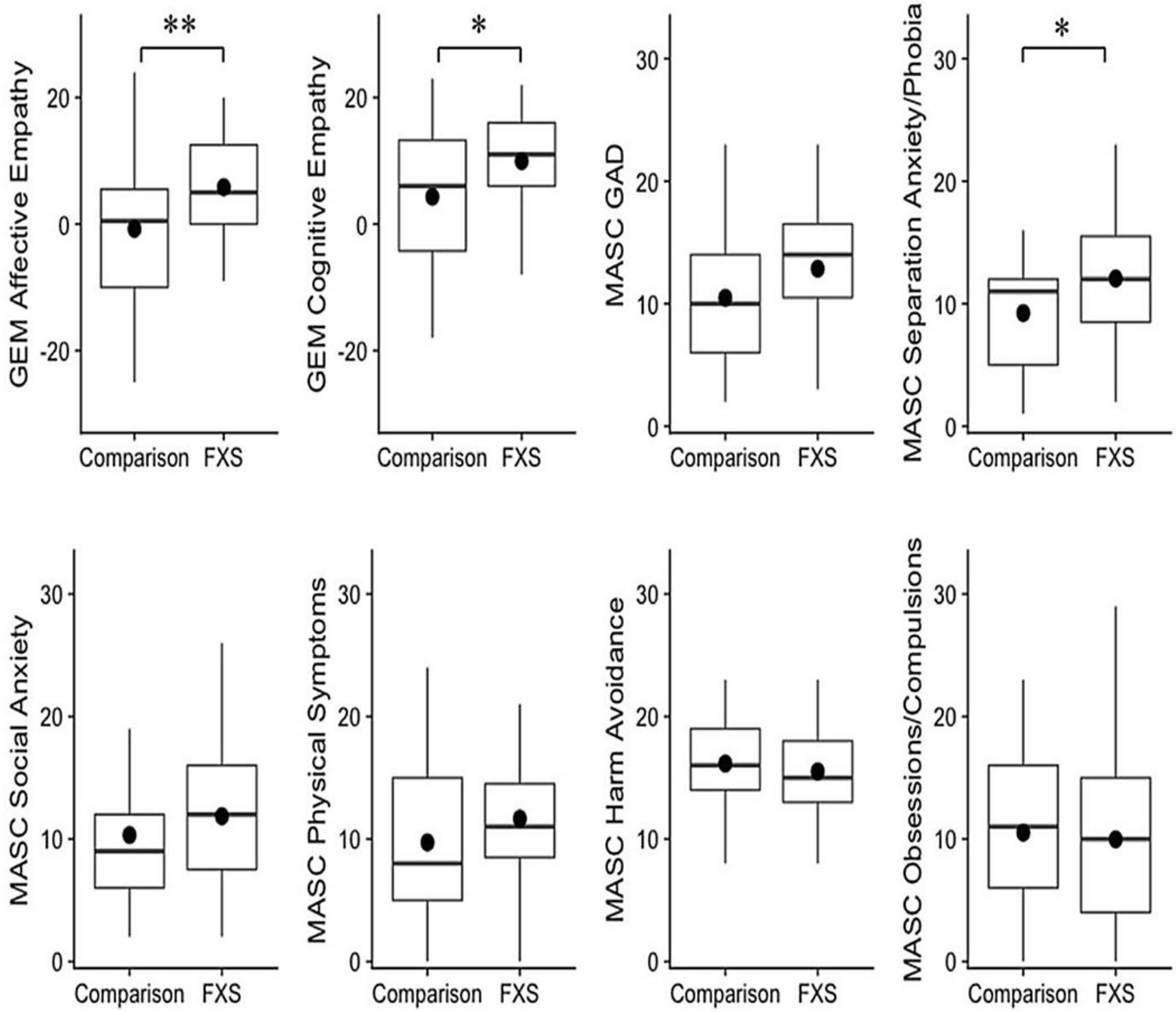

Figure 2.

Group differences in empathy and anxiety.

Note. FXS = Fragile-X Syndrome; GAD = Generalized Anxiety Disorder; GEM = Griffith Empathy Measure; MASC = Multidimensional Anxiety Scale for Children. The black horizontal line inside of the box represents the median. The black dot represents the mean. Higher values reflect higher scores. ** $p<.01$, * $p<.05$

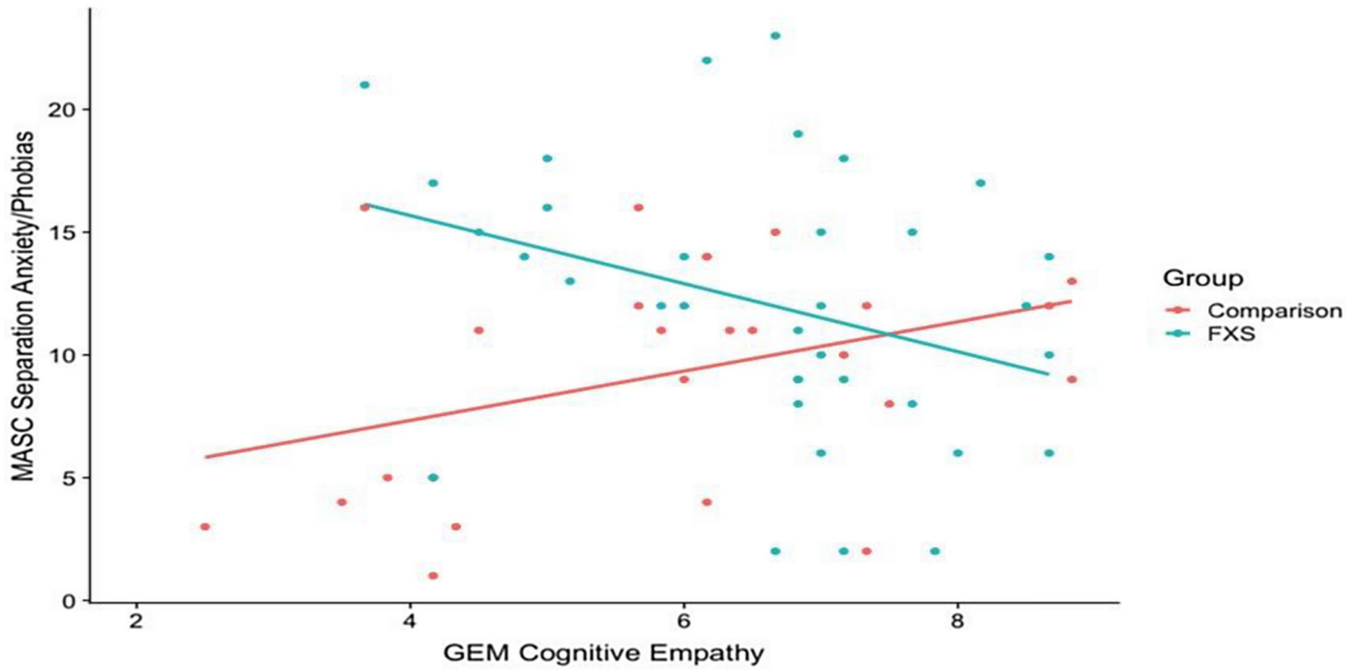

Figure 3.
Interaction between group status and cognitive empathy in predicting separation anxiety/ phobia symptoms.
Note. FXS = Fragile X Syndrome; GEM = Griffith Empathy Measure; MASC = Multidimensional Anxiety Scale for Children.

Table 1.

Descriptive statistics for age, verbal IQ, adaptive behaviors, and autism behaviors

	Total Sample			FXS Group			Comparison Group		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Age	10.51	2.65	6.03-16.31	10.58	2.86	6.03-16.31	10.43	2.37	6.50-15.21
DAS Verbal IQ	82.12	17.36	31-114	79.70	17.93	33-114	85.38	16.27	31-112
Vineland Communication	79.03	13.50	44-108	80.49	14.64	44-108	77.06	11.74	54-100
Vineland Daily Living Skills	82.93	12.96	57-118	84.60	12.09	65-108	80.69	13.93	57-118
Vineland Socialization	79.49	12.73	51-110	80.81	12.48	54-110	77.72	12.91	51-98
ADOS-2 Social Affect	5.91	4.64	0-19	6.58	4.70	1-19	5.00	4.49	0-16
ADOS-2 Restricted and Repetitive Behaviors	1.01	1.32	0-5	1.02	1.42	0-5	1.00	1.19	0-4
ADOS-2 Overall Total	6.92	5.30	0-21	7.60	5.37	1-21	6.00	5.15	0-17

Note. ADOS-2=Autism Diagnostic Observation Schedule, Second Edition; DAS=Differential Abilities Scale; FXS=Fragile X Syndrome.

Table 2.

Descriptive statistics for empathy and anxiety

	Total Sample			FXS Group			Comparison Group		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
GEM Affective Empathy	3.03	10.65	−25-24	5.84	9.21	−19-20	−0.75	11.41	−25-24
GEM Cognitive Empathy	7.55	9.79	−18-23	9.95	8.08	−8-22	4.31	11.02	−18-23
MASC Generalized Anxiety Disorder	11.87	5.67	0-23	12.86	5.48	0-23	10.48	5.75	2-23
MASC Separation Anxiety/Phobias	10.88	5.34	1-23	12.06	5.57	2-23	9.24	4.61	1-16
MASC Social Anxiety	11.22	6.14	2-26	11.86	6.14	2-26	10.32	6.15	2-26
MASC Physical Symptoms	10.85	6.39	0-31	11.66	6.39	0-31	9.72	6.34	0-24
MASC Harm Avoidance	15.78	4.10	3-23	15.51	4.35	3-23	16.16	3.77	8-23
MASC Obsessions/Compulsions	10.20	6.81	0-29	9.97	7.10	0-29	10.52	6.51	0-23

Note. GEM=Griffith Empathy Measure; MASC=Multidimensional Anxiety Scale for Children; FXS=Fragile X Syndrome.

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Table 3.

Regression model predicting MASC Separation Anxiety/Phobias

	MASC Separation Anxiety/Phobias			
	B	**SE**	***β***	***p***
Intercept	10.84	0.67		<001
Group status	3.38	1.36	.32	.016
Affective Empathy	0.05	0.06	.11	.431
Cognitive Empathy	−0.09	0.07	−.15	.242
Group x Affective Empathy	0.22	0.12	.23	.080
Group x Cognitive Empathy	−0.38	0.14	−.33	.011

Note. MASC=Multidimensional Anxiety Scale for Children. For Group status, the comparison group was coded as −0.5 and the FXS group was coded as 0.5 (Kraemer and Blasey, 2004).