Journal of Autism and Developmental Disorders (2020) 50:3957–3966
https://doi.org/10.1007/s10803-020-04459-7

ORIGINAL PAPER

Restricted and Repetitive Behaviors in Males and Females with Fragile X Syndrome: Developmental Trajectories in Toddlers Through Young Adults

Lauren J. Moskowitz[1] · Elizabeth A. Will[2] · Conner J. Black[2] · Jane E. Roberts[2]

Published online: 27 March 2020

Abstract
There is limited research on the trajectory of restricted and repetitive behaviors (RRBs) in fragile X syndrome (FXS), with previous studies only examining males and/or examining RRBs as a unitary construct rather than delineating subtypes of RRBs. Thus, we described the trajectory of five subtypes of RRBs in 153 males and females with FXS (aged 1–18 years) with repeated measurement over time (445 total assessments). Multilevel modeling was used to test age-related differences in RRB subtypes between males and females with FXS, controlling for nonverbal IQ. Results showed that lower-order Sensory-Motor behaviors decreased over time for both males and females, while there was no significant change in the higher-order RRBs. The trajectory between males and females differed for Self-Injury.

Keywords Fragile X syndrome · Repetitive behavior · Developmental trajectory · Sensory motor behaviors · Restricted interests · Self-injurious behavior

Developmental Trajectories of Restricted and Repetitive Behaviors in Males and Females with Fragile X Syndrome

Fragile X syndrome (FXS) is the most common heritable cause of intellectual disability (ID), with an estimated prevalence of approximately 1 in 4000–5000 males and 1 in 6000–8000 females (Coffee et al. 2009; Hunter et al. 2014). FXS is caused by a cytosine-guanine-guanine (CGG) repeat expansion on the *Fragile X Mental Retardation-1* (*FMR1*) gene on the X chromosome, resulting in a loss of production of Fragile X Mental Retardation Protein (FMRP), which is considered to be responsible for the physical and behavioral phenotype of FXS. Because FXS is an X-linked disorder, females are differentially affected, and often experience reduced symptomatology and lower rates of comorbid ID (Hagerman and Hagerman 2002; Reiss and Dant 2003). In addition to ID, FXS is also associated with a complex phenotypic profile that includes impairments in language and communication (Abbeduto et al. 2007), elevated physiological arousal (Klusek et al. 2013), socially avoidant behavior and anxiety (Cordeiro et al. 2011; Ezell et al. 2019; Roberts et al. 2019a, b), aggressive and self-injurious behavior (SIB) (Hall et al. 2008; Hessl et al. 2008), and restricted and repetitive behaviors (RRBs) (Lachiewicz et al. 1994). While many aspects of the FXS behavioral phenotype have been relatively well characterized, patterns of RRBs across age and in the context of sex and cognitive ability remain poorly characterized.

RRBs are highly prevalent in FXS, with elevated rates in FXS compared to other genetic syndromes associated with ID (Moss et al. 2009). In fact, virtually all males with FXS exhibit repetitive motor movements (Hall et al. 2016; Hessl et al. 2008) and the vast majority are reported to demonstrate repetitive questions (i.e., 76%; Woodcock et al. 2009), compulsions (i.e., 74%; Hall et al. 2008), and self-injurious behaviors (i.e., 58–71%; Hall et al. 2008, 2016). RRBs can directly interfere with day-to-day functioning and impede an individual's ability to learn from and attend to his or her environment (Leekam et al. 2011; Richler et al. 2010). Accordingly, it is critical to understand the nature, extent,

✉ Lauren J. Moskowitz
Moskowil@stjohns.edu

[1] Department of Psychology, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, USA

[2] Department of Psychology, University of South Carolina, Columbia, SC, USA

and trajectory of RRBs in FXS to adequately develop and implement targeted approaches to treatment.

From the existing empirical longitudinal work on RRBs in FXS, it is clear that there are differential trends in RRBs depending on age, but also measurement. Restricted interests and sensory-motor RRBs are reported as the most problematic in boys with FXS (Hall et al. 2016; Oakes et al. 2016; Roberts et al. 2008), compared to SIB and compulsions (Oakes et al. 2016; Wolff et al. 2012). Further, rates of RRBs appear to be higher earlier in development, but may decrease over time (Cochran et al. 2015). Decreasing trends are dependent, however, on the categorization of specific RRBs or lack thereof. Specifically, Cochran et al. (2015) reported decreases in overall RRBs (rather than across subtypes of RRBs) in males with FXS, whereas Sabaratnam et al. (2003) found specific increases in preference for sameness (i.e., changes in routine) over time and Crawford et al. (2018) found that most RRB's remained stable over time, with exceptions in repetitive questioning and restricted conversations. Thus, it is important to consider age-related trends in multiple subtypes of RRBs rather than just broad RRB (i.e., single category) because this latter approach may mask differential trends across subtypes of RRBs, which are unique and distinct categories of behavior (Bishop et al. 2013; Richler et al. 2010). Moreover, age-related trends in RRBs should be considered within more discrete developmental periods (e.g., childhood) rather than spanning very wide developmental windows (4–47 years, Cochran et al. 2015; 6–47 years, Crawford et al. 2018; and 6–76 years, Sabaratnam et al. 2003). A more refined demarcation in age will better characterize developmentally relevant trends and accurately inform targeted (i.e., developmentally sensitive) intervention.

There are additional factors that may influence RRBs, such as cognitive ability and sex. In terms of cognitive ability, several cross-sectional studies have found that lower IQ scores are associated with increased severity of ASD symptomatology in males with FXS (Bailey et al. 1998, 2008; Hall et al. 2010; Loesch et al. 2007; McDuffie et al. 2010) and that the severity of RRBs decreases as nonverbal IQ (NVIQ) increases in boys with FXS (Thurman et al. 2015). However, in a longitudinal study of boys with FXS between 6 and 10 years old, NVIQ was negatively related to Restricted Interests (a specific subtype of RRB) 18 months later (Oakes et al. 2016). In addition, variations in levels and trends of RRBs in FXS are found due to sex. This is consistent with expected differences in the overall FXS phenotype between males and females, given that females tend to be less affected overall, including in cognitive ability (Hagerman and Hagerman 2002; Reiss and Dant 2003). Females with FXS generally exhibit lower rates of overall problem behaviors (Freund et al. 1993) and RRBs compared to males (Hall et al. 2016). The existing empirical work on RRBs in FXS, which generally only includes males (Cochran et al. 2015; Crawford et al. 2018; Oakes et al. 2016) and fails to examine cognitive functioning (Cochran et al. 2015; Crawford et al. 2018), offers an incomplete characterization of the broad FXS phenotype, particularly given evidence of variation in RRBs by cognitive ability (Oakes et al. 2016), subtype (Oakes et al. 2016), and sex (Hall et al. 2008, 2016). Thus, further characterization of age-related trends in RRBs subtypes, while also accounting for sex-related trends and cognitive ability over time, is warranted.

Goals of the Present Study

Documenting the profile and developmental trajectory of RRBs is critical for advancing targeted interventions for this population as well as understanding the optimal ages on which to focus intervention efforts. As such, the main goal of the present study is to examine RRBs in a large group of children with FXS in order to ascertain a more thorough characterization of RRBs across age, sex, and subtype of RRB. Furthermore, given the likely influence of cognitive ability (Oakes et al. 2016), it is important to characterize RRBs across these factors while controlling for nonverbal IQ. Examining developmental trends in RRBs across various subtypes while considering additional factors of sex and cognitive ability will provide a more nuanced, fine-grained analysis of the ways in which specific subtypes of RRBs change or remain stable over time, which has implications for the development of interventions.

Methods

Participants

Participants included 153 youth diagnosed with FXS (see Table 1 for descriptive statistics) who completed between 1 and 5 ($M = 2.04$, $SD = 1.03$; total of 445) assessments between the ages of 1 and 18 years old. The sample had 192 (43.1%) observations in the toddler/preschool range, 126 (28.3%) in the school-aged range, and 127 (28.5%) in the adolescent range. FXS diagnosis was confirmed through genetic report revealing greater than 200 CGG repeats (i.e., full mutation FXS). Participant data was collected across multiple studies focused on early development in children with FXS at both the University of South Carolina (USC) and the University of North Carolina (UNC). Participants were included if they had at least one time point with data across all main variables.

Table 1 Participant demographic information

	Female ($n = 29$; obs. = 95)		Male ($n = 134$; obs. = 357)		Total ($n = 153$; obs. = 445)	
	Mean	SD	Mean	SD	Mean	SD
Age at initial enrollment (months)	55.46	44.78	87.11	55.98	80.57	55.32
Full scale IQ	71.14	19.10	52.38	11.22	56.70	15.57
Sensory motor	3.44	3.65	5.77	4.04	5.29	4.07
Restricted interests	0.80	1.20	1.78	1.69	1.58	1.65
Self-injury	1.82	2.99	3.01	3.41	2.76	3.36
Compulsive	3.47	3.75	3.60	4.44	3.57	4.30
Ritualistic sameness	3.82	4.40	5.00	5.22	4.76	5.08

Measures

Measures of Cognition

The *Mullen Scales of Early Learning* (*MSEL*; Mullen 1995) is a developmental measure used to assess cognitive abilities in 0–68 month-year-old children. This measure has been standardized across 1849 children in the United States and has satisfactory internal consistency (0.75–0.83) and test–retest reliability (0.76–0.84). Acceptable concurrent validity has been shown across a variety of other standardized test (Mullen 1995). Specifically, the MSEL assesses cognitive abilities across five domains: Gross Motor, Fine Motor, Visual Reception, Receptive Language, and Expressive Language. The composition of Fine Motor and Visual Receptions create a nonverbal composite score.

The *Differential Abilities Scales—Second Edition* (*DAS*; Elliott et al. 2007) is a measure designed to assess cognitive abilities in children between 2:6 and 17:11 years of age. The measure has been standardized across 3480 children in the United States and has excellent internal consistency (0.90–0.95) and satisfactory test–retest reliability (0.79–0.94). Acceptable concurrent validity across a wide range of other standardized measures (Elliot 2007). A nonverbal composite score can be calculated by using Matrices and Picture Similarities.

The *Leiter-R* (Roid and Miller 1997) is a measure of nonverbal intellectual ability in children between 2 and 20 years 11 months of age. The measure has been standardized across a sample of 1719 children across the United States and has acceptable internal consistency (0.75–0.90) and test–retest reliability (0.83–0.96). The Leiter-R has acceptable concurrent validity across a wide range of other standardized tests (Roid and Miller 1997). The nonverbal composite is created using four subtests: Figure Ground, Form Completion, Sequential Order, and Repeated Patterns.

Because the *MSEL*, *DAS*, and *Leiter-R* are inherently different and potentially non-comparable, but necessary at different ages in the study, Z-scores were computed from nonverbal IQ composite scores. This approach establishes a best approximation of equivalence across these measures and was subsequently used as a covariate in all models.

Measure of RRBs

The *Repetitive Behavior Scale—Revised* (*RBS-R*; Bodfish et al. 2000) was used to measure RRBs in participants with FXS. The *RBS-R* is a 43-item caregiver-report questionnaire that assesses a range of restricted and repetitive behaviors. Each item is scored on a four-point Likert scale ranging from 0 (behavior does not occur) to 3 (behavior occurs and is a severe problem). The *RBS-R* provides both a total score and six subscale scores, with the subscales conceptually derived rather than empirically derived through factor analysis. The six subscales of the *RBS-R* are: (1) *Stereotyped Behavior* (6 items; e.g., movements or actions of the whole body, head, hand/finger, etc. that are repeated in a similar manner; covering eyes or ears), (2) *Self-Injurious Behavior* (8 items; e.g., hits self, bites self, rubs or scratches self), (3) *Compulsive Behavior* (8 items; e.g., arranging/ordering, completeness, checking, repeating), (4) *Ritualistic Behavior* (6 items; performing activities of daily living in a similar manner; e.g., insists on certain play activities, repeats same topics during social interaction), (5) *Sameness Behavior* (11 items; resistance to change, insisting that things stay the same; e.g., resists changing activities; difficulty with transitions, insists on sitting at the same place), and (6) *Restricted Behavior* (4 items; e.g., fascination, preoccupation with one subject or activity, strongly attached to one specific object). The mean item score for each subscale (i.e., the "subscale score") ranges from 0 to 3.

The *RBS-R* was normed on individuals with intellectual disability and many studies have evaluated the factor structure of the *RBS-R* in individuals with ASD (Bishop et al. 2013; Harrop et al. 2014; Lam and Aman 2007; Mirenda et al. 2010). At the time of the present study, existing work has validated a 5-factor structure for the RBS (Bishop et al. 2013), and these were thus used in the present study.

These five factors were: (1) Sensory Motor, (2) Restricted Interests, (3) Self-injury, (4) Compulsive, and (5) Ritualistic/Sameness. These five factors are very similar to the six RBS-R subscales, with the biggest change being that the two subscales of Compulsive and Ritualistic behavior are essentially combined into one factor. This 5-factor structure made more sense conceptually to us than using the 6 subscales, given that many of the items from the *RBS-R* Ritualistic Behavior subscale (e.g., insists on certain pre-bedtime routines, insists on eating/drinking only certain things, insists on taking certain routes/paths) appear to overlap with items from the Sameness subscale (e.g., insists on walking in a particular pattern, insists on same routine, household, school, or work schedule every day).

Procedure

Ethical approval was obtained from both the University of South Carolina and the University of North Carolina institutional review board. Participants were recruited through local and national organization serving FXS populations. The majority of data was collected in each participant's home. After completion of each time point, participants received a brief developmental report and monetary compensation.

Analytic Approach

A multilevel modeling approach was used to test age-related differences in repetitive.

behavior domains between males and females with FXS controlling for nonverbal IQ. We used random slopes and random intercepts models because we anticipated individual variation in the level and trend of repetitive behavior over time. In the primary models, age was mean-centered ($M = 78.34$ months) and an age-by-sex interaction term was included. Significant age-by-sex interactions were further probed by re-centering age (Preacher et al. 2006) to determine at what specific ages males and females with FXS differed in their RRBs.

Results

Sensory-motor behavior

Sensory-motor models indicated that both males and females showed decreasing repetitive sensory-motor behaviors over time (see Fig. 1, Table 2), controlling for NVIQ. Males displayed more atypical repetitive sensory-motor behaviors than females that was evident at 78-months ($b = 3.02$; $p < 0.001$) and remained consistently higher than females across age as the age-by-sex

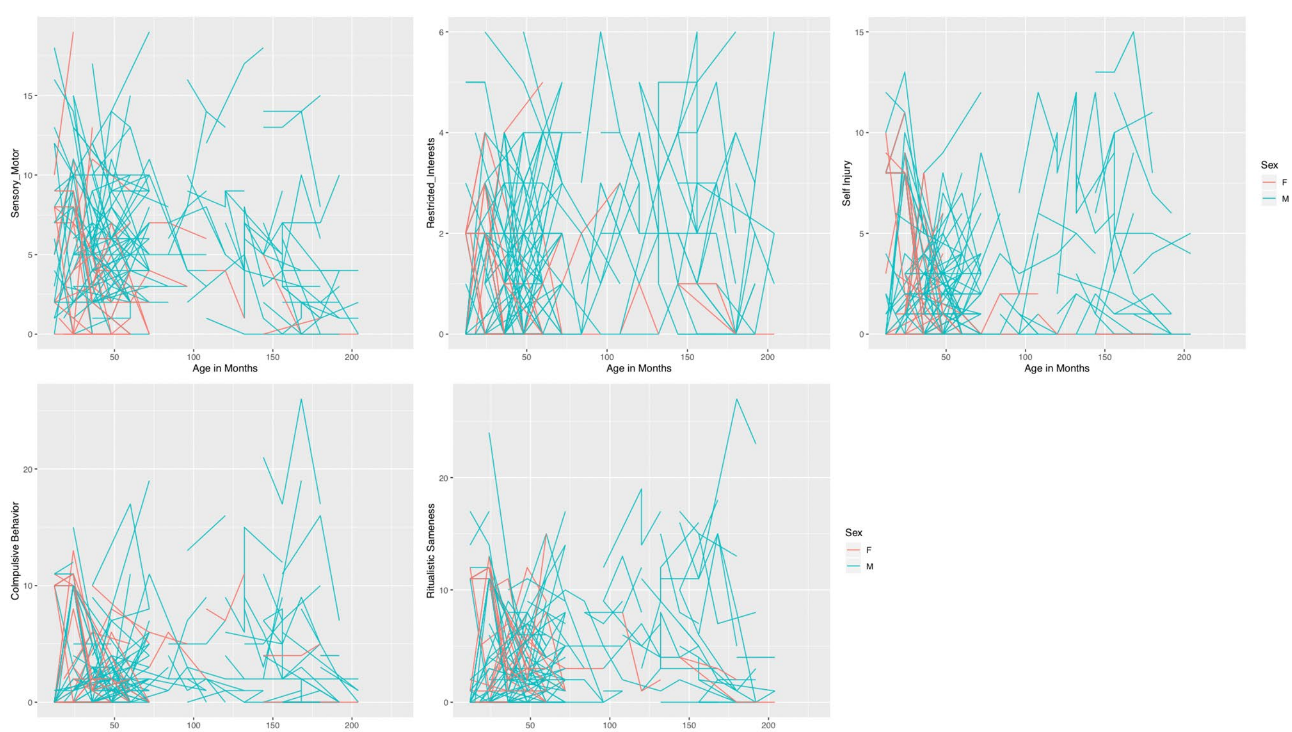

Fig. 1 Longitudinal trajectories of repetitive behaviors in males and females with FXS

Table 2 RBS model results

	Sensory motor			Restricted interests			Self-injury			Compulsive			Ritualistic sameness		
	b	*SE (b)*	*p*	*b*	*SE (b)*	*p*	*b*	*SE (b)*	*p*	*b*	*SE (b)*	*p*	*b*	*SE (b)*	*p*
Intercept	2.87	0.66	< .0001	0.77	0.27	.005	0.27	0.52	.611	2.33	0.67	< .001	2.85	0.79	< .001
Age	− 0.03	0.01	.041	− 0.00	0.00	.391	− .03	0.01	.002	− 0.02	0.01	.237	− 0.02	0.02	0.22
NVIQ	− 0.13	0.23	.575	− 0.08	0.09	.401	0.17	0.19	.347	0.51	0.24	0.031	0.32	0.28	.245
Male	3.03	0.74	< .0001	1.02	0.31	.001	2.42	0.58	< .0001	1.18	0.75	.119	1.86	0.88	0.036
Age:Male	0.01	0.01	.452	0.01	0.01	.234	0.03	0.01	.008	0.02	0.07	.155	0.03	0.02	.088

interaction was not significant ($b = 0.01$; $p = 0.45$; see Fig. 1). NVIQ was not a significant predictor of sensory-motor behavior for males ($b = 0.13$; $p = 0.576$) or females ($b = -0.13$; $p = 0.575$) with FXS.

Restricted Interests

Models for the restricted interest domain indicated no significant change across age for either males or females; however, it was noted that there was a trend for males to increase over time while the females demonstrated the tendency for a reduction over time (see Fig. 1, Table 2). Males displayed greater restricted interests at 78-months ($b = 1.02$; $p = 0.001$) than females and this persisted across age as the age-by-sex interaction was non-significant ($b = 0.006$; $p = 0.234$). NVIQ was also not a significant predictor of restricted interests for males ($b = -\ 0.08$; $p = 0.403$) or females ($b = -\ 0.08$; $p = 0.403$) with FXS.

Self-Injury

Self-injury models revealed that these behaviors changed over time and that males displayed more self-injurious behaviors than females by 78-months ($b = 2.42$; $p < 0.001$). The age-by-sex interaction term was significant ($b = 0.03$; $p = 0.008$), indicating a difference in the effect of age on self-injurious behavior between males and females. The results indicated that males demonstrated a stable and very slight increasing trend in their self-injury over time, whereas females demonstrated a sharp decrease in their self-injurious behavior over time ($b = -\ 0.04$; $p = 0.003$; see Fig. 1). Results from probing the age-by-sex interaction indicated that differences between males and females in their self-injurious behavior emerged at 48-months old ($b = 1.32$; $p = 0.01$) and became greater over time, with males scoring almost 2-points higher than females on self-injury domain by 60-months ($b = 1.76$; $p = 0.001$). NVIQ was not a significant predictor of self-injury for males ($b = 0.18$; $p = 0.346$) or females ($b = 0.17$; $p = 0.347$) with FXS.

Compulsive Behavior

Results from the compulsive behavior model indicated that these behaviors did not change over time ($b = -\ 0.02$; p = − 0.237) with no differences between males and females at any point in development (see Table 2 and Fig. 1). NVIQ was a significant predictor of compulsive behavior for males with FXS ($b = 0.51$; $p = 0.031$), such that an increased standard deviation in NVIQ was associated with a half-point increase in compulsive behavior scores for males. NVIQ was also a significant predictor of compulsive behavior for females with FXS ($b = 0.51$; $p = 0.0310$), such that each increase in standard deviation of IQ is associated with a half-point increase in compulsive behavior for females.

Ritualistic/Sameness

Results from the Ritualistic-Sameness models revealed that these behaviors did not change over time ($b = -\ 0.02$; $p = 0.221$). Sex effects were present at 78-months ($b = 1.86$; $p = 0.036$) with males demonstrating more ritualistic/sameness behaviors than females. The age-by-sex interaction approached significance ($b = 0.03$; $p = 0.088$). Results from subsequent models probing this interaction indicated a greater difference in ritualistic-sameness behavior between males and females at older ages. That is, no significant differences were identified prior to 78-months, but males and females were significantly different later on in their development, such that differences became greater each subsequent year, with males scoring significantly higher at 84-months ($b = 2.05$; $p = 0.03$) and 96-months ($b = 2.45$; $p = 0.03$) (see also Fig. 1 and Table 2). NVIQ was not a significant predictor of ritualistic/sameness behavior for males ($b = 0.32$; $p = 0.25$) or females ($b = 0.32$; $p = 0.245$) with FXS.

Summary

In general, males and females with FXS demonstrated differential trends in their RRB profiles over time. While both decreased in sensory-motor behaviors across age, males were significantly and consistently higher in these behaviors over time. Males also demonstrated higher rates of restricted interests, self-injury, and ritualistic-sameness behavior than females, though degree of differences varied somewhat across development. Compulsive behavior was one area that lacked age-related trends and sex differences, indicating this may not be prominent repetitive behavior in the FXS phenotype. However, higher NVIQ was associated with slight increases in compulsive behavior in males and females with FXS.

Discussion

Trajectory of RRBs Over Time

The primary aim of the present study was to examine the trajectories of RRBs over time in males and females with FXS from toddler age through early adulthood. We found that age, sex and NVIQ were related to RRBs in a somewhat complicated and nuanced manner. The results also suggested different patterns for lower versus higher order behaviors. These findings are important both for understanding the trajectory of RRBs across childhood through early adulthood but also to direct targeted treatments in terms of timing and specificity.

Specifically, we found developmental stability across "higher-order" (i.e., more complex, cognitively mediated) RRB domains, including Restricted Interests, Compulsive Behaviors, and Ritualistic/Sameness Behaviors, in males and females with FXS. These findings are consistent with previous research, which has identified minimal change in RRBs over time (Cornish et al. 2012; Crawford et al. 2018; Hernandez et al. 2009) or with chronological age (McDuffie et al. 2010; Thurman et al. 2015) for males with FXS. Whereas our results show stability in these three "higher-order" subtypes of RRBs, some prior research found a decrease in overall RRBs (Cochran et al. 2015) or in a single RRB item (Crawford et al. 2018; Sabaratnam et al. 2003). Discrepancies in developmental trends between our study and these prior studies are likely due to our more specific delineation of RRB subtypes, rather than broad RRBs measured as a unitary construct (Cochran et al. 2015), and/or differences in sample size and characteristics (i.e., age range, sex) relative to prior work (Sabaratnam et al. 2003).

In terms of lower-order RRBs (those requiring fewer advanced executive skills), we identified decreases in Sensory Motor behaviors over time, for both males and females, and a sharp decrease in Self-Injury over time for females. These results also substantiate previous cross-sectional research that found age-related decreases in Sensory Motor RRBs, specifically in the repetitive use of objects and hand/finger mannerisms, for youth with FXS + ASD (McDuffie et al. 2010). The decreasing trend in SIB for females, while males showed a relatively stable but slight increase in SIB over time, is also consistent with prior cross-sectional work on males and females with FXS (Symons et al. 2010) and a longitudinal study on males with FXS (Crawford et al. 2019).

Influences of Sex and IQ

Results indicate that males and females with FXS broadly demonstrated different trends in their RRB profiles over time, with Compulsive behaviors as the exception. More specifically, our results indicated sex differences, with Sensory-Motor behaviors, Restricted Interests, Self-injury, and Ritualistic/Sameness behavior elevated in males. These findings are consistent with prior cross-sectional work identifying higher rates of behavior across these domains in males compared to females with FXS (Hall et al. 2010; Symons et al. 2010), which confirmed the expectation that males would be more severely affected given the nature of this X-linked disorder. While examining RRBs in the context of comorbid ASD in FXS was beyond the scope of the present study, higher rates of RRBs in males could be accounted for by the fact that males with FXS show higher rates of ASD symptomatology than females with FXS (Clifford et al. 2007; Hall et al. 2008, 2010). Given prior work identifying that compulsions are more prevalent in boys with FXS compared to girls (Hall et al. 2008, 2010), it was somewhat surprising that no sex-related differences were identified in Compulsive behavior in the present study; however, this could again be due to the longitudinal nature of our study versus prior research.

We were also surprised to find that nonverbal IQ was not a significant predictor of Sensory-Motor behavior, Restricted Interests, SIB, or Ritualistic/Sameness behavior for males or females with FXS, given previous findings that the severity of RRBs decreases as NVIQ increases in boys with FXS (Thurman et al. 2015). However, we did find that NVIQ was a predictor of Compulsive behavior, in that higher NVIQ was associated with slight increases in Compulsive behavior in both males and females with FXS. This suggests that individuals with FXS who have milder ID may be more likely to engage in Compulsive behavior (e.g., ordering, completeness, checking) than individuals with a greater severity of ID, which mirrors prior work on compulsive behaviors in ASD (Bishop et al. 2006). Although prior work found no effect of full-scale IQ on the prevalence of or on the number of compulsions displayed by males or females with FXS (Hall et al. 2008), the results of the present study likely differ due to our use of nonverbal IQ instead of full-scale IQ, and/or due to the longitudinal design of our study.

Strengths, Limitations, and Future Research Directions

Our study is among the first to delineate developmental trends in RRBs in a large sample ($N = 153$) of youth with FXS spanning toddlerhood through middle childhood and adolescence. Additionally, this is the first longitudinal study on RRBs to include both males and females with FXS while directly examining sex differences in age-related trends in RRBs. Further, we also examined these trends while accounting for NVIQ. Finally, we examined RRBs across a validated factor structure (Bishop et al. 2013) of specific RRB subtypes, rather than broad/overall RRB, using a measure specific to RRBs rather than ASD (Bodfish et al. 2000; Scahill et al. 2015). Given that the ASD-specific measures used in prior research (e.g., *ADI-R*, *SCQ*) were designed to identify abnormalities relevant to diagnosing and screening for ASD, these measures capture RRBs broadly in the context of ASD symptomatology rather than subtle differences and changes in behavior specific to RRBs. This is an important distinction, given that RRBs are common across many genetic disorders associated with ID and are not unique to ASD.

Despite the present study's strengths, it is not without limitations. First, the use of a parent-report questionnaire might not produce the most accurate representation of RRBs in individuals with FXS. Although parent-report questionnaires can yield information about RRBs across a wide range of contexts, they are nevertheless subjective, and it is possible that higher-functioning individuals or younger children may exhibit more subtle RRBs that might not be as noticeable (Bishop et al. 2006; Esbensen et al. 2009). Thus, future studies should code RRBs from direct observation at several time points to more objectively record frequency, subtype, and severity of RRBs and corroborate the findings from this study, as has been done in ASD (Harrop et al. 2014). A second limitation of the present study is that our sample included a small subgroup of 12-month-old infants, and the *RBS-R* is not designed for infants (Wolff et al. 2014). Therefore, the *RBS-R* includes some items which may not be developmentally appropriate for this age group, such as compulsive item/object counting. Future research on RRBs in FXS should use a measure designed for this younger population, such as the *Repetitive Behavior Scale for Early Childhood* (*RBS-EC*; Wolff et al. 2016). However, inclusion of this very young group allowed us to examine trends over a large age span in childhood.

A third limitation is that the present study used multiple cognitive tests to assess NVIQ (with relatively unknown convergent validity between measures), although this is often the case in studies that include children of different ages and ability levels (Bishop et al. 2006). Related to this point, it is possible that correlating RRBs with NVIQ rather than verbal IQ (VIQ) or full-scale IQ (FSIQ) could be a limitation, given that relative strengths in verbal skills have been found in FXS, at least in terms of receptive verbal skills (Thurman et al. 2015). However, some individuals with FXS are nonverbal or minimally verbal. Given that we have NVIQ as our only measure of cognition on approximately 25% of the sample, using NVIQ in the analysis allowed us to represent the full range of males and females with FXS, including those individuals with FXS who have difficulty understanding verbal instructions and providing verbal responses (see Cornish et al. 2012). This use of NVIQ is in line with previous research on RRBs in FXS (Oakes et al. 2016; Thurman et al. 2015).

Finally, given that only a small subset of the participants in the present study had data available to confirm an ASD diagnosis, we were unable to consider ASD status of participants when analyzing our results. This is important, given that there may be a different profile and trajectory of RRBs for individuals with FXS who also have ASD versus those who do not have ASD (see Crawford et al. 2018). Thus, future research on the longitudinal course of RRBs in FXS should account for comorbid ASD, especially in light of the theory that children with FXS who meet diagnostic criteria for ASD may meet criteria because of elevated repetitive motor behavior (Wolff et al. 2012). Related to this, given that we did not include a comparison group with other developmental disabilities (e.g., ASD, Down syndrome), it is unclear the extent to which our findings are specific to FXS. Future research on the trajectory of RRBs in FXS could benefit from including comparison groups as well as from examining RRBs in sub-groups of individuals with FXS (e.g., FXS-Only versus FXS+ASD, FXS+anxiety).

Summary and Implications

The current study details the trajectory of RRBs in males and females with FXS from toddler age to young adulthood. Specifically, we found that both males and females with FXS demonstrated improvement in repetitive Sensory-Motor behaviors (which, along with SIB, are often classified as "lower-order" RRBs), but that Restricted Interests, Compulsive behaviors, and Ritualistic/Sameness behaviors ("higher-order" RRBs) did not significantly improve over time in our sample. This provides further support for previous research suggesting that RRBs should not be viewed as a unitary construct (Richler et al. 2010). We also demonstrated sex differences in the trajectories of certain subtypes of RRBs, as males demonstrated consistently higher levels of Sensory-Motor behaviors, Restricted Interests, and Ritualistic-Sameness behaviors over time and more stability in SIB compared to females. It is important for future studies to investigate which variables—such as anxiety and hyper- or hypo-arousal—are predictive of these different RRB trajectories.

Understanding life-course changes and sex differences in RRBs for those with FXS, especially females who are traditionally underrepresented in research, has important implications for the creation of targeted treatments for this population. Although some RRBs might not warrant intervention and can even be seen as a strength to be harnessed, other RRBs represent a significant barrier to learning and social functioning, serve as a major source of parental stress, and—in the case of SIBs—are physically harmful. Our finding that higher-order RRBs did *not* improve over time in individuals with FXS suggests that these behaviors might be particularly important to target in intervention. After all, some researchers have suggested that higher-order RRBs can be even more impairing than lower-order RRBs to both individuals with ASD (Bodfish et al. 2000) and their caregivers (South et al. 2005), although it is unclear if the same is true for those with FXS. While there is a lack of intervention research that is specifically focused on addressing RRBs in individuals with ASD (Uljarević et al. 2017), with even fewer intervention studies targeting higher- than lower-order RRBs (Boyd and Wakeford, 2013; Harrop et al. 2014), non-medical intervention studies targeting RRBs in FXS are virtually nonexistent. In fact, a systematic review of behavioral interventions in FXS identified studies that targeted SIB, but not any other RRBs (Moskowitz and Jones 2015). Given the lack of improvement in Restricted Interests, Compulsive behaviors, and Ritualistic/Sameness behaviors over time, developing interventions to address these specific subtypes of RRBs might be the most beneficial future direction for individuals with FXS.

Acknowledgments We gratefully acknowledge the families who participated in this study for their time and dedication. We also wish to thank Megan Braconnier and Iris Garza, who assisted with manuscript preparation.

Author Contribution LJM conceptualized the manuscript, wrote the initial draft of the manuscript, participated in the design of the study and interpretation of the data, and reviewed and revised the manuscript. EAW performed the statistical analysis, participated in interpretation of the data, wrote the Results section, created the Figures, and helped revise the manuscript. CJB participated in conducting the statistical analysis, assisted with interpretation of the data, and drafted the Methods section. JER conceived of and designed the larger longitudinal study from which the data were drawn, participated in the design and interpretation of the data for this study, and revised the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abbeduto, L., Brady, N., & Kover, S. T. (2007). Language development and fragile X syndrome: Profiles, syndrome-specificity, and within-syndrome differences. *Mental Retardation and Developmental Disabilities Research Reviews, 13*(1), 36–46.

Bailey, D. B., Jr., Mesibov, G. B., Hatton, D. D., Clark, R. D., Roberts, J. E., & Mayhew, L. (1998). Autistic behavior in young boys with fragile X syndrome. *Journal of Autism and Developmental Disorders, 28*(6), 499–508.

Bailey, D. B., Jr., Raspa, M., Olmsted, M., & Holiday, D. B. (2008). Co-occurring conditions associated with FMR1 gene variations: Findings from a national parent survey. *American Journal of Medical Genetics Part A, 146*(16), 2060–2069.

Bishop, S. L., Hus, V., Duncan, A., Huerta, M., Gotham, K., Pickles, A., et al. (2013). Subcategories of restricted and repetitive behaviors in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 43*(6), 1287–1297.

Bishop, S. L., Richler, J., & Lord, C. (2006). Restricted and repetitive behaviors and non-verbal IQ in children with autism spectrum disorders. *Journal of Child Neuropsychology, 12*(4–5), 247–267.

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties in repetitive behavior in autism: Comparisons to mental retardation. *Journal of Autism and Developmental Disorders, 30*(3), 237–243.

Clifford, S., Dissanayake, C., Bui, Q. M., Huggins, R., Taylor, A. K., & Loesch, D. Z. (2007). Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *Journal of Autism and Developmental Disorders, 37*(4), 738–747.

Cochran, L., Moss, J., Nelson, L., & Oliver, C. (2015). Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X, and Cri du Chat syndromes: Results from a 2.5 year follow-up. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 169*(2), 188–197.

Coffee, B., Keith, K., Albizua, I., Malone, T., Mowrey, J., Sherman, S. L., et al. (2009). Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. *American Journal of Human Genetics, 85*(4), 503–514.

Cordeiro, L., Ballinger, E., Hagerman, R., & Hessl, D. (2011). Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: Prevalence and characterization. *Journal of Neurodevelopmental Disorders, 3*, 57–67.

Cornish, K., Cole, V., Longhi, E., Karmiloff-Smith, A., & Scerif, G. (2012). Does attention constrain developmental trajectories in fragile X syndrome? A 3-year prospective longitudinal study. *American Journal on Intellectual and Developmental Disabilities, 117*(2), 103–120.

Crawford, H., Karakatsani, E., Singla, G., & Oliver, C. (2019). The persistence of self-injurious and aggressive behavior in males with fragile X syndrome over 8 years: A longitudinal study of prevalence and predictive risk markers. *Journal of Autism & Developmental Disorders, 49*(7), 2913–2922.

Crawford, H., Moss, J., Stinton, C., Singla, G., & Oliver, C. (2018). Overactivity, impulsivity and repetitive behaviour in males with fragile X syndrome: Contrasting developmental trajectories in those with and without elevated autism symptoms. *Journal of Intellectual Disability Research, 62*(8), 672–683.

Elliott, C. D. (2007). *Differential ability scales* (2nd ed.). San Antonio, TX: Harcourt Assessment.

Esbensen, A. J., Seltzer, M. M., Lam, K. S. L., & Bodfish, J. W. (2009). Age-related differences in restricted repetitive behaviors in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*(1), 57–66.

Ezell, J., Hogan, A., Fairchild, A., Hills, K., Klusek, J., Abbeduto, L., et al. (2019). Prevalence and predictors of anxiety disorders in adolescent and adult males with autism spectrum disorder and fragile X syndrome. *Journal of Autism & Developmental Disorders, 49*(3), 1131–1141.

Freund, L. S., Reiss, A. L., & Abrams, M. T. (1993). Psychiatric disorders associated with fragile X in the young female. *Pediatrics, 91*(2), 321–329.

Hagerman, R. J., & Hagerman, P. J. (2002). *Fragile X syndrome: Diagnosis, treatment, and research* (3rd ed.). Baltimore: Johns Hopkins University Press.

Hall, S., Lightbody, A. A., & Reiss, A. L. (2008). Compulsive, self-injurious and autistic behavior in children and adolescents with fragile X syndrome. *American Journal on Mental Retardation, 113*(1), 44–53.

Hall, S. S., Barnett, R. P., & Hustyi, K. M. (2016). Problem behaviour in adolescent boys with fragile X syndrome: Relative prevalence, frequency and severity. *Journal of Intellectual Disability Research, 60*(12), 1189–1199.

Hall, S. S., Lightbody, A. A., Hirt, M., Rezvani, A., & Reiss, A. L. (2010). Autism in fragile X syndrome: A category mistake? *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(9), 921–933.

Harrop, C., McConachie, H., Emsley, R., Leadbitter, K., & Green, J. (2014). Restricted and repetitive behaviors in autism spectrum disorders and typical development: Cross-sectional and longitudinal comparisons. *Journal of Autism and Developmental Disorders, 44*(5), 1207–1219.

Hernandez, R. N., Feinberg, R. L., Vaurio, R., Passanante, N. M., Thompson, R. E., & Kaufmann, W. E. (2009). Autism spectrum disorder in fragile X syndrome: A longitudinal evaluation. *American Journal of Medical Genetics Part A, 149A*, 1125–1137.

Hessl, D., Tassone, F., Cordeiro, L., Koldewyn, K., McCormick, C., Green, C., et al. (2008). Brief report: Aggression and stereotypic behavior in males with fragile x syndrome—moderating secondary genes in a "single gene" disorder. *Journal of Autism and Developmental Disorders, 38*(1), 184–189.

Hunter, J., Rivero-Arias, O., Angelov, A., Kim, E., Fotheringham, I., & Leal, J. (2014). Epidemiology of fragile X syndrome: A systematic review and meta-analysis. *American Journal of Medical Genetics Part A*, *164*(7), 1648–1658.

Klusek, J., Martin, G. E., & Losh, M. (2013). Physiological arousal in autism and fragile X syndrome: Group comparisons and links with pragmatic language. *American Journal on Intellectual and Developmental Disabilities, 118*(6), 475–495.

Lachiewicz, A. M., Spiridigliozzi, G. A., Gullion, C. M., Ransford, S. N., & Rao, K. (1994). Aberrant behaviors of young boys with fragile X syndrome. *American Journal on Mental Retardation, 98*(5), 567–579.

Lam, K. S., & Aman, M. G. (2007). The repetitive behavior scale-revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 37*(5), 855–866.

Leekam, S. R., Prior, M. R., & Uljarevic, M. (2011). Restricted and repetitive behaviors in autism spectrum disorders: A review of research in the last decade. *Psychological Bulletin, 137*(4), 562–593.

Loesch, D. Z., Bui, Q. M., Dissanayake, C., Clifford, S., Gould, E., Bulhak-Paterson, D., et al. (2007). Molecular and cognitive predictors of the continuum of autistic behaviours in fragile X. *Neuroscience & Biobehavioral Reviews, 31*(3), 315–326.

McDuffie, A., Abbeduto, L., Lewis, P., Kim, J. S., Weber, A., & Brown, W. T. (2010). Autism spectrum disorder in children and adolescents with fragile X syndrome: Within syndrome differences and age-related changes. *American Journal on Intellectual and Developmental Disabilities, 115*(4), 307–326.

Mirenda, R., Smith, I. M., & Vaillancourt, T. (2010). Validating the repetitive behavior scale-revised in young children with autism spectrum disorder. *Journal of Autism Developmental Disorders, 40*(12), 1521–1530.

Moss, J., Oliver, C., Arron, K., Burbidge, C., & Berg, K. (2009). The prevalence and phenomenology of repetitive behavior in genetic syndromes. *Journal of Autism and Developmental Disorders, 39*(4), 572–588.

Mullen, E. M. (1995). *Mullen scales of early learning* (pp. 58–64). Circle Pines, MN: AGS.

Oakes, A., Thurman, A. J., McDuffie, A., Bullard, L. M., Hagerman, R. J., & Abbeduto, L. (2016). Characterising repetitive behaviours in young boys with fragile X syndrome. *Journal of Intellectual Disability Research, 60*(1), 54–67.

Preacher, K. J., Curran, P. J., & Bauer, D. J. (2006). Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *Journal of Educational and Behavioral Statistics, 31*(4), 437–448.

Reiss, A. L., & Dant, C. C. (2003). The behavioral neurogenetics of fragile X syndrome: Analyzing gene–brain–behavior relationships in child developmental psychopathologies. *Development and Psychopathology, 15*(4), 927–968.

Richler, J., Huerta, M., Bishop, S. L., & Lord, C. (2010). Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. *Development and Psychopathology, 22*(1), 55–69.

Roberts, J. E., Crawford, H., Hogan, A. L., Fairchild, A., Tonnsen, B., Brewe, A., et al. (2019b). Social avoidance emerges in infancy and persists into adulthood in fragile X syndrome. *Journal of Autism & Developmental Disorders, 49*(9), 3753–3766.

Roberts, J. E., Crawford, H., Will, E. A., Hogan, A. L., McQuillin, A., Tonnsen, B. L., et al. (2019a). Infant social avoidance predicts autism but not anxiety in fragile X syndrome. *Frontiers in Psychiatry, 10*, 199.

Roberts, J. E., Mankowski, J. B., Sideris, J., Goldman, B. D., Hatton, D. D., Mirret, P. L., et al. (2008). Trajectories and predictors of the development of very young boys with FXS. *Journal of Pediatric Psychology, 34*(8), 827–836.

Sabaratnam, M., Murthy, N. V., Wijeratne, A., Buckingham, A., & Payne, S. (2003). Autistic-like behaviour profile and psychiatric morbidity in fragile X Syndrome: A prospective ten-year follow-up study. *European Child & Adolescent Psychiatry, 12*(4), 172–177.

Scahill, L., Aman, M. G., Lecavalier, L., Halladay, A. K., Bishop, S. L., Bodfish, J. W., et al. (2015). Measuring repetitive behaviors as a treatment endpoint in youth with autism spectrum disorder. *Autism, 19*(1), 38–52.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive behavior profiles in Asperger syndrome and high-functioning autism. *Journal of Autism and Developmental Disorders, 35*(2), 145–158.

Symons, F. J., Byiers, B. J., Raspa, M., Bishop, E., & Bailey, D. B., Jr. (2010). Self-injurious behavior and fragile X syndrome: Findings from the national fragile X survey. *American Journal on Intellectual and Developmental Disabilities, 115*(6), 473–481.

Thurman, A. J., McDuffie, A., Kover, S. T., Hagerman, R. J., & Abbeduto, L. (2015). Autism symptomatology in boys with fragile X syndrome: A cross sectional developmental trajectories comparison with nonsyndromic autism spectrum disorder. *Journal of Autism and Developmental Disorders, 45*(9), 2816–2832.

Uljarević, M., Arnott, B., Carrington, S. J., Meins, E., Fernyhough, C., McConachie, H., et al. (2017). Development of restricted and repetitive behaviors from 15 to 77 months: Stability of two distinct subtypes? *Developmental Psychology, 53*, 1859–1868.

Wolff, J. J., Bodfish, J. W., Hazlett, H. C., Lightbody, A. A., Reiss, A. L., & Piven, J. (2012). Evidence of a distinct behavioral phenotype in young boys with fragile X syndrome and autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(12), 1324–1332.

Wolff, J. J., Botteron, K. N., Dager, S. R., Elison, J. T., Estes, A. M., Gu, H., et al. (2014). Longitudinal patterns of repetitive behavior in toddlers with autism. *Journal of Child Psychology and Psychiatry, 55*(8), 945–953.

Wolff, J. J., Boyd, B. A., & Elison, J. (2016). A quantitative measure of restricted and repetitive behaviors for early childhood. *Journal of Neurodevelopmental Disorders, 8*, 27.

Woodcock, K. A., Oliver, C., & Humphreys, G. W. (2009). Associations between repetitive questioning, resistance to change, temper outbursts and anxiety in Prader-Willi and Fragile-X syndromes. *Journal of Intellectual Disability Research, 53*, 265–278.