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

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Abstract

Restricted and repetitive behaviors (RRBs) frequently occur in individuals with fragile X syndrome (FXS). However, there is limited research focused on the trajectory of RRBs in FXS, and this work has only examined males with FXS and/or has examined RRBs as a unitary construct rather than delineating specific subtypes of RRBs. Thus, we aimed to develop a profile of the trajectory of five subtypes of RRBs in both males and females with FXS. Participants were 153 individuals 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, in terms of trajectory, both males and females with FXS showed a decrease in lower-order Sensory-Motor behaviors over time, while there was no significant change in the higher-order Restricted Interests, Compulsive behaviors, or Ritualistic/Sameness behaviors over time for either males or females. The trajectory between males and females differed for Self-Injury; males demonstrated a stable and very slight increasing trend in their SIB over time, whereas females showed a sharp decrease in their SIB over time. Higher nonverbal IQ was associated with slight increases in compulsive behavior. Understanding how RRBs change over time and the predictors of RRB in FXS has implications for the advancement of targeted interventions.

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 4,000–5,000 males and 1 in 6,000–8,000 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

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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 & Hagerman, 2002; Reiss & Dant, 2003). In addition to ID, FXS is also associated with a complex phenotypic profile that includes impairments in language and communication (Abbeduto, Brady, & Kover, 2007), elevated physiological arousal (Klusek, Martin, & Losh, 2013), socially avoidant behavior and anxiety (Cordeiro, Ballinger, Hagerman, & Hessel, 2011; Ezell et al., 2019; Roberts et al., 2019a, 2019b), aggressive and self-injurious behavior (SIB) (Hall, Lightbody, & Reiss, 2008; Hessel et al., 2008), and restricted and repetitive behaviors (RRBs) (Lachiewicz, Spiridigliozzi, Gullion, Ransford, & Rao, 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, Oliver, Arron, Burbidge, & Berg, 2009). In fact, virtually all males with FXS exhibit repetitive motor movements (Hall, Barnett, & Hustyi, 2016; Hessel et al., 2008) and the vast majority are reported to demonstrate repetitive questions (i.e., 76%; Woodcock, Oliver, & Humphreys, 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, Huerta, Bishop, & Lord, 2010). Accordingly, it is critical to understand the nature, extent, 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, Moss, Nelson, & Oliver, 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; Bailey, Raspa, Olmsted, & Holiday, 2008; Hall, Lightbody, Hirt, Rezvani, & Reiss, 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, McDuffie, Kover, Hagerman, & Abbeduto, 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 & Hagerman, 2002; Reiss & Dant, 2003). Females with FXS generally exhibit lower rates of overall problem behaviors (Freund, Reiss, & Abrams, 1993) and RRBs compared to males (Hall et al., 2016). The existing empirical work on RRB's 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.

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 (.75-.83) and test-retest reliability (.76-.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, Murray, & Pearson, 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 (.90-.95) and satisfactory test-retest reliability (.79-.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 & 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 (.75-.90) and test-retest reliability (.83-.96). The *Leiter-R* has acceptable concurrent validity across a wide range of other standardized tests (Roid & 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 & Aman, 2007; Mirenda, Smith, & Vaillancourt, 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 5 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, Curran, & Bauer, 2006) to determine at what specific ages males and females with FXS differed in their RRBs.

Results

Sensory-motor behaviour

Sensory-motor models indicated that both males and females showed decreasing repetitive sensory-motor behaviors over time (see Figure 1, Table 2), controlling for NVIQ. Males

displayed more atypical repetitive sensory-motor behaviors than females that was evident at 78-months ($b = 3.02$; $p < .001$) and remained consistently higher than females across age as the age-by-sex interaction was not significant ($b = 0.01$; $p = .45$; see Figure 1). NVIQ was not a significant predictor of sensory-motor behavior for males ($b = 0.13$; $p = .576$) or females ($b = -0.13$; $p = .575$) 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 Figure 1, Table 2). Males displayed greater restricted interests at 78-months ($b = 1.02$; $p = .001$) than females and this persisted across age as the age-by-sex interaction was non-significant ($b = 0.006$; $p = .234$). NVIQ was also not a significant predictor of restricted interests for males ($b = -0.08$; $p = .403$) or females ($b = -0.08$; $p = .403$) 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 ($b = 2.42$; $p < .001$). The age-by-sex interaction term was significant ($b = 0.03$; $p = .008$), 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 Figure 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 ($b = 1.32$; $p = .01$) and became greater over time, with males scoring almost 2-points higher than females on self-injury domain by 60-months ($b = 1.76$; $p = .001$). NVIQ was not a significant predictor of self-injury for males ($b = .18$; $p = .346$) or females ($b = 0.17$; $p = .347$) with FXS.

Compulsive behaviour

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 Figure 1). NVIQ was a significant predictor of compulsive behavior for males with FXS ($b = 0.51$; $p = .031$), 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 ($b = 0.51$; $p = .031$), 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 ($b = 1.86$; $p = .036$) with males demonstrating more ritualistic/sameness behaviors than females. The age-by-sex interaction approached significance ($b = 0.03$; $p = .088$). 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 ($b = 2.05; p = .03$) and 96-months ($b = 2.45; p = .03$) (see also Figure 1 and Table 2). NVIQ was not a significant predictor of ritualistic/sameness behavior for males ($b = 0.32; p = .25$) or females ($b = .32; p = .245$) 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, or 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, Cole, Longhi, Karmiloff-Smith, Scerif, 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, Byiers, Raspa, Bishop, & Bailey, 2010) and a longitudinal study on males with FXS (Crawford, Karakatsani, Singla, & Oliver, 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; Hall et al., 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 milder ID with FXS 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, Richler, & Lord, 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 study 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, Seltzer, Lam, & Bodfish, 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, Boyd, & Elison, 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, McDuffie, Hagerman, Josol, & Abbeduto, 2017). 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, Cole, Longhi, Karmiloff-Smith, & Scerif, 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, 2004) and their caregivers (South, Ozonoff, & McMahon, 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 & 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 & 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.

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Figure 1.
Longitudinal Trajectories of Repetitive Behaviors in Males and Females with FXS

Table 1.

Participant Demographic Information

	Female (<i>n</i> =29; obs.=95)		Male (<i>n</i> =134; obs.=357)		Total (<i>n</i> =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

Table 2.

RBS model Results

	Sensory Motor			Restricted Interests			Self-Injury			Compulsive			Ritualistic Sameness		
	<i>b</i>	<i>SE(b)</i>	<i>p</i>	<i>b</i>	<i>SE(b)</i>	<i>p</i>	<i>b</i>	<i>SE(b)</i>	<i>p</i>	<i>b</i>	<i>SE(b)</i>	<i>p</i>	<i>b</i>	<i>SE(b)</i>	<i>p</i>
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