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Adaptive Skill Trajectories In Infants With Fragile X Syndrome

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ADAPTIVE SKILL TRAJECTORIES IN INFANTS WITH FRAGILE X SYNDROME

by

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ABSTRACT

This study examined longitudinal trajectories of adaptive behavior in infants with fragile X syndrome (FXS), compared to typical development (TD) and infant siblings of children diagnosed with autism (ASIBs). Additional analysis were conducted to examine the differences in trajectories for males and females with FXS, and to identify if a profile of strengths and weaknesses appeared across domains by 24 months in males with FXS. Participants included 76 male infants assessed up to 4 times between 6 and 24 months of age. A sample of 12 females with FXS was also included for the comparative sex analysis. Infants with FXS displayed lower initial adaptive behavior across all domains, and slower growth rates than both comparison groups. Differences in initial status and growth rates were different between males and females depending on the domain measured. No significant profile of strengths and weaknesses was identified in infants with FXS at 24 months.

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LIST OF ABBREVIATIONS

ADOS..... Autism Diagnostic Observation Schedule

AOSI .....Autism Observation Scale for Infants

ASD..... Autism Spectrum Disorder

ASIB .....Younger Sibling of Child with Autism

FXS .....Fragile X Syndrome

TD .....Typically Developing Controls

CHAPTER 1

INTRODUCTION

Fragile X syndrome (FXS) is a rare single gene disorder that occurs at a rate of approximately 1 in 5000 in males (Coffee et al., 2009). FXS, caused by a CGG repeat expansion on the FMR1 gene, results in almost universal intellectual disability, and a comorbid diagnosis of autism spectrum disorder in approximately 60% of individuals (Harris et al., 2008). While a diagnosis of FXS can be made prenatally, the average age of diagnosis remains at around 3 years of age in the absence of a family history (Bailey, Raspa, Bishop, & Holiday, 2009) highlighting a significant delay to detection, which may result in the loss of access to early intervention. Early intervention is especially important given that delays in cognitive, motor and language development have been detected by 9 months of age for infants with FXS (Roberts et al., 2009). Additionally, a recent paper (Roberts, Tonnsen, McCary, Caravella & Shinkareva, under review) identified significantly greater levels of autism symptomatology in infants with FXS than typically developing controls and younger siblings of children diagnosed with autism (ASIB) by 12 months of age, highlighting the early emergence of atypical social skills by the end of the first year of life in many infants with FXS. Despite the importance of early identification and treatment, only a handful of studies exist that characterize the infant behavioral and adaptive behavior phenotype in FXS.

Adaptive behavior consists of a range of skills that encompass an individual's ability to function independently in their environment, to take care of themselves and get along with others (Cicchetti & Sparrow, 1990). Adaptive development is typically sequential, with foundational skills developing in infancy and young childhood, which allow for the emergence of more complex skills into adulthood. Therefore, the mastery of early adaptive skills is essential for developing the skills necessary for later independence. Adaptive behavior profiles are of importance to the study of FXS given the almost universal cognitive impairment present in FXS, and the inclusion of adaptive behavior impairments in the conceptualization of intellectual disability. Additionally, adaptive behaviors have been found to be the strongest predictor of independence in adulthood in individuals with FXS (Hartley et al., 2011), therefore understanding the early development of these skills can assist in treatment planning and prognostic indicators. Adaptive skills measure an individuals' ability to translate learned skills into consistent independent use in home, school, community and vocational settings, therefore they are essential to lifelong independence, an important goal for many individuals with disabilities.

It has been established that individuals with FXS exhibit adaptive behavior deficits, often equal to one half of their chronological age. These deficits appear as early as toddlerhood (McCary, Machlin, & Roberts, 2014; Rogers, Wehner, & Hagerman, 2001) and are maintained throughout childhood (Fisch, Simensen, & Schroer, 2002; Hahn, Brady, Warren, & Fleming, 2015; Hatton et al., 2003) and early adolescence (Frolli, Piscopo, & Conson, 2014; Klaiman et al., 2014). Although impaired overall in comparison to chronological age matched peers, research has aimed to identify patterns

of strengths and weaknesses among individuals with FXS. A consistent pattern of strengths and weaknesses in adaptive skills in FXS has not been established in the literature. Some research suggests a relative strength in daily living skills (Dykens et al., 1996; Hatton et al., 2003), while others report strengths in the domain of socialization (Frolli et al., 2014; Klaiman et al., 2014). In direct contrast, daily living skills (Frolli et al., 2014) and socialization have been identified as a weakness in other reports (Hahn et al., 2015; Klaiman et al., 2014) The most consistent finding across studies appears to be a relative weakness in the area of adaptive communication (Dykens et al., 1996; Frolli et al., 2014; Klaiman et al., 2014; Rogers et al., 2001). These contrasting findings may reflect the varying age groups with which the previous studies were conducted, suggesting that patterns of strengths and weaknesses may change across development. Less is known about the domain of adaptive motor development in FXS, given that it has been excluded from many previous analyses due to the norm scores being limited to children under the age of 6.

In addition to domains of strengths and weaknesses, questions about growth in adaptive skills over time have been an important area of research in FXS. Limitations exist in the consistency across work in methodology (i.e. linear growth models vs. mean comparisons/correlations) and score types used in analyses (i.e. raw scores/age equivalent vs. standard scores). These inconsistencies contribute to what appear to be contradictory findings. A summary of the primary findings of this body of work is presented in Table 1.1. Research that has utilized raw or age equivalent scores has reported overall growth in adaptive skills through middle childhood in males with FXS, with plateaus or declines evidenced thereafter. Hatton and colleagues (2003) and Hahn and colleagues (2015) used

hierarchical linear modeling to examine adaptive skill development from toddlerhood (i.e., 1-2 years old) through middle childhood (i.e., 10 -11 years old). Both studies reported growth in adaptive functioning across time. A cross-sectional study by Dykens and colleagues (1996) also examined children with FXS between the ages of 1 and 10, and reported a positive relationship between age and composite adaptive behavior, suggesting increasing skill acquisition with age. Additionally, both Dykens et al. (1996) and Hahn et al., (2015) results suggest a slowing, plateau or slight loss of adaptive skills for individuals with FXS beginning around the age of 10. Although the studies by Hatton et al. (2003), Hahn et al. (2015) and Dykens et al. (1996) included children as young at 1, 2, and 2 years old respectively, average ages of the participants at first time point in each study were 6.3, 2.8 and 3.8 years respectively, limiting the inference of these findings to children under the age of 2.

In contrast to these studies reporting growth in skills in individuals with FXS, research utilizing standard scores has reported mixed findings. Fisch et al. (2002) and Frolli et al. (2014) utilized repeated measures designs with 2 and 3 time points respectively. Fisch (2002) and colleagues reported declines in all domains of adaptive behavior standard scores between the ages of 5 and 11 years while Frolli and colleagues (2014) reported increases between the ages of 9 and 15 in the domains of communication and socialization, while daily living skills remained constant. With a significantly larger sample and age range that encompassed both age cohorts in the previously reviewed two studies (2-18 years), Klaiman and colleagues (2014) utilized hierarchical liner modeling of standard scores and identified declines in all domains over time, which contradicts the findings reported by Frolli et al. (2002). These contradictory findings may be due in part

to the contrasting analytical methods, with Frolli et al.'s (2002) work examining discrete changes between two time points finding growth of at most 7 standard score points over time, while Klaiman et al.'s (2015) paper utilized growth models which intentionally smooth small changes between time points to identify an average growth trajectory. Taken together this body of work suggests that rates of growth in adaptive behavior in FXS are slower than would be expected of typically developing peers, resulting in overall delays across all domains.

In addition to time, predictors of adaptive behavior skills examined in the literature include autism symptomatology and sex. Fragile X syndrome has the highest known penetrance of autism spectrum disorder of any known single gene disorder. Symptoms of autism appear to compound the impact of FXS on adaptive behavior skill development. Multiple studies have reported more severe adaptive skill impairment in individuals with FXS who exhibit higher levels of autistic features (Cohen, 1995; Hahn et al., 2015; Hatton et al., 2003; Hustyi et al., 2014; Rogers et al., 2001). Across these studies, the gap between chronological age and age equivalent increases proportionally over time, with differences in age equivalent scores of a few months for toddlers with and without a co-morbid ASD diagnosis (Hatton et al., 2003; Rogers et al., 2001) resulting in gaps of over two years by the time individuals reach 10 years old (Hatton et al., 2003).

Across multiple studies (Hahn et al., 2015; Hatton et al., 2003; Klaiman et al., 2014) girls with FXS exhibit less severe impairments in their adaptive behavior development, and appear to gain skills at a faster rate than their chronologically age matched male counterparts. Similarly, research has also found that females with FXS evidence more independence in adulthood than FXS males, which is directly related to

their adaptive skill development (Hartley et al., 2011). This is consistent with other work supporting a overall milder impairment in females with FXS likely due to the presence of their second X chromosome, which is unaffected by the FMR1 mutation (Hagerman, Rivera, & Hagerman, 2008; Huddletson, Visootsak, & Sherman, 2014).

Adaptive Development in Infancy. Research examining early development in infants with FXS is limited, with no work currently published examining adaptive skill development in the first two years of life. This is due, in part, to the delay to diagnosis present in many families, with the average age around 3 years of age and the overall rarity of the disorder. However, given that FXS can be diagnosed prenatally or at birth, prospective research can follow those detected early in life to gather essential information about the time course of early development. Similar prospective models have become extensively used with ASIBs, allowing researchers to measure behaviors and developmental patterns in infancy before a diagnostic decision about autism can be confidently made.

Given the elevated risk of ASD in both ASIBs (20%) (Ozonoff et al., 2011) and FXS infants (60%), ASIBs serve as an important comparison group at high risk for developing autism. However, research examining adaptive behavior in infant ASIBs is also limited. The authors identified two studies that reported analysis of adaptive behavior in ASIBs less than 2 years old (Estes et al., 2015; Toth, Dawson, Meltzoff, Greenson, & Fein, 2007). One compared 20-month-old ASIBs without ASD to an age matched low risk control group, and identified lower mean scores on all adaptive behavior domains, with the exception of communication in the high risk group, when compared to the control group. These findings suggest that even when autism does not

develop, ASIBs evidence lower adaptive functioning than low risk children. In contrast, Estes and colleagues (2015) did not find differences between unaffected ASIBs and low risk controls on adaptive behavior scores between 6 and 24 months of age. These contradictory findings may represent the inherent heterogeneity in ASIB samples (Landa, Gross, Stuart, & Bauman, 2012; Ozonoff et al., 2014) given the vast variability in outcome functioning in this high-risk group, these two samples of ASIBs presented in these studies may not be equivalent in behavioral phenotype.

In summary, adaptive behaviors in children with FXS appear to be delayed, emerging as early as toddlerhood. Adaptive skill growth appears to peak by middle childhood with overall adaptive functioning reaching maximum age equivalent levels of between 5 to 7 years old (Dykens et al., 1996; Hatton et al., 2006). Additionally, autism symptomatology appears to lead to more severe impairment in adaptive functioning in individuals with FXS. Sex also appears to have an impact on adaptive skill development, with girls with FXS gaining skills at a faster rate than males resulting in overall higher skill acquisition. However, research has not yet investigated adaptive skills in infancy to determine when these deficits first appear, how these skills develop across the first two years of life, their relationship with early emerging symptoms of autism, and how this differs between males and females. To our knowledge, no study has utilized a prospective longitudinal design to examine adaptive behavior development in infants with FXS.

Current Study. This study aims to address gaps in the literature by examining adaptive behavior development in FXS infants with 4 research questions:

1. Do adaptive behavior trajectories differ between infants with FXS, ASIBs and a typically developing control group? We hypothesize that infants with FXS will

evidence lower levels of adaptive functioning beginning at 9 months and exhibit slower growth rates than both comparison groups.

2. Is autism symptom severity related to growth in adaptive behavior skills across the first two years of life in infants with FXS syndrome? We hypothesize that elevated autism symptomatology will be related to slower rates of adaptive skill acquisition over time.
3. Do infants with FXS at 24 months show specific strengths or weaknesses in particular areas of adaptive behavior functioning? We hypothesize that infants with FXS will show strengths in the domains of socialization and motor skills, while showing weaknesses in the areas communication and daily living.
4. Do males and females with FXS show differences in adaptive skill trajectories in the first two years of life? We hypothesize that female infants with FXS will evidence higher initial adaptive skills and faster growth rates than males with FXS.

Table 1.1 Summary of Literature Examining Adaptive Behavior in Fragile X Syndrome Across Development

First Author	Year	FXS n	Sex	Metric	Sample	Age	Analysis	Primary Conclusions
Dykens	1996	132 Group 1 = 44 Group 2 = 42 Group 3 = 28 Group 4 = 16	Males	Age equivalent scores	Cross-sectional	Group 1: 1-5 Group 2: 6-10 Group 3: 11-15 Group 4: 16-20	Correlation	Age and scores are positively correlated between 1-5 years, and 6-10 years. No correlation between age and scores were found between 11-20 years.
Hatton	2003	70	60 Males 10 females	Age equivalent scores	Longitudinal (2-8 time points m = 4.4)	1-11, mean = 6.3 years	HLM	Positive growth in overall adaptive skill acquisition over time.
Hahn	2015	55	44 Males 11 Females	Raw Scores	Longitudinal, 3 to 5 time points (M = 4.87)	2-10 years	HLM	Positive growth through middle childhood, with some evidence of minor declines.
Klaiman	2014	275	186 Males 89 Females	Standard scores	Longitudinal (1-4 times points)	Time 1: 9.12 years	HLM	Standard scores decreased over time. This decrease was greater in males than females.
Frolli	2014	47	Males	Standard scores	Longitudinal, 3 time points	Time 1: 9-11 years (M = 10.25 years) Time 2: 11-13 years Time 3: 13-15 years	Repeated measures ANOVA	Domains of Communication and Socialization increased over time, daily living skills remained stable.
Fisch	2002	18 Group 1= 8 Group 2 = 10	Males	Standard Scores	Longitudinal (2 time points, 2 cohorts)	Group 1: M = 5 years Group 2: M = 8 years	Repeated Measures MANOVA	Declines in adaptive behavior composite over time in both age cohorts.

CHAPTER 2

METHOD

Participants

Participants included 76 male infants who are part of a larger longitudinal study on identification of early behavioral and biomarkers of autistic features in infants at high risk for developing ASD. The primary focus of this study was infants with FXS (n= 25). Comparison groups included infant siblings of children already diagnosed with autism (ASIB) (n=27), and children with no family history of ASD, who are at low risk of developing the disorder, and display typical development at 24 months (Typically Developing, TD) (n= 24).

A prospective longitudinal design was utilized. Infants were seen at 6 *(M*=6.43, *SD* =0.67), 9 (*M*=9.29, *SD* =0.56), 12 months (*M*=12.61, *SD* =0.81) and 24 months (*M* = 24.75, *SD* = 0.92) In total, data from 215 assessments are included in the analyses, 57 FXS, 86 ASIB and 72 TD. Characteristics of the sample are presented in Table 2.1. Variability in the age of assessment was present given the design of the primary study that focused on 9, 12 and 24 months across the three groups while a complementary study extended these assessments to 6 months but focused on the ASIBs and TD groups only, with 6 month assessments in the FXS group conducted opportunistically. All infants included in the study had between 1 and 4 assessments, with 83% of participants having at least 2 assessments. A subset of 12 female infants with FXS, who were seen at the

same time intervals was added to the sample to facilitate preliminary analysis of sex differences in adaptive skill trajectories.

For infants in the FXS group, confirmation of the diagnosis was documented by a genetic report. For the infants in the ASIB group, confirmation of a diagnosis of ASD in the older sibling was confirmed through a review of a diagnostic report that was completed by a licensed psychologist or physician with knowledge of the diagnosis of ASD. To meet eligibility criteria for the low risk TD group, the infant could have no documented history of ASD in the family and display typical development at 24 months. Typical development was defined as no developmental delay (Mullen Early Learning Composite > 85) and an absence of elevated autism features (ADOS-2 severity score < 4). Exclusion criteria for all participants included diagnosis of a medical condition (other than FXS), premature birth before 37 weeks or birth weight less than <2000 grams, families whose predominant language in the home was not English and infants who were adopted.

Participants were most commonly recruited through passive means such as letters and pamphlets distributed through community settings, such a pediatricians offices and parent groups. To target the FXS and ASIB cohorts, recruitment materials were sent through listservs, parent support groups, social media groups, and service provision centers exclusive to these two populations. Additionally, collaborations with researchers having access to samples with FXS and utilization of the University of North Carolina Fragile X research registry were essential for recruitment of the FXS sample.

Measures

Adaptive Behavior. The Vineland Adaptive Behavior Scales- II, Survey Form (Sparrow et al., 2005), is a semi-structured caregiver interview designed to measure an individual's current adaptive behavior functioning in four domains, Communication, Socialization, Daily Living Skills and Motor Skills. Individual items are scored on the frequency with which the individual completes the behavior independently, usually (2), sometimes (1), or never (0). Raw scores for each domain are determined by a sum of the item scores. Higher scores indicate higher levels of adaptive skill development. Raw scores will be utilized in all growth curve analyses in this paper due to the fact that standard scores will already be corrected for time (i.e. standardization by age), making true growth in skills more difficult to measure in a linear growth model. Standard scores (M = 100, SD = 15) will be utilized in the profile analysis to improve interpretability, given that raw scores cannot be directly compared across domains.

The Vineland has been validated for individuals from birth to 99 years of age. Out of the entire norming sample of over 1000 individuals, 470 infants between 0 to 2 years were included. Mean reliability scores on the four domains for this age group is as follows: communication= .91, daily living skills = .84, socialization = .92, motor skills = .93.

Autism Symptomatology in Infancy. The Autism Observation Scale for Infants (AOSI) (Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008) is a direct observation scale designed to identify behaviorally observed symptoms of autism in infants 6 to 18 months of age. Throughout the 20-minute measure, infants are engaged in two free play sessions, and behavioral presses from the examiner designed to target

specific behaviors, including visual tracking and disengagement, social engagement, sensory behaviors and vocalizations. Behaviors are rated on a scale from 0 to 3 (0 = typical response/absence of atypical response, 3 = great atypicality) and a total score is calculated. Total scores of 9 or more denote a behavioral presentation that signifies autism risk and has been found to be predictive of a best estimate diagnosis of autism at 3 years of age (Bryson, 2005). Total scores on the AOSI at 12 months are used in the analysis.

Autism Symptomatology at 24 months. The Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al., 2012) is a play based semi-structured assessment designed to press for social interaction to rate the presence of behaviors consistent with a diagnosis of autism spectrum disorder. Five modules are available (Toddler, 1-4) which differ based on the child's age and language level. Behaviors are generally rated on a 0-3 scale (0 = typical response/absence of atypical response, 3 = great atypicality), and a total score is calculated. To compare scores across modules, a calibrated severity score can be obtained from the total score on each module. Calibrated severity scores are used in the analyses as a measure of autism symptom severity. A subset of 19 infants with FXS received an ADOS at 24 months consistent with the study design. The remaining FXS participants (n=5) are missing ADOS data at 24 months, due to their not yet aging to 24 months at the time of this analysis (n=4), or a missing ADOS administration at 24 months (n=1).

Developmental Level. The Mullen Scales of Early Learning (Mullen) is a standardized developmental assessment for children ages 0-60 months that measures skills in five areas of development, expressive language, receptive language, fine motor,

gross motor and visual reception. Each domain has a T-score of 50 and a standard deviation of 10. A summary standard score, called the early learning composite (ELC) is generated from the domains (with the exclusion of gross motor). The ELC has a mean of 100, and standard deviation of 15. ELC was used to rule out developmental delays in the TD group.

Procedure

Families participated in informed consent at their first visit, and all procedures were conducted in compliance with the USC Institutional Review Board. At the 6 and 12-month visits, infants and their families came to lab at the University of South Carolina. While at their visit, the Vineland, Mullen and AOSI were collected. Trained graduate students and research staff administered Vinelands and Mullens. AOSIs were administered by research staff who obtained official administration and coding reliability (>80%) with the developers of the measure. To minimize travel burden on the families, research staff traveled to the family's homes to administer all measures for the 9 and 24 month visits where procedures were identical to those administered in the lab environment. In lieu of the AOSI at the 24 month visit, participants were administered an ADOS-2 by research reliable administrators. A sample of 20% of all AOSI and ADOS administration were scored from tapes of the administrations for inter-rate reliability. Participants were compensated for their time.

Data Analysis

Statistical Analysis was completed using R (R Core Team, 2013). Descriptive statistics were used to characterize the sample. To address the study's primary aims of examining trajectories of adaptive skill development, multilevel modeling was used.

Multilevel modeling is ideal for these analyses given its robustness to uneven time points and missing data. Age was centered at 9 months (Age in Months– 9) so that the intercept is interpreted as the average predicted adaptive behavior functioning at 9 months of age. Slopes and intercepts were allowed to vary randomly. Separate models were estimated for each of the 4 Vineland domains, Communication, Socialization, Daily Living and Motor skills. Assumptions of homogeneity of variance and multivariate normality were examined visually with no violations identified. All parameter estimates without accompanying p-values reported in the text are statistically significant at a .05 alpha level.

To examine profiles of adaptive behavior skills across domains, a one sample Hotelling's T-square profile analysis was conducted at the 24-month time point. Lastly, trajectories of all domains on the Vineland were compared between males and female infants with FXS with multilevel models. Given the small sample sizes for females (n=12) and greater missing data, those results are presented as preliminary.

Table 2.1 Sample Characteristics

Variable Age in Months	FXS n=25	TD n=24	ASIB n=27
Sample Size			
6	6	17	15
9	14	21	21
12	17	16	27
24	20	18	23
Age			
6	6.64 (1.05)	6.28 (0.52)	6.51 (0.65)
9	9.45 (0.76)	9.13 (0.37)	9.35 (0.55)
12	12.74 (0.92)	12.29 (0.39)	12.72 (0.89)
24	25.02 (1.03)	24.63 (0.93)	24.62 (0.79)
Vineland[1]			
24	75.10 (9.48)	97.50 (9.08)	91.96 (8.27)
Mullen[2]			
24	57.50 (9.81)	105.93 (14.03)	85.52 (17.28)
AOSI[3]			
12	10.76 (5.52)	4.88 (3.72)	7.41 (4.57)
ADOS[4]			
24	6.16 (3.08) (n=19)	1.53 (0.74) (n=15)	4.09 (2.6) (n=22)

[1]Adaptive Behavior Composite
[2]Early Learning Composite
[3]AOSI Total Score
[4]ADOS Calibrated Severity Score

CHAPTER 3

RESULTS

Research Question 1: Do adaptive behavior trajectories differ between infants with FXS, ASIBs and a typically developing control group?

At 9 months of age, infants with FXS evidenced lower adaptive socialization skills compared to both comparison groups, scoring on average 7 points lower than TD infants (β =7.13, SE = 1.29) and 6 points lower than ASIBs (β = 5.73, SE = 1.28). These differences become greater with time, as TD (β = 0.95, SE = 0.26) and ASIBs (β = 0.52, SE = 0.25) gain adaptive socialization skills at a faster rate than FXS infants.

Differences in adaptive communication skills are also evident by 9 months in FXS infants. On average, FXS infants score 7 points lower than TD infants (β = 6.62, SE = 1.03) and 5 points lower than ASIBs (β = 4.70, SE = 1.02). Growth rates also differed, with TD (β = 1.84, SE = 0.31) and ASIB (β = 1.03, SE = 0.29) infants gaining adaptive communication skills at a faster rate than infants with FXS.

Differences in daily living skills were also evident by 9 months of age in FXS infants, who scored on average 3 points lower than both TD (β = 3.42, SE = 0.70) and ASIBs (β = 2.85, SE = 0.69). Growth rates also differed, with TD (β = 0.88, SE = 0.15) and ASIB (β =0.52, SE = 0.14) infants gaining daily living skills at a faster rate than infants with FXS.

Adaptive motor skills were lower in FXS infants at 9 months of age, with FXS infants scoring on average 11 points lower than TD infants (β = 10.69, SE = 1.91), and 6

points lower than ASIBs (β = 6.49, SE = 1.88). FXS infants gained skills at a slower rate than both TD (β = 0.72, SE = 0.19) and ASIBs (β = 0.91, SE = 0.18). Results from these 4 models are presented in Figure 3.1.

Research Question 2: Is autism symptom severity related to growth in adaptive behavior skills across the first two years of life in infants with FXS?

Two separate growth models were run to examine the relationship between adaptive behavior and autism symptomatology at 12 and 24 months, respectively. A subset of 17 infants received the AOSI. Across all domains, AOSI scores were not related to adaptive behavior scores at 9 months or growth rates. A subset of 19 infants with FXS has ADOS scores. Across all domains, average adaptive behavior scores at 9 months were not related to autism symptom severity at 24 months. However, symptom severity at 24 months was related to growth in adaptive behavior for the domains of socialization (β = -0.11, SE = 0.05), communication (β = -0.15, SE = 0.06) and approaching statistical significance in daily living (β = -0.06, SE = 0.03, p = .06). Across these three domains, higher autism severity scores were related to slower rates of growth in adaptive skills. Autism symptom severity was not related to growth rates in the adaptive motor skills domain (0.82).

Research Question 3: Do infants with FXS show specific strengths or weaknesses in particular areas of adaptive behavior functioning at 24 months of age?

A one-sample profile analysis was run to examine the hypothesis of flatness across domains of adaptive functioning using Hotelling's T-square. Results indicated that the profile was flat (p = .41), suggesting that at 24 months infants with FXS do not yet show a distinct profile of strengths or weaknesses across the four domains of adaptive

functioning. Means and 95% confidence intervals across the four domains are presented in Figure 3.2.

Research Question 4: Do males and females with FXS show differences in adaptive skill trajectories in the first two years of life?

To examine sex differences in adaptive behavior trajectories in infancy in FXS, a sample of 12 female infants with FXS was added to the sample of 25 males with FXS. Growth trajectories were compared for males and females with FXS across all domains of adaptive functioning. At 9 months of age, females were found to have higher scores in the domains of socialization (β = - 8.13, SE =2.84) and motor (β =-9.90, SE = 3.23). Rates of change for both of these domains were not significant. The opposite relationships were found in the communication and daily living domains, where initial scores at 9 months were not found to be different between the sexes, however females gained skills at faster rates than males in both communication (β = -0.60, SE = 0.27) and daily living (β = -0.43, SE = 0.15) leading to greater discrepancies in scores as the infants got older. These trajectories are presented in Figure 3.3.

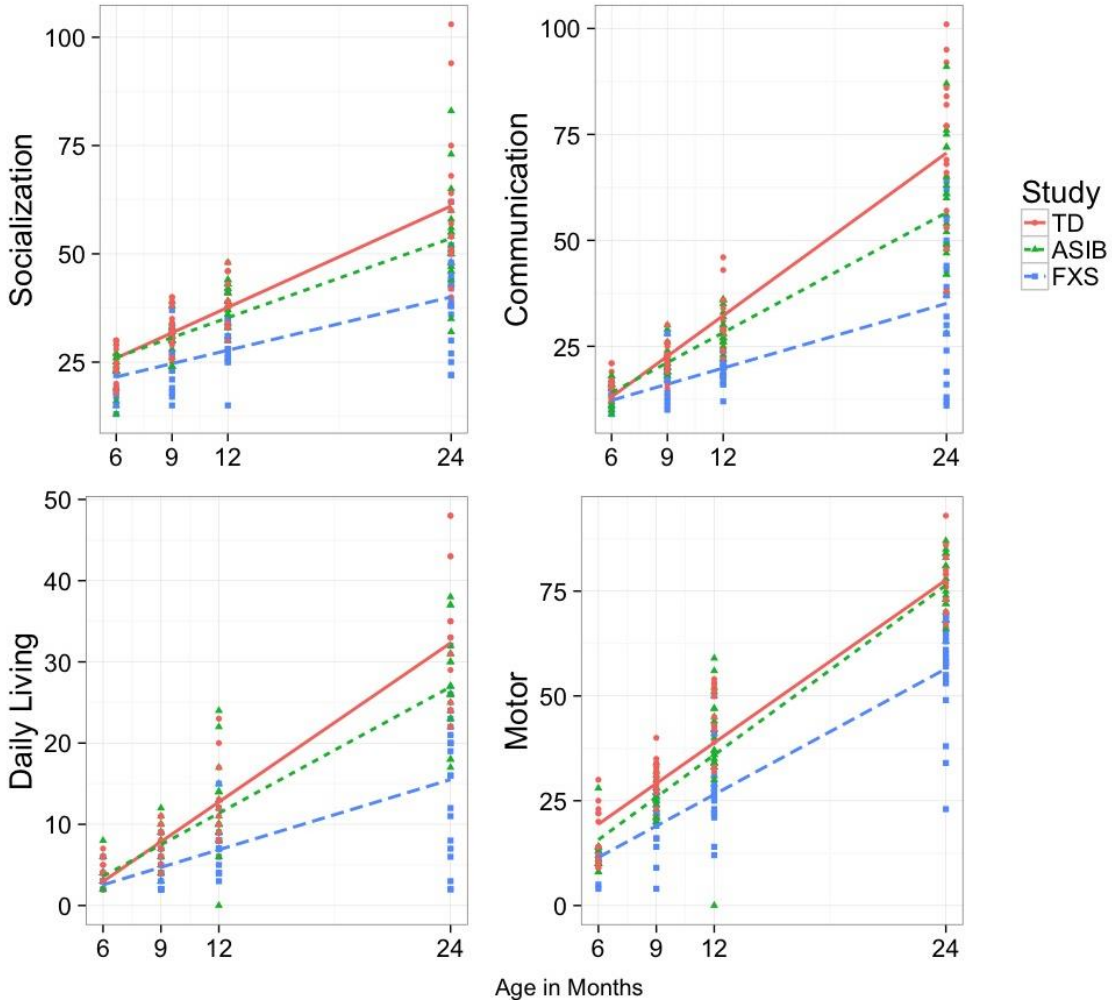

Figure 3.1 Average linear growth trajectories of raw adaptive behavior scores by risk group.

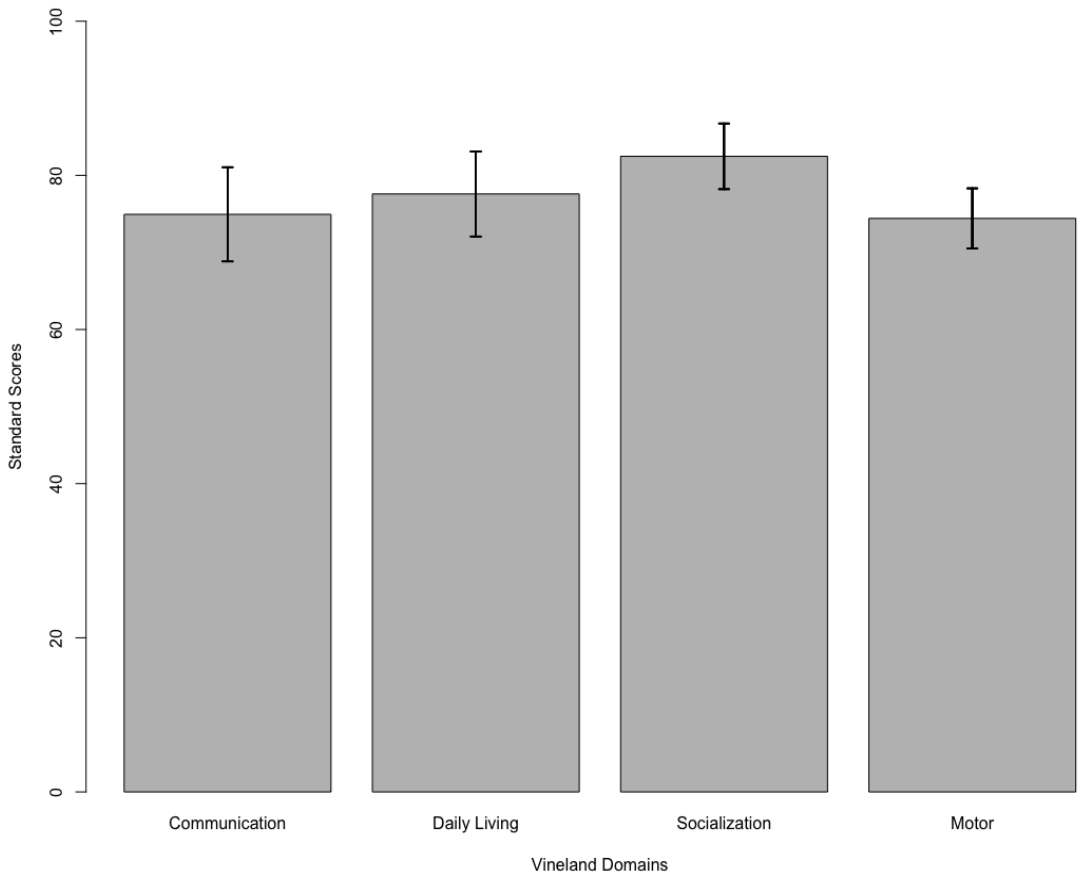

Figure 3.2 Mean standard score values at 24 months across Vineland domains in males with FXS.

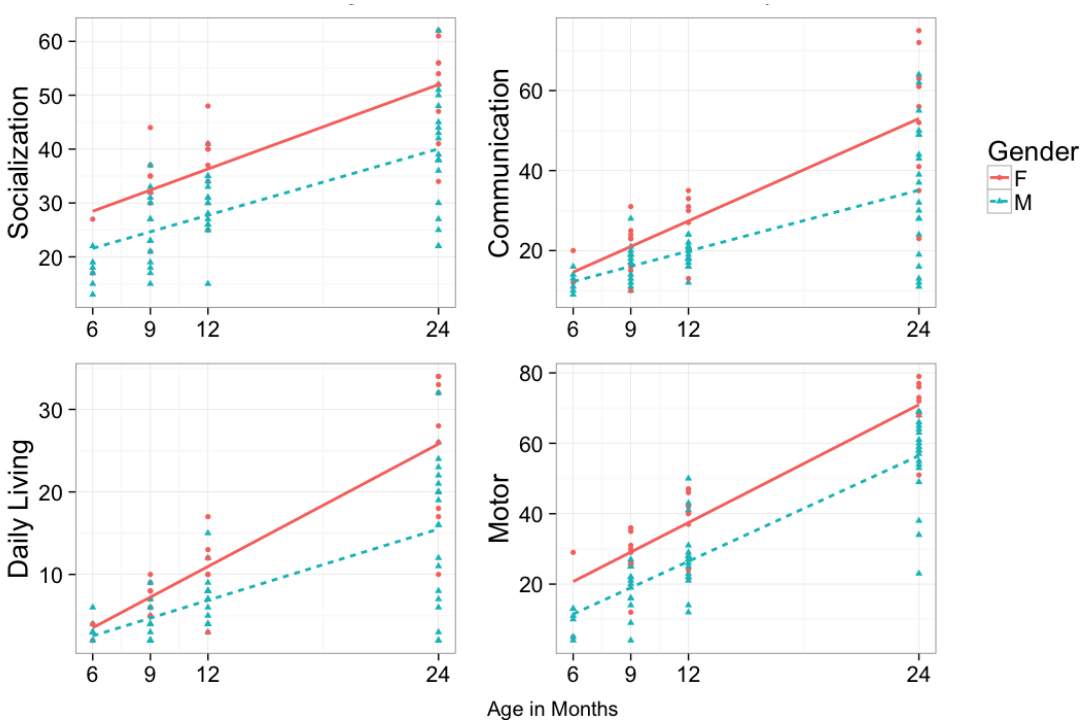

Figure 3.3 Average linear growth trajectories of raw adaptive behavior scores by sex.

CHAPTER 4

DISCUSSION

This paper is the first prospective longitudinal study to examine adaptive skills in infants with FXS, and the first to incorporate any data on infants less than 12 months of age. Through the use of multilevel modeling and single sample profile analysis, adaptive behavior trajectories and profiles were explored. Given the importance of adaptive skills for independent functioning, and the low rates of independence in adults with FXS (Hartley et al., 2011) understanding the presentation and growth of these skills during early development can inform targets for treatment and provide prognostic indicators beginning in infancy.

Adaptive Behavior Trajectories

Consistent with our hypothesis, infants with FXS evidenced lower adaptive skills across all domains at 9 months of age, compared to both ASIB and TD infants. These deficits increased over time, evidenced by the slower rates of growth on all domains, than both comparison groups. The magnitude of difference in the rates was greater between the FXS and TD, than FXS and ASIB groups across all domains, with the exception of gross motor in which ASIBs gained skills at a slightly faster rate than TDs (however their means scores at 24 months were almost indistinguishable). The magnitude of difference in growth was largest in the communication domain, where TD infants gained skills at almost double the rate of FXS infants. These findings highlight significant delays in adaptive communication skills for infants with FXS, which mirror the delays found in

direct evaluation of language development where delays are evident in both expressive and receptive language skills by 9 months of age (Roberts et al., 2009).

While direct comparison of these findings to previous research is challenging given the limited published work on adaptive skill development in FXS before the age of 2, our findings are consistent with the positive growth identified by studies including a handful of children below the age of 2 (Dykens et al., 1996; Hahn et al., 2015; Hatton et al., 2003), suggesting that although growth rates may be slower than TD peers, infants with FXS are showing overall growth in adaptive skills beginning in infancy. This is a promising providing evidence of aptitude for growth in this population, even if rates are below age expectations.

Of interest, the magnitude of difference in growth rates between ASIB and FXS infants was approximately half that of TD and FXS infants in all domains, except gross motor. Therefore, the ASIBs in our sample appear to be falling somewhere in between the FXS and TD infants in their rate of acquisition of adaptive skills, as a whole. The ASIB comparison group included in this analysis is similar to other work examining ASIBs in that it is heterogeneous in developmental presentation at 24 months, with 52% children having a score of 4 or higher on the ADOS and 43% evidencing development delays. Even with these delays, ASIBs grew at a faster rate than FXS infants, highlighting a more significant delay in adaptive skill development in infants with FXS, than other high-risk populations.

Adaptive Behavior and Autism Symptomatology

Measures of autism symptom severity at both 12 and 24 months were not related to initial adaptive behavior functioning at 9 months of age, suggesting that early adaptive

skill acquisition is generally consistent across all infants with FXS, regardless of their later presentation of autism symptomatology. Surprisingly, autism symptomatology at 12 months was not related to trajectories of adaptive development in any domain. In contrast, increasing symptom severity at 24 months was related to decreases in growth rates in the domains of socialization, communication and daily living skills. These findings are consistent with previous work that reported negative relationships between autism symptomatology and adaptive skill growth (Hahn et al., 2015; Hatton et al., 2003). The only domain in which this relationship was not evident was the motor skills domain. The relationship between early motor skills and autism symptomatology in young children with FXS is complex. Recent work has identified that atypical motor behaviors measured by the AOSI differentiate infants with FXS from ASIBs, however 80% of infants with FXS display poor motor control at 12 months, regardless of autism outcomes at 24 months (Roberts et al., under review), suggesting that atypicalities in this domain may be universal in infants with FXS. Other work has shown a strong relationship between fine motor development on the Mullen and autism symptomatology (Roberts, 2009) in young children with FXS. This finding may be related to the significant imitation burden required of early fine motor tasks on the Mullen, which has been found to be a significant deficit in young children with autism and infants with FXS with elevated autism symptomatology (Rogers, Hepburn, Stackhouse, & Wehner, 2003). In contrast, the motor skills captured on the Vineland have less to do with immediate imitation, rather they measure the use of hands and fingers when completing activities of daily living (e.g., taking items out of a container, turning pages in a book, opening doors). Of note, previous work has not considered gross motor development in these

relationships, which is combined with fine motor to create the motor domain on the Vineland. Future work may want to focus on teasing apart the relationships between the subdomains of gross and fine motor adaptive skills, and autism symptomatology in FXS to help elucidate the relationship between these sets of skills as they may help identify a specific risk phenotype in FXS. In contrast, the results presented in this paper may suggest that adaptive motor skills may be a not specific indicator of autism in FXS, rather a deficit across the group as a whole.

Strengths and Weaknesses in Adaptive Behavior Domains

In contrast to previous research in older individuals with FXS that reports profiles of strengths and weaknesses in adaptive skills, our study did not identify any differences in standard scores across the four domains of adaptive functioning when examined at the 24-month time point. The flat profile at 24 months may represent global delays across areas of adaptive functioning, consistent with findings of global delays across all areas of developmental/cognitive functioning in FXS (Roberts, Hatton, & Bailey, 2001; Roberts, McCary, Shinkareva, & Bailey, 2016; Roberts et al., 2009). Strengths identified in older children with FXS may be the result of a more focused intervention in a particular adaptive skill area resulting in improvements, while others remain unaugmented therefore appearing to be "weaknesses" in these individuals. In contrast, individuals with FXS may gain adaptive skills at an uneven rate across development, evidencing different profiles of strengths and weaknesses at specific periods of development which would be consistent with the literature in older children with FXS. Future work should focus on examining the emergence of strengths and weaknesses in adaptive behavior in FXS, and identifying predictors of these shifts in profiles.

Sex Differences in Adaptive Skill Development

The final aim of this paper was to present preliminary findings on the differences in adaptive skill development between male and female infants with FXS. Findings from the analysis suggest that females with FXS evidence higher scores in the domains of adaptive socialization and motor skills at 9 months of age. Rates of growth were not different in these domains, suggesting that males and females gained skills at a similar rate therefore maintaining the discrepancy of higher scores in females through 24 months. In direct contrast, differences in initial scores were not identified between males and females in the communication and daily living domains, while growth rates did differ. This finding suggests that initial skills are similar between the sexes in communication and daily living, with the gap between the sexes widening with age as females gain skills at a faster rate than males. Across all domains, these trajectories result in higher skill acquisition in females with FXS by 24 months of age. While these results are limited by the small sample size of females with FXS in the analysis, they are consistent with previous work showing greater skills, and faster rates of growth in females with FXS (Hahn et al., 2015; Klaiman et al., 2014). Future work should aim to replicate these findings in a larger sample of infant females with FXS.

Conclusion

In conclusion, infants with FXS show deficits across all domains of adaptive functioning as early as 9 months of age and slower rates of growth in these skills across the first two years of life when compared to TD and ASIB age matched peers. Additionally, growth in these skills is impacted by autism symptom severity measured at 24 months, but not at 12 months or in the domain of motor development. No distinct

profile of strengths and weaknesses is evident across adaptive behavior domains at 24 months in FXS. Lastly, preliminary findings suggest that females and males with FXS have similar initial skill levels in the domains of daily living and communication, while evidencing higher scores in the domains of motor and socialization. While initial scores rates of growth may vary across the domains between the sexes, females evidence higher scores in all domains by 24 months of age.

Limitations

While this is the first longitudinal study to examine trajectories of adaptive behavior in infants with FXS, a few limitations exist. While using raw scores in longitudinal models is ideal when attempting to measure true change over time, the use of raw scores also have some weaknesses. Raw scores on the Vineland can be conceptualized as a representation of the number of skills that an individuals has mastered (e.g. 2 points = 1 skill performed at independence or 2 skills at partial independence), however they cannot be compared across domains given differing expectations in skill acquisition across domain and age. Therefore, clinical interpretation of some of the parameter estimates reported in this paper is limited. Additionally, the study is inherently limited by the generally small range of adaptive skills expected of young children as measured by the Vineland, therefore reducing the range of possible scores, especially at the earliest time points.

This study is also limited by the small number of data points at 6 months in FXS and the small overall sample size of females with FXS. While multilevel modeling is robust to missing data and uneven data collection over time, time points with fewer data points to estimate from will be inherently more biased. Future research in infants with

FXS should aim to collect a larger sample size at 6 months of age to more fully understand these early anchors of these trajectories, while also focusing on collecting a larger sample of females. Given the rarity of FXS, and the challenge of identifying children, especially females with the disorder, at those early time points, we suspect this will continue to be a limitation in FXS infant research for the foreseeable future

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