

2018

The Emergence Of Early Visual Attention Profiles In Infants At High Risk For Autism Spectrum Disorder

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THE EMERGENCE OF EARLY VISUAL ATTENTION PROFILES IN INFANTS AT
HIGH RISK FOR AUTISM SPECTRUM DISORDER

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For the Degree of Doctor of Philosophy in

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2018

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ACKNOWLEDGEMENTS

I offer my sincerest thanks to my advisor and mentor, Dr. Jane Roberts, for her encouragement, advice, and guidance over the past years. Her dedication to my training and insightful leadership pushed me to develop my skills not only as a clinician, but also a researcher and a writer. I am grateful for the opportunities you provided me over the years to gain a wide breadth of experiences, while also allowing me to specialize and develop in my areas of interest, to become a more critical, principled researcher. I would also like to thank Dr. Kimberly Hills for selflessly giving her time and support toward my clinical and research training. You set an excellent example as a clinician and educator, and without your guidance I would not be the clinician I am today. I am also most appreciative of the efforts of my other committee members: Dr. Kate Flory and Dr. Erik Drasgow, who kindly gave their time, expertise, and guidance to better my work. I thank you for your words of encouragement and insightful comments. I am indebted to the former and current members of the University of South Carolina Neurodevelopmental Disorders Lab. I am incredibly lucky to have been a part of such a dedicated, outstanding team and thank all of you for your friendship and support throughout my graduate school training. In particular, I would like to thank Alexis Brewe, Kayla Smith, and Allison Vittes for their help with coding for this dissertation. I also owe a special thanks to Dr. Sam McQuillin for his guidance and knowledge on the statistical approaches utilized in this dissertation. I gratefully acknowledge the support that I received from the Ralph H. Tindall Dissertation Award. On a personal note, I would like to thank my family and

close friends for their unconditional support and for grounding me through this process. Importantly, I would like to recognize the children and families who gave their time so generously so that this work could be completed.

ABSTRACT

This dissertation is comprised of two manuscripts focused on early social and nonsocial attention in children at-risk for developing autism spectrum disorder (ASD): infants with fragile X syndrome (FXS) and infants with an older sibling diagnosed with autism (ASIBs). Each manuscript will present original research: the first will consist of a cross-sectional and longitudinal examination of attention to objects in infants with FXS and infant ASIBs parsed apart by their ASD diagnostic outcomes in comparison to a group of typically developing (TD) infants, and how developmental trajectories of object attention predict later ASD symptom severity and diagnostic outcomes. The second will extend this line of research by examining cross-sectional and longitudinal trajectories of social and nonsocial attention in these at-risk groups parsed apart by their diagnostic outcomes as compared to TD infants, and how these trajectories impact later ASD symptom severity and diagnostic outcomes. These manuscripts will address the extent to which early social and nonsocial attention impairments differentiate these at-risk groups for developing ASD prior to the typical age of diagnosis and how trajectories of social and nonsocial attention are linked to ASD symptomology and outcomes. The results of these studies have implications for informing early diagnostic efforts, identifying early behavioral phenotypes, and in the development of syndrome specific interventions.

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CHAPTER 1: DEVELOPMENT OF OBJECT ATTENTION IN INFANTS AT-RISK FOR AUTISM SPECTRUM DISORDER

1.1 SUMMARY

Impairments in object attention in infancy have been identified as a significant predictor of later social functioning relative to later ASD diagnostic outcomes. Infant ASIBs are at high genetic risk for developing ASD in addition to infants with FXS. Both of these high-risk groups have been found to demonstrate impairments in their object attention in infancy; however, their impairments have yet to be examined from a cross-syndrome approach. The present study is the first to examine object attention trajectories in infants with FXS and infant ASIBs based on their ASD diagnostic outcomes in relationship to typically developing same-aged peers. Cross-sectional analyses revealed that differences in object attention were identified at 9 and 24 months of age within the four groups of high-risk infants and the TD infants, but not at 12 months. Longitudinally, infants with FXS and infant ASIBs who did not go on to develop ASD demonstrated significant declines in their object attention across 9 to 24 months, whereas infants with FXS and infant ASIBs who later went on to develop ASD demonstrated increases in their object attention across 9 to 12 months. Increasing object attention trajectories across 9 to 24 months of age were predictive of increased ASD symptoms later in life with object attention trajectories across 9 to 24 months differing the high-risk infants from those who go on to receive a diagnosis of ASD and those who do not.

1.2 INTRODUCTION

With prevalence rates of ASD increasing to 1 in 68 children and 1 in 42 boys (CDC, 2016), early identification of ASD symptoms is key to the development and implementation of early interventions. Despite evidence that ASD symptoms are typically present within the first few years of life (Dahlgren & Gillberg, 1989; De Giacomo & Fombonne, 1998; Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013), most children with ASD are not diagnosed until four years of age or later (CDC, 2016; Charman & Baird, 2002; Shattuck et al., 2009). Literature suggests that early attention behaviors may be directly related to the emergence of social impairments associated with ASD (Chawarska, Ye, Shic, & Chen, 2016; Swettenham et al., 1998). The present study examines early developmental trajectories of visual object attention from a cross-syndrome approach in infants at high genetic risk for developing ASD, including (1) infants with an older sibling diagnosed with ASD (ASIBs) and (2) infants with FXS compared to (3) typically developing controls.

Evidence indicates that impairments in object attention, specifically increased object attention, is a significant predictor of later social functioning relative to ASD (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Rice, Moriuchi, Jones, & Klin, 2012) and in FXS (Roberts, Hatton, Long, Anello, & Colombo, 2012; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012). It is unclear, however, if object attention profiles are similar across ASD and FXS as there has been no cross-syndrome comparisons conducted to date. Delineation of syndrome-specific object attention profiles can further the current literatures understanding of how the phenotypic profiles of ASD and FXS overlap or differ by identifying if early object attention behaviors are related to later

diagnostic outcomes. Ultimately, these findings can help provide evidence for the development of targeted interventions, specifically at what age we should potentially intervene and what skills should be targeted, within these at-risk populations. Below, ASD and FXS will be discussed briefly in addition to a review of the salient literature reflecting the current understanding of object attention for each disorder.

Object Attention in ASD

ASD is diagnosed through observing impairments in the development of specific social and communication skills, the presence of repetitive and stereotyped behaviors, and restricted interests (APA, 2013). Through parental reports, analyzing retrospective videos of children with a diagnosis of ASD, and prospective studies, research has shown that ASD symptoms are present in up to 50% of infants during the first year of life with 80% of parents reporting abnormalities by the time the child reaches two years of age (Dahlgren & Gillberg, 1989; DeGiacomo & Fombonne, 1998; Turner-Brown et al., 2013). One of the hallmark early impairments in ASD is abnormal attention, including increased object attention (Klin et al., 2002; Zwaigenbaum et al., 2005). For example, Jones and Klin (2013) found that high-risk infants later diagnosed with ASD demonstrate a decline in object attention from 2 to 12 months, similar to TD controls, with an increase in object attention beginning at 12 months and continuing to 24 months, deviating from their TD peers. A majority of the literature has focused on object attention in relationship to social attention based on the social motivation theory within ASD (Dawson, Web, McPartland, 2005; Dawson et al., 2002). This theory suggests that early impairments in social attention alter social learning experiences that are responsible for the development of preferred attention to social stimuli (e.g., looking at people) compared to other things

in the environment (e.g., toys, objects in the room). In other words, early deficits in the imbalance of social and nonsocial attention (e.g., increased attention to objects and decreased attention to social stimuli) can result in downstream negative effects on the development of appropriate socialization skills later in life (e.g., avoiding eye contact with people).

Due to the disconnect between presenting symptoms in the first two years of life and the average age of diagnosis nearly two years after the emergence of symptoms, research has begun utilizing longitudinal studies with infants identified as high genetic risk for ASD that have an older sibling diagnosed with ASD (ASIB). ASIBs are an ideal group given the established genetic component and high familial risk of ASD found in the literature (Garon et al., 2009). Additionally, ASIB's provide insight into the broad autism phenotype (BAP) through those who do not go on to meet diagnostic criteria for ASD but may still present with a variation of ASD symptoms (Bolton, Macdonald, Pickles, & Rios, 1994). Furthermore, the BAP has been found to emerge through mechanisms such as developmental delays (Charman et al., 2016) or language delays (Ozonoff et al., 2014) in the ASIB literature. Overall, ASIBs are at higher risk of developing ASD than typical children with no older sibling diagnosed. Although the underlying causes of the higher risk are unknown, genetic factors are highly implicated with prevalence rates for infant siblings reported to range from 2-28% with most studies indicating a risk of around 18% (CDC, 2016; Messinger et al., 2015; Gronborg, Schendel, & Parner, 2013). Within the current literature on ASIB populations, researchers have examined this group longitudinally until ASD diagnostic determination is made (Jones & Klin, 2013); whereas others have examined this group from solely as an at-risk

perspective independent of later diagnoses (Dewaele, Demurie, Warreyn, & Roeyers, 2015). The present study utilizes both mechanisms.

Within the ASIB literature, object attention deficits have been documented within the social attention literature (Jones & Klin, 2013, Pierce et al., 2016, Shic et al., 2011), with significant differences emerging as early as nine months of age and continuing into early school ages. However, findings within the literature are highly variable. For example, increased attention to geometric patterns or to background elements (e.g., toys, parts of the room) have been found to be predictive of later ASD diagnoses and increased ASD symptom severity (Pierce et al., 2016; Shic et al., 2011). Conversely, some groups have found increased attention to objects in ASIBs, but these differences were not related to diagnostic outcomes in ASD (Chawarska, Macari, Powell, DiNicola, & Shic, 2016). Within the ASD literature, toddlers' attention to objects may be context dependent where explicit cues for dyadic engagement (e.g., face-to-face interaction coupled with child-direct speech) increased their attention to objects (Chawarska, Macari, & Shic, 2012).

To date, there has been limited longitudinal research on object attention in ASIB populations. Object attention in infants later diagnosed with ASD has been shown to decline slowly beginning around 2 months of age until 12 months, and then rise from there until 24 months, where object attention appears to double in comparison to typical controls (Jones & Klin, 2013). Similarly, ASIBs have demonstrated stable levels of object attention from 6 to 9 months with an increase in object attention from 9 to 12 months (Chawarska, Macari, et al., 2016). Although other literature suggests that object attention differences can be found earlier in life, Jones and Klin's (2013) findings suggest these differences may not be apparent until later in life. Additional research is needed

from a longitudinal perspective to further decipher object attention trajectories in infants who are at high risk for ASD.

Conflicting research has also suggested that ASIB populations who later receive a diagnosis of ASD do not differ from typically developing peers in their object attention (Chawarska, Macari, & Shic, 2013; Hutman, Chela, Gillespie-Lynch, & Sigman, 2012). One group found that high-risk infants for ASD, who did not have outcome data, did not differ from low-risk infants in their attention to objects (Dewaele et al., 2015). Another group found no significant group differences in object (e.g., toys) attention at 6 months of age across low-risk, high-risk typically developing, high-risk atypically developing, and ASD infants (Chawarska et al. 2013). Similarly, Hutman and colleagues (2012) found no significant group differences in 12 month old infants' attention to objects (toys) during toy play and caregiver distress conditions across low-risk typically developing, high-risk typically developing, other concerns, and ASD infants. The controversy in findings suggests that these early visual attention differences may be subtler than previously assumed in infants who are at-risk for later developing ASD. Furthermore, the studies described above all use cross-sectional methodologies which may play a role in their conflicting findings adding to the notion that object attention may be better understood from a longitudinal perspective. The present study addresses this by using both methodologies to compare findings.

The majority of the current literature has examined object attention integrated within measures of social attention (e.g., attention to a person or examiner) in comparison to where else infants at high risk for ASD look (e.g., objects, background). Some groups (Koterba, Leezenbaum, & Iverson, 2014; Ozonoff et al., 2008) have explicitly examined

object exploration (e.g., gaze behaviors, object manipulation, mouthing) in these high-risk infants with an emphasis on atypical visual object exploration. Interestingly, this literature has suggested that atypical visual object exploration is associated with repetitive and restricted behaviors typically found in ASD (Ozonoff et al. 2008). Similar to these findings in infants, other groups have found that preschoolers with ASD significantly attended to objects identified as being of high-autism interest or of circumscribed interest over social stimuli (Sasson & Touchstone, 2014; Sasson et al. 2011). Together, these results suggest atypical object attention patterns may be a distinctive characteristic of the ASD phenotype relative to restricted and repetitive behaviors, not just social communication concerns. Given these findings, the present study examines overall ASD symptoms in addition to examining restricted and repetitive behaviors and social communication symptoms separately to potentially understand how these two ASD specific areas may play different roles in the development of object attention.

Limitations in the Current Literature. In the literature discussed above, all studies utilized eye tracking to measure object attention; however, these results have yet to be evaluated through naturalistic observation to confirm their ecological validity. The advances in technology, such as implementation of eye tracking, have contributed to the ability of our field to quantify abnormalities in visual attention, which appears to derail the development of later socialization skills (for review, see Guillon, Hadjikhani, Baduel, Rogé, & Rogé, 2014). Although researchers are attempting to use more naturalistic, real life stimuli in their eye tracking measures, their findings may not generalize to real life

situations given participants can perform differently in lab-based, experimental video tasks compared to more natural social situations.

To the author's knowledge, there has been no research examining how object attention using eye-tracking mechanisms and video stimuli compares to natural, real-life social interactions in infants. One study utilizing typically developing undergraduates examined differences in social attention across a live interaction and a videotaped interaction (Freeth, Foulsham, & Kingstone, 2013). These authors found that decreased looking at the examiner was associated with increased ASD traits only during the videotaped interaction, not during the live interaction. Additionally, another study utilizing undergraduates found that participants looked at the videotaped examiner in a waiting room more than when the examiner was physically present (Laidlaw, Foulsham, Kuhn, Kingstone, & Purves, 2011). Furthermore, they found that increased social skills were associated with increased head turns toward the physically present examiner; whereas no relationship was found between social skills and head turns toward the videotaped examiner. Overall, these findings suggest that context may be important when examining visual attention and caution should be exercised when using only a video presented stimulus as a substitute for real life social situations, which is the case in the current eye-tracking literature. Given the surge of eye tracking studies in the current literature, the present study will be one of the first to utilize a naturalistic, lab based procedure with physically present social and object stimuli to measure object attention rather than a videotaped interaction. These mechanisms may further our current understanding of the development of visual attention patterns in infants at high-risk for ASD.

In addition to the predominate use of eye-tracking to measure object attention, the majority of the literature has utilized cross-sectional methods in an attempt to understand how visual attention appears at a specific time point in relationship to their diagnostic outcomes (Chawarska et al., 2012, 2013; Hutman et al., 2012; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011). As mentioned previously, there is high variability within the currently literature's findings with regards to visual attention being predictive of ASD outcomes. Researchers have looked as early as 6 months (Chawarska et al., 2013) up to preschool ages (Sasson & Touchstone, 2014). However, as pointed out by Jones and Klin's (2013) findings, differences in object attention may be too subtle to identify at a specific age point and may be better understood from a developmental or longitudinal perspective. The present study presents both cross-sectional and longitudinal data on object attention to provide a comparison of the findings within and across both methodologies.

Overall, atypical object attention has been documented in ASIBs, with some literature (Jones & Klin, 2013) suggesting these differences may be subtler than previously thought. Due to the discrepancy in findings, additional research is needed in an effort to understand object attention in this high-risk population. Additionally, most of the literature includes cross-sectional methodologies with relatively little literature examining object attention explicitly. Furthermore, very little research has examined how developmental trajectories of object attention emerge in infants at-risk for ASD and its predictive value on later outcomes. The present study aims to address these deficits by utilizing behavioral coding of object attention in a more naturalistic, play-based task from

a cross-sectional and longitudinal perspective while examining the influence of ASD outcomes on infants at high-risk for ASD.

Object Attention in Fragile X Syndrome. As noted earlier, no studies to date have contrasted object attention in ASIBs to other clinical groups at-risk for developing ASD. Fragile X syndrome is the leading known genetic cause of intellectual disability associated with a mutation on an unstable trinucleotide (CCG) repeat expansion on the fragile X mental retardation 1 (FMR1) gene (Hagerman & Hagerman, 2002; Hall et al., 2009). FXS has a variable clinical phenotype, typically affecting males with the full mutation more than females, making it ideal within this population to look at males and females separately. Due to the documented differences in males compared to females with FXS (Hagerman et al., 2017), the current study explicitly focuses on infant males with FXS. FXS is characterized by mild to severe ID with a series of other deficits including: anxiety, social deficits, abnormalities in communication, gaze aversion, inattention, impulsivity, aggression and hyperactivity (Cordeiro et al., 2010).

Similar to ASIBS, infants with FXS are also at high risk for developing ASD with comorbidity rates as high as 60-70% in males with FXS compared to 30-60% in all children with FXS (Klusek et al., 2014; Talisa, Boyle, Crafa, & Kaufmann, 2014; Thurman et al., 2014). With these high comorbidity rates, there is a strong association between FXS and ASD. Furthermore, there are significant deficits in visual attention regulation across the developmental lifespan in FXS (Scerif et al., 2012). Within the FXS literature, atypical social attention has been well documented in children and adults (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Hessler, Glaser, Dyer-Friedman, & Reiss, 2006; Roberts, Weisenfeld, Hatton, Heath, & Kaufmann, 2007) with some research

suggesting social attention in children with FXS is related to increased ASD severity (Hall et al., 2015); however, very little research has been done on object attention in FXS or with infants.

To date, one study has examined object attention in infants at high risk for ASD (i.e., infants with FXS) and its association to later autism symptoms (Roberts et al., 2012). Results suggest that infants with FXS display atypical object attention across multiple measures over time and that increased object attention was associated with more severe autism symptoms. Specifically, infants with FXS displayed longer look durations toward objects and extended latencies to disengage their attention from the toy object in comparison to TD infants at 12 months of age. Additionally, increased look durations to the toy object in the FXS infants were associated with increased autism symptoms at 12 and 18 months of age. However, this study lacked the ability to compare the FXS infants' trajectories (9 to 18 months) to a typically developing control group or other high-risk group for developing ASD (e.g., ASIBs). Given the established risk of FXS meeting criteria for ASD, it is an ideal group to examine the development of object attention in comparison to other high-risk groups for ASD. Understanding early object attention pathways in FXS can potentially provide information into the similarities or differences within and across the phenotypic profiles of ASD and FXS.

The Present Study

The aim of the present study is to expand upon the previous literature (Roberts et al., 2012) by examining behavioral trajectories of object attention in infants who are at high-risk for ASD, including both (1) infant males with FXS and (2) infant male ASIBs, in comparison to (3) typically developing (TD) infant males within and across 9 to 24

months of age. Furthermore, the infants with FXS and infant ASIBs were parsed apart based on their ASD outcomes (e.g., FXS+ASD and ASIB+ASD) to examine how these outcomes differentiate their object attention patterns not only across groups, but within groups to create a total of five groups of male infants: (1) FXS, (2) FXS+ASD, (3) ASIB, (4) ASIB+ASD, and (5) TD. Additionally, the present study utilizes behavioral observation approaches to measure object attention, which will contribute to the lack of literature utilizing non-eye tracking, videotaped methodology. Lastly, the present study will be utilizing both a cross-sectional and longitudinal approach to characterize early age-specific time points and developmental trajectories of object attention in two genetically high-risk groups, which has not yet been done to date. This will help address if the subtleties of atypical object attention can be identified at specific age points during infancy or if they are better understood from a longitudinal perspective.

Furthermore, the present study aims to examine how object attention trajectories predict later ASD symptoms and diagnoses at 24 months of age. Analyses will be conducted to examine how object attention trajectories predict ASD outcomes at 24 months within the entire FXS and ASIB sample from a categorical diagnostic perspective in addition a continuous symptom-based perspective. The benefit of examining ASD symptoms continuously and categorically will allow us to see if object attention trajectories are predictive of ASD at any level across the spectrum, or if there are specific clinical subgroups, based on diagnostic outcomes, who have significantly different trajectories. Within the literature on FXS, ASD has been examined categorically through diagnostic measures (Hatton et al., 2006; Wolff et al., 2012) and continuously through symptom severity scores (McDuffe, Thurman, Hagerman, & Abbeduto, 2015). Each of

these analyses will provide different information about the behavioral phenotype of FXS and ASIBs in relationship to object attention. For example, continuously we may find as object attention increases, ASD symptoms also increase, adding information to our understanding of the BAP. Categorically, we may find that infants' object attention differentiates the high-risk infants based on their later ASD diagnoses, as some of the previous literature has suggested (Jones & Klin, 2013; Shic et al., 2011). The present study's specific research questions and hypotheses are as follows:

1. How do infants with FXS, infants with FXS+ASD, infant ASIBs, infant ASIBs+ASD, and TD infants differ in their object attention at each standard assessed age point (9, 12, and 24 months) while controlling for developmental level?
 - a. It is hypothesized that infants with FXS and infants with FXS+ASD will spend significantly more time attending to objects at each age time point (9, 12, and 24 months) compared to infant ASIBs, infant ASIBs+ASD, and typically developing infants.
 - b. It is hypothesized that infant ASIBs and infant ASIBs+ASD will spend significantly more time attending to objects at each age time point (9, 12, and 24 months) compared to TD infants.
2. How do infants with FXS, infants with FXS+ASD, infant ASIBs, infant ASIBs+ASD and TD infants differ in their object attention trajectories across 9, 12, and 24 months of age controlling for developmental level?
 - a. It is hypothesized that infants with FXS and infants with FXS+ASD will demonstrate increased slopes of object attention beginning at 9

months and continuing through 24 months of age in comparison to infant ASIBs, infant ASIBs+ASD, and TD infants.

- b. It is hypothesized that infant ASIBs and infant ASIBs+ASD will demonstrate increased slopes of object attention beginning at 9 months and continuing through 24 months of age in comparison to TD infants.
3. How do trajectories of object attention predict ASD diagnostic outcomes and symptomology at 24 months in infants with FXS and infant ASIBs?
 - a. It is hypothesized that trajectories of object attention across 9 to 24 months of age will differentiate the high-risk infants who develop ASD from those who do not at 24 months.
 - b. It is hypothesized that trajectories of increasing object attention across 9 to 24 months will be predictive of increased ASD symptoms within the high-risk groups (infants with FXS and infant ASIBs).

1.3 METHOD

Participants

Data were drawn from a longitudinal study conducted at the University of South Carolina and initially included 3 groups of males: (1) infants with FXS, (2) infant ASIBs, and (3) typically developing (TD) controls. All Infants were required to be full term (37 weeks or later) and reside with their biological mothers. Infants with FXS were recruited to participate through a national registry for FXS research and ongoing research studies. Infants with FXS had the FMR1 full mutation based on genetic reports (CCG repeats of greater than 200 on the FMR1 gene). Infants were enrolled in our high risk ASIB group if they were the full biological sibling of an older child with a documented diagnosis of

autism and no diagnosed genetic or medical conditions. Both our ASIB and control group of TD infants were recruited locally through advertising around schools and community centers. Based on parent report, the TD control group had no developmental or genetic concerns, and no family history of ASD. Additionally, developmental skills were confirmed to be in the average range for the TD group via their developmental testing in this study as detailed below. Participants were excluded from the study if they had a pre-existing condition (e.g. cerebral palsy, seizure disorder) or if they had hearing or vision impairments that would impact the results of this study. Each participant was assessed 1-3 times at the following time points: 9 months, 12 months, and 24 months. While the aim was for all participants to be enrolled at 9 months and to be assessed at all three time points, some were not enrolled until 12 or 24 months of age. Additionally, a few participants missed assessments due to family schedule conflicts. Outcome data were collected at the 24-month assessment for each of the participants.

Participants include 25 infant males with FXS, 25 infant male ASIBs, and 33 TD infant males with a total of 195 observations across groups (75.64% White, 10.26% Black or African American, 12.82% more than one race, and 1.28% race unknown or not reported; mean income = \$79,548.71, SD =\$51,335.87). Infants with FXS have a total of 46 observations, infant ASIBs have a total of 66 observations, and TD infants have a total of 83 observations. Not all participants in the study were assessed at three age points, and few have not yet been seen for their 24-month assessment, resulting in some missing data. Additionally, some missing data occurred due to video malfunctions, the attention task not being video recorded or conducted, or the child's mother was not present for the assessment (N =13; FXS=4, ASIB=5, TD=4). Clinical Best Estimate (CBE) diagnoses

were utilized to differentiate the FXS and ASIB groups based on their diagnostic outcomes into those with FXS+ASD, only FXS, only ASIBs, and infant ASIBs+ASD. Participants' CBE's were determined by expert clinicians based on several measures including development, behavioral questionnaires, family/medical history, and gold standard measures for ASD. Although participants' CBE's were evaluated at 24 months of age, a reliable and sensitive diagnosis can be established at this age point with diagnostic stability rates around 82% (Ozonoff et al., 2015). Within the TD group, four participants were removed due to their CBE's suggesting ASD diagnoses and one participant was removed due to having below average cognitive scores (a standard score below 77.5 in either verbal and/or nonverbal cognitive domains). The retained sample included 28 TD infants, 17 infant ASIBs, 8 infant ASIBs+ASD, 10 infants with FXS, and 15 infants with FXS+ASD for a total of 178 observations across all five groups. For participant descriptive statistics, refer to Table 1.1.

Measures

Attention to Objects. The Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith & Rothbart, 1996) is a standardized, observational based measure that is used to assess temperament and involves the administration of several games for infants aged 6 months to 3 years. The Lab-TAB is a reliable and valid paradigm that has been utilized across several laboratories including samples of TD children (Brooker et al., 2013), ASIBS (Garon et al., 2009), and FXS (Tonnsen et al., 2013). All participants were administered the Lab-TAB at 9, 12, and 24 months of age. The present study utilized the unstructured toy play task to assess participants' duration of attention to objects. Prior to the presentation of the toy (e.g., set of toy keys), the infant is seated in a high chair or

booster seat and placed in front of a table with no stimulus with the examiner and parent seated on either side of them. The participant was required to be in a neutral state for at least 15 seconds (e.g., not crying, upset, or yawning) prior to the toy presentation. Also, the infant must have shown interest in the keys (e.g., looking at them, manipulating them) for the experiment to continue or a substitute toy was presented if the infant did not show interest in the toy keys. Once the toy was presented, the infant is allowed 3 minutes of unstructured toy play with the examiner and parent instructed to remain neutral and to not engage with the child other than to pick up the keys if they are dropped and to re-present them. A second examiner video records the task which is then later coded offline using Noldus Observer XT 10.5 (Noldus Information Technology, 2010).

Gaze behaviors were examined and coded for each participant as a measure of attention during the task. Trained research assistants, upon establishing an initial reliability standard of at least 80% agreement across three consecutive videos, coded the offline behavioral data. Reliability was maintained through a master coder who coded 20% of the data with a Cohen's kappa coefficient of 0.80 across all codes. The current Cohen's kappa coefficient for data coded for this study is 0.85 which is considered almost perfect agreement (Viera & Garrett, 2005). Five attention variables that were coded include: (1) looking at the parent, (2) looking at the experimenter, (3) looking away (child is looking anywhere else not defined in other behaviors), (4) looking at the object (e.g. toy keys), and (5) attention obscured (when both eyes are not visible lasting longer than 1 second). All of the attention variables were coded if they happened for at least 1 second or longer across the entire duration of the task with each behavior having an onset and offset. There were two steps in the coding process. First, each attention

variable is coded to represent the duration of seconds each behavior was exhibited by the participants. Second, the duration of seconds for each behavior was then used to create a proportion of time spent in each behavior which accounts for slight variation in the total amount of time for the task. None of the participants had more than 10% of data coded as attention obscured. The proportion of attention to objects (looking at the object) is the primary dependent variable in this study. Due to the nature of the task being intended to measure object attention with instructions for the examiners and parent to remain neutral and not interact with the infant, only attention behaviors toward the object/keys were analyzed in the present study.

Developmental Level. The Mullen Scales of Early Learning (MSEL; Mullen, 1995) is an assessment used to measure cognitive and motor ability in children. The MSEL has five scales that measure the following domains: Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language. The median split-half internal consistency for each of the scales ranges from 0.75 to above 0.80 (Mullen, 1995). Test-retest reliability coefficients range from 0.70 to 0.80 (Mullen, 1995). The MSEL was administered to all participants at each time point (9, 12, and 24 months). In line with existing studies indicating a relationship between both verbal and non-verbal ability to object attention and autism features (Chawarska et al., 2016; Ozonoff et al., 2008), two scores were calculated from the Mullen: a verbal developmental quotient (VDQ) using the expressive and receptive language subtest scores and a nonverbal developmental quotient (NVDQ) from the fine motor and visual reception subtest scores. Consistent with this existing work, these developmental quotients will be derived by taking the mean mental age from the subtests to calculate a

ratio IQ (Mental Age/Chronological Age X 100). Both the VDQ and the NVDQ were examined for their relationship with the independent and dependent variables. Furthermore, the typically developing infants were required to perform in the average range when tested on the MSEL at each time point they were assessed, resulting in one participant being dropped from the final sample.

Autism Symptomology. The Autism Diagnostic Observation Schedule – Toddler Module (ADOS-T; Lord et al., 2012) is a semi-structured, standardized observational measure of behavioral symptoms significant to ASD (e.g., communication, social interaction, and repetitive behaviors and interests) for minimally verbal children aged 12-30 months. Forty-one items are assessed on a four-point scale with 14 of those items going into the diagnostic algorithm providing three ranges of concern (Little to No, Mild to Moderate, and Moderate to Severe risk). The ADOS-T has been shown to have excellent sensitivity and specificity in a previous validation study completed by Luyster et al. (2009). Additionally, strong psychometric properties have been found with the ADOS-T, including inter-rater reliability of 84% as measured by mean exact agreement (Luyster et al. 2009; Lord et al., 2012). Stability of receiving a clinical diagnosis that confirmed or ruled out ASD through the ADOS-T has been shown to be stable when reevaluated one to two years later (Guthrie et al. 2013). Examiners were all trained to achieve research reliability of at least 80%. Ongoing reliability scoring for ADOS-T protocols within our research lab is 82.74% and 82.50% for the diagnostic algorithm. While the majority of the participants (94%) were assessed with the ADOS-T at 24 months of age, five participants were administered the Module 1 of the ADOS (2 FXS, 3

ASIB; Lord, Luyster, Gotham, & Guthrie, 2012) at the onset of the project when the ADOS-T was not yet available.

Due to utilizing different modules of the ADOS and the advantage of using scores on a continuum, we utilized Calibrated Severity Scores (CSS) that were developed by Gotham, Pickles, and Lord (2009; ADOS-2) and Elser et al. (2015; ADOS-T) to provide levels of autism symptomology. The CSS are intended to provide a marker of severity of autism symptoms on a scale of 1 to 10 relative to age and language level based on ADOS raw total scores. Across modules, between 1 and 3 represent non-spectrum classification, while 4 through 5 represent autism spectrum classification and 6 through 10 represent an autism classification. For the present study, CSS will be interpreted continuously as a measure of autism symptom severity within the FXS and ASIB groups. Lower CSS are associated with fewer social communication and repetitive behavior concerns. To complement the analyses using the CSS as a continuous measure of ASD symptom severity, we also examined relationships across groups based on categorical designations of being diagnosed with ASD (categorical yes/no) using participants CBE's. These analyses were conducted to examine how trajectories of object attention differ by diagnostic outcomes in addition to how these trajectories predict ASD symptoms as measured by CSS at 24 months. Including both continuous and categorical measures of ASD is a strength given different theoretical and measurement dimensions as outlined previously.

Procedures

Participants were assessed in either their home or in the lab based on their age. They were assessed at the lab on the university campus at 12 months of age and in their

homes at 9 and 24 months of age. A team of two trained examiners completed the assessments. The unstructured play task was administered alongside a larger standardized protocol with a fixed sequence order. Behavioral coding was completed offline through video recordings of the assessment by trained research staff. The current study focuses on proportion of object attention through gaze behaviors.

Data Analysis

Analyses were conducted in R version 3.3.3 to address the present study's research questions. First, data were examined for outliers, nonnormality, linearity, and homoscedasticity. Object attention was positively skewed, however, the residuals approached a normal distribution deeming transformation to be unnecessary. One TD participant was found to be a significant outlier with respect to his VDQ and was removed from the analyses. Next, correlations were examined to identify if any significant relationships existed among any variables being included in the models. Participants' proportion of object attention was not significantly correlated with any of the independent variables (VDQ, NVDQ, ADOS CSS). Participants' ADOS CSS was found to significantly correlate with their NVDQ ($r=-0.37$) and their VDQ ($r=-0.50$). Additionally, a priori post hoc analyses were conducted to examine if the current sample size, although small, would have the power to find effects. Results of the power analysis suggested a 9% chance of finding a small effect (0.1), 54% chance of finding a medium effect (0.3), and a 95% chance of finding a large effect (0.5).

To answer the first research question, analyses utilized ANCOVA's to examine cross-group differences in proportion of object attention at each standard age time point (9, 12, and 24 months) while controlling for VDQ and NVDQ. To answer the second

research question, piecewise multilevel modeling (MLM) was utilized to examine trajectories of proportion of objection attention across all five groups and standard age (9, 12, and 24 months) time points. MLM is ideal for examining these trajectories as it can account for nesting of observations within individuals and permit cross-individual differences in the number of assessments. In this model, participants' proportion of object attention over time were nested within four clinical groups. Proportion of object attention was predicted by participants' standard age, a dummy coded vector for Time 1 to Time 2 (9-12 months) and Time 1 to Time 3 (9-24 months), change from Time 1-2, change from Time 1-3, group status, and covariates for NVDQ and VDQ. This model was chosen to evaluate the trajectories of proportion of object attention across standard age (9-24 months) due to a potential nonlinear relationship occurring for some groups. Formulaic representations of the first and second level of this model are found in Equations 1 and 2 below.

Equation 1: Level 1 model for longitudinal analysis of proportion of object gaze, Y

$$Y = \beta_0 + \beta_1 (\text{Time 1 to Time 2}_j) + \beta_2 (\text{Time 1 to Time 3}_j) + \beta_3 (\text{Group}_j) + \beta_4 (\text{Group}_j) * (\text{Time 1 to Time 2}_j) + \beta_5 (\text{Group}_j) * (\text{Time 1 to Time 3}_j) + \beta_6 (\text{VDQ}_j) + \beta_7 (\text{NVDQ}_j) + \beta_8 (\text{ADOS CSS}) + r_{ij}$$

Equation 2: Level 2 model for longitudinal analysis of proportion of object gaze

$$\beta_0 = \gamma_{00} + \mu_0$$

$$\beta_1 = \gamma_{00} + \mu_1$$

$$\beta_2 = \gamma_{00} + \mu_2$$

In Equation 1, the intercept can be interpreted as the mean value of the control group (TD) at Time 1 (9 months) with VDQ, NVDQ, and ADOS CSS at zero. The main

effects of standard age are observed in the interaction terms between group and the two dummy coded variables. Trajectories of proportion of object attention from 9 to 12 months are seen in the coefficient “Group*Time 1 to Time 2” in Equation 3 and can be interpreted as the relative difference between the TD control group and the five high-risk groups object attention at 12 months of age. Trajectories of proportion of object attention from 9 to 24 months are seen in the coefficient “Group*Time 1 to Time 3” in Equation 3 and can be interpreted as the relative difference between the TD control group and the four high-risk groups object attention at 24 months. Equation 2 shows the level 2 random error added to control for clustering associated with participants.

To answer the third research question, participants’ slopes for 9 to 12 months and 9 to 24 months from Equation 1 will be extracted to represent their trajectories of object attention. Using regression and ANOVA models, participants’ slopes will be used to examine if trajectories of object attention are predictive of later ASD symptomology and ASD diagnostic outcomes within the two groups at high-risk for ASD (FXS and ASIBs). The high-risk sample (all infants with FXS and infant ASIBs) was split into those who have ASD and those who do not based on their CBE data for the categorical analyses. For the continuous analyses, the high-risk sample was examined as a whole. Additionally, the Overall, Social Affect (SA), and Restricted Repetitive Behavior (RRB) CSS were examined independently to assess if object attention is predictive of general or specific symptoms relative to ASD for the continuous analyses.

1.4 RESULTS

Cross-Group Comparisons for Object Attention

Participant groups were examined for significant differences in proportion of object attention at each age point (9, 12, and 24 months) while controlling for VDQ and NVDQ by including them in the models. At nine months of age, an ANCOVA revealed marginally significant group difference in participants' proportion of object attention, $F(4,44)=2.27$, $p=0.076$, $\eta^2= 0.17$. Pairwise comparisons suggest infants with FXS ($M=85.36$, $SE=9.73$) spent more time attending to the object compared to infants with FXS+ASD ($M=55.52$, $SE=9.85$) and infant ASIBs+ASD ($M=55.52$, $SE=7.35$). At twelve months of age, no significant group differences were found in the proportion of object attention across groups, $F(4,53)=0.82$, $p=0.519$, $\eta^2= 0.06$. At 24 months of age, significant group differences appeared in the proportion of object attention across groups, $F(4,50)=2.65$, $p=0.044$, $\eta^2= 0.17$. Pairwise comparisons suggest TD infants ($M=76.85$, $SE=6.14$) spent more time visually attending to the object in comparison to the ASIB group ($M=56.01$, $SE= 5.39$) at 24 months of age.

Overall, as shown in Figure 1.1, differences in object attention were identified at 9 months and 24 months across the 5 groups of infants. Specifically, infants with FXS spent more time attending to the toy object than infants with FXS+ASD and infant ASIBs+ASD at 9 months; whereas, only TD infants and ASIB infants appeared to differ at 24 months with TD infants attending to the object longer. Furthermore, despite the small sample sizes across some groups, medium effect sizes were observed at 9 and 24 months of age. Lastly, object attention at 12 months did not differ across groups.

Object Attention Trajectories Across Age and Group

Piecewise MLM's were utilized to estimate how object attention changes across 9 to 12 and 9 to 24 months of age while controlling for VDQ and NVDQ (Table 1.2) across the 4 groups of participants in comparison to their TD peers. Results of the model suggest infants with FXS+ASD ($\beta=31.22$, $SE=11.35$, $t=2.75$, $p=0.006$) and infant ASIBs+ASD ($\beta=19.83$, $SE=10.96$, $t=1.81$, $p=0.071$) demonstrate significant increases in their object attention between 9 and 12 months compared to their TD peers. Infants with FXS and infant ASIBs did not demonstrate significant changes in their object attention between 9 and 12 months of age in relation to their TD peers. Conversely, infants with FXS ($\beta=-26.69$, $SE=13.80$, $t=-1.93$, $p=0.054$) and infant ASIBs ($\beta=-20.78$, $SE=10.25$, $t=-2.03$, $p=0.043$) demonstrated marginally significant and significant declines in their object attention from 9 to 24 months in comparison to their TD peers. Infant ASIBs+ASD and infants with FXS+ASD did not demonstrate significant changes in their object attention across 9 to 24 months of age. As shown in Figure 1.2, the results from the piecewise model are supported through graphing each groups' marginal means at each age point.

Overall, both high-risk groups who went on to develop ASD (FXS+ASD and ASIBs+ASD) exhibited significant increases in their object attention across 9 to 12 months of age compared to their TD peers. Conversely, both high-risk groups who did not go on to develop ASD (FXS and ASIBs) exhibited marginally significant declines in their object attention across 9 to 24 months relative to their TD peers.

Object Attention Trajectories Predicting ASD Outcomes at 24 Months

ASD Symptomology Outcomes. Linear regression analyses were utilized to examine if trajectories of object attention are predictive of ASD symptoms at 24 months

of age within the high-risk infants (infants with FXS, FXS+ASD, ASIBs, and ASIBs+ASD). For participants' overall ASD symptoms, change in object attention across 9 to 12 months is not a significant predictor ($\beta=1.16$, $SE=1.71$, $t=0.68$, $p=0.504$), whereas, participants' change in object attention from 9 to 24 months is a significant predictor ($\beta=0.11$, $SE=0.04$, $t=2.88$, $p=0.006$), $F(1,46)=0.46$, $p=0.50$, $R^2=0.01$; $F(1,46)=8.31$, $p=0.006$, $R^2=0.15$, respectively. Similarly, for participants' Social Affect, change in object attention from 9 to 12 months is not a significant predictor ($\beta=1.36$, $SE=1.68$, $t=0.81$, $p=0.423$), whereas change in object attention from 9 to 24 months is a significant predictor ($\beta=0.12$, $SE=0.04$, $t=3.26$, $p=0.003$), $F(1,46)=0.65$, $p=0.423$, $R^2=0.01$; $F(1,46)=10.63$, $p=0.003$, $R^2=0.18$, respectively. Lastly, for participants' Restricted and Repetitive Behaviors, change in object attention from 9 to 12 months is not a significant predictor ($\beta=2.24$, $SE=1.64$, $t=1.37$, $p=0.177$), whereas change in object attention from 9 to 24 months is a marginally significant predictor ($\beta=0.08$, $SE=0.04$, $t=2.00$, $p=0.052$), $F(1,46)=1.88$, $p=0.177$, $R^2=0.04$; $F(1,46)=4.01$, $p=0.052$, $R^2=0.08$, respectively.

Overall, participants who demonstrate increases in their object attention across 9 to 24 months of age also show increases in their overall ASD symptoms and across the core sub-symptoms (social affect and restricted, repetitive behaviors). Conversely, changes in object attention across 9 to 12 months of age were not significantly predictive of ASD symptomology at 24 months of age.

ASD Diagnostic Outcomes. Two ANOVA models were utilized to examine differences in infants at high-risk for ASD trajectories of object attention based on their diagnostic outcomes. For participants' change in object attention from 9 to 12 months, no

significant group differences were found, $F(1,47)=0.46$, $p=0.501$, *partial* $\eta^2= 0.01$. For participants' change in object attention from 9 to 24 months, significant group differences were found, $F(1,47)=4.53$, $p=0.039$, *partial* $\eta^2= 0.09$. Specifically, the high-risk infants who did not develop ASD demonstrated a decrease in their object attention ($M=-5.56$, $SD=2.04$), whereas high-risk infants who did develop ASD demonstrated an increase in their object attention across 9 to 24 months of age ($M=0.91$, $SD=2.26$).

As shown in Figure 1.3, both groups of high-risk infants (with ASD and without) exhibit similar object attention trajectories across 9 to 12 months. However, significant group differences appear in object attention trajectories across 9 to 24 months of age. High-risk infants without ASD exhibit declines in their object attention in contrast to high-risk infants with ASD who exhibit increases in their object attention across 9 to 24 months.

1.5 DISCUSSION

The present study is one of the first to examine the development of object attention utilizing a cross-syndrome approach with two genetically high-risk groups for ASD: infants with FXS and infant ASIBs. Additionally, the present study examined object attention trajectories and their relationship to ASD symptoms and diagnostic outcomes within the two high-risk infant groups. Within the ASIB literature, impairments in object attention have been identified as emerging around 9 months of age (Chawarska, Macari, et al., 2016) in addition to being predictive of later social impairments relative to ASD (Klin et al., 2002; Rice et al., 2012). Similar findings have also been identified in the FXS literature, with differences in object attention emerging around 12 months of age also being related to ASD symptoms (Roberts et al., 2012). However, it is unclear if

object attention profiles found in ASIBs and FXS infants are similar or different given both groups are at high risk for developing ASD. Identifying the development of object attention in these high-risk groups individually, in addition to the relationship of object attention on their ASD outcomes, will further the current literatures understanding of their phenotypic profiles and help with developing targeted interventions.

Cross-Group Comparisons for Object Attention. The first aim of the present study was to examine differences in object attention at 9, 12, and 24 months of age across typically developing infants and four clinical groups: ASIBs, ASIBs+ASD, FXS, and FXS+ASD infants. At nine months, object attention was found to significantly differentiate the FXS from the FXS+ASD and ASIBs+ASD groups, with infants with FXS spending more time attending to the toy object. Descriptively, the FXS+ASD and ASIB+ASD groups exhibited less object attention than ASIBs, FXS, and typically developing infants; however, infants with FXS and ASIB infants exhibited more object attention than their TD peers, potentially demonstrating specific phenotypic profiles emerging at nine months of age. Conversely, these differences then disappeared at twelve months with no differences in object attention emerging across all five groups. However, at 24 months, object attention only significantly differentiated the typically developing infants and the ASIB infants. Similar, but inverted trends at 9 months were observed at 24 months with infants with FXS+ASD and ASIBs+ASD attending to the toy object more than infants with FXS and ASIBs. In general, ASD outcomes in the high-risk infants (FXS+ASD and ASIB+ASD) appears to play a role in their object attention development with increased attention at 9 months and decreased attention at 24 months.

These data also suggest that infants with FXS and ASIBs demonstrate similar object attention profiles regardless of ASD status at 9, 12, and 24 months of age.

Object Attention Trajectories. Given the variability found in the object attention literature between cross-sectional and longitudinal methods, the present study then examined object attention trajectories across 9 to 24 months of age in comparison to the results described above. Although not statistically significant in the cross-sectional models, the trends identified above were identified statistically from a longitudinal perspective. Specifically, the FXS+ASD and ASIB+ASD infants demonstrated increases in their object attention across 9 to 12 months in comparison to their TD peers; however, the ASIB and FXS groups demonstrated decreases in their object attention across 9 to 24 months of age. The results concur with the cross-sectional analyses suggesting similar object attention profiles across the high-risk groups based on their ASD outcomes. Interestingly, the ASIB+ASD and the FXS+ASD appear to differentiate across 12 to 24 months, descriptively, and may potentially point to an age in development where their attention profiles begin to diverge. Overall, the present study's results point to significant overlap across the phenotypic profiles with regards to object attention development in early infancy.

Object Attention and ASD Outcomes. As highlighted thus far, object attention development appears to differentiate the high-risk groups (FXS and ASIBs) based on ASD outcomes, but the present study also examined if their trajectories predict their ASD outcomes at 24 months. Findings suggest that as object attention increases over time, the high-risk infants' ASD symptoms at 24 months also increase. Diagnostically, results suggest that changes across 9 to 24 months in object attention are predictive of the high-

risk infants developing ASD at 24 months of age. Visually, the high-risk sample appears to diverge around 12 months of age, with the non-ASD group (FXS and ASIBs only) attending to the toy object significantly less and the ASD group (FXS+ASD and ASIB+ASD) increasing their attention to the toy object over time. In general, not only do object attention profiles differ within the high-risk group based on ASD status, these early attention trajectories are also predictive of increased ASD symptomology and ASD diagnostic outcomes.

The present study's findings align with the current literatures understanding of object attention in the ASIB population, but is one of the first to look at object attention in isolation and in relation to other high-risk populations. Similar to Klin and Jones' (2013) findings, our ASIB sample that went on to develop ASD exhibited increases in their object attention beginning at 9 months, rather than 12, and continuing into 24 months of age. Furthermore, similar to Rice et al. (2012), increased object attention was related to increased ASD symptom severity. Additionally, these findings add to the literature suggesting that ASIBs and ASIBs+ASD's object attention is different than their TD peers at specific age points in addition to longitudinally beginning in the first year of life and continuing into the second year. Lastly, infant ASIB's object attention appears to be impaired as early as nine months and can take on a different trajectory based on their ASD outcomes and severity of symptoms.

Within the FXS literature, this is the first study to look at object attention longitudinally and in comparison to other high-risk populations. Expanding on Roberts et al. (2012), the present study's results suggest infants with FXS, regardless of ASD outcomes (FXS and FXS+ASD), differ from their typically developing peers at and

across 9 to 24 months of age. Additionally, object attention trajectories were identified as an early predictor of a later ASD diagnosis and increased ASD symptomology in FXS at 24 months. Both the present study and Roberts et al. (2012) were able to demonstrate the predictive relationship between object attention and ASD outcomes despite one using an ASD symptom scale and the other using an ASD diagnostic measure.

Conversely to Roberts et al. (2012), object attention appeared to be relatively similar to the TD infants at 12 months of age. Despite utilizing the same measure of visual attention, this could be due to the present study's typical sample being different given their typical sample spent less time attending to the object at 12 months compared to our typical sample at 12 months. Additionally, the FXS samples across both studies are were relatively similar, even though Roberts and colleagues (2012) did not parse apart their FXS sample based on ASD outcomes, suggesting the measure of object attention was quite stable across two independent samples. Furthermore, similar nonlinear trajectories of object attention in FXS observed in the present study were also observed in the FXS group across 9 to 18 months in Roberts et al. (2012). The large drop in object attention observed in the present study's sample from 12 to 24 months may have also been observed by Roberts and colleagues (2012) had they followed their sample beyond 18 months. Overall, both studies provide evidence for impairments in object attention emerging as early as nine months of age in infants with FXS with the present study suggesting different trajectories of object attention depending on their ASD symptom severity and diagnostic outcomes.

In conclusion, the present study's findings on object attention have complemented the literature within the ASIB population suggesting differential object attention

trajectories emerging as early as nine months of age with these trajectories being predictive of later ASD outcomes. Furthermore, the present study has begun to explore the development of object attention in FXS, also suggesting differential trajectories emerging at nine months that were similar to ASIBs and also predictive of later ASD outcomes. Interestingly, as also suggested by Roberts et al. (2012), both infants with FXS and ASIBs object attention trajectories highly overlap, in addition to the FXS+ASD and ASIB+ASD object attention trajectories, suggesting a common profile despite both groups being etiologically different.

The present study provides several research and clinically relevant implications. First, the study builds on the current ASIB literature suggesting early impairments in object attention; however, the need to begin investigating the effectiveness of early interventions within this population still exists. A recent review of the current literature on interventions implemented within the ASIB population suggests positive findings on the short-term outcomes of social engagement and communication through parent-mediated interventions (Bradshaw, Steiner, Gengoux, & Koegel, 2015). As the field continues to reveal evidence suggesting ASD can be identified in high-risk infants, the ability to intervene at these early ages is also crucial to improving outcomes. Additionally, since FXS can be identified prenatally or even at birth, this can be an ideal population to investigate the effectiveness of early interventions if research continues to support similar object attention trajectories across both high-risk groups.

Limitations. While the present study builds on the object attention literature in genetically high-risk infants, and there are several strengths to this work including a prospective longitudinal design and cross-syndrome comparisons, there are also

limitations. Given the present study parsed the two high-risk groups based on their clinical outcomes, this significantly reduced the sample size. Additionally, examining object attention in groups similar to FXS matched on developmental level (e.g., Down syndrome) would be useful to see how these findings are unique or similar to other developmental disorders. Furthermore, as mentioned previously, this study utilized only males with FXS due to the high variation across gender within FXS, suggesting these results cannot be generalized to females with FXS. Lastly, the use of behavioral coding to collect object attention data in an attempt to keep the context natural can result in more error across observations than the precision of utilizing methods such as eye tracking.

Summary and Future Directions. Object attention impairments appear to emerge as early as nine months of age in infants at high genetic risk for ASD across two distinct etiologies. These impairments can vary depending on their ASD outcomes, but are still impaired relative to typically developing peers. Infants with FXS and infant ASIBs demonstrate remarkably similar object attention profiles regardless of ASD outcomes and despite them being etiologically different. Furthermore, these impaired object attention trajectories across 9 to 24 months are predictive of ASD outcomes and increased symptomology, suggesting the need for early intervention in an attempt to improve clinical outcomes.

Future research can build on the use of cross-syndrome approaches to investigate early impairments in infants at-risk for developing ASD. Additionally, the use of biobehavioral models (e.g., behavior and physiological data) can expand on these findings providing a more detailed understanding of the development of attention. Furthermore, investigating these trajectories prior to 9 months and beyond 24 months

can widen the developmental lens that we currently understand within attention, including object attention, in these high-risk samples. Additionally, future research can compare more naturalistic methods of attention and eye tracking to validate the substantial amount of literature utilizing eye tracking methodology. Lastly, results of this study can be utilized toward the development of targeted interventions to increase quality of life in these high-risk infants.

Table 1.1

Demographic and behavioral variables at person level

Group	<i>n</i> Participants	Mean	SD	Min	Max
FXS					
<i>n</i> Assessments	10	1.68	0.72	1.00	3.00
Average VDQ	10	60.30	15.80	30.80	92.26
Average NVDQ	10	75.97	14.79	52.08	108.60
FXS+ASD					
<i>n</i> Assessments	15	1.52	0.71	1.00	3.00
Average VDQ	15	49.53	20.79	16.21	92.26
Average NVDQ	15	63.83	19.83	30.85	100.78
ASIB					
<i>n</i> Assessments	17	1.77	0.72	1.00	3.00
Average VDQ	17	82.23	18.90	35.93	128.69
Average NVDQ	17	98.51	20.70	47.08	130.58
ASIB+ASD					
<i>n</i> Assessments	8	1.91	0.81	1.00	3.00
Average VDQ	8	79.48	17.02	35.58	106.33
Average NVDQ	8	102.09	18.34	69.29	142.39
TD					
<i>n</i> Assessments	28	1.79	0.80	1.00	3.00
Average VDQ	28	98.49	14.86	77.87	140.59
Average NVDQ	28	107.60	16.41	77.84	154.36

Note. FXS=fragile X syndrome; ASD= autism spectrum disorder; ASIB= infants with an older sibling diagnosed with ASD; TD=typically developing; VDQ= verbal developmental quotient; NVDQ= nonverbal developmental quotient

Table 1.2

Piecewise multilevel models examining change in object attention across age and group in comparison to typically developing infants

Variable	β	<i>SE</i>	<i>t</i>	<i>p</i>
Intercept	62.73	12.71	4.83	0.000**
VDQ	0.02	0.11	0.15	0.882
NVDQ	0.02	0.11	0.11	0.909
ADOS-2 CSS	0.30	0.87	0.35	0.728
9 to 12 months	-3.39	6.09	-0.56	0.578
9 to 24 months	4.89	6.96	0.70	0.482
FXS	14.54	9.59	1.47	0.143
9 to 12 months	-4.10	11.34	-0.36	0.718
9 to 24 months	-26.69	13.80	-1.93	0.054*
FXS+ASD	-13.83	10.25	-1.35	0.178
9 to 12 months	31.22	11.35	2.75	0.006**
9 to 24 months	8.85	11.81	0.75	0.454
ASIB	3.52	6.93	0.51	0.612
9 to 12 months	3.59	9.12	0.39	0.694
9 to 24 months	-20.78	10.25	-2.03	0.043**
ASIB+ASD	-11.82	8.58	-1.38	0.169
9 to 12 months	19.83	10.96	1.81	0.071*
9 to 24 months	16.37	13.71	1.19	0.233

Note. FXS=fragile X syndrome; ASD= autism spectrum disorder; ASIB= infants with an older sibling diagnosed with ASD; VDQ= verbal developmental quotient; NVDQ= nonverbal developmental quotient; ADOS-2= Autism Diagnostic Observation Schedule, Second Edition; CSS= Calibrated Severity Scores; *= $p < 0.10$; **= $p < 0.05$

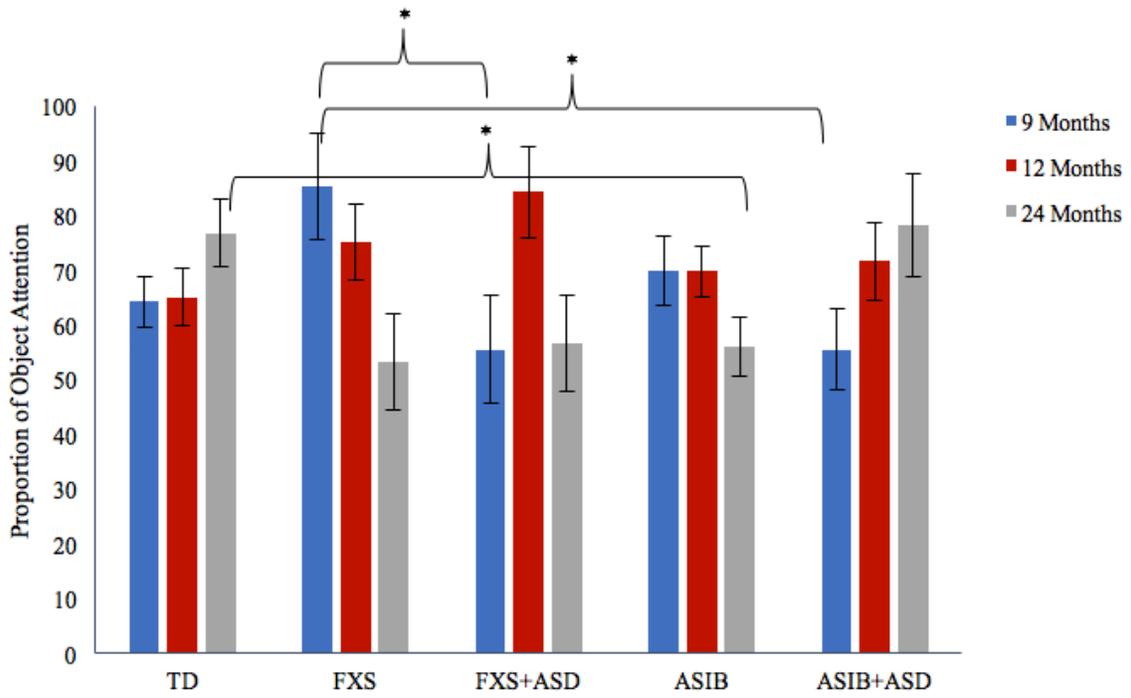


Figure 1.1 Proportion of Object Attention Across Groups and Within Chronological Age with Standard Error Bars (± 1); $*=p<0.05$

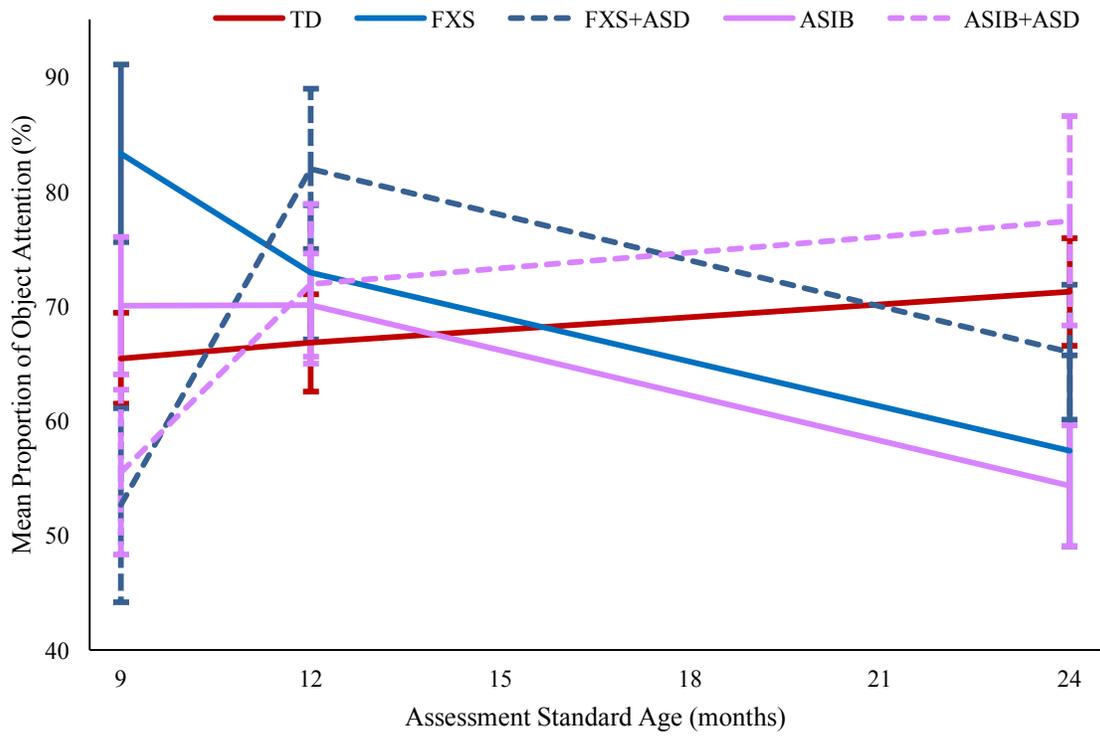


Figure 1.2 Marginal Means of Object Attention Across Group and Chronological Age with Standard Error Bars (± 1).

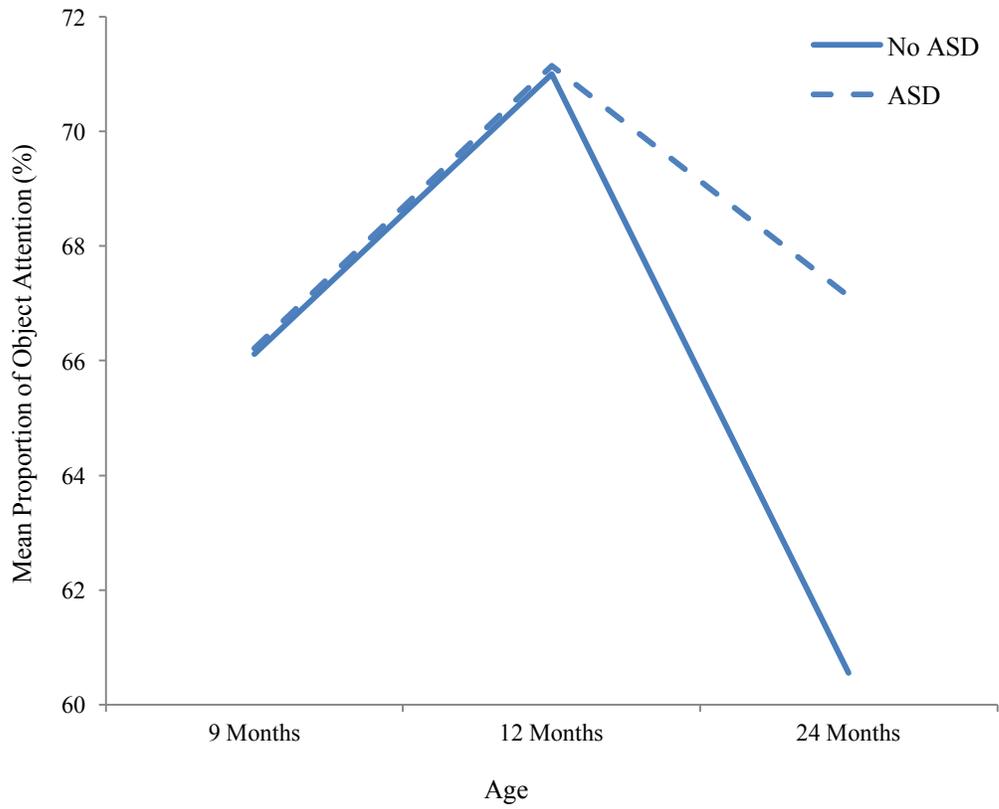


Figure 1.3 Mean Levels of Proportion of Object Attention Across Age in High-Risk Infants Based on ASD Outcomes

CHAPTER 2: DEVELOPMENT OF SOCIAL AND NONSOCIAL ATTENTION DURING THE FIRST YEAR OF LIFE IN INFANTS AT-RISK FOR AUTISM SPECTRUM DISORDER

2.1 SUMMARY

Early social and nonsocial attention impairments have been identified as significant predictors of social functioning within ASD. Infant ASIBs and infants with FXS have both been found to be at high genetic risk for developing ASD. Despite ASIBs being shown in the literature to have early social and nonsocial attention impairments, no research to date has examined if similar social attention deficits appear in infants with FXS; however, nonsocial attention impairments in infancy have been identified in FXS. Furthermore, no study to date has investigated the development of attentional profiles from a cross-syndrome perspective. The present study is the first to examine social and nonsocial attention profiles in infant ASIBs and infants with FXS parsed apart based on their ASD diagnostic outcomes in comparison to typically developing same-aged peers utilizing multiple methodological approaches within the first year of life. Results revealed that differences in social and nonsocial attention were identified at 6 and 12 months of age, but not 9 months. Longitudinally, infants with FXS and infant ASIBs exhibited distinct social and nonsocial attention profiles; however, they were similarly impacted based on their ASD outcomes. Social and nonsocial attention trajectories did not predict later ASD outcomes or symptoms; however, ASD outcomes did decrease social and increase nonsocial attention within both high-risk groups.

2.2 INTRODUCTION

Attention in infancy is a central mode of communication prior to grasping, crawling, walking, or talking while remaining one of the most important channels of interpersonal exchange (Harel, Gordon, Geva, & Feldman, 2011). Social attention is important for early development because of its role in establishing social engagement, the formation of attachment relationships, and development of joint attention skills (Ibanez et al., 2008). Social and nonsocial attention in infants has been shown to be an early indicator of developmental and cognitive outcomes, both in clinical and typical populations (Colombo et al., 2004). The present study examines early trajectories of social and nonsocial attention from a cross-syndrome approach in infants at high-genetic risk for developing ASD: (1) infants with an older sibling diagnosed with ASD (ASIBs) and (2) infants with fragile X syndrome (FXS), compared to (3) typically developing controls. Given the lack cross-syndrome comparisons of social and nonsocial attention in the literature, it is unclear if the social and nonsocial attention profiles of these high-risk groups are distinct or similar. Delineation of syndrome-specific social and nonsocial attention profiles will further the current understanding of how these phenotypic profiles overlap or differ and potentially provide information for the development and implementation of targeted interventions (e.g., what skills should interventions be targeting and when we should start to intervene).

Social and Nonsocial Attention in ASD

ASD is diagnosed through observing impairments in the development of social and communication skills, the presence of repetitive and stereotyped behaviors, and restricted interests (APA, 2013). Although ASD is typically not diagnosed in children

until four years-of-age or later (CDC, 2016; Charman & Baird, 2002; Shattuck et al., 2009), evidence suggests that ASD symptoms are present in up to 50% of infants during the first year of life with 80% of parents reporting abnormalities by the time the child reaches two years of age (Dahlgren & Gillberg, 1989; DeGiacomo & Fombonne, 1998; Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013). Given the disconnect between presenting symptoms of ASD in the first two years of life and the average age of diagnosis not occurring until age four (Christensen et al., 2016), current research has been utilizing longitudinal studies with infants identified as high-risk for ASD that have an older sibling diagnosed with ASD (ASIBs). With the established genetic component and high familial risk of ASD found in the ASIB literature (Garon et al., 2009), this is an ideal group to use to study the early development of ASD. Additionally, ASIBs allow for researchers to examine the development of the broad autism phenotype (BAP), or those who exhibit symptoms of ASD but their symptoms are not significant enough to meet diagnostic criteria (Bolton, Macdonald, Pickles, & Rios, 1994). Although the underlying causes of the higher risk for developing ASD in ASIBs are unknown, prevalence rates for these at-risk infants are reported to range from 2-28% of the infant sibling population with most studies suggesting a risk of around 18% (CDC, 2014; Messinger et al., 2015; Gronborg, Schendel, & Parner, 2013). Researchers have examined ASIBs both longitudinally until diagnostic determination is made (Jones & Klin, 2013) and from solely an at-risk perspective independent of later diagnoses (Dewaele, Demurie, Warreyn, & Roeyers, 2015).

Within the past few years, previous research has found that infant ASIBs significantly differ in their social and nonsocial attention abilities with these differences

emerging as early as two months of age (Jones & Klin, 2013). Additionally, some literature has identified decreased attention to social stimuli being present in infants ASIBs as young as 6 months (Chawarska, Macari, & Shic, 2012; Shic, Macari, & Chawarska, 2014) with similar findings occurring during the second year of life (Chawarska, Ye, Shic, & Chen, 2015; Pierce et al., 2016; Pierce, Conant, Hazin, Stoner, & Desmond, 2011; Shic et al., 2011) and into preschool ages (Sasson et al., 2011; Shi et al., 2015). Specifically, research has identified decreases in attention to eyes, increases in mouth and body attention, and increases in background and object attention (Chawarska, Macari, & Shic, 2013; E. J. H. Jones et al., 2016; W. Jones & Klin, 2013; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011). However, decreases in social attention does not automatically result in increased object attention (Chawarska et al., 2013). Furthermore, specific facets of social attention have been identified as potentially salient risk markers including: using specific dyadic cues (using child-directed speech and making eye-contact; Chawarska et al., 2012) or preference for geometric patterns or objects related to circumscribed interests (Pierce et al., 2016, 2011; Sasson et al., 2011; Shi et al., 2015). Conversely, some studies have found that ASIBs later diagnosed with ASD do not differ at all in their social and nonsocial attention (Elsabbagh et al., 2013; Elsabbagh et al., 2014; Hutman, Chela, Gillespie-Lynch, & Sigman, 2012; Sasson & Touchstone, 2014). Despite the inconsistent findings in the literature, there is evidence to suggest abnormalities in social and nonsocial attention can appear early in infancy well before the age of diagnosis in these infants who go on to receive a diagnosis of ASD.

Limitations in the Current Literature. The majority of the literature has chosen to utilize cross-sectional analyses to examine social and nonsocial attention. The use of

cross-sectional analyses could play a role in the variability of findings based on what age point researchers choose to examine. Of the select longitudinal studies, evidence has pointed to social and nonsocial attention being quite salient across infancy and not necessarily distinct enough to identify at a specific age point (Jones & Klin, 2013). For example, the cross-sectional literature has identified differences in social attention at 6 months but not at 12 months in the same sample (Jones et al., 2016). Due to the limited amount of research examining social and nonsocial attention utilizing longitudinal methods, additional research is needed to help decipher these variable findings within the substantive cross-sectional literature. The present study aims to add to the current literature on social and nonsocial attention utilizing ASIBs along with both cross-sectional analyses at several age points and longitudinal analyses while comparing across findings.

Advances in technology over the past decade have allowed us to quantify abnormalities in social and nonsocial attention in children and adults with ASD that appear to derail the development of socialization (for review, see Guillon, Hadjikhani, Baduel, Rogé, & Rogé, 2014). The literature discussed above primarily utilized the methodology of eye tracking; however, these results have yet to be replicated through naturalistic observation techniques to confirm their ecological validity. Although researchers are attempting to use more naturalistic stimuli within their eye tracking paradigms, their findings may not generalize to real life interactions and situations. One study utilizing a group of undergraduates to examine differences in social attention across methodology suggests that experimental context may be important when examining social and nonsocial attention and caution should be exercised when using only a video

presented stimulus as a substitute for real life (Freeth, Foulsham, & Kingstone, 2013). Given the surge of eye tracking studies in the current literature, the present study aims to replicate some of their findings utilizing a naturalistic (e.g., face-to-face) interaction as part of a standardized ASD assessment measure.

Social and Nonsocial Attention in Fragile X Syndrome. Fragile X syndrome (FXS) is caused by a mutation on an unstable trinucleotide (CCG) repeat expansion on the fragile X mental retardation 1 (FMR1) gene, which is located on the long arm of the X chromosome (Hagerman & Hagerman, 2002). FXS is the most common inheritable genetic cause of intellectual disability and affects approximately one in 3500 males (McDuffie et al., 2015). Due to the documented differences in males compared to females with FXS (Hagerman et al., 2017), the current study explicitly focuses on infant males with FXS. FXS is characterized by mild to severe ID with a series of other deficits including anxiety, social deficits, and abnormalities in communication, gaze aversion, inattention, impulsivity, aggression, and hyperactivity (Cordeiro et al., 2013).

Similar to ASIBs, there is high comorbidity of FXS and ASD with about 50-75% of children with FXS meeting criteria of ASD (Abbeduto, McDuffie, & Thurman, 2013; Clifford et al., 2007; Klusek et al., 2014). Overall, males with FXS who meet diagnostic criteria for ASD are at-risk for markedly poorer outcomes compared to those with only FXS (Abbeduto, McDuffie, & Thurman, 2013; Hartley et al., 2011). Understanding of the underlying mechanisms for the perceived comorbidity of ASD and FXS is controversial with some scholars hypothesizing that ASD symptoms in children with FXS are due to different mechanisms than those found in children with ASD alone (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; McDuffie et al., 2015). More research is needed to

distinguish the phenotypic profiles of children with ASD alone, children with FXS alone, and children with comorbid diagnoses of FXS and ASD to further the understanding of the impact of ASD symptoms and comorbid ASD diagnoses within and across individuals with FXS.

In infants with FXS, deficits in social communication have been identified as one of the earliest and most apparent features relative to early markers of ASD (Hogan et al., 2017). Specifically, infants with only FXS have been described as having a delay in social development coupled with some strengths in their socialization skills (e.g., sustaining eye-contact); whereas infants with FXS and a comorbid diagnosis of ASD have been described as having aberrant social development with a clear absence of social behaviors (e.g., reduced eye contact, limited social interest, and lack of social smiling). Furthermore, specific aspects within social communication have been identified as potentially differentiating infants with FXS and infant ASIBs including: social babbling, eye-contact, social interest and affect, and social referencing (Roberts, Tonnsen, McCary, Caravella, & Shinkareva, 2016). Given similar social communication deficits have been identified as potential early markers for ASD in both infants with FXS and infants ASIBs, these are two phenotypically different, but ideal groups to compare with respect to their early development and ASD outcomes.

In addition to general social communication deficits, social gaze avoidance in interactions is a particularly predominate behavioral feature of individuals with FXS. In a sample of 12- to 28-year-old males, eye tracking during a naturalistic conversation task revealed they could engage in social gaze approximately 20% of the time during a 10-minute conversation task (Hall et al., 2015). Interestingly, this study also found higher

levels of autism symptoms associated with greater impairments in social gaze for their control sample. The majority of the current literature focuses on general socialization or social gaze avoidance behaviors in FXS utilizing adolescents and adults, similar to Hall et al. (2015). Generally speaking, attention is a relative weakness in boys with FXS compared to their TD peers and can be subsequently related to ASD symptoms (Scerif et al., 2012). In comparison to ASD research, no work has been done to examine the specific aspect of early social attention in infants and young children with FXS. One study has examined early nonsocial attention in infants with FXS and found infants with FXS spent majority of their time attending at a toy object with increased nonsocial attention relating to increased ASD symptoms (Roberts et al., 2012). However, this study did not include another ASD high-risk group and did not examine social attention profiles in these FXS infants. With FXS having substantial phenotypic overlap with ASD and clearly documented early socialization deficits relative to ASD, examining how social and nonsocial attention emerges within this population serves as a gateway to identify biological mechanisms within ASD.

The Present Study

The aim of the present study is to examine early behavioral trajectories of social and nonsocial attention in infants who are at high genetic risk for ASD, including both (1) infants with FXS and (2) infant ASIBs in comparison to (3) TD controls across 6 to 12 months of age. The two high-risk groups (e.g., infants with FXS and infants with ASD) were parsed apart based on their ASD outcomes to create a total of five groups of infants: (1) FXS, (2) FXS+ASD, (3) ASIBs, (4) ASIBs+ASD, and (5) TD infants. Furthermore, the present study will utilize naturalistic observation approaches coupled with cross-

sectional and longitudinal analyses to examine how social and nonsocial attention emerges and differs across the four clinical groups in comparison to their TD peers.

The present study also aims to examine how social and nonsocial trajectories predict ASD symptoms and ASD diagnoses at 24 months of age within the high-risk infants (FXS and ASIBs). Specifically, analyses will be conducted examining how these trajectories influence ASD outcomes from a categorical perspective (ASD diagnostic outcomes) and from a continuous perspective (ASD symptom severity). The benefit of examining ASD in ASIBs and FXS continuously and categorically will allow us to see if social and nonsocial attention trajectories are predictive of ASD at any level across the spectrum, or if there are significantly different trajectories within the high-risk sample (FXS and ASIBs) based on their diagnostic outcomes. Within the literature on FXS, ASD has been examined categorically through diagnostic measures (Hatton et al., 2006; Wolff et al., 2012) and continuously through symptom severity scores (McDuffe, Thurman, Hagerman, & Abbeduto, 2015). Each of these analyses will provide different information about the behavioral phenotype of FXS and ASIBs in relationship to social and nonsocial attention. The present study's specific research questions and hypotheses are as follows:

1. How do infants with FXS, infant with FXS+ASD, infant ASIBs, infant ASIBs+ASD, and TD infants differ in their social and nonsocial attention at each standard assessed age point (6, 9, and 12 months)?
 - a. It is hypothesized that infants with FXS and infants with FXS+ASD will demonstrate increased proportions of nonsocial attention and decreased social attention across each age time point (6, 9, and 12 months) compared to infant ASIBs, infant ASIBs+ASD, and TD infants.

- b. It is hypothesized that infant ASIBs and infant ASIBs+ASD will demonstrate increased proportions of nonsocial attention and decreased social attention across each age time point (6, 9, and 12 months) compared to TD infants.
2. How do infants with FXS, infant with FXS+ASD, infant ASIBs, infant ASIBs+ASD and TD infants differ in their social and nonsocial attention trajectories across 6, 9, and 12 months of age?
 - a. It is hypothesized that infants with FXS and infants with FXS+ASD will demonstrate increased slopes of nonsocial attention and decreasing slopes of social attention beginning at 6 months and continuing through 12 months of age in comparison to ASIB, ASIB+ASD, and TD infants.
 - b. It is hypothesized that infant ASIBs and infant ASIBs+ASD will demonstrate increased slopes of nonsocial attention and decreased slopes of social attention beginning at 6 months and continuing through 12 months of age in comparison to TD infants.
3. How do trajectories of social and nonsocial attention predict ASD diagnostic outcomes and ASD symptoms at 24 months in infants with FXS and infant ASIBs?
 - a. It is hypothesized that trajectories of social and nonsocial attention across 6 to 12 months of age will differentiate the high-risk infants who develop ASD from those who do not at 24 months.
 - b. It is hypothesized that increased trajectories of nonsocial attention and decreased trajectories of social attention across 6 to 12 months will be

predictive of elevated ASD symptoms at 24 months of age in infants later diagnosed with ASD.

2.3 METHOD

Participants

Data were drawn from two longitudinal studies on infant development in FXS conducted at the University of South Carolina. The first study included infants with FXS, infant ASIBs, and TD infants assessed at 9, 12, and 24 months of age. The second study was a supplemental study and included infant ASIBs and TD infants assessed at 6 months of age that then were enrolled in the first study. For the present study, participants included three groups of male infants: (1) infant with FXS, (2) infant ASIB, and (3) TD infants as controls (75.64% White, 10.26% Black or African American, 12.82% more than one race, and 1.28% race unknown or not reported; mean income = \$79,548.71, SD =\$51,335.87). All of the participants were assessed 1-4 times around the following ages: 6, 9, 12, and 24 months, with some of the participants entering the study at different time points (e.g., 6, 9 or 12 months). While it was the aim for all participants to be enrolled at either 6 or 9 months, some were not enrolled until 12 months of age. Additionally, some families missed assessments due to scheduling conflicts.

All infants were required to be full term (37 weeks or later) and reside with their biological mothers. Infants with FXS were recruited nationally through a registry of FXS research and through other ongoing research studies. Genetic reports were obtained to verify a full mutation diagnosis of FXS (CCG repeats of greater than 200 on the FMR1 gene). Infant ASIBs were enrolled if they had an older sibling with documentation of a diagnosis of ASD. Based on parental report, the TD group had no family history of ASD.

Infants enrolled in the ASIB and TD groups were verified through parental report to not have any documented developmental delays or diagnosed genetic or medical conditions at study entry. Both ASIB and TD control groups were recruited locally through advertising around schools, medical offices, and community centers. Participants were excluded from the study if they had a pre-existing condition (e.g. cerebral palsy, seizure disorder) or if they had hearing or vision impairments that would impact the results of this study. Each participant was assessed 1 to 3 times at the following time points: 6 months, 9 months, and 12 months. While the aim was for all the participants to be assessed as all three time points, some were not enrolled until 9 or 12 months of age. Additionally, a few families missed assessments due to family schedule conflicts. Outcome data were obtained at their 24-month assessment.

Participants include 19 infants with FXS, 26 infant ASIBs, and 23 TD infants with a total of 148 observations across groups. Infants with FXS have a total of 39 observations, infant ASIBs have a total of 59 observations, and TD infants have a total of 50 observations. Not all participants in the study were assessed at all three age points, and a few have not yet been seen for their 24-month assessment, resulting in some missing data and the inability to separate them for the five group analyses. Furthermore, some missing data occurred due to video malfunctions or the attention task not being video recorded or conducted ($N=5$; FXS=1, ASIB=1, TD=3). Clinical Best Estimate (CBE) diagnoses were utilized to differentiate the FXS and ASIB groups based on their diagnostic outcomes into those with FXS +ASD, only FXS, only ASIBs, and ASIBs+ASD. Participants' CBE's were determined by expert clinicians based on several measures including developmental and behavioral measures, family/medical history, and

gold standard measures for ASD. Although participants' CBE's were evaluated at 24 months of age, a reliable and sensitive diagnosis can be established at this age point with diagnostic stability rates around 82% (Ozonoff et al., 2015). Within the TD group, two participants were excluded from the analyses due to their CBE's suggesting ASD diagnoses. The retained sample included 10 infants with FXS, 9 infants with FXS+ASD, 13 infant ASIBs, 10 ASIBs+ASD, and 17 TD infants. For participant statistics, refer to Table 2.1.

Measures

Social and Nonsocial Attention. Participants were assessed with Autism Observation Scale for Infants (AOSI; Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008) at 6, 9 and 12 months of age. The AOSI is typically used as a direct, play-based observational measure to detect and monitor early signs of autism as they emerge in infants 6 to 18 months identified as high-risk for ASD. It encompasses a standard set of semi-structure activities to provide a socially interactive context in which a trained examiner engages the infant in play, while conducting a set of systematic presses to elicit certain target behaviors. When the AOSI is administered, participants are seated at a table in their mother's lap across from and facing a trained examiner. Within the set of semi-structured activities, there are two Free Play sessions where the examiner provides the child with several toys to interact with and also attempts to interact with the child (e.g., rolling a ball back and forth, playing blocks, looking at a picture book). Each Free Play session typically lasts between 3 to 5 minutes. The AOSI is video recorded by a second examiner and these Free Play sessions were later coded offline by trained examiners using Noldus Observer XT 10.5 (Noldus Information Technology, 2010).

Gaze behaviors were coded for each participant during both Free Play sessions across assessments as a measure of attention. Trained research staff, upon establishing an initial reliability standard of at least 80% agreement across three consecutive videos, coded the behavioral data offline. A master coder maintained the reliability and coded 20% of the data with a Cohen's kappa coefficient of ≥ 0.80 across all codes. The current kappa coefficient for data coded in the study is 0.84, which is considered almost perfect agreement (Viera & Garret, 2005). Five attention variables that were coded include: (1) looking at the parent, (2) looking at the experimenter, (3) looking away (child is looking anywhere else not defined in other behaviors), (4) looking at toys (e.g. toys used in the AOSI), and (5) attention obscured (when both eyes are not visible lasting longer than 1 second). All of the attention variables were coded if they happened for at least 1 second or longer across the entire duration of the Free Play task with each behavior having an onset and offset. Each attention variable was then extracted for every participant to represent a proportion of time in seconds that the behavior was exhibited. After coding and extracting the attention data, attention behaviors were compared between the first and second Free Play session to examine if differences in attention exist across sessions (e.g., did they warm up in the second Free Play compared to the first that resulted in more social or nonsocial attention). No significant differences were found; therefore, both Free Play sessions attention behaviors were combined and averaged for each participant.

Data were then combined to represent proportions of social stimuli (looking at parent and/or examiner) and looking at nonsocial stimuli (looking at toys) for the present study. Any participant who had more than 10% of their coded as obscured were planned to be dropped from the final analyses; however, none of the participants met this

criterion. Due to the variability among social initiations of the examiners and parents during the AOSI Free Play tasks, an additional code was included in all analyses counting the frequency of social bids by examiners and parents to control for this variability. Using criteria by Kochanska and Aksan (2004), a social bid is defined as any verbal or nonverbal attempt to engage a child. Utilizing this definition and behavioral descriptions, social bids were coded as either a verbal (remark, vocalization, question, request directed toward the child) or nonverbal (gesture request, pointing, showing, smile, or touch directed at the child) social bid in an attempt to engage each child in the task (Kochanska & Aksan, 2004; Willemsen-Swinkels & Buitelaar, 2000). The proportions of social and nonsocial attention were utilized as the dependent variables in the present study. The total number of social and nonsocial bids were included in all statistical models to control for examiner variability.

Developmental Level. Participants were assessed with the Mullen Scales of Early Learning (MSEL; Mullen, 1995) at each assessment (6, 9, and 12 months). The MSEL is an assessment used to measure cognitive and motor ability in children and is comprised of five scales that measure the following domains: Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language. Two different scores were constructed from scores obtained on the Mullen: a verbal developmental quotient (VDQ) using the expressive and receptive language scores and a nonverbal developmental quotient (NVDQ) from the motor and visual reception scores. Developmental ages for each domain within the developmental quotients will be averaged together to calculate a ratio verbal IQ ($\text{Mental Age} / \text{Chronological Age} \times 100$). Infants in the TD group performed in the average range when tested on the MSEL. The

median split-half internal consistency for each of the scales ranges from 0.75 to above 0.80 (Mullen, 1995). Test-retest reliability coefficients range from 0.70 to 0.80 (Mullen, 1995).

Autism Symptomology. The Autism Diagnostic Observation Schedule – Toddler Module (ADOS-T; Lord et al., 2012) was administered to majority of the participants (93%) at 24 months of age to provide outcome data. Five participants were administered the Autism Diagnostic Observation Schedule, Second Edition - Module 1 (Lord, Luyster, Gotham, & Guthrie, 2012) due to the ADOS-T not being available at the beginning of data collection. The ADOS-T is a semi-structured, standardized observational measure of behavioral symptoms significant to ASD (e.g., communication, social interaction, and repetitive behaviors and interests) for minimally verbal children aged 12-30 months. The ADOS-T consists of forty-one items scored on a 0 to 3 scale with a higher score indicating greater severity of autism symptoms. Fourteen of the forty-one items comprise the diagnostic algorithm to provide three ranges of concern: Little to No, Mild to Moderate, and Moderate to Severe risk. Examiners are required to reach research reliability prior to the administration of the ADOS-T. Reliability is achieved after coding three consecutive previously administered ADOS-T's at 80% agreement in scores and then administering and coding two of their own ADOS-T's. Ongoing reliability scoring for ADOS-T protocols within our research lab is 82.74% and 82.50% for the diagnostic algorithm. Within the literature, the ADOS-T has demonstrated excellent sensitivity and specificity (Luyster et al., 2009) and strong psychometric properties with an inter-rater reliability of 84% as measured by mean exact agreement (Luyster et al. 2009; Lord et al., 2012). Additionally, stability of receiving a clinical diagnosis of confirmation of or ruled

out ASD that utilized the ADOS-T remained when reevaluated one to two years later (Guthrie et al. 2013).

Although the present study utilizes two different ADOS modules, Gotham, Pickles, and Lord (2009) and Else et al. (2015) developed Calibrated Severity Scores (CSS) to standardize ADOS raw total scores across modules. These scores intend to provide a marker of severity of autism symptoms relative to age and language level. Scores range from 1 to 10 with scores between 1 and 3 representing non-spectrum classification, 4 to 5 representing autism spectrum, and 6 through 10 representing an autism classification. For the present study, CCS was utilized on a continuous scale to represent autism symptom severity within the FXS and ASIB groups. To complement the continuous analyses using CSS, categorical analyses were also utilized to examine how trajectories of social and nonsocial attention differ by diagnostic outcomes at 24 months. Including both continuous and categorical analyses is a strength given the different theoretical and measurement dimensions outlined previously.

Procedures

Participants were assessed in either their home or in the lab based on their age. They were assessed at the lab on the university campus at 12 months of age and in their homes at 6, 9 and 24 months of age. A team of two trained examiners complete the assessments. The AOSI was administered alongside a larger standardized protocol with a fixed sequence order. Behavioral coding was completed offline through video recordings of the assessment by trained research staff. The current study focuses on the proportion of social and nonsocial attention through gaze behaviors.

Data Analysis

Analyses were conducted in R version 3.3.3 to address the present study's research questions. First, data were examined for outliers, nonnormality, linearity, and homoscedasticity. Social and nonsocial attention were positively skewed, however, the residuals approached a normal distribution deeming transformation to be unnecessary. One TD participant was found to be a significant outlier with respect to his VDQ and was removed from the analyses. Next, correlations were examined to identify if any significant relationships existed among any variables being included in the models. Participants' proportion of social and nonsocial attention was not significantly correlated with any of the independent variables (VDQ, NVDQ, Verbal Bids, Nonverbal Bids, ADOS CSS). Participants' ADOS CSS was found to significantly correlate with their NVDQ ($r=-0.33$) and their VDQ ($r=-0.36$). Given VDQ and NVDQ were not significantly related to participants social and nonsocial attention, these variables were not included in the models to reduce the likely of losing power since we parsed the groups apart into smaller groups based on their ASD outcomes and we controlled for verbal and nonverbal bids. It should be noted that all the models were ran including VDQ and NVDQ to compare across findings and the findings did remain the same; however, one of the piecewise multilevel models (MLM) would not converge including VDQ and NVDQ. Lastly, a priori post hoc analyses were conducted to examine if the current sample size, although small, would have the power to find effects. Results of the power analysis suggested an 8% chance of finding a small effect (0.1), 44% chance of finding a medium effect (0.3), and a 91% chance of finding a large effect (0.5).

To answer the first research question, analyses utilized ANCOVA's to examine cross-group differences in their proportion of social and nonsocial attention at each standard age time point (6, 9, and 12 months) while controlling for verbal bids and nonverbal bids. To answer the second research question, piecewise MLM was utilized to examine trajectories of proportion of social and nonsocial attention across all five groups and standard age (6, 9, and 12 months) time points. MLM is ideal for examining these trajectories as it can account for nesting of observations within individuals and permit cross-individual differences in the number of assessments. In this model, participants proportion of social and nonsocial attention overtime were nested within four clinical groups. Proportion of social and nonsocial attention was predicted by participant's standard age, a dummy coded vector for Time 1 to Time 2 (6-9 months) and Time 1 to Time 3 (6-12 months), change from Time 1-2, change from Time 1-3, group status, and covariates for NVDQ and VDQ. This model was chosen to evaluate the trajectories of proportion of object attention across standard age (6-12 months) due to a potential nonlinear relationship occurring for some groups. Formulaic representations of the first and second level of this model are found in Equations 1 and 2 below.

Equation 1: Level 1 model for longitudinal analysis of proportion of social and nonsocial attention, Y

$$Y = \beta_0 + \beta_1 (\text{Time 1 to Time 2}_j) + \beta_2 (\text{Time 1 to Time 3}_j) + \beta_3 (\text{Group}_j) + \beta_4 (\text{Group}_j) * (\text{Time 1 to Time 2}_j) + \beta_5 (\text{Group}_j) * (\text{Time 1 to Time 3}_j) + \beta_6 (\text{Verbal Bids}_j) + \beta_7 (\text{Nonverbal Bids}_j) + r_{ij}$$

Equation 2: Level 2 model for longitudinal analysis of proportion of social and nonsocial attention

$$\beta_0 = \gamma_{00} + \mu_0$$

$$\beta_1 = \gamma_{00} + \mu_1$$

$$\beta_2 = \gamma_{00} + \mu_2$$

In Equation 1, the intercept can be interpreted as the mean value of the control group (TD) at Time 1 (6 months) with verbal bids and nonverbal bids at zero. The main effects of standard age are observed in the interaction terms between group and the two dummy coded variables. Trajectories of proportion of social and nonsocial attention from 6 to 9 months are seen in the coefficient “Group*Time 1 to Time 2” in Equation 3 and can be interpreted as the relative difference between the TD control group and the five high-risk groups object attention at 9 months of age. Trajectories of proportion of social and nonsocial attention from 6 to 12 months are seen in the coefficient “Group*Time 1 to Time 3” in Equation 3 and can be interpreted as the relative difference between the TD control group and the five high-risk groups social and nonsocial attention at 12 months. Equation 2 shows the level 2 random error added to control for clustering associated with participants.

To answer the third research question, participants’ slopes for 6 to 9 months and 6 to 12 months from Equation 1 will be extracted to represent their trajectories of social and nonsocial attention. Using regression and ANOVA models, participants’ slopes will be used to examine if trajectories of object attention are predictive of later ASD symptomology and ASD diagnostic outcomes within the two groups at high-risk for ASD (FXS and ASIBs). The high-risk sample was split into those who have ASD and those

who do not based on their CBE data. For the continuous analyses, the high-risk sample was used as a whole. The Overall, Social Affect (SA), and Restricted Repetitive Behavior (RRB) CSS are examined independently to assess if social and nonsocial attention is predictive of general or specific symptoms relative to ASD for the continuous analyses.

2.4 RESULTS

Cross-Group Comparisons

Social Attention. Participant groups were examined using ANCOVA's for significant differences in their proportion of social attention at each age point (6, 9, and 12 months) while controlling for verbal bids and nonverbal bids by including them in the models. At six months of age, significant group differences were found in participant's proportion of social attention, $F(4,18)=5.47$, $p=0.005$, $\eta^2= 0.50$. Pairwise comparisons suggest that infants with FXS ($M=31.21$, $SE=5.21$) demonstrated significantly more social attention in comparison to TD infants ($M=7.44$, $SE=2.26$), infant ASIBs ($M=4.98$, $SE=3.04$), and infant ASIBs+ASD ($M=7.32$, $SE=2.42$). Infants with FXS+ASD ($M=14.39$, $SE=3.69$) were not significantly different from the other four groups. At nine months of age, no significant group differences were found, $F(4,42)=0.35$, $p=0.84$, $\eta^2= 0.03$. At twelve months of age, a significant effect of group was found in participant's proportion social attention, $F(4,51)=4.09$, $p=0.006$, $\eta^2= 0.23$. Pairwise comparisons suggest infants with FXS ($M=17.57$, $SE=2.42$) spent significantly more time attending to the social stimuli in comparison to infant ASIBs+ASD ($M=9.05$, $SE=2.12$). Marginally significant differences were found between the infant ASIBs+ASD and the TD infants ($M=13.35$, $SE=1.85$). Infants with FXS+ASD ($M=11.87$, $SE=2.48$) and infant ASIBs ($M=9.05$, $SE=2.12$) were not significantly different from the other groups. See Figure 2.1.

Nonsocial Attention. Participant groups were examined using ANCOVA's for significant differences in their proportion of nonsocial attention at each age point (6, 9, and 12 months) while controlling for verbal bids and nonverbal bids by including them in the models. At six months of age, significant group differences were found, $F(4,18)=3.71$, $p=0.002$, $\eta^2=0.43$. Pairwise comparisons suggest that infants with FXS ($M=53.60$, $SE=9.22$) demonstrated marginally significantly less attention toward nonsocial stimuli in comparison to TD infants ($M=88.72$, $SE=4.01$). Infant ASIBs ($M=86.96$, $SE=5.37$), infants ASIBs+ASD ($M=85.41$, $SE=4.28$), and infants with FXS+ASD ($M=72.66$, $SE=6.54$) were not significantly different from the other groups. At nine months, no significant group differences were found, $F(4,42)=0.18$, $p=0.95$, $\eta^2=0.02$. At twelve months of age, significant group differences were found, $F(4,51)=2.81$, $p=0.035$, $\eta^2=0.16$. Pairwise comparisons suggest significant group differences between infants with FXS ($M=78.37$, $SE=3.21$) and infant ASIBs+ASD ($M=92.77$, $SE=3.27$). Marginally significant group differences were found between the ASIB+ASD infants and the TD infants ($M=81.31$, $SE=2.46$). Infant ASIBs ($M=84.47$, $SE=2.81$) and infants with FXS+ASD ($M=81.92$, $SE=3.29$) were not significantly different from the other groups.

Summary. Unexpectedly, infants with FXS demonstrated significantly higher rates of social attention and lower rates of nonsocial attention in comparison to the other groups at six and twelve months of age. The infants with FXS+ASD showed higher rates of social and relatively lower rates of nonsocial attention similar to their FXS peers; however, they were not significantly different from the other groups of infants. Additionally, all five groups were relatively similar in their social and nonsocial attention at 9 months of age. At 12 months, infant ASIBs+ASD demonstrated significantly lower

rates of social and higher rates of nonsocial attention in comparison to TD and FXS infants.

Trajectories Across Age and Group

Social Attention. Piecewise MLM's were utilized to examine how social attention changes across 6 to 12 months of age while controlling for verbal bids and nonverbal bids (Table 2.2) across the 4 clinical groups of participants in comparison to their TD peers. Results of the model suggest infants with FXS were significantly different on average in their change across time (6 to 9 and 6 to 12 months; $\beta=11.24$, $SE=5.75$, $t=2.00$, $p=0.047$) and that all participants demonstrated marginally significant changes in their social attention across 6 to 9 months ($\beta=4.84$, $SE=2.65$, $t=1.83$, $p=0.068$). Additionally, infants with FXS demonstrated significant changes in their social attention from 6 to 9 months ($\beta=-13.12$, $SE=5.91$, $t=-2.21$, $p=0.028$), whereas infant ASIBs+ASD demonstrated marginally significant changes in their social attention across 6 and 12 months of age ($\beta=-7.57$, $SE=3.93$, $t=-1.93$, $p=0.054$) in comparison to their TD peers. Infants with FXS+ASD and infant ASIBs did not demonstrate significant changes in their social attention across 6 to 9 month or 6 to 12 months in comparison to their TD peers. As shown in Figure 2.2, the results from the piecewise model are supported through graphing each groups marginal means at each age point.

Nonsocial Attention. Piecewise MLM's were utilized to examine how nonsocial attention changes across 6 to 12 months of age while controlling for verbal bids and nonverbal bids (Table 2.3) across the 4 clinical groups of participants in comparison to their TD peers. Unfortunately, running the model to include all variables (as shown in the data analysis section) resulted in the model not converging due to the study's small

sample size; however, parsing apart 6 to 9 months and 6 to 12 months into separate equations allowed for the model to converge. When examining participants' trajectories from 6 to 9 months, results suggest infants with FXS demonstrated marginally significant changes in their nonsocial attention on average across time ($\beta=-6.93$, $SE=4.12$, $t=-1.68$, $p=0.093$) along with all groups on average demonstrating marginally significant changes in their nonsocial attention from 6 to 9 months, ($\beta=-6.02$, $SE=3.28$, $t=-1.83$, $p=0.067$). When examining participants' change in nonsocial attention from 6 to 12 months, infant ASIBs+ASD demonstrated significant changes in their nonsocial attention ($\beta=9.06$, $SE=5.68$, $t=1.96$, $p=0.050$). As shown in Figure 2.2, the results from the piecewise model are supported through graphing each groups' marginal means at each age point.

Summary. Overall, all participants demonstrated significant changes in their social attention across 6 to 9 months. In infants with FXS, they exhibited the most change in their social attention over time, with a significant decline emerging across 6 to 9 months of age. Additionally, infant ASIBs+ASD exhibited a significant decline in their social attention across 6 to 12 months of age. Descriptively, you can see that both groups of infants with FXS (FXS and FXS+ASD) exhibited higher rates of social attention at 6 months and 12 months in comparison to their TD peers; however, the FXS+ASD infants' social attention rates are relatively lower than their FXS only peers. Conversely, the infant ASIBs (ASIBs and ASIBs+ASD) exhibited similar rates of social attention at 6 months compared to their TD peers and then lower rates at 9 and 12 months; however, similar to the infants with FXS+ASD, the ASIBs+ASD social attention rates were also relatively lower than their ASIB only peers.

For nonsocial attention, all groups exhibited changes in their social attention from 6 to nine months with infants with FXS, in general, exhibiting marginally significant changes in their social attention compared to their TD peers. Conversely to the social attention data, the nonsocial attention data did not differentiate as many groups except for the infant ASIBs+ASD, which demonstrated a significant incline in their object attention across 6 to 12 months. Descriptively, all the clinical groups exhibited increases in their nonsocial attention across 6 to 12 months while the TD infants demonstrated a decline overtime.

Trajectories Predicting Autism Symptomology at 24 Months

ASD Diagnostic Outcomes.

Social Attention. Linear regression analyses were utilized to examine if trajectories of social attention are predicative of ASD symptoms at 24 months of age within in the high-risk infants (FXS, FXS+ASD, ASIBs, and ASIBs+ASD). For participants' overall ASD symptoms, change in social attention across 6 to 9 months ($\beta=0.22$, $SE=0.17$, $t=1.35$, $p=0.185$) and across 6 to 12 months ($\beta=-0.18$, $SE=0.14$, $t=-1.24$, $p=0.223$) were not significant predictors, $F(1,40)=1.82$, $p=0.185$, $R^2=0.02$; $F(1,40)=1.53$, $p=0.223$, $R^2=0.01$, respectively. Similarly, for participants' Social Affect symptoms, change in social attention across 6 to 9 months ($\beta=0.26$, $SE=0.16$, $t=1.64$, $p=0.109$) and 6 to 12 months ($\beta=-0.18$, $SE=0.14$, $t=-1.31$, $p=0.199$) were not significant predictors, $F(1,40)=2.69$, $p=0.109$, $R^2=0.04$; $F(1,40)=1.71$, $p=0.199$, $R^2=0.02$, respectively. Lastly, for participants Restricted and Repetitive Behaviors, change in social attention across 6 to 9 months ($\beta=-0.03$, $SE=0.17$, $t=-0.20$, $p=0.843$) and 6 to 12

months ($\beta=0.14$, $SE=0.14$, $t=1.01$, $p=0.319$) were not significant predictors, $F(1,40)=0.04$, $p=0.843$, $R^2=0.000$; $F(1,40)=1.02$, $p=0.319$, $R^2=0.000$, respectively.

Nonsocial Attention. Linear regression analyses were utilized to examine if trajectories of nonsocial attention are predictive of ASD symptoms at 24 months of age within the high-risk infants (FXS, FXS+ASD, ASIBs, and ASIBs+ASD). For participants' overall ASD symptoms, change in nonsocial attention across 6 to 9 months ($\beta=-0.26$, $SE=0.22$, $t=-1.15$, $p=0.257$) and across 6 to 12 months ($\beta=-0.29$, $SE=0.36$, $t=-0.79$, $p=0.433$) were not significant predictors, $F(1,40)=1.32$, $p=0.257$, $R^2=0.01$; $F(1,40)=0.63$, $p=0.433$, $R^2=0.01$, respectively. Similarly, for participants' Social Affect symptoms, change in social attention across 6 to 9 months ($\beta=-0.18$, $SE=0.14$, $t=-1.31$, $p=0.199$) and 6 to 12 months ($\beta=-0.38$, $SE=0.35$, $t=-1.09$, $p=0.283$) were not significant predictors, $F(1,40)=1.71$, $p=0.199$, $R^2=0.02$; $F(1,40)=1.19$, $p=0.283$, $R^2=0.01$, respectively. Lastly, for participants' Restricted and Repetitive Behavior symptoms, change in social attention across 6 to 9 months ($\beta=-0.04$, $SE=0.22$, $t=-0.20$, $p=0.846$) and 6 to 12 months ($\beta=-0.28$, $SE=0.35$, $t=-0.78$, $p=0.439$) were not significant predictors, $F(1,40)=0.04$, $p=0.846$, $R^2=0.000$; $F(1,40)=0.61$, $p=0.439$, $R^2=0.000$, respectively.

Summary. Overall, participants' change in social and nonsocial attention across 6 to 9 and 6 to 12 months was not predictive of overall ASD symptoms in infants at high risk for developing ASD. Similarly, participants' change in social and nonsocial attention across 6 to 9 and 6 to 12 months was not predictive of Social Affect or Restricted and Repetitive Behavior symptoms.

ASD Diagnostic Outcomes.

Social Attention. Two ANOVA models were utilized to examine differences in infants at high-risk for ASD trajectories of social attention based on their diagnostic outcomes. For participants' change in social attention across 6 to 9 months, no significant group differences were found, $F(1,40)=2.30$, $p=0.137$, $\eta^2= 0.05$. Similarly, for participants' change in social attention across 6 to 12 months, no significant group differences were found, $F(1,40)=1.75$, $p=0.194$, $\eta^2= 0.04$.

Nonsocial Attention. Two ANOVA models were utilized to examine differences in infants at high-risk for ASD trajectories of nonsocial attention based on their diagnostic outcomes. For participants' change in nonsocial attention across 6 to 9 months, no significant group differences were found, $F(1,40)=1.53$, $p=0.223$, $\eta^2= 0.04$. Similarly, for participants' change in social attention across 6 to 12 months, no significant group differences were found, $F(1,40)=0.40$, $p=0.530$, $\eta^2= 0.01$.

Summary. Overall, participants' change in social and nonsocial attention across 6 to 9 and 6 to 12 months did not differentiate the high-risk infants who later developed ASD from the high-risk infants who did not go on to develop ASD at 24 months. Similar to the piecewise models, the participants' marginal means based on their diagnostic outcomes were graphed (Figure 2.3). Despite not finding statistically significant results between the groups, descriptively, we can see both groups exhibit slightly different trajectories. Specifically, the infants with ASD exhibit a decline in their social attention, whereas the infants without ASD rates of social attention remain relatively stable. Similarly, both groups of infants exhibited increasing rates of nonsocial attention; however, the infants with ASD nonsocial attention rates were slightly higher.

2.5 DISCUSSION

The present study, to the author's current knowledge, is the first to examine social and nonsocial attention utilizing a cross-syndrome approach in two groups of infants at high genetic risk for ASD: infants with FXS and infant ASIBs. Furthermore, the present study also examined if trajectories of social and nonsocial attention across 6 to 12 months were predictive of later ASD symptoms and diagnostic outcomes at 24 months within the high-risk sample. Within the current literature, evidence suggests that infant ASIBs exhibit deficits in social attention with a preference for nonsocial stimuli in comparison to their TD peers along with these impairments being linked to later ASD outcomes (Chawarska et al., 2016; Hall et al., 2015; Jones & Klin, 2013; Shic et al., 2011).

Similarly, infants with FXS have also demonstrated increased rates of nonsocial attention in comparison to their TD peers with these impairments being related to elevated ASD symptoms in toddlerhood (Roberts et al., 2012). Although individuals with FXS have been shown in the literature to exhibit general deficits in social communication (Hogan et al., 2017; Roberts et al., 2016) and social gaze avoidance (Hall et al., 2015), there has yet to be any literature published looking specifically at the early development of social attention. Additionally, given the high genetic risk for ASD in FXS (Abbeduto, McDuffie, & Thurman, 2013; Clifford et al., 2007; Klusek et al., 2014), this is an ideal group to examine how ASD impacts specific facets of development within FXS. Furthermore, it is unclear how the phenotypic profiles of social and nonsocial attention in FXS with ASD compare to other high genetic risk groups (e.g., ASIBs). Some groups argue that idiopathic ASD and FXS are two distinct disorders with FXS presenting with mild social and communication impairments, whereas others argue they are similar with

significantly overlapping profiles (Abbeduto, McDuffie, & Thurman, 2014; Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Kau et al., 2004; Kaufmann et al., 2004).

Cross-Group Comparisons for Social and Nonsocial Attention. The first aim of the present study utilized cross-sectional mechanisms to examine how infants with FXS and infant ASIBs, parsed apart by their ASD outcomes, differed in their social and nonsocial attention compared to their TD peers at 6, 9, and 12 months of age. Unexpectedly, infants with FXS demonstrated the highest rates of social attention and the lowest rates of nonsocial attention at 6 and 12 months of age; however, still atypical from their TD peers as hypothesized. Additionally, infants with FXS+ASD exhibited similar trends in their social and nonsocial attention as their FXS only peers; however, these rates were lower and relatively similar to the other clinical and typical groups. Furthermore, our results were comparatively similar to those found by Jones et al. (2016) who identified differences at 6 but not 12 months of age in a group of ASIB infants. In the present study, differences in groups were identified at 6 months and 12 months, but not at 9 months of age adding to the hypothesis of potentially disrupted social and nonsocial attention at one age point that then subsides at another in the infants with FXS and ASIBs+ASD. Unexpectedly, infant ASIBs and infant ASIBs+ASD were relatively similar to their TD peers with the exception of ASIBs+ASD exhibiting significantly lower social attention at 12 months in comparison to their TD peers also as hypothesized. Overall, specific subgroup patterns were not easily identified despite parsing the groups apart by their diagnostic outcomes, adding to the complexity of attempting to understand the development of social and nonsocial attention from a cross-sectional perspective. Depending on what age point researchers may choose to examine can potentially alter

their findings; however, these findings may imply specific time points when deficits begin to emerge or reemerge in these high-risk infants.

Social and Nonsocial Attention Trajectories. Given the variability found in the social and nonsocial attention literature between cross-sectional and longitudinal methods, the present study examined social and nonsocial attention trajectories across 6 to 12 months of age in comparison to the results described above. Although the cross-sectional analyses did not clearly identify within and across group trends, the longitudinal models picked up on potentially differing trends across the ASIB and FXS groups. In the present study's sample, it appears the added ASD diagnosis derailed and plateaued the infants with FXS+ASD's social attention trajectories in comparison to those infants with FXS only beginning as early as 6 months of age. Specifically, infants with FXS exhibited higher rates of social attention overall, but a general decline across time in comparison to the lower, stable rates observed in those with FXS+ASD. Similar inverse patterns were identified with respect to nonsocial attention across groups suggesting the added ASD diagnosis decreased social and increased nonsocial attention over time. Given this is the first paper to examine social attention in infants with FXS and FXS+ASD, replication is needed to validate these trajectories; however, their nonsocial attention trajectories appear relatively similar to Roberts et al. (2012) findings despite this study not parsing the infants with FXS apart by their ASD outcomes. Specifically, Roberts et al. (2012) also found nonlinear trends of object attention across 9 to 18 months and both studies range of proportion of nonsocial attention are similar.

Interestingly, the infant ASIBs and ASIBs+ASD exhibited inverse trends of social and nonsocial attention in comparison to the FXS and FXS+ASD sample. Specifically,

infant ASIBs and ASIBs+ASD exhibited similar social and nonsocial attention profiles across 6 to 9 months, but different from their TD peers. Across 9 to 12 months, the groups appear to diverge with a general decline in social attention and incline in nonsocial attention emerging overall in comparison to their TD peers. Similar social and nonsocial attention patterns identified in the FXS and FXS+ASD infants also emerged in the infant ASIBs+ASD and infant ASIBs. The added ASD diagnosis appears to derail and differentiate the ASIB and ASIB+ASD groups around 9 months; whereas the ASD diagnosis appears to impair social and nonsocial attention development in the infants with FXS and FXS+ASD as early as 6 months. Additionally, although the ASIB group did not have a diagnosis of ASD, their rates of social attention were also lower than their TD peers across time potentially providing evidence for the broader autism phenotype (BAP; Bolton et al., 1994) and its emergence in infancy. Lastly, the TD infants exhibited the lowest rates of social and highest rates of nonsocial attention at 6 months but as expected developmentally, the TD infant's social attention increased and their nonsocial attention declined over time.

Overall, the present study's results, with respect to the ASIB population, were comparatively similar to the current literature suggesting decreasing rates of social and increasing rates of nonsocial attention across 6 to 12 months coupled with differing trends emerging for the ASIB groups based on their ASD outcomes (Chawarska et al., 2016; Hall et al., 2015; Jones & Klin, 2013; Shic et al., 2011). The infant ASIBs were relatively similar to their TD peers with the infant ASIBs+ASD statistically standing out over time potentially implying the added diagnosis of ASD further impairs their social and nonsocial attention development. Although the infants with FXS and FXS+ASD

exhibited inverse trends in social and nonsocial attention overtime, both groups with a comorbid diagnosis of ASD exhibited lower rates of social and higher rates of nonsocial attention. Despite both groups exhibiting different attentional profiles, which adds evidence to the groups being two etiologically distinct disorders, comorbid ASD diagnoses appear to impair both groups similarly.

Social and Nonsocial Attention and ASD Outcomes. As highlighted throughout the present study, the current literature suggests early visual social and nonsocial attention should differentiate the high-risk groups (FXS and ASIBs) based on their ASD outcomes. The present study identified salient differences within the high-risk groups based on their ASD outcomes with respect to their social and nonsocial attention development across 6 to 12 months. However, another aim of the present study was to identify if trajectories of social and nonsocial attention within the high-risk infants predicts their later ASD diagnostic outcomes and symptomology. Inconsistent with our hypotheses, our findings suggest that infants with FXS and infant ASIBs trajectories of social and nonsocial attention do not predict later ASD diagnoses or increased ASD symptomology at 24 months of age as predicted.

Despite being different from our hypotheses, as shown in Figure 3 and in the longitudinal analyses, we can visually see the two groups exhibiting similar trends but those with comorbid ASD diagnoses demonstrate decreased social and increased nonsocial attention overtime. The present study is not the first to find attentional trajectories do not predict ASD outcomes in the ASIB literature (Elsabbagh et al., 2013). Given the high prevalence rates of ASD in FXS (Abbeduto, McDuffie, & Thurman, 2013; Clifford et al., 2007; Klusek et al., 2014), we generalized the ASIB literature's

findings onto the FXS literature since this is the first paper to examine early social attention in FXS. However, Roberts et al. (2012) found that increased rates of nonsocial attention at 12 months was indicative of increased ASD symptoms at 24 months. The differences in our findings could be due to the present study looking within both groups of high-risk infants rather than explicitly the FXS group.

In conclusion, the present study identified different trends of social and nonsocial attention across the two groups of high-risk infants: infants with FXS and infant ASIBs. Despite both groups exhibiting differing trends of social and nonsocial attention, comorbid ASD diagnoses impaired both groups similarly. The present study added evidence to the hypothesis of FXS and ASD being two etiologically distinct groups; however, similarly impacted by ASD. Furthermore, the present study provides evidence for social and nonsocial attention as potential prognostic indicators of ASD emerging in these high-risk groups that can be used for when and how to provide early intervention in these high-risk groups. Although social and nonsocial attention was not predictive of later ASD diagnostic outcomes and symptomology, both groups of infants exhibited different trajectories of social and nonsocial attention when parsed apart by their diagnostic outcomes. However, generally speaking, both groups exhibited an overall decline in social and increase in nonsocial attention

The present study provides several research and clinically relevant implications. First, the present study builds upon the current ASIB literature suggesting early impairments of social and nonsocial attention not only in ASIB infants but also within ASIB infants who go on to develop ASD. Furthermore, the present study builds on the notion pointed out by Jones & Klin (2013) that these visual attention profiles may be

more salient than we think and examining from a cross-sectional perspective may not be sensitive enough to pick up on these differences depending on what age you choose to assess. The present study also provided new information about visual attention development in infants with FXS and validated some of the findings identified by Roberts et al. (2012). Despite literature continuing to point to deficits in social and nonsocial attention in infants with FXS and infant ASIBs, there still lies a need to develop effective interventions for these high-risk infants in an attempt to remediate the potentially long term effects on later socialization skills. A recent review of the current literatures interventions implemented within the ASIB population suggests positive findings on the short-term outcomes of social engagement and communication through parent-mediated interventions (Bradshaw, Steiner, Gengoux, and Koegel, 2015). The ability to identify deficits in these high-risk populations early on, despite potentially not receiving an ASD diagnosis until preschool ages, is hopeful for the ability to intervene early and potentially improve long-term outcomes. Since FXS can be identified prenatally or at birth, this is an ideal population to study the effectiveness of early interventions if research continues to support similar deficits specific to ASD within these high genetic risk populations for ASD.

Limitations. While the present study builds on the current social and nonsocial attention literature within FXS and ASIB populations, and there are several strengths to this work including a prospective longitudinal design and cross-syndrome comparisons, there are also limitations to be mindful of when interpreting and generalizing the results. First, sample size is an apparent limitation given we parsed the high-risk samples apart by their diagnostic outcomes, thus reducing our power to find significant effects; however,

significant effects were found, but more potentially salient differences may have been identified with a larger sample size. Additionally, drawing on other groups similar to FXS from a developmental standpoint (e.g., Down Syndrome) to compare how visual attention develops across developmentally delayed populations would be beneficial. Furthermore, the present study only focused on males ultimately limiting the generalization of these findings to females. Lastly, although a strength of the present study given the majority of the current literature utilizes eye-tracking methodology, the present study's use of behavioral coding to collect visual attention data in an attempt to keep the context natural can result in more error across observations than the precision of eye-tracking methodologies.

Summary and Future Directions. Social and nonsocial attention impairments appear to emerge as early as six months in infants at high genetic risk for ASD across two etiologically distinct groups. These impairments can vary based on their ASD outcomes within and across groups (e.g., FXS and ASIBs). Infant's with FXS and infant ASIBs presented with distinctive social and nonsocial attention profiles; however, both groups were affected by ASD similarly exhibiting lower social and higher nonsocial rates of attention if they went on to receive a diagnosis of ASD at 24 months. Despite both groups being equally affected by ASD outcomes, their early trajectories of social and nonsocial attention in the first year of life was not predictive of later ASD diagnostic outcomes or symptomology.

Future research can build upon the use of cross-syndrome approaches to investigate early developmental profiles of social and nonsocial attention in infants at-risk for developing ASD. Additionally, the use of biobehavioral models (e.g., behavior

and physiological data) can expand on these findings by providing insight into whether what we are seeing behaviorally aligns with what these infants experience biologically and provide a holistic picture to visual attention development. Furthermore, expanding the study age down further and follow the infants later to get a larger picture of social and nonsocial attention development in these high-risk populations. Future research could also compare naturalistic approaches to measuring visual attention and eye tracking methodology in infants in an effort to validate the substantial literature utilizing eye tracking in comparison to real world interactions. Lastly, results of this study can be utilized to inform the development of interventions targeted to remediate early attentional deficits in these high-risk infants and ultimately increase quality of life long-term.

Table 2.1

Demographic and behavioral variables at person level

Group	<i>n</i> Participants	Mean	SD	Min	Max
FXS					
<i>n</i> Assessments	10	1.55	0.60	1.00	3.00
Average VDQ	10	67.47	18.29	38.94	96.75
Average NVDQ	10	89.27	18.80	65.43	132.92
FXS+ASD					
<i>n</i> Assessments	9	1.68	0.75	1.00	3.00
Average VDQ	9	63.46	13.10	40.13	79.37
Average NVDQ	9	80.94	21.75	48.15	108.60
ASIB					
<i>n</i> Assessments	13	1.65	0.75	1.00	3.00
Average VDQ	13	81.90	14.24	57.58	104.02
Average NVDQ	13	105.98	20.89	62.38	130.58
ASIB+ASD					
<i>n</i> Assessments	10	1.89	0.80	1.00	3.00
Average VDQ	10	76.14	10.78	66.72	106.30
Average NVDQ	10	106.16	13.97	82.79	134.91
TD					
<i>n</i> Assessments	17	1.73	0.72	1.00	3.00
Average VDQ	17	95.73	14.50	78.00	129.24
Average NVDQ	17	114.58	13.42	88.68	135.47

Note. FXS=fragile X syndrome; ASD= autism spectrum disorder; ASIB= infants with an older sibling diagnosed with ASD; TD=typically developing; VDQ= verbal developmental quotient; NVDQ= nonverbal developmental quotient

Table 2.2

Piecewise multilevel models examining change in social attention across age and group in comparison to typically developing infants

Variable	β	<i>SE</i>	<i>t</i>	<i>p</i>
Intercept	7.57	3.05	2.49	0.013**
Verbal Bid	0.05	0.05	0.95	0.344
Nonverbal Bid	-0.01	0.06	-0.23	0.819
6 to 9 Months	4.84	2.65	1.83	0.068*
6 to 12 Months	3.79	2.64	1.43	0.152
FXS	11.12	5.75	2.00	0.047**
6 to 9 Months	-13.11	5.94	-2.21	0.028**
6 to 12 Months	-6.34	5.64	-1.12	0.261
FXS+ASD	0.17	4.71	0.04	0.973
6 to 9 Months	-2.99	5.03	-0.60	0.552
6 to 12 Months	-1.47	4.89	-0.30	0.765
ASIB	-1.49	4.04	-0.37	0.713
6 to 9 Months	0.31	4.44	0.07	0.945
6 to 12 Months	-2.82	4.17	-0.68	0.500
ASIB+ASD	-1.89	3.71	-0.51	0.611
6 to 9 Months	-0.62	3.92	-0.16	0.875
6 to 12 Months	-7.60	3.93	-1.93	0.054*

Note. FXS=fragile X syndrome; ASD= autism spectrum disorder; ASIB= infants with an older sibling diagnosed with ASD; *= $p < 0.10$; **= $p < 0.05$

Table 2.3

Piecewise multilevel models examining change in nonsocial attention across age and group in comparison to typically developing infants

Variable	β	<i>SE</i>	<i>t</i>	<i>p</i>
<i>Model 1: 6 to 9 Months</i>				
Intercept	87.18	3.74	23.32	0.00**
Verbal Bid	-0.06	0.08	-0.72	0.471
Nonverbal Bid	-0.04	0.10	-0.37	0.715
6 to 9 Months	-6.03	3.28	-1.84	0.067*
FXS	-6.93	4.12	-1.68	0.093*
6 to 9 Months	8.85	5.71	1.55	0.122
FXS+ASD	-2.22	4.07	-0.54	0.587
6 to 9 Months	5.84	5.85	1.00	0.319
ASIB	1.77	3.67	0.48	0.631
6 to 9 Months	1.64	5.52	0.30	0.766
ASIB+ASD	6.57	3.76	1.75	0.081*
6 to 9 Months	-3.53	5.11	-0.69	0.490
<i>Model 2: 6 to 12 Months</i>				
Intercept	84.59	3.59	23.55	0.00**
Verbal Bid	-0.08	0.08	-1.04	0.299
Nonverbal Bid	-0.03	0.09	-0.29	0.776
6 to 12 Months	1.78	3.22	0.55	0.581
FXS	-3.37	4.82	-0.70	0.486
6 to 12 Months	-0.01	5.44	-0.01	0.999
FXS+ASD	1.30	5.03	0.26	0.797
6 to 12 Months	-0.91	5.67	-0.16	0.874
ASIB	1.80	4.58	0.39	0.695
6 to 12 Months	2.07	5.19	0.40	0.691
ASIB+ASD	1.88	4.36	0.43	0.667
6 to 12 Months	9.91	5.05	1.96	0.050**

Note. FXS=fragile X syndrome; ASD= autism spectrum disorder; ASIB= infants with an older sibling diagnosed with ASD; *= $p < 0.10$; **= $p < 0.05$

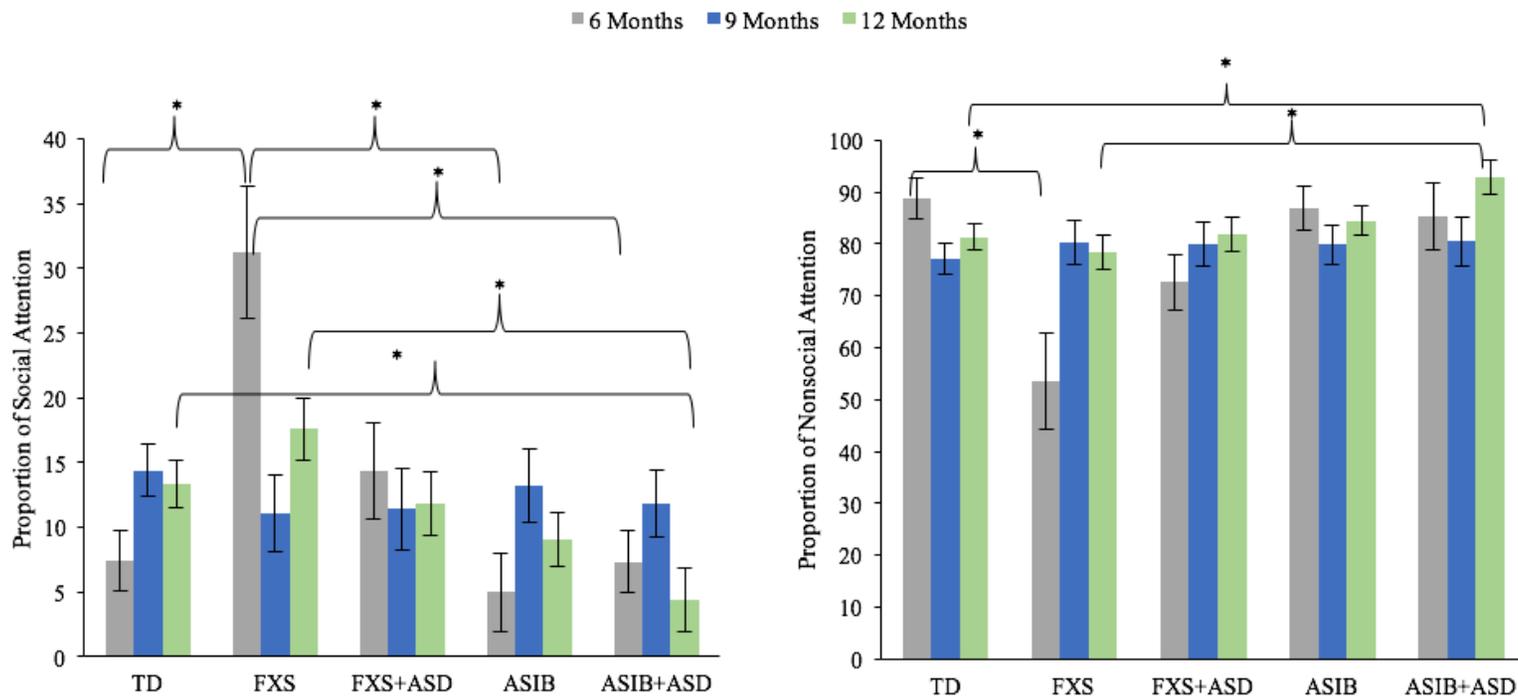


Figure 2.1 Proportion of Social and Nonsocial Attention Across Groups Within Chronological Age with Standard Error Bars (± 1); $*=p<0.05$.

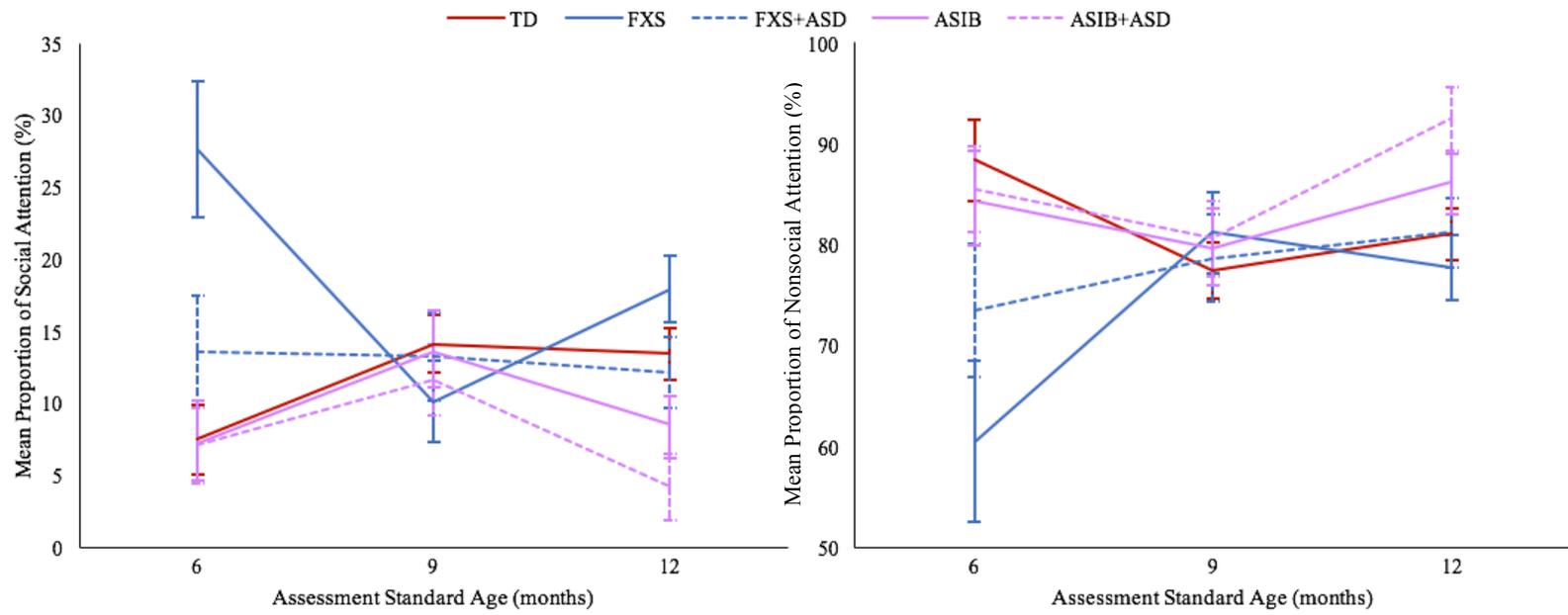


Figure 2.2 Social Attention and Nonsocial Attention Across Group and Age with Standard Error Bars (± 1)

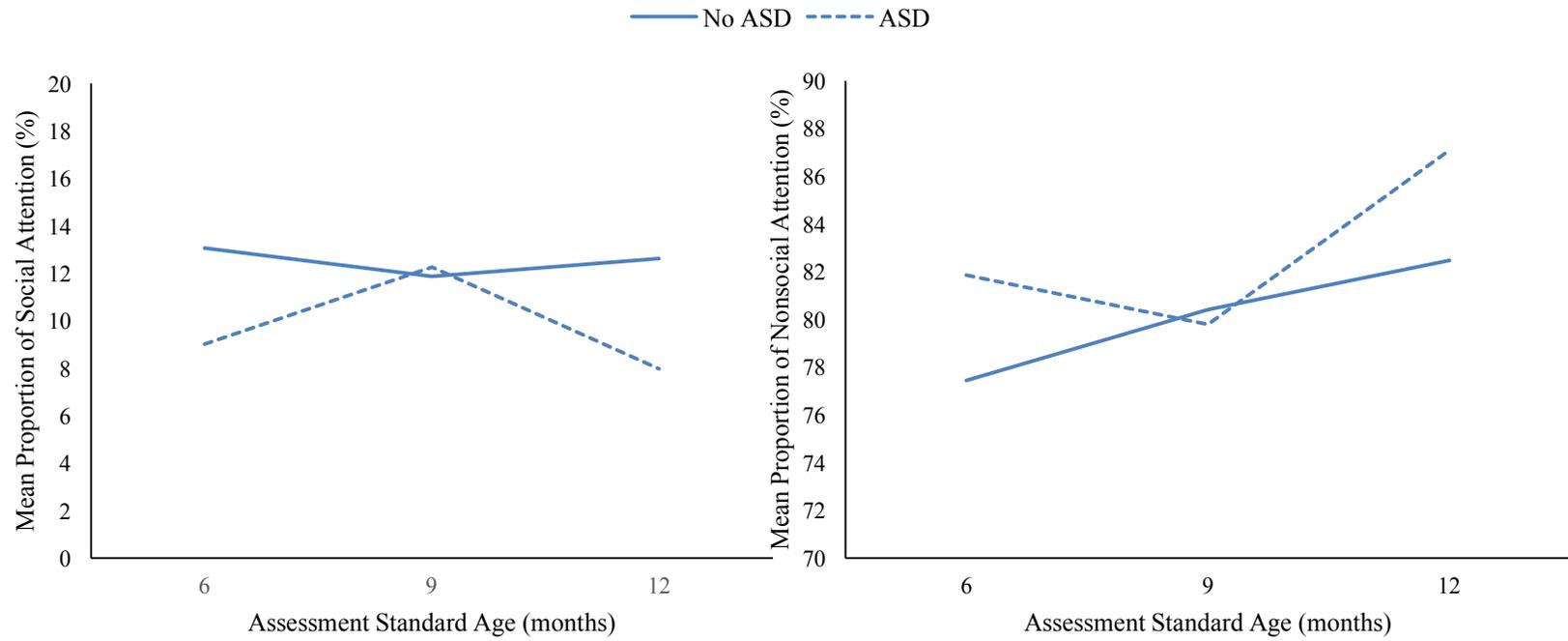


Figure 2.3 Proportion of Social and Nonsocial Attention Across Age in High-Risk Infants Based on ASD Outcomes

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