CHAPTER 9

My Baby Has Just Been Diagnosed with Fragile X Syndrome

What Is There to Know?

Susan M Rivera, Jane E Roberts, Anne C Wheeler, and Randi J Hagerman

I. RECEIVING THE DIAGNOSIS

The diagnosis of fragile X syndrome (FXS) can feel overwhelming at first because the initial information that you hear is 'intellectual disability and autism.' Many healthcare providers are unfamiliar with this diagnosis and this can be frustrating for the family; hopefully, this book will help to educate them and you. If your pediatrician is unfamiliar with the diagnosis they can refer you to a specialist in your area and there are many Fragile X Clinic and Research Centers around the country and internationally organized by the National Fragile X Foundation (NFXF) that can be helpful in the treatment of your child. There are also many parent support groups established around the world (see the website www.fragilex.org and Chapter 12); contact with these families can be reassuring and supportive with constructive advice for you and for your child.

It is important to know that there is great variability in the involvement from FXS related to the characteristics of the mutation (mosaicism and methylation status) in the males and activation ratio (the percentage of cells that have the normal X as the active X) in the females and these concepts are discussed in Chapters 3 and 4. The environment also has a great influence on the development of your child. You as parents can do much to stimulate the development of your child through your interactions, especially language stimulation, reading to them daily, and playing with your child to enhance social development. Excellent programs about how to stimulate the development of your child can be found in the Naturalistic Behavior Intervention Therapy (NBIT) programs that have been developed for the field of autism and they are discussed in Chapter 2 (Vismara et al. 2019). Whether your child has autism or not, a child with FXS can benefit from all that you do at home and also individualized therapy from a speech and language pathologist, occupational therapist, physical therapist, and an early interventionist. This multimodality therapy can begin even in the first year of life. Your pediatrician can also discuss supplements and medications as outlined in Chapter 5. Very common problems such as night awakenings even into the second year of life can respond well to treatment, such as melatonin.

It is important for parents to take care of themselves because lack of sleep, postpartum depression, or feeling overwhelmed, stressed or anxious can be treated and help is available. Since the diagnosis of FXS can also lead to involvement of other family members from the premutation and/or the full mutation, this can also be overwhelming and your physician can guide you and other family members into treatment as outlined in Chapters 7 and 8.

Perhaps the most important aspect of children with FXS is that they are loving, usually always happy, typically have a great sense of humor, and very special, such that they bring a wonderful presence to the families. In this chapter we review much of the research carried out in babies and toddlers with FXS. If you are reading this chapter and you have a newly diagnosed child with FXS, welcome to the family.

The Role of Newborn Screening

Newborn screening initiatives are designed to identify neonates with conditions that require rapid response in order to reduce the likelihood of severe disabilities or death. However, in recent years there has been an increase in discussions regarding inclusion of conditions on newborn screening (NBS) panels that don't require immediate medical attention but that could, nevertheless, benefit from very early identification. FXS has been at the center of these conversations for a couple of reasons.

First, there are no obvious signs of FXS at birth. However, symptoms of reflux, recurrent emesis and hypotonia are common. Developmental delays are reported to emerge as early as 6 months of age. Despite early parental concerns, the average age of diagnosis is 3 years of age for males with FXS and even later for females (Bailey et al. 2009). This delayed diagnosis often is the end result of a financially and emotionally demanding diagnostic odyssey for parents (Okoniewski et al. 2019). Children may be delayed in receiving appropriate early intervention services and, frequently, parents will have another child with FXS before they get the genetic diagnosis for their older child. Second, rapid progression in the understanding of the molecular mechanisms of changes in the fragile X mental retardation 1 (*FMR1*) gene have led to the development of several potential therapeutics for FXS (Bassell and Gross, 2008; Bear, Huber, and Warren 2004; Dölen et al. 2007; Nakamoto et al. 2007) and these therapeutics are discussed in more detail in Chapter 5.

As these promising treatments move through the clinical trial pipeline a consensus among researchers and clinicians is that the scenario most likely to lead to significant long-term positive outcomes would be implementation of the treatments very early. Without prenatal or newborn screening, however, it will be extremely difficult to test the efficacy of these very early interventions. This 'catch 22' is a significant challenge for treatment development in rare disorders like FXS because these conditions cannot be on traditional NBS panels without evidence of an effective treatment, but a treatment cannot be properly tested for efficacy without very early identification.

A novel voluntary NBS program has been established in North Carolina to try to address this catch 22 scenario. *Early Check* is a research program that is providing free expanded newborn screening for conditions that are not eligible for traditional newborn screening programs but that are thought to benefit from very early diagnosis and/or need early identification of infants in order to prove the efficacy of an intervention or therapeutic program. FXS is one of two inaugural conditions included on the Early Check panel.

Families who receive a diagnosis of FXS in their newborn through the Early Check program will receive genetic counseling, information about the condition, ongoing surveillance of the child's development and behavior, and referrals to early intervention programs. In addition, a targeted early intervention program will be offered and as clinical trials for novel therapeutics are approved for infants, families will be provided with information about how to participate.

II. WHAT IS KNOWN FROM RESEARCH ON INFANTS AND TODDLERS WITH FXS?

Cognitive Profile

Language/Communication. Usually one of the first noticeable symptoms by parents and pediatricians, language delays are also perhaps the most prevalent of early symptoms in FXS. Most boys display significant language delays by 9 months, and almost all children with FXS exhibit both receptive and expressive language delays by 12 months (Mirrett et al. 2004; Hatton et al. 2009; Roberts et al. 2009). Parents report the average age of first words for boys with FXS is around 26–28 months, a full year later than what is expected for typical development (Hinton et al. 2013; Roberts, Mirrett, and Burchinal, 2001). Although language abilities do appear to improve over time (Kover et al. 2015), nearly half of children with FXS age 18–36 months in one study were found to be non-verbal (Brady et al. 2006). As with older children with FXS, more emerging autism symptoms are associated with more severe language impairments (Roberts et al. 2009).

Additional delays in nonverbal communication and social reciprocity are also apparent early on, with limited communicative functions and gestures demonstrated in 9–12-month-olds with FXS based on retrospective video analysis (Marschik et al. 2014). Infants and toddlers who use fewer gestures to communicate were found to have lower vocabulary 2 years later (Flenthrope and Brady 2010).

In a recent series of case studies Hogan et al. (2017) found that in nearly all infants with FXS assessed (n = 8), measurable increases in repetitive behaviors and impairments in cognitive and adaptive skills were evident by 9 months of age. For those who went on to receive an autism spectrum disorder (ASD) diagnosis (n = 4), deficits in social communication were the earliest and most predictive symptom. In contrast to those with FXS without ASD and typically developing infants, those with co-morbid ASD demonstrated less eye contact, less social interest, less social smiling, and no social babbling. The authors suggest that deficits in social communication may be one of the key early symptoms suggesting co-morbid ASD and greater severity in impairments for infants with FXS.

Motor Development. Delays in all motor milestones have been reported for boys with FXS, with sitting, crawling, and walking occurring on average 2–4 months later than typically expected (Roberts, Hatton, and Bailey 2001). This may be especially true for infants who go on to have co-morbid ASD (Hinton et al. 2013). Sensory-motor delays may be even more of an issue for babies with FXS early on, as evidenced by a retrospective video analysis conducted on infants who later went on to receive a diagnosis of FXS, autism, or other developmental disabilities (Baranek et al. 2005). Those children with FXS who were more likely to have later developmental issues displayed more repetitive leg movements, posturing and less sophistication/more repetitive use of objects at 9–12 months. Further, in a study comparing infants with FXS to those with or at risk for ASD and typical controls, infants with FXS were more likely to display motor atypicalities on the Autism Observation Schedule for Infants (AOSI) than all other groups (Roberts et al. 2016b).

Brain Development

Much of what is known about brain development in FXS is through longitudinal studies utilizing magnetic resonance imaging (MRI) brain imaging methods. For example, Hazlett and colleagues (Hazlett et al. 2012) studied 53 boys with FXS across two timepoints, between ages 2–3 and 4–5 years, compared to a group of typically developing and developmentally delayed controls. They found that the children with FXS showed a specific enlargement in temporal lobe white matter, cerebellar gray matter, and caudate nucleus, but significantly smaller amygdala. Other studies have found that frontal and

temporal brain regions that are implicated in social cognition (medial prefrontal cortex, anterior cingulate, superior temporal sulcus, temporal pole, and the amygdala) are smaller in FXS than in idiopathic autism or typically developing controls (Hoeft et al. 2011). These findings of initial overgrowth of some brain regions in FXS, and undergrowth of others, are consistent with studies of the mouse model of fragile X (e.g., Harlow et al. 2010) demonstrating that the protein product of the fragile X gene (*FMR1* protein-FMRP) inhibits the generation of progenitor neurons (brain cells that are capable of dividing a limited number of times and have the capacity to differentiate into different brain cell types.) Thus, a lack of FMRP, as seen in FXS, might result in an increased proliferation of progenitor cells and subsequent brain overgrowth. Likewise, FMRP has been shown to regulate the loss, maturation and formation of dendritic spines (small protrusion from a neuron's main cell body that typically receive input from other brain cells), which may result in some brain regions being larger, and others smaller, in children with FXS (Grossman et al. 2010).

Cognition and Visual Processing

Much is now known about the cognitive and visual processing abilities in infants and toddlers with FXS. Many of the early studies were retrospective in design, and used standardized assessments, often collected under different conditions and at different ages across subjects (Hay 1994). In one study that employed a prospective longitudinal design, Bailey and colleagues used standardized neuropsychological testing to examine the early developmental trajectories of males with FXS, demonstrating that the overall rate of development in FXS boys was approximately half of that expected for typically developing children (Bailey, Hatton, and Skinner 1998).

One of the first longitudinal studies in FXS reported on the developmental and behavioral characteristics of 26 boys with fragile X syndrome between the ages of 12 and 36 months showing an increase in the developmental skills of male toddlers with FXS over time (assessed via multiple standardized assessments) accompanied by a broad range of variability within the sample, with global developmental delays evident by 12 months of age in some children, but not evident in others until later ages (Roberts, Hatton, and Bailey 2001). In general, these researchers found motor skills to be least delayed, and communication skills to be most delayed.

Work on older children with FXS gave researchers abundant clues that pointed to a specific deficit in visual processing, particularly in tasks requiring visuo-spatial abilities. For example, one study examined tasks requiring visual construction, such as the manipulation of blocks or triangles to recreate an abstract pattern, and found that boys with FXS (7–14 years old) performed worse than typical controls, but comparable to boys with Down syndrome (DS) (Cornish, Munir, and Cross 1999). In contrast, on the object assembly task in which pieces of a puzzle are arranged to construct a meaningful pattern, the Gestalt closure task, and the visuo-spatial memory task, the FXS group performed similar to the typical group, while DS children performed significantly worse than both other groups. Overall, these results suggest that visual deficits in FXS are specific to tasks involving visuo-spatial construction rather than a generalized perceptual impairment. Given what is known about vision in the brain, this would indicate damage in the 'vision-for-action' pathway of the parietal lobe of the brain, the so-called 'dorsal stream' (Milner and Goodale 2006).

In one of the first studies of visual processing in very young children with FXS, Scerif et al. (2004) investigated selective visual attention (the ability to attend to relevant, and ignore irrelevant visual stimuli) in 2- and 3-year-olds with FXS compared to children with Williams Syndrome (WS). The main finding for the FXS group was a perseverative error of touching targets that had previously been found. Another study examined oculomotor control (ability to inhibit saccades toward suddenly appearing peripheral stimuli–prosaccades, and direct them instead to contralateral locations–antisaccades) in

typically developing toddlers and toddlers with FXS (Scerif et al. 2004). Consistent with the above finding of inhibitory deficits, they found that toddlers with FXS failed to suppress prosaccades toward the cue during the test trials.

More recent work has employed infrared eye tracking methodology, and classic methods from vision science research, to identify the brain pathways that are most affected by the *FMR1* gene. For example, one study tested the so-called 'dorsal stream deficit' hypothesis in FXS. According to this hypothesis, visual information going from the primary visual cortex to the parietal lobe (dorsal stream), which carries information related to movement and spatial relationships between objects, should be more impacted in aberrant development than information going from visual cortex to the temporal lobe (ventral stream) which carries information related to object identification and recognition. One study examined this hypothesis by showing infants with FXS stimuli on an eye tracker. One side of the screen showed striped visual gradients that were either static or moving, luminance-defined (first-order) or texture-defined (second-order) and that had one of 4 visual contrast levels, while the other side of the screen was gray. The higher the visual contrast, the easier the stripes are to see, and the more likely infants will look to the side of the screen containing the stripes. With this classic method, researchers were able to get a 'psychophysical function' on each infant. In other words, determine how high the contrast level must be in order for the infant to look to the correct side of the screen 75% of the time or more. Results showed that infants with FXS (who had a mean chronological age of 24 months and a mean mental age of 14 months) displayed significantly higher detection thresholds only for the second-order, moving stimuli compared to mental age-matched typically developing controls (Farzin et al. 2008). What these findings demonstrated is that while ventral stream processing (as predicted) is intact in infants with FXS, the aspects of dorsal stream processing that are affected are those involved in 'attentive tracking' (Ashida, Seiffert, and Osaka 2001; Cavanagh 1992; Derrington, Allen, and Delicato 2004; Seiffert and Cavanagh 1998) . A network of several cortical areas, including parietal and frontal regions, is believed to be engaged in attentive tracking (Culham et al. 1998) and may mediate the perception of second order motion. Notably, the same attentive tracking deficits seen in infants with FXS were also observed in infants with the FX premutation (Gallego, Burris, and Rivera 2014).

In another paper, researchers used the 'violation of expectation' method to assess infants' visual response to expected versus unexpected outcomes following a brief dynamic (dorsal stream) or static (ventral stream) occlusion event on an eye tracker. Results indicated that infants with FXS could maintain the identity of static, but not dynamic, object information during occlusion (Farzin and Rivera 2010).

Other studies by the same group investigated the question of what *aspects* of attentive tracking (spatial or temporal) were affected in infants with FXS. In one eye tracking experiment, they psychophysically measured the limits of **spatial** attention using a visual crowding paradigm involving orientation to upright vs. inverted 'Mooney' faces (visual stimuli consisting of smooth, rounded patches of black and white that, when processed holistically, look like a face.) It was found that both infants with and without FXS prefer upright Mooney faces (just as infants prefer *real* upright human faces) and that infants with FXS did not differ from typically developing infants in their 'spatial resolution of attention' – in other words, as those upright vs. inverted faces got farther out into the visual periphery, both infants with FXS and typically developing infants showed less and less preference to the upright face (Farzin, Rivera, and Whitney 2011).

In another experiment the same group of researchers investigated the resolution of **temporal** attention in infants with FXS. This experiment used a 'flicker' eye tracking task in which the screen was split into four quadrants, and one of the quadrants flickered out of phase with the others. This flickering was presented at one of four temporal frequencies: 0.2, 0.5, 1, or 2Hz. At slower rates, the target (i.e., the quadrant flickering out of phase) is more easily seen because it is easier to individuate the black and white states, but at frequencies faster than an individual's threshold level, all squares appear to be flickering

identically (i.e., the phase cannot be individuated.) Results of this experiment showed that typically developing infants were able to identify the out-of-phase flicker up to a rate of 1Hz, whereas infants with FXS could do so only up to 0.5Hz, indicating that infants with FXS experience drastically reduced resolution of temporal attention (Farzin et al. 2011).

A key component of dynamic processing is orienting – a perceptual ability that requires disengagement from one visual stimulus to fixate on a second. Such visual orienting of attention has been studied in infants and toddlers with FXS using eye-tracking methodology and a classic 'gap-overlap' task (Chernenok et al. 2019). During this task, there are two types of trials. On 'gap' trials, there is central stimulus that elicits fixation, but then disappears before a target one side of the screen (peripheral target) appears, imposing a visual gap between stimuli. On overlap trials, the central stimulus elicits fixation but then remains present when the peripheral target appears, creating visual competition. A gap effect emerges when latencies to shift to the peripheral target are longer in overlap versus gap conditions. Results from this study indicated typically developing infants and toddlers showed the expected gap effect, where children were slower to orient to peripheral targets on overlap trials than on gap trials. In contrast, in the FXS group, saccadic latencies between gap and overlap trials were not significantly different, indicating no significant gap effect. These findings suggest disrupted attentional engagement patterns in FXS that may be underlying impairments in attention orienting, and suggest potential targets for attention training in this population.

In summary, research findings haves taught us that infants with FXS appear to have intact ventral stream functioning (which is responsible for basic object recognition and color perception) and that dysfunctions of the dorsal stream appear to be limited to those motion-related visual events that implicate *attentive tracking* mechanisms, or keeping track of objects over space and time. Further, we have learned that with respect to attentive tracking, it appears to be the **temporal** aspects that are most affected.

Temperament

Temperament refers to a characteristic 'style' of behavior that can be observed as early as infancy. Temperament is believed to be innate and is typically consistent over time and across settings such as school and home. The primary constructs associated with temperament include negative affect, surgency and effortful control, and these constructs appear to be similarly expressed in young children with FXS as they are in neurotypical children (Roberts et al. 2014).

Negative affect refers to negative emotions such as fear, sadness, and frustration, and elevated negative affect in neurotypical infants has been shown to predict anxiety during the preschool and school age years (Brooker, Kiel, and Buss 2016). Elevated negative affect has also been linked to predict autism in high risk samples (Grant et al. 2009). Interestingly, negative affect appears to either be no different or lower than neurotypical children (Shanahan et al. 2008; Tonnsen et al. 2019) during the first two years of life but to increase steadily across the infant and preschool years in males with FXS more than females with FXS, or children with the premutation (Low Kapalu and Gartstein 2016; Tonnsen et al. 2019; Wall et al. 2019). A subgroup of infants with FXS have been described to have high levels of negative affect or elevated fear and sadness that was associated with elevated symptoms of anxiety but not ASD (Tonnsen et al. 2013a; Wall et al. 2019).

Surgency refers to traits such as activity level, impulsivity, shyness, and social approach that are present in infancy. Elevated surgency has been found to predict attention deficit hyperactivity disorder (ADHD) in neurotypical samples (De Pauw and Mervielde, 2011). In FXS, surgency has been described as somewhat lower (Low Kapalu and Gartstein 2016; Tonnsen et al. 2019) or similar to neurotypical infants and toddlers (Grefer et al. 2016). However, increased impulsivity and activity level, two aspects of a surgent temperament, have been associated with ADHD in young males with FXS (Grefer et al. 2016).

Effortful control is the ability to suppress an automatic response in order to perform a response that is believed to be desired or adaptive. For example, the ability to self-regulate emotional or behavioral responses is part of effortful control such as being able to wait for a reward rather than demanding the reward be presented immediately. In typical development, effortful control begins to emerge during the toddler and preschool years. Elevated effortful control is associated with positive social and cognitive outcomes while lower levels may predict poor social or academic outcomes as well as anxiety or ADHD. In preschool males with FXS, effortful control was found to be lower than a neurotypical control group (Low Kapalu and Gartstein 2016) and did not increase over time as it did with the controls (Robinson et al. 2018). Lower effortful control was not associated with adaptive behavior, *FMR1* gene function, or ASD symptoms in that study.

While temperament is not considered 'good' or 'bad,' it is important to consider the match of your young child's temperament to the demands of the situation. For example, there is not a treatment for temperament, it is a matter of observing your child and seeing what situations are challenging and what are supportive. For example, children who are high in negative affect or surgency might have more challenges transitioning between activities or places so it might be a good idea to allow time and support transitions.

Arousal

Physiological hyperarousal refers to an elevated state of activation across one or more physiological systems such as elevated autonomic function (e.g., higher heart rate) or increased salivary cortisol. While elevated arousal in the face of challenge is an adaptive response, chronic hyperarousal can negatively affect attention, heighten social-emotional reactivity and reduce performance. Hyperarousal has been described as a trait of many children and adults with FXS; however, direct links between arousal and behavior or outcomes in FXS are limited, and there are only a handful of studies with very young children. In one of the few studies to include infants and toddlers with FXS, evidence suggested that elevated heart rate and reduced respiratory sinus arrhythmia (RSA: associated with the rest and restorative function) were linked to elevated social fear (Tonnsen et al. 2013b). Elevated autonomic arousal has also been documented to be related to increased severity of ASD features across the infant and toddler years (Tonnsen et al. 2013b; Roberts et al. n.d.).

Elevated arousal in FXS may be subtle or absent in the early years, and it may be evident in certain situations and not others. Parents can tune in to their child's arousal level by observing their responses and trying to adapt to them. Elevated physiological arousal can be expressed through hand flapping, crying, facial flushing, elevated activity, or heightened emotional or behavioral reactivity. For example, a child who has elevated arousal will likely have a difficult time settling down to pay attention to therapy or to sleep. One response that parents might consider is to provide soothing or calming activities prior to situations that might be difficult for their child to manage given elevated physiological arousal (e.g., music, pacifier, feeding). These strategies have not been tested as effective in FXS; however, they are strategies that have been shown to reduce arousal and promote regulation in neurotypical children (Ostlund et al. 2017).

Autism Spectrum Disorder in FXS

There is a clear association of ASD with FXS with multiple research studies reporting that a large proportion of children and adults with FXS meet diagnostic criteria for ASD or display a high degree of elevated features of ASD. Most of this research has focused on males with FXS; however, there are some studies that include or focus on females as well. The rates of ASD in FXS vary across studies with a range of between 30% and 75% of males and 20–41% of females reported as meeting criteria for ASD (Abbeduto et al. 2019; Lee et al. 2016). In preschool-aged children with FXS, the rate of ASD is reported to be approximately 35% (Hazlett et al. 2012; Rogers, Wehner, and Hagerman 2001) but a recent report suggests that

the rate may be as high as 60% (Roberts et al. n.d.) It is important to note that diagnoses of ASD in males with FXS obtained through research studies may not align with clinical diagnoses in the community suggesting that parents, educators and treatment specialists in the community may focus more on the features of FXS and less on whether both FXS and ASD are present (Klusek, Martin, and Losh 2014). Given that the presence of ASD in FXS is associated with increased impairment, early detection of ASD is important.

A valid diagnosis of ASD is typically not determined until a child is 2 to 3 years of age; however, early signs and predictors of ASD have been reported in non-syndromic ASD (ASD not associated with FXS or another syndrome). The presence of ASD in very young children or early signs of ASD in infants or toddlers with FXS is of increasing focus in research. An initial study indicated that 53% of 12-month-old infants with FXS displayed elevated features of ASD (Roberts et al. 2016b). In addition, another study indicated that features of ASD may be common in 9-month-old infants with FXS but may not be strong indicators of a later diagnosis of ASD (Hogan et al. 2017). However, a consistent elevated presence of ASD features across both 9 and 12 months of age does appear to be a marker of high risk for a later diagnosis of ASD (Hogan et al. 2017; Robertset al. 2016b; Roberts et al. 2019).

Atypical motor movement, motor skills and poor social-communication appear to be the most salient features during the infant and toddler years that signal high risk for a diagnosis of ASD in those with FXS later in life. Specifically, hand flapping and poor motor control (Roberts et al. 2016b), and delayed fine and gross motor skills that are beyond cognitive delays are suggested as potential red flags for a later diagnosis of ASD (Will, Bishop, and Roberts, 2019). Reduced eye contact and social avoidance during the infant and toddler years have also been identified as early signs of later diagnoses of ASD (Roberts et al. 2019). Finally, as described earlier, elevated physiological arousal or 'hyperarousal' has been linked to increased risk for ASD diagnoses (Roberts et al. 2012; Roberts et al. n.d)

While the precise age at which early signs of ASD can be accurately detected in infants with FXS is not yet known, several reports suggest that early signs of ASD are present and detectable in the first 12 months of life (Hogan et al. 2017; Roberts et al. 2016a; Roberts et al. n.d.; Will et al. 2019). However, these signs are often subtle and difficult to separate from overall developmental delays, which makes this work challenging. Also, given the rather limited range of behaviors that infants display and the fact that development unfolds over time in a sequenced manner with more advanced skills reliant on the foundation of skills established earlier in time, the detection of early signs of ASD in infants and toddlers with FXS is very challenging because some signs will emerge earlier than others given the developmental nature of this disorder.

It should be noted that a number of early developmental features may not be associated with ASD in infants and toddlers with FXS and may just signal overall developmental delay that is a known feature of FXS. These include early gesture development (Rague et al. 2018) and the initiation of joint attention (Brewe et al. 2018). However, there is some evidence that while gesture frequency may not discriminate ASD-risk in 12-month-olds with FXS, the function of gestures might be an important factor with fewer gestures, either in initiation or response, meaning that this patient is at high risk for ASD (Hughes et al. 2019).

III. WHAT TREATMENTS AND INTERVENTIONS HAVE BEEN STUDIED?

Pharmacological Interventions

Drug trials in children under the age of 2 years are understandably limited. There have, however, been some drug trials in older children with FXS – as young as 2 up to about 16 years of age. Those studies include the use of sertraline (a selective serotonin reuptake inhibitor, or SSRI, often used to treat depression and anxiety disorders); metformin (a drug originally FDA-approved for its effects in lowering blood glucose levels in patients with type 2 diabetes); and minocycline (a tetracycline antibiotic typically used

to fight bacteria in the body). In each case, some improvements were seen in children with FXS, to include improved motor and visual perception seen with the use of low-dose sertraline (Greiss Hess et al. 2016); improvements in language development and decreased lethargy and stereotypy seen with the use of metformin (Biag et al. 2019); and improved Clinical Global Impression seen with the use of minocycline (Leigh et al. 2013).

Behavioral Interventions

While most behavioral interventions in FXS, such as the parent-implemented spoken language intervention described by Abbeduto and colleagues (McDuffie et al. 2016; Nelson et al. 2018) have been implemented in older, school-aged children, 2 are particularly relevant to infants and toddlers with FXS.

Parent-infant fragile X Intervention (PIXI): As part of the Early Check program, researchers are testing various models of behavioral interventions to support the development and well-being of newborns with FXS and their families This intervention program, named '**P**arents and **I**nfants with fragile **X** **I**ntervention (PIXI)' uses empirically based strategies and processes for supporting responsive and sensitive parenting as well as recognizing and intervening when atypical behaviors emerge. At the time of this writing, the PIXI intervention is currently being tested in both in-person and telehealth-based formats with the intention of providing support and interventions for newly diagnosed infants anywhere in the country.

ESDM: A recent pilot study evaluated efficacy and acceptability of an autism intervention model, the parent-delivered Early Start Denver Model (P-ESDM), for use in young children with FXS (Vismara et al. 2019). Four parent–child dyads participated in the study. The children with FXS were between the ages of 25 and 40 months.

Parents showed improved in P-ESDM fidelity, implemented intervention goals to increase child learning, and found the experience moderately to highly acceptable. All four parents reported gains in their children's language skills. Overall, this pilot study showed potential for this therapy to help young children with FXS.

SUMMARY

In summary, we have learned much about the cognitive and emotional development of infants and toddlers with FXS. More information is on the horizon as pediatricians continue to push the diagnosis of FXS in younger children, and researchers continue to develop protocols for assessing and studying younger children. Although we have presented a broad overview of the developmental profiles present in FXS, it is important to keep in mind that each child's development is unique, and the features seen in one child with FXS may differ from those in another. The best outcomes for infants and toddlers with FXS will come from being sensitive to the unique strengths and challenges of each child, and working with healthcare and intervention providers to provide each child with the resources that will be best suited to his or her needs.

REFERENCES

Abbeduto L, Thurman AJ, McDuffie A et al. (2019) ASD Comorbidity in fragile X Syndrome: symptom profile and predictors of symptom severity in adolescent and young adult males. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3796-2.

Ashida H, Seiffert AE, Osaka N (2001) Inefficient visual search for second-order motion. *Journal of the Optical Society of America A*. https://doi.org/10.1364/josaa.18.002255.

Bailey DB, Hatton DD, Skinner M (1998) Early developmental trajectories of males with fragile X syndrome. *American Journal on Mental Retardation*. https://doi.org/10.1352/0895-8017(1998)103<0029:EDTOMW>2.0.CO;2.

Bailey DB, Raspa M, Bishop E, Holiday D (2009) No change in the age of diagnosis for fragile X syndrome: findings from a national parent survey. *Pediatrics*. https://doi.org/10.1542/peds.2008-2992.

Baranek GT, Danko CD, Skinner ML et al. (2005) Video analysis of sensory-motor features in infants with fragile X syndrome at 9–12 months of age. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-005-0008-7.

Bassell GJ, Gross C (2008) Reducing glutamate signaling pays off in fragile X. *Nature Medicine*. https://doi.org/10.1038/nm0308-249.

Bear MF, Huber KM, Warren ST (2004) The mGluR theory of fragile X mental retardation. *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2004.04.009.

Biag HMB, Potter LA, Wilkins V et al. (2019) Metformin treatment in young children with fragile X syndrome. *Molecular Genetics and Genomic Medicine*. https://doi.org/10.1002/mgg3.956.

Brady N, Skinner D, Roberts J, Hennon E (2006) Communication in young children with fragile X syndrome: a qualitative study of mothers' perspectives. *American Journal of Speech-Language Pathology*. https://doi.org/10.1044/1058-0360(2006/033).

Brewe AM, Reisinger DL, Adlof SM, Roberts JE (2018) Initiating joint attention use in infants at high-risk for autism spectrum disorder. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.12539.

Brooker RJ, Kiel EJ, Buss KA (2016) Early social fear predicts kindergarteners' socially anxious behaviors: direct associations, moderation by inhibitory control, and differences from nonsocial fear. *Emotion*. https://doi.org/10.1037/emo0000135.

Cavanagh P (1992) Attention-based motion perception. *Science*. https://doi.org/10.1126/science.1523411.

Chernenok M, Burris JL, Owen E, Rivera SM (2019) Impaired attention orienting in young children with Fragile X syndrome. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2019.01567.

Cornish KM, Munir F, Cross G (1999) Spatial cognition in males with fragile-X syndrome: evidence for a neuropsychological phenotype. *Cortex*. https://doi.org/10.1016/S0010-9452(08)70799-8.

Culham JC, Brandt SA, Cavanagh P, Kanwisher NG, Dale AM, Tootell RBH (1998) Cortical fMRI activation produced by attentive tracking of moving targets. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.1998.80.5.2657.

De Pauw SSW, Mervielde I (2011) The role of temperament and personality in problem behaviors of children with ADHD. *Journal of Abnormal Child Psychology*. https://doi.org/10.1007/s10802-010-9459-1

Derrington AM, Allen HA, Delicato LS (2004) Visual mechanisms of motion analysis and motion perception. *Annual Review of Psychology*. https://doi.org/10.1146/annurev.psych.55.090902.141903.

Dölen G, Osterweil E, Rao BSS et al. (2007) Correction of fragile X syndrome in mice. *Neuron*. https://doi.org/10.1016/j.neuron.2007.12.001.

Farzin F, Whitney D, Hagerman RJ, Rivera SM (2008) Contrast detection in infants with fragile X syndrome. *Vision Res* 48: 1471–1478. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18457856.

Farzin F, Rivera SM (2010) Dynamic object representations in infants with and without fragile X syndrome. *Front. Hum. Neurosci.* https://doi.org/10.3389/neuro.09.012.2010.

Farzin F, Rivera SM, Whitney D (2011) Resolution of spatial and temporal visual attention in infants with fragile X syndrome. *Brain: A Journal of Neurology*. https://doi.org/10.1093/brain/awr249.

Flenthrope JL, Brady NC (2010) Relationships between early gestures and later language in children with fragile X syndrome. *American Journal of Speech-Language Pathology*. https://doi.org/10.1044/1058-0360(2009/09-0018).

Gallego PK, Burris JL, Rivera SM (2014) Visual motion processing deficits in infants with the fragile X premutation. *Journal of Neurodevelopmental Disorders*. https://doi.org/10.1186/1866-1955-6-29.

Grant VV, Bagnell AL, Chambers CT, Stewart SH (2009) Early temperament prospectively predicts anxiety in later childhood. *Canadian Journal of Psychiatry*. https://doi.org/10.1177/070674370905400506.

Grefer M, Flory K, Cornish K, Hatton D, Roberts J (2016) The emergence and stability of attention deficit hyperactivity disorder in boys with fragile X syndrome. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.12226.

Greiss Hess L, Fitzpatrick SE, Nguyen DV et al. (2016) A randomized, double-blind, placebo-controlled trial of low-dose sertraline in young children with fragile X syndrome. *Journal of Developmental and Behavioral Pediatrics*. https://doi.org/10.1097/DBP.0000000000000334.

Grossman AW, Aldridge GM, Lee KJ et al. (2010) Developmental characteristics of dendritic spines in the dentate gyrus of Fmr1 knockout mice. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.07.090.

Harlow EG, Till SM, Russell TA, Wijetunge LS, Kind P, Contractor A (2010) Critical period plasticity is disrupted in the barrel cortex of Fmr1 knockout mice. *Neuron*. https://doi.org/10.1016/j.neuron.2010.01.024.

Hatton DD, Wheeler A, Sideris J et al. (2009) Developmental trajectories of young girls with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-114.3.161.

Hay DA (1994) Does IQ decline with age in fragile-X? A methodological critique. *American Journal of Medical Genetics*. https://doi.org/10.1002/ajmg.1320510412.

Hazlett HC, Poe MD, Lightbody AA et al. (2012) Trajectories of early brain volume development in fragile X syndrome and autism. *Journal of the American Academy of Child and Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2012.07.003.

Hinton R, Budimirovic DB, Marschik PB et al. (2013) Parental reports on early language and motor milestones in fragile X syndrome with and without autism spectrum disorders. *Developmental Neurorehabilitation*. https://doi.org/10.3109/17518423.2012.704414.

Hoeft F, Walter E, Lightbody AA et al. (2011) Neuroanatomical differences in toddler boys with fragile X syndrome and idiopathic autism. *Archives of General Psychiatry*. https://doi.org/10.1001/archgenpsychiatry.2010.153.

Hogan AL, Caravella KE, Ezell J, Rague L, Hills K, Roberts JE (2017) Autism spectrum disorder symptoms in infants with fragile X syndrome: a prospective case series. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-017-3081-9.

Hughes KR, Hogan AL, Roberts JE, Klusek J (2019) Gesture frequency and function in infants with fragile x syndrome and infant siblings of children with autism spectrum disorder. *Journal of Speech, Language, and Hearing Research*. https://doi.org/10.1044/2019_JSLHR-L-17-0491.

Klusek J, Martin GE, Losh M (2014) Consistency between research and clinical diagnoses of autism among boys and girls with fragile X syndrome. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.12121.

Kover ST, McCary LM, Ingram AM, Hatton DD, Roberts JE (2015) Language development in infants and toddlers with fragile X syndrome: change over time and the role of attention. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-120.2.125.

Lee M, Martin GE, Berry-Kravis E, Losh M (2016) A developmental, longitudinal investigation of autism phenotypic profiles in fragile X syndrome. *Journal of Neurodevelopmental Disorders*. https://doi.org/10.1186/s11689-016-9179-0.

Leigh MJS, Nguyen DV, Mu Y et al. (2013) A randomized double-blind, placebo-controlled trial of minocycline in children and adolescents with fragile x syndrome. *Journal of Developmental and Behavioral Pediatrics*. https://doi.org/10.1097/DBP.0b013e318287cd17.

Low Kapalu CM, Gartstein MA (2016) Boys with fragile X syndrome: investigating temperament in early childhood. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.12304.

Marschik PB, Vollmann R, Bartl-Pokorny KD et al. (2014) Developmental profile of speech-language and communicative functions in an individual with the preserved speech variant of Rett syndrome. *Developmental Neurorehabilitation*. https://doi.org/10.3109/17518423.2013.783139.

McDuffie A, Machalicek W, Bullard L et al. (2016) A spoken-language intervention for school-aged boys with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-121.3.236.

Milner D, Goodale M (2006) *The Visual Brain in Action*. https://doi.org/10.1093/acprof:oso/9780198524724.001.0001.

Mirrett PL, Bailey DB, Roberts JE, Hatton DD (2004) Developmental screening and detection of developmental delays in infants and toddlers with fragile X syndrome. *Journal of Developmental and Behavioral Pediatrics*. https://doi.org/10.1097/00004703-200402000-00004.

Nakamoto M, Nalavadi V, Epstein MP, Narayanan U, Bassell GJ, Warren ST (2007) Fragile X mental retardation protein deficiency leads to excessive mGluR5-dependent internalization of AMPA receptors. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0707484104.

Nelson S, McDuffie A, Banasik A, Tempero Feigles R, Thurman AJ, Abbeduto L (2018) Inferential language use by school-aged boys with fragile X syndrome: effects of a parent-implemented spoken language intervention. *Journal of Communication Disorders*. https://doi.org/10.1016/j.jcomdis.2018.02.007.

Okoniewski KC, Wheeler AC, Lee S et al. (2019) Early identification of fragile X syndrome through expanded newborn screening. *Brain Sciences*. https://doi.org/10.3390/brainsci9010004.

Ostlund BD, Measelle JR, Laurent HK, Conradt E, Ablow JC (2017) Shaping emotion regulation: attunement, symptomatology, and stress recovery within mother–infant dyads. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21448.

Rague L, Caravella K, Tonnsen B, Klusek J, Roberts J (2018) Early gesture use in fragile X syndrome. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/jir.12498.

Roberts JE, Bradshaw J, Will EA, Hogan AL, McQuillin SD, Hills KJ (in press) Prevalence and emergence of autism in fragile X syndrome across the first years of life.

Roberts J, Crawford H, Hogan AL et al. (2019) Social avoidance emerges in infancy and persists into adulthood in fragile X syndrome. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-019-04051-8.

Roberts Jane E, Hatton DD, Bailey DB (2001) Development and behavior of male toddlers with fragile X syndrome. *Journal of Early Intervention*. https://doi.org/10.1177/105381510102400306O1.

Roberts Jane E, Mankowski JB, Sideris J et al. (2009) Trajectories and predictors of the development of very young boys with fragile X syndrome. *Journal of Pediatric Psychology*. https://doi.org/10.1093/jpepsy/jsn129.

Roberts Jane E, McCary LM, Shinkareva SV, Bailey DB (2016a) Infant Development in Fragile X Syndrome: Cross-Syndrome Comparisons. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-2737-1.

Roberts Jane E, Tonnsen BL, McCary LM, Caravella KE, Shinkareva SV (2016b) Brief report: autism symptoms in infants with fragile X syndrome. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-2903-5.

Roberts Jane E, Tonnsen BL, Robinson M, McQuillin SD, Hatton DD (2014) Temperament factor structure in fragile X syndrome: The Children's Behavior Questionnaire. *Research in Developmental Disabilities*. https://doi.org/10.1016/j.ridd.2013.11.024.

Roberts Jane E, Tonnsen B, Robinson A, Shinkareva SV (2012) Heart activity and autistic behavior in infants and toddlers with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-117.2.90.

Roberts Joanne E, Mirrett P, Burchinal M. (2001) Receptive and expressive communication development of young males with fragile X syndrome. *American Journal on Mental Retardation* 106: 216–230. Retrieved from http://www.aamr.org/index.shtml.

Robinson M, Klusek J, Poe MD, Hatton DD, Roberts JE (2018) The emergence of effortful control in young boys with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-123.2.89.

Rogers SJ, Wehner EA, Hagerman RJ (2001) The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioral Pediatrics* **22**: 409–417.

Scerif G, Cornish K, Wilding J, Driver J, Karmiloff-Smith A (2004) Visual search in typically developing toddlers and toddlers with fragile X or Williams syndrome. *Dev Sci* **7**: 116–130.

Seiffert AE, Cavanagh P (1998) Position displacement, not velocity, is the cue to motion detection of second-order stimuli. *Vision Res* **38**: 3569–3582. https://doi.org/S0042-6989(98)00035-2 [pii].

Shanahan M, Roberts J, Hatton D, Reznick J, Goldsmith H (2008) Early temperament and negative reactivity in boys with fragile X syndrome. *Journal of Intellectual Disability Research*. https://doi.org/10.1111/j.1365-2788.2008.01074.x.

Tonnsen BL, Malone PS, Hatton DD, Roberts JE (2013a) Early negative affect predicts anxiety, not autism, in preschool boys with fragile X syndrome. *Journal of Abnormal Child Psychology*. https://doi.org/10.1007/s10802-012-9671-2.

Tonnsen BL, Shinkareva SV, Deal SC, Hatton DD, Roberts JE (2013b) Biobehavioral indicators of social fear in young children with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*. https://doi.org/10.1352/1944-7558-118.6.447.

Tonnsen BL, Wheeler AC, Hamrick LR, Roberts JE (2019) Infant temperament in the FMR1 premutation and fragile X syndrome. *Journal of Clinical Child and Adolescent Psychology*. https://doi.org/10.1080/15374416.2018.1514613.

Vismara LA, McCormick CEB, Shields R, Hessl D (2019) Extending the parent-delivered early start denver model to young children with fragile X syndrome. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3833-1.

Wall CA, Hogan AL, Will EA, McQuillin S, Kelleher BL, Roberts JE (2019) Early negative affect in males and females with fragile X syndrome: implications for anxiety and autism. *Journal of Neurodevelopmental Disorders*. https://doi.org/10.1186/s11689-019-9284-y.

Will EA, Bishop SL, Roberts JE (2019) Developmental divergence: motor trajectories in children with fragile X syndrome with and without co-occurring autism. *Journal of Neurodevelopmental Disord*ers. https://doi.org/10.1186/s11689-019-9281-1.