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Early identification of autism in fragile X syndrome: a review

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Abstract

Fragile X syndrome (FXS) is the leading genetic cause of autism, accounting for approximately 5% of autism cases with as many as 50% of individuals with FXS meeting DSM-IV-TR criteria for autistic disorder. Both FXS and idiopathic autism (IA) are attributed to genetic causes; however, FXS is an identified single gene disorder whereas autism is a complex disorder with multiple potential causes, some of which have been identified. Studies in IA have focused on the prospective longitudinal examination of infant siblings of children with autism as a target group due to their high risk of developing the disorder. We propose that this same model be applied to the study of infants with FXS. There is a lack of research focusing on the early development of autism within FXS and debate in the literature regarding how to best conceptualise this co-morbidity or whether it should be considered a co-morbid condition at all. Studying the emergence and stability of autism in infants with FXS has multiple benefits such as clarifying the underlying mechanisms of the development of autism in FXS and solidifying similarities and differences between co-morbid FXS with autism and IA. Infant research in both IA and FXS are discussed as well as conclusions and implications for practice and future research.

Keywords

autism; fragile X; intellectual disability; methodology in research

Introduction

Fragile X syndrome (FXS) is the leading known genetic cause of autism, accounting for approximately 5% of autism cases (Hagerman *et al*. 2008). In individuals with the full mutation, approximately 30–50% meet full DSM-IV-TR criteria for autism with 60–74% meeting criteria for an autism spectrum disorder (Kaufmann *et al*. 2004; Clifford *et al*. 2007; Hall *et al*. 2008; Harris *et al*. 2008; Bailey *et al*. 2009). Additionally, over 90% of individuals with FXS display some form of atypical behaviour characteristic of autism including social interaction (e.g. avoidant eye contact, social withdrawal, social anxiety) and repetitive and stereotyped behaviours (Hernandez *et al*. 2009).

Both FXS and idiopathic autism (IA; not FXS-related) are attributed to genetic causes (Muhle *et al*. 2004); however, FXS is an identified single gene disorder whereas autism is a

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complex disorder with multiple potential causes, some of which have been identified (Kelleher & Bear 2008; Darnell *et al*. 2011). Studies in IA have focused on the prospective longitudinal examination of infant siblings of children with autism as a target group due to their high risk of developing the disorder (13.6–28%; Landa *et al*. 2007; Stone *et al*. 2008; Ozonoff *et al*. 2011). We propose that this same model be applied to the study of infants with FXS as they, too, are at increased risk for the development of autism. Studying the emergence and stability of autism in infants with FXS has multiple benefits such as clarifying the underlying mechanisms of the development of autism in FXS and solidifying similarities and differences between co-morbid FXS and autism and IA. Infant research in both IA and FXS are discussed as well as conclusions and implications for practice and future research.

Autism

Autistic disorder is the most debilitating subgroup of a larger category known as pervasive developmental disorders (PDD; American Psychiatric Association 2000) characterised by impairments in social interaction and verbal and non-verbal communication, and restricted, repetitive and stereotypic patterns of behaviour, interests and activities. Although there is considerable variability in individual symptoms, core deficits in social communication and restricted and repetitive behaviours are hallmarks of the disorder (Tager-Flusberg 2010). Genetic studies of autism suggest that the majority of autism cases may be explained by a large number of variable genetic risk factors, each conferring a small risk. Thus, autism likely requires multiple risk genes that interact with each other and the environment (Tager-Flusberg 2010).

Autism is estimated to affect approximately 1 in 110 (1 in 70 males) individuals, and the lifetime cost per capita in the USA is approximately $3.2 million (Ganz 2007; Rice 2009). It is a disorder that affects families from a range of backgrounds and ethnicities. Autism is typically not diagnosed until three years of age, with an average age of diagnosis of 5.7 years, despite the ability to reliably diagnose at 2 years of age (Shattuck *et al*. 2009).

Research on behavioural intervention and neuro-plasticity suggests that amelioration of symptoms or even prevention of the disorder is plausible given the detection and treatment of infants before the full syndrome develops (Dawson 2008).

Early identification of idiopathic autism

Two waves of research on the early features of IA exist. The initial wave consists of retrospective parent reports and home video analysis that have identified behaviours that distinguish children with autism from their non-autistic peers during the first year of life. The second wave of research consists of prospective, longitudinal studies following high-risk infants from the first year of life through early childhood in order to examine their development over time. One of the most prominently studied high risk autism group is infants with older siblings with a clinical diagnosis of autism. Prospective research designs offer several strengths such as early assessment of participants, longitudinal monitoring of behaviour, limited reliance on recall, and the ability to elicit and measure certain behaviours under standardised conditions (Zwaigenbaum *et al*. 2005).

In a prospective, longitudinal study of 65 high-risk infant siblings, Zwaigenbaum *et al*. (2005) found that high-risk infant siblings who later met diagnostic criteria for autism were reported on parent ratings of temperament to have more frequent and intense distress reactions at 12 months of age as well as longer durations of orienting to objects; and at 24 months of age rated as having less attention shifting, less inhibitory control, and less positive anticipation and affective responses than a control group. Additionally, infants' ability to disengage attention at 12 months on a visual orienting task predicted autism classification at 24 months of age.

Similarly, Garon *et al*. (2009) followed 138 high-risk infant sibs from 6–12 until 36 months of age to further establish an association between early behavioural characteristics and autism. The researchers found two factors that best discriminated between high-risk infant sibs who did and did not meet criteria for autism and low-risk controls: Behavioural Approach and Effortful Emotion Regulation. In predicting autism status at 36 months, Garon *et al*. (2009) found that both temperament factors significantly predicted membership for all three groups (high-risk infant sibs with autism, high-risk infant sibs without autism, and low-risk controls) with Behavioural Approach significantly distinguishing between high-risk infant sibs with autism and high-risk infant sibs without autism. When comparing high-risk infant sibs with autism to low-risk controls, Effortful Emotion Regulation was most significant, indicating both factors had relevance to understanding the emergence of autism.

Bryson *et al*. (2007) described nine infants who met diagnostic criteria for autism by the age of 36 months. Six cases were distinguished by marked behavioural changes very early in development, which continued and/or were more evident by 18 months of age. Between 6 and 12 months of age, participants became more difficult to engage socially and an increase in visual fixation on objects was notable, in addition to increased repetitive and atypical motor behaviours. There was a trend towards greater irritability, less tolerance of intrusions, increased negative affect/proneness to distress, difficulties with self-regulation, and difficulties with being comforted or settled by others between 6 and 12 months of age.

Collectively, these studies indicate that particular patterns of behaviour and reactivity emerge in infancy and may predict IA in early childhood. Although group differences at 6 months of age do not appear to be predictive of autism status, group differences as early as 12 months of age are predictive of later outcomes, indicating the potential benefit of intervention at this time. Relatively few studies have been conducted examining early behaviour and later outcomes in children with disabilities, and studies in autism are increasing. Examining the emergence of autism over time is critical to elucidate the stability of behaviours and indicators for later development of both IA and autism in FXS.

Early identification in fragile X syndrome

Fragile X syndrome is the leading cause of inherited intellectual disability affecting approximately 1 in 3600 individuals across gender, race and ethnicity (Hagerman *et al*. 2009). The syndrome results from repetition in the CGG trinucleotide sequence at Xq27.3 on the long arm of the X chromosome which alters function of the *FMR*1 gene responsible

for production of fragile X mental retardation protein (FMRP). FMRP is vital for normal brain functioning in all persons including adequate learning and memory. The reduction of FMRP is assumed to be the cause of various outcomes associated with FXS such as intellectual disability, autistic behaviour, social problems and anxiety (Weiler *et al*. 1997; Bailey *et al*. 2001b).

Diagnosis of FXS is based on molecular genetic testing of the *FMR*1 gene. Six to 45 CGG repeats are considered normal, 45–54 repeats is considered the 'gray zone', while 55–200 repeats represents the *FMR*1 premutation. Greater than 200 CGG repeats is considered the full mutation in which there is hypermethylation of the *FMR*1 gene, which reduces FMRP production and results in physical, cognitive and behavioural aspects of FXS. Individuals with the full mutation may have complete methylation of the *FMR*1 gene or partial methylation referred to as 'mosaicism'. Both premutation and full mutation carriers can exhibit signs of FXS with individuals with the *FMR*1 premutation showing more psychiatric characteristics such as depression and anxiety, and fewer cognitive deficits (Franke *et al*. 1996).

Characteristic physical features of FXS include an elongated face, large ears, prominent jaw, macro-cephaly, macroorchidism, flat feet, a narrow high-arched palate and hyperextensible joints (Hagerman 1999). Although these are prominent physical features later in development, they are often not obvious at birth and during early infancy (Hagerman 1999). The first sign of FXS is typically late attainment of developmental milestones; however, these developmental delays are difficult to differentiate from other developmental disabilities (Maes *et al*. 2000). General delays include deficits in motor skills, increased initial social avoidance, and decreased social withdrawal compared with age and IQ matched controls (Kau *et al*. 2000). Motor skills tend to be the least delayed while communication and cognitive skills are the most delayed (Roberts *et al*. 2001a). Recent studies have also found deficits in visual attention and visual processing in infants with FXS (Farzin *et al*. 2008, 2011).

Although the average age of first concern (12 months), confirmation of developmental delay (19 months) and start of early intervention services for individuals with FXS (19 months) have decreased since 2001, the average age of diagnosis for FXS remains relatively stable at 38 months of age, an average of over 2 years after first concern (Bailey *et al*. 2009). Bailey *et al*. (2009) conducted a national survey which found that 22% of parents of children with FXS were informed that their child was developing normally upon first presenting concerns (12 months) to a healthcare professional. Only 14% of parents were referred to a specialist and, of those, 9% received a diagnosis other than FXS, and 4% were referred for FXS testing (Bailey *et al*. 2009). Thus, early identification of FXS is clearly challenging from multiple dimensions.

A characteristic cognitive profile is emerging in individuals with FXS. The majority of males exhibit cognitive deficits in the moderate to severe range, with stronger verbal than visual–spatial abilities (Bailey *et al*. 2004). Atypical early development of attention has also been well documented (Cornish *et al*. 2007; Scerif *et al*. 2007; Sullivan *et al*. 2007; Ornstein *et al*. 2008). These cognitive deficits can be mediated by the level of FMRP expression, so

that males with higher FMRP expression may exhibit higher cognitive abilities than males with little to no FMRP expression (Hagerman 1999; Tassone *et al*. 1999). Several studies have demonstrated that the IQ of individuals with FXS declines over time; yet, consensus is that the decline in scores is primarily due to suboptimal growth rather than a true decline or loss of skills (Fisch *et al*. 2002; Skinner *et al*. 2004). Individuals with FXS display a relative strength in self-help and daily living skills and a deficit in socialisation and communication adaptive skills (Hatton *et al*. 2003). Of note, autistic behaviour is associated with lower scores on measures of adaptive behaviour (Hatton *et al*. 2003).

FXS and autism

Autism is one of the most severe behaviour abnormalities observed in FXS. As noted above, 30–50% of individuals with the full mutation meet full DSM-IV-TR criteria for autism with 60–74% meeting criteria for an autism spectrum disorder (Bailey *et al*. 2000; Kaufmann *et al*. 2004; Philofsky *et al*. 2004; Clifford *et al*. 2007; Hall *et al*. 2008; Harris *et al*. 2008). Co-morbid FXS and autism is indicative of worse developmental outcomes (Bailey *et al*. 2000, 2001a; Rogers *et al*. 2001; Kau *et al*. 2004), leading to overall greater impairment in cognition and adaptive behaviour skills and more severe aberrant behaviour than FXS without autism. Recent work with larger longitudinal samples that span a broad age range suggest that autistic behaviours increase slowly but significantly over time (Hatton *et al*. 2006) as do associated social avoidance behaviours (Roberts *et al*. 2007).

Causal mechanisms of autism in fragile X syndrome

The underlying mechanism of autism in FXS is unknown; however, there are multiple hypotheses including social anxiety and neuropsychological processing, which encompasses executive functioning and theory of mind. The primary hypothesis is that *FMR*1 gene dysfunction leads to reduced FMRP resulting in atypical brain development in regions associated with autistic behaviour. Indeed, evidence has recently emerged indicating that brain regions associated with social cognition (Hoeft *et al*. 2011) and emotion processing (Hazlett *et al*. 2009) are dissociable in preschool males with FXS compared with typical controls; however, differences between preschool boys with FXS and those with IA were in the opposite direction, suggesting different pathogenic mechanisms for these two disorders that share a common set of behaviours (Hazlett *et al*. 2009; Hoeft *et al*. 2011). Likewise, findings suggest no brain differences between those with FXS and autism compared with those with FXS without autism (Hazlett *et al*. 2009; Hoeft *et al*. 2011).

Studies examining the role of FMRP have conflicting results. Bailey *et al*. (2000) found that the level of FMRP did not correlate with the presence or absence of autism, suggesting that autism within FXS may be related to genetic or environmental factors that could be additive to the *FMR*1 mutation; however, Hatton *et al*. (2006), using an expanded sample, found that FMRP did correlate with the level of autistic behaviour. In other studies, no relationship between autistic behaviour and FMRP was found after controlling for IQ (Hessl *et al*. 2001; Loesch *et al*. 2007; Harris *et al*. 2008). Autistic behaviour in FXS has also been attributed to hyperarousal secondary to reduced FMRP (Cohen 1995), and evidence has emerged supporting this relationship (Roberts *et al*. 2001b, 2009; Hall *et al*. 2008). Whether

hyperarousal is a mediating factor regarding the presence of autism in FXS is not yet fully understood.

García-Nonell *et al*. (2008) hypothesised that there is an additive effect beyond FMRP that relates to autism and that individuals with FXS and a secondary medical or genetic syndrome are at increased risk for autism. Using retrospective analysis and chart review, these researchers found that there were twice as many participants with medical conditions in the co-morbid FXS and autism group versus those with FXS alone, and this difference was statistically significant. When including individuals with only seizures as a secondary condition there were still twice as many participants in the co-morbid group, but this was not statistically significant (García-Nonell *et al*. 2008). These findings indicate that there may be an additive function to FMRP that leads to autistic behaviours. These behaviours could be due to general damage affecting the brain or to a secondary gene dysregulation. Berry-Kravis *et al*. (2010) confirm these results in demonstrating that autism is significantly associated with seizures that occur in individuals with FXS and this relationship impacts cognitive and behavioural function. Additionally, a similar pattern has been reported in the *FMR*1 premutation (Chonchaiya *et al*. 2011). Clearly, the presence of autism in FXS is related to additional effects beyond FMRP, including other genetic and environmental effects that are independent of, or interact with, the FXS genotype and phenotype (Harris *et al*. 2008).

Debates regarding autism in fragile X syndrome

While clear consensus exists regarding the shared phenomenology between FXS and IA, a number of debates regarding diagnostic and treatment issues exist. Two of the primary debates in FXS centre around questions of whether autism in FXS represents a continuum, with only those most severely affected meeting criteria for autism, and whether autism in FXS is the same or different than IA. Some investigators have recently questioned the current diagnostic approach of applying criteria for a behavioural disorder, autism, to a clearly defined neurogenetic disorder, FXS. These arguments hold that when diagnostic criteria for autism are met by individuals with FXS, they are often met in different ways than IA (Hall *et al*. 2010), and that it is a ‘category mistake’ to diagnose children with FXS with autism given the distinction between diagnosing autism in a known genetic disorder (i.e. FXS) versus doing so when the aetiology is unknown (i.e. IA). Likewise, Harris (2011) proposes a focus on brain-behaviour relationships targeting advancement of behavioural phenotyping in neurogenetic disorders precluding application of DSM-IV diagnostic behavioural criteria to identified disorders such as FXS. He proposes that FXS is a neural model and phenocopy of autism and should not be considered a genetic model for autism.

In contrast to these views, a number of investigators report findings indicating highly similar profiles between individuals with FXS and autism versus IA and apply categorical or dimensional ratings of autism in FXS (Bailey *et al*. 2004; Kau *et al*. 2004; Kaufmann *et al*. 2004; Lewis *et al*. 2006). Rogers *et al*. (2001) found that children with FXS fell into two distinct groups based on autism symptomology using the ADOS, ADI-R and DSM-IV. One group of children with FXS met criteria for autism and was indistinguishable from a matched group of children with IA, and the second group of children with FXS did not meet

criteria for autism and were highly similar to a matched group with other developmental delays. In a more recent study Hoeft *et al*. (2011) examined brain–behaviour profiles in young boys with IA and FXS broken into groups with and without autism. They reported greater problem behaviours in IA compared with FXS as a whole group with similar levels of repetitive behaviour and IQ. In comparisons of IA to FXS with autism, scores were not different in social and communication on the ADOS, communication on the ADI-R, repetitive behaviour and IQ; however, ADI measures of social function on the ADI-R were more impaired in IA than FXS with autism. Of interest, imaging results indicated brain differences between groups with IA resembling controls more closely than groups with FXS with and without autism (Hoeft *et al*. 2011). Clearly, brain–behaviour relationships in IA and FXS are complex, and there is insufficient evidence to resolve these debates at this time.

One of the primary limitations to this work that hampers advancement of these debates is the limited number of studies including samples of FXS with and without autism to controls with IA. In the study by Hall *et al*. (2010), their intent was to determine whether the classification of autism in FXS is appropriate. However, they only included a FXS sample and relied on reference sample norms to provide comparisons to individuals with autism which limited some of their core findings. Another limitation to this debate is the paucity of study taking developmental factors into consideration (Harris 2011). Clearly, there is a need for specificity of both behaviour and underlying mechanisms to inform the debate regarding whether autism in FXS is the same as idiopathic autism and whether these distinctions should be made solely at the behavioural level or include aetiology as an exclusionary factor. We believe these discussions can be informed through research comparing infants at risk for IA and those with FXS who later do and do not develop autism. Debates regarding diagnostic specification have treatment implications in that standard treatments for autism may not be ideal for individuals with FXS and autism if there are different underlying mechanisms accounting for the behavioural expression (Hall *et al*. 2010).

Early indicators of autism in fragile X syndrome

Similar to IA, studies of children with FXS in the first year of life have recently begun to emerge, and few longitudinal studies of behaviour in FXS during the first five years of life have been published. Cross-sectional studies are inconsistent with regard to continuity and change in the profile of problem behaviour in FXS. Some suggest age related changes with behaviour problems described as subtle or absent during the infant and toddler years yet emerging and intensifying in early childhood (Hatton *et al*. 1999; Hepburn & Rogers 2001; Bailey *et al*. 2001a; Hatton & Roberts 2004; Baranek *et al*. 2008). Recently, Brock & Hatton (2010) distinguished four parent-questionnaire items that, when used as a screening instrument for autism, exhibited adequate sensitivity (82%) and specificity (79%) regarding the severity of autistic behaviour. The four items of interest addressed social avoidance, response to joint attention, stereotyped object use and social withdrawal (Brock & Hatton 2010).

In a study of development in young boys with FXS, Roberts *et al*. (2009) followed 55 boys with FXS between the ages of 8 and 48 months. Results indicated that the boys' rate of development was significantly lower than chronological age expectations, an expected

finding based on what we know about cognitive development in FXS. Of interest, no slowing in the rate of development was found as reported in other studies (Fisch *et al*. 2002; Skinner *et al*. 2004). Autistic behaviour was negatively associated with development and, importantly, developmental delays were evident as early as 9 months of age, consistent with work in IA (Stone *et al*. 2007; Brian *et al*. 2008).

In a study utilising retrospective video analysis, Baranek *et al*. (2005) examined sensory-motor patterns in a cross-sectional study of infants with FXS (n = 11) in order to distinguish them from infants with autism (n = 11), other developmental delays (n = 10) and typically developing infants (n = 11) at 9–12 months of age. Results indicated a pattern of sensory-motor features such as repetitive leg movements, posturing and repetitive use of objects was associated with FXS and indicated similarities with the developmental delay group. Two features that best discriminated FXS from autism were reduced level of object play skills and reduced amount of repetitive play skills. FMRP correlated with looking at the camera and object play. In a follow-up longitudinal study of sensory-processing in infants with 13 males with FXS (Baranek *et al*. 2008), results indicated that sensory processing problems (both hyper- and hyporesponsiveness) were evident very early in development. An unexpected shift from sensory hyporesponsivity in early infancy to hyper-responsivity in toddlerhood and preschool was evident highlighting the need to conduct in-depth studies of infants with FXS and not presume a downward age extension of the phenotype is valid.

Roberts *et al*. (2011) examined the relationship of visual attention to autistic behaviour in infants with FXS as atypical visual attention is shown to be a robust indicator of autism in IA (Zwaigenbaum *et al*. 2005). In their sample of 13 infants with full mutation FXS and 10 typically developing controls, Roberts *et al*. (2011) found that infants with FXS displayed a flat trajectory from 9 to 18 months of age, in contrast to the expected normative changes (Bornstein 1998; Courage *et al*. 2006). Additionally, infants with FXS had increased heart rate consistent with reported patterns of systematic hyper-arousal (Roberts *et al*. 2001b; Hall *et al*. 2008). At 12 and 18 months of age, increased look duration was associated with increased severity of autistic behaviour, and blunted change in latency to disengage attention between 9 and 12 months of age also related to increased autistic behaviours similar to findings in IA (Zwaigenbaum *et al*. 2005) indicating there may be core features that are shared in both populations.

Roberts *et al*. (2012) examined the relationship between the severity of autistic behaviour and physiological arousal in 31 males with FXS, aged 8 to 40 months. Cross-sectional analyses indicated autistic behaviour was associated with cardiovascular indicators of hyperarousal. However, an age-related shift in arousal was evident with elevated autistic behaviour associated with lower heart rate at younger ages and elevated heart rate at older ages. Results suggest a relationship between physiological arousal and autistic behaviour that emerges and is unstable within the first year of life, lending evidence that observed behavioural characteristics may be rooted in abnormal physiological regulation associated with abnormal brain development secondary to *FMR*1 dysfunction.

Tonnsen *et al*. (in press) prospectively compared early indicators of anxiety and autistic behaviour in infants with FXS over time. In a sample of 26 boys with full mutation FXS,

results indicated that temperament constructs of fear and soothability were related to anxiety outcomes and the change over time of sadness was also related to anxiety outcomes. However, temperament measures did not relate to autistic behaviour in this sample. Preliminary analyses with a behavioural measure of facial fear indicate a potential relationship with autistic behaviour with decreased facial fear being associated with increased autistic behaviour.

Summary and conclusions

Fragile X syndrome is the most common known genetic cause of autism, and the co-morbidity of autism in FXS is extremely high (Hagerman *et al*. 2008). Individuals with both autism and FXS experience greater impairments in social interactions and communication and delays in adaptive and cognitive development (Bailey *et al*. 2000, 2001a; Rogers *et al*. 2001; Kau *et al*. 2004; Hernandez *et al*. 2009). It remains unclear, however, whether co-morbid FXS and autism is a distinct phenotype of FXS or a continuum of features and how the mechanisms underlying autism in FXS are shared or distinct from IA (Rogers *et al*. 2001; Bailey *et al*. 2004; Kau *et al*. 2004; Kaufmann *et al*. 2004; Hall *et al*. 2010; Harris 2011). The effects of co-morbid autism and FXS are deleterious, so the need to measure risk factors well and early is of great importance. Given this, FXS is proposed as an ideal population to study early indicators of autism due to the high-risk status and genetic relevance to the field of IA. Studies of early indicators of autism in FXS may aid in the earlier identification of children with FXS and the provision of necessary services. To date, little research has been conducted involving the direct comparison with individuals with autism, FXS, and autism and FXS (Bailey *et al*. 2004). Thus, understanding early indicators of autism in children with FXS is a pertinent area of study.

Although the literature on the co-morbidity of FXS and autism is extensive, few published studies have examined early indicators of autism in an infant sample longitudinally. In fact, studies examining early indicators as a basis for understanding later behavioural problems have only recently begun (Shanahan *et al*. 2008; Roberts *et al*. 2011). Studying emerging characteristics in FXS is critical for understanding if early features in infants with FXS are associated with later autistic behaviours as reported in IA. To date, studies that have been conducted lend evidence to the fact that indicators of autism exist as early as 12 months of age in males with FXS, and replicate findings in IA that implicate difficulties with disengagement of attention and shifts in behaviour between 6 and 12 months of age in the later development of autism (Zwaigenbaum *et al*. 2005; Baranek *et al*. 2008; Roberts *et al*. 2011).

Diagnosis and treatment implications

There are significant diagnostic and treatment implications to this work. Given the elevated level of autism diagnoses in FXS, it is critical that we have a clear understanding of these early behavioural indicators to guide diagnostic and treatment efforts. This is particularly relevant given evidence that the infant FXS phenotype may differ from that describing older-aged children and adults (Baranek *et al*. 2008; Roberts *et al*. 2011). Traditional approaches to autism diagnosis are inadequate for identifying children early, as gold standard diagnostic tools have rarely been applied to children under the age of two

(Zwaigenbaum *et al*. 2005). A focus on early discrete indicators, such as activity, anger or attention, versus meeting a cut-off score may be more informative for the identification of autism in those at high risk for the disorder as the primary barrier to diagnosis is a lack of understanding of the early phenotypes (Brock & Hatton 2010). Routine developmental screening for all children may be the best strategy to detect delays in infants with both FXS and autism. Additionally, for individuals with FXS, a differential autism diagnosis may be helpful to provide prognostic information and guide treatment efforts (Roberts *et al*. 2009).

Not only can behavioural treatments for autistic behaviours potentially remediate phenotypic features in FXS, but pharmacological treatments for FXS may be beneficial for the subgroup that demonstrates autistic behaviours, which may lead to decreased cases of autism in this population (Berry-Kravis *et al*. 2011). Studies have indicated many similarities in GABA and glutamate dysregulation, which can be reversed with targeted pharmacological treatments (Fatemi & Folsom 2011). Additionally, studies examining the effects of lithium and anticonvulsant medication lend promise to the idea that these medications may also prevent autistic like behaviours by treating the underlying cause of such behaviours (García-Nonell *et al*. 2008). FMRP dys-function is not unique to FXS and reduced FMRP found in adults with autism suggests that targeted pharmacological treatments for FXS may be beneficial to remediate symptoms of autism, particularly mGluR inhibitors and lithium (Fatemi & Folsom 2011).

Future research

Because of the importance of early identification of risk markers for the development of autism both in IA and FXS, future research is necessary to help solidify and replicate findings of these early risk markers. Having comparison groups of both typically developing infants as well as those at high-risk for IA will add information regarding the sensitivity and specificity of early indicators, both behavioural and physiological. Inclusion of comparison groups will also contribute to our understanding of differences in the developmental trajectories of these indicators. Using DSM-IV-TR-based diagnostic measures of autism is also of critical importance in order to differentiate clinical subgroups.

Larger and more representative samples are necessary to increase the generalisability of findings. However, recruiting infants within the first year of life is challenging, considering the average age of diagnosis of FXS is 38 months (Bailey *et al*. 2009). Additionally, retaining participants over a period of years is difficult and costly. Future research should incorporate more experimental measures eliciting expression of behaviour markers such as activity and attention. A more systematic and experimental approach for measuring these constructs may elucidate relationships with autism missed by the use of parent ratings alone.

Benefits of the study of autism in fragile X syndrome

There are several benefits to studying the early emergence of both IA and autism within FXS. The latent heterogeneity of IA is often under investigated, and clarifying the early mechanisms and solidifying similarities and differences between these two populations is of utmost importance. Understanding early indicators of autism may lead to earlier provision of services and potentially amelioration of symptoms (Dawson 2008). Existing evidence

suggests that 6–12 months is a critical developmental period, and further study of early development can help determine the validity of such findings.

Within FXS, earlier diagnosis of both FXS and autism is important for intervention and family planning. There are fundamental differences between these groups that may exist at early ages and studying early development in FXS can help elucidate underlying mechanisms of autistic behaviours and contribute to discussion of how the phenotypic expression of autism in FXS is shared or distinct from IA. If the phenotypic expression is similar in FXS as in IA, then targeted treatment and outcomes could be similar in both groups. Importantly, examining change over time is critical as evidence suggests the phenotype in infancy is not simply a downward extension of that in early childhood (Baranek *et al*. 2008; Shanahan *et al*. 2008) and important age-related factors have emerged during the infant–toddler developmental period (Roberts *et al*. 2012).

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edn, text revised. American Psychiatric Association; Washington, DC.: 2000.

Bailey DB Jr, Hatton DD, Mesibov G, Ament N, Skinner M. Early development, temperament, and functional impairment in autism and fragile X syndrome. Journal of Autism and Developmental Disorders. 2000; 30:557–67.

Bailey DB Jr, Hatton DD, Skinner M, Mesibov G. Autistic behaviour, FMR1 protein, and developmental trajectories in young males with FXS. Journal of Autism and Developmental Disorders. 2001a; 31:165–74. [PubMed: 11450815]

Bailey DB Jr, Hatton DD, Tassone F, Skinner M, Taylor AK. Variability in FMRP and early development in males with FXS. American Journal on Mental Retardation. 2001b; 1:16–27. [PubMed: 11246709]

Bailey, DB., Jr; Roberts, JE.; Hooper, SR.; Hatton, DD.; Mirrett, PL.; Roberts, JE., et al. Research on FXS and autism: implications for the study of genes, environments, and developmental language disorders.. In: Rice, ML.; Warren, SF., editors. Developmental Language Disorders: From Phenotypes to Etiologies. Erlbaum; Mahway, NJ.: 2004. p. 121-53.

Bailey DB Jr, Raspa M, Bishop E, Holliday D. No change in the age of diagnosis for FXS: findings from a national parent survey. Pediatrics. 2009; 142:527–33. [PubMed: 19581269]

Baranek GT, Cassandra DD, Skinner ML, Bailey DB Jr, Hatton DD, Roberts JE, et al. Video analysis of sensory-motor features in infants with fragile X syndrome at 9-12 months of age. Journal of Autism and Developmental Disorders. 2005; 35:645–56. [PubMed: 16172809]

Baranek GT, Roberts JE, David FJ, Sideris J, Mirrett PL, Hatton DD, et al. Developmental trajectories and correlates of sensory processing in young boys with FXS. Physical and Occupational Therapy in Pediatrics. 2008; 28:79–98. [PubMed: 18399048]

Berry-Kravis E, Raspa M, Loggin-Hester L, Bishop E, Holiday D, Bailey DB Jr. Seizures in fragile X syndrome: characteristics and comorbid diagnosis. American Journal of Intellectual and Developmental Disabilities. 2010; 6:461–72.

Berry-Kravis E, Knox A, Hervey C. Targeted treatments for fragile X syndrome. Journal of Neurodevelopmental Disorders. 2011; 3:193–210. [PubMed: 21484200]

Bornstein, MH. Stability in mental development from early life: methods, measures, models, meanings, and myths.. In: Simion, F.; Butter-worth, G., editors. The Development of Sensory, Motor, and Cognitive Capacities in Early Infancy: From Perception to Cognition. Psychology Press/Taylor & Francis; Hove, England/Erlbaum, UK.: 1998. p. 301-32.

Brian J, Bryson SE, Garon N, Roberts W, Smith IM, Szatmari P, et al. Clinical assessment of autism in high-risk 18 month olds. Autism. 2008; 12:433–56. [PubMed: 18805941]

Brock M, Hatton D. Distinguishing features of autism in boys with fragile X syndrome. Journal of Intellectual Disability Research. 2010; 54:894–905. [PubMed: 20704635]

Bryson SE, Zwaigenbaum L, Brian J, Roberts W, Szatmari P, Rombough V, et al. A prospective case series of high-risk infants who develop autism. Journal of Autism and Developmental Disorders. 2007; 37:12–24. [PubMed: 17211728]

Chonchaiya W, Au J, Schneirder A, Hessl D, Harris SW, Laird M, et al. Increased prevalence of seizures in boys who were probands with the FMR1 premutation and comorbid autism spectrum disorder. Human Genetics. 2011; 131:1–9. [PubMed: 21706341]

Clifford S, Dissanayake C, Bui QM, Huggins R, Taylor AK, Loesch DZ. Autism spectrum phenotype in males and females with fragile X full mutation and permutation. Journal of Autism and Developmental Disorders. 2007; 37:738–47. [PubMed: 17031449]

Cohen IL. A theoretical analysis of the role of hyperarousal in the learning and behaviour of fragile X males. Mental Retardation and Developmental Disabilities Research Reviews. 1995; 1:286–91.

Cornish K, Scerif G, Karmiloff-Smith A. Tracing syndrome-specific trajectories of attention across the lifespan. Cortex. 2007; 43:672–85. [PubMed: 17710820]

Courage ML, Reynolds GD, Richards JE. Infants' attention to patterned stimuli: developmental change from 3 to 12 months of age. Child Development. 2006; 77:680–95. [PubMed: 16686795]

Darnell JC, Van Driesche SJ, Zhang C, Hung KYS, Mele A, Fraser CE, et al. FMRP stalls ribosomal translocation on mRNAs linked to synaptic function on and autism. Cell. 2011; 146:247–61. [PubMed: 21784246]

Dawson G. Early behavioural intervention, brain plasticity, and the prevention of autism spectrum disorder. Developmental Psychopathology. 2008; 20:775–803.

Farzin F, Whitney D, Hagerman RJ, Rivera SM. Contrast detection in infants with fragile X syndrome. Vision Research. 2008; 48:1471–8. [PubMed: 18457856]

Farzin F, Rivera SM, Whitney D. Resolution of spatial and temporal visual attention in infants with fragile X syndrome. Brain. 2011; 134:3355–68. [PubMed: 22075522]

Fatemi SH, Folsom TD. The role of fragile X mental retardation protein in major mental disorders. Neuropharmacology. 2011; 60:1221–6. [PubMed: 21108954]

Fisch GS, Simensen R, Schroer RJ. Longitudinal changes in cognitive and adaptive behaviour scores in children and adolescents with the fragile X mutation or autism. Journal of Autism and Developmental Disorders. 2002; 32:107–14. [PubMed: 12058838]

Franke P, Maier W, Iwers B, Hautzinger M, Froster UG. Fragile X carrier females: evidence for a distinct psychopathological phenotype? American Journal of Medical Genetics. 1996; 64:334–9. [PubMed: 8844076]

Ganz ML. The lifetime distribution of the incremental societal costs of autism. Archives of Pediatric and Adolescent Medicine. 2007; 161:343–9.

García-Nonell C, Ratera ER, Harris S, Hessl D, Ono MY, Tartaglia N, et al. Secondary medical diagnosis in fragile X syndrome with and without autism spectrum disorder. American Journal of Medical Genetics Part A. 2008; 146A:1911–6. [PubMed: 18627038]

Garon N, Bryson SE, Zwaigenbaum L, Smith IM, Brian J, Roberts W, et al. Temperament and its relationship to autistic symptoms in a high-risk infant sib cohort. Journal of Abnormal Child Psychology. 2009; 37:59–78. [PubMed: 18704676]

Hagerman, RJ. FXS.. In: Hagerman, RJ., editor. Neurodevelopmental Disorders. Oxford University Press; Oxford: 1999. p. 61-132.

Hagerman RJ, Rivera SM, Hagerman PJ. The fragile X family of disorders: a model for autism and targeted treatments. Current Pediatric Reviews. 2008; 4:40–52.

Hagerman RJ, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, et al. Advances in the treatment of FXS. Pediatrics. 2009; 123:378–90. [PubMed: 19117905]

Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behaviour in children and adolescents with fragile X syndrome. American Journal on Mental Retardation. 2008; 113:44–53. [PubMed: 18173299]

Hall SS, Lightbody AA, Hirt M, Rezvani A, Reiss AL. Autism in fragile X syndrome: a category mistake? Journal of the American Academy of Child and Adolescent Psychiatry. 2010; 49:921–33. [PubMed: 20732628]

Harris SW. Brain and behaviour in fragile X syndrome and idiopathic autism. Archives of General Psychiatry. 2011; 68:295–305. [PubMed: 21041609]

Harris SW, Hessl D, Goodlin-Jones B, Ferranti J, Bacalman S, Barbato I, et al. Autism profiles of males with FXS. American Journal on Mental Retardation. 2008; 113:427–38. [PubMed: 19127654]

Hatton, DD.; Roberts, JE. Early Intervention Strategies for Young Children with FXS. Palm Springs; CA: Feb. 2004 2004 Behaviour and Social Emotional Regulation in Fragile X Syndrome..

Hatton DD, Bailey DB Jr, Hargett-Beck MQ, Skinner M, Clark RD. Behavioural style of young boys with FXS. Developmental Medicine and Child Neurology. 1999; 41:1–8.

Hatton DD, Wheeler AC, Skinner ML, Bailey DB Jr, Sullivan KM, Roberts JE, et al. Adaptive behaviour in children with FXS. American Journal on Mental Retardation. 2003; 108:373–90. [PubMed: 14561110]

Hatton DD, Sideris J, Skinner M, Mankowski J, Bailey DB Jr, Roberts JE, et al. Autistic behaviour in children with FXS: prevalence, stability, and the impact of FMRP. American Journal of Medical Genetics Part A. 2006; 140A:1804–13. [PubMed: 16700053]

Hazlett HC, Poe MD, Lightbody AA, Gerig G, Macfall JR, Ross AK, et al. Teasing apart the heterogeneity of autism: same behaviour, different brains in toddlers with fragile X and autism. Journal of Neurodevelopmental Disorders. 2009; 1:81–90. [PubMed: 20700390]

Hepburn, SL.; Rogers, SJ. Temperament in children with FXS.. Paper presented at the Gatlinburg Conference on Research in Developmental Disabilities; Charleston, SC.. 2001.

Hernandez RN, Feinberg RL, Vaurio R, Passanante NM, Thompson RE, Kaufmann WE. Autism spectrum disorder in FXS: a longitudinal evaluation. American Journal of Medical Genetics Part A. 2009; 149A:1125–37. [PubMed: 19441123]

Hessl D, Dyer-Friedman J, Glaser B, Wisbeck J, Barajas RG, Taylor A, et al. The influence of environmental and genetic factors on behaviour problems and autistic symptoms in boys and girls with FXS. Pediatrics. 2001; 108:314–19.

Hoeft F, Walter E, Lightbody AA, Hazlett HC, Chang C, Piven J, et al. Neuroanatomical differences in toddler boys with fragile X syndrome and idiopathic autism. Archives of General Psychiatry. 2011; 68:295–305. [PubMed: 21041609]

Kau AS, Reider EE, Payne L, Meyer WA, Freund L. Early behaviour signs of psychiatric phenotypes in FXS. American Journal on Mental Retardation. 2000; 105:266–99.

Kau AS, Tierney E, Bukelis I, Stump M, Kates W, Trescher W, et al. Social behaviour profile in young males with FXS: characteristics and specificity. American Journal of Medical Genetics. 2004; 126:9–17. [PubMed: 15039968]

Kaufmann WE, Cortell R, Kau A, Bukelis I, Tierney E, Gray R, et al. Autism spectrum disorder in FXS: communication, social interaction, and specific behaviours. American Journal of Medical Genetics Part A. 2004; 129A:225–34. [PubMed: 15326621]

Kelleher RJ III, Bear MF. The autistic neuron: troubled translation? Cell. 2008; 135:401–6. [PubMed: 18984149]

Landa RJ, Holman KC, Garrett-Mayer E. Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. Archives of General Psychiatry. 2007; 64:853–64. [PubMed: 17606819]

Lewis P, Abbeduto L, Murphy M, Richmond E, Giles N, Bruno L, et al. Cognitive, language, and social-cognitive skills of individuals with fragile X syndrome with and without autism. Journal of Intellectual Disability Research. 2006; 50:532–45. [PubMed: 16774638]

Loesch DZ, Bui QM, Dissanayake C, Clifford S, Gould E, Bulhak-Paterson D, et al. Molecular and cognitive predictors of the continuum of autistic behaviours in fragile X. Neuroscience and Biobehavioral Reviews. 2007; 31:315–26. [PubMed: 17097142]

Maes B, Fryns JP, Ghesquiere P, Borghgraef M. Phenotypic checklist to screen for FXS in people with mental retardation. Mental Retardation. 2000; 28:207–15. [PubMed: 10900928]

Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004; 113:e472–3486. [PubMed: 15121991]

Ornstein PA, Schaaf JM, Hooper SR, Hatton D, Mirrett P, Bailey DBJ. Memory skills of boys with fragile X syndrome. American Journal on Mental Retardation. 2008; 113:453–65. [PubMed: 19127656]

Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, et al. Recurrence risk for autism spectrum disorders: a baby sibling research consortium study. Pediatrics. 2011; 128:e1–e8. [PubMed: 21690117]

Philofsky A, Hepburn SL, Hayes A, Hagerman R, Rogers SJ. Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. American Journal on Mental Retardation. 2004; 109:208–18. [PubMed: 15072521]

Rice C. Prevalence of autism spectrum disorders. Autism and Developmental Disabilities Monitoring Network Survey Summary. 2009; 58:1–20.

Roberts JE, Boccia ML, Bailey DB Jr, Hatton DD, Skinner M. Cardiovascular indices of physiological arousal in boys with FXS. Developmental Psychobiology. 2001a; 29:107–23. [PubMed: 11568881]

Roberts JE, Hatton DD, Bailey DB Jr. Development and behaviour of male toddlers with fragile X syndrome. Journal of Early Intervention. 2001b; 24:207–23.

Roberts JE, Weisenfeld LA, Hatton DD, Heath M, Kaufmann WE. Social approach and autistic behaviour in children with FXS. Journal of Autism and Developmental Disorders. 2007; 37:1748–60. [PubMed: 17180715]

Roberts JE, Mankowski JB, Sideris J, Goldman BD, Hatton DD, Mirrett PL, et al. Trajectories and predictors of the development of very young boys with fragile X syndrome. Journal of Pediatric Psychology. 2009; 8:1–10.

Roberts JE, Hatton DD, Long ACJ, Anello V, Colombo J. Visual attention and autistic behaviour in infants with fragile X syndrome. Journal of Autism and Developmental Disorders. 2011; 42:937–46. [PubMed: 21720726]

Roberts JE, Tonnsen BL, Robinson AR, Shinkareva SV. Heart activity and autistic behavior in infants and toddlers with FXS. American Journal on Intellectual and Developmental Disabilities. 2012; 117:90–102. [PubMed: 22515825]

Rogers S, Wehner E, Hagerman R. The behavioural phenotype in fragile X: symptoms of autism in very young children with FXS, idiopathic autism, and other developmental disorders. Journal of Developmental and Behavioural Pediatrics. 2001; 22:409–17.

Scerif G, Cornish K, Wilding J, Driver J, Karmiloff-Smith A. Delineation of early attentional control difficulties in fragile X syndrome: focus on neurocomputational changes. Neuropsychologia. 2007; 45:1889–98. [PubMed: 17254617]

Shanahan M, Roberts J, Hatton D, Reznik J, Goldsmith H. Early temperament and negative reactivity in boys with FXS. Journal of Intellectual Disability Research. 2008; 52:842–54. [PubMed: 18498331]

Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, et al. Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; 48:463–4. [PubMed: 19395900]

Skinner M, Hooper S, Hatton DD, Roberts JE, Mirrett P, Schaaf J, et al. Mapping nonverbal IQ in young boys with FXS. American Journal of Medical Genetics Part A. 2004; 132A:25–32. [PubMed: 15551333]

Stone WL, McMahon CR, Yoder PJ, Walden TA. Early social-communicative and cognitive development of younger siblings of children with autism spectrum disorders. Archives of Pediatric and Adolescent Medicine. 2007; 161:384–90.

Stone WL, McMahon CR, Henderson LM. Use of the Screening Tool for Autism in Two-Year-Olds (STAT) for children under 24 months: an exploratory study. Autism:The International Journal of Research and Practice. 2008; 12:557–73. [PubMed: 18805947]

Sullivan K, Hatton D, Hammer J, Sideris J, Hooper S, Ornstein PA, et al. Sustained attention and response inhibition in boys with fragile X syndrome: measures of continuous performance. American Journal of Medical Genetics B Neuropsychiatric Genetics. 2007; 144B:517–32.

Tager-Flusberg H. The origins of social impairments in autism spectrum disorders: studies of infants at risk. Neural Networks. 2010; 23:1072–6. [PubMed: 20800990]

Tassone R, Dyer PD, Lampe M, Willemsen R, Oostra B, Hagerman RJ, et al. FMRP expression as a potential prognostic indicator in FXS. American Journal of Medical Genetics. 1999; 84:250–61. [PubMed: 10331602]

Tonnsen BL, Malone P, Hatton D, Roberts JE. Negative affect predicts anxiety, not autism, in young boys with fragile X syndrome. Journal of Abnormal Child Psychology. (in press).

Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, et al. Fragile X mental protein is translated near synapses in response to neurotransmitter activation. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94:5395–400. [PubMed: 9144248]

Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioural manifestations of autism in the first year of life. International Journal of Neuroscience. 2005; 23:143–52.