

CHAPTER 2

Fragile X Syndrome as a Multilevel Model for Understanding Behaviorally Defined Disorders

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INTRODUCTION

Neurodevelopmental disorders of known genetic origin, like fragile X, Williams, and Down syndromes, can serve as multidisciplinary, multilevel models for understanding the neurodevelopmental mechanisms and the origins of other disorders that are currently defined only at the behavioral level (e.g., dyslexia, attention-deficit/hyperactivity disorder [ADHD]; autism spectrum disorder [ASD]), with one critical proviso: they are considered within a truly developmental framework. Indeed, special emphasis will be given throughout this chapter on the importance of the developmental perspective on neurodevelopmental disorders. It is crucial for researchers always to recall that early genetic modifications—whether deletions, translocations, duplications, or mutations—are likely to affect neurocognitive functioning from the very outset of development and to have complex interactions and widespread cascading effects over time on the resulting phenotype. For example, research on infants with disorders of known genetic origin has highlighted the importance of investigating empirically the very early developmental profile of each syndrome during infancy, rather than assuming a priori that the cognitive profile in adults is representative of earlier deficits and abilities (Karmiloff-Smith, 1998; Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith, 1999). So, researchers always need to keep in mind a clear distinction between the

mature, developed, relatively stable brain and the dynamically changing developing brain (Karmiloff-Smith, 2010). Thus, while genetic disorders can provide unique insights into how relatively well understood genetic modifications, molecular pathways, and systems neuroscience influence cognition, these complex interactions cannot be fully understood outside their developmental context (Doherty, Shimi, & Scerif, 2015).

In this chapter, we take the case of one such neurodevelopmental disorder of known genetic origin, fragile X syndrome (FXS), to discuss a number of broad issues that emerge from the comparison with disorders that are behaviorally defined (see Farran & Karmiloff-Smith, 2012, for a similar approach using Williams syndrome as the model disorder). First, we provide a short summary of the genetic, neurocognitive, and behavioral characteristics of FXS, with special emphasis on the complex interplay between developmental stability and developmental change. Second, using longitudinal data, we discuss the ostensibly surprising fact that despite being a monogenetic disorder, there are wide within-syndrome individual differences in the phenotypic outcomes of individuals with FXS. The longitudinal findings highlight the existence of within-syndrome developmental trajectories that diverge over time as well as the importance of identifying both risk and protective environmental factors that influence these outcomes. Then we focus on cross-syndrome comparisons

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of the similarities and differences in social and cognitive problems of children with FXS with those of children with two behaviorally defined disorders, ADHD and ASD. We conclude with a strong emphasis on the usefulness of cross-syndrome comparisons and a discussion of how this approach can be used as a model for understanding other genetic disorders in which within-syndrome variability has not been as thoroughly investigated, particularly within a longitudinal framework.

THE FRAGILE X GENOTYPE AND PHENOTYPE

Genetically, FXS is caused by the silencing of a single gene on the X chromosome, and in males who are carriers of the full mutation it results in an almost complete absence of the protein product linked to this gene in typical development. Phenotypically, the syndrome is associated with significant attentional, memory, and sociocognitive deficits that turn out to be more severe than would be predicted given levels of overall developmental delay. This therefore makes FXS an ideal model in which to study the effects of protein networks on the developmental trajectories of attentional control and memory at multiple levels, from the cellular to the systems and cognitive neuroscience, and how they impact on specific cognitive domains such as social cognition (see Belmonte & Bourgeron, 2006; Bourgeron, 2009; Scerif & Karmiloff-Smith, 2005, for a discussion of this interdisciplinary approach). Nonetheless, at all levels, scientists must take into account the developmental constraints acting over time if we are to reach a full understanding of the resulting phenotype. In the following paragraphs, we characterize FXS at these different levels.

Constituting the most common inherited form of intellectual disability, FXS has a prevalence of approximately 1 in every 4,000 males and 1 in every 8,000 females, although more recent figures estimate a general prevalence closer to 1 in 2,500 (Crawford, Acuña, & Sherman, 2001; Hagerman, 2008). It results from a large trinucleotide CGG repeat expansion in the 5' untranslated region of the *FMR1* gene at site Xq27.3. While typically developing individuals usually have approximately 30 CGG repeats at this site, premutation carriers present with around 55–200 repeats, and individuals with the full mutation have over 230 repeats (Maddalena et al., 2001). In this chapter, we will concentrate on full mutation carriers because of the greater wealth of developmental findings to date (but see Bourgeois et al., 2009; Cornish, Kogan, Li, Turk, Jacquemont, & Hagerman, 2009; Cornish et al., 2008; for fascinating research that now reveals unsuspected

impairments also in premutation carriers, and their developmental progressions from childhood into young and late adulthood). The extensive CGG repeat expansion in full mutation carriers gives rise to epigenetic changes, such as methylation of the *FMR1* gene promoter, and thus transcriptional silencing of the *FMR1* gene itself, which then results in a reduction of FMRP, the fragile X mental retardation protein (Verkerk et al., 1991). Because of the location of the *FMR1* on the X chromosome, males are usually more severely affected than females, the latter being more resilient because they have two X chromosomes, only one of which is randomly inactivated (Grigsby, Kemper, Hagerman, & Myers, 1990).

Phenotypically, individuals with FXS present with a number of physical features: prominent ears, a long narrow face, flat feet, joint laxity, and macro-orchidism (Hagerman, Van Housen, Smith, & McGavran, 1984). However, while these features are not especially obvious in early development, they become more evident with growing maturation. By contrast, developmental delay in cognitive and motor milestones is more obvious during the early stages of development, and is often what alerts clinicians to the possibility of a neurodevelopmental disorder in families with newly diagnosed children and no previous FXS births (Bailey, Skinner, Hatton, & Roberts, 2000). By contrast, given the inherited nature of the syndrome, if there is already an older child with FXS in the family, babies are screened for FXS during fetal or early postnatal life even in the absence of overt physical signs.

In terms of cellular modifications, FXS results in numerous anatomical and functional changes at the level of synaptic connectivity. Post-mortem studies have identified immature dendritic spines in neurons (Hinton, Brown, Wisniewski, & Rudelli et al., 1991; Rudelli et al., 1985). Interestingly from an evolutionary perspective, the *FMR1* gene has high conservation across species (Verkerk et al., 1991), which has made it possible for animal models to investigate in greater depth the changes that arise from the loss of FMRP. For example, *fmr1* knockout mice develop dense, immature dendritic spines that are very similar to those observed in human patients (Comery et al., 1997; Grossman, Aldridge, Weiler, & Greenough, 2006). Additional murine research has revealed that FMRP binds selectively to mRNA in the postsynaptic spaces of dendritic spines, thereby repressing synaptic translation by stalling ribosomal translocation. In typical development, FMRP de-represses translation in response to synaptic activity, making the synthesis of crucial synaptic plasticity proteins possible. The FXS loss of FMRP thus constrains this response and, because deficits in synaptic plasticity

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correlate with memory and learning problems, it has been argued that such deficits are the main cause of the resulting FXS phenotype. In particular, mGluR dependent long-term depression (LTD), a major form of synaptic plasticity, is thought to constitute the impaired neurological pathway involved in the FXS behavioral symptoms (Bear, Huber, & Warren, 2004). Furthermore, it has been demonstrated that mGluR LTD is indeed altered in *Fmr1* knockout mice (Huber, Gallagher, Warren, & Bear, 2002), and that mGluR antagonists can indeed enhance cognitive and behavioral outcomes (Yan, Rammal, Tranfaglia, & Bauchwitz, 2005), as well as rescuing immature dendritic spine morphology (Michalon et al., 2012; Nakamoto, Nalavadi, Epstein, Narayanan, Bassell, & Warren, 2007). The successes of the murine intervention studies with these antagonists have now resulted in relatively successful clinical trials with human patients using drugs to target the mGluR LTD pathway (Berry-Kravis et al., 2009). However, while atypical synaptic function and anatomy are characteristic of most animal models of FXS, an examination of different studies that have used *Fmr1* knockout mice reveals that these synaptic phenotypes are in fact transient and appear developmentally only within short time windows. This means that their effects are dependent upon the temporal expression of *Fmr1* (Meredith, Dawitz, & Kramvis, 2012), stressing again the importance of a developmental perspective on such questions. In sum, although there is a single and well-understood genetic cause of FXS, there is wide variation in phenotypic outcome in this population. This is likely to be due to a combination of individual temporal expression dynamics together with differing timing of environmental impacts, something to which we will turn our attention in a subsequent section.

BRAIN-BEHAVIOR RELATIONS IN FRAGILE X

The investigation of human patients with FXS at the systems level has yielded interesting links between genes, brain, and behavior. For example, memory impairments, particularly working memory, correlate with FMRP levels in FXS as well as with abnormal brain activation in regions that are critical for memory functions (Menon, Kwon, Eliez, Taylor, & Reiss, 2000). Moreover, during attention and impulse control tasks, FMRP also has been shown to correlate with the atypical recruitment of dorso-striatal networks (Hoefl, Hernandez, Parthasarathy, Watson, Hall, & Reiss, 2007; Menon, Leroux, & White, 2004). These studies tend to lend support to the hypothesis that FMRP is required for the brain to react rapidly in

the service of executive function and working memory tasks (Lightbody & Reiss, 2009). Additionally, evidence is accruing to suggest that reduced FMRP is associated with reduced amygdala volume as well as reduced amygdala activation during emotion processing tasks (Hessl et al., 2011). Furthermore, recent research with mouse models suggests a general neural imbalance between excitation and inhibition across the whole brain in FXS (D'Hulst et al., 2006; Gibson, Bartley, Hays, & Huber, 2008). An exciting area of open research would be to investigate such an imbalance in humans by measuring the levels of excitatory and inhibitory neurochemicals, such as GABA and glutamate, in individuals with FXS using magnetic resonance spectroscopy. These findings point to a serious problem in individuals with FXS, because it is known that the excitatory/inhibitory balance is critical for optimal functioning at the neural level, both in terms of region specificity and across developmental time.

Much of the early research on the FXS brain was done on older children and adults, but recently structural imaging studies have targeted very young children with the syndrome (Haas et al., 2009; Hoefl et al., 2008, 2010, 2011). This should in time make possible the much earlier diagnosis of FXS, identifying in infants precocious neural markers of atypical brain development. For example, in a longitudinal study by Hoefl and collaborators (2010) on 1–3-year-old boys with FXS, gray and white matter volumes were measured over a 2-year period. The researchers identified areas of the brain in which gray matter volumes were either enlarged (caudate, thalamus, and fusiform gyri) or reduced (cerebellar vermis), and this held across both time points, thereby highlighting from a very early point in development quite stable regional effects in the brains of individuals in this population. Interestingly, other brain regions revealed initial gray matter volume that was similar to that of typically developing controls (orbital gyri, basal forebrain, and thalamus), but which subsequently increased in size in FXS, again stressing the need for a developmental perspective when considering the atypical brain (Karmiloff-Smith, 2010). In contrast to gray matter volumes, white matter volumes of fronto-striatal regions were greater in FXS compared with typically developing controls at the first time point, and, in this case, the differences did not remain stable but increased over time. In general, then, these results underscore how structural (and probably functional) abnormalities within different brain regions develop differently over time in FXS, reflecting again time-dependent effects of *FMRI* silencing. Such effects are very similar to those already highlighted in the context of murine models of FXS.

COGNITIVE AND BEHAVIORAL PATTERNS IN FRAGILE X

Individuals with the full FXS mutation present with a very characteristic cognitive and behavioral profile across development, despite the existence of strong individual variation. Males are usually severely impaired intellectually, with an average IQ as low as 41, whereas those males with incomplete *FMRI* inactivation can turn out to be less affected (Merenstein, Sobesky, Taylor, Riddle, Tran, & Hagerman, 1996). Males also have quite severe communication difficulties, including significant language delay coupled with social awkwardness alongside hyperactivity, inattention, impulsivity, and anxiety. By contrast, females—even those with the full mutation—tend to present with less deficits (due to their unaffected second X chromosome), often having only moderate and in some cases no intellectual impairment at all. However, social problems are frequently part of the female FXS phenotype, but unlike the co-occurring symptoms in males with FXS, social impairments in girls and women are more likely to be accompanied by anxiety or depression (Freund, Reiss, & Abrams, 1993).

Noteworthy is the fact that subtle behavioral and cognitive delays and deficits are evident in infancy, with parents becoming concerned about their children's symptoms on average as early as 9–13 months of age. However, clinical confirmation of the atypical developmental pathways often has to wait until the child is considerably older, that is, on average around 21–24 months of age, with in many cases a full diagnosis of FXS not happening until as late as 32–35 months of age (Bailey, Skinner, Hatton, & Roberts, 2000; Bailey, Skinner, & Sparkman, 2003). The early signs at around 9–12 months of age include decreased object play, increased leg stereotypies, and atypical postures. In fact, these quite subtle symptoms have been shown actually to be able to yield a FXS diagnosis in infancy with some 73% accuracy (Baranek et al., 2005). Furthermore, scientific research has revealed that already in infancy, those with FXS demonstrate poor response inhibition (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004, 2007), poor saccadic eye-movement control (Scerif, Karmiloff-Smith, Campos, Elsabbagh, Driver, & Cornish, 2005), and prolonged visual attention to objects or what is known as sticky fixation (Roberts, Hatton, Long, Anello, & Colombo, 2012). In subsequent FXS development, school children and adolescents also display poor response inhibition (Sullivan, Hatton, & Hammer, 2007) and atypical patterns of visual attention (Hooper, Hatton, & Baranek, 2000; Munir, Cornish, & Wilding, 2000a, 2000b). Finally,

executive function is clearly deficient in FXS in childhood, with concomitant memory impairments (Lanfranchi, Cornoldi, & Drigo, 2009). All of these characteristic problems continue into adulthood; nonetheless, the most serious cognitive impairments have been shown to reside in executive function and visual-spatial attention in this syndrome (Cornish, Munir, & Cross, 2001).

INSIGHTS FROM LONGITUDINAL STUDIES OF FRAGILE X

Attentional control has been a particular area of FXS research, but hitherto mainly only in cross sectional designs. Here, we provide data from a longitudinal approach that yielded deeper insights into the FXS phenotype. It is indeed longitudinal research that has highlighted two crucial factors affecting the cognitive phenotype of individuals with the full mutation. The first concerns differences in attentional biases that tend to alter cognitive development from the very outset for children with this genetic disorder. One important way of targeting the attentional domain is to compare younger and older individuals with FXS (Cornish et al., 2007; Scerif et al., 2004, 2005, 2007), and especially to do so within a longitudinal design (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012; Cornish et al., 2013; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012). The second resides in the fact that, as we mentioned earlier, even in seemingly simple monogenic disorders like FXS, the resulting phenotype displays significant phenotypic variability across individuals, as for instance demonstrated by studies of individual differences in saccadic eye-movement control in young children with FXS between 12 and 36 months of age (Scerif et al., 2005). Moreover, variability also exists in how abilities actually change longitudinally over developmental time in FXS (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Cornish et al., 2012; Scerif et al., 2012). There is clearly no simple one-to-one mapping between the mutated gene and the resulting phenotype.

Noteworthy is that fact that studies of neurodevelopmental disorders have produced a new emphasis on theory development, highlighting the need to go beyond group comparisons and trace instead domain-specific or even task-specific developmental trajectories, by plotting, say, numerical or linguistic functioning against individuals' verbal or nonverbal ability levels (e.g., Thomas, Annaz, Ansari, Scerif, Jarrold, & Karmiloff-Smith, 2009). Basically, this involves a new focus on within-syndrome individual differences. There is indeed a glaring absence

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of studies tracking change over developmental time, that is, longitudinally. For example, even though striking attentional difficulties had already been demonstrated in children with FXS, even when compared with a much younger typically developing group of children matched on overall developmental level (Cornish et al., 2007; Scerif et al., 2004, 2005, 2007), the cross sectional design did not make it possible to ascertain whether the severity of attentional difficulties increased over developmental time or remained stable. This was because the experimental instruments available to measure attention in younger and older individuals were often very different in nature and the outcomes across age were difficult to compare directly. Moreover, although the FXS cognitive phenotype has been extensively examined via cross sectional research, far fewer studies have probed longitudinal changes not only within attention but also in terms of other sensory and cognitive domains (e.g., Baranek et al., 2008; Roberts et al., 2009; Skinner et al., 2005). In other words, studies that simultaneously target the FXS phenotype both longitudinally and in a cross-domain design have been sadly lacking.

However, very recent research using the longitudinal approach has yielded new insights. For example, although we know that significant delays in attentional control are present in boys with FXS, this turns out not to be a case of developmental arrest. Instead, dynamic trajectories of delayed development have now been identified. For example, using a combined cross sectional and prospective longitudinal design, we examined early profiles of attention and working memory impairment in FXS (Cornish et al., 2013). When investigated only in cross sectional designs, significant weaknesses emerged for boys with FXS, with no clear improvement over chronological age. By contrast, when we examined the same issues in a longitudinal design, we were able to reveal that, although clearly impaired, the improvements that occurred over time in boys with FXS paralleled the slope of improvement that we witnessed in typically developing children. In other words, while cross sectional approaches would have called on an interpretation of developmental arrest, the longitudinal studies yielded developmental improvements, albeit delayed compared with TD controls, in both attention and working memory. While confirming previous cross sectional findings of deficits in attentional control and working memory compared with what would be expected given their general level of developmental delay, the Cornish and collaborators' longitudinal study (2013) additionally revealed improvements over developmental time that a simple cross sectional comparison would have masked. The longitudinal study also measured other aspects of the FXS

cognitive profile (i.e., nonverbal intelligence) and revealed unique insights that would again have been missed in cross sectional approaches. For instance, cross sectional studies of nonverbal IQ scores, measured by the Leiter International Performance Scale-R (Roid & Miller, 1997), had tended to point to a potential plateau or even decline with age, whereas our longitudinal trajectories measured with growth scores (an analogue of raw scores that takes into account repeated presentations and item difficulty) highlight instead an albeit small yet significant improvement over developmental time (Cornish et al., 2012).

What about lower level perceptual rather than cognition-level functions? Are these unimpaired in FXS? Studies with adults (Van der Molen et al., 2012) and also with infants with FXS (Farzin, Whitney, Hagerman, & Rivera, 2008) suggest that visuospatial attention impairments may in fact be underpinned by atypical lower level perceptual abilities. Again, longitudinal data are crucial in evaluating whether low-level perceptual processing differences do in fact lead over developmental time to atypical higher level processing. This yet again highlights the need for more longitudinal approaches to understanding the complexities of neurodevelopmental disorders like FXS.

In addition to the aforementioned striking group-level deficits, clinicians working with individuals with FXS tend to identify striking individual differences in attention outcomes, with some individuals much more seriously affected by inattention than others, even when they have equivalent levels of IQ. Again, longitudinal studies following sufficiently large samples could start to dissect the within-syndrome FXS variability, because they enable researchers to go beyond correlational measures, and ask instead how within-syndrome variability predicts subsequent outcomes. This was indeed our approach in the longitudinal study referred to above. We measured visual, auditory, and multimodal attention in young boys with FXS, aged between 4 and 10 years of age at time 1 and again 12 months later at time 2 (Scerif et al., 2012). We also assessed behavior in these boys through standardized teacher questionnaires targeting dimensions that are relevant to symptoms of ADHD (e.g., Conners Teacher Rating Scales; Conners, 1997). The results showed that the children with FXS attended less well than mental-age matched typically developing boys and had greater difficulties with auditory stimuli than with visual ones. In addition, unlike typically developing children, the boys with FXS did not benefit from multimodal information. Importantly from the perspective of individual differences, early visual attention markers in boys with FXS were significant predictors of their later ADHD symptomatology, highlighting the

need to identify the drivers of differing developmental trajectories for individual children within this seemingly homogeneous group if measured cross sectionally. Interestingly, while visual attention was a significant longitudinal predictor of ADHD symptoms in the boys with FXS (Scerif et al., 2012), it was auditory attention that predicted later symptoms related to ASD (Cornish et al., 2012).

THE CHALLENGES OF COMORBIDITY

Individuals with FXS present with a particularly high risk for comorbid symptoms, which are found in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Indeed, some 50–90% of patients with FXS have autistic-like traits such as tactile defensiveness, poor eye contact, hand flapping, hand biting, and speech perseveration (Bailey et al., 1998; Baumgardner, Reiss, Freund, & Abrams, 1995; Kerby & Dawson, 1994). Strikingly, about 25–47% of individuals with FXS actually meet the diagnosis for ASD (Bailey et al., 1998; Demark, Feldman & Holden, 2003; Rogers, Wehner, & Hagerman, 2001). Moreover, FXS has been identified as the most common known genetic cause of ASD, with between 1 and 2% of individuals with ASD having the full FXS mutation (Devlin & Scherer, 2012).

A similar situation obtains for ADHD. Some 74% of individuals with FXS meet the criteria for an ADHD diagnosis (Backes, Genç, Schreck, Doerfler, Lehmkuhl, & von Gontard, 2000), making ADHD the most common comorbid condition diagnosed alongside FXS (Tranfaglia, 2011). Despite these high risk factors for ASD and ADHD, we have consistently noted in earlier sections that behavioral outcomes across individuals with FXS are highly variable, making the investigation of the factors causing individual differences in these symptoms of both theoretical and clinical importance. What factors are involved in the developmental trajectories in many children with FXS to cause them to present with social and cognitive control problems similar to those experienced by children diagnosed with ASD and ADHD, while at the same time there exist other children with FXS who do not display these particular socio-cognitive problems? One research advantage stems from the fact that both FXS and ASD are diagnosed around the same age and substantially earlier than the diagnosis of ADHD (usually only diagnosed in the early school years), making FXS an ideal model for assessing high risk early in development. Indeed, comorbidity in disorders of known genetic origin can serve as models for understanding other disorders that are diagnosed only on

behavioral measures, because the genetic disorders can be diagnosed much earlier in development. This is not unique to FXS, of course. Genetic disorders such as Williams syndrome are also characterized by high risk for ADHD symptoms (Rhodes, Riby, Matthews, & Coghill, 2011) and also receive very early diagnosis, often at or shortly after birth. The same holds for infants with Down syndrome. Given the early, and possibly perinatal diagnoses, neurodevelopmental disorders like FXS, Williams syndrome and Down syndrome can be considered models of high risk for those behaviorally defined disorders. However, given the developmental unfolding and variability of these difficulties within and across syndromes, understanding high risk requires moving away from static snapshots, even of individual differences, to developmental trajectories. Furthermore, systematic longitudinal comparisons across these genetically distinct groups with commonly high risk for those behavioral symptoms could lead us to understand the differing developmental trajectories leading to those symptoms.

Nonetheless, the promise of insights from genetic disorders that, like FXS, are diagnosed early and carry a high risk for ASD or ADHD is not necessarily straightforward.

Comorbidity With ASD

A first set of questions that obviously must be raised are the following: Are the comorbid autistic-like traits in FXS really the same as those existing in individuals with idiopathic ASD? Or do they constitute instead the severe end of a continuum of cognitive impairment and behavioral difficulties present in more affected individuals? Separating these two interpretations is not an easy endeavor yet is clearly critical for the development of behavioral and pharmacological treatments that address the core impairments in ASD, ADHD, and FXS. Several researchers have attempted to address this question using behavioral measures. While some have identified similar profiles of autistic traits in both individuals with FXS and those with idiopathic ASD (Bailey et al., 1998), others argue that behavioral profiles are in fact distinct in the two populations (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; Kaufmann et al., 2004; McDuffie, Thurman, Hagerman, & Abbeduto, 2014). For example, McDuffie and colleagues (2014) designed a study whereby groups of individuals with idiopathic ASD and individuals with FXS were matched on three different criteria: (1) on chronological age regardless of comorbidity (i.e., some members of the FXS group met and others did not meet the ASD diagnostic criteria); (2) on diagnosis (chronological age matches, taking all

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the participants with FXS who had received a comorbid ASD diagnosis); and (3) on severity (chronological age together with severity levels of the ASD diagnosis). The three groups were then compared on the basis of their scores on the ADI-R, a tool commonly used in the diagnosis of ASD, which yields a variety of scores within three categories: reciprocal social interaction, communication, and restricted interests/stereotypical behaviors. Comparing idiopathic ASD and comorbid FXS/ASD, the study identified a number of significant differences in scores, for instance, for social smiling and complex behaviors. However, studies based solely on behavior can be problematic, because they tend to match individuals according to ASD severity, or ASD diagnostic criteria, which themselves are behaviorally defined, and then compare groups based on behaviorally defined ASD symptomatology and measures of adaptive behaviors. The risk of circularity is obvious.

Circularity can be surmounted by opting for a different level of analysis, i.e., neurobiological and molecular variation between FXS and ASD or ADHD, using both human and animal models. Taking again the example of ASD, researchers need to raise the very question of why genetically defined FXS would lead to ASD-like symptoms. Here, the major response stems from research that has found that many of the targets of FMRP are indeed the products of genes that have also been implicated in ASD (Darnell et al., 2011). This has caused scientists to argue that FXS leads to ASD or autistic-like symptoms via downstream mechanisms of FMRP. Recent modeling studies have lent support to this claim by modeling how FMRP targets not only contribute to an ASD outcome, but they do so via a number of distinct etiologies. These include single, rare, highly penetrant disruptions in a subgroup of embryonically expressed FMRP targets, as well as multiple less penetrant disruptions with cumulative effects in a subgroup of FMRP targets up-regulated in adolescence and adulthood (Steinberg & Webber, 2013). Such an explanatory framework suggests that *FMR1* silencing would put individuals with FXS at higher risk for comorbid ASD if accompanied by other downstream hits that are also involved in ASD risk factors. This gives rise to a further question: why does non-idiopathic ASD, which may or may not result from genetic disruption downstream of FMRP, share symptoms with genetically defined FXS? This is where animal models become critical. Indeed, molecular work on mice is beginning to shed light on this issue. Research using a common ASD mouse model, the NLGN3 KO mouse, has succeeded in creating the same synaptic phenotype as in FXS (Baudouin et al., 2012). Thus, despite distinct etiologies, FXS and at least

one example of nonsyndromic ASD share a core neurobiological phenotype, opening the doors to explore shared therapeutic intervention studies. Moreover, scientists have argued that the notion of shared genetic and neural mechanisms is actually supported also by behavioral findings. For example, Rogers and collaborators (2001) studied two subgroups of young children with FXS between the ages of 21 and 48 months, one of which performed similarly to children with developmental delay but not ASD, and the other whose performance was similar to a group with idiopathic ASD. To explain the subgroup findings, the authors argue that these differences occur because the FXS mutation represents high risk for all individuals, but it is not deterministic; additional mutations are likely to work synergistically with the FXS mutation to result in comorbid ASD. In spite of the demonstration of shared genetic and neural mechanisms, there are numerous other functional and anatomical differences between individuals with FXS and those with idiopathic ASD, which supports a contrasting view, that is, that comorbid ASD in FXS may be distinct from those in nonsyndromic, idiopathic ASD (Hazlett et al., 2009). Further in-depth research is clearly necessary to decide between these competing theories. Although variation in the behavioral profiles of individuals with FXS alone, FXS together with comorbid ASD, and idiopathic ASD obviously complicates the picture, the investigation of the genetic and cellular mechanisms of ASD risk in FXS may yield a better understanding of comorbidity in general as well as of the heterogeneous presentation of symptoms across individuals, ultimately resulting in targeted therapeutic interventions based on biological differences.

Comorbidity With ADHD

Very similar approaches need to be taken to understand the mechanisms responsible for the presence of hyperactivity and inattention mechanisms in ADHD and comorbid FXS/ADHD (Scerif & Baker, in press). Idiopathic ADHD is associated with both functional and structural abnormalities of a distributed right lateralized corticostriatal network implicated in inhibitory control. Interestingly, these atypicalities overlap significantly with those implicated by functional imaging studies of inhibitory control problems in FXS (e.g., Hoesft et al., 2007). Early reports of localized structural abnormalities have since been complemented by large-scale studies of cortical development over time (Shaw et al., 2007). Such longitudinal studies have also pinpointed the differences in prefrontal cortical thickness across patients with ADHD that tend to predict

later clinical outcome (Shaw et al., 2006). Functional abnormalities of these circuits in ADHD have also been clearly established: fMRI studies using classical inhibitory control tasks (e.g., go/no-go task, stop-signal reaction time) yield reduced activation of inferior prefrontal cortex and caudate nucleus compared with healthy age-matched controls (Durstun et al., 2003), a finding that mirrors the abnormalities found in FXS (Hoeft et al., 2007). Electrophysiological studies also indicate that children with ADHD differ from controls at multiple time points in the information processing cascade leading to the inhibition of a response or when resolving conflict (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). Again, very similar findings have emerged from electrophysiological studies of adolescents and adults with FXS (van der Molen et al., 2012).

At the level of neurotransmission, the involvement of striatal circuits in ADHD is strongly supported by the fact that methylphenidate (MPH), a dopamine reuptake inhibitor, alleviates symptoms in the majority of affected cases (Volkow, Wang, Fowler, & Ding, 2005). Interestingly, MPH has been shown also to be the most effective pharmacological intervention for treating ADHD-like symptoms in individuals with FXS (Roberts et al., 2011). Intriguingly, recent findings from genome-wide association studies have considerably changed prevailing views on which key genes might be associated with risk for ADHD (Franke, Neale, & Faraone, 2009). Rather than the expected dopaminergic candidates, it is genes involved in neurodevelopmental networks for neurite outgrowth that seem to be more heavily implicated (Poelmans, Pauls, Buitelaar, & Franke, 2011). This turns out to be consistent with recent evidence from the study of rare copy-number variants in ADHD, suggesting that intrinsic neurotransmitter systems, and more specifically metabotropic glutamatergic pathways, are likely to be involved in ADHD risk (Elia et al., 2012). Importantly, these very pathways overlap with those compromised in FXS, suggesting at least one neural pathway of risk for hyperactivity/inattention that is shared between idiopathic ADHD and FXS.

In summary, the high risk for ADHD- and ASD-like symptoms in FXS has attracted the attention of scientists studying those behaviorally defined neurodevelopmental disorders, because multilevel studies of FXS could contribute to a much earlier understanding of the developmental trajectories in the normal population that lead to compromised outcomes in confirmed diagnoses of ADHD or ASD. The longitudinal assessment of very young children with FXS, before their behavioral problems become consolidated, would be especially helpful in this respect, in

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that it could lead to the identification of potential modifiable protective factors (e.g., environmental inputs such as parent-child interaction and teaching practices). However, this again puts us squarely in the important debate as to whether ADHD and ASD symptoms in FXS are similar to or different from those in idiopathic cases of ADHD and ASD. We argue that a focus on both overlapping and distinct neural mechanisms may advance this debate, especially if it also takes into account potential differences in developmental timing.

RELATIONSHIPS TO THE PRINCIPLES OF DEVELOPMENTAL PSYCHOPATHOLOGY

Throughout this chapter, we have focused in particular on a specific neurodevelopmental disorder and its comparison with other genetic disorders. However, because of their identified etiology, disorders like FXS, WS and DS offer inroads into the broader and more general principles of developmental psychopathology as a whole (Cicchetti & Toth, 2009). First, their study is increasingly interdisciplinary, bridging scientists who work at complementary levels of enquiry: from cellular neuroscience to systems neuroscience, developmental and cognitive psychology, as well as clinical implementation (e.g., see Fung, Quintin, Haas, & Reiss, 2012, for a review of mechanistic comparisons between FXS and WS). Second, work on specific genetic disorders and their comparison identifies new challenges for developmental cognitive neuroscientists working with neurotypical individuals: if they play such an important role in shaping atypical development (e.g., Karmiloff-Smith et al., 2012), how do typical low-level mechanisms such as attentional biases impact memory and learning trajectories over developmental time (see Scerif & Wu, 2014, for emerging implications in the field of typical attention research)? Third, because the early genetic diagnosis increasingly precedes the emergence of childhood difficulties and it is clear that not all children with disorders like FXS, WS and DS develop full-blown ADHD or ASD, may offer insights into pathways to protection and resilience. Fourth, in addition to discovering multilevel processes leading to maladaptive and adaptive life span outcomes, researchers in this area now have a range of interdisciplinary tools to ameliorate poor outcomes. Although recent efforts have focused on pharmacogenetics (e.g., Jacquemont et al., 2014), there is also growing interest in complementary effective and syndrome-specific psychosocial therapies (Turk, 2011). We turn to these translational implications in a later section.



FUTURE DIRECTIONS: THE IMPORTANCE OF LONGITUDINAL COMPARISONS ACROSS SYNDROMES OF KNOWN GENETIC ORIGIN

Throughout this chapter, we have argued for the importance of taking a syndrome of known genetic origin to gain a deeper understanding of those neurodevelopmental disorders which are currently only defined in terms of patterns of behavioral deficits. Yet, cross-syndrome comparisons amongst genetic syndromes themselves also turn out to be particularly useful. For example, it is frequently the case that individuals with different genetic syndromes end up with the same behavioral scores on a task. Can we take it that the underlying cognitive and/or neural processes are the same? Not necessarily. Indeed, in a series of cross-syndrome comparisons of genetic syndromes including FXS, Down syndrome (DS) and Williams syndrome (WS), we have revealed different cognitive and neural processes even when scores fall within the normal range on standardized tasks such as the Benton or Rivermead face processing tasks (Karmiloff-Smith et al., 2004). Other studies, e.g., examining sensitivity to numerical displays in infants with genetic syndromes such as DS and WS, revealed different trajectories of saccadic eye movements even though total looking time scores were equivalent across the two syndromes (Karmiloff-Smith, 2012). In comparisons of FXS and WS (e.g., Scerif et al., 2004), we demonstrated the existence of different patterns underlying equivalent behavioral scores. Such subtle differences are crucial to inform both theory and intervention, and underline the importance of syndrome-specific treatment schedules. In general, comparisons across syndromes yield subtle impairments that a focus on a single syndrome would not necessarily reveal. Ultimately, future research in developmental psychopathology should target prospective longitudinal designs that directly compare dynamically changing profiles and trajectories across disorders of identified genetic etiology, at all their interacting levels. Detailed prospective work on developmental dynamics at each level will need to be increasingly complemented by interdisciplinary collaborations bringing together clinicians and researchers working on animal models, systems neuroscience, and developmental psychology.

TRANSLATIONAL IMPLICATIONS

Translational research has been defined as “research designed to address how basic behavioral processes inform the diagnosis, prevention, treatment and delivery of

services for mental illness and, conversely, how knowledge of mental illness increases our understanding of basic behavioral processes” (National Advisory Mental Health Council, 2000, p. iii). The convergence between basic scientists and clinicians in the area of genetic disorders is still in its infancy. However, we believe that a cross-syndrome developmental cognitive neuroscience approach will be pivotal in devising intervention attempts that are truly syndrome-specific, rather than focused on a collection of individual behavioral symptoms. To take hyperactivity and inattention, until now the most commonly used approach to treat them in the context of FXS has been stimulant-based treatment (Roberts, Miranda, et al., 2011). A similar approach has characterized the treatment of hyperactivity in WS (Rhodes et al., 2011). In contrast, researchers and clinicians alike have been calling for a mechanism- and syndrome-specific approach to treatment, and one that is sensitive to individual and developmental differences within the spectrum of individuals with FXS (Jacquemont et al., 2014; Turk, 2011). We believe that similar translational implications apply to other neurodevelopmental disorders of identified genetic etiology and high risk of behavioral difficulties. If these difficulties continue to be treated as disparate symptoms, rather than the complex outcomes of multilevel developmental dynamics, treatment approaches will not be optimized to the specific needs of individuals with genetic disorders.

CONCLUDING THOUGHTS

In this chapter we have highlighted the importance of both cross-syndrome comparisons and within-syndrome variability. Indeed, despite very high risk, FXS is not of necessity associated with impairment. In fact, some children with the full FXS mutation function quite well. This is true in the case not only of females, who have the additional unaffected X that may act as a protective factor, but also of some males. So, something protects a limited number of boys from risk, which is why we believe that the case of young children with a diagnosis of FXS constitutes an interesting more general model in which to assess early predictors of risk and resilience, as well as early predictors of declining or improving neurocognitive trajectories (Hernandez et al., 2009; Rogers, Wehner, & Hagerman, 2001). This is particularly true of comorbidity with ASD- and ADHD-like symptomatology. Other syndromes of known genetic origin (e.g., Williams syndrome) have also been used as models for a more general consideration of neurocognitive disorders (D’Souza et al.,

2014; Farran & Karmiloff-Smith, 2012; see also Scerif & Wu, 2014). Cross-syndrome comparisons can also be rich sources of information at multiple levels of description (Karmiloff-Smith et al., 2012).

Here, we used the example of fragile X syndrome to illustrate a number of broad points that emerge from the study of genetic syndromes. We overviewed what is known about the FXS genotype and phenotype in terms of cellular, neural, cognitive, and behavioral aspects of the syndrome, in particular emphasizing its developmental nature. Critically, we discussed how recent longitudinal data emphasize the need to focus on variability in outcomes for affected individuals, even in the face of a monogenic disorder. As mentioned above, there is indeed no one-to-one mapping between genetic mutation and phenotypic outcome, but rather a complex, time-dependent pathway across developmental time. The findings on FXS highlight the need to understand diverging developmental trajectories, predictors of greater risk, mechanisms of resilience and environmental protective influences. In summary, we argue that, because they present biologically well-dissected information about genetic origin, syndromes like FXS lend themselves particularly well to study of the high risk of impairment for common behaviorally defined disorders, like ADHD and ASD (see Scerif & Baker, in press, for a review of how this approach might inform an understanding of ADHD risk). However, to understand trajectories leading to good or poor outcomes, as well as their overlap or differences across disorders, a developmentally inspired approach is critical and needs to go beyond behavioral outcomes and be underpinned by knowledge of the developmental cognitive neuroscience of each disorder.

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