FRAGILE X SYNDROME AND ASSOCIATED DISORDERS

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I. Introduction

The past decades have witnessed staggering advances in the fields of molecular genetics, cognitive neuroscience, neuropsychiatry, and brain imaging. Collectively, these findings have pushed forward a new generation of research aimed at exploring the dynamic interplay between gene expression, developmental brain pathways, and neurocognitive profiles beginning in infancy and moving across the lifespan. These new discoveries have been facilitated by advances on several fronts. New methods are now available for viewing brain activity in real time, there is
expanding information on the complexities of individual genes and gene-environment interactions, analysis of the domain processes included under the broad umbrella of “cognition” has become more finetuned, and ingenious methods have been advanced for measuring typical and atypical development of these processes. In essence, this research provides a platform to elucidate the complex journey from cell to systems thus allowing a more precise clinical diagnosis alongside a much clearer understanding of the behavioral phenotype as it develops across childhood and into adulthood. Most important, these new findings push forward targeted clinical and educational interventions that recognize disorder-specific strengths and challenges at major stages of developmental transitions, for example, from preschool to primary school and from primary school to high school and then into the workplace.

Fragile X syndrome (FXS) is a well documented neurodevelopmental disorder but it is rarely defined by its clinical features alone. Although still lacking consensus, recent estimates indicate a frequency of approximately 1 per 2500 children world-wide will be affected by FXS (Hagerman, 2008). In some (but certainly not all) children, there is a characteristic constellation of physical features that include an elongated face, large prominent ears, and forehead, and in males, postpubertal macroorchidism (Cornish, Levitas, & Sudhalter, 2007; Lachiewicz, Dawson, & Spiridigliozzi, 2000). More subtle features can include narrow intereye distance, a highly arched palate of the mouth, and hyperextensible joints. However, the wide variability in manifestation in both boys and girls makes a diagnosis based on physical features alone almost impossible. It is precisely because of their relatively “normal” appearance that many affected children are not diagnosed with FXS until relatively late in their development. Undoubtedly, the most defining feature, especially in boys, is developmental delay and the resulting cognitive–behavioral phenotype, most notably the attentional control difficulties, language impairments, and autistic-like features that can accompany the syndrome from very early in development (Cornish, Scerif, & Karmiloff-Smith, 2007; Cornish, Turk, & Hagerman, 2008).

Of significant interest is that it is caused by a single gene being switched off on the X chromosome resulting in a characteristic profile that includes developmental delay alongside chronic and pervasive attention and executive function difficulties. Furthermore, this same gene is one of the few known genetic causes of autism, one of the most prevalent and debilitating of childhood psychiatric disorders.
II. Genetic Profile

An emerging family of DNA mutations known as trinucleotide repeat expansions is responsible for causing a range of cognitive and clinical consequences such as Huntington disease, Friedreich’s ataxia, and FXS. The fragile X mental retardation 1 (FMR1) gene is a fascinating gene located at the long arm of the X chromosome. This gene contains a cytosine, guanine, guanine (CGG) triplet repeat region that when expanded can result in a continuum of fragile X disorders. Normal CGG repeat sizes correspond to between 7 and 55 repeats, with 30 repeats being the most common. When expanded to >200 repeats (large expansion) the FMR1 gene is turned off leading to the lack of the fragile X mental retardation protein (FMRP), and results in the neurodevelopmental disorder known as FXS. Because FMRP is involved in normal brain development, through its impact on synaptic formation and function, the absence of FMRP results in the characteristic intellectual impairment and cognitive profile associated with this disorder and represents one of the few known single gene causes of autism.

Due to genetic variation in the form of X-inactivation (when one of the two X chromosomes remains inactive and the other active) girls with FXS, compared to boys, produce a broader range of cognitive abilities and have IQ’s ranging from moderate to the normal range. In contrast, this is not an issue of concern in FXS males whose impairment, without the protection of X-inactivation, shows greater severity. For this reason, we will focus on boys and girls separately.

Most recently, interest has focused on more common, medium size expansions between 55 and 200 CGG repeats (referred to “carrier status”). This research is especially important given the relative frequency of these expansions in the general population calculated as 1 in 130 to 250 females and 1 in 260 to 800 males (Song, Lee, Li, Koo, & Jung, 2003). Until recently carriers were believed to be “phenotypic free”, that is without any known cognitive deficits. However, there is a now well documented subtle profile of cognitive strengths and weaknesses, notably in males, that can mirror those found in those individuals with the large CGG expansion (FXS). See Cornish, Turk, et al. (2008) for a review of these findings.

III. Neural Profile

Alongside a greater understanding of the genetic underpinnings of FXS, an increasing number of studies have begun to explore how the absence of FMRP impacts on early brain development. This research has been
facilitated by a variety of new methods that have increasingly allowed neuroscientists to obtain high-resolution images of the structure and activity of the brain. These brain images can capture “snapshots” of brain activity in order to determine which areas are active during task performance. These innovative findings that have begun to enhance our understanding of the typical and atypical developing brain and the complex networks that drive brain maturation across the lifespan.

In typically developing children, the findings from a wealth of new data, made possible by newer imaging technologies, demonstrate the feasibility of imaging the typical brain. The work of Casey and colleagues is testament to the high caliber of research currently being undertaken in this field and the possibilities of this research to push forward our understanding the role of genes on brain development (e.g., Casey, Soliman, Bath, & Glatt, 2010). However, there is still some way to go in providing comparable data of atypical brain development in children with significant cognitive impairment. The most successful studies have tended to use participants with relative higher IQs within the borderline to normal range (therefore skewing the population sample) and there is also a tendency for studies to incorporate older childhood and adolescent samples rather than younger age groups. There are obvious reasons for this but by focusing solely on later outcomes we may be tapping only the end-state rather than exploring age changes in brain maturation over the course of development. In FXS, structural and functional neuroimaging studies highlight a vulnerability of specific brain regions in males and females. For example, there is a decreased size of the posterior vermis of the cerebellum (Mostofsky et al., 1998; Reiss, Aylward, Freund, Joshi, & Bryan, 1991). Other brain areas whose function is affected by FMR1 status include the caudate nucleus (Eliez, Blasey, Freund, Hastie, & Reiss, 2001) and the hippocampus (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997; Reiss, Lee, & Freund, 1994). Findings of several studies established a correlation between identified structural abnormalities and the degree of cognitive impairment. For example, posterior vermis volumes were found to be positively correlated with performance on specific measures of intelligence, visual–spatial ability, and executive function suggesting a role of this structure in determining performance on these tasks (Mostofsky et al., 1998).

Alongside structural imaging studies, functional magnetic resonance imaging (fMRI) has been the neuroimaging technique of choice for investigating brain structure/function associations in both typically and atypical development. However, studies employing fMRI to investigate FXS are to date limited to female participants (e.g., Kwon et al., 2001). Nevertheless, findings have already demonstrated potential in defining
the underlying neural etiology of atypical cognitive functioning associated with the disorder, and in some instances as a function of FMRP expression. For example, both Rivera, Menon, White, Glaser and Reiss (2002) and Kwon et al. (2001) demonstrated that reduced parietal activation recorded in adults with FXS was related to \textit{FMRI} protein expression, with possible implications for the visual–spatial and attentional control difficulties reported at the cognitive level. In addition, Tamm, Menon, Johnston, Hessl and Reiss (2002) used fMRI to demonstrate that deficits in cognitive interference during a counting Stroop task may be the result of atypical recruitment of fronto-parietal brain regions. However, the majority of published research has tended to focus on females with a skew toward later adolescence/early adulthood. The reason for this is that FXS females are much less intellectually impaired than their male counterparts and are therefore more able to perform a broader range of cognitive tasks using this technique.

To date, Reiss and colleagues provide the only examples of fMRI studies conducted in both young males and females with FXS with a specific focus on attention control. Using a traditional Go–No Go paradigm, requiring participants to view a series of letters and respond with a key press to every letter except the letter X for which they had to withhold a response, findings indicate that fronto-striatal regions, known to be involved in response inhibition, are especially affected in FXS irrespective of gender. For example, Hoeft \textit{et al.} (2007) compared performance in FXS male adolescents (mean age 15.4 years) and two control groups, an IQ matched developmental delayed group and a typically developing group matched on chronological age. Their findings are noteworthy in two respects: first, Go–No Go performance by FXS males, unlike that of controls males, was not associated with increased activation in the right fronto-striatal regions. Second, successful performance was instead associated with increased activation levels in the left fronto-striatal network. The pattern of these findings led the authors to make the tantalizing conclusion that response inhibition in FXS may be guided by compensatory processes brought about by a complex interaction between the effects of the \textit{FMRI} gene on early brain maturation, with particular vulnerability in the fronto-striatal network. A similar prefrontal dysfunction has also observed in a study of females with FXS (mean age 15.9 years) using the same Go–No Go paradigm (Menon, Leroux, White, & Reiss, 2004). Undoubtedly, these intriguing findings await further exploration but they clearly demonstrate that at least by adolescence, FXS is associated with anomalous brain development in regions that involve core attention components, in this case attentional control. Future studies will undoubtedly explore brain regions in other cognitive domains.
IV. Cognitive Profile

A. ISSUES OF COMPLEXITY

A core issue of complexity in research that includes defining disorder-specific profiles in children with intellectual impairment is to what extent are (a) behaviors more dependent on the overall degree of impairment, that is, disorder-general deficits no matter what the specific cause (e.g., processing speed differences or low IQ) and (b) which behaviors reflect impairment unique to a particular disorder (syndrome-specific) and/or cognitive domain, that is, domain-specific deficits (such as inhibitory control difficulties or difficulties in face processing) (see Cornish, Bertone, Kogan, Scerif, & Chaudhuri, 2010 for a more detailed discussion). Cornish in a 10-year collaboration with Wilding, Scerif, and Karmiloff-Smith, have exquisitely teased apart the cognitive phenotypes across three genetic disorders of mental retardation: FXS, Williams syndrome (a disorder that results from a micro-deletion on one copy of chromosome 7 involving between 25 and 30 genes), and Down syndrome (DS) (a disorder that results from a trisomy of chromosome 21). Together this research has been able to further clarify which behaviors across multiple disorders are more dependent on the overall degree of intellectual impairment, no matter what the specific cause, and which reflect impairment unique to a particular genetic disorder. It is therefore critical that research incorporates cross-syndrome perspectives to allow a more finer-tuned disorder-specific profile to emerge. In the section below, we will demonstrate how illuminating this approach has been in elucidating the unique nature of cognitive deficits in FXS.

A second issue of complexity relates to the use of standardized versus experimentally driven paradigms to tap cognitive functioning in atypical populations. All too frequently researchers in this field rely on measures that assess global cognitive functions usually through IQ batteries initially developed for determining the range of functioning in the normal population. As a result, they can mask important yet subtle profiles. For example, standardized tasks are specifically designed to be appropriate in their demands and level of difficulty for a typically developing population. Participants are assumed to be able to understand the instructions, to be motivated to carry out the tasks, to focus for the full duration of the task, and to match various other assumptions. There is no certainty that such assumptions hold when the task is given to participants with a neurodevelopmental disorder; poor performance can occur for a variety of reasons in such cases, not only the inadequacy of the component process or processes that are engaged by the task, and the task may simply be too difficult for the target population. Conversely,
a task that is appropriate for a group with cognitive delay may be too easy for a typically developing group. In contrast, experimental measures are developed to be appropriate for developmentally disordered groups such that floor effects can be avoided in those with cognitive delay and also sufficiently sensitive to avoid ceiling effects in the typically developing control groups. There is an emerging literature providing excellent published examples of different types of novel experimental paradigms that include number (Ansari, Donlan, & Karmiloff-Smith, 2007), attention (e.g., Cornish, Munir, & Wilding, 2001a; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004), working memory (e.g., Purser & Jarrold, 2005), and face processing (e.g., Karmiloff-Smith et al., 2004). We argue that the development of novel experimental paradigms that can tease apart subtle features of performance within and between cognitive domains will facilitate a greater understanding of disorder-specific strengths and difficulties that more generalized measure of cognitive function struggle to isolate.

A third issue is the critical role of development itself in producing phenotypic profiles. The pioneering work of Karmiloff-Smith (e.g., Karmiloff-Smith, 2009; Karmiloff-Smith et al., 1998) set the stage for a new generation of research that has focused on charting the developmental trajectories across different neurodevelopment disorders beginning in late infancy and moving across childhood into early adulthood. One of the most prevailing assumptions is that cognitive development in atypical populations represents a static, somewhat “frozen” trajectory of proficiencies and deficiencies that rarely change with increasing age. Thus, one would expect to observe no or minimal age changes in performance across development. However, this assumption has been challenged by recent findings from a number of developmental studies that have shed further light on the possible dynamic role of development in shaping disorder-specific profiles from childhood all the way through to adulthood (see Karmiloff-Smith, 2009, for theoretical perspectives; Thomas et al., 2009). In the section below, we highlight some exciting studies that have incorporated a cross-syndrome perspective in order to identify disorder-specific profiles alongside some emerging findings that have used a developmental approach to address the question of whether cognitive performance in FXS is associated with developmental freeze or developmental change.

B. PROFILE

In FXS, X-linkage means that males are especially vulnerable to the full effects of the condition at the brain and cognitive levels. In boys, almost all present with IQ’s within the mild–severe range of impairment with
profiles emerging as young as 3 years of age (Skinner et al., 2005). In girls, there is a much broader profile with some girls showing only subclinical learning disabilities (Bennetto & Pennington, 2002) whilst approximately 25% display more significant cognitive impairment (most with mild intellectual disability and rare individuals with moderate intellectual disability) similar in profile to boys with FXS. The X-inactivation status of the FXS female is seen as the major contributor to the heterogeneity of intellectual disability and the broad range of cognitive deficits. However, a decade of research has confirmed that FXS is not defined by the degree of intellectual impairment but rather by a unique “profile” of cognitive strengths and difficulties that differentiate FXS from other neurodevelopmental disorders (e.g., autism, DS, Williams syndrome). A key discovery has been to demonstrate the importance of looking beyond the general effects of developmental delay on intellectual functioning in order to identify the distinct pathways and processes that represent the FXS cognitive profile.

Early studies in the 1980s reported findings that began to explore cognitive functioning using traditional IQ tests to examine potential discrepancies between verbal and nonverbal performance in FXS. These early findings set the scene for research programs beginning in the 1990s and continuing to the present day, with which researchers began to unravel more finely-tuned profiles of cognitive dysfunction—more “skill-specific” rather than “global” in nature (see Cornish, Sudhalter, & Turk, 2004 for a review of these changes in perspectives.) More specifically, by using novel experimental measures that are designed for children with differing levels of intellectual ability and with a focus on delineating performance across a single cognitive domain, such as visuo-spatial or attention, findings revealed unique profiles that differentiate neurodevelopmental disorders from each other and from typically developing children.

In the working memory domain, boys with FXS have a relative strength in verbal memory especially for recalling meaningful information with long or short delays compared to much weaker visual–spatial working memory (Munir, Cornish, & Wilding, 2000). This profile differs to that of other disorders of known genetic origin (e.g., DS and Williams syndrome) (Cornish, Wilding, & Grant, 2006; Wilding & Cornish, 2004). In the visuo-spatial domain, boys and girls with FXS have core deficits in their ability to navigate their environment but are proficient in their ability to process local information; a profile that differs from that of children with DS (Cornish, Munir, & Cross, 1998; Cornish, Munir, & Cross, 1999). In the language domain, weaknesses in speech fluency characterized by repetitive and impulsive speech (Belser & Sudhalter, 2001; Cornish et al., 2004), are often accompanied by difficulties with grammar and pragmatics (e.g., Abbeduto et al., 2004), a profile that contrasts with the language profile of Williams syndrome which is
characterized by a relative proficiency in language overall, but with subtle impairments across all language subdomains (Grant, Valian, & Karmiloff-Smith, 2002; for reviews see Karmiloff-Smith & Thomas, 2003; Laing et al., 2002; Thomas & Guskin, 2001).

Finally, in the attention domain research has produced some striking findings. Notably, the degree of inhibitory impairment displayed in FXS appears to be significantly different from that shown in children with DS, children with Williams syndrome, and typically developing comparison children (e.g., Munir et al., 2000; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2007; Scerif et al., 2004). Using a novel computerized paradigm developed by Wilding (e.g., Wilding, Munir, & Cornish, 2001), and modified by Scerif et al. (2004), in which a child has to locate individual “monsters” amongst specific hidden targets (known as visual search), toddlers, and children with FXS show a pervasive inability to switch attention set, from a previously reinforced stimulus pattern to a new one. The degree of perseverative impairment is a hallmark feature of FXS and persists across the lifespan (Cornish, Scerif, et al., 2007). Thus, the apparently simple operation of inhibiting the response just made in order to proceed to the next one is crucial in any chain of behavior and is disastrously impaired in FXS.

Loesch et al. (2003) have also reported a specific deficit in attentional control in adult FXS males; and the findings from recent studies of individuals who are carriers of FXS strongly indicate inhibitory control difficulties that cannot be accounted for by general developmental delay, because these males display IQ’s within the normal range of ability (e.g., Cornish, Li, et al., 2008; Grigsby et al., 2008).

From a developmental perspective, few studies have sought to examine age trajectories in cognitive performance across different time points in the same cohort of FXS children. To date, the majority of published studies have tended to incorporate a cross-sectional design to explore age trajectories. Although such data provide important clues to possible changes in performance between cohorts of different ages, it can only ever provide a snapshot of performance in time, but, however traced, cannot provide information on developmental change. Using a longitudinal methodology, performance can be explored within a live and dynamic context that can address, for the first time, whether cognitive profiles in FXS change over time or whether profiles remain “frozen” after reaching a developmental plateau. Focusing on the attention and working memory domains, preliminary data from Scerif and colleagues suggests that performance although delayed with respect to chronological age and developmental level is nonetheless dynamic, not static, showing improvements over a 12-month period in the same pattern as observed in typically developing children. This profile is suggestive of developmental change not developmental freeze (e.g., Cornish, Cole, Karmiloff-Smith, & Scerif, submitted).
V. Social and Behavioral Profiles

The social and behavioral profiles of children with FXS include core difficulties in anxiety and hyperarousal and many features also overlap considerably with Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) and so will be discussed alongside these two other disorders.

A. SOCIAL ANXIETY AND HYPERAROUSAL

Hypersensitivity, social anxiety, and hyperarousal are recognized as early prominent behavioral features of children with FXS and are present in both boys and girls. Even though there is a desire for social contact (Simon & Finucane, 1996; Turk & Cornish, 1998), children with FXS show social anxiety, with delay in initiating interaction, gaze avoidance, and failure to understand gaze direction (e.g., Garrett, Menon, MacKenzie, & Reiss, 2004). However, the majority of children with FXS, although tending to avoid social interactions, will offer what is now classically termed the “FXS handshake,” whereby an initial wish to communicate socially, with a “handshake,” a socially acceptable remark or even brief initial eye contact, is coupled with active and even persistent gaze avoidance. In a recent physiological study by Hall, Maynes and Reiss (2009) that involved 50 boys and girls with FXS participating in an intense “social interaction” session, the authors observed significant gaze avoidance at session onset which slightly decreased over the course of the session itself. Furthermore, eye avoidance was not associated with atypical cardiovascular activity suggesting a window of opportunity for social skill interventions. The constellation of behavioral symptoms clearly suggests that children with FXS may be overwhelmed by the demands created by social involvement, novel or unexpected situations and changes, even by the common transitions of daily life. It is not surprising therefore that huge interest has focused on the association between FXS and autism.

B. AUTISTIC SPECTRUM DISORDER BEHAVIORS

There are currently very few single-gene disorders for which there is a certainty of the involvement of autism; FXS is one. Identified as one of the most common of childhood psychiatric disorders, recent studies of autism prevalence report rates of 38.9 per 10,000 in a birth cohort
of children (Baird et al., 2006), 18.9 per 10,000 in preschool children (Chakrabarti & Fombonne, 2005), and 20.5 per 10,000 (Gillberg, Cederlund, Lamberg, & Zeijlon, 2006). Defined by a constellation of behaviors encompassing deficits in reciprocal social interaction, communication, and repetitive, stereotyped and restricted patterns of behavior or interests, autism has intrigued researchers and clinicians for decades. Impairments in eye contact, social aloofness, and a difficulty in understanding the intentions and perspective of others can result in difficult social interactions regardless of degree of cognitive impairment.

Although still controversial, a plethora of studies using a variety of standardized measures (e.g., ADOS-G, ADI-R, CARS) indicate a range of 24–33% of FXS children will fulfill a clinical diagnosis of autism and almost all children with FXS will display some features of autism (e.g., Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Bailey, Hatton, Skinner, & Mesibov, 2001; Bailey et al., 1998). However, similarities in behavioral characteristics do not always imply identical cognitive mechanisms and by default identical treatment approaches. Accumulating evidence suggests that although some “core” characteristics appear to unite FXS and autism, these same characteristics also serve very different functions and are suggestive of disparate mechanisms underlying the profiles of these two disorders. For example, poor eye gaze is a key characteristic of both the FXS and autism profiles and yet appears to serve quite different purposes. In autism, abnormal eye gaze is especially evident in social interactions and appears to be motivated both by a lack of understanding of the social situation itself and by the absence of a desire to communicate. In contrast, eye gaze behavior in FXS does not appear to be motivated by a lack of social awareness or a desire to communicate but is more likely due to the hyperarousal caused by social interactions. Thus despite a growing mutual relationship this eye gaze avoidance may persist. As already suggested, research suggests that FXS is associated with a unique pattern of hyperarousal and social anxiety that can cause them to avert their eyes in a social situation (to avoid the sensory stimulation of eye contact) but may still wish to communicate socially (Cornish et al., 2004; Wolff, Gardner, Paccla, & Lappen, 1989).

C. ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attentional problems are the most frequently cited behavioral characteristics in FXS, affecting both boys and girls but to quite different degrees of involvement depending on whether there is an associated
developmental delay. However, for many children the severity of symptoms is such that it often leads to a clinical diagnosis of ADHD. In the largest nation-wide parent survey to date of children with FXS, Bailey and colleagues report findings on 976 boys and 259 girls. Of these, parents identified inattentive behaviors as a significant problem in 84% of boys and 67% of girls (Bailey, Raspa, Olmsted, & Holiday, 2008). However, further analysis revealed that of those girls who were reported as having a developmental delay, 82% had also been diagnosed with attention problems, a figure comparable with the incidence reported in males. This elevated incidence of attention problems associated with FXS is striking and further detailed assessments are needed to establish the range of inattentive behaviors across the lifespan and whether they are gender-specific or even disorder-specific. Currently, elevated rates of attention difficulties have tended only to be reported in FXS boys using both standardized rating scales (e.g., Child Behavior Checklist [CBCL]) (Cornish, Munir, & Wilding, 2001b; Hatton et al., 2002; Sullivan et al., 2006) and clinical interview (e.g., Parental Account of Childhood Symptoms Interview). Although at first blush the pattern of symptoms seems to mirror those of ADHD children without FXS, a classic study by Turk (1998) was the first to suggest different profiles. Turk compared the ADHD profiles of 49 FXS boys (aged 4–16 years) to that of 45 boys with DS (aged 4–16 years), and 42 boys with intellectual disability of an unknown cause (aged 4–16 years). Although both groups of boys showed similar levels of motor activity, the boys with FXS show significantly more inattentiveness, restlessness, fidgetiness, distractibility, and impulsive tendencies suggestive of DSM-IV ADHD predominantly inattentive type. These findings and others that have followed this initial study (e.g., Cornish et al., 2001a) suggest that we need to question the extent to which symptom overlap implies common etiologies, or whether so-called “commonalities” in overt phenotypic behavioral outcomes actually reflect different underlying cognitive and brain processes that diverge from the normal pattern over developmental time and across syndromes. If this is the case, then intervention approaches both clinical and educational, need to be disorder-specific focusing on the biological mechanisms and their multiple manifestations at the behavioral and cognitive levels.

VI. Interventions

Alongside the tremendous growth in our new knowledge on the causes and cognitive outcomes of children with FXS there is a critical need to develop resources packages that can bridge the gap between this
generation of new scientific knowledge and the uptake and utilization of these discoveries by educators, clinicians, and affected families. A possible explanation for this discrepancy may lie in the lack of available resource tools that provide up-to-date and accessible information on the range and specificity of cognitive, behavioral, and social profiles and the interventions that will promote optimal and flexible learning strategies across different environments (the home, school, community, and workplace). Resources need also to target core transition periods and be flexible enough to accommodate developmental changes such that clinicians and teachers do not make the *a priori* assumption that what works effectively in a preschool child with FXS will be equally as effective in a teenager with FXS. It cannot be a “one size fits all” approach to intervention.

A. PSYCHOPHARMACOLOGICAL TREATMENT APPROACHES

There is no single treatment or intervention for FXS, rather treatment approaches focus on specific problems and behaviors. One approach has been to target problem behaviors that also occur in other developmental disorders for which treatment is well established. In children with ADHD, in which core symptoms overlap in FXS, the most intensive research activity has focused on the efficacy of stimulant medication to facilitate symptom reduction. There is good reason for this, notably that stimulant medications do have a markedly beneficial effect on alleviating inattentive and hyperactive behaviors by increasing dopamine levels that are thought to be reduced in ADHD. Findings from animal and human research clearly demonstrate that lower levels of dopamine in the prefrontal cortex can impact on behaviors that include hyperactivity and attentional control (e.g., Biederman & Spencer, 2008; Levy, 2008). The stimulant medication of choice, world-wide, is *methylphenidate* (MPH) which is a catecholaminergic stimulant that increases dopamine levels in the brain by blocking their reuptake. However, as with all stimulant medications there are potential adverse effects although treatment appears to be successful in reducing ADHD symptoms in the short-term (Huss, Poustka, Lehmkuhl, & Lehmkuhl, 2008) with good tolerance for its side effects, especially with careful monitoring of dosage amounts. However, evidence on the long-term effects of MPH treatment in terms of dosage and reduction in behavioral symptoms is still needed.

In FXS, despite advances in our understanding of the behavioral phenotype there is a surprising lack of empirical research on the effectiveness of psychopharmacological treatments. At the core root of these concerns are the issues surrounding safety and tolerability of medication
and, in particular, the noted elevated risk of developing adverse effects to MPH above and beyond that seen in children with ADHD alone (e.g., Research Units on Pediatric Psychopharmacology Autism Network, 2005). There is also a concern that the intellectual impairment coupled with disorder-specific psychiatric or motor anomalies may produce more variable and inefficient responses to MPH than for children with ADHD symptoms in the general school population; hence, studies are relatively scarce (see Cornish & Wilding, 2010 for further exploration of these issues).

Of the few published studies on FXS, stimulant medication has been shown to improve symptoms of ADHD. For example, an early study by Hagerman and her colleagues remains one of the only studies to date to assess the effectiveness of MPH in children with FXS using a placebo, double-blind crossover trial (Hagerman, Murphy, & Wittenberger, 1988). Findings indicated that MPH was tolerated by over two-thirds of participants, with beneficial effects noted on ratings of inattentive behaviors and social skills. However, in younger children stimulants can result in symptoms of irritability and behavior problems (Hagerman et al., 2009). Given this side-effect, alternative pharmacological treatments for reducing ADHD symptoms in FXS have recently been explored. For example, Torrioli et al. (2008) used a double-blind parallel study design to assess the effect of L-acetylcarnitine (LAC; a nonstimulant agent) versus placebo in children with FXS and a dual diagnosis of ADHD aged between 6 and 13 years (mean age 9.18 years). All children were assessed at baseline and after 1, 6, and 12 months of treatment. Preliminary findings demonstrated that LAC did significantly reduce hyperactive behavior and increase attention in boys with FXS across all time points. Clearly, however, there is a critical need for more detailed investigations that assess a broad range of psychopharmacological interventions and their efficacy in treating ADHD symptoms in FXS.

In terms of other aspects the FXS phenotype, selective serotonin reuptake inhibitors (SSRIs) have been suggested as a pharmacological treatment for anxiety, and may be helpful in reducing symptoms for some individuals with FXS (50% or more of cases) (Berry-Kravis & Potanos, 2004; Hagerman et al., 2009). Recently, Hagerman and colleagues have suggested low dose antipsychotic drugs such as risperidone, may help to reduce high levels of aggression, mood instability, and severe tantrums (Hagerman et al., 2009). However, as with all pharmacological approaches to treatment, neuroleptic drugs such as risperidone can be associated with significant side effects such as dystonic reactions (e.g., tremor, muscular rigidity, and motor restlessness), and weight gain with ultimate risk of metabolic problems such as diabetes.
Alongside pharmacological interventions, behavioral and cognitive based treatment approaches can be effective in reducing symptoms of ADHD. One of the core advantages of behavioral treatments is that they address a broader range of difficulties than those directly related to the clinical symptoms of ADHD: hyperactivity, impulsivity, and distractibility. For example, the deleterious impact of ADHD on academic functioning, on social and family relationships, and on adherence to societal rules is well documented. It is therefore important that treatment, if it is to be of maximal effect, includes the child, their teachers, and parents, and that techniques can be transferable across different settings. For children with ADHD, modifying parental expectations and facilitating strategies to cope more effectively with challenges has proved a useful tool in reducing the impact of ADHD at home. In brief, such programs generally comprise weekly training sessions that aim to provide parents with skills to recognize and address problem behaviors (e.g., monitoring problem behaviors, setting rules, reinforcing positive behaviors). Antshel and Barkley (2008) provide an excellent review of this type of procedure. In recent years, an emerging body of research has begun to explore how intensive computerized training methods can improve the amount of information that children with ADHD can attend to and are able to retain and process. Klingberg et al. (2005); see also www.cogmed.com tested the efficacy of a 25-day computerized training program consisting of visuo-spatial tasks (referred to as “Robomemo”). Children aged 7–12 years diagnosed with ADHD were divided into treatment and control groups; the treatment group was trained with increasing levels of task difficulty while the control group remained on the lowest level throughout the training period. At the end of the training period (5–6 weeks after initial assessment), and again 3 months later, the children were tested on abilities unrelated to the training task (e.g., forward and backward spatial span, digit span). The treatment group was superior on all measures at both testing points, and parents, but not teachers, rated them as having reduced inattention and hyperactivity/impulsivity. Holmes, Gathercole and Place (2008; see also Gathercole, 2008) also assessed the efficacy of Robomemo and found substantial benefits for children with ADHD.

To what extent these techniques can be transferred to children with FXS is as yet unknown. It is therefore disappointing to see virtually no studies that have focused on the efficacy of psychosocial treatment approaches to reducing the effects of inattention and hyperactivity in atypical populations other than in children and adolescents with ADHD alone. Given that there is now clear consensus that intellectual impairment does
not necessarily imply global cognitive delay, alongside the reluctance of many professionals to rely solely on medication to alleviate ADHD symptoms, it is critical that research evaluates the effectiveness of behavior modification approaches that target disorder-specific profiles both in terms of short- and long-term outcomes. In FXS, the high level of stress experienced by most parents would suggest that interventions aimed at reducing stress levels by providing behavioral techniques that lead to reductions in problem behaviors, for example, those presented by severe inattention and hyperactivity, may be extremely beneficial. Likewise, adapting computer-based interventions similar to those used in ADHD children to facilitate working memory and attentional control may be especially beneficial to children with FXS. For example, developing strategies that tap into their strength for meaningful information and their natural affinity for computers (requires no eye contact) is likely to promote considerable improvement in cognitive functioning. See Hall (2009) for a summary of current behavior treatment approaches for FXS.

C. COGNITIVE BEHAVIOR THERAPY

Despite being a primary treatment approach for anxiety problems, considerably less research has been undertaken on the efficacy of cognitive behavior therapy for anxiety in children with ID. However, some have emphasized the importance of this approach to treatment (Dagnan & Jahoda, 2006; Lindsay, 1999; Lindsay, Neilson, & Lawrenson, 1997) and although the applicability of cognitive behavior therapy as a treatment approach with children and young people with intellectual disability has been questioned, particularly for those with severe ID, there is a growing body of literature demonstrating that with modification it is possible and indeed desirable, to use these therapeutic techniques to assist people with intellectual disability (Hatton, 2002; Whitehouse, Tudway, Look, & Kroese, 2006). For example, it has been demonstrated that the ability to link thoughts and feelings (a critical skill in cognitive behavior therapy) can be taught to adults with a mild degree of ID in a single therapy session (Bruce, Collins, Langdon, Powlitch, & Reynolds, 2010), although there is some evidence that with declining verbal ability it is more difficult to successfully apply cognitive techniques (Joyce, Globe, & Moody, 2006; Sams, Collins, & Reynolds, 2006).

In contrast to the literature on cognitive behavioral approaches to treatment of mental health problems in ID, there is comparatively more evidence supporting the efficacy of this approach for the treatment of anxiety in children and adolescents with Asperger’s Disorder and high
functioning autism (Chalfant, Raee, & Carroll, 2007; Lang, Regester, Lauderdale, Ashbaugh, & Haring, 2010; Moree & Davis, 2010; Sofronoff, Attwood, & Hinton, 2005; Wood et al., 2009). However, there is a marked lack of controlled trials with children and young people with low-functioning autism and other developmental disorders including FXS.

As already stated, it is puzzling how few early behavioral interventions are currently for children with FXS. With positive results in terms of developmental skills, language, social communication, adaptive behavior, and reduction of behavior problems in young children with autism (Corsello, 2005; Dawson et al., 2010; Green et al., 2010; Kasari, Freeman, & Paparella, 2006; Rogers, 1996), it is not clear why similar intervention studies have not been undertaken in FXS syndrome. Similarly, training parents of children with autism to implement treatment programs has also demonstrated gains in communicative behavior, parent communication style, reduction in behavior problems, improved parent–child interaction, and decreases in parent stress and mental health problems (McConachie & Diggle, 2005; Tonge et al., 2006; Whittingham, Sofronoff, Sheffield, & Sanders, 2009). This approach to treatment delivery is well established as useful in the reduction of behavior and emotional problems in children with ID without autism (e.g., Ciechomski, Jackson, Tonge, King, & Heyne, 2001; Hudson et al., 2003; Plant & Sanders, 2007). These approaches to intervention are likely to be of considerable benefit to children with FXS and their families.

In terms of enhancing social communication skills, approaches already developed for children and young people with autism are also likely to be helpful for children with FXS. The use of social stories (Lorimer, Simpson, Smith Myles, & Ganz, 2002; Moore, 2004; Reynhout & Carter, 2006; Scattone, Wilczynski, Edwards, & Rabian, 2002; Thiemann & Goldstein, 2001) and training in emotion recognition and theory of mind skills (Howlin, Baron-Cohen, & Hadwin, 1999; Ozonoff & Miller, 1995) may be helpful in improving social interactions in children and young people with FXS. Social skills training programs for children adolescents with autism have demonstrated some efficacy, namely in improving children’s knowledge of social skills, increasing number of social engagements, improving greeting behaviors, improving play skills, and overall improvements in social skills (Barry et al., 2003; Beaumont & Sofronoff, 2008; Krasny, Williams, Provencal, & Ozonoff, 2003; Laugeson, Frankel, Mogil, & Dillon, 2009; Laushey & Heflin, 2000). However, to date, this social skills research is limited to children with Asperger’s Disorder and high functioning autism. Evaluations of these approaches to intervention in FXS are urgently needed; crucially along with the identification of characteristics which best predict successful outcomes.
In conclusion, research clearly shows that treatments to alleviate problem behaviors and improve cognitive functioning in children with ADHD and autism can be extremely effective. Although less researched there is reason to believe that similar techniques, with modifications, may be as useful in FXS. The key is for interventions to begin as early as possible in development and to use an approach that combines both a judicious use of psychopharmacological medications alongside intensive behavioral therapy.

**VII. Summary and Future Directions**

Infants, children, and adolescents with FXS represent a unique constellation of strengths and challenges that impact across developmental time affecting cognitive, social, and behavioral functioning. The past decade has seen tremendous advances in our understanding of this disorder and its dynamic interplay across multiple levels: the molecular, the brain, the cognitive, and the behavioral. Most recently, there has been a push in three core directions, all of which need more thorough and rich data if we are to facilitate a new generation of translational research that will be of tremendous advantage to clinicians, teachers, and affected families.

The **first** is a need for more longitudinal research that will trace developmental changes in cognitive abilities from early infancy and across different neurodevelopmental disorders. For example, our own work on FXS and DS children in the domain of **attention** has shown that despite large overall delay and greater adult difficulties with selective attention, individuals with DS showed improvements by adulthood, whereas those with FXS did not, especially for measures tapping inhibitory control (e.g., Cornish, Scerif, *et al.*, 2007). We are currently completing one of the few studies to date that have charted cognitive and behavioral inattention in FXS toddlers and young children (Scerif, Cornish & Karmiloff-Smith, funded by the Wellcome Trust, UK).

The **second** is the critical need to create an awareness that FXS does not always occur in isolation but that many children also present with symptoms that resemble more common disorders such as ADHD and autism. However, research needs to carefully investigate whether commonalities in symptomatology infer common causal mechanisms. The research to date suggests that different pathways characterize different disorders even though at first blush all share common behavior end-states, for example, ADHD symptoms. This has huge implications for treatment and for the necessity of disorder-specific interventions and approaches.
The third relates to treatment approaches. More specifically to the need for clinical trials (currently underway) that target problem behaviors through appropriate medications. However, there is a huge need to evaluations of behavioral and psychosocial interventions that can be used as early as possible by parents and educators in order to promote success and social inclusion across the academic trajectory. Clearly, early diagnosis of FXS is crucial if educational and clinical interventions are to have maximum impact in enabling children with FXS to develop to their maximum potential.

In conclusion, we are moving along the next decade of exciting discoveries that will ultimately demonstrate, in even finer-tuned detail, how variations in a single gene such as the FMR1 gene result in specific cognitive and behavioral profiles and identify their time course across development.

REFERENCES


