MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *10: 11–16 (2004)*

ATTENTION AND LANGUAGE IN FRAGILE X

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Fragile X syndrome (FXS) is a well-recognized cause of mental retardation and developmental delay in males. Alongside the well-documented clinical characteristics of the condition, recent advances in technology and methodology have begun to define FXS at a number of different levels: genetic, brain structure and function, cognition, and behavior. This article suggests that the FXS phenotype is not merely a juxtaposition of spared and impaired functions but rather may be characterized by an inhibitory control deficit that interferes with the individual's ability to modulate output causing perseverative responding across various skill areas. It is further suggested that an inability to modulate arousal may be at least one cause for the inhibitory control deficit that typifies the FXS phenotype. The approach to understanding atypical development outlined here holds exciting promise for future research in FXS and other developmental disorders.

MRDD Research Reviews 2004;10:11–16.

Key Words: fragile X syndrome; attention processing; speech; executive functions

INTRODUCTION

Fragile X syndrome (FXS) is a well-recognized cause of mental retardation and developmental delay in males and to a lesser extent in females. In recent years, it has become one of the most widely researched and well documented of genetic conditions. At a genetic level, it is now established that the FMR1 gene is the major contributor to the pathogenesis of FXS and that the key issues relate to a lack of messenger RNA (mRNA) and a lack or absence of the protein product of the FMR1 gene—FMRP. The extent to which these discoveries explain some of the phenotypic outcomes in FXS are beginning to be unraveled with the application of more finely tuned neuropsychological and neuropsychiatric approaches to understanding atypical development.

Alongside these advances, recent progress in brain imaging techniques, most notably functional magnetic resonance imaging (fMRI) and event-related potential (ERP), has provided exciting opportunities to further delineate the impact of the FMR1 gene on brain development and the resulting cognitive system. For example, recent work by Reiss and colleagues [e.g., Rivera et al., 2002; Tamm et al., 2002] have provided the first published demonstration that fMRI can be sufficiently sensitive to measure the role of the FMR1 gene expression and neural activity. Interestingly, both Rivera et al. [2002] and Tamm et al. [2002] noted unusual activation patterns in the prefrontal cortex in FXS females compared to unaffected controls. Similarly, recent ERP studies have also revealed unusual frontal activations also among FXS females when compared to controls [Cornish et al., 2003; Hagerman, 2002]. Further evidence of anomalous lateralization in FXS was reported in a recent study using magnetoencephalography (MEG) technology to assess auditory evoked responses in a sample of adult males and females with FXS. In this study Rojas et al. [2001] report abnormally large amplitude sensory evoked responses alongside an alteration in auditory cerebral lateralization in their FXS adults compared to controls.

In addition to the impact of genetic and brain factors, Hessl et al. [2001] have reported the potential impact of environmental factors (e.g., rated effectiveness of educational and therapeutic inventions) in determining behavioral outcomes in boys with FXS.

Taken together, these findings provide strong support for an interactive role across many systems: from the genetic to the neurological systems to the cognitive and the affective systems and then to the behavioral and environmental systems. In this article we focus on describing the recent advances in our understanding of the cognitive phenotype in FXS. Crucially, we speculate that the constellation of proficiencies and deficiencies across cognitive domains do not represent a catalog of spared and impaired functions specified from infancy onward. Instead, the range of phenotypical outcomes we observe in FXS could result from the dynamic interplay among multiple systems originating from the biological and interacting all the way from the gene expression to the cognitive and behavioral endstates [Karmiloff-Smith, 1998].

COGNITIVE PROFICIENCIES AND DEFICIENCIES IN FXS

The past 2 decades have witnessed an explosion of research studies that have attempted to isolate the core cognitive impairments in FXS. Early studies using traditional IQ tests suggested a slight verbal–nonverbal discrepancy with better ver-

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Received 30 March 2003; Accepted 13 June 2003
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/mrdd.20003

bal IQ scores than performance IQ scores in both boys and girls [e.g., Dykens et al., 1987; Kemper et al., 1986; Miezejeski et al., 1986; Theobald et al., 1987; Veenema et al., 1987]. Detailed examination of the profile of the IQ performance reveals that FXS individuals typically performed worse on tasks that required placing information in a serial or temporal order (e.g., series of digits, motor movements, and spatial construction) compared to tasks that involved integrating information in a holistic, gestaltlike manner (e.g., perceptual closure).

In the 1990s researchers began to unravel an even more finely tuned profile of cognitive dysfunction—more "skill specific" rather than "global" in nature. This included particular weaknesses in short-term memory for complex, sequential information [e.g., Freund and Reiss, 1991; Hodapp et al., 1992; Jakala et al., 1997; Schapiro et al., 1995]; visuoconstructive and visuospatial skills [Cornish et al., 1998; 1999; Freund and Reiss, 1991; Mazzocco et al., 1993]; planning and verbal fluency [Mazzocco et al., 1993, 1994]; and perseverative, repetitive, impulsive speech [Ferrier et al., 1991; Sudhalter et al., 1990]. In contrast, performance on tasks that required short-term memory for simple, meaningful information [Schapiro et al., 1995], visuoperceptual integration (gestalt processing) [Cornish et al., 1999; Hodapp et al., 1992], face and emotion recognition [Simon and Finucane., 1996; Turk and Cornish., 1998], and syntax [Scarborough et al., 1991; Sudhalter et al., 1992] were not as severely impaired with performance equivalent to developmental age but not chronological-age control children.

A number of interesting issues emerge from these findings. First is that the pattern of results, although strongly indicative of a unique profile of strengths and difficulties across and within cognitive domains in FXS, does not infer brain function that can be described as comprising "intact" alongside "impaired" systems. If this were the case then we would see skills that tap cognitive strengths performed at a comparable level to those of age-matched, typically developing children. In most studies, as highlighted in the profile above, a cognitive "strength" is likely to infer a developmental age equivalent performance rather than a chronological age performance. This notion has been further expanded in a series of recent pioneering studies by Karmiloff-Smith and colleagues [e.g., Karmiloff-Smith et al., 2003; Paterson et al., 1999] of toddlers and children with Williams syndrome. Examination of the Williams syndrome profile reveals domains of relative proficiency (face processing and language) alongside other serious impairments. However, finer tuned analysis of these areas of proficiency indicates that even where performance is equivalent to normal developing children, the cognitive processes by which such proficiency is achieved are different and atypical.

Second, the pattern of the cognitive profile is consistent in both males and females although in females we see a wider phenotypic diversity, especially in relation to intellectual functioning. The modulating role of the X activation ratio (the ratio of active normal X chromosomes to normal inactive X chromosome) may account for some of the individual variation among females, but the literature remains inconsistent as to whether the activation ratio serves as a predictor of overall intellectual impairment or a predictor of specific cognitive deficits [Cornish et al., 1998; De Vries et al., 1996; Reiss et al., 1995; Taylor et al., 1994]. It may also be conceivable that there are important gene–gene interactions ("epistasis") that have yet to be identified. However, what is especially striking is the number of similarities in the cognitive profile of males and females even when individual differences are taken into account.

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Third, there is the possibility of more generalized physiological dysregulation contributing to the prevailing FXS phenotype. However, in actuality there is little, if any, empirical evidence for this over and above anecdotal clinical reports. Also, such a hypothesis cannot explain the specificity of the profile of strengths and weaknesses that have been documented repeatedly. Nevertheless, there is the possibility of this process contributing nonspecifically by accentuating the cognitive, emotional and behavioral features that have been described. Thus, we acknowledge the possible contribution of quantitative (hyperarousal) as well as qualitative (neurocognitive) factors in our model. These contributing factors are not mutually exclusive.

In an attempt to integrate these findings into a cohesive model we propose a core deficit in behavioral inhibition may account for a large percentage of the observed strengths and weaknesses in FXS. Specifically, deficits in sequential on-line processing [e.g., Freund and Reiss 1991] and working (short-term) memory [e.g., Jakala et al., 1997; Munir et al., 2000a] alongside deficits in repetitive, perseverative speech [Ferrier et al., 1991] can arise because of reduced inhibitory control. Crucially, if such a low-level impairment is present during prenatal development, for example, then we would expect an impact through development across multiple levels (genetic, brain, cognitive, environment, and behavioral) to produce the phenotypic outcomes we associate with FXS. In a series of recent studies researchers have sought to test this notion that inhibitory weakness is a core feature of FXS.

ATTENTION PROBLEMS IN FXS

At the behavioral level, the most striking and consistent primary behavioral features identified in young FXS children are attentional and hyperactivity problems that include the behavioral triad of severe and persistent inattention, overactivity, and impulsivity [e.g., Baumgardner et al., 1995; Fryns et al., 1984; Hagerman, 1987]. The triad of symptoms leads to many FXS children, especially boys, being clinically diagnosed with attention deficit/hyperactivity disorder (ADHD). When boys with FXS are compared with age and developmentally matched boys who have mental retardation of unknown cause, they show similar levels of motor activity [Turk, 1998]. However, the boys with FXS show significantly more inattentiveness, restlessness, fidgetiness, distractibility, and impulsive tendencies. Furthermore, these features do not improve spontaneously over time, emphasizing the critical need for early identification and intervention. The closest diagnostic category the FXS boys conform to, given their similar rates of overactivity compared to matched non-FXS boys, is that of "ADHD"—predominantly inattentive type. It is also of note that psychostimulant medications (e.g., methylphenidate,

Ritalin) for the attentional deficits and impulsiveness have been reported as producing positive outcomes [Hagerman, 2002; Hagerman et al., 1988].

At the cognitive level, Munir et al. [2000b] compared performance of boys with FXS and Down syndrome as well as typically developing children on a range of neuropsychological measures of attention (selective, divided, sustained). The researchers concluded that the FXS group differed from the other groups in their ability to plan and to organize visual search, to shift attention from one target type to another or from one concept to another. Additionally the FXS group demonstrated a delay in responding and a greater inability to inhibit task irrelevant responses in comparison to the control groups. These deficits were more pronounced for tasks that required higher attentional capacity suggesting a pattern of deficit broadly encompassing "*executive function*" (EF). Indeed, the pattern of this finding in males compliments an already emerging literature reporting EF deficits in the cognitive phenotype of FXS females [e.g., Bennetto et al., 2001; Mazzocco et al., 1993, 1994; Sobesky et al., 1996; Tamm et al., 2002; Thompson et al., 1994]. Similarly, EF deficits alongside deficits in working memory and visuospatial skills have also been reported in adult men with FXS [Cornish et al., 2001b].

In recent years, however, the heterogeneity of EF has been recognized and there is a growing consensus that EF encompasses a range of functions, including "planning" "inhibition", "set-shifting," and "working memory" [Pennington, 1997]. To date, these different components have not been disentangled. Moreover, FXS is not unique in presenting with executive difficulties and other neurodevelopmental disorders, most notably autism [Pennington and Ozonoff, 1996; Turk and Graham, 1997] and ADHD [Sergeant et al., 2002; Turk, 1998]. The extent to which the pattern and severity of EF deficits differs across syndromes has yet to be revealed. However, in a series of recent studies of young males with FXS there has been an attempt to understand the EF deficit at a more finely grained level. Using a novel, computerized paradigm to explore the range of attentional problems, Wilding, Cornish, and Munir (2002) found that boys with FXS demonstrated significantly greater problems in their ability to switch visual attention and to inhibit repetitive behavior, resulting in more perseverative errors compared to boys with Down syndrome and typically developing control children matched to the FXS group on developmental level and chronological age. Specifically, the greatest number of errors occurred when the task involved switching from one target type to another in a sequence. One possible explanation for these findings is that they represent a fundamental weakness of FXS in switching attention that could be ascribed to a weakness in inhibitory functions. Given that switching and inhibition are widely regarded as key components of EF, these findings suggest that weaknesses in aspects of EF are crucial components of attentional problems. This conclusion is further supported by recent studies on much younger children with FXS. Scerif et al. [2003], for example, found a similar profile of perseveration errors (repeating successful responses) in a sample of toddlers with FXS and Hooper et al. [2000] report deficits in selective attention and working memory in FXS boys as young as four years of age. However, simply proposing "inhibition" as the primary explanation to account for the different types of weaknesses is only an initial step toward understanding the attentional deficit in FXS.

One possible explanation for the pattern of findings is that they represent a fundamental weakness of FXS in switching attention that could be ascribed to a weakness in inhibitory functions. Given that switching and inhibition are widely regarded as key components of EF, these findings suggest that weaknesses in aspects of EF are crucial components of attentional problems.

Clearly other possibilities remain, including a primary deficit in sensory modulation that is not related to executive function. Ayres [1972] first referred to a "tactile defensiveness syndrome" in which normally innocuous tactile stimuli were apparently interpreted as dangerous and triggered inappropriate "fight or flight" type reactions. Subsequent work in this area [e.g., Ayres, 1979; Baranek et al., 1997; Royeen and Lane, 1991] broadened the concept to that of "sensory defensiveness," which denoted a symptom profile that could include avoidance of, or hypersensivity to, various types of touch, sound, light, smell, taste, and movement. More recently, the term *sensory-modulation disorder* has been used to refer to cases characterized by inappropriate (either hyper- or hyporesponsive) reactions to stimuli [Dunn, 1997; Cohn et al., 2000]. These sensory modulation deficits are thought to underlie such behavioral problems as distracted, impulsive, or disorganized behavior; abnormal activity levels, anxiety, and emotional lability resulting in deficient social participation; self-regulation; and inadequate perceived competence [Cohn et al., 2000]. Early clinical observations of individuals with FXS suggested that they often exhibit abnormal responses to sensory stimulation and that these abnormal responses may be related to anxiety or arousal [Braden, 1992; Scharfenaker et al., 1991]. Thus, the inability to normally regulate arousal provides another useful framework for understanding many of the behavioral symptoms of FXS. Although the underlying physiological basis of such impaired arousal regulation is not well understood, Berry-Kravis [1992] has speculated that the hypersensitivity to sensory stimuli, as well as impaired habituation and working memory problems, that is also seen in FXS may be related to the abnormal regulation of cyclic AMP production by the FMR-1 gene.

SPEECH AND CONVERSATIONAL LANGUAGE

Though males with FXS appear to demonstrate relatively spared vocabulary and syntactic knowledge, their conversational language has been the subject of much study. The types of atypical language that are produced most often by individuals with FXS but most notably males during conversational interactions include tangential language [Sudhalter and Belser, 2001], perseverative language [Sudhalter et al., 1990], repetitive speech [Belser and Sudhalter, 2001], and tendency toward delayed echolalia [Turk and Graham, 1997]. Tangential language refers to off-topic questions, responses, or

comments that do not logically follow the preceding conversational thread. Perseverative language refers to the reintroduction of favorite topics over and over, even in the presence of conflicting conversational demands. Repetitive speech refers to the repetition of sounds, words, or phrases within an utterance or conversational turn. One explanation that awaits empirical study for the cause of these atypical productions is that individuals with FXS have an inability to normally regulate arousal [Belser and Sudhalter, 2001; Miller et al., 1999]. For instance, it has been demonstrated that males with FXS react more strongly than those without FXS to many forms of environmental and social stimuli, and the hyperarousal that results can take an unusually long time to abate. As a result, individuals with FXS are prone to long periods of sustained hyperarousal, especially during social interactions. A maladaptive response to this sustained arousal would be to restrict the number and length of one's verbal output. This could lead to selective mutism. In fact, Hagerman et al. [1999] described selective mutism in sisters with FXS. However, despite the use of such social avoidance strategies, there are times when males with FXS are required to talk and otherwise interact actively with their social environment. Under such circumstances, specific types of atypical language are commonly observed.

TANGENTIAL AND PERSEVERATIVE LANGUAGE

We have suggested elsewhere [Belser and Sudhalter, 1995; Sudhalter and Belser, 2001] that hyperarousal, in conjunction with diminished inhibitory control, is one explanation for the production of perseverative and tangential language seen in individuals with FXS. In some very preliminary data presented in Belser and Sudhalter [1995] it was demonstrated that in males with FXS, eye contact predicted higher skin conductance level and greater rates of spontaneous skin conductance responses, indicative of arousal. This arousal in turn was associated with the emergence of atypical language in males with FXS. Neither increased skin conductance activity nor production of atypical language in the presence of eye contact was observed in the subjects with Down syndrome or ADHD.

There is also the issue of high rates of shyness and social anxiety in otherwise friendly and empathic individuals who understand the nature of social interaction. Ordinarily, excitatory and inhibitory processes exist in balance within the nervous system, resulting in stable, well-controlled behavior. Because both hyperarousal and impaired inhibitory control are characteristic of individuals with FXS, such imbalance is easily triggered by either physical or social stimulation within their environment. We suggest that the effect on language production is to free impulsive tendencies to talk about favorite or highly associated topics regardless of the conversational demands. Tangential language occurs when the association between previous and current utterances is personal or otherwise unknown to the conversational partner. Perseverative language occurs when favorite topics are impulsively reintroduced into a conversation, independently of the current context, presumably because they are well rehearsed and their use provokes less social anxiety than new unfamiliar information. This finding and explanation is similar to that given by Scerif et al. (2003), who described perseverative errors in a sample of toddlers with FXS.

REPETITIVE SPEECH

In addition to the atypical types of language described above, another common linguistic characteristic of males with FXS is repetitive speech. Once an individual has acquired some language he must learn how to communicate fluently (i.e., with appropriate rate, rhythm, and articulation) within a social setting. The Neuropsycholinguistic Theory of Language Production [Perkins et al., 1991] is one of many theories that describe how speakers are able to accomplish this. According to this theory, fluent speech requires the coordination of two independently operating neural systems: one that controls linguistic processes, such as selecting the appropriate vocabulary and syntax to convey a desired thought, and another that controls paralinguistic process, such as generating the appropriate facial expression, intonation, and rhythm to indicate the speaker's emotion and intent. Dysfluent speech is thought to occur when the coordination between these systems becomes impaired, causing them to become desynchronized. We believe that the hyperarousal experienced by individuals with FXS creates the conditions required for repetitive speech to occur. We have suggested elsewhere [Belser and Sudhalter, 2001] that anxiety triggered by the expectations of conversational participation may cause a child to develop rapid speech. Rapid speech has been associated with heightened anxiety and arousal [Siegman, 1978] and is a recognized phenotypic characteristic of individuals with FXS [Hanson et al., 1986; Borghgraef et al., 1987]. This rapid speech may result in the individual beginning an utterance prematurely, causing the linguistic elements of that utterance to lead the paralinguistic elements. When the neuropsycholinguistic system senses that this occurs, it causes the speaker to stall for time by repeating a selected phoneme, word, or phrase until the associated paralinguistic elements have had a chance to catch up and synchrony is restored. As with the production of atypical language, the hyperarousal that leads to dysfluent repetitive speech may be triggered by either environmental stimulation or conversational demands. Thus, we argue the characteristic atypical language of individuals with FXS is likely to be caused by their hyperarousal and impaired inhibitory control systems. These deficits work in tandem to affect language production in several important ways. By making it difficult to block impulsive verbal behavior, these problems lead to language that is inappropriately perseverative and tangential. Hyperarousal also promotes rapid speech, which can lead to the production of repetitive dysfluencies—so-called cluttering.

THE NATURE AND RELEVANCE OF THE SOCIAL DYSFUNCTION

Studies of social impairments in FXS [Turk and Graham, 1997; Aziz et al., 2003; Das and Turk, 2002] confirm the impossibility of "pigeonholing" the majority of individuals with FXS as having autism. It has long been recognized that it is the paradoxical juxtaposition of a friendly sociable (albeit often shy, socially anxious, and socially avoidant) personality with certain "autistic-like" communicatory and ritualistic features that is the hallmark of most with FXS. What are we to make of this? First, at a clinical level, it is immediately clear that there is far more to social and communicatory dysfunction that simply having or not having autism. Second, it is necessary to acknowledge the different yet complementary natures of etiological diagnosis on the one hand (e.g., FXS) and clinical/phenomenological diagnosis on the other (e.g., autistic spectrum disorder). Third, the repeatedly identified profile of social, communicatory, and ritualistic dysfunction in those with FXS [Turk, 1992] is once again consistent with underlying executive dysfunction, neurobehavioural inhibition deficits, hyperarousal, and heightened anxiety states. The inhibition

deficits are evidenced in such social phenomena as the active and odd, disinhibited yet socially anxious, naive and socially inappropriate tendencies of many with FXS. Frequent echolalia, repetitive speech [Ferrier et al., 1991], and hand flapping in response to anxiety and excitement [Turk and Graham, 1997] are further evidence of this. Thus we have a model for an underlying set of developmental neurocognitive deficits as underlying delays and distortions in a range of developmental domains—social, communicatory, ritualistic/obsessive, fine and gross motor, attentional, and even executive.

In conclusion, there have been tremendous advances over the past decade and a half in our understanding of the FXS. We can now identify the gene that causes the disorder. We are beginning to understand the effect of lack or absence of the gene product on cognition. Finely tuned neuropsychological and neuropsychiatric approaches have led us to understand that the FXS phenotype should not be viewed merely as a catalog of spared and impaired cognitive functions. Rather, the emerging behavioral and neurocognitive findings pertaining to attentional, social, and speech profiles in FXS suggest possible core impairments in inhibitory control with subsequent inability to regulate arousal effectively. The hyperaroused state may then cause neural connections to become activated, even those that are unimportant to the particular task or demand of the moment. This "irrelevant" activation interferes with executive functioning by interfering with the FXS individual's ability to inhibit, switch, or update a response effectively. We believe that the findings resulting from this period of intense research activity can inform clinical and behavioral interventions (pharmacotherapy, behavioral management, and education) as well as contribute to the scientific knowledge of a condition that affects many thousands of individuals. Through better definition of the cognitive phenotype, in combination with current progress in brain imaging techniques and molecular studies, the next decade should continue to hold exciting promise for reseach of FXS and other neurodevelopmental disorders. ■

ACKNOWLEDGMENT

We thank Cary Kogan (Department of Psychology, McGill University) for insightful comments on earlier versions of this article.

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