Published in final edited form as:

Wiley Interdiscip Rev Cogn Sci. 2014 ; 5(4): 501–508. doi:10.1002/wcs.1296.

Cognitive Aspects of Fragile X syndrome

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Abstract

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability. It is primarily caused by the expansion of a CGG trinucleotide repeat located in the 5' untranslated region of the X-linked *FMRI* gene. Individuals with FXS present with variable intellectual quotients (IQs) ranging from the average to the severe intellectual disability level. A range of neurocognitive strengths and challenges are observed in individuals with FXS. This article provides an overview of our current understanding related to cognition and FXS. Cognitive functioning levels, profiles, and IQ trajectories are discussed. Limitations of existing neuropsychological measures are described.

Fragile X syndrome (FXS) is the leading inherited cause intellectual disability and it is associated with a range of social, behavioral, and cognitive impairments [1, 2],[3]. The primary cause of FXS is the expansion of a CGG trinucleotide repeat located in the 5' untranslated region of the X-linked *FMRI* gene [1, 4]. Expansions of 200 CGG repeats or greater lead to abnormal hypermethylation of the repeats and the surrounding regulatory region. As a consequence, *FMRI* gene is silenced. Thus, this full mutation leads to the absence of the fragile X mental retardation protein (FMRP). Individuals with 55 – 200 CGG repeats are classified as premutation carriers. In this case, the repeats are not methylated and FMRP is unaffected. However, as the repeat length increases to the 100s, the level of FMRP is sometimes reduced[5, 6] due to the inefficiency of translation[7]. However, it is relatively uncommon that levels are reduced to a point that may be pathogenic[8]. The reduction or absence of FMRP has been associated with the clinical features (i.e., limitations of cognitive, behavioral, social functioning) of FXS[9],[10].

Given that the mutation is located on the X chromosome, males are typically affected to a greater degree with a prevalence of approximately 1 in 4000 as compared to 1 in 8000 in females[11-15]. Herein, we review the current literature on cognition in FXS, describe the

cognitive profiles of males and females, and discuss implications for future research and practice.

COGNITIVE FUNCTIONING IN FXS

Cognitive functioning, as measured by standardized psychological and neuropsychological measures ranges from the average to the severely intellectually disabled range in the FXS population. Based on current research, a proportion of the variability in IQ can be linked to FMRP status and gender. Relatively few studies have been published examining the trajectory of IQ related to individuals with FXS. The cross sectional and longitudinal studies reviewed varied according to measures, comparison groups, and demographics (i.e., age, gender, FMRP status) limiting the ability to draw comparisons across studies. Key findings related to cognition and FXS are presented in Table 1.

IQ and FMRP status

As described above, studies have shown a relationship between intellectual quotient (IQ) and the level of FMRP, with higher levels of FMRP being associated with less cognitive involvement.[2, 10] Higher cognitive functioning is typically noted in females since they have one normal *FMR1* allele on their second X chromosome. In males, three genetically different groups have been studied with regard to cognitive functioning: full methylation (i.e., no production of FMRP); methylation mosaic (i.e., both methylated and unmethylated *FMR1* genes present); and full mutation/premutation mosaics (i.e., presence of both full and premutation repeat length alleles)[10]. Individuals with full methylation, typically score within the intellectually disabled range with scores ranging from mild to moderate, although in some instances, severe intellectual disability has also been reported[2, 9, 16]. For individuals mosaic for methylation status or repeat allele status, IQ ranges of borderline to low average have been reported with average to low-average cognitive functioning being documented in a few males with partial methylation[2]. Tassone et al.[10] found a significant correlation between full scale IQ and FMRP expression in males with partially methylated full mutations and to a lesser degree, those mosaics with pre and full mutations. These findings provide evidence of the role of FMRP and cognitive performance in males with FXS.

In females, the amount of FMRP also appears to relate to level of cognitive functioning[16]. However, as females have two X chromosomes, one of the chromosomes is inactivated, or turned-off in each cell. The level of cognitive functioning in females with FXS varies based on the proportion of cells with the unaffected *FMR1* allele in comparison to those with the full mutation. As such, females with FXS are typically less affected than their male counterparts with reported IQ scores from the average to intellectually disabled range[17] with most demonstrating borderline to low-average IQ (i.e., scores between 70 and 90[1]).

IQ TRAJECTORIES IN FXS

Researchers have identified a decline in IQ score with increasing age in the FXS population [2, 18-20]. The IQ decline was observed in participants with FXS when compared to those with other genetic or developmental conditions as well as mental age matched typical

controls (Table 1). For example, in a retrospective study of cognitive functioning in males and females with FXS[19], significant IQ declines were observed in males with FXS as compared to controls with non FXS-related behavior or developmental concerns. However, the IQ decline was not observed in females with FXS as compared to non-FXS controls[19]. Fisch et al.,[20] conducted a longitudinal study of cognitive and adaptive functioning children with the *FMRI* full mutation, Williams-Beuren Syndrome, and Neurofibromatosis Type 1 focusing on gender effects. The Stanford-Binet, 4th edition (SB-IV) and Vineland Adaptive Behavior Scale (VABS) were administered twice within a two-year interval to children between the ages of 4 and 16. A significant decline in IQ scores was reported for children with FXS, with a greater decline for males, as compared to children with other genetic conditions.

A longitudinal study of cognitive and adaptive functioning in children and adolescents with FXS and those with autism revealed an IQ decline in both groups [18]. Consistent with previous findings, the IQ decline was more significant in males with FXS. Participants were tested at two time points within a two-year period. Children with autism initially tested prior to the age of six years demonstrated stable test-retest IQ scores while the IQ decline persisted in participants with FXS. Adaptive functioning decline was observed in both groups.

While it has been previously reported that children and adolescents with FXS experience cognitive decline, later findings suggest that lower IQ score trajectories for individuals with FXS are not indicative of cognitive regression[2]. Fisch et al.[20] concluded that individuals with intellectual disabilities caused by genetic conditions present with a more gradual cognitive developmental trajectory and appear to plateau as compared to age-matched peers. This trajectory may account for the perceived cognitive decline. Indeed, the IQ decline is a reflection of the difference in rate of skill acquisition between individuals with FXS and their neurotypical peers [21, 22]. Given the slower rate of development of some individuals with FXS, test-retest IQ decline could be a function of the nature of cognitive assessments. As chronological age increases, different skills are assessed. Therefore, individuals with FXS appear to lose skills across time.

COGNITIVE PROFILES

It is important to investigate the cognitive profile of individuals with FXS in order to build upon their strengths and develop targeted educational and medical interventions specific to their needs[23]. Individuals with FXS demonstrate a unique pattern of cognitive strengths and limitations with some similarities across gender[21, 24]. Relative weaknesses have been observed in the areas of executive function [22], visual memory/perception, visual-spatial reasoning, and visual-motor coordination [21], short-term memory [23]. Verbal reasoning and simultaneous processing tasks have been noted as areas of relative strength [16, 21, 24]. For example, in a study of males with FXS (n = 49), Backes et al.[16] identified a relative strength on the simultaneous processing scale versus sequential processing scale utilizing Kaufman Assessment Battery for Children (K-ABC) as compared to a control group of males with tuberous sclerosis (n = 16). The study also revealed a significant strength related to acquired knowledge as compared to general intelligence as measured by the K-ABC

mental processing scale. The cognitive profile was revealed after a recalculation of scales using the participants' developmental age norms in lieu of chronological age norms, which yielded no significant difference. This study highlights floor effects, one of the challenges associated with assessing cognitive functioning in the FXS population. A floor effect occurs when there is a finite lower limit on a particular instrument and the majority of the data points cluster at the lower end. This limits the variance of scoring and produces a skewed distribution if scores are recorded at the lower limit. In essence, the distribution is truncated at this low limit. As such, floor effects limit the clinical value of psychometric instruments.

Freund and Reiss[23] utilized the Stanford-Binet, Fourth Edition (SB-IV) to examine the cognitive profile of males and females with FXS to determine whether or not a similar cognitive profile was observed across genders. They hypothesized that both groups would present with stronger verbal facility and relative weaknesses in quantitative, visual-spatial, and short-term memory skills. In general, verbal and quantitative reasoning tasks require an individual to access information acquired through formal education. In the SB-IV, these tasks comprised the Crystallized Knowledge cluster. Abstract or visual reasoning tasks measure an individual's ability to solve novel problems utilizing visual motor and visual-spatial/perceptual abilities. On the SB-IV, short-term memory was measured with visual and auditory tasks in both abstract and meaningful contexts. The findings revealed a relative strength in crystallized abilities in males with FXS with verbal reasoning skills being significantly higher than short-term memory skills. Results for females with FXS were inconclusive with evenly distributed abilities being revealed based on the standard interpretation of SB-IV scores. Using an exploratory analysis, females demonstrated a relative weakness in short-term memory for nonverbal sequential tasks and a relative strength in verbal-based short-term memory tasks for sequential material. In contrast to previous findings, no deficits in quantitative reasoning were revealed for males or females with FXS.

Executive Function

In recent years, Executive Function (EF) has become an area of interest with respect to cognitive functioning in individuals with FXS. Executive function was originally investigated in patients with frontal lobe damage[25]. Clinicians observed that individuals with frontal lobe damage had difficulty with control and regulation of certain aspects of behavior linked to performing activities essential to normal functioning.[25] There is some evidence to support the existence of discrete skills sets that comprise executive function[25, 26]. Executive function is defined as the underlying processes that conduct goal-directed and future oriented behaviors such as inhibition, working memory, set-shifting, cognitive flexibility, planning and cognitive efficiency[27].

EF deficits in the area of inhibition overlap with associated clinical features of the FXS phenotype such as hyperactivity and impulsivity[28]. Executive function deficits also have been revealed in the areas of working memory and shifting. Weaknesses in working memory limit an individual's ability to hold, manipulate, and process new information. Shifting refers to the ability to disengage in a previous task and actively engaging in a new task while overcoming the desire to maintain the initial behavior[25]. Researchers have investigated the

degree to which EF deficits are implicated in learning and behavioral difficulties observed in the FXS population.

Much of the research related to EF and FXS has been conducted with females. This could be due in part to the fact that there is more variability in cognitive functioning in females.[29] In addition, they are more likely to tolerate the testing procedures. As males with FXS are typically more cognitively impaired than females, it is difficult to determine whether lower EF performance is indicative of underlying weaknesses in EF skills or a function of lower global intellectual functioning[29]. Key studies related to executive function in FXS are presented below.

Previous studies of females with FXS have revealed significant deficits on multiple measures of executive functioning (e.g., Wisconsin Card Sorting Test, Contingency Naming Test, Visual-Verbal Test)[29]. Bennetto et al.[29] conducted two studies of EF with females with FXS. In the first study, females with FXS aged 18 to 45 were compared to premutation carriers and unaffected females who grew up in families with FXS. Females with FXS scored significantly lower on IQ measures than the comparison groups. While females with FXS performed lower on tasks of executive functioning, spatial ability, and visual memory; it was unclear if these findings were attributable to variation in IQ or indicative of a distinct neurocognitive profile for females with FXS. The results of the ANCOVA indicated that women with the full mutation demonstrated significantly poorer performance on EF tasks as compared to premutation and control groups. EF deficits were maintained in a follow-up study with age-and IQ- matched peers. The findings provided evidence of EF weaknesses in women with the full mutation.

Kirk, Mazzocco, and Kover[30] examined working memory and shifting using the Contingency Naming Test in girls with FXS or Turner Syndrome. Similar to the findings of adult females with FXS; the study revealed executive dysfunction related to cognitive flexibility and working memory in girls with FXS compared to IQ matched peers.[30] However, IQ remained a significant factor when evaluating the level of EF difficulties among FXS participants. The preliminary findings indicate that it may be beneficial to target EF interventions females with FXS.

As described above, less is known about the role of EF in males with full mutation. Early researchers examining EF in males with FXS were unable to determine the level of EF functioning due to floor effects [31]Hooper and colleagues [27] investigated EF in young males with FXS between the ages of 7 and 13 as compared to mental age matched peers. Boys with FXS performed significantly lower on tasks related to inhibition, working memory, cognitive flexibility, set-shifting, and planning. Performance on the aforementioned tasks was influenced by mental age. Researchers also have observed working memory deficits in a subsequent study of in boys with FXS[32] The authors hypothesized that boys with FXS would demonstrate global working memory delays. However, the results indicated the participants performed better on visual-spatial sketchpad tasks (i.e., Leiter-R Spatial Memory and Leiter-R Reverse Memory) rather than phonological loop tasks.(Woodcock-Johnson, 3rd Edition [WJ-III] memory for Words, WJ-

III Numbers Reversed, WJ-III Auditory Working Memory). These findings provide essential information for intervention development and assessment.

LIMITATIONS OF NEUROPSYCHOLOGICAL TESTS

As described above, one of the challenges in examining cognitive functioning in individuals with FXS is the limitation of current cognitive and neuropsychological assessment tools [24]. Many of the widely used IQ measures are often less sensitive to individuals in the lower range of cognitive functioning. For example, due to floor effects, individuals with variable performance within the intellectually disabled range on a measure of cognitive ability could be assigned similar standard scores. This occurs due to the conversion of raw scores to scaled scores and ultimately standard scores, which washes out variation at the floor of the test.

Hessl et al. [33] investigated the sensitivity of the Wechsler Intelligence Scale for Children, Third Edition (WISC III) in children with FXS between the ages of 6 and 17. The researchers were able to circumvent the floor effects typically observed in standardized cognitive measures through a z-score normalization procedure. The authors obtained raw score data from the test publisher to calculate each participant's deviation from the norm sample using a z-score transformation. The procedure was validated through correlations between the new z-score transformation scores versus standard scores with the Vineland Adaptive Scales and a measure of FMRP. They were able to demonstrate a normal distribution using the z-score transformation, which resulted in the elimination of floor effects. This procedure is promising and could have implications for FXS research given the variability of IQ and tendency towards floor effects in many of the commonly used standardized measures of intellectual functioning.

There are limitations to the use of IQ tests in research and clinical practice for individuals with a greater degree of cognitive impairment due to their limited ability to complete certain aspects of the tests. This is particularly challenging in the FXS population as intellectual disability as well as executive dysfunction related to inhibition tend to limit their ability to complete test procedures. For example, Hooper et al. [27] found that several participants were unable to complete the EF tasks despite having a mental age of 48 months or above.

Knox and colleagues [28] investigated the feasibility and utility of the Test of Attentional Performance in Children (KiTAP) to measure attention and inhibition in individuals with FXS. The authors highlighted the need for reliable measures of EF that can be consistently completed by individuals with FXS irrespective of mental age. Scores derived from four of the eight KiTAP subtests were deemed feasible for the majority of participants. The scores obtained had an acceptable range and distribution, correlated with other well-known behavioral questionnaires, and demonstrated adequate psychometric properties (i.e., test-retest, basal, ceiling, learning effects) [28]. These findings are promising and contribute to the knowledge base regarding outcome measures for future clinical trials and intervention studies.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent studies have explored the cognitive profile of males and females with FXS[16, 23, 29]. In general, relative strengths have been identified in verbal ability, acquired knowledge, long-term memory for verbal information, and simultaneous processing. Relative weaknesses in cognitive processing and have been revealed in sequential processing, auditory visual-perceptual short-term memory, numerical facility, and tasks related to executive function (e.g., attention, set-shifting, cognitive flexibility, etc.). While cognitive profiles are beginning to emerge, more studies are needed to replicate preliminary findings and to explore the relationships between the neurocognitive profile and genotype of FXS.

Over the past few years, there has been substantial advancement in our understanding of cognition in FXS as a result of advances in our ability to characterize the genotype and phenotype of FXS and explore its potential associations with respect to cognitive functioning. For example, researchers are able to determine methylation status, FMRP expression, and the X activation ratio in females[3] (i.e., the proportion of cells with the normal FMR1 allele on the active X chromosome). With scientific advancement, researchers have identified significant correlations between FMRP and cognitive functioning with higher levels of FMRP being associated with a greater degree of cognitive functioning in males and females.

Furthermore, there has been progress in the area of longitudinal studies examining IQ trajectory. Several methodological issues were identified in early longitudinal IQ studies such as small sample size, use of different IQ measures, the assessment interval between testing, reliance on cross-sectional studies, and floor effects with standardized IQ measures. The use of small sample sizes and cross-sectional studies limits interpretation and generalization of findings. The use of different IQ measures is potentially problematic as it is unclear whether or not different cognitive measures are assessing the same construct[3]. The time between assessments is also important to consider when interpreting the findings of longitudinal studies. For instance, the time period of the suspected decline should be adequately covered within the assessment time points of the study[2]. Finally, the limitation of floor effects, as described above, is particularly problematic for individuals with moderate to severe intellectual disabilities. Recent studies have addressed the aforementioned challenges through improvements in study design, methodology, and statistical procedures. More studies are needed to continue to enhance our understanding of the underlying causes of the decline in IQ scores for individuals with FXS.

Our understanding of cognitive profiles of individuals with FXS has the potential to contribute to research and clinical practice in a variety of ways. In the area of research, the development of more sensitive cognitive measurements and procedures can provide guidance in identifying efficacious medical and behavioral treatments, especially related to pharmacological clinical trial studies in FXS. Further, characterization of the cognitive profile of individuals with FXS has potential to influence the development of targeted interventions for parents, educators, and therapists as well as school-based interventions that utilize those areas of strength to buffer relative challenges in cognitive functioning for individuals with FXS.

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Table 1

Study	Subjects	N	Age Range	Measures	Key Findings
Kemper et al., 1988	Males and females with full mutation and IQ matched clinical sample	20	4 – 12 years	K-ABC (Kaufman Assessment Battery for Children)	Relative strength in Simultaneous processing, achievement, matrix analogies. Weakness in arithmetic
Fruend & Reiss, 1991	Males and females with full mutation	34	3 – 24 years	SB-IV (Stanford-Binet, Fourth Edition)	Weaknesses in quantitative skills and short-term memory recall for visually presented abstract stimuli for both genders. Relative strengths in verbal labeling and comprehension; deficits in spatial visualization and visual-motor coordination for males. Relative weakness in short-term memory for nonverbal, sequential material and strength on verbally based short-term memory task for sequenced information for females.
Wright-Talamante et al., 1996	Males with full mutation (fully methylated, mosaic, and partially unmethylated), females with full mutation, and clinical controls	51	Chart review -Not included	Wechsler, SB, K-ABC	IQ decline in FXS males compared to controls; No significant IQ decline in FXS females as compared to controls; IQ decline varied based on methylation status for males
Fisch et al., 1996	Males with full mutation	24	3 – 15 years	SB-IV	Declines in IQ in 75%. Declining scores due to relative inability to keep pace with age-normed peers
Tassone et al., 1999	Males with full mutation (fully methylated, mosaic, and partially unmethylated), females with full mutation, permutation, and normal controls	80	1 – 60 years	Leiter, Wechsler, K-ABC, SB	FMRP expression correlated with IQ in mosaic males, partially methylated full mutation males, and full mutation females
Backes et al., 2000	Males with full mutation and controls with tuberous sclerosis	49	5 – 16 years	K-ABC, CBC (Child Behavior Checklist), Clinical interview	FXS profile-strengths in acquired knowledge and simultaneous processing
Bennetto et al., 2001	Females with full mutation and permutation/ FXS family member controls	165	8 – 45 years	WAIS-R (Wechsler Adult Intelligence Scale, Revised)	Significantly lower IQ revealed for women with FXS; relative weakness on Arithmetic, subtest; Relative strength on Picture Completion subtest
Fisch, Simensen, & Schroer, 2002	Males with full mutation and age-matched peers with ASD		2 – 18 years	SB-IV	IQ lower in FXS; steeper decline, did not stabilize over time
Kogan et al., 2009	Males with full mutation and mental age matched cohort with DS	15	11 – 23 years	Modified Wisconsin General Apparatus Test	Limitations in object discrimination learning and reversal tasks; strengths in egocentric spatial learning and reversal tasks; poor visual-working memory
Fisch et al., 2010	Males and females with full mutation, Williams-Beuren Syndrome, and Neurofibromatosis Type 1	65	4 – 16 years	SB-IV VAB (Vineland Adaptive Behavior Scales)	Longitudinal decline in IQ in FXS; lower in males; Significant DQ decline in FXS not significantly lower in females than males
Van der Molen et al., 2010	Males with full mutation	43	18 – 48 years	Snijders and Oomen Non-Verbal Intelligence Test (SON), PPVT (Peabody Picture Vocabulary Test); TVK (Talltest voor Kinderen); RAKIT (Revised Amsterdam Children Intelligence Test); CANTAB	Weakness on measures of reasoning-and performance abilities confined to abstract item content, relatively strong on measures of visuo-perceptual recognition and vocabulary. Significant weakness for verbal short-term memory. Suggested a fundamental deficit in executive control.