Differential Impact of the FMR-1 Full Mutation on Memory and Attention Functioning: A Neuropsychological Perspective

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Abstract

■ Memory and attention processing were examined in a group of 15 adult Fragile-X syndrome (FXS) males with Fragile-X mental retardation 1 (FMR-1) full mutation and compared to two control groups: a learning disabled (LD) control and a normal functioning control. Performance was assessed across a wide range of tasks including working memory, recognition memory, selective attention, sustained attention, and attentional switching. All three groups performed at a comparable level on recognition memory tasks, and the Fragile-X males and LD control group performed worse than the control group on tasks of working memory and sustained attention. On a task of executive function, the Fragile-X males demonstrated a significant deficit in comparison to the LD control group and the normal control group, but performed better than the LD control group and at a comparable level to the control group on tasks of selective attention. Molecular analyses of the lymphocyte DNA provided little evidence for a correlation between expansion size and performance on tasks of memory and attention. The findings from the present study are discussed in the context of functional neuroimaging and brain–behavior–molecular correlates. ■

INTRODUCTION

Fragile-X syndrome (FXS) represents the most common inherited cause of intellectual disabilities in males, with an estimated incidence of 1 in 4,000 live births (Turner, Webb, Wake, & Robinson, 1996), somewhat lower than earlier prevalence estimates of 1 per 1,500. The syndrome is associated with an X chromosome fragile site at Xq27.3 and involves the abnormal amplification of a small DNA fragment, containing a repeat of the trinucleotide CGG located in the promoter region of the Fragile-X mental retardation 1 (FMR-1) gene (Fu et al., 1991; Verkerk et al., 1991). In the general population, this triple repeat region contains between 6 and 58 repeats. In individuals with the syndrome (full mutation), the region becomes greatly expanded to >200 triple repeats, the gene becomes methylated and FMR-1 mRNA fails to be transcribed. There is also the absence of detectable FMR-1 protein (FMRP), which is now thought to play a critical role in early brain development and subsequent lateralization of function. In contrast, individuals with the premutation (''normal transmitting males'' and ''carrier females'') have a triple repeat region that is somewhere between 59 and 200 repeats and although instability is emphasized as the number of CGG repeats increases, it can be carried with apparently little or no phenotypic effect in either males or females.

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The Neuropsychological Phenotype

Deficits associated with spatial performance, short-term memory, and inattention are well documented in young boys with FXS (e.g. Cornish, Munir & Cross, in press; Turk, 1998; Freund & Reiss, 1991). Specifically, these deficits include visuospatial skills, nonverbal short-term memory, and deficits in higher control processes of attention such as the ability to plan and organize information. Comparatively few studies have documented the pattern of deficit in attention and memory processes in adult males with FXS although preliminary evidence suggests that short-term (''working memory'') memory may be more severely affected in adult full mutation males compared to adult premutation males (Jakala et al., 1997). Crowe and Hay (1990) found a similar pattern of memory deficit in Fragile-X males when their performance on the Digit Span task was compared to performance of Down's Syndrome (DS) adult males. There is also some suggestion that the memory profile for Fragile-X males may be strongly determined by the nature of the material to be remembered (Maes, Fryns, Van Walleghem, & Van den Berghe, 1994) and that information presented in a meaningful context may be more accurately recalled than information presented in an abstract context (Munir, Cornish, & Wilding, 1999). There is as yet no published data that has examined the different cognitive components of attentional functioning in adult FXS males, although there is now

accumulating evidence of modularity in the organization of attention. For instance, selective attention refers to the ability to select relevant stimuli while ignoring or inhibiting irrelevant information; while divided attention refers to the ability to attend to more than one source of information simultaneously (Corbetta, Miezin, Dobmeyer, Shulman, & Peterson, 1991); and sustained attention refers to maintaining information over a period of time (Posner & Dehaene, 1994). Neuroanatomic studies suggest these different aspects of attention are subserved by different regions of the brain (Corbetta et al., 1991). Preliminary findings by Munir, Cornish, and Wilding (1998) suggest that young Fragile-X boys have a specific pattern of deficit in attention processing and executive functioning (i.e., attentional switching, inhibiting and manipulating mental representation of tasks and goals).

Identifying why these specific cognitive processes should be especially affected in FXS is still unknown. One possible explanation is that Fragile-X males have abnormalities within those brain regions that mediate cognitive functions typically impaired in the disorder. Evidence from in vivo magnetic resonance imaging (MRI) studies of full-mutation Fragile-X males and females have reported deviations in the size of the cerebellar vermis, fourth ventricle, and right and left hippocampal volumes (Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Reiss, Lee, & Freund, 1994). Minor abnormalities in temporal lobe structures have also been reported (Jakala et al., 1997) and in a recent study of seven Fragile-X males using single photon emission computerized tomography (SPECT), the most frequent finding was a hypofusion of the inferior of the frontal lobes (Guerreiro et al., 1998).

The extent to which the neuropsychological deficits can be explained at a molecular level has also received considerable attention, although the findings remain controversial. While correlations between intellectual level and the number of CGG triple repeat length in the FMR-1 gene have been reported (Rousseau, Heitz, Tarlton, Macpherson, & Mamgren, 1994; Loesch, Huggins, & Chin, 1993), the findings are not consistent (Fisch et al., 1996; Baumgardner, Reiss, Freund, & Abrams, 1995). Recent evidence is more indicative of a task-specific rather than global affect upon cognitive performance of CGG repeat length in males and females with the full mutation (Cornish, Munir, & Cross, 1998, 1999; Jakala et al., 1997).

The Present Study

The main objectives of the study were twofold: first, to determine the nature of impairment on a range of traditional memory and attention tasks in adult males with the FMR-1 full mutation. The comparison groups chosen for this study were adult males with DS (LD) (trisomy 21) matched with the FXS group for chronological age (CA) and mental age (MA). This LD group was specifically included because DS represents a distinct chromosome abnormality other than FXS; and because both disorders represent two of the most common causes of mental retardation for which etiology is known. A normal comparison group matched as closely as possible on the intellectual level was included to establish baseline data. Tasks tapped two components of memory (working memory and recognition memory) and three components of attention (selective attention, sustained attention, and executive function). The second objective was to examine the extent to which molecular characteristics of the FMR-1 mutation, specifically CGG repeat length, predict the pattern of memory and attention performance in males with FXS.

RESULTS

Table 1 provides a summary of findings across the four groups.

Verbal mental age (VMA) did not differ significantly between the groups [$F(2, 44) = 1.70$; *ns*), with all groups performing at a comparable level. A multivariate analysis of variance (MANOVA) was performed across the three subject groups and across tasks. There was a significant main effect of group ($F = 22.51$; $df = 2$; $p < .0001$) with the normal control group performing better than the LD groups. There was also a significant group by task interaction ($F = 20.01$; $df = 14$; $p < .0001$) indicating that any differences between the subject groups were task-specific. In order to explore these interactions further, nine separate MANOVAs, one for each task, was performed across the groups. To reduce the likelihood of Type I errors, the Bonferroni correction test was applied where only those results meeting an alpha level of $0.05/9 = 0.005$ were considered statistically significant.

Performance differed significantly between the subject groups on all attention tasks: Elevator Counting task ($F = 7.11$; $df = 2$; $p < .002$); Map Search task: Map 1 ($F = 18.59$; $df = 2.42$; $p < .0001$), Map 2 ($F = 23.05$; $df = 2$; $p < .0001$), and Map 3 ($F = 27.62$; $df = 2.39$; $p < .0001$); and the WCST ($F = 11.97$; $df = 2$; $p < .0001$). On the memory tasks, performance differed significantly between groups on the Digit Span task ($F = 15.31$; $df = 2$; $p < .0001$) and on the Spatial Memory task ($F = 18.52$; $df = 2$; $p < .0001$). There was no significant differences on the Recognition Memory for Pictures task ($F = 2.87$; $df = 2.42$; *ns*) and on the Recognition Memory for Faces task ($F = 1.60$; $df = 2$; *ns*). Post hoc Newman–Keuls tests revealed that on a task of selective attention, the LD control group performed significantly poorer than the FXS group and the normal control group. In contrast, on a task of executive function, the FXS group made significantly more perseverative errors compared to the LD control group and the normal controls. On tasks of working memory and sustained attention, both

Table 1. Comparison of Participants with FXS, DS (LD), and Normal Controls (NC)

Neuropsychological Measures	*FXS*	*LD Control*	*NC*	*Significance Tests (unadjusted alpha)*	*Post hoc Test*
Memory					
Digit Span	5.66 (3.10)	6.86 (6.33)	15.66 (6.14)	$p < .0001$	NC > LD, FXS
Spatial Memory	7.27 (3.57)	4.26 (2.08)	11.66 (4.06)	$p < .0001$	NC > LD, FXS
Memory for Pictures	7.20 (4.50)	7.66 (3.61)	9.93 (0.25)	*ns*	
Memory for Faces	3.80 (2.04)	3.80 (2.04)	4.40 (0.73)	*ns*	
Selective Attention					
Map Search I	30.07 (14.04)	13.06 (5.06)	31.80 (3.77)	$p < .001$	LD < FXS, NC
Map Search II	23.40 (5.86)	13.60 (5.76)	25.53 (5.76)	$p < .001$	LD < FXS, NC
Map Search III	53.46 (17.15)	27.46 (9.74)	57.13 (6.06)	$p < .0001$	LD < FXS, NC
Sustained Attention (Vigilance)					
Elevator Counting	3.35 (2.87)	3.60 (3.29)	6.53 (0.74)	$p < .002$	NC > LD, FXS
Executive Function					
WCST	13.40 (7.65)	9.26 (4.25)	4.33 (0.90)	$p < .0001$	FXS, LD < NC; FXS < LD

FXS = Fragile-X syndrome; DS (LD) = Down's syndrome (learning disabled).

the FXS group and the LD control group performed at a comparable level but were significantly poorer than the normal controls.

Cognitive–Molecular Correlations

Table 2 summarizes the standard regression coefficients (β) corresponding to the correlations between chronological age (CA), mental age (MA), and CGG repeat length, and task performance on the Fragile-X groups and control groups.

The variance in cognitive performance across each of the cognitive tasks that can be predicted from CA and MA was determined by regression analysis. The independent contributions of CA, MA, and CGG repeat length to cognitive performance in the FXS group was determined by stepwise analysis. In the FXS group, analysis revealed that FMR-1 repeat length did correlate with specific cognitive skills, namely those that involved recognition memory (Recognition for Pictures task, $p < .05$) with a trend towards significance on tasks that involved selective attention (Map Search task (2), $p < .07$) and vigilance (Elevator Counting task, $p < .061$). The direction of all these correlations indicated that performance improved as the number of CGG repeats increased. The unexpected direction of these findings would suggest a chance occurrence and indeed, a Bonferroni correction would have nullified the results. There were no other significant correlations (see Table 2).

DISCUSSION

This paper presents results from a study of task performance on a range of memory- and attention-processing measures in adult males with FXS and two control groups. The findings indicate a task-specific rather than global deficit in memory and attention skills with greatest impairment on a task that requires the ability to switch attention set from a previously reinforced stimulus pattern to a new one. In contrast to the LD controls and normal controls, FXS males displayed significant perseverative impairments on the Wisconsin Card Sorting Task (WCST), failing due to a tendency to continue to sort along the previously correct set. Marked impairment on this task is typically associated with executive dysfunction, and reflects an inability to effectively generate and coordinate successful performance on complex tasks. Interestingly, research by Mazzocco, Pennington, and Hagerman (1993) report a similar deficit in executive function in adult females with Fragile-X. The present study therefore extends this finding to include adult males. In contrast, deficits on measures of sustained attention (Elevator Counting task) and working memory (Digit Span task and Spatial Memory task) were not specific to FXS, their performance being comparable to

Table 2. Correlations of Neuropsychological and Molecular Characteristics by Participant Group

Dependent Variable	*Independent Variable*	*Fragile-X Syndrome (FXS)*		*Learning disabled Controls (LD)*		*Normal Controls (NC)*	
		β	*p*	β	*p*	β	*p*
Memory							
Digit Span	CA	−.183	*ns*	295	*ns*	.140	*ns*
	MA	.932	< .001	.643	< .005	.464	*ns*
	Repeat length	−.004	*ns*				
Spatial Memory	CA	.101	*ns*	−.047	*ns*	.334	*ns*
	MA	−.196	*ns*	−.521	*ns*	.277	*ns*
	Repeat length	−.231	*ns*				
Recognition for Pictures	CA	−.240	*ns*	.204	*ns*	.502	*ns*
	MA	.783	< .001	.223	*ns*	.107	*ns*
	Repeat length	.506	< .05				
Recognition for Faces	CA	−.002	*ns*	.145	*ns*	.183	*ns*
	MA	.627	< .01	.256	*ns*	.273	*ns*
	Repeat length	.445	*ns*				
Selective Attention							
Map Search 1	CA	−.189	*ns*	.081	*ns*	.227	*ns*
	MA	.545	< .03	.160	*ns*	.453	*ns*
	Repeat length	.349	*ns*				
Map Search 2	CA	−.054	*ns*	.182	*ns*	.026	*ns*
	MA	.474	*ns*	.037	*ns*	.556	< .05
	Repeat length	.476	< .07				
Map Search 3	CA	.136	*ns*	.153	*ns*	.149	*ns*
	MA	.609	< .03	.105	*ns*	.599	< .05
	Repeat length	.241	*ns*				
Sustained Attention (Vigilance)							
Elevator Counting	CA	−.116	*ns*	.596	< .02	.569	< .02
	MA	.873	< .001	.193	*ns*	.603	< .02
	Repeat length	.509	< .06				
Executive Function							
WCST	CA	.272	*ns*	−.520	*ns*	.056	*ns*
	MA	.625	< .01	.041	*ns*	.063	*ns*
	Repeat length	.073	*ns*				

CA = chronological age; MA = mental age.

the LD controls but worse than the normal controls. The pattern of deficit may well indicate a generalized attentional delay across tasks that specifically involve the holding of information for a short time span (in the order of seconds), irrespective of mode of input (i.e., verbal or visuospatial). Using the working memory model developed by Baddeley (1986, 1990) in which short-term processing of information is divided into a three-unit system: the central executive, which is assumed to be an attentional controlling system of limited capacity, and its two slave systems: the phonological loop, which stores and rehearses verbal information and whose capacity is limited by the speed at which the articulation can be performed, and the visual–spatial sketch pad, which processes and manipulates visual and spatial information. It could be argued that impairment to the central executive underlies the deficits in working memory and that these impairments result from the generalized effects of mental retardation on brain development, possibly in regions involved in sustained attention, rather than from a specific genetic mechanism. The failure of the present study to find any group differences on tasks of recognition memory and selective attention (parallel search) serves further to support a hypothesis of differential impact on cognitive performance in FXS.

The extent to which the profile of attention and memory skills found in FXS males in the present study can be predicted by the molecular characteristics of the FMR-1 full mutation (CGG repeat length) was also addressed. Overall, our findings do not confirm a link between number of CGG repeats and performance on tasks of working memory, selective attention, sustained attention, and executive function. This finding even extended to tasks which FXS males performed weakest on. To some extent, the absence of a relationship is not surprising given the failure of recent studies to confirm an association between repeat length and performance on other finely tuned aspects of cognitive functioning (Cornish et al., 1998, 1999). It is interesting that on more global measures of intellectual ability such as standardized IQ tests (i.e., WAIS), studies have reported a significant association with repeat length (Jakala et al., 1997; Rousseau et al., 1994). One explanation for this discrepancy could be that repeat length may be a predictor of overall intellectual functioning but not a predictor of specific cognitive deficits (i.e., executive dysfunction), which instead result from methylation and inactivation of the FMR-1 gene once a threshold expansion of 200 repeats has been reached.

The present findings suggest that if there is a molecular basis underpinning the attention deficits, the effect is selective and is not generalized to all aspects of attention functioning. This is consistent with recent neuroimaging studies that have indicated that the FMR-1 mutations affect the growth and development of specific brain regions (e.g., Guerreiro et al., 1998; Jakala et al., 1997; Reiss et al., 1994). These findings are also consistent with a hypothesis of modularity of cognitive systems within brain organization with differing aspects of attention and memory processing subserved by different regions of the brain. In addition to highlighting the importance of teasing out cognitive components of tasks, the present study also adds to the wider picture of distinct patterns of neuropsychological functioning associated with specifically genetically disordered syndrome groups. Future studies might extend these findings to include genetic disorders for which profiles are emerging, as well as bring together findings from functional neuroimaging, molecular genetics, and neuropsychology as a means of determining the process of the brain–behaviour–molecular correlates.

METHODS

Participants

Participants were 15 adult males with FXS (FMR-1 full mutation) (age range 18–28 years; mean age 23.4 years); 15 adult males with learning disabilities (DS males—age range 18–27 years; mean age 24.1 years); and 15 control males (NC) matched on VMA and therefore, biologically younger than the Fragile-X group (age range 12–15 years; mean age 13.41 years). All participants were classified as right-handed as measured by the McManus et al. (1988) hand preference battery.

All participants with FXS and participants with DS were recruited from UK parent support groups and all were currently living within home environments. None were living in institutional settings and none were receiving medication.

Molecular analysis of the Fragile-X males were performed on DNA extracted from a 10-ml peripheral blood sample. Genotyping was by hybridization with the probe OX1.9 on Southern blots of *Eco*RI+*Eag*I double digests of lymphocyte DNA. The process reveals the size of the CGG expansions and the methylation status. Where expansions were detected as smears or multiple bands, the largest and smallest methylated expansions were recorded, as well as the average (the midpoint of the smear, or the band, which represented the most prevalent expansion size). All males were classified as fully methylated with the full mutation.

In all cases, a letter explaining the research, together with a consent form, was sent to parents of participants. To allow for the possible effect of higher verbal skills than nonverbal skills in individuals with FXS, intellectual level was assessed using the British Picture Vocabulary Scales (Dunn, Dunn, Whetton, & Pintilie, 1982) that produces a VMA for each participant.

Measures

The measures chosen for this study assessed the varying cognitive demands of attention and memory

processing. All were taken from the neuropsychological literature.

Assessment of Memory Skills

Working Memory

The Spatial Memory task (Kaufman & Kaufman, 1983; K-ABC) requires the immediate recall of visually presented objects arranged randomly on a page. The total number of correctly recalled object locations was taken as the total correct score, with a maximum score of 21.

The Digit Span task (Weschler, 1992; WISC-III-R) requires the immediate recall of increasingly longer sequences of digits presented auditory. The total number of correct trials was taken as the total correct score, with a maximum score of 16.

Recognition Memory

The Picture Recognition task (Wilson, Cockburn, & Baddeley, 1985; RBMT) requires recall of 10 visually presented picture of objects from 10 distracters after a filled delay. Each picture was presented one at a time in a specified order. The total number of correctly recognized pictures was taken as the total correct score, with a maximum score of 10.

The Face Recognition task (Wilson et al., 1985; RBMT) requires recall of five visually presented photographs of faces from five distracters The total number of correctly recognized faces was taken as the total correct score, with a maximum score of 5.

Assessment of Attention Skills

Selective Attention

The Map Search task (Robertson, Ward, Rideway, & Nimmo-Smith, 1994; TEA) is a timed, visual search task that requires searching a map (Philadelphia area, US) for a total of 2 min for symbols of knives and forks paired together (version A) and circling them with a pen. After 1 min, participants were given a different colored pen to enable targets located in 1 min versus 2 min to be counted. Three scores were recorded: the total number of correctly circled symbols in the first minute (Map1), the total number of correctly circled symbols in the second minute (Map2), and the combined total number (Map3), with a maximum score of 80.

Sustained Attention

The Elevator Counting task (Robertson et al., 1994; TEA) requires each participant to silently count a series of monotones heard on an audiotape. The task consists of a scenario where the participant imagines he is travelling in an elevator and each floor he passes a tone is heard, which has to be counted in order to find out which floor the elevator stops. Participants were asked to report the number at the end of each trial. There are seven trials in total with a maximum score of 7.

Executive Function

The WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) requires the development of appropriate problem-solving strategies across changing stimulus conditions. In the shortened version of the task, there are a total of 64 cards, each containing geometrical figures that may vary according to three features: color, number, and form. Each participant is instructed to match each card with one of four target cards without being informed of the correct criterion. The only information they are told is whether they have decided correctly or incorrectly. When 10 consecutive cards have been arranged correctly, the criterion is changed without informing the participant. The task proceeds until three rating categories have been successfully completed, or all 64 cards have been sorted. The number of perseverative errors was obtained for the analysis.

Each participant was tested individually in a quiet, private room. The battery took approximately 1 hr to complete and was administered in one session.

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