Brain and Cognition 69 (2009) 551–558

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Lifespan changes in working memory in fragile X premutation males

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ARTICLE INFO

Article history:
Accepted 20 November 2008
Available online 27 December 2008

Keywords:
Fragile X syndrome
Fragile X tremor and ataxia syndrome
Premutation status
Working memory
Central executive
Phonological loop
Visual–spatial sketchpad
Development
Aging

ABSTRACT

Fragile X syndrome is the world's most common hereditary cause of developmental delay in males and is now well characterized at the biological, brain and cognitive levels. The disorder is caused by the silencing of a single gene on the X chromosome, the *FMR1* gene. The premutation (carrier) status, however, is less well documented but has an emerging literature that highlights a more subtle profile of executive cognitive deficiencies that mirror those reported in fully affected males. Rarely, however, has the issue of age-related declines in cognitive performance in premutation males been addressed. In the present study, we focus specifically on the cognitive domain of working memory and its subcomponents (verbal, spatial and central executive memory) and explore performance across a broad sample of premutation males aged 18–69 years matched on age and IQ to unaffected comparison males. We further tease apart the premutation status into those males with symptoms of the newly identified neurodegenerative disorder, the fragile X-associated tremor/ataxia syndrome (FXTAS) and those males currently symptom-free. Our findings indicate a specific vulnerability in premutation males on tasks that require simultaneous manipulation and storage of new information, so-called executive control of memory. Furthermore, this vulnerability appears to exist regardless of the presence of FXTAS symptoms. Males with FXTAS symptoms demonstrated a more general impairment encompassing phonological working memory in addition to central executive working memory. Among asymptomatic premutation males, we observed the novel finding of a relationship between increased CGG repeat size and impairment to central executive working memory.

1. Introduction

Fragile X syndrome (FXS) has been a well-recognized common genetic cause of developmental disabilities for over 25 years. Previously known as the Martin-Bell syndrome, FXS represents the world's most common form of inherited intellectual disability, with most recent estimates suggesting that 1 in 2500 are affected (Crawford et al., 2002; Hagerman, 2008; Kooy, Willemsen, & Oostra, 2000; Turner, Webb, Wake, & Robinson, 1996). By virtue of its single gene etiology, fragile X represents an important model for understanding the impact of early gene expression on the development and normal functioning of the central nervous system. The syndrome is caused by a defect in the fragile X mental retardation 1 gene (*FMR1*), located near the end of the long arm of the X chromosome. The *FMR1* gene carries a CGG trinucleotide repeat in the 5′ untranslated region and abnormal expansion above a threshold of 200 CGG repeats in males is almost always associated with intellectual impairment. In unaffected individuals there are between 7 and 54 repeats, with 30 repeats found on the most common allele. In fully affected individuals the CGG regions expands to over 200 repeats resulting in the loss of the encoded protein, the fragile X mental retardation protein—FMRP. When the CGG repeats expand to between 55 and 200 an individual is referred to as carrying a "premutation". Both males and females can be carriers of the premutation. At the molecular level, individuals with premutation alleles actually produce increased levels of *FMR1* mRNA (Tassone, Hagerman, Chamberlain, & Hagerman, 2000; Tassone, Hagerman, Taylor et al., 2000). These *FMR1* mRNA levels range from 2 to 10 times normal levels and increase with increasing CGG repeat size over the premutation range (Tassone, Hagerman, Taylor et al., 2000). In the majority of individuals with

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doi:10.1016/j.bandc.2008.11.006

the premutation, FMRP levels are within normal limits (Tassone, Hagerman, Chamberlain et al., 2000). At the cognitive level, it was initially assumed fragile X carriers were indistinguishable from those who were unaffected. However, there is now converging evidence to suggest that there are identifiable cognitive strengths and weaknesses in this population that mirror the 'signature' of individuals with the full mutation who are cognitively impaired (see Cornish, Hagerman, & Turk, 2008 for a review). What is especially significant about these new findings is that impairments occur in the absence of intellectual disability (Cornish et al., 2005; Cornish, Li et al., 2008; Grigsby, Brega et al., 2006; Loesch et al., 2003; Moore et al., 2004). Furthermore, the recent discovery of an additional premutation 'signature', known as, fragile X tremor and ataxia syndrome (FXTAS) (Hagerman & Hagerman, 2007; Hagerman et al., 2001; Jacquemont et al., 2003), suggests that the premutation, at least in males, may well diverge into two dissociable pathways: one that leads to FXTAS and one that results in a milder phenotype (Cornish, Li et al., 2008; Hay, 2008). It is possible that the former effect can be related to the toxicity of increased levels of mRNA that can cause cell death and brain atrophy over time, and eventually the full clinical picture of FXTAS. The latter effect may be primarily related to the mild reduction in FMRP level associated with the premutation condition, which results in a subtle yet measurable fragile X phenotype including inhibition and attentional problems. The specific timing of when the impact of these molecular events becomes measurable at a behavioral level is hitherto unknown.

Because of the variability in CGG repeat length in this population, it is also possible to examine correlations between repeat length and cognitive performance to infer gene–behavior relationships. Several studies have begun to explore potential relationships between subthreshold repeat length and degree of cognitive impairment. An initial study examining cognitive performance in 14 female premutation carriers revealed that these participants had Full Scale IQs within the average range (Allingham-Hawkins et al., 1996). Further analysis of the potential correlation between CGG repeat length and measures of cognitive ability similarly indicated no significant impairment. (Johnston et al., 2001) also examined the relationship between IQ and expansion size in 85 female premutation carriers (Johnston et al., 2001). Consistent with the earlier study, there were no significant correlations between expansion size and IQ. In contrast, results of the proportion of fibroblasts expressing the unaffected *FMR1* gene as the active form were positively correlated with Full Scale IQ. A more recent study examining both male and female premutation carriers examined IQ scores in 66 males and 217 females with a range of CGG repeat expansions (Allen et al., 2005). Only a nominal amount of the variance (4%) in Verbal IQ scores could be explained by the CGG repeat length and only in female carriers.

Rather than focusing on general measures of cognition, which may mask domain-specific impairments, other studies have examined specific cognitive functions that are known to be impaired in individuals with the full mutation. These include: cognitive inattention, visual–spatial processing, social cognition and executive cognitive functioning (e.g. Cornish et al., 2005; Cornish, Li et al., 2008; Grigsby et al., 2008). For example, Cornish et al. (2005) investigated aspects of social cognition in premutation male carriers and found the performance of premutation males compared to comparison males matched on chronological age and IQ was significantly poorer on measures that required recognition of complex emotions. This relative impairment was found to be over and above that which might be anticipated on the basis of IQ scores. However, the authors found no correlation between CGG repeat length and social cognitive measures. The one cognitive domain that does appear to show sensitivity to CGG repeat length is the domain of inhibition where larger repeat sizes correlate with greater impairment (Cornish, Li et al., 2008). The authors speculated that increasingly large mRNA transcripts of the *FMR1* gene may damage highly susceptible neural networks, in particular, those associated with the right inferior frontal cortex. Intriguingly, this study was also the first to demonstrate an important trajectory of cognitive deficit in premutation carrier males that appears to begin early in adulthood and become progressively more severe across the lifespan. Furthermore, when one differentiates premutation males with and without FXTAS symptoms the inhibition deficit is more pronounced in those males with FXTAS symptoms suggesting that the disruption of inhibitory control may serve as a useful neurological soft sign preceding more generalized and profound effects associated with FXTAS (i.e., brain atrophy, ataxia, peripheral neuropathy, progressive intention tremor, dementia) reported in older patients (>50 years) (Hagerman & Hagerman, 2004; Jacquemont et al., 2004; Jacquemont, Hagerman, Hagerman, & Leehey, 2007).

In sum, whereas there is little evidence to suggest that measures of genetic severity correlate with general IQ scores, when specific domains of cognition are evaluated, emerging evidence demonstrates a relationship between severity of performance and CGG repeat length that is domain specific. These findings highlight the importance of selecting cognitive measures that tap known weaknesses in fragile X syndrome when studying genetic–neurocognitive relationships. The relatively high prevalence of the fragile X premutation in the general population, estimated to be 1 in 259 females (Rousseau, Rouillard, Morel, Khandjian, & Morgan, 1995) and 1 in 813 males (Dombrowski et al., 2002), highlights the necessity of investigating the effect of premutation involvement on cognitive development and functioning.

1.1. Present study

In the present study, we focus on the cognitive domain of working memory as described by Baddeley (1986). Working memory involves the temporary storage of information in mind or 'online', while processing the same or other information. Baddeley's model of working memory comprises three main components: the central executive, the phonological loop, and the visual–spatial sketchpad. More recently an episodic buffer has been added to the model (Baddeley, 2000). The central executive controls information performing complex mental operations such as planning, manipulation, and organization. It is a limited-capacity system involved in regulatory control of working memory. Two 'slave systems', the phonological loop and the visuo-spatial sketchpad are limited-capacity, material specific stores that are involved in the maintenance of verbal and visuo-spatial materials, respectively. Both stores are subject to rapid decay. At the brain level, an increasing body of neuroimaging findings indicates dissociations between working memory tasks that employ maintenance (corresponding to the phonological and visuo-spatial components) and those that employ manipulation (corresponding to the central executive component). In the former, a network of parietal, dorsal premotor and the ventral lateral frontal regions, lateralized to the left for verbal tasks and to the right for spatial tasks, have consistently been implicated (Wager & Smith, 2003; Henson, Burgess, & Frith, 2000). In the latter, the dorsal and ventral lateral prefrontal cortex, anterior prefrontal cortex, the bilateral premotor, and the lateral and medial superior parietal cortices have been implicated (D'Esposito et al., 1999; Wager & Smith, 2003).

Disruptions to one or more of these working memory components has been extensively documented across a wide range of neurodevelopmental disorders including Down syndrome (Brock & Jarrold, 2005; Jarrold, Baddeley, & Hewes, 1999; Vicari, Bellucci, & Carlesimo, 2006), William syndrome (Devenny et al., 2004; Vicari, Bellucci, & Carlesimo, 2003), and fragile X syndrome (Cornish, Munir, & Cross, 2001; Hooper et al., 2008; Jakala et al., 1997; Lan-