CORTEX 44 (2008) 628–636

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/cortex

Research report

Age-dependent cognitive changes in carriers of the fragile X syndrome

Kim M. Cornish[a,b,*], Lexin Li[c], Cary S. Kogan[d], Sebastien Jacquemont[e], Jeremy Turk[f], Ann Dalton[g], Randi J. Hagerman[h,i] and Paul J. Hagerman[i,j]

[a]Neuroscience Laboratory for Research and Education in Developmental Disorders, McGill University, Montreal, Canada
[b]Department of Neurology and Neurosurgery, McGill University, Montreal, Canada
[c]Department of Statistics, North Carolina State University, Raleigh, USA
[d]School of Psychology, University of Ottawa, Ottawa, Canada
[e]Service de génétique médicale, CHU de Nantes, Nantes, France
[f]Department of Clinical Developmental Sciences, St George's Hospital Medical School, London, UK
[g]Sheffield Molecular Genetics Service, Sheffield Children's NHS Trust, Sheffield, UK
[h]Department of Pediatrics, University of California at Davis, School of Medicine, Sacramento, CA, USA
[i]M.I.N.D. Institute, UC Davis Health System, Sacramento, CA, USA
[j]Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis, CA, USA

ARTICLE INFO

Article history:
Received 27 April 2006
Reviewed 26 June 2006
Accepted 20 November 2006
Action editor Mike Anderson
Published online 23 December 2007

Keywords:
Fragile X syndrome
Fragile X permutation
Fragile X-associated tremor/ataxia syndrome (FXTAS)
Cognition
Attention

ABSTRACT

Fragile X syndrome is a neurodevelopmental disorder that is caused by the silencing of a single gene on the X chromosome, the fragile X mental retardation 1 (*FMR1*) gene. Affected individuals display a unique neurocognitive phenotype that includes significant impairment in inhibitory control, selective attention, working memory, and visual–spatial cognition. In contrast, little is known about the trajectory and specificity of any cognitive impairment associated with the fragile X premutation (i.e., "carrier status") or its relationship with the recently identified neurodegenerative disorder, fragile X-associated tremor/ataxia syndrome (FXTAS). In the present study, we evaluated a broad sample of 40 premutation males (PM) aged 18–69 years matched on age and IQ to 67 unaffected comparison males (NC). Performance was compared across a range of cognitive domains known to be impaired in fragile X syndrome (i.e., "full mutation"). Tremor was also assessed using a self-report neurological questionnaire. PM displayed statistically significant deficits in their ability to inhibit prepotent responses, differentiating them from NC from age 30 onwards. With increasing age, the two groups follow different trajectories, with PM developing progressively more severe problems in inhibitory control. This deficit also has a strong co-occurrence in males displaying FXTAS-related symptomatology ($p < .001$). Selective attention was also impaired in PM but did not show any disproportionate aging effect. No other cognitive deficits were observed. We conclude that an inhibitory deficit and its impact across the lifespan are specifically associated with the fragile X premutation status, and may be a precursor for development of a more severe form of cognitive impairment or dementia, which has been reported in patients with the diagnosis of FXTAS.

* *Corresponding author*. Neuroscience Laboratory for Research and Education in Developmental Disorders, 3700 McTavish Street, Montreal, Quebec H3A-1Y2, Canada.
E-mail address: kim.cornish@mcgill.ca (K.M. Cornish).
0010-9452/$ – see front matter
doi:10.1016/j.cortex.2006.11.002

1. Introduction

Fragile X syndrome is the most common hereditary cause of developmental delay in males affecting one in 4000 live births (de Vries et al., 1998; Kooy et al., 2000; Turner et al., 1996). The syndrome is caused by a defect in the fragile X mental retardation 1 (*FMR1*) gene, located near the end of the long arm of the X chromosome. The *FMR1* gene carries a CGG trinucleotide repeat region that in unaffected individuals is usually in the range of 7–60 repeats. However, in fragile X syndrome there is an expansion of these repeats to over 200, known as the *full mutation*. At this so-called threshold level, the *FMR1* gene is no longer transcribed, resulting in a lack of the encoded protein, the fragile X mental retardation protein (FMRP). It is the absence of FMRP during early brain development that results in the characteristic cognitive phenotype associated with this syndrome.

Until recently, individuals who carry *FMR1* allele expansions with between 55 and ~200 repeats, classified as *premutation* for fragile X syndrome (i.e., *carrier status*), were generally thought to be free from phenotypic effects. However, apparently premutations can be unstable across successive generations eventually giving rise to the fragile X full mutation with further expansion past threshold (O'Donnell and Warren, 2002). Both males and females can be carriers of fragile X syndrome. The absence of observable phenotypic differences in carriers of fragile X stands in marked contrast the effects of the full mutation (>200 repeats), which results in the moderate to severe mental retardation characteristic of fragile X syndrome. However, more recent molecular data demonstrate that the moderately expanded CGG repeat region of the gene that occurs in premutation alleles, results in both elevated *FMR1* mRNA levels and slight to moderate reductions in FMRP levels (Tassone et al., 2000a, 2000b). The high prevalence of the fragile X premutation in the general population, estimated to be one in 259 females (Rousseau et al., 1995) and one in 813 males (Dombrowski et al., 2002), highlights the necessity of investigating the effect of this condition on cognitive development and functioning. Importantly, there is some evidence that clinically affected carriers display some of the same physical and emotional features typically associated with fragile X syndrome (Hagerman and Hagerman, 2002; Johnston et al., 2001), albeit with far less severity.

One example of the emerging phenotype in carriers of fragile X syndrome is the identification of a novel neurodegenerative disorder, the fragile X-associated tremor/ataxia syndrome (FXTAS), recently identified within a subgroup of older male carriers (>50 years) (Hagerman et al., 2001; Leehey et al., 2003 but see Kogan et al., 2007). FXTAS is specifically associated with the fragile X carrier status and results in striking neuropathology that includes generalized brain atrophy; white matter disease, particularly associated with the middle cerebellar peduncles (MCPs) (Brunberg et al., 2002) as well as eosinophilic intranuclear inclusion bodies in neurons and astroglial cells in broad distribution throughout the CNS (Greco et al., 2002; Hagerman et al., 2003). It is important to note that FXTAS is associated only with carriers of fragile X and then only within a subset of carrier males' aged 50 and over. To date, there is no evidence to suggest that FXTAS is associated with the fragile X full mutation.

The pathogenic mechanism of FXTAS is believed to be a toxic "gain of function" resulting from the elevated, abnormally large *FMR1* mRNA. Specifically it is thought to result from sequestration of increased amounts of proteins that normally bind to the *FMR1* mRNA (Hagerman and Hagerman, 2004). The pathologic mechanisms differ between fragile X syndrome and the premutation condition. Clinical involvement in the premutation condition might arise from two sources, lowered FMRP levels and elevated mRNA levels, with potentially dissociable effects on cognitive functioning. In contrast, clinical involvement in fragile X syndrome arises from the lack of FMRP.

To date, few studies exist that have explicitly examined the pattern of cognitive deficit that may be present in individuals with the fragile X premutation and fewer still that have delineated the premutation males (PM) cognitive phenotype (Cornish et al., 2005; Loesch et al., 2003a, 2003b). Preliminary findings from these studies suggest a neuropsychological profile that includes impairment of social cognition (Cornish et al., 2005), alongside deficits in planning of goal-directed behaviour and in executive functions (Loesch et al., 2003a, 2003b). In stark contrast, the profile of adult males with the *FMR1* full mutation, i.e., fragile X syndrome, is now well documented with substantial evidence supporting the idea that this condition is not simply characterized by global mental retardation. Rather, the fragile X neuropsychological profile can be described as comprising uneven abilities within and across cognitive domains that remain stable into adulthood. Relative strengths in vocabulary (Abbeduto et al., 2003), verbal working memory (Jakala et al., 1997), and long-term memory for meaningful and learned information (Cornish et al., 2001; Freund and Reiss, 1991) are accompanied by relative weaknesses in executive control (Cornish et al., 2001, 2007; Loesch et al., 2003a), selective and sustained attention (Cornish et al., 2001), visual working memory and visual–motor processing (Crowe and Hay, 1990; Kogan et al., 2004).

The extent to which this profile – or some variation thereof – is present in the carriers of fragile X syndrome is the focus of the present study. As discussed, previous research has demonstrated an association between ataxia/tremor and premutation carriers in older men in the form of FXTAS (Hagerman and Hagerman, 2004; Jacquemont et al., 2003). Previous publications have also reported many cases of mild to severe dementia in older males carriers of the premutation whether these patients were ascertained through neurology clinics (Van Esch et al., 2005), or through family studies of fragile X syndrome (Hagerman et al., 2001). Here, we examine aspects of cognition known to be affected in full mutation fragile X males, through a cross-section of the lifespan of PM. We raise the possibility that – as with motor control – there is a trajectory of specific and clinically important cognitive deficits that while initially subtle, progress to culminate in significant functional impairments with increasing age. We also address the extent to which potential FXTAS symptoms impact upon cognitive performance and whether there are specific weaknesses across or within cognitive domains that precede the onset of ataxia/tremor. We also explore whether individuals with the premutation allele may vary in their risk of developing more serious effects of CGG repeat expansion in