Research in Developmental Disabilities 31 (2010) 426–439

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Profiling Fragile X Syndrome in males: Strengths and weaknesses in cognitive abilities

M.J.W. Van der Molen [a,*], M. Huizinga [a], H.M. Huizenga [a], K.R. Ridderinkhof [a], M.W. Van der Molen [a], B.J.C. Hamel [b], L.M.G. Curfs [c,d], G.J.A. Ramakers [a,e]

[a] Department of Developmental Psychology, University of Amsterdam, The Netherlands
[b] Department of Clinical Genetics, University of Nijmegen, The Netherlands
[c] GROW School for Oncology and Developmental Biology, Maastricht University, The Netherlands
[d] Department of Clinical Genetics, Academic Hospital Maastricht, The Netherlands
[e] Netherlands Institute for Neuroscience, Royal Netherlands Academy of Science, The Netherlands

ARTICLE INFO

Article history:
Received 30 September 2009
Received in revised form 6 October 2009
Accepted 16 October 2009

Keywords:
Fragile X Syndrome
Cognitive profile
Model-based cluster analysis
Subgroups
Executive control

ABSTRACT

The present study examined the cognitive profile in Fragile X Syndrome (FXS) males, and investigated whether cognitive profiles are similar for FXS males at different levels of intellectual functioning. Cognitive abilities in non-verbal, verbal, memory and executive functioning domains were contrasted to both a non-verbal and verbal mental age reference. Model-based cluster analyses revealed three distinct subgroups which differed in level of functioning, but showed similar cognitive profiles. Results showed that cognitive performance is particularly weak on measures of reasoning- and performal abilities confined to abstract item content, but relatively strong on measures of visuo-perceptual recognition and vocabulary. Further, a significant weakness was found for verbal short-term memory. Finally, these results indicated that the choice of an appropriate reference is critically important in examining cognitive profiles. The pattern of findings that emerged from the current cognitive profiling of FXS males was interpreted to suggest a fundamental deficit in executive control.

1. Introduction

Fragile X Syndrome (FXS) is the most frequently reported inherited type of mental retardation in males (Turner, Webb, Wake, & Robinson, 1996), and is most often caused by transcriptional silencing of the Fragile X Mental Retardation 1 (FMR-1) gene (Fu et al., 1991; Oostra & Chiurazzi, 2001; Verkerk et al., 1991). In the FXS full mutation this single-gene defect results in reduced or absent FMR-1 protein (FMRP) expression (Koukoui & Chaudhuri, 2007). FMRP is argued to be specifically involved in synaptic and dendritical refinement during early brain development (Christie, Akins, Schwob, & Fallon, 2009). Absence of FMRP is primarily associated with abnormal maturation of synaptic connectivity (Oostra & Chiurazzi, 2001), and is argued to be the primary cause of the cognitive deficits frequently observed in FXS (Loesch, Huggins, & Hagerman, 2004; Visootsak, Warren, Anido, & Graham, 2005). Although the cognitive profile of FXS males has been extensively studied over the years, little is known about the relation between performance level and cognitive profile. The goal of the present study was: (a) to examine the cognitive profile of FXS full mutation males of different performance levels over a wide range of cognitive abilities; and (b) to investigate whether such a cognitive profile would be similar for FXS males of different levels of performance.

* Corresponding author at: University of Amsterdam, Department of Psychology, Developmental Psychology Section, Roetersstraat 15, 1018 WB Amsterdam, The Netherlands. Tel.: +31 20 525 6828; fax: +31 20 639 0279.
E-mail address: M.J.W.vanderMolen@uva.nl (M.J.W. Van der Molen).

0891-4222/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ridd.2009.10.013

Over the years, the neuropsychological phenotype of full mutation FXS has been well documented and is characterized by a general impairment in cognitive performance, with some cognitive abilities more strongly affected than others (Cornish, Turk, & Hagerman, 2008; Hodapp, Dykens, Ort, Zelinsky, & Leckman, 1991; Maes, Fryns, Van Walleghem, & Van den Berghe, 1994). Relative strengths in cognitive performance are frequently reported for vocabulary capacity (Dykens, Hodapp, & Leckman, 1987; Maes et al., 1994; Philofsky, Hepburn, Hayes, Hagerman, & Rogers, 2004), visuo-perceptual abilities (Cornish, Munir, & Cross, 1999; Hodapp et al., 1992; Maes et al., 1994), and the processing and recall of simultaneous and meaningful information (Backes et al., 2000; Dykens et al., 1987; Freund & Reiss, 1991; Maes et al., 1994; Munir, Cornish, & Wilding, 2000a; Powell, Houghton, & Douglas, 1997). In contrast, consistent deficits have been reported for verbal short-term memory (Freund & Reiss, 1991; Munir et al., 2000a), visuo-spatial memory (Munir et al., 2000a), linguistic processing (Abbeduto, Brady, & Kover, 2007; Abbeduto & Hagerman, 1997; Ferrier, Bashir, Meryash, Johnston, & Wolff, 1991), selective and divided attention (Munir, Cornish, & Wilding, 2000b; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2007; Wilding, Cornish, & Munir, 2002), and the processing of sequential and abstract information (Dykens et al., 1987; Freund & Reiss, 1991; Powell et al., 1997).

Accumulating evidence suggests a fundamental deficiency in executive control (Cornish, Sudhalter, & Turk, 2004b; Cornish et al., 2004b; Wilding et al., 2002). That is, those processes that provide top-down guidance for orchestrating the more basic cognitive processes to accomplish goal-directed behavior. Executive control exerts its influence on cognition by modulating information processing in different cognitive modalities, driven by a prefrontal neural network (Miller & Cohen, 2001; Posner & Petersen, 1990; Posner & Rothbart, 2007). Importantly, deficits in executive control have their repercussions for performance across a wide range of cognitive abilities. Illustrative in this respect is that within the domain of executive function FXS males show difficulties in inhibiting pre-potent responses (Cornish, Scerif, & Karmiloff-Smith, 2007; Hooper et al., 2008; Loesch et al., 2003; Munir et al., 2000b; Wilding et al., 2002), impaired cognitive flexibility (e.g., task-switching; Cornish, Munir, & Gross, 2001; Hooper et al., 2008; Woodcock, Oliver, & Humphreys, 2009), and weak problem solving abilities (Hooper et al., 2008; Maes et al., 1994). In addition, within the domain of working memory, deficits have been attributed to a general limitation in working memory capacity (Munir et al., 2000a; Ornstein, Schaaf, Hooper, Hatton, & Mirrett, 2008). That is, the amount of attention available to maintain and manipulate information, mediated by executive control processes. Furthermore, the pattern of deficits reported for more complex verbal abilities (e.g., perseverations in speech; Abbeduto & Hagerman, 1997) and non-verbal reasoning abilities (processing of abstract information; Maes et al., 1994), seem to implicate a specific deficit for cognitive abilities relying on executive control. Together, these findings point to inefficient executive control as a core-deficit in FXS males.

The observed pattern of strengths and weaknesses in FXS cognitive functioning may suggest a specific cognitive profile for FXS. That is, the cognitive profile in FXS might well be different from cognitive profiles seen in other mental retardation syndromes (Cornish et al., 2007, 2008). However, syndrome-specificity of a cognitive profile is also determined by heterogeneity in cognitive performance levels. More specifically, FXS males functioning at higher performance levels may be characterized by a different cognitive profile compared to FXS males functioning at lower performance levels. Such differences constrain the notion of syndrome-specific cognitive profiles. For example, FXS is characterized by an increased heterogeneity in the level of intellectual functioning, corresponding to moderate-to-severe levels of mental retardation (Abbeduto et al., 2007; Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Dykens et al., 1987; Loesch et al., 2004; Mazzocco, 2000). The question arises whether high-functioning FXS males show similar or distinct strengths and weaknesses in cognitive performance relative to low-functioning FXS males.

The primary objective of the present study was to examine the relative strengths and weaknesses in a wide range of cognitive abilities in FXS full mutation males functioning at different performance levels. More specifically, we investigated whether such a cognitive profile would differ between FXS males of different performance levels. Cognitive performance was examined in a large sample of FXS males for the following cognitive domains: non-verbal (reasoning and performal) abilities, verbal abilities, memory performance, and aspects of executive function. Test results were converted into mental age (MA) equivalents, which allowed for comparing between cognitive abilities within, as well as between participants. To interpret the cognitive abilities in terms of relative strengths and weaknesses, each performance measure was contrasted to a non-verbal and verbal MA reference measure (NVMA and VMA respectively). Two reference measures were employed to avoid interpretation-bias resulting from comparison to a single reference measure. For example, reference to a single measure of intelligence can result in serious interpretation problems, as this reference or cognitive ability could reveal as a significant strength or weakness (see Mottron, 2004, for a detailed discussion on this issue).

Since full mutation males share the same genetic cause of mental retardation, we expected that FXS males functioning at different performance levels would show similar cognitive profiles. In addition, based upon previous studies on cognitive functioning in FXS males, we anticipated FXS males to be more impaired on tasks that require higher levels of executive control. Thus, specific deficits were expected for cognitive abilities relying on executive functions and working memory processes. These deficits were expected to be evident for all FXS males, regardless of cognitive performance level. In contrast, relative strengths were expected for visuo-perceptual recognition (i.e., Gestalt closure) and vocabulary.

2. Method

2.1. Participants

The present study included 43 adult males, ranging in age from 18 to 48 years (mean age = 28.7, SD = 8.5). Participants were recruited through the Dutch Fragile X Parent Network. The FXS full mutation was established by DNA testing. All