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

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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.
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 Bergh, 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
participants were free from additional diagnosed psychiatric disorders, based on DSM-IV-TR classifications (American Psychiatric Association, 2000), and had normal or corrected-to-normal vision. None of the participants were taking (prescribed) medication. Informed consent was obtained from parents or legal guardians. The protocol for this study was reviewed and approved by the ethical review committee of the university.

2.2. Measures

A test battery was assembled from neuropsychological and intelligence tests for children to assess non-verbal (reasoning and performal) abilities, verbal abilities, memory performance, and aspects of executive function. Tests were selected based upon the following criteria: (1) tests should preferably cover a wide (MA) age range to enable assessment of both higher- and lower-functioning individuals; (2) tests (with the exception of verbal measures) should preferably be independent of verbal output by the participants to enable inclusion of individuals with limited or absent speech. Raw scores were converted into MA equivalents, and, unless indicated otherwise, the variable of interest was the number of items answered correctly. A schematic overview including psychometric characteristics of the test battery is presented in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Measures administered</th>
<th>Cognitive ability assessed</th>
<th>Descriptives</th>
<th>Floor effects</th>
<th>MA (SD)</th>
<th>CA (SD)</th>
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<tr>
<td><strong>Reference measures</strong></td>
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<tr>
<td>SON-R total score</td>
<td>Non-verbal intelligence</td>
<td>0%</td>
<td>4.86 (1.32)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td>PPVT-III</td>
<td>Verbal ability</td>
<td>0%</td>
<td>7.87 (2.63)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td><strong>Non-verbal measures</strong></td>
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<td><strong>Reasoning abilities</strong></td>
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<tr>
<td>SON-R Situations</td>
<td>Concrete reasoning</td>
<td>0%</td>
<td>6.05 (2.55)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td>SON-R Analogies</td>
<td>Abstract sorting</td>
<td>0%</td>
<td>4.11 (1.15)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td>SON-R Categories</td>
<td>Concrete sorting</td>
<td>0%</td>
<td>5.23 (1.74)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<td>K-ABC Conceptual Thinking</td>
<td>Concept formation</td>
<td>0%</td>
<td>5.27 (1.59)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<td>RAKIT Picture Recognition</td>
<td>Visuo-perceptual recognition</td>
<td>0%</td>
<td>9.61 (2.60)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td><strong>Performal abilities</strong></td>
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<tr>
<td>SON-R Puzzles</td>
<td>Concrete object assembly</td>
<td>0%</td>
<td>5.53 (1.27)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td>SON-R Mosaics</td>
<td>Abstract object assembly</td>
<td>0%</td>
<td>4.27 (1.31)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td>SON-R Patterns</td>
<td>Abstract drawing (copying)</td>
<td>0%</td>
<td>4.48 (1.07)</td>
<td>28.91 (8.70)</td>
<td>43</td>
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<tr>
<td><strong>Verbal measures</strong></td>
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<tr>
<td>TvK Word Production</td>
<td>Expressive vocabulary</td>
<td>48%</td>
<td>8.21 (1.51)</td>
<td>28.03 (7.52)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>TvK Sentence Construction</td>
<td>Grammar (sentence production)</td>
<td>33%</td>
<td>6.06 (1.74)</td>
<td>28.21 (7.61)</td>
<td>29</td>
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<tr>
<td>RAKIT Production of Ideas</td>
<td>Verbal fluency</td>
<td>35%</td>
<td>6.18 (2.67)</td>
<td>28.11 (8.59)</td>
<td>28</td>
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<tr>
<td>RAKIT Telling Stories</td>
<td>Verbal association and reasoning</td>
<td>44%</td>
<td>4.75 (1.61)</td>
<td>27.04 (7.45)</td>
<td>24</td>
<td></td>
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<td><strong>Memory measures</strong></td>
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<tr>
<td>K-ABC II Number Recall</td>
<td>Verbal STM</td>
<td>30%</td>
<td>3.70 (1.16)</td>
<td>28.03 (7.52)</td>
<td>30</td>
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<tr>
<td>CANTAB Spatial Span</td>
<td>Visuo-spatial STM (sequential)</td>
<td>53%</td>
<td>5.50 (1.12)</td>
<td>27.55 (8.19)</td>
<td>20</td>
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<tr>
<td>K-ABC I Spatial Memory</td>
<td>Visuo-spatial STM (simultaneous)</td>
<td>68%</td>
<td>6.60 (1.93)</td>
<td>26.85 (7.79)</td>
<td>13</td>
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<tr>
<td>CANTAB SWM</td>
<td>Working memory (self-ordered search)</td>
<td>47%</td>
<td>5.02 (1.43)</td>
<td>26.43 (6.51)</td>
<td>23</td>
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</tr>
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<td>CANTAB SRM</td>
<td>Spatial recognition memory</td>
<td>63%</td>
<td>4.53 (0.59)</td>
<td>30.13 (8.97)</td>
<td>16</td>
<td></td>
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<tr>
<td>CANTAB PRM-I</td>
<td>Recognition memory (instant recall)</td>
<td>53%</td>
<td>5.97 (1.56)</td>
<td>25.65 (7.41)</td>
<td>20</td>
<td></td>
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<tr>
<td>CANTAB PRM-D</td>
<td>Recognition memory (delayed recall)</td>
<td>44%</td>
<td>6.42 (1.57)</td>
<td>27.79 (8.70)</td>
<td>24</td>
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<tr>
<td>RAKIT Learning Names</td>
<td>Associative learning</td>
<td>16%</td>
<td>7.38 (2.83)</td>
<td>27.89 (7.55)</td>
<td>36</td>
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<td><strong>Executive Function measures</strong></td>
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<tr>
<td>CANTAB IED</td>
<td>Cognitive flexibility</td>
<td>35%</td>
<td>7.38 (2.13)</td>
<td>27.36 (8.69)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>CANTAB SOC</td>
<td>Planning</td>
<td>63%</td>
<td>7.44 (3.61)</td>
<td>28.63 (8.25)</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Note: Abbreviations: STM = short-term memory; MA = mental age; CA = chronological age; SD = standard deviation from the mean.

1 The SON-R total score is the weighted average of performance on the six SON-R subtests. The SON-R total score was considered as a representative contrast value for subtest comparison, based on the finding that strengths and weaknesses within the SON-R profile remain identical whenever the SON-R total score was employed as a contrast value subtest comparison, or when the SON-R subtest were contrasted against each other (i.e., with the SON-R total score excluded as contrast value).
more widely used intelligence batteries, such as the Stanford Binet (Thorndike, 1973) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; Harris, 1982; Moore et al., 1998; Wechsler, 1963). Also, the SON-R is rated as "good" on reliability by the Committee On Test Affairs Netherlands (COTAN; Evers, 2001; Evers, Van Vliet-Mulder, & Groot, 2000). Furthermore, the SON-R has proven to be particularly useful to assess non-verbal intelligence in children with (mental) disabilities (Janke & Petermann, 2006; Jenkinson, Roberts, Dennehy, & Tellegen, 1996). The SON-R subtests do not require verbal output by the participant, which enables inclusion of participants with limited or absent speech.

Verbal mental age. The Dutch version of the Peabody Picture Vocabulary Test, third edition (PPVT-III-NL; Schlichting, 2004), was used to index receptive vocabulary and to provide a reference for VMA. The PPVT has proven to be an adequate and reliable instrument for assessing verbal ability, and it accurately predicts full scale IQ and verbal IQ measures on the Wechsler Adult Intelligence Scale (Bell, Lassiter, Matthews, & Hutchinson, 2001). Moreover, although verbal responses are not required, the PPVT can still provide an estimate of verbal ability. The PPVT has been frequently used as an indicator of VMA in developmental studies (e.g., Cornish et al., 1999; Kogan et al., 2009).

2.2.2. Non-verbal reasoning abilities

Concrete reasoning. The SON-R subtest “Situations” was employed as a measure of concrete non-verbal reasoning ability. Drawings of specific (ecologically relevant) situations were presented. These drawings consist of a blank square, leaving out a specific part of a situation or object. Participants are required to choose the correct (i.e., the most sensible) picture from multiple options.

Abstract sorting. The SON-R subtest “Analogies” was employed as a measure of abstract reasoning ability. Participants are required to sort geometric colored tokens according to shape, color or size, or on more difficult items, according to a transformation rule that has to be detected.

Concrete sorting. The SON-R subtest “Categories” was employed as a measure of sorting ability confined to ecologically relevant objects. The participant is required to sort cards depicting objects, according to a category rule (e.g., tables versus chairs).

Concept formation. Concept formation or implicit reasoning was measured using the subtest “Conceptual Thinking” from the Kaufman Assessment Battery for Children, second edition (K-ABC II; Kaufman & Kaufman, 1983a, 1983b). Participants have to identify (by pointing) the odd object amongst a series of objects that belong to the same class or category.

Visuo-perceptual recognition. The subtest “Picture Recognition” of the Revised Amsterdam Children Intelligence Test (RAKIT; Bleichrodt, Drenth, Zaal, & Resing, 1984, 1987) was employed to assess visuo-perceptual abilities (i.e., Gestalt closure). Participants are instructed to denominate incompletely drawn pictures of objects. Reliability and validity of the RAKIT have been rated as “good” by the COTAN.

2.2.3. Performal abilities

Concrete object assembly. The SON-R subtests “Puzzles” was used to assess the ability to copy or rearrange visual meaningful stimuli. Participants are required to assemble a puzzle depicting a meaningful picture.

Abstract object assembly. The SON-R subtest “Mosaics” was used to assess the ability to copy abstract visual patterns using colored blocks.

Abstract drawing. The SON-R subtest “Patterns” was employed to assess visuo-constructive abilities involved in drawing geometric shapes. Participants are asked to copy geometric shapes with increasing difficulty.

2.2.4. Verbal abilities

Expressive vocabulary. Expressive vocabulary was measured with the subtest “Word Production” from the Dutch Language Test for Children (Taaltest voor Kinderen (TVK); Van Bon, 1982). While looking at a picture from a booklet, a prompting sentence is provided related to that picture. The participant is required to complete this sentence with a correct word.

Sentence production. The TVK subtest “Sentence Construction” was used to assess grammatical abilities necessary for correct sentence construction. While looking at a drawing (e.g., a picture of a cat on a car), participants are provided with a corresponding, but incongruent sentence (e.g., “the cat is on the car”). The participant has to change word order to form the correct sentence (e.g., “the cat is on the car”).

Verbal fluency. The RAKIT subtest “Production of Ideas” was used to assess semantic fluency. Participants are required to produce as many words as possible within 1 min related to a specific category (e.g., “what can you find in a store?”).

Verbal reasoning. The RAKIT subtest “Telling Stories” was used to assess verbal reasoning and expressive speech by means of two pictures presented on an A4 sized sheet (e.g., a scene in a garden and in a living room). Participants are required to denominate as many objects as possible, as well as verbalize object relations and the plot of the story.

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2 The RAKIT (Bleichrodt et al., 1984, 1987) is a Dutch intelligence test for children aged 4–12 years, and is based on Thurstone’s (1938) theory of cognitive abilities. The RAKIT has a high concurrent validity (.86) with the WISC-R for total IQ.

3 The TVK (Van Bon, 1982) is a Dutch language assessment battery for children aged 4–9 years. The TVK comprises subtests which assess a broad range of receptive and productive verbal abilities. The TVK taps phonological, morphological, syntactical, and semantical aspects of grammatical competence. Appropriate reliability has been reported for the subtests “vocabulary production test” and “sentence production test” (Resing, Evers, Koomen, Pameijer, & Bleichrodt, 2005).
Participants were tested individually in a quiet room. The SON-R test was administered to all participants during the first test session. Four test sessions (with a duration of maximally 1.5 h each) were scheduled for administration of the test battery.

2.3. Procedure

Planning. Spatial planning and problem solving abilities were assessed with the CANTAB subtest “Stockings of Cambridge” (SOC). The SOC is a computerized analogue to the “Tower of London” (Shallice, 1982), and consists of two visual displays containing three colored balls placed as stacks in stockings. The goal situation (upper half of the screen) has to be memorized by the participant. The variable of interest is the number of correctly recalled objects.

Cognitive flexibility. The CANTAB subtest “Intra-Extra Dimensional Set-Shift” (IED) was used to assess rule acquisition and reversal (cognitive flexibility). This subtest consists of a total of nine stages, assessing various set-shifting paradigms (e.g., simple discrimination, simple reversal, intra-dimensional set-shift (and reversal), or extra-dimensional set-shift (and reversal)). The variables of interest are the number of completed stages, the total number of errors committed, and the number of trials completed.

2.2.6. Executive function

Visual recognition memory. The K-ABC subtest “Spatial Memory” (Kaufman & Kaufman, 1983a) was used to assess visuo-spatial recognition memory. Participants are required to carefully look at a sequence of five squares presented in different locations on a touch screen. Thereafter, two squares are presented simultaneously, and participants have to indicate which square was positioned at the exact location of one of the previous squares. The variable of interest is the percentage of correctly recalled locations.

Visuo-spatial STM (simultaneous). The CANTAB subtest “Pattern Recognition Memory” (PRM) was administered to assess visual recognition memory. Twelve geometric patterns are presented sequentially. Subsequently, two patterns are presented and the participant is asked to point to the pattern previously seen (recall mode). The recall mode is presented either immediately (PRM-I) or with a 20-min delay (PRM-D). Both versions were used in this study. The PRM-I was taken to provide an index of short-term recognition memory, whereas the PRM-D was taken as a measure of long-term recognition memory. For both versions, the variable of interest is the percentage of correctly recalled patterns.

Associative learning. The RAKIT subtest “Name Learning” was used to assess associative-learning capacity. Participants are presented with a booklet containing pictures of cats or butterflies. For each picture a corresponding name is provided, which has to be memorized by the participant. The variable of interest is the number of correctly recalled objects.

Verbal STM for sequential information was assessed using the subtest “Number Recall” (digit span forward), adopted from the Kaufmann Assessment Battery for Children, second edition (K-ABC II; Kaufman & Kaufman, 1983b).

Visuo-spatial STM (sequential). Visuo-spatial STM for sequential information was assessed using the subtest “Spatial Span” of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Strauss, Sherman, & Spreen, 2006). During this computerized analogue to the Corsi Block Tapping test (Corsi, 1972), participants are required to correctly copy a sequence of highlighted squares on a computer touch screen. After correctly copying a sequence of squares, the subsequent sequence is increased with an additional square. The variable of interest is the maximum length of the correctly recalled sequence of squares.

Verbal STM for sequential information was assessed using the subtest “Number Recall” (digit span forward), adopted from the Kaufmann Assessment Battery for Children, second edition (K-ABC II; Kaufman & Kaufman, 1983b).

Visuo-spatial STM (simultaneous). The K-ABC subtest “Spatial Memory” (Kaufman & Kaufman, 1983a) was used to assess visuo-spatial STM capacity for the location of meaningful information. During each trial, a sheet is presented for five seconds, depicting several objects/animals within a specific spatial arrangement. After the five seconds, an empty matrix is presented, and participants have to point to the location of the recalled stimuli within the matrix. A trial is scored correct when the location of all stimuli is recalled correctly.

Working memory (self-ordered search). The CANTAB subtest “Spatial Working Memory” (SWM) was employed to assess the ability to retain and update visuo-spatial information in working memory. On this subtest, analogous to the self-ordered pointing task of Petrides and Milner (1982), participants are required to search for tokens (hidden in boxes) by a process of search and elimination. Participants are instructed to collect the tokens by opening the boxes, and are told that a box remains empty once a token has been collected from that box. Therefore, to employ an efficient search strategy, participants have to keep in mind the boxes in which they have previously found a token. The variable of interest is the number of errors (total errors) committed.

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2.2.6. Executive function

Cognitive flexibility. The CANTAB subtest “Intra-Extra Dimensional Set-Shift” (IED) was used to assess rule acquisition and reversal (cognitive flexibility). This subtest consists of a total of nine stages, assessing various set-shifting paradigms (e.g., simple discrimination, simple reversal, intra-dimensional set-shift (and reversal), or extra-dimensional set-shift (and reversal)). The variables of interest are the number of completed stages, the total number of errors committed, and the number of trials completed.

Planning. Spatial planning and problem solving abilities were assessed with the CANTAB subtest “Stockings of Cambridge” (SOC). The SOC is a computerized analogue to the “Tower of London” (Shallice, 1982), and consists of two visual displays containing three colored balls placed as stacks in stockings. The goal situation (upper half of the screen) has to be copied by moving balls around in the experimental display (lower half of the screen). Items differ in the level of difficulty, as the number of moves required to copy the goal situation increases. The variable of interest is the number of problems solved with the minimum number of moves needed.

2.3. Procedure

Parents and primary caregivers of the participants were contacted by telephone to screen for possible behavioral or medical problems of the participant group. All participants were scheduled for the complete neuropsychological assessment. Four test sessions (with a duration of maximally 1.5 h each) were scheduled for administration of the test battery. Participants were tested individually in a quiet room. The SON-R test was administered to all participants during the first test session. Four test sessions (with a duration of maximally 1.5 h each) were scheduled for administration of the test battery.

4 The CANTAB is a widely used computerized tool for the assessment of frontal and medial temporal lobe dysfunctions. The CANTAB subtests included in this study were derived from the ‘child battery’, appropriate for children aged 4–12 years. Normative data for these subtests have been extended by De Luca et al. (2003) and Luciana and Nelson (2002). Indices of reliability have been reported by Lowe and Rabbitt (1998). For a detailed description of the CANTAB-subtests included in this study, the reader is referred to Luciana and Nelson (1998).
session. CANTAB subtests were administered during the final test session on a 12-inch Paceblade Slimbook Tablet PC, running the Windows XP operating system. The remaining subtests were administered in a second and third test session. The order of test administration was equal for all participants. Based on the participants’ performance level (e.g., performance at a subtests’ floor level), assessment could be shortened to two or three sessions.

2.4. Data analysis

Data analysis was performed in three steps: (1) participants performing below the subtests’ floor level were excluded from the analyses. The proportion of participants performing below floor level is presented in Table 1 for each test; (2) to determine whether the sample consisted of one or more subgroups, we performed a model-based cluster analysis (Fraley & Raftery, 2002). This analysis compares several ways of clustering by means of the Bayesian Information Criterion (BIC; Fraley & Raftery, 2003). The solution with the lowest BIC value yields the best description of the data. Model-based clustering compares solutions with different numbers of subgroups, as well as solutions with different constraints on the covariance matrices between subgroups. These constraints may both pertain to the equality of covariance matrices between subgroups as well as to the covariance structure within subgroups; (3) in order to examine relative strengths and weaknesses in FXS cognitive functioning, repeated-measures analyses of variance (ANOVA) were conducted in which all measures were contrasted to the NVMA or VMA reference measures. The cognitive profile was established by using a simple contrast method, which compares each cognitive ability to the two reference measures.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc, Version 15.0, 2006). Greenhouse-Geisser correction was used whenever the assumption of sphericity was violated, but uncorrected dfs are reported for transparency. A Bonferroni correction was employed to reduce the likelihood of Type 1 errors. In view of the large number of statistical tests performed, effects were considered significant at \( p < .01 \).

3. Results

3.1. Floor performance

Exploration of the data was conducted for all participants to ensure that statistical analyses were performed only on the data for participants performing above floor level. Table 1 presents the proportion of participants performing below floor level for each subtest. It can be seen that performance below floor level is most frequent for STM, working memory and EF subtests. Inspection of the data indicated that none of the participants performed above floor level on all of the tests administered. The analyses were confined to the participants who performed above floor level.

3.2. Subgroup differences

3.2.1. Model-based cluster analysis

To determine whether our sample of FXS participants consisted of two or more subgroups (e.g., high- versus low-performers) a model-based cluster analysis was performed. The analysis was restricted to those subtests that provided within-range MA data for all participants (N = 43); that is, Concrete Reasoning, Abstract Sorting, Concrete Sorting, Concept Formation, Visuo-Perceptual Recognition, Concrete Object Assembly, Abstract Object Assembly, Abstract Drawing, and Receptive Vocabulary (VMA). Results indicated that our sample could best be described by three distinct subgroups (BIC = –1346.88, BIC of one-group model with unrestricted covariance –1358.11). In this solution the data are modeled as uncorrelated within subgroups.

Next, we examined whether these subgroups could be differentiated in terms of level of performance, and we investigated whether the cognitive profiles differed between subgroups. Hence, two mixed design repeated measures ANOVAs were performed with Subtests (10) as within-subjects factor and Subgroup (3) as between-subjects factor. ANOVAs were performed using either NVMA or VMA as reference measure (simple contrast). Chronological age was included as a covariate to determine whether differences in functioning are better explained by chronological age than by Subgroup.

3.2.2. Between subgroup analysis

First, between-subject analyses were performed in order to determine significant differences in MA performance levels between subgroups on the subtests. Results showed a main effect of Subgroup, \( F(2, 39) = 123.94, p < .0001, \eta^2_p = .86 \). MA performance levels differed significantly between subgroups for all subtests (all p’s < .01), except for Concrete Object Assembly and Abstract Sorting (no significant differences between Subgroups 2 and 3). Importantly, the subgroup differences could not be attributed to chronological age, \( F(1, 39) = .41, p = .524, \eta^2_p = .01 \). In Fig. 1 it can be seen that Subgroup 1 (n = 10) contained the ‘high-performing’ participants, Subgroup 2 (n = 15) the ‘intermediate-performing’ participants, and Subgroup 3 (n = 18) the ‘low-functioning’ participants.

3.2.3. Non-verbal mental age reference analysis

The ANOVA showed a main effect of Subtests, \( F(9, 351) = 6.95, p < .0001, \eta^2_p = .15 \), indicating a profile of strengths and weaknesses relative to the NVMA reference measure. For all Subgroups, relative strengths were observed for Visuo-Perceptual
Recognition and VMA, whereas a relative weakness was found for Abstract Drawing (all \( p < .01 \)). The ANOVA yielded a significant interaction effect between Subgroup and Subtests, \( F(168, 351) = 4.41, p < .0001, \eta^2_p = .18 \), indicating that profiles differed between subgroups. In Fig. 1 it can be seen that for the low-performing subgroup a relative strength was observed for Concrete Object Assembly. For the high-performing subgroup, a relative strength was observed for Concrete Reasoning Abilities whereas weaknesses were observed for Abstract Sorting and Abstract Drawing (all \( p's < .01 \)). Strengths and weaknesses in non-verbal (reasoning and performal) abilities relative to the NVMA reference are presented in Table 2 for each subgroup.

3.2.4. Verbal mental age reference analysis

The ANOVA with VMA as reference measures yielded a main effect of Subtests, \( F(8, 312) = 6.81, p < .0001, \eta^2_p = .15 \), indicating a profile of strengths and weaknesses. For all Subgroups significant weaknesses were observed for Abstract Object Assembly, \( F(1, 39) = 11.89, p < .001, \eta^2_p = .23 \), Abstract Sorting, \( F(1, 39) = 9.73, p < .01, \eta^2_p = .19 \), and Abstract Drawing, \( F(1, 39) = 15.01, p < .0001, \eta^2_p = .28 \). The analysis yielded also a significant interaction between Subgroups and Subtests \( F(16, 312) = 4.41, p < .0001, \eta^2_p = .18 \). Subsequent analyses indicated that weaknesses in Concrete Object Assembly and Concept

![Cognitive profiles of high- (n = 10), intermediate- (n = 15) and low-performing (n = 18) FXS males.](image)

**Table 2**

Strengths and weaknesses in non-verbal abilities for high-, intermediate-, and low-performing FXS males, relative to NVMA and VMA.

<table>
<thead>
<tr>
<th>Neuropsychological measures</th>
<th>NVMA contrast</th>
<th>VMA contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subgroup df F ratio Effect</td>
<td>Contrast result</td>
</tr>
<tr>
<td>Reasoning abilities</td>
<td></td>
<td>size ( \eta^2_p )</td>
</tr>
<tr>
<td>Concrete reasoning (CR)</td>
<td>HP 2 8.05* .29  CR &gt; NVMA</td>
<td></td>
</tr>
<tr>
<td>Abstract reasoning (AR)</td>
<td>HP 2 7.03* .27  AR &lt; NVMA</td>
<td></td>
</tr>
<tr>
<td>Sorting (S)</td>
<td>All 1 9.91* .20  S &gt; NVMA</td>
<td></td>
</tr>
<tr>
<td>Concept formation (CF)</td>
<td>All 1 ns .29  VR &gt; NVMA</td>
<td></td>
</tr>
<tr>
<td>Visual recognition (VR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performing abilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concrete object assembly (COA)</td>
<td>LP 2 5.87* .23  COA &lt; NVMA</td>
<td></td>
</tr>
<tr>
<td>Abstract object assembly (AOA)</td>
<td>ns .23</td>
<td></td>
</tr>
<tr>
<td>Abstract drawing (AD)</td>
<td>HP 2 13.79* .41  AD &lt; NVMA</td>
<td></td>
</tr>
</tbody>
</table>

* Significant at \( p < .01 \).

** Significant at \( p < .001 \).

*** Significant at \( p < .0001 \).
Formation (all p’s < .0001) were only evident for high- and intermediate-functioning participants. Table 2 presents the strengths and weaknesses in non-verbal (reasoning and performal) abilities relative to the VMA reference measure for each subgroup.

In sum, the current pattern of findings indicate that both high-, intermediate- and average-functioning FXS males have cognitive profiles that are characterized by strengths in concrete reasoning, and concrete performal abilities. Weaknesses are observed for abstract reasoning, and abstract performal abilities. Interestingly, the subgroup profiling indicates that these strengths and weaknesses are more pronounced for high-functioning FXS males. Thus, not only their strengths are more pronounced, but also their weaknesses are more prominent relative to the lower-functioning subgroups. Finally, separate analyses with NVMA and VMA as reference measures, demonstrated the importance of including an additional reference measure in order to avoid bias in interpreting a cognitive ability as strength versus weakness.

3.3. Verbal abilities

Performance on the verbal fluency and verbal reasoning subtests yielded a considerable number of floor effects, hence valid performance for all verbal subtests could only be established for 18 participants. Repeated measures ANOVAs were performed on the following verbal subtests as within-subjects variables: Receptive (VMA) and Expressive Vocabulary, Sentence Production, Verbal Fluency and Verbal Reasoning, again using the VMA and NVMA references as simple contrasts to determine strengths and weaknesses in verbal abilities. Results are presented in Fig. 2.

VMA reference. The ANOVA with Subtests (4) as within-subject variables and the VMA reference as simple contrast yielded a significant main effect of Subtests, F(4, 68) = 21.06, p < .0001, η² = .55, indicating a profile of strengths and weaknesses. Relative to the VMA reference, within-subject contrast analysis revealed significant weaknesses for Sentence Production, F(1, 17) = 43.09, p < .0001, η² = .72, Verbal Fluency, F(1, 17) = 8.39, p < .01, η² = .33, and Verbal Reasoning, F(1, 17) = 118.96, p < .0001, η² = .86. The ANOVA with the VMA reference yielded no significant strengths.

NVMA reference. Additionally, a separate ANOVA was performed with Subtests (5) as within-subject variables and the NVMA reference as simple contrast. VMA was also included in the analysis as a fifth within-subject variable. Results yielded a significant main effect of Subtests, F(5, 85) = 15.96, p < .0001, η² = .60. Relative to NVMA, significant strengths were found for Receptive Vocabulary (VMA), F(1, 17) = 87.33, p < .0001, η² = .84, Expressive Vocabulary F(1, 17) = 244.38, p < .0001, η² = .94, and Sentence Production F(1, 17) = 11.20, p = .004, η² = .40. The ANOVA with the NVMA reference yielded no significant weaknesses.

Current findings revealed a clear pattern of strengths and weaknesses in the verbal abilities of our FXS participants. Relative to the VMA reference, however, they showed considerable deficits on Sentence Production, Verbal Fluency and Verbal Reasoning. These apparent weaknesses were less clear when NVMA was used as a reference.

3.4. Memory performance

Performance on the memory subtests was examined in 16 participants who did not show floor performance on any of these tests. The following subtests were included as within-subjects variables in the ANOVA: Verbal STM,
3.4. Memory function

Fig. 3 presents MA performance on the memory Subtests, referenced to NVMA and VMA.

NVMA reference. An ANOVA was performed with Subtests (3) as within-subjects variables and the NVMA reference as simple contrast. Results yielded a significant main effect for Subtests, \( F(3, 45) = 21.72, p < .0001, \eta^2_p = .59 \). A significant strength was found for Associative Learning \( F(1, 15) = 21.35, p < .0001, \eta^2_p = .59 \), and a significant weakness for Verbal STM, \( F(1,15) = 23.12, p < .0001, \eta^2_p = .61 \).

VMA reference. Additionally, a separate ANOVA was performed with Subtests (3) as within-subjects variables and VMA as simple contrast. Again, results yielded a significant main effect for Subtests, \( F(3, 45) = 32.62, p < .0001, \eta^2_p = .69 \). A significant weakness was demonstrated for Verbal STM, \( F(1, 15) = 89.74, p < .0001, \eta^2_p = .86 \). Furthermore, a significant weakness was found for Visuo-Spatial STM, \( F(1, 15) = 35.31, p < .0001, \eta^2_p = .70 \). To examine the robustness of NVMA and VMA as reference measures, a paired samples t-test was performed to examine whether NVMA and VMA also differed in this specific sub-sample of FXS males. A significant difference between NVMA and VMA, \( t(15) = -7.55, p < .0001 \) was found. Also, in this sample of FXS males, VMA is a significant strength relative to NVMA.

In sum, STM for auditory sequential information processing shows as a significant weakness within FXS memory performance when compared to both NVMA and VMA, whereas Visuo-Spatial STM only shows as a weakness when compared to VMA. Interestingly, associative learning is not a weaknesses when compared to VMA, implicating a relative strength in long-term memory performance confined to the rehearsal of ecologically relevant information.

3.5. Executive function

Performance on the EF subtests was examined in 15 participants who did not show floor effects on any of these tests. The Cognitive Flexibility and Planning subtests were both included as within-subjects variables in the ANOVA. Fig. 4 presents MA performance on these EF subtests, referenced to NVMA and VMA.

NVMA reference. An ANOVA was performed with Subtests (2) as within-subjects variables and NVMA as simple contrast. Results yielded no significant main effect for Subtests, \( F(2, 28) = 3.14, p = .06, \eta^2_p = .18 \). This finding suggests that Cognitive Flexibility and Spatial Planning abilities do not demonstrate as significant strengths or weaknesses relative to the NVMA reference measure. However, contrasted to NVMA, cognitive flexibility just failed to reach significance \( (p = .013) \).

VMA reference. An additional ANOVA was performed with Subtests (2) as within-subjects variables and the VMA reference as simple contrast. The analysis with VMA as reference yielded a significant main effect for Subtests, \( F(2, 28) = 12.16, p < .0001, \eta^2_p = .47 \). Both Cognitive Flexibility \( F(1, 14) = 19.08, p < .01, \eta^2_p = .58 \), and Planning, \( F(1, 14) = 16.51, p < .01, \eta^2_p = .54 \), showed as significant weaknesses relative to VMA.

Again, to examine the robustness of NVMA and VMA as reference measures, a paired samples t-test was performed to examine whether NVMA and VMA also differed in this specific sub-sample of FXS males. Results again yielded a significant
difference between NVMA and VMA, \( t(14) = -7.87, p < .0001 \). Also, in this sample of FXS males, VMA can be considered as a significant strength relative to NVMA.

In sum, the analyses on the EF measures with the NVMA and VMA reference contrast further demonstrated the importance of including an additional reference measure to avoid possible interpretation-bias in interpreting strengths and weaknesses in cognitive abilities. That is, also as resulted from the EF analysis, referencing to NVMA and VMA has a differential impact on interpreting a cognitive ability as strength or weakness.

4. Discussion

The current study aimed at determining the specific profile of relative strengths and weaknesses of cognitive functioning in a large sample of full mutation FXS males. Our primary aim was to investigate whether subgroups could be identified in our sample of FXS males and to examine whether these subgroups would show distinguishable cognitive profiles. By means of an extensive neuropsychological assessment, we found that FXS is associated with a disharmonic cognitive profile, characterized by domain-specific strengths and weaknesses. In addition, we identified three FXS subgroups that differed in the level of cognitive performance and showed subtle, but significant differences in terms of their strengths and weaknesses profiles. The strengths in cognitive performance are related to concrete (i.e., meaningful) item content, whereas weaknesses refer to abstract item content. Subsequently, subgroup profiling in the current study leads to the notion of a robust cognitive profile in FXS males, regardless of the level of performance.

We first consider the observation of floor performance on the administrated subtests, which could provide the context for interpreting the strengths and weaknesses in FXS cognitive performance. Floor performance is likely to result from the MA range of a particular subtest or test battery. Indeed, performance at floor level was observed primarily for subtests with a relatively small MA range (e.g., 4–12 years), whereas subtests yielding above floor performance had larger MA ranges (e.g., 2–17 years). Discarding MA range, the patterning of floor performance is relevant to the cognitive profiling of FXS. To a large extent, floor performance was related to subtests assessing complex verbal abilities (e.g., verbal fluency and verbal reasoning), STM, working memory, and aspects of executive functions. In contrast, subtests yielding above floor performance were related to non-verbal reasoning, performal abilities, visuo-perceptual recognition, and receptive vocabulary. Interestingly, this patterning is consistent with the cognitive profile obtained from above floor performance. Thus, FXS participants performed particularly poor on subtests used to assess verbal STM, visual STM, verbal fluency and verbal reasoning. These apparent weaknesses are in line with previous studies reporting disproportionate deficits in verbal and visual STM (Munir et al., 2000a) and verbal fluency and verbal reasoning (Abbeduto et al., 2007).

A major aim of the present study was cognitive sub-typing of our sample of FXS males. Model-based cluster analysis identified three subgroups corresponding to high-, intermediate-, and low-functioning individuals. These subgroups were both similar and different. They were similar in that all three subgroups could be characterized by a cognitive profile showing a pronounced dissociation between concrete versus abstract non-verbal reasoning and performal abilities. More specifically, the cognitive profile across subgroups showed significant strengths in visuo-perceptual recognition and concrete sorting abilities relative to the NVMA reference. This pattern of findings is in line with previous studies reporting relative intact visuo-perceptual abilities and processing of meaningful information (Cornish et al., 1999; Dykens et al., 1987; Maes et al., 1994). However, the subgroups were different in that the dissociation between concrete versus abstract non-
The current study contributes to the recent literature indicating that FXS males perform particularly poor on tasks with a high demand on executive control (see Hooper et al., 2008, for a review). First, FXS males performed poorly on verbal fluency and verbal reasoning tasks. These findings are in accord with previous studies reporting deficits in verbal fluency and verbal reasoning abilities (Abbeduto et al., 2003, 2007; Roberts, Mirrett, & Burchinal, 2001). Verbal fluency is generally referred to as the ability to generate novel verbal responses, and the ability to switch between semantic or phonemic categories (Turner, 1999). Furthermore, it has been argued that verbal fluency tasks require the ability to successful inhibit inappropriate verbal responses and to update verbal responses (Henry & Crawford, 2004). In this regard, weaknesses in verbal fluency observed in the present study are interpreted in terms of deficits in executive control processes involved in regulating and generating accurate verbal responses. Similarly, impairments in verbal reasoning have been argued to depend more on higher-order effortful selection and organization of ideas, rather than automatized, easy selective processes (Sluis, De Jong, & Van der Leij, 2007).

Second, the current pattern of findings point to serious deficits in STM and working memory processes in our sample of FXS participants. This finding is consistent with previous observations that performance on working memory tasks is particularly weak in FXS males (Munir et al., 2000a). Tasks in the current study required the ability to update information with new incoming information, as well as the ability to employ an effective, self-ordered search strategy to keep track of items previously inspected. Updating and self-ordered search are frequently postulated to dependent on executive control (Baddeley, 1996; Miyake, Friedman, Emerson, Witzki, & Howarter, 2000; Tubau, Hommel, & López-Moliner, 2007). The current findings revealed that associative learning ability for concrete information was relatively spared in our sample of FXS males. The associative learning task used in the current study required successful encoding and retrieval of familiar verbal labels which corresponded to concrete visual stimuli (i.e., pictures of cats and butterflies). Recently, it has been suggested that encoding processes recruited during associative learning can be considered as distinct cognitive processes from those recruited during working memory tasks (Kaufman, DeYoung, Gray, Brown, & Mackintosh, 2009). In addition, it has been suggested that associative learning and working memory rely on different neural substrates (Ranganath, 2006). Subsequently, it could be argued that associative learning imposes less demand on executive control than working memory processes.

Third, assuming that executive control is deficient in FXS males, our participants should perform poorly on executive function tasks. The current test battery included two aspects of executive function, Cognitive Flexibility and Planning. Consistent with previous studies examining executive functioning in FXS males (Hooper et al., 2008; Kogan et al., 2009; Loesch et al., 2003; Munir et al., 2000b; Woodcock et al., 2009), the current results showed poor performance on both tests, but only when referenced to VMA. When NVMA was taken as a reference, performance on Cognitive Flexibility and Planning was not particularly poor. It should be noted, however, that the IED test used for examining cognitive flexibility consists of two parts requiring intra- versus extra-dimensional shifts, respectively. Intra-dimensional shifting requires visuo-perceptual abilities (e.g., object recognition, stimulus discrimination) that have been observed to be relatively spared in the current sample of FXS males. In contrast, extra-dimensional shifts have been argued to involve shifting between contextual or cognitive sets (Geurts, Corbett, & Solomon, 2009; Ravizza & Carter, 2008), and, thus, impose a higher demand on executive control (Miyake et al., 2000). Only a few participants were able to complete this part of the IED task, which is consistent with the alleged executive control deficit in FXS males. In regard to the Planning task, it should be noted that only 37% of the participants were able to complete this task. This proportion is similar to the proportions that Hooper et al. (2008) observed for FXS boys performing on planning tasks. The failure of FXS individuals to complete planning tasks is interpreted to suggest deficient executive control (see also Kogan et al., 2009; Loesch et al., 2003; Munir et al., 2000b).

Finally, the observation that performance on the executive function tasks is poor when performance on these tasks is referenced to VMA but not NVMA points to the importance of selecting the appropriate reference when examining strengths and weaknesses in FXS individuals. The current study indicates that the reference issue goes beyond the domain of executive

Spearman (see Tucker-Drob, 2009) suggested that, at low ability levels, a scarcity of effortful selection and organization of ideas, rather than automatized, easy selective processes (Sluis, De Jong, & Van der Leij, 1999). Furthermore, it has been argued that verbal fluency tasks require the ability to successful inhibit inappropriate verbal responses and to update verbal responses (Henry & Crawford, 2004). In this regard, weaknesses in verbal fluency observed in the present study are interpreted in terms of deficits in executive control processes involved in regulating and generating accurate verbal responses. Similarly, impairments in verbal reasoning have been argued to depend more on higher-order effortful selection and organization of ideas, rather than automatized, easy selective processes (Sluis, De Jong, & Van der Leij, 2007).

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Finally, the observation that performance on the executive function tasks is poor when performance on these tasks is referenced to VMA but not NVMA points to the importance of selecting the appropriate reference when examining strengths and weaknesses in FXS individuals. The current study indicates that the reference issue goes beyond the domain of executive
functioning. That is, taking VMA as a reference, performance on tasks requiring non-verbal reasoning, performal abilities, working memory or executive function was particularly weak in our sample of FXS participants. Taking NVMA as a reference, the current findings showed relative strengths for expressive vocabulary and simple grammatical abilities. Compared to VMA, however, these abilities showed up as weaknesses. In this regard, the use of VMA as a reference may underestimate the “true” level of functioning of FXS individuals, whereas the use of NVMA may overestimate their abilities. Obviously, when studying strengths and weaknesses in cognitive functioning, errors related to over- and underestimation biases are prevalent (cf. Burack, Iarocci, Bowler, & Mottron, 2002; Mottron, 2004). Given the absence of a golden standard, it is recommended here to use both VMA and NVMA as a safeguard against estimation biases.

In conclusion, the present study contributes to the existing FXS literature by reporting four main findings: (1) the cognitive profiling of FXS resulted in three distinct subgroups, which differed in terms of performance level; (2) the cognitive profiles of these subgroups are both similar and subtly different. Strengths refer to concrete information processing and weaknesses to abstract information processing. Both strengths and weaknesses were somewhat more pronounced for the subgroup functioning at a relatively higher level; (3) to a large extent, deficits in cognitive abilities are dependent on executive control processes. This finding contributes to the recent literature suggesting a fundamental deficiency of higher-level cognitive processes; (4) the present study illustrated the importance of choosing an appropriate reference in order to determine strengths and weaknesses in cognitive performance. Future studies should aim at teasing apart these higher-level executive control processes from lower-level cognitive processes, and subsequently relate them to underlying neural mechanisms. Such studies should take advantage of electrophysiological and brain-imaging techniques. In combination with neurobiological investigations on the determinants of abnormal FXS brain development, the specific cognitive profile associated with FXS could then be further defined in terms of an endophenotype.

Acknowledgements

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