

# Ageing and cognition in men with fragile X syndrome

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Päijät-Hämeen Rahasto

**Abstract****Background:** Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability. The aim of our longitudinal study was to describe ageing-related cognitive changes in men with FXS.**Method:** A neuropsychologist determined the raw scores (RSs) of 19 men with FXS twice with the Leiter International Performance Scale at an average interval of 22 years. The ages of the participants at baseline ranged from 16 to 50 (mean 27) years.**Results:** At follow-up, the RSs improved in two men, remained the same in two men and declined in 15 men. Overall, the RS of the study group deteriorated by an average 4 points in RSs ( $p < .001$ ).**Conclusion:** Cognitive ageing in men with FXS started earlier than that in men in the general population; in many cases, cognitive ageing in men with FXS began before middle age, usually without any medical or other underlying cause.**KEYWORDS**

ageing, cognitive development, fragile X syndrome, intellectual disability

## 1 | INTRODUCTION

Fragile X syndrome (FXS, OMIM number 309550) is the most common inherited cause of intellectual disability (ID), with a prevalence ranging from 1/3,600 to 1/6,000 (ArvioPeippo & Simola, 1997; Hagerman, 2002; Schneider, Ligsay, & Hagerman, 2013). FXS is caused by a mutation in the *FMRI* gene on the long arm of the X chromosome, and it manifests mainly in males as an ID syndrome (Hagerman, 2002; Verkerk et al., 1991).

Young boys with FXS show delayed psychomotor development, and their ID diagnosis is usually established before school age. During childhood and adolescence, the average level of intelligence in boys is equivalent to a moderate ID but can vary from borderline to severe disability (Fisch et al., 2012; Huddleston, Visootsak, & Sherman, 2014; Quintin et al., 2016). Boys and young men show relative strengths in tasks requiring visual “matching” (recognition of similar type objects), simultaneous processing and verbal reasoning, whereas executive

functions such as planning, attention and visual-motor coordination are relatively weaker cognitive domains (Hooper et al., 2008; Huddleston et al., 2014; Reiss & Hall, 2007; Van der Molen et al., 2010). Further, they have difficulties in tasks requiring visual and short-term memory recall and visual-spatial reasoning (Lanfranchi, Cornoldi, Drigo, & Vianello, 2009; Reiss & Hall, 2007; Schwarte, 2008). Their IQ often declines as they transition into adulthood. This is most often due to the slower rate of cognitive development compared to that of their typically developing age-matched peers and is not due to mental decline (Fisch et al., 2012; Hall, Burns, Lightbody, & Reiss, 2008; Hessler et al., 2009; Quintin et al., 2016; Wright-Talamante et al., 1996). Individuals with FXS are often shy and are wary of new people, and one-third present with autistic features (Chonchaiya, Schneider, & Hagerman, 2009; Utari et al., 2010; Seritan, Ligsay, & Hagerman, 2016; Siegel & Smith, 2010). Those with autism spectrum disorder as an adjunctive comorbidity may show a more severe level of ID than those without comorbidities (Chonchaiya et al., 2009; Skinner et al., 2005).

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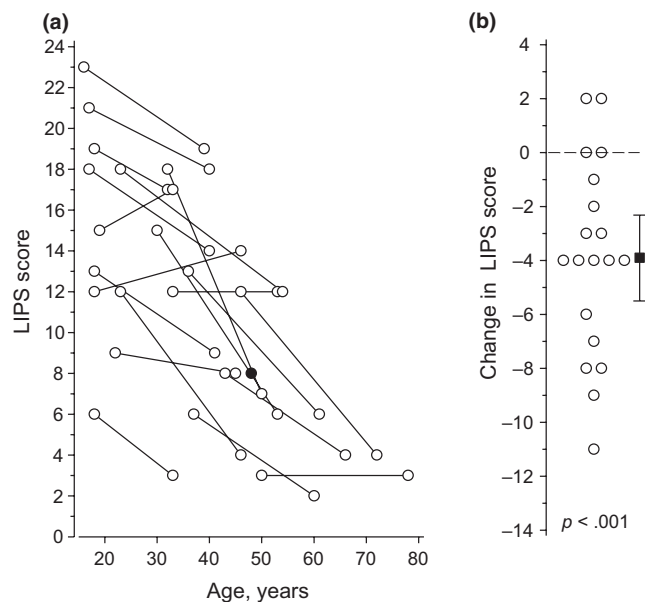
To date, we know little about ageing-related cognitive changes in people with ID (Carr, 2005; Strydom et al., 2010; Seritan et al., 2016; Schneider et al., 2013). During recent decades, the life expectancy of people with ID has increased, and thus, it has become possible to map ageing-related cognitive changes in this subpopulation (Arvio, Salokivi, & Bjelogrić-Laakso, 2017; Arvio, Salokivi, Tiitinen, & Haataja, 2016; Westerinen et al., 2016). The aetiology of ID is known to determine how cognitive skills and abilities develop during childhood and adolescence. Consequently, the aetiology can also be assumed to influence mental ageing (Cornish, Scerif, & Karmiloff-Smith, 2007; Fisch et al., 2012; Quintin et al., 2016).

Multiple studies have demonstrated that some ID syndromes are risk factors for memory disorders. For instance, Down syndrome is a significant risk factor for early-onset Alzheimer's disease (Coppus et al., 2006; Evenhuis, 1990; McCarron et al., 2017; Strydom et al., 2010), and Williams syndrome (WS) is a risk factor for vascular dementia (Sauna-aho, Bjelogrić-Laakso, Siren, & Arvio, 2018). Less is known about the link between FXS and memory disorders. In a single cross-sectional FXS study based on the medical reports of 44 men (mean age 50 years), approximately 20% presented memory problems, and 9% presented a decline in functional ability (Utari et al., 2010). In our recent study, we screened dementia-associated signs in 62 adults with Down syndrome (mean age 52 years), 22 adults with WS (mean age 55 years) and 44 men with FXS (mean age 54 years). We found that these signs were frequent in individuals with Down syndrome and senior-aged individuals (70+) with WS but not in those with FXS (Sauna-aho et al., 2018). In another study, we followed the adaptive skills of 34 boys and men with FXS for 20 years. They learned new adaptive skills until the age of 25 years; these skills remained in adulthood but began to decline after the age of 50 years due largely to the weakening of motor skills (Arvio, 2016).

In our previous FXS studies, the focus was on the development of dementia and adaptive behaviours. The objective of this follow-up study was to ascertain how ageing affects the cognition of men with FXS.

## 1.1 | Study group and method

Finland is divided into 16 state-supported regional full-service districts for individuals who have intellectual disabilities. In 1994, we examined all 30 known men (age 15+ years) with a DNA blood test (Southern blot) confirmed FXS living in the South-Häme district (Arvio & Laine, 1995). All our study members had full mutation and got the diagnosis of ID before school age, and none had movement disorder. There were no cases with mosaicism. Of these 30 men, 21 completed neuropsychological assessment by the Leiter International Performance Scale (LIPS) between 1985 and 2004, and the nine oldest men underwent five other tests. We invited the 21 men who were assessed with the LIPS to enrol this study. The first author, a clinical neuropsychologist, made the final assessments



**FIGURE 1** (a) The raw scores, assessed by the Leiter International Performance Scale, of 19 men with fragile X syndrome according to chronological age at baseline and at the end of the study. The black circle represents the mental age of a deceased man assessed by the Leiter International Performance Scale. (b) The individual change in mental age raw score, assessed by the Leiter International Performance Scale, of the 19 study men with fragile X syndrome per follow-up year. Whiskers represent the 95% confidence interval of the mean change

in 2018, and the average follow-up period was 22 years (range 14–33 years) (Figure 1a).

The LIPS test measures general intelligence and is strictly structured, facilitating its use for MA determination with individuals with autistic features or for people with attention difficulties (Carr, 2005; Skinner et al., 2005). The LIPS (the first edition) assessments are based on visual material, and the instructions are pantomimed (Leiter, 1979). The easiest tasks measure the person's ability to combine similar colours and images, and the more complex tasks assess the person's ability to classify images belonging to the same concept class, complete forms, understand number concepts and continue sequential orders. When a person fails in all tasks, his/her MA is 13 months whereas every single successfully completed task of the LIPS adds three months to a person's MA. Besides, the MAs when also reported the raw scores (RSs) which was the number of tasks passed by a study subject. In addition to administering the LIPS assessment, the first author interviewed the study participants as well as their family members or close care providers to determine the participant's functional ability.

The fourth author, a specialist in ID medicine and a child neurologist, has followed the state of health of the study members since 1981.

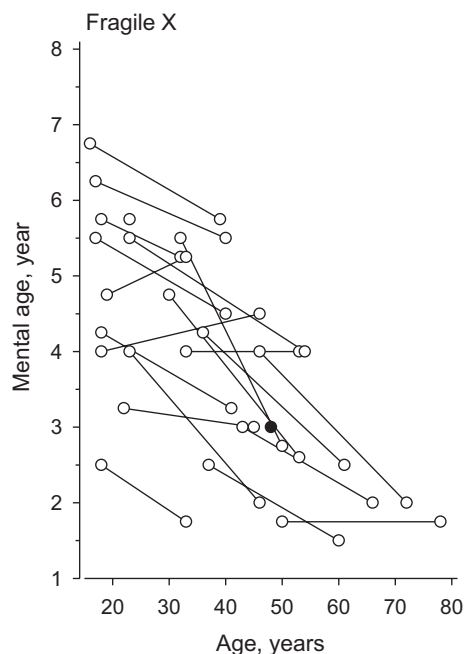
The within-subject (repeated measures) statistical comparisons were performed by permutation tests. Confidence intervals were obtained by bias-corrected bootstrapping (5,000 replications).

Research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki 2002. The ethics committee of the Pirkanmaa University Hospital evaluated our research plan, and the Päijät-Häme Joint Municipal Authority granted research authorization. Written informed consent to participate in the study was obtained from all participants or their representative.

## 2 | RESULTS

Of the 21 men with FXS invited to participate in the study, one refused to participate in the final survey, and one died before the last assessment at the age of 65 years from status epilepticus. At baseline, the chronological age in the study group ranged from 17 to 50 (mean 27) years, and at the end, the ages ranged from 32 to 78 (mean 49) years. Two men had autism spectrum disorder, three men had focal epilepsy, and three had mitral valve prolapse as comorbid conditions. No man showed signs of Alzheimer's, vascular dementia or other memory deficit.

Figures 1a and 2 present each participant's individual RSs and MAs according to chronological age at baseline and at the end of the study, and Figure 1b presents their positive (improvement), plateau (no change) or negative change (decline) of RS. The RS of the deceased man at the baseline assessment at the age of 48 years was eight (MA 3 years) (Figures 1a and 2, black circle). During the follow-up, the RSs of two men (baseline ages 19 and 32 years) improved, and the RSs of two men (baseline ages 34 and 50 years)



**FIGURE 2** The mental ages, assessed by the Leiter International Performance Scale, of 19 men with fragile X syndrome according to chronological age at baseline and at the end of the study. The black circle represents the mental age of a deceased man assessed by the Leiter International Performance Scale

remained the same. In 15 men, RSs declined. Of these 15 men, 13 men showed no cause for mental decline on the basis of neurological and clinical examinations. The epileptic seizure frequency of a 37-year-old man with RS decline increased, and a 49-year-old man with RS decline suffered psychotic symptoms. The study group's mean RS at baseline was 13.05 (MA 4.4 years) and at the end was 9.42 (MA 3.4 years). Overall, the RS of the study group deteriorated by an average of 4 points. ( $p < .001$ ) (Figure 1b).

The deterioration was evident especially in tasks requiring simultaneous processing, non-verbal reasoning, simple problem-solving and cognitive reasoning. The tasks that required matching pictures according to two or more features (e.g. colour and form) or their purpose (e.g. candle and lamp—both are used for lighting) were too difficult to solve at follow-up despite the success at baseline. This was also the case in understanding number concepts beyond two and in matching forms from the smallest to the biggest if the model and the matched pictures were not identical (e.g. circles on the model and squares on the pictures).

Along with these findings, detailed interviews revealed an increased need for support and guidance, a decreased amount of time spent alone without assistance, less interest in social interactions with peers or going out and a greater level of fatigue.

## 3 | DISCUSSION

FXS, the most common X-linked chromosomal ID syndrome, was identified over 40 years ago (Camerino, Mattei, Mattei, Jaye, & Mandel, 1983; Turner, Till, & Daniel, 1978), but most longitudinal studies on FXS include only young boys and men (Cornish et al., 2007; Fisch et al., 2012; Quintin et al., 2016; Schneider et al., 2013). In Finland and probably also in other countries, numerous adults with an ID have not been evaluated systematically for the cause of their disability; thus, there are many unidentified FXS cases. The FXS screening in our catchment area was performed in the early 1990s (Arvio et al., 1997), and since then, we have followed these men on a regular basis (Arvio, 2016). The more we know about the clinical picture of adults, the easier it becomes to recognize unidentified individuals with FXS to improve their care and hopefully their quality of life. An additional benefit arising from the identification of inherited disorders such as FXS is related to the genetic counselling of families, the significance of which is of utmost importance. Considering the rarity of FXS, the size of the study group was reasonable, although ideally it should have been larger.

Individuals with intellectual disabilities probably form the most heterogeneous group of people representing numerous genetic and acquired aetiologies. IQ is represented by a mathematical proportion; the definition of IQ is based on a Gaussian or normal distribution, where the mean is 100 and the standard deviation in most tests is 15. ID is diagnosed if IQ and assessed adaptive abilities are at least 2 standard deviations below the mean (70 or less) during developmental age and the portion is 2.28% of the total sample. IQ in the ID subpopulation ranges from 0 to 69, and the MA ranges from 0 to approximately

12 years, while IQ among the general population ranges from 85 to 115(±15), and the mean MA is approximately the same as chronological age up to 16 years. Intelligence tests are designed for the general population, and test batteries are standardized for certain age groups, such as toddlers, pre-school children, school-aged children and adults. Those with mild ID can be assessed with tests designed for adults, whereas tests designed for younger age groups better serve people with more severe ID but do not reveal their IQ. In addition, the cognitive profile of people with intellectual disabilities is often uneven, and therefore, those with poor verbal skills cannot be assessed with spoken instructions. The LIPS assessment makes an exception to this rule since unlike other neuropsychological tests, and it is applicable to a wide age group from two-year-old children to adults and does not contain spoken instructions. Thus, the strength of our study is the long follow-up performed using the same test method at baseline and at the end. We used the number of passed tasks to make the assessments comparable at different ages.

Our earlier study revealed that the adaptive skills of these same men improved until the age of 25 years and began to decline after the age of 50 years. This study unexpectedly showed that in many men, cognitive skills declined much earlier than adaptive skills. This was evident especially in the two youngest men, aged 16 and 17 years, who, at baseline, had the study group's highest RSs (23 and 22, respectively), but before the ages of 32 and 39 years, their RSs had declined (to 21 and 17, respectively) (Figure 2). The decline became evident in tasks requiring simultaneous processing, non-verbal reasoning and simple problem-solving. The RS and MA of the eldest man remained the same between ages 50 and 79 years (Figure 1 and 2). Unfortunately, we found no documentation of his cognition from his adolescence and youth. However, these observations suggest that at least the non-verbal cognitive skills of men with FXS often start to decline in early adulthood, and most are not associated with any medical or other cause. A brain scan of all the men with mental decline would have been informative, but it would have required general anaesthesia; thus, without a clinical indication, it would have been unethical to perform.

Longitudinal studies on the general population indicate that the adverse impact of ageing on cognition becomes evident only after the age of 60 years and, in some instances, only after the age of 70 years. Processing speed slows even earlier, starting at the age of 55 years according to longitudinal studies (Salthouse, 2009, 2010, 2012, 2016; Schai & Willis, 2010). Skills requiring crystallized abilities, which are largely verbally learned and well mastered, are retained longer. Skills that are associated more with visual perception, processing speed and problem-solving ability, and so-called fluid abilities, tend to be more vulnerable to the weakening effects of ageing (Rönnlund & Nilsson, 2006; Salthouse, 2010; Schaie, 2005). This follow-up study demonstrates that the cognitive developmental trajectory in adults with FXS diverges from the typical developmental trajectory, as the cognitive skills of FXS men start to noticeably weaken before middle age.

Based on our earlier study, the cognitive trajectory in adulthood varies depending on the genetic ID syndrome. A 20-year follow-up

study of people with WS showed that verbal performance strengthened in early adulthood and remained relatively stable up to the age of 45–50 years but then declined rather rapidly. However, the so-called fluid, non-verbal abilities were found to remain stable until at least the age of 55 years (Sauna-aho et al., 2018; Sauna-aho, Bjelogrić-Laakso, Siren, Kangasmäki, & Arvio, 2019). Compared to people with WS, the fluid, non-verbal cognitive abilities of FXS men seem to decline earlier.

## 4 | CONCLUSION

In the most common inherited ID syndrome, FXS, the cognitive development trajectory of adulthood diverges from typical cognitive ageing, which in the general population starts after the age of 60 or 70 years. In our study, the cognitive functioning in men with FXS began to deteriorate in young adulthood, although the risk for dementia did not increase during their lifetime. As cognitive capacity declines, the need for help in their daily routines increases; this should be considered in the provision of social and healthcare services.

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## CONFLICT OF INTEREST

No conflicts of interest have been declared.

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