Viewpoint

Fragile X – A challenge to models of the mind and to best clinical practice

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ABSTRACT

Cornish et al. (2008, this issue) provide an excellent review of Fragile X a common but very complex cause of intellectual disability. They report on a cohort of such males of normal intelligence quotient (IQ) and socioeconomic status (SES), but who have deficits in selective attention and growing impairment in response inhibition. This paper has theoretical views for our models of the mind and clinical implications for families where Fragile X may never have been considered as a possible cause of some of the problems in male and female family members and possibly as well for other disorders such as attention deficit hyperactivity disorder (ADHD) and autism.

I can remember the first time I encountered Fragile X. As part of one of our twin studies in the late 1970s, we had a family where the twin girls had significant learning problems and their brother was intellectually disabled. Shortly after we assessed them, the mother let us know that they had been diagnosed with some new genetic disorder – Fragile X. Checking their test results I saw amazingly large disparities between scores on some verbal and performance subtests and this led to 15 years research with my colleague Danuta Loesch (e.g., Loesch et al., 1993). Of course we now know that Fragile X is associated with dizygotic twinning (Healey et al., 1997) and the neuropsychological research into such disparities has advanced well beyond our initial paper (Crowe and Hay, 1990).

I start on this nostalgic note because in my view Fragile X has still not received its due recognition outside clinical genetics. While two of the authors, Randi and Paul Hagerman, have long championed both research and clinical care, like me many researchers simply “fell” into Fragile X research by accident. It is a very common inherited disorder associated with a bewildering array of neuropsychological and neuropsychiatric impairments that pose some interesting challenges to models of the mind, as well as some still unanswered clinical questions: is Fragile X a neurodegenerative disorder with a decline in cognitive functioning, and if so, what should the individual and the family be told? There have long been discussions of methodological issues which may limit conclusions about whether intelligence quotient (IQ) itself declines in Fragile X (Hay, 1994).

The authors begin with a very good review of where Fragile X is nowadays. It is a complex disorder genetically in that it is...
a repeat of three deoxyribonucleic acid (DNA) base pairs, CGG (cytosine–guanine–guanine) in a region of the X chromosome. Most of us have less than 60 repeats, while those with the full disorder have more than 200 copies, where the gene is methylated (shut down) and the Fragile X mental retardation protein (FMRP) no longer produced. This paper is concerned with those who have between 55 and 200 repeats and who are carriers and in the premutational (PM) state. Thus males can be carriers unlike conventional X-linked disorders. Cornish et al. (2008, this issue) compared 40 PM males with can be carriers unlike conventional X-linked disorders. are carriers and in the premutational (PM) state. Thus males no longer produced. This paper is concerned with those who have between 55 and 200 repeats and who are carriers and in the premutational (PM) state. Thus males can be carriers unlike conventional X-linked disorders. Cornish et al. (2008, this issue) compared 40 PM males with a carefully age-matched group of non-affected males on a very extensive battery covering five areas of neuropsychological functioning. There were very different results on two areas, namely response inhibition characterised by such tasks as the Stroop and on selective attention. On the latter, all males deteriorated in performance as they got older and the PM males were consistently worse. On response inhibition, the PM males got progressively worse after the age of 30. And these were all males of normal IQ.

As the authors point out, problems with response inhibition are not unique to Fragile X and may be important markers for other disorders such as attention deficit hyperactivity disorder (ADHD). What is interesting here is the strong correlation (.49) between response inhibition problems and the number of CGG repeats and also the relation to a recently described neurodegenerative disorder, Fragile X associated tremor/ataxia disorder (FXTAS) found in some Fragile X males age 50. Indeed the authors go so far as to claim that response inhibition may be a marker for those destined to develop this disorder and they relate this to diminished activity of the protein, FMRP and its effects on the right inferior frontal cortex. Thus rather than the all or none effects usually seen in genetic disorders, we have quantitative change in gene, then protein, then neuropsychological impairment and (putatively) a brain region and a neurodegenerative condition.

There are three main messages in this paper:

Firstly to think more about who may be in the PM phase of Fragile X. These are men of normal IQ and of similar socioeconomic status (SES) and occupational status to the matched controls. Yet they have consistent differences in selective attention and growing impairment in response inhibition. Fragile X may never have even been considered in their family, especially as physical signs are subtle. Asking about female relatives who are shy and have learning problems or male relatives with some degree of intellectual disability may be enough to warrant the DNA test for the number of repeats which is much more reliable than the cytogenetic assessment used when I first got involved in this area.

Secondly what does it say about the determinants of components of cognition? Is it appropriate to think of something as specific as response inhibition, being independent of the other areas of neuropsychological functioning which do not show the same association with number of CGG repeats, nor the same increasing impairment compared with controls? In the presence of normal IQ, what does such a quantitative change in functioning say about the role of response inhibition and selective attention in contributing to IQ and SES achievement?

Thirdly, does this provide an exemplar for other behavioural disorders? The authors did refer to response inhibition as also being one of the more robust endophenotypes for ADHD and Zametkin et al. (2001) did discuss Fragile X as a useful model for neuropsychological and neuroanatomical changes in ADHD. There may be even more parallels. Randi Hagerman has long discussed the association of autistic-like features with Fragile X and there is growing work on deficits in social reciprocity in children with ADHD and even possible links between Autism and ADHD (Holtmann et al., 2005). While children with autism have often been screened for Fragile X, is it worth considering screening for the number of CGG repeats in children and adults presenting with a broader range of psychopathologies? However, there have to be caveats about extending this approach to concepts such as response inhibition which has complex relationships with different behavioural disorders (Dyck et al., 2004).

I thank the authors for this article. It has certainly brought me up to date with the recent advances in Fragile X and demonstrated just how subtle are the neuropsychological effects of this complex but common disorder. Hopefully it will encourage more to venture into Fragile X as a challenging area of research. There is also a duty to help families. During my time working on Fragile X, I would say the diagnosis “rippled” through families as more and more members discovered the implications of a disorder of which they had never heard. These people deserve the most accurate information on the neuropsychological implications and the possibility of the neurodegenerative FXTAS. The disorder remains complex but one where the genetic counsellors and the neuroscientists should be able to work together to provide families with the most recent information. This article helps.

References


