

## Delineation of early attentional control difficulties in fragile X syndrome: Focus on neurocomputational changes

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### Abstract

Fragile X syndrome (FXS) is due to the silencing of a single X-linked gene and it is associated with striking attentional difficulties. As FXS is well characterised at the cellular level, the condition provides a unique opportunity to investigate how a genetic dysfunction can impact on the development of neurocomputational properties relevant to attention. Thirteen young boys with FXS and 13 mental-age-matched typically developing controls performed a touch-screen-based search task that manipulated the similarity between targets and distractors and their heterogeneity in size. Search speed, path and errors were recorded as multiple measures of performance. Children did not differ in overall search speed or path when searching amongst distractors, but striking error patterns distinguished children with FXS from controls. Firstly, although clear markers of previously found targets remained on screen, children with FXS perseverated on touching previous hits more than typically developing controls, consistent with the well-documented inhibitory deficits in adults with the disorder. Secondly, they could accurately discriminate single target-distractor pairs, but, when searching a complex display, they touched distractors more often than control children when distractors were similar to targets and especially so when these were infrequent, highlighting difficulties in judging relative size and allocate attentional weight independently of stimulus frequency. Thirdly, their performance was also characterised by inaccuracies in pointing, suggesting additional motor control deficits. Taken together, the findings suggest that fragile X syndrome affects the early development of multiple processes contributing to efficient attentional selection, as would be predicted from an understanding of the neurocomputational changes associated with the disorder.

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Fragile X syndrome (FXS) is the most common form of inherited mental retardation in males, with an incidence estimated at 1 in 4,000–9,000 (Crawford, Acuna, & Sherman, 2001). It is associated with the silencing of a single gene, the Fragile X Mental Retardation gene (FMR1, Verkerk et al., 1991). The cellular physiology and the cortical patterns of expression of the protein associated with FMR1 have been recently mapped out, making fragile X syndrome a unique model to investigate the relationships between the silencing of a single gene and the development of neurocognitive dysfunction (e.g., Jin & Warren, 2003; Reiss & Dant, 2003). Furthermore, an increasingly large

number of individuals with the condition are now diagnosed early in childhood (Bailey, Roberts, Mirrett, & Hatton, 2001), highlighting the need to study processes leading to very early deficits in cognitive functioning.

Serious problems of inattention and hyperactivity are clinically diagnostic of fragile X syndrome across the lifespan (Cornish, Sudhalter, & Turk, 2004; Hagerman & Hagerman, 2002; Turk, 1998). Adults and older children with the syndrome differ from typically developing individuals and those with other genetic disorders in their inability to inhibit task-irrelevant repetitive responses (Cornish, Munir, & Cross, 2001; Munir, Cornish, & Wilding, 2000; Wilding, Cornish, & Munir, 2002). Recently, even toddlers with fragile X syndrome demonstrated difficulties in executive control (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004). When assessed with a

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touch-screen-based task that required searching for targets amongst a variable number of distractors that were more or less similar to the targets in size, toddlers with FXS repeatedly touched targets that they had already found, suggesting difficulties in inhibiting previously successful responses, a pattern that mirrored the errors by older children with FXS (Wilding et al., 2002). Deficits in inhibiting inappropriate eye-movements in an analogue of the antisaccade task were also demonstrated in infants with FXS as young as 12 months old (Scerif et al., 2005).

What are the neural correlates of these seeming life-long difficulties with executive control? Adult women with fragile X syndrome have shown dysfunctional activation of prefrontal and parietal cortices during multiple tasks requiring executive control (e.g., Cornish, Swainson, et al., 2004; Menon, Leroux, White, & Reiss, 2004; Tamm, Menon, Johnston, Hessel, & Reiss, 2002). In order to understand these findings at the systems level, it is crucial to appreciate the cellular pathophysiology of FXS at least in basic terms. The Fragile X Mental Retardation gene (FMR1) codes for a protein (FMRP) that plays a key role in the post-synaptic refinement of dendritic spine morphology following the excitation of metabotropic glutamatergic receptors, type I (Bagni & Greenough, 2005; Bear, Huber, & Warren, 2004). FMRP acts as a translational repressor by regulating translation of multiple dendritic mRNAs involved in synaptic development and function (Brown et al., 2001), so that loss of FMRP is associated with immature dendritic spine morphology (e.g., Irwin et al., 2002) and dysregulation of other neurotransmitter pathways (e.g., monoamines, Gruss & Braun, 2004; Zhang et al., 2005). These morphological and functional changes seem ubiquitous across cortex, but they may be particularly disruptive for the development of executive functions, because these are supported by circuits that rely more extensively on these structural changes and neuromodulatory functions, as seems to be the case for prefrontal cortices and the networks to which they belong (refer to Scerif et al., 2005; Scerif & Karmiloff-Smith, 2005, for further details on this argument). However, an understanding of the neurobiology of the syndrome also predicts that executive difficulties should not be the sole characteristic cognitive deficit in FXS: multiple cognitive processes may be affected by the changes in neurocomputational properties associated with FMR1 silencing and its related cascade of molecular events. Widespread effects of changes in low-level computational properties, rather than selective effects on specific high-level cognitive functions, have indeed already been suggested to account for the complex cognitive profile in fragile X syndrome (Cornish, Turk, et al., 2004). The challenge remains to understand why certain cognitive processes are more affected than others, and why deficits co-occur in this disorder.

Multiple deficits do indeed seem to accompany prominent executive difficulties in toddlers with FXS. Scerif et al. (2004) asked typically developing toddlers, toddlers with FXS and toddlers with Williams syndrome (WS, another genetic disorder characterised by attentional difficulties) to search for targets amongst distractors that varied in number and were either similar or dissimilar to targets in terms of size. Search performance by toddlers with FXS was characterised by striking repetitive errors on previously found targets compared to the other groups, but

also by a larger number of erroneous touches on distractors compared to typically developing controls, with toddlers with WS producing the greatest number of such errors. This suggested atypical processing of target-distractor similarity for toddlers with FXS or WS during search, despite the fact that these children could accurately discriminate single target-distractor pairs. These errors were particularly surprising for toddlers with FXS, given that older children with FXS (aged between 8 and 15 years of age) never confused targets and distractors in a variant of this task that required target-distractor discriminations through a categorical distinction (vertically as opposed to horizontally oriented stimuli of two different colours) (Wilding et al., 2002), rather than requiring a relative size judgment (Scerif et al., 2004). However, the study design did not allow investigating in detail all possible sources of these difficulties for children with FXS, and we therefore aimed to do so here.

The relative salience of targets is affected both by whether distractors are similar to targets and by whether distractors can be grouped into homogeneous sets (Duncan & Humphreys, 1989; Humphreys, Quinlan, & Riddoch, 1989). In fact, the effects of these two manipulations of target salience can be relatively independent of each other. For example, some patients with visual agnosia are atypically affected by the similarity of targets and distractors, but not by distractor heterogeneity, presumably because disadvantages associated with the latter depend on different processes, such as the disruption of Gestalt grouping of distractors (Humphreys, Riddoch, Quinlan, Price, & Donnelly, 1992). Older children with FXS display relative strengths in perceptual grouping (Cornish, Munir, & Cross, 1999). Therefore, target-distractor similarity and distractor heterogeneity may vary in the extent to which they impact on the efficiency of search in fragile X syndrome. Employing heterogeneous search displays for the first time afforded an additional empirical question. Infrequent items in a search display appear relatively more salient because computations of salience depend on the difference between an element and any other elements in the display (Cave & Wolfe, 1990) and between that element and neighbouring elements (Wolfe, 1994). Differences in salience for infrequent items account for strong effects of relative ratios across distractor types, with infrequent distractors receiving greater attentional weight and appearing more salient than frequent ones (e.g., Shen, Reingold, & Pomplun, 2000). Therefore, employing search displays composed of heterogeneous distractors would enable us to test the degree to which children are affected by the relative salience of distractors regardless of their similarity to targets.

In sum, we sought to extend earlier characterisations of control difficulties in older children with FXS (Wilding et al., 2002) and in toddlers with FXS (Scerif et al., 2004) by investigating in detail search performance in young children with FXS, with a particular emphasis on all their errors and on assessing the effects of target and distractor salience. We therefore manipulated concurrently, for the first time, target-distractor similarity, distractor heterogeneity and the relative proportion of distractors of various types. Firstly, if young children with FXS display early difficulties analogous to those in older individuals with the syndrome, their search performance should be characterised by repetitive errors. Secondly, if their ability to evaluate target and

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