Title: Trajectories of Crystallized and Fluid Reasoning and the Influence of Biological and Environmental Factors in Females with Fragile X Syndrome

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Introduction: Fragile X syndrome (FXS) is caused by a mutation in the \textit{FMR} 1 gene on the X chromosome, which leads to decreased levels of its associated protein (FMRP). Reduced FMRP leads to atypical synaptic development (Tassone, 2014), and, as a consequence, an array of cognitive, behavioral, and emotional impairments. Because FXS is an X-linked condition, females with FXS are more mildly affected than males, on average. At the group level, both males and females with FXS show less severe impairments in the ability to access verbal information acquired through explicit learning (so-called crystallized intelligence) and more severe impairments in the ability to solve novel problems that are less dependent on explicit instruction (so-called fluid intelligence). Due, in part, to X inactivation, there is a considerable variability in terms of severity of affectedness among females, ranging from cognitive skills in the typical range to about 33\% of females having an intellectual disability (Huddleston, Visootsak, & Sherman, 2014). Relative to males with FXS, there have been few investigations focused on females with FXS, in part due to the differences in prevalence and variability observed between the two sexes. The present project is focused on understanding the determinants of cognitive development in females with FXS.

Method: The current longitudinal study was designed to investigate (1) trajectories of fluid reasoning (assessed through the Repeated Patterns and Sequential Order subtests of the Leiter) and crystallized ability (assessed through a measure of expressive vocabulary) in females with FXS ($n=16$, ages 10-15 years at enrollment, at four annual assessments), and (2) the relative influences of biological factors (FMRP levels and the activation ratio; i.e., proportion of active Xs carrying the full mutation and family-environmental factors (perceived closeness in the mother-child relationship, maternal psychological distress, maternal educational, and maternal IQ).

Results: Results showed that level of fluid intelligence was linked to a lower activation ratio, higher FMRP levels, closer mother-child relationship, and lower maternal psychological distress. In contrast, level of crystallized intelligence was related to closer mother-child relationship and lower maternal psychological distress. In terms of longitudinal change, age-related gains were observed in fluid reasoning ($\beta=2.0, p=0.02$) and crystallized abilities ($\beta=5.2, p<0.001$). Individual change over time in fluid reasoning was exclusively predicted by FMRP levels ($\beta=4.7, p<0.001$) and activation ratio ($\beta=-1.4, p=0.01$). In contrast, change over time in crystallized ability was solely predicted by the closeness in the mother-child relationship ($\beta =0.8, p=0.01$) and maternal level of education ($\beta =7.5, p<0.001$).

Discussion: Our results are consistent with previous literature (Dyer-friedman et al., 2002; Kover, Pierpont, Kim, Brown, & Abbeduto, 2013) in suggesting that, in females with FXS, the level and rate of change in fluid reasoning during adolescence is particularly susceptible to the impact of biological factors. This reflects the role that FMRP plays in frontostriatal and prefrontal development. Thus, pharmacological treatments targeting these areas may improve fluid reasoning abilities. In contrast, the fact that level and rate of change in crystallized ability is sensitive only to environmental factors suggests that it is a potential target of efforts to enrich the family environment.

References/Citations: