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Developmental trajectories of executive functions in young males with fragile X syndrome

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ABSTRACT

Background: Executive functions (EF) have been identified as impaired in FXS, but few studies have examined their developmental trajectories.
Aims: The primary aim of this longitudinal study was to examine the development of EF in young males with FXS compared to Mental Age (MA)-matched controls.
Methods and Procedures: The sample comprised 56 boys with FXS (ages 7–13 years), and 48 MA-matched typical boys (ages 4–8 years). EF tasks included measures of inhibitory control, working memory, cognitive flexibility/set-shifting, problem solving/planning, and processing speed. Tasks were administered at three time points over five-years.
Outcomes and Results: The MA-Matched Typical boys significantly outperformed the FXS boys on all EF tasks, with the FXS Group showing a pattern of slow, but positive growth on most EF tasks. For working memory tasks, significant interactions were noted between MA and autism symptom severity, and MA and medication status. The probability of task completion increased with higher MA.
Conclusions and Implications: These findings contribute to our understanding of the development of EF in this population. They also lay the foundation for use of EF tasks in treatment efforts, particularly with respect to documenting improvements and practice effects, and in understanding associations with targeted developmental outcomes.

What this paper adds?

This is one of the first investigation of the developmental unfolding of various EF in boys with FXS using longitudinal methodology and an empirically based, multidimensional model of EF. Tracking the EF developmental trajectory over a five-year time span, the findings from this study provide strong evidence for core global delays in EF in FXS boys, and add a missing piece to the FXS EF development literature. The results also provide guidance for the assessment of various EF in children with FXS. Given this

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phenotypic set of findings, the use of such measures would be critical in the assessment of individuals with FXS, particularly given the challenges of conducting assessments with this population (Hessl et al., 2009). Assessment practices should include measures of EF, especially those that are developmentally sensitive, as EF undoubtedly contribute to much of the cognitive, behavioural, and affective dysregulation that can be manifest in this population across the ages (Raspa, Wheeler, & Riley, 2017). Knowing that most, if not all, EF show slowed growth over time also portends the need for early intervention in an effort to change these developmental trajectories in a positive fashion. Further, these findings provide much needed information regarding potential tasks to be employed in clinical trials. The findings from this study provide important details about the performance of young boys with FXS on these specific tasks as well as what might be expected from the developmental trajectories of these tasks without the implementation of controlled interventions.

1. Introduction

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability (Hagerman, 2008) and is caused by mutations of the fragile X mental retardation-1 (FMR-1) gene. The FMR-1 gene is located on the X chromosome. In its typical form, the gene contains somewhere between 5–55 trinucleotide (CGG) repeats, while there are approximately 56–200 repeats for the premutation form of the gene wherein individuals do not show the prototypic clinical symptoms of FXS. For the full mutation of the gene, CGG repeats are greater than 200, and there is complete methylation of the *FMR1* gene and little to no production of the Fragile X Mental Retardation Protein (FMRP). FMRP is critical for brain development (Hall, Dougherty, & Reiss, 2016; Hoeft et al., 2008; Peng et al., 2013), and its lack of production contributes to the characteristic neurocognitive features seen in many individuals with FXS (Raspa et al., 2017; Van der Molen et al., 2010). With the FMR1 protein prominently expressed in the frontal brain regions, the domain of executive functions (EF) has been of keen interest to investigators exploring phenotypic neurocognitive functions in FXS.

1.1. An overview of EF development

Executive Functions represent a multidimensional y of cognitive abilities that support the execution of goal-directed behaviours (Friedman & Miyake, 2017). Many of the control processes associated with EF have been described in conceptual and empirical models going back over 25 years, and have been variously described as consisting of two (Carlson, Moses, & Claxton, 2004); three (Pennington, 1997), four (Denckla, 1996; Espy, 2004), and six factors (Daigneault, Braun, & Whitaker, 1992). Executive processes are critical to the integrity of many learning and social-behavioural functions (Cragg & Gilmore, 2014; Devine & Hughes, 2014; Fuhs, Nesbitt, Farran, & Dong, 2014; Martin, Quintin, Hall, & Reiss, 2016; Richland & Burchinal, 2013). In addition to being important to learning and social-behavioural functions, EF have a developmental basis that will have differential effects on learning and behaviour over time with both neurological (e.g., Hall et al., 2016; Peng et al., 2013) and environmental factors (e.g., poverty) contributing to the developmental integrity of EF (Ardilia, Rosselli, & Matute, 2005; Blair, Raver, Berry, & The Family Life Project Investigators, 2014; Cuevas et al., 2014; Hackman, Gallop, Evans, & Farah, 2015; Raver, Blair, Willoughby, & The Life Project Key Investigators, 2013).

1.1.1. Development of EF in young children

The development of EF is complex, given the multidimensionality of the EF construct noted above, and it is even more poignant for the young child. Not only are young children more difficult to assess more generally, the limited availability of developmentally appropriate measures and their associated interpretation remain of keen interest to both clinicians and researchers. This interest is accentuated even further when questions pertaining to the development of EF in young children with disabilities are posed, and it is important for such questions to be raised, particularly for children with intellectual/developmental disabilities as far less is known about the development of EF in these populations. In general, previous studies have shown that in typically developing preschool children there is positive, but differential growth of various executive functions (Blair, Zelazo, & Greenberg, 2005; Hongwanishkul, Happaney, Lee, & Zelazo, 2005), with this growth laying the foundation for future growth into the school-age years (Brocki and Bohlin (2004).

1.2. EF in fragile X syndrome

To date, there have been only a few explorations of EF in young males with FXS, possibly due to the challenges inherent in their lower functioning and subsequent acquisition of reliable assessment data (Garner, Callias, & Turk, 1999). Despite these measurement challenges, a number of investigators have described disproportionate EF deficits in males with FXS in the domains of inhibitory control, different types of attention (e.g., selective, divided, sustained, shifting) (Tonnsen, Grefer, Hatton, & Roberts, 2015; Wilding, Cornish, & Munir, 2002), set-shifting (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004), working memory (Baker et al., 2011; Lanfranchi, Cornoldi, Drigo, & Vianello, 2009; Munir, Cornish, & Wilding, 2000), and behavioural regulation (Loesch et al., 2003) when compared to chronological-age and mental age-matched typicals as well as selected disability groups (e.g., Williams Syndrome, Down Syndrome).

Hooper et al. (2008) examined the EF in 54 boys with fragile X syndrome (FXS), ages 7–13 years, when compared to that of a group of typically developing boys matched on MA and ethnicity. Results revealed a differential level of task completion, with only 25.9% being able to complete a set-shifting task, but 94.4% being able to complete a word span task. Additionally, when compared to the MA matched typical boys, boys with FXS demonstrated disproportionate impairments in inhibitory control, working memory,