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Developmental trajectories of attentional control in preschool males with fragile X syndrome

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ABSTRACT

Attention problems are among the most impairing features associated with fragile X syndrome (FXS). However, few studies have examined behavioral development of inhibitory control in very young children with FXS. We examined attentional control in 3–6 year boys with FXS using both an experimental inhibitory control paradigm and parent-report of attention problems. Study 1 examined attentional control in FXS compared to comparison groups matched on chronological and mental age. To determine the stability of impairments over time in FXS, Study 2 examined patterns of developmental change in an expanded longitudinal sample. Across studies, males with FXS demonstrated persistent impairments in inhibitory control and parent-reported attention problems. Inhibitory control was related to, but not solely driven by, lower mental age. Although parent-rated attention problems remained stable across ages, inhibitory control improved with time. Children with more severe attention problems often displayed initially poorer inhibitory control. However, these trajectories also improved more rapidly with age. Our findings indicate that despite persistent deficits in attentional control in young children with FXS, multi-method assessment can be used to capture developmental growth that should be further supported through early, targeted intervention.

1. Introduction

Fragile X syndrome is the most common heritable form of intellectual disability, affecting 1:4000–6000 individuals. Fragile X is caused by a CGG repeat expansion on the promotor region of the *FMR*1 gene, resulting in reduced production of fragile X mental retardation protein necessary for mRNA transcription and synaptic plasticity. Among males with FXS, over 90% are diagnosed with comorbid conditions such as attention problems, anxiety, and autism symptomatology (Bailey, Raspa, Olmsted, & Holiday, 2008; Sullivan et al., 2006). In light of these high rates of behavior problems and the known genetic mechanisms of FXS, studying developmental psychopathology within FXS lends insight into complex interactions among genetics, experience, and behavior.

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Attention problems are among the earliest and most impairing features associated with FXS, presenting in early infancy and toddlerhood (Cornish, Scerif, & Karmiloff-Smith, 2007; Roberts, Hatton, Long, Anello, & Colombo, 2011) and potentially "constraining" later neurocognitive development (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012). Attention involves multiple dimensions; including orienting, maintenance and regulation; which are reflected at both behavioral and neurocognitive levels. Behavioral indicators are often reported in terms of meeting criteria for an attention-related disorder such as attention deficit hyperactivity disorder (ADHD). In FXS, 54–74% of males meet behavioral ADHD diagnostic criteria and over 80% receive attention-related diagnoses or treatment (Bailey et al., 2012, 2008). Although children with FXS are reported to exhibit both inattentive and hyperactive symptoms (Bailey et al., 2008; Sullivan et al., 2006; Wheeler et al., 2014), within-group analyses suggest greater deficits in inattentive compared to hyperactive and oppositional symptoms in school-aged children (Cornish et al., 2012). As measured by behavior rating scales, attention symptoms in FXS are relatively stable in childhood (Cornish et al., 2012; Hatton et al., 2002) but appear to decrease into late adolescence and adulthood (Wheeler et al., 2014), consistent with findings of decreased attention-related medication use in adults versus children (Bailey et al., 2012).

Importantly, profiles of behavioral attention problems in school-aged children with FXS have been linked to early neurocognitive deficits within the FXS phenotype, with particular deficits noted in inhibitory control (Cornish et al., 2012; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012). Inhibitory control is defined as the ability to inhibit a prepotent or predominant response (Barkley, 1997), a skill that develops across childhood and into adulthood with maturation of ventral fronto-striatal circuitry (Durston et al., 2002). Although inhibitory control improves with age, inhibitory control abilities of children with FXS relative to same-aged peers remains relatively stable across childhood (Kochanska, Murray, & Coy, 1997), thus children with early impairments are likely to also experience continued difficulties later in life. Inhibitory control is central to a variety of daily tasks during the preschool period, such as taking turns during games and listening to a complete question before answering. Unsurprisingly, children who fail to inhibit predominant responses in these types of situations are vulnerable to poorer academic and socio-emotional experiences, as inhibition is critical to participation in both academic learning environments and healthy social networks (Blair & Razza, 2007; Kochanska et al., 1997).

The intersection of inhibitory control and both academic and socio-emotional functioning is particularly relevant for individuals with FXS who often exhibit co-occurring attention, learning, and socio-emotional challenges (Bailey et al., 2008). Previous attention studies suggest school-age children with FXS exhibit poor inhibition through greater errors on tasks that require sustaining or switching attention (Cornish et al., 2007; Scerif et al., 2012; Sullivan et al., 2007), even in comparison to children with Down syndrome (Cornish et al., 2007; Munir, Cornish, & Wilding, 2000), Williams syndrome (Cornish et al., 2007), and Prader Willi syndrome (Woodcock, Oliver, & Humphreys, 2009). These cross-syndrome comparisons indicate a relatively specific vulnerability to poor inhibitory control within the FXS phenotype contrasted to other neurodevelopmental disorders. These deficits likely emerge early in development, as toddlers with FXS often perseverate on previously selected items during visual search activities (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2007) and show greater numbers of reflexive saccades on inhibitory visual saccade tasks (Cornish et al., 2007; Scerif et al., 2005). Given the pervasive nature and early emergence of these impairments, it is likely that poor inhibitory control contributes to cascading academic and socio-emotional challenges associated with FXS (Cornish et al., 2012).

A number of important advances have improved our understanding of the nature and timing of these inhibitory control deficits. First, contrasting attention in FXS to various comparison groups has informed understanding of the underlying mechanisms and specificity of attention deficits. Cross-sectional studies in young children have contrasted FXS groups to children without known genetic conditions, matched on both chronological and mental age (Scerif et al., 2004, 2007, 2005), supporting conclusions that attentional control is atypical based on chronological age, yet impairments are not solely driven by lower intellectual abilities. In addition, cross-syndrome comparisons suggest that specific attention-related deficits appear unique to FXS, indicating mores severe inhibitory control impairments in FXS compared to other neurodevelopmental disorders (Cornish et al., 2007; Munir et al., 2000; Woodcock et al., 2009). In addition to the rich information afforded by multiple matching strategies, there has been increased emphasis on longitudinal characterization of attentional trajectories across childhood, consistent with evidence that disorders emerge from complex, nonlinear influences rather than global, static impairments (Karmiloff-Smith, 2009). Several recent studies in FXS have identified developmental changes in attentional control that were only detectable using longitudinal data (Cornish et al., 2012; Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Scerif et al., 2012), highlighting the critical importance of capturing within-individual patterns of change over time.

It is increasingly recognized that early detection and treatment of attention problems holds promise for maximizing positive outcomes (Halperin, Bédard, & Curchack-Lichtin, 2012). Given the critical role of attention and inhibitory control in academic and socio-emotional development (Blair & Razza, 2007; Kochanska et al., 1997) and its known impairments in FXS (Cornish et al., 2007; Scerif et al., 2012; Sullivan et al., 2007), early interventions are likely to improve outcomes in young children with FXS. However, tailoring interventions to this population first requires understanding of the developmental course of attentional control during early childhood. Although several comprehensive, longitudinal studies of attention have been conducted in children with FXS (Cornish et al., 2012: FXS $n = 48$, $\bar{x}$ initial age = 8.17 years; Cornish et al., 2013: FXS $n = 21$, $\bar{x}$ initial = 8.75 years; Roberts et al., 2011: FXS $n = 13$, initial = 9–12 m; Scerif et al., 2012: FXS $n = 21$, $\bar{x}$ initial = 8.6 years), studies focused in early childhood have predominantly examined attentional phenotype through cross-sectional comparisons, most commonly using computerized visual attention tasks rather than behavioral measures