Published in final edited form as:

Am J Intellect Dev Disabil. 2018 March ; 123(2): 89–102. doi:10.1352/1944-7558-123.2.89.

The Emergence of Effortful Control in Young Boys With Fragile X Syndrome

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Abstract

Effortful control, or the ability to suppress a dominant response to perform a subdominant response, is an early-emerging temperament trait that is linked with positive social-emotional development. Fragile X syndrome (FXS) is a single-gene disorder characterized by hallmark regulatory impairments, suggesting diminished effortful control. This study compared the development of effortful control in preschool boys with FXS ($n=97$) and typical development ($n=32$). Unlike their typical peers, the boys with FXS did not exhibit growth in effortful control over time, which could not be accounted for by adaptive impairments, *FMR1* molecular measures, or autism symptoms. These results contribute to our understanding of the childhood phenotype of FXS that may be linked to the poor social-emotional outcomes seen in this group.

Keywords

Fragile X syndrome; effortful control; temperament; autism; FMR1; FMRP

Childhood temperament, or individual differences in reactivity and self-regulation, is a reliable predictor of a range of developmental outcomes (Rothbart & Derryberry, 1981) that has proven useful in distinguishing clinical groups (Samyn, Roeyers, & Bijttebier, 2011). Thus, the study of early temperament profiles can inform later patterns of risk and resiliency in at-risk groups. Temperament is comprised of many dimensions, such as impulsivity, shyness, soothability, inhibitory control, and pleasure intensity (Rothbart, Ahadi, Hershey, &

Fisher, 2001). These characteristics are thought to be innate and relatively stable, yet are influenced by developmental, biological, and experiential factors (Rothbart & Bates, 1998). Parent rating scales are the primary means of measuring temperament (Gagne, Van Hulle, Aksan, Essex, & Goldsmith, 2011). Evidence suggests that parent-rated temperament profiles can be captured within three core domains: (1) negative affectivity, which reflects negative emotional reactivity or emotional dysregulation; (2) surgency, which is characterized by consistent high activity level, rapid response initiation, risk taking behaviors, and ease in novel social situations; and (3) effortful control, or the ability to suppress a dominant response to perform a subdominant response (Rothbart, Ahadi, & Evans, 2000; Rothbart, Ahadi, Hershey, & Fischer, 2001; Posner & Rothbart, 2000; Putnam, Garstein, & Rothbart, 2006).

This study focuses on the developmental change in effortful control in fragile X syndrome (FXS), a genetic disorder whose phenotype includes the hallmark features of impaired self-regulation and poor attention control—features that are consistent with low levels of effortful control. The development of this temperament domain has not been studied in young children with FXS, although early effortful control has been linked with a number of cognitive, behavioral, and social-emotional outcomes that are of particular relevance to FXS. These include attention, academic achievement, social competence and cognition, self-regulation in adolescence and adulthood, and risk for psychopathology (Ayduk, Mendoza-Denton, Mischel, & Downey, 2000; Carlson & Moses, 2001; Shoda, Mischel, & Peake, 1990; Rothbart, Ellis, Rueda, & Posner, 2003).

Fragile X Syndrome

FXS is the leading cause of inherited intellectual disability, affecting as many as 1 in 2,500 males (Fernandez-Carvajal et al., 2009; Hagerman, 2008). The disorder is caused by an expanded number of CGG nucleotide repeats on the *Fragile X Mental Retardation-1 (FMR1)* gene of the X chromosome (Crawford, Acuna, & Sherman, 2001). These mutations reduce the expression of the Fragile X Mental Retardation Protein (FMRP), an essential protein for cognitive development (Crawford et al., 2001; Hatton et al., 2006). Individuals with 200 or more CGG repeats have the full mutation, which causes the gene to methylate and subsequently reduces FMRP production, causing the behavioral and cognitive phenotype of FXS.

Development is highly impacted by FXS; most individuals with FXS fall in the moderate range of intellectual disabilities (Bailey, Raspa, Olmsted, & Holiday, 2008; Roberts, Mirrett, P., & Burchinal, 2001; Roberts, McCary, Shinkareva, & Bailey, 2016). Adaptive behaviors are also impaired, with growth significantly slower than age-based expectations (Hatton et al., 2003; McCary, Machlin, & Roberts, 2013). In addition to cognitive and adaptive deficits, the core behavioral phenotype of FXS includes symptoms such as inattention, hyperactivity, and impulsivity (Sullivan et al., 2006), as well as a number of autistic symptoms, such as poor eye contact, stereotypic behaviors, atypical sensory responses, and social-communication impairments (Hatton et al., 2006; Kaufmann et al., 2004; Klusek, Martin, & Losh, 2014a). Individuals with FXS have a high risk for autism spectrum disorder (ASD); ~60% of males and ~30% of females with FXS meet criteria for ASD (Garcia-Nonell et al.,

2008; Klusek, Martin, & Losh, 2014b). FXS may serve as a useful model for studying temperament, as individuals with this disorder are characterized by common genetic characteristics (i.e., the *FMR1* mutation), physiological dysregulation, and distinct cognitive and behavioral profiles (i.e., adaptive behavior deficits and heightened autism symptoms). The study of these temperament profiles within FXS may inform patterns of risk and resilience relevant to other clinical populations that have less clearly-defined mechanisms, as well as typical development more generally.

Role of Effortful Control in Development

Effortful control is the ability to suppress a dominant response to perform a subdominant response (Posner & Rothbart, 2000) and reflects an innate predisposition for self-regulation (Diamond, 2013). In typical development, the developmental trajectory of effortful control is well-established, with emergence observed in the toddler years and large improvements occurring between 2 and 3 years, reflecting, in part, neural development particularly in the prefrontal cortex (Blair & Diamond, 2008; Kochanska, Murray, & Harlan, 2000; Li-Grining, 2007). After 4 years the rate of effortful control growth slows (Jones, Rothbart, & Posner, 2003; Murphy, Eisenberg, Fabes, Shepard & Guthrie, 1999).

Although effortful control increases across early childhood, this temperament trait is considered as generally innate, with children showing moderate stability in their rank order of effortful control levels across early childhood (Kochanska & Knaack, 2003). Research shows that several skills underlie effortful control, including inhibitory control, attention focusing, perceptual sensitivity, low-intensity pleasure, and smiling/laughter (Rothbart, Ahadi, & Hershey, 1994; Rothbart et al., 2001). These skills assist individuals in regulating behaviors that are typically driven by affect (Rothbart, Ellis, Rueda, & Posner, 2003). Therefore, it is not surprising that high levels of effortful control have been linked with a number of social-emotional outcomes, which include elevated metacognition (Carlson & Moses, 2001), social competence, self-regulation, enhanced adjustment, and decreased levels of psychopathology (Rothbart et al., 2003).

Effortful control impacts both behavioral and emotional development and, when impaired, it can lead to increased risk for negative outcomes. Specifically, lower levels of effortful control increase the risk for problem behavior and psychopathology (Nigg, 2006; Muris & Ollendick, 2005) with strong support that low levels of effortful control relate to elevated externalizing behaviors and internalizing behaviors (Eisenberg, Valiente, Cumberland & Liew, 2009; Eisenberg et al., 2005; Murray & Kochanska, 2002). This factor is inversely related to externalizing problems in the presence of high negative emotionality (Eisenberg & Fabes, 1992). Furthermore, the risk for depression is increased when individuals display extremely low levels of effortful control combined with high negative emotionality (Nigg, 2006). Internalizing symptoms have also been found to relate to low levels of attentional effortful control, which is a subfactor focusing on the attention mechanisms (Eisenberg et al., 2009; Eisenberg et al., 2005). Strong links have also been found between effortful control and attention deficit hyperactivity disorder, specifically with inattentive symptoms (Nigg, Goldsmith, & Sachek, 2004) and lower levels of effortful control in toddlerhood are

predictive to increased parent-reported attention problems at age 4 (Murray & Kochanska, 2002).

Effortful control has also been shown to be the only temperament construct to differentiate children with autism spectrum disorder (ASD) from typically developing children ages 3 to 10 with reduced levels of effortful control in children with ASD (Konstantareas & Stewart, 2006). Furthermore, in a prospective study investigating early temperament profiles in infants at increased risk for ASD due to having an older sibling with ASD, children who were diagnosed with ASD at 3 years of age displayed an “Effortful Emotion Regulation Profile” marked by lower positive affect, higher negative affect, and difficulty controlling attention and behavior when compared to controls (Garon et al., 2009). Similarly, infants at high risk for ASD showed reduced effortful control at 14 and 24 months old compared to controls (Clifford, Hudry, Elsabbagh, and Johnson, 2013). Altogether, these findings underscore the important role of effortful control in social and behavioral development as well as the possible link to later behavioral outcomes.

Effortful Control in FXS

Very little is known about the nature, development, or consequences of effortful control, or temperament more generally, in individuals with FXS. FXS is a disorder marked by cognitive deficits and social impairments; thus, determining the developmental trajectory of effortful control in this population will shed light on mechanistic underpinnings of impairments. Existing evidence suggests that temperament profiles are variable but relatively stable across early to middle childhood for males with FXS (Hatton, Bailey, Hargett-Beck, Skinner, & Clark, 1999); however, temperament profiles in toddlers and preschool-aged boys with FXS may differ from those observed at older ages (Shanahan, Roberts, Hatton, Reznick, & Goldsmith, 2008). The temperament factor structure in FXS appears highly similar to typically developing controls (Roberts, Tonnsen, Robinson, McQuillin, & Hatton, 2014), and temperament profiles do not appear to be influenced by developmental level or the severity of ASD features (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Hatton et al., 1999). Also, temperament does not appear to predict ASD features in young boys with FXS; yet, the emergence of anxiety may be linked to early elevations of negative affect (Tonnsen, Malone, Hatton, & Roberts, 2013) with elevated arousal and blunted arousal modulation implicated mechanistically (Roberts, Boccia, Hatton, Skinner, & Sideris, 2006; Roberts et al., 2013).

Of the few studies examining temperament in children with FXS, none have focused on effortful control, although some have examined constructs that comprise effortful control, such as response inhibition, attention, and executive functioning (e.g., Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012; Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Cornish, Suderhalter, & Turk, 2004; Hooper, Hatton, Baranek, Roberts & Bailey, 2000; Wilding, Cornish, & Munir, 2002). These studies show that, relative to typically developing children, children with FXS exhibit impairments in executive functioning as young as 4 years of age, which include deficits in inhibition, working memory, planning, and flexibility (Hooper et al., 2008). Executive functioning differences are also observed when compared to children with other intellectual disabilities; boys with

FXS show decreased inhibition of irrelevant responses and repetitive behaviors, poorer visual planning and organization and decreased attention shifting compared to boys with Down syndrome (Wilding, et al., 2002). Although evidence consistently points towards executive function impairments in FXS, longitudinal studies suggest developmental delays rather than a developmental freeze. For instance, Cornish and colleagues (2012; 2013) show that, despite lower levels of attentional control relative to controls, school-aged boys with FXS do show growth within this domain over time, albeit at a slower rate than their peers. Thus, prior research suggests overall difficulties in effortful control in FXS, and further investigation of effortful control is needed to define early development in this domain in children with FXS.

The Present Study

Although the FXS phenotype consists of hallmark features that suggest low levels of effortful control, the developmental trajectory—change and continuity—of effortful control in children with FXS has not been studied. Evidence that effortful control is similar or divergent from patterns of typically developing children or those with ASD, for example, would advance our understanding of the FXS phenotype and could generate hypotheses for study in other populations (e.g., is the relationship between adaptive behavior and effortful control in FXS similar or different from that in other clinical and non-clinical samples?). Furthermore, it is unclear what biological and behavioral mechanisms support effortful control development in FXS. This work will also lend insight into the potential impact of *FMR1* gene dysfunction on individual differences in reactivity and self-regulation, informing mechanistic underpinnings and the development of targeted treatments.

Two research questions guided this study: (1) How does effortful control develop across early childhood in boys with FXS compared to boys with typical development? and (2) Do adaptive behavior skills, ASD symptom severity, or FMRP influence the rate of effortful control growth in boys with FXS? We hypothesized that effortful control would increase over time across both groups, with a slower rate and lower level observed in the boys with FXS, and that effortful control would be predicted by FMRP but not by adaptive behavior or ASD symptom severity.

Methods

Participants

Ninety-seven boys with FXS completed 1 to 5 annual assessments between the ages of 1.3 and 9.4 years, for a total of 235 evaluations. Thirty-two boys with typical development (TD) were assessed annually 1 to 2 times between 1.3 and 4.8 years of age, for a total of 53 evaluations. The age of the participants at study entry and number of observations varied given inclusion of data across multiple studies as outlined below; Figure 1 shows the age distributions for each of the groups at study entry. The number of repeated observations varied across participants, with 22 boys with FXS participating in 1 assessment point, 27 contributing data from 2 repeated assessments, 38 from 3 repeated assessments, 5 from 4 repeated assessments, and 5 from 5 repeated assessments (235 observations total). In the TD group, 32 boys participated in one assessment point and 21 participated in 2 repeated

assessments (53 observations total). Analyses involving group comparisons were restricted to the 1.5–5.0 year period to avoid interpreting results outside of the range of the TD data (within-group analyses involving the participants with FXS included the full range of data), and the analysis technique employed does not require a balanced number of participants across groups (see Data Analysis). The sample was primarily Caucasian (100% of TD and 82% of FXS, with the remaining FXS sample 10% African American, 6% Mixed Race, 1% American Indian or Alaskan native, and 1% Native Hawaiian or other Pacific Islander). Participant characteristics are outlined in Table 1.

Participants were drawn from an extant dataset comprised of data from a series of longitudinal studies of FXS conducted at the University of North Carolina at Chapel Hill. Participants with data from a parent-rated temperament questionnaire, parent interview of adaptive behaviors, and examiner ratings of ASD symptoms severity were selected for inclusion. Participation in the broader study included multi-day assessments of a number of family and child characteristics. Participants were drawn primarily from the Southeastern region of the United States and recruitment was through genetic clinics, developmental assessment centers, and word of mouth. Genetic reports were obtained to confirm the diagnosis of full mutation FXS. All procedures were approved by the university Institutional Review Board (IRB) and informed consent was obtained from participants' parents.

Measures

Effortful control.—The Toddler Behavior Assessment Questionnaire- Revised (TBAQ-R; 16–35 months; Rothbart, Ellis, Rueda, & Posner, 2003) and the Children's Behavior Questionnaire (CBQ; 3–7 years; Rothbart, Ahadi, Hershey, & Fisher, 2001) assessed temperament constructs across the ages per standard practice in longitudinal studies. Mothers completed the questionnaire corresponding to their child's current age at each assessment. Each questionnaire requires the mother to rate how typical a given behavior is for her child, on a scale of "1" (extremely untrue) to "7" (extremely true). Sample items include: "Can easily stop an activity when s/he is told 'no'" (inhibitory control domain) and "Notices even little specks of dirt on objects" (perceptual sensitivity domain). The TBAQ-R consists of 239 items, with subscales consisting of 9–10 items each. The CBQ is a 195-item questionnaire with subscales typically comprised of 12–13 items. Raw scores for each subscale are computed by tallying the scores for each item and dividing the total by the number of items in the subscale. The psychometric properties of these scales have been extensively evaluated and suggest strong convergent and discriminate validity, interrater reliability, intracorrelations, and heterotypic continuity or differences in behavior over time of temperament factors across the effortful control composite (Putnam et al., 2006). A composite score for effortful control was obtained using the following procedure: first, trait expression scores on the TBAQ-R and CBQ subscales were normalized by computing *z*-scores. Then, based on previous factor analytic studies, an effortful control composite score was computed for each participant by taking the mean of the following normalized scales: attention focusing, low-intensity pleasure, smiling and laughter, perceptual sensitivity and inhibitory control (Rothbart, Ahadi, Hershey, & Fisher, 2001). To facilitate interpretation, *z* scores of the composite effortful control scale were computed (a score of "0" represents performance at the sample mean). Internal consistency of the effortful control composite was

evaluated with Cronbach's alpha, with $\alpha = 0.68$ for children less than 3 years old, who received the TBAQ-R form. For older children who received the CBQ, $\alpha = 0.71$ for 3–4 year olds, 0.78 for 4–5 year olds, and 0.67 for children older than 5 years. Within the FXS group, α was 0.70 in children under 3 who received the TBAQ-R. Internal consistency on the CBQ within the FXS group was $\alpha = 0.58$ for 3–4 year olds, 0.71 for 4–5 year olds, and 0.64 for children older than 5 years.

Adaptive behavior.—The Vineland Adaptive Behavior Scale—Expanded Interview Form (VABS; Sparrow, Balla, Cicchetti, & Doll, 1984) was administered as a developmental index. The VABS is a semi-structured parent interview that assesses the domains of communication, socialization, daily living skills, and motor skills. The VABS significantly and positively correlates with measures of cognitive ability and mental age in children with autism (Wells, Condillac, Perry, & Factor, 2009; Freeman, Del'Homme, Guthrie, & Zhang, 1999) and was used in the present study as a proxy for developmental level. Given that the current study represents a secondary analysis, the VABS was the best index of developmental level that was available across all participants. Standard scores for the Adaptive Behavior Composite were used.

ASD symptoms.—The Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980) was used to measure behavioral symptoms of ASD. The scale was completed by masters- and PhD-level examiners who were trained on the instrument. Ratings were based on direct observations of the child across multiple days, information gleaned from parent interviews, and review of parent rating scales, consistent with administration guidelines. Examiners came to a consensus before assigning a score for each item. The CARS includes ratings in 15 areas relevant to ASD, including social behaviors, activity level, adaptation, and communication. Composite scores range from 15–60 and have been used in prior research to index ASD severity within a number of developmental disorders, including FXS (e.g., Hatton et al., 2006; Rellini, Tortolani, Trillo, Carbone, & Montecchi, 2004; Sloneem, Oliver, Udwin, & Woodcock, 2011). Composite scores of 30 or above are consistent with an ASD diagnosis (26% of participants with FXS scored within this range for the present study). The CARS is a well-established measure with high internal consistency ratings (>0.90), interrater reliability estimates around 0.71, test-retest reliabilities ranging from 0.77–0.90, and sensitivity and specificity values of 0.88 or higher (Schopler et al., 1980).

FMR1 molecular measures.—FMRP expression was determined through blood smears that were analyzed via immunocytochemistry (Willemsen et al., 1995). This test analyzes 200 lymphocytes per child for the occurrence or nonoccurrence of FMRP, resulting in a percentage of lymphocytes that are producing FMRP.

Data Analysis

A mixed effects linear model was fit in SAS 9.4 (SAS Institute, 2013) to test for group differences in effortful control. Mixed models incorporate both fixed and random effects to account for between- and within-subject variation, and the use of a mixed model in this study allowed us to adjust for multiple data points from some subjects in determining group

differences in the development of effortful control during early childhood (Singer & Willett, 2003; Liu, 2016; Verbeke, & Molenberghs, 2009). An advantage of mixed models is that they do not require a balanced number of participants across groups when examining fixed effects (Gibbons, Hedeker & DuToit, 2010; Wu, 2009). In the present study, the greater number of collection points for the FXS group does not bias the estimates of fixed effects, but rather, allows for a more precise estimate for this group (see Littell, Stroup, & Freund, 2002, page 161). Group, age at testing, and their interaction were regressed on effortful control. Random slopes and intercepts were included in the model. To aid in illustration, estimates were calculated at 1.5, 3.2, and 5.0 years. These time points were chosen based on the oldest and youngest ages that overlapped across the two cohorts, and the mid-point between these points (3.2 years). To avoid interpreting results outside the range of the data, results involving comparison with the TD group were restricted to the 1.5–5.0 year period. A nonlinear model allowing for exponential change was also fit to test for nonlinear change; the AIC and BIC both indicated that the linear model was a better fit for the data. The measurements in our TD sample were limited to two repeated observations; although some texts recommend a minimum of three repeated observations to test nonlinear effects, there are differing opinions among methodologists regarding this requirement (see Discussion).

Mixed models were also used to test developmental level, ASD symptom severity, and FMRP as predictors of development of effortful control within the group with FXS. In these analyses, the full range of available data on the FXS group was used. Age, the predictor of interest, and the interaction with age were regressed on effortful control in separate models to determine their individual contributions. Age, ASD symptoms, and developmental level were grand mean centered at 3.2 years, 25 points, and 59 points respectively. FMRP was log transformed to correct for skewedness. All models included random slopes and intercepts. Denominator degrees of freedom were calculated using the Kenward-Roger approximation (Kenward & Roger, 1997).

Results

The Development of Effortful Control in FXS and TD in Early Childhood

The boys with TD showed higher levels of effortful control than the boys with FXS ($\beta = 1.11$, $p < 0.001$), as shown in Figure 1. Examination of the slopes indicated that the boys with TD showed significant gains in effortful control during early childhood ($\beta = .28$, $p = .009$) while the boys with FXS showed no change in effortful control over the same period of time ($\beta = -.03$, $p = .360$), as shown in Table 2. Estimates of group differences in the level of effortful control at 1.5 years, 3.2 years, and 5.0 years indicated that the gap between the groups magnified over time (see Table 3).

Predictors of Effortful Control Development in FXS

Within the FXS group, autism symptom severity was a significant predictor of overall level of effortful control, with greater autism symptoms associated with lower effortful control ($\beta = -.051$, $p < .001$; see Table 4). Neither adaptive behavior nor FMRP were related to the level of effortful control ($\beta = .008$, $p = .401$; $\beta = -.631$, $p = .334$, respectively). The interaction with time was not significant for any of the predictors ($ps > .250$), indicating that autism symptom

severity, adaptive behavior, and FMRP did not affect the rate of effortful control growth over time.

Discussion

Effortful control is a core temperament trait associated with the development of prosocial behavior and optimal cognitive and social outcomes, with increasing focus on the complex environmental, genetic, and neural bases of its development. The development of effortful control in early childhood represents a critical phase given evidence that poor executive function and self-regulation are often exacerbated across the preschool and early school years (Blair & Diamond, 2008). As such, the study of early temperament profiles in high-risk clinical groups can lend insight into patterns of risk and resilience, strengthening prevention efforts and informing pivotal intervention targets.

Very little is known about the development of effortful control across early childhood in FXS, a genetic condition marked by intellectual disability, poor social outcomes and deficits in inhibition, arousal regulation, and attention control. The present study contrasted the development of effortful control during early childhood in boys with FXS to boys with TD of a similar age. Consistent with our hypothesis, results indicated diminished effortful control in boys with FXS during early childhood, which is consistent with several well-documented features of the FXS profile that reflect low levels of effortful control (e.g., disinhibition, attentional deficits, and arousal dysmodulation). Of note, we report that effortful control is lower in the boys with FXS across the age span of our study emerging as young as 18 months of age with increasing divergence from controls with TD. While we anticipated lower levels of effortful control in the boys with FXS, we did not expect the levels to be as low as we report, or for the divergence from TD controls to be present this young. Thus, our findings are particularly striking given that typical development is characterized by relatively low levels and high variability of effortful control at 18–24 months-of-age (Kochanska, Murray, & Harlan, 2000; Putnam et al., 2006). Yet, young boys with FXS display significantly lower levels of effortful control even during these very first years of life when developmental delays in FXS are often presumed to be milder with increasing severity of delay across early to middle childhood.

Contrary to our hypothesis, autism symptom severity predicted the level of effortful control, which differs somewhat from previous evidence showing that temperament profiles of boys with FXS were similar to those with idiopathic ASD and temperament profiles did not differ between boys with FXS who showed low versus high levels of ASD symptoms (Bailey et al., 2000). However, our study represents a younger sample of children with FXS and our findings align with studies of young children with idiopathic ASD and familial high-risk for ASD. In the current study, the boys with FXS and elevated ASD symptoms showed reduced effortful control during early childhood, which is consistent with studies of idiopathic ASD showing effortful control as the most salient predictor of ASD in regards to temperament (Hepburn & Stone, 2006; Konstantareas & Stewart, 2006). Additionally, our findings align with early temperament profiles in infants and toddlers with familial high-risk for ASD, where reduced effortful control is evident at 14 and 24 months in infant siblings of children with ASD (Clifford, et al., 2013) and distinguishes siblings (high risk) who were diagnosed

with ASD from non-ASD siblings controls at 36 months (Garon et al., 2009). Thus, our findings are consistent with studies of younger children with idiopathic ASD. Other methodological differences may also explain discrepancies with the Bailey et al. (2000) findings, as we examined continuous ASD symptoms as opposed to dichotomized groups and used the Rothbart scales of temperament while previous studies used the Carey scales, which have different theoretical bases. The Rothbart scales represent temperament as constitutionally based individual differences in reactivity and self-regulation with a strong cognitive component, while the Carey scales are based on work by Thomas and Chess with temperament represented as a behavioral style.

Unlike boys with TD who demonstrated increased effortful control with age, those with FXS exhibited a flat developmental profile of effortful control, with no gains over time. This finding was unexpected as we assumed that boys with FXS would demonstrate some improvement over time albeit at a slower rate than that of the boys with TD. This is consistent with patterns observed using experimental measures of attentional control in older school-aged boys with FXS (e.g., Cornish et al., 2012; 2013). Discrepant findings may be related to a number of factors, including the younger age of the boys included in the present sample, the use of direct-assessment versus parent-report tools, and differences in the constructs measured across studies as attention is only one domain within the larger construct of effortful control. Although ASD symptom severity was related to the level of effortful control in the boys with FXS, it did not influence the development of this skill over time, suggesting that the lack of improvement in effortful control during early childhood is independent of comorbid ASD features in boys with FXS. It is plausible that the lack of effortful control change observed in the FXS group is accounted for by delayed cognitive development, as the majority of boys with FXS have an intellectual disability (Bailey et al., 2008). However, adaptive impairment was not associated with the reduced level or lack of growth in our sample, consistent with existing work indicating no association between developmental level and the level or growth across temperament domains in older 4–8 year old boys with FXS (Hatton et al., 1999).

These results suggest an atypical and maladaptive profile of effortful control in young males with FXS that likely contributes to the social difficulties, problem behaviors and cognitive deficits experienced by this group. Our finding of a complete lack of improvement in effortful control across time is important to refine the early developmental phenotype in FXS and to contribute to targeted treatment efforts. The significant impairments in effortful control documented here and the lack of improvement over time suggest that poor effortful control is a robust feature of early development in FXS, perhaps suggesting that individuals with FXS have a biological predisposition for low effortful control, which is consistent with Rothbart's theoretical model and empirical evidence in non-FXS samples (Blair & Diamond, 2008). Yet, FMRP, an index of the amount of protein produced by the *FMR1* gene, was not related to the level or growth of effortful control in FXS, which was contrary to our hypothesis given prior evidence showing an association between FMRP and executive functioning, a cognitive skill related to effortful control (Loesch, Huggins, & Hagerman, 2004). The divergent findings may be related to sample characteristics as the Loesch study included females and covered almost the full range of possible FMRP expression whereas the present study included only males with a more limited range. Both the current study and

Loesch et al. (2004) estimated FMRP level by counting the percent of lymphocytes staining positive for FMRP. Future studies incorporating new technological advances that allow for quantitative measurement of actual FMRP levels will provide a more sensitive index of FMRP levels, clarifying relationships. Other indicators of *FMR1* molecular-genetic function, such as the extent of gene methylation or the number of CGG repeats, may also help determine the role of *FMR1* in the development of effortful control.

This study has several limitations. First, our TD sample was small and we were limited to two repeated observations for this group, which may have impacted our ability to detect nonlinear change. Although three or more waves of data are often recommended when using growth models to estimate the functional form of change (e.g., Singer & Willet, 2003), there is some disagreement among methodologists as to whether this is a requirement, particularly when the focus is on estimating group-level trajectories as opposed to individual change. Our methodological approach is consistent with prior work where nonlinear change was tested from two waves of data (e.g., Braams, Duijvenvoorde, Peper, and Crone, 2015; Peters, Peper, Van Duijvenvoorde, Braams, Crone, 2017), however, a TD sample that consisted of more waves of data from a larger number of individuals would have been ideal to ensure that potential nonlinear growth patterns were not overlooked. Second, the present study included a sample of children younger than 6 years and therefore does not represent the full range of childhood. Our sample of was also primarily Caucasian, which may limit generalizability to more diverse groups. Also, the inclusion of comparison groups matched on mental age rather than chronological age might more finely characterize developmental effects (although the results presented here suggest that developmental level, broadly indexed by adaptive behavior, was not related to effortful control in FXS). Additional research may include the use of experimental measures of effortful control, which may provide complementary estimates of effortful control abilities in addition to parent report. In particular, maternal ratings of effortful control behaviors may have been negatively biased by knowledge of their child's diagnosis. Lastly, due to the link found between autism symptom severity and effortful control level, additional research employing calibrated severity metrics of ASD symptomatology (such as Autism Diagnostic Observation Schedule-2; Lord et al., 2012) may further define this relationship.

In conclusion, the current study shows that effortful control is not only diminished within FXS compared to children with TD, but that effortful control in FXS does not increase over time with deficits emerging within the second year of life. While ASD symptom severity is associated with lower levels of effortful control, the lack of effortful control growth in FXS could not be accounted for by ASD symptoms. Due to increased social-emotional difficulties, cognitive impairments, and problem behaviors in children with FXS, treatment efforts may focus on building skills linked with effortful control such as impulse control, behavior regulation, and attention control. Indeed, one of the first behavioral studies to target executive function (e.g., working memory) is currently underway using a computer-based training program with outcomes in cognition and behavior being monitored for individuals with FXS 8–18 years of age (www.ucmdmc.ucdavis.edu).

Acknowledgments

This research was supported by the Office of Special Education and Rehabilitative Services of the U.S. Department of Education (H324C010007) and the National Institutes of Health (5F32DC013934; 5R01MH090194; 5R01HD40602; 5R01HD024356). We would like to acknowledge M. Lee Van Horn for his assistance with the statistical analyses for an earlier draft of this manuscript. We thank the children and families who participated in this research.

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Figure.

Effortful control in boys with FXS and TD across age

Table 1

Descriptive statistics at initial assessment

Variable	<i>n</i>	FXS	<i>n</i>	TD
		<i>Mean (SD)</i>		<i>Mean (SD)</i>
Age (years)	97	3.82 (2.07)	32	2.58 (0.64)
Effortful Control Composite (raw score)	97	4.16 (0.58)	32	4.67 (0.48)
Effortful Control Composite (standard score)	97	−0.17 (0.95)	32	0.75 (0.60)
VABS-ABC	82	60.41 (11.49)	--	--
CARS	81	26.95 (5.69)	--	--
FMRP	49	9.83 (8.82)	--	--

Note. VABS-ABC = Vineland Adaptive Behavior Scale-Adaptive Behavior Composite Standard Score; CARS = Childhood Autism Rating Scale; FMRP = Fragile X Mental Retardation Protein; Potential Effortful Control Composite raw scores range from 1–7.

Table 2

Change in effortful control across early childhood in boys with FXS and TD

	Estimate	SE	DF	t-value	p-value
FXS slope	−0.03	0.03	85.2	−0.89	0.377
TD slope	0.28	0.11	221	2.63	0.009

Table 3

Test of group differences in effortful control between boys with FXS and TD at 1.5, 3.2, and 5.0 years

Age (years)	Estimate	SE	DF	t-value	p-value
1.5	0.579	0.246	282	2.35	0.019
3.2	1.113	0.162	126	6.87	<0.001
5.0	1.678	0.265	276	6.34	<0.001

Table 4

Regression coefficients from mixed model examining autism symptom severity as a predictor of effortful control in FXS

Effect	Estimate	SE	DF	t-value	p-value
Intercept	0.027	0.077	93.6	0.35	0.724
Age	−0.008	0.033	79.7	−0.23	0.817
CARS	−0.051	0.009	169.0	−5.36	<.001
CARS*Age	0.003	0.005	201.0	0.58	0.560

Note. CARS = Childhood Autism Rating Scale