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# Trajectories and Psychiatric Consequences of Inhibitory Control in Young Males With Fragile X Syndrome

Erin Hunt

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TRAJECTORIES AND PSYCHIATRIC CONSEQUENCES OF  
INHIBITORY CONTROL IN YOUNG MALES WITH FRAGILE X SYNDROME

by

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Bachelor of Science  
Fordham University, 2017

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## **Abstract**

Inhibitory control (IC), the ability to suppress inappropriate responses, emerges late in the first year of life and improves across typical development, concurrent with brain maturation. The development of IC is critical to various social-emotional and behavioral functions, with IC deficits being linked to numerous psychiatric conditions, including attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Fragile X syndrome (FXS) is a single-gene disorder characterized by IC deficits, and elevated rates of ADHD and ASD, making it a useful model for understanding the early development and consequences of IC. In this longitudinal study, we characterized IC trajectories across multiple time points between 16 and 71 months of age in young males with FXS (n=80) relative to neurotypical controls (n=49). To explore the association between psychiatric features and IC, we identified a subsample of 48 children with longitudinal IC data and an outcome assessment for ADHD and ASD symptoms at age 5 (FXS: n=26, neurotypical: n=22). Results indicated that, compared to their neurotypical peers, young males with FXS exhibit IC deficits as early as 18 months, with group differences increasing through age 5. Additionally, we determined that lower IC levels at 18 months were associated with later ADHD symptoms and attenuated growth in IC over time was associated with later ASD symptoms in male children with FXS. These findings help refine early developmental phenotypes of FXS and highlight IC as a potential target for early detection and intervention of ASD and ADHD symptoms in male children with FXS.

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### **List of Abbreviations**

ADHD .....	Attention-Deficit/Hyperactivity Disorder
ASD.....	Autism Spectrum Disorder
FXS .....	Fragile X Syndrome
IC.....	Inhibitory Control
NT .....	Neurotypical

## **Chapter 1: Introduction**

### **Inhibitory Control in Development**

Inhibitory control (IC) is the voluntary ability to withhold inappropriate responses and behaviors; it is a foundational component of executive functioning (EF), a multi-faceted construct which underlies self-regulation and goal-directed behavior (Diamond, 2013; Friedman et al., 2008; Garon et al., 2008; Miyake et al., 2000; Zelazo et al., 2008; Zelazo & Muller, 2011). The emergence of IC in early childhood can be well conceptualized according to neuroconstructivist and broader developmental theories (Hodapp, et al., 1990; Karmiloff-Smith, 2006). The neuroconstructivist theory stipulates that processes at various levels, including genetic, neural, cognitive, and behavioral, exert bidirectional influences on each other across development. Indeed, increasing specialization and efficiency of information processing and behavioral control across the first few years of life is simultaneously supported by and reinforces the rapid development of the prefrontal cortex and increasing connectivity among neural structures (Buss & Spencer, 2014; Kochanska et al., 2000; Rothbart & Posner, 2001). Further, the development of inhibitory control and underlying neural structures enables the development of higher-order cognitive functions and more sophisticated goal-directed activity and emotion regulation (Zelazo & Cunningham, 2007).

In this study, we examine the trajectory and consequences of early IC development in male children with Fragile X syndrome (FXS), a single-gene disorder with high prevalence of IC deficits and associated psychiatric disorders including

attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Examining IC as a potential early risk marker may improve our understanding of the multifinality of psychiatric outcomes, such as ADHD and ASD symptoms, in individuals with FXS and may contribute to identifying mechanistic underpinnings of these behaviorally-defined disorders (Friedman et al., 2008).

Inhibitory control emerges late in the first year of life, improves steadily, and becomes increasingly differentiated from other behavioral abilities over time in neurotypical development (see Garon et al., 2008 for review; Diamond, 2013; Hongwanishkul et al., 2005; Rothbart et al., 2007). The expected improvement with age in regulatory abilities such as IC results in greater heterogeneity of these abilities across individuals, with rank-order stability, the maintenance of one's position relative to the group over time, of IC between individuals across development being largely attributed to genetic factors (Gagne & Saudino, 2016; Putnam et al., 2008). Both task performance and parent ratings of IC show demonstrated improvement across early childhood (Petersen et al., 2016, Putnam et al., 2006). For example, Carlson (2005) examined performance of 2- to 6-year-olds on a battery of commonly used EF tests and found age-related improvements in IC task performance across this age range. Though there is no consensus on the age at which IC is fully mature (Petersen et al., 2016), findings by Macdonald et al. (2014) indicate that children commit fewer inhibition errors on an IC task, therefore successfully inhibiting a dominant response, and engage in more self-correction of errors, demonstrating greater awareness of errors, with age from ages 5 to 8 years. Moreover, maturation and differentiation of inhibitory control and higher-order executive functions continues through adolescence and into early adulthood

(Constantinidis & Luna, 2019; Ordaz et al., 2013; Shing et al., 2010). Previous research has also revealed sex differences in IC, with males evidencing similar or lower parent ratings of IC and performing more poorly on IC tasks compared to their female peers (Eisenberg et al., 2005; Garon et al., 2016; Memisevic & Sinanovic, 2014; Thorell et al., 2004).

Inhibitory control contributes to the development of social-emotional skills and self-regulation (Kochanska et al., 2000). Indeed, greater IC in childhood has been linked to a number of prosocial behaviors and skills, including social competence, committed compliance, and theory of mind (Carlson et al., 2004; Dyson et al., 2012; Eisenberg et al., 2007; Eisenberg & Spinrad, 2004; Lengua, 2003; Liew et al., 2004; Rhoades et al., 2009; Rothbart & Bates, 2006; Spinrad et al., 2012). Greater IC also mitigates risk for the development of psychiatric disorders and poor adjustment outcomes, with high levels of IC predicting decreased incidence of internalizing and externalizing behaviors (Kim-Spoon et al., 2019; Lengua, 2003; Muris & Ollendick, 2005; Rhoades et al., 2009). Furthermore, IC impairments have been associated with diminished self-regulatory skill development, poor emotion regulation, and the development of behavior problems (Brunsdon & Happé, 2014; Carlson & Wang, 2007; Diamond, 2013; Espy et al., 2011; Miyake & Friedman, 2012). Further research is needed to confirm whether IC is a useful marker and target for the early detection and prevention of specific psychiatric phenotypes. Mapping the development of IC in early childhood is crucial to elucidating when deviant trajectories become apparent and thus identifying sensitive periods for intervention. Targeted intervention of IC in early childhood may have the cascading

effects of altering a child's developmental trajectories and therefore possibly minimizing achievement gaps or health inequities (Diamond, 2015).

### **Psychiatric Outcomes Associated with IC: ADHD and ASD**

**ADHD.** An extensive body of research upholds that IC deficits underly the development of ADHD (Barkley, 1997). For example, DePauw and Mervielde (2011) found that, compared to neurotypical children, children with ADHD exhibited lower IC and effortful control, the broader temperamental regulatory domain which encompasses IC of behavioral responses as well as voluntary management of attentional control processes in service of self-regulation (Rothbart, 2007). Further, lower inhibitory control (i.e., effortful control) was predictive of both internalizing and externalizing symptoms in both groups of children, though the effect was more pronounced in children with ADHD (DePauw & Mervielde, 2011). Inhibitory control has also been shown to predict subclinical levels of hyperactivity three years later in school-aged children, suggesting IC may be a sensitive early marker of ADHD symptoms (Thorell et al., 2004). Inhibitory control deficits may also be relatively specific to ADHD, as Skogan et al. (2015) determined that parent-rated IC distinguished preschoolers with ADHD from those with oppositional defiant disorder or anxiety. Further, it is likely that poor IC early in life may signal genetic risk for later ADHD-related problems, as phenotypic covariance between parent-rated IC and ADHD symptoms at 24 months has been largely attributed to common genetic underpinnings (Gagne et al., 2011). Similar to those findings, heritability estimates of IC in middle childhood, a period when many psychiatric conditions become apparent, suggest that IC impairment may be characteristic of a

particular subgroup of individuals with a familial form of ADHD (Crosbie et al., 2008; Nigg et al., 2004).

**ASD.** Because past research involving youth with ASD has mostly focused on global executive deficits or specific impairments in mental flexibility or shifting, the presence of IC deficits in ASD is less clear than research on ADHD (Gardiner et al., 2017; Gioia et al., 2002; Hill, 2004; Konstantareas & Stewart, 2006; Smithson et al., 2013; Zantinge et al., 2017). Consistent with the aims of the current paper, previous studies have found that parent-rated inhibitory control (i.e., effortful control) differentiated children with and without ASD and predicted ASD symptoms longitudinally (Garon et al., 2016; Konstantareas & Stewart, 2006). Gardiner et al. (2017) also determined that poor IC in children with ASD was related to greater ASD symptom severity. Other studies documenting lower parent-rated IC in children, however, have failed to detect an association between IC and ASD symptoms (Bishop & Norbury, 2005). Sex differences in IC may also differ in the context of ADHD and ASD. Whereas neurotypical males evidence poorer IC ratings and performance relative to female children and adolescents, females with ASD demonstrate poorer response inhibition relative to males with ASD and neurotypical females (Eisenberg et al., 2005; Lemon et al., 2011; Moilanen et al., 2010; Thorell et al., 2004). For instance, female children and adolescents show slower and less accurate response inhibition, an effect moderated by ADHD trait scores, with greater differences in younger females compared to males (Crosbie et al., 2013). Finally, it is well-established that children at high risk for developing ASD evidence morphological brain differences as early as infancy (Hazlett et al., 2017).

## **Genetic Model of IC Impairment: Fragile X Syndrome**

Fragile X syndrome (FXS) is a single-gene disorder identified by an expansion of the CGG repeat sequence on the long arm of the X chromosome. Though cognitive and behavioral profiles vary across individuals with FXS, the majority of males with FXS have intellectual disability, and the phenotype is also characterized by significant social impairments, internalizing and externalizing behaviors, and elevated rates of ADHD and ASD (Bailey et al., 2008; Baumgardner et al., 1995; Center for Disease Control [CDC], 2021; Hatton et al., 2002; Roberts et al., 2020; Sullivan et al., 2006). Specifically, as many as 61% of preschoolers with FXS meet DSM-5 criteria for ASD and nearly 80% experience ADHD-related symptoms (Bailey et al., 2008; Roberts et al., 2020).

Additionally, ADHD and ASD symptoms commonly co-occur in individuals with FXS, similar to what is seen in the general population (Sinzig et al., 2009; Crawford et al., 2018; Ames & White, 2011; Visser et al., 2016; Smith et al., 2012). The presence of one or both of these co-morbidities is associated with reduced quality of life for children with FXS and their families (Bailey et al., 2008).

Inhibitory control deficits are central to the behavioral phenotype of young males with FXS. Further, inhibitory control deficits documented in young males with FXS cannot be fully explained by general developmental delays (Cornish et al., 2007, 2013; Hooper et al., 2008; Kapalu & Gartstein, 2016; Munir et al., 2000; Scerif et al., 2005, 2007; Sullivan et al., 2007; Tonnsen et al., 2015; Wilding et al., 2002). This is consistent with reports of poorer verbal and nonverbal IC in children with intellectual disability relative to mental age (MA)- and chronological age (CA)-matched peers (Danielsson et al., 2012; Spaniol & Danielsson, 2021). Males with FXS have exhibited lower

performance relative to MA-matched males on various IC-related tasks, including distractor interference, delay of gratification, stop signal, and antisaccade tasks (Cornish et al., 2007; Munir et al., 2000; Scerif et al., 2007; Tonnsen et al., 2015). Still, little is understood about how IC develops very early in male children with FXS. Prior work suggests that IC deficits are likely present by toddlerhood in males with FXS, increasing over time (Robinson et al., 2008). Specifically, neurotypical males demonstrate growth in inhibitory control (i.e., effortful control) over time, whereas children with FXS evidence a flat trajectory of inhibitory control (Robinson et al., 2018) These low levels of inhibitory control in children with FXS were associated with greater ASD symptoms (Robinson et al., 2018), highlighting the importance of examining IC as an early indicator of ASD. However, despite clear evidence of IC deficits in young males with FXS, to date no study has specifically examined IC *longitudinally* in early childhood or investigated IC as a predictor of later psychiatric symptoms (e.g., ADHD, ASD) in male children with FXS.

### **Present study**

In sum, it remains unclear how IC develops across early childhood or the cascading impacts of early IC differences/delays in males with FXS. The present study aimed to shed light on this question by examining IC abilities longitudinally from 16 months to 71 months in males with FXS and neurotypical males. The primary aim of the study was to characterize early IC trajectories and determine when IC deficits become apparent in young males with FXS relative to neurotypical peers. We hypothesized that, compared to their neurotypical peers, male children with FXS would exhibit early emerging IC deficits which would become more striking across early childhood. The



second aim of the study was to determine whether early levels and/or changes in IC over time were related to ADHD and ASD symptom severity at age 5 in both groups. We hypothesized that IC growth across early development would be associated with both ADHD and ASD symptoms in young males with FXS.

## Chapter 2: Method

### Participants

*Sample 1:* To characterize IC trajectories across early development and determine when IC deficits become apparent in children with FXS, we identified a sample of 129 eligible male participants, (FXS:  $n=80$ , neurotypical:  $n=49$ ) using extant data from two longitudinal studies of early development in children with FXS (R01MH090194; R01MH107573; PI: Roberts). The sample included all individuals who were assessed between 16 and 71 months (1-5 observations per child), for a total of 286 observations (FXS:  $n=174$ ; neurotypical:  $n=112$ ). This age range was chosen because IC emerges around the end of the first year of life and matures steadily, becoming increasingly coherent over this age range (Kochanska et al., 2000).

*Sample 2:* To determine whether early IC trajectories predicted ADHD and ASD symptom severity at age 5, we identified 48 children from the initial dataset who had both IC trajectory data across early childhood and an outcome assessment that characterized ADHD and ASD symptom severity at 5 years of age (FXS:  $n=26$ , neurotypical:  $n=22$ ; see Table A.5). The age of outcome was selected as 5 years of age because ASD and ADHD symptoms have been shown to emerge and stabilize by this age (Lord, 1995; O'Neill et al., 2014; Ozonoff et al., 2015; Riddle et al., 2013; Van Daalen et al., 2009).

Recruitment for the larger longitudinal studies was completed via research, parenting, and social media internet sites along with postings in the community and collaborations among research groups. Inclusion criteria for participation were: a)

gestational age of at least 37 weeks, b) English as the household primary language, c) no other known medical conditions. Neurotypical children with a family history of ASD or related disorders (e.g., FXS, tuberous sclerosis) or with a diagnosis of ID, ADHD, and ASD were excluded (described below). FXS status was confirmed via genetic report. Because FXS is less common in females, and because females are generally less severely affected cognitive, behavioral, and social domains, only males were included in the present study (Bailey et al., 2008; Hatton et al., 2006; Klusek et al., 2014; Lee et al., 2016; Rinehart et al., 2011).

## **Measures**

**Inhibitory control (IC).** IC was assessed via the inhibitory control subscale from the Rothbart Scales of Temperament. Parents completed the Early Childhood Behavior Questionnaire (*ECBQ*; Putnam et al., 2006) for children ages 18 to 36 months and the Children's Behavior Questionnaire (*CBQ*; Rothbart et al., 2001) for children ages 36 months and older. The creation of these measures was informed by theory of temperamental continuity, and they have been previously used together in longitudinal examinations of temperament in neurotypical children (Joyce et al., 2016; Posner & Rothbart, 2000; Spinrad et al., 2012). A meta-analysis examining the developmental validity of IC measures supported the utility of the IC subscale of the CBQ in examining individual differences in IC (Petersen et al., 2016). Further, a confirmatory factor analytic study of the CBQ in males with FXS retained a three-factor model of temperament, similar to that demonstrated by Rothbart and colleagues (2001), demonstrating its valid use with this population (Roberts et al., 2014). IC scores range from 1-7, with higher scores indicating greater IC ability.

**ADHD Symptom Severity.** ADHD symptom severity was measured at the outcome assessment using the Child Behavior Checklist for Ages 1½-5 (*CBCL*; Achenbach & Rescorla, 2000), a parent rating scale of emotional and behavioral functioning, which has been used previously with children with FXS (Grefer et al., 2016; Hatton et al., 2002; Sullivan et al., 2006). As suggested by the test publishers, raw scores on the DSM-oriented Attention Deficit/Hyperactivity (ADHD) Problems subscale range from 0 to 12 and were used as the outcome variable, with higher scores reflecting more severe ADHD symptoms. This subscale has demonstrated high inter-rater and test-retest reliability ( $r=.96$ ;  $r=.93$ ; Nakamura et al., 2009).

**ASD Symptom Severity.** ASD symptom severity was assessed at the outcome assessment via the Autism Diagnostic Observation Schedule, Second Edition (*ADOS-2*; Lord et al., 2012), a play-based, semi-structured socio-behavioral assessment and gold-standard tool for the diagnosis of ASD which has been extensively used to measure ASD symptoms in individuals with FXS (Abbeduto et al., 2019; Klusek et al., 2014; Roberts et al., 2018; Wall et al., 2019). Calibrated severity scores (CSS) were included in analyses as a continuous measure of ASD symptom severity. CSS scores range from 1-10, with higher scores indicating more severe ASD symptoms.

**Developmental Level.** Developmental level was measured via the Mullen Scales of Early Learning (*MSEL*; Mullen, 1995), a standardized assessment of developmental abilities in early childhood. The MSEL Early Learning Composite (ELC) is comprised of fine motor, visual reception, receptive language, and expressive language domains and is utilized as an index of general developmental level in the current study. The inclusion of ELC in our statistical models was not supported; however, it is included in the present

study for descriptive purposes. Additionally, a nonverbal developmental quotient (NVDQ) was computed as the (average of visual reception and fine motor age equivalents)/chronological age\*100.

## **Procedures**

Procedures were approved by the Institutional Review Boards at the University of South Carolina and the University of North Carolina at Chapel Hill. Prior to study enrollment parents provided written informed consent. As part of the larger longitudinal studies, children were assessed at 18, 24, 36, 48, 60, and 72 months using a standard research protocol consisting of various developmental and clinical measures. Assessments took place either in the child's home or in a research lab setting. Parent-report measures assessing IC and ADHD symptoms were mailed home and completed prior to each assessment. The ADOS-2 was administered by research reliable personnel. ADOS-2 module was determined according to participant age and expressive language abilities. As part of the study protocol, a clinical best estimate (CBE) diagnosis (i.e. ASD, non-ASD developmental delay, no clinical features), adapted from standard procedures (Lord et al., 2012; Lord et al., 2006), was determined based on a review of data by a multidisciplinary team including a licensed psychologist who is a research-reliable trainer for the ADOS-2. Although a small subset of neurotypical males exhibited symptoms of ASD or ADHD as is expected in a community sample, we confirmed that none met diagnostic criteria for ASD or ADHD according to this CBE process. However, NT children with higher or clinically-significant levels of psychiatric symptoms according to the CBCL or ADOS-2 were retained in the present sample and regarded as reflecting the true spectrum of typical functioning.

## Statistical Analysis Plan

Prior to running the analyses to test the primary aims of the study, we calculated descriptive analyses to characterize the groups. For Sample 1, Groups were matched on CA using a pseudo-randomized matching process. This process involved a) assigning a random number to each observation; b) splitting the dataset into quartiles; c) sorting by random number and number of observations available for each participant; and d) systematically trimming to remove cases, resulting in groups with minimal differences in (Cohen's  $d=-.20$ ) and similarly distributed CA. Participants from Sample 1 were included in Sample 2 if they had available outcome data (i.e., ADHD symptoms, ASD symptoms) at age 5. Additionally, Sample 2 NT and FXS groups were matched on chronological age (Cohen's  $d=-.21$ ). In addition, all data were examined for linearity and normality using data visualization, Q-Q plots, boxplots, and Shapiro-Wilk test of normality ( $p>.05$ ). Levene's test was used to assess the assumption of homogeneity of variance. MSEL ELC scores were positively skewed for the FXS group and violated the assumption of homogeneity of variance across groups for both Sample 1 and 2. Violations to the assumption of normality as indicated by significant results on the Shapiro-Wilk test was found for ADHD symptoms in the FXS group and ASD symptoms in the TD group. As expected, ASD symptoms violated the assumption of homogeneity of variance across groups. Transformation of skewed variables did not improve the model, therefore untransformed variables were retained. No assumptions were found to be violated for the remaining variables.

Demographic frequencies and descriptive statistics for Aim 1 are included in Tables A.1 and A.2. Differences between groups on all primary variables of interest were

evaluated descriptively via effect sizes (i.e., Cohen's  $d$ ) in order to reduce Type I error through multiple comparisons (Tables A.4 and A.5). In addition, data visualization was used to characterize the clinical distribution of ASD and ADHD scores across groups (see Figure B.1). Bivariate correlations were computed to determine whether cognitive ability (i.e., MSEL ELC) should be included as a covariate. There was a small yet significant correlation between IC and ELC in the FXS group, ( $r(144)=.21, p=.011$ ), but not the neurotypical group, ( $r(83)=.14, p=.160$ ). To be conservative, ELC was included as a covariate in the initial linear mixed model, however there was no significant main effect of ELC, suggesting that cognitive ability could not significantly account for group differences identified in IC. This pattern is consistent with prior research involving individuals with ID (Spaniol & Danielsson, 2021). Accordingly, ELC was not included in the final linear mixed model which also maximized statistical power.

To characterize IC growth across early development and determine when IC deficits become apparent in young males with FXS, we employed a linear mixed model using the *lme4* package in R (Bates et al., 2015; RStudio Team, 2016) examining IC across age (16-71 months). A linear model was chosen given the majority of participants completed two assessments and data visualization indicated a linear relationship between IC and chronological age. This type of modeling allows for within- and between-subject variance over time and is flexible to variable timing and frequency of assessments, as is the case in our sample (Singer, 1998). Group, age, and a group\*age interaction were included as predictors, with age specified as a level-1 predictor nested within participant and centered at the earliest timepoint of 18 months and group as a level-2 predictor.

Specifying a 2-level model enabled us to control for interdependence of child IC over time. Random effects were estimated for the intercept and slope.

To examine whether IC at 18 months (intercept) or developmental trajectories of IC (slope) across early childhood are associated with ADHD and/or ASD symptom severity at age 5, individual regression lines were fit to the longitudinal IC data for each participant and subject-specific IC slope and intercept were extracted (Table A.4). We employed partial correlation analyses to determine whether IC intercept or IC slope was a more salient predictor of specific psychiatric symptoms (i.e., ADHD, ASD symptoms). We chose a partial correlation approach because it estimates the unique variance accounted for by each predictor in each outcome, while removing the effects associated with other predictors (i.e. IC slope, IC intercept). This analytic approach effectively reduces the chance of reporting spurious associations between variables that are better explained by the effects of other related variables. The present study utilizes a developmental approach to understanding inhibitory control in early childhood and its' relationship with later psychiatric symptoms. Accordingly, determining whether overall levels versus growth rates of IC better predicts psychiatric symptom severity may inform both our understanding of the mechanisms underlying behavioral symptom expression in neurodevelopment as well as direct timing of interventions aimed at improving IC. Bivariate correlations were computed to determine whether cognitive ability (i.e., MSEL ELC, MSEL NVDQ) should be included as a covariate. Given NVDQ was moderately related to ASD symptoms for the FXS group ( $r(24) = -.47, p = .015$ ), it was included as a covariate in partial correlation analyses examining the association between ASD symptoms and IC parameters for the FXS group.



## Chapter 3: Results

### Descriptive Analyses

Demographic characteristics for Sample 1 are shown in Table A.1. Maternal education and income were included for participants with available data. For participants with income data available at multiple assessments, the average income was included. A greater proportion of mothers of NT children completed a bachelor's degree or higher. Income was similarly distributed across FXS and NT groups. Compared to the NT group, the FXS group exhibited lower IC at each time point (Table A.2). Based on averaged parameters extracted from individual regression lines, the FXS group demonstrated lower IC slope and intercept in both Samples 1 and 2 (Tables A.4 and A.5), which also indicates Sample 2 is representative of the larger Sample 1.

For Sample 2, large effect size estimates indicated that the FXS group showed considerably lower developmental ability and nonverbal developmental quotient, and higher levels of ADHD and ASD symptoms at age 5 compared to neurotypical males (Table A.5).

### IC Maturation Across Early Development

A linear mixed model tested the effect of group on IC across age (see Table A.3). Results indicated a significant main effect of group, ( $b=0.69$ ,  $t(76.72)=3.15$ ,  $p=.002$ ), indicating significant differences in IC between males with FXS and neurotypical males at 18-months old. A significant age-by-group interaction, ( $b=0.02$ ,  $t(70.71)=3.09$ ,  $p=.003$ ), was also found, suggesting a difference in the rate of IC maturation between

males with FXS and neurotypical males. Results indicated that neurotypical males increased in IC, whereas males with FXS demonstrated flat trajectories over time (see Figure B.2), suggesting increasing group differences in IC across development.

### **Associations Between IC Maturation in Early Development and ADHD & ASD Symptoms at Age 5**

**FXS Group.** Partial correlation analyses were run to determine the relationship between each IC parameter (i.e., slope, intercept) and ADHD symptoms, controlling for the other parameter. Results of the partial correlations showed that, controlling for IC intercept, there was a trend between IC slope and ADHD symptoms, ( $r_{\text{partial}} = -0.41$ ,  $p=.052$ ). Comparatively, the significant bivariate correlation between IC slope and ADHD symptoms, not controlling for IC intercept, ( $r = -.43$ ,  $p=.038$ ), suggests the relationship between IC slope and ADHD is at least in part explained by IC intercept (Figure B.3). Alternatively, when controlling for IC slope, the partial correlation between IC intercept and ADHD symptoms, ( $r_{\text{partial}} = -0.46$ ,  $p=.027$ ), was significant, suggesting the association between IC intercept and ADHD is not better explained by the association between either of these variables with IC slope (Figure B.4). Together these results suggest that greater ADHD symptoms in young males with FXS are more so related to low early levels of IC (i.e., IC intercept) rather than restricted growth in IC over time (i.e., IC slope).

Partial correlation analyses revealed a significant correlation between IC slope and ASD symptoms, ( $r_{\text{partial}} = -0.63$ ,  $p<.001$ ), controlling for NVDQ, suggesting the association between IC slope and ASD symptoms is not better explained by the association between either of these variables with NVDQ (Figure B.5). When controlling

for IC slope and NVDQ, the partial correlation between IC intercept and ASD symptoms was non-significant, ( $r_{\text{partial}} = -0.03$ ,  $p = .896$ ; see Figure B.6). These findings indicate that less growth in IC across early development (i.e., IC slope) is associated with greater ASD symptoms at age 5 in young males with FXS, whereas low early levels of IC (i.e., IC intercept) is unrelated to ASD symptom severity in this group.

**NT Group.** Partial correlation analyses were run to determine the relationship between each IC parameter (i.e., slope, intercept) and ADHD symptoms, controlling for the other parameter. Results of the partial correlations identified a strong and significant correlation between IC slope and ADHD symptoms (Figure B.3), controlling for IC intercept, ( $r_{\text{partial}} = -0.66$ ,  $p < .001$ ), suggesting the association between IC slope and ADHD symptoms is not better explained by the association between either of these variables with IC intercept. The association between IC intercept and ADHD symptoms, controlling for IC slope, was also significantly and strongly correlated, ( $r_{\text{partial}} = -0.70$ ,  $p < .001$ ), suggesting the association between IC intercept and ADHD symptoms is not better explained by the association between either of these variables with IC slope (Figure B.4). Similar to findings for the FXS group, these results suggest that low early levels of IC (i.e., IC intercept) and restricted growth in IC over time (i.e., IC slope) are both associated with greater ADHD symptoms in neurotypical male children. For neurotypical males, when accounting for IC intercept, the partial correlation between IC slope and ASD symptoms was non-significant, ( $r_{\text{partial}} = -0.22$ ,  $p = .328$ ; see Figure B.5). Similarly, when accounting for IC slope, the partial correlation between IC intercept and ASD symptoms was non-significant in the neurotypical group, ( $r_{\text{partial}} = 0.22$ ,  $p = .333$ ; see

Figure B.6). These findings suggest no association between early levels or growth in IC across early childhood with ASD symptoms in neurotypical male children.

## **Chapter 4: Discussion**

The present study aimed to determine whether and when young males with FXS differ from their neurotypical peers in parent ratings of IC. To our knowledge, this is the first study to specifically map within-individual trajectories of IC across the toddler and preschool years in male children with FXS relative to neurotypical male children, as well as to examine these trajectories as potential predictors of different psychiatric features in these groups. Overall, findings indicate that IC abilities among young males with FXS differ from their neurotypical peers as early as 18 months of age and that these differences widen across early childhood. Additionally, whereas low early levels and flat trajectories of IC across early childhood are associated with greater ADHD symptoms at age 5 in neurotypical development, low early levels of IC are related to greater ADHD symptoms and flatter trajectories of IC are associated with greater ASD symptoms at age 5 in young males with FXS.

In the present study, males with FXS demonstrated significantly lower IC than neurotypical males as early as 18 months of age, the youngest age at which we could detect differences given our sample age and study design. This confirms that IC is in fact delayed in boys with FXS, representing a true neurocognitive deficit. These findings are consistent with previous reports of impaired IC performance in school-aged males with FXS (Cornish et al., 2007; Hooper et al., 2008; Munir et al., 2000; Scerif et al., 2007; Sullivan et al., 2007; Wilding et al., 2002), but demonstrate the emergence of IC delays earlier in development. In addition to evidence of IC divergence from typical

development by 18 months of age, males with FXS also demonstrated slow gain of IC skills, with the group mean trajectory showing a flat but slightly downward trend across development (Figure B.2). This aligns with previous work demonstrating slower EF growth across childhood and adolescence in males with FXS (Cornish et al., 2013; Hooper et al., 2018; Tonnsen et al., 2015). Further, our findings are also consistent with prior work showing stagnant growth in regulatory abilities in males with FXS (Robinson et al., 2018). In summary, results indicate that the IC delays in males with FXS are evident as early as the second year of life and slow growth in IC causes increasing divergence from typical development over time.

Early IC difficulties and a lack of improvement in IC across early childhood likely set the stage for several social and behavioral impairments central to the FXS phenotype, such as low social competence, difficulties with self-regulation, and poor adjustment outcomes such as increased internalizing and externalizing symptoms. Our results indicated that lower IC levels at 18 months were associated with greater ADHD symptoms at age 5 in young males with FXS. Further, 18-month IC levels were associated with age 5 ADHD symptoms in young males with FXS regardless of whether their IC improved, stagnated, or declined over time. These findings are seemingly at odds with evidence of increasing expression of ADHD symptoms with age in individuals with FXS (Grefer et al., 2016). Collectively our results suggest that early delays in IC at 18 months may serve as a prognostic marker for later ADHD-related symptomatology in males with FXS, replicating evidence of longitudinal predictive validity and specificity of IC to ADHD in children with both low and high familial risk for ASD (Brocki et al., 2007; Campbell & Von Stauffenberg, 2009; Shephard et al., 2019). Ultimately, our

findings support a broader ADHD subtype in young males with FXS that is characterized by neurocognitive deficits, rather than a model of heterogeneity, in which only some individuals with ADHD demonstrate IC impairments (Sonuga-Barke 2002; Nigg et al., 2004). For the NT group, IC levels at 18 months and growth in IC across childhood were both related to ADHD symptom severity at age 5. Interestingly, despite lower levels of ADHD symptoms on average in the NT group, cross-group comparison of correlation coefficients suggests both IC levels and growth are more strongly associated with ADHD symptoms in the NT group compared to the FXS group.

Regarding ASD symptoms, findings suggest that flatter IC trajectories, but not initial IC levels, were related to ASD symptoms in male children with FXS; further, this association was independent of initial IC levels and NVDQ. These results reflect a more nuanced association between IC and ASD than has been previously described (Gardiner et al., 2017; Konstantareas & Stewart, 2006). Previous studies reporting no significant associations between age-related improvements in regulatory abilities and ASD symptoms in children with FXS (Robinson et al., 2018) may be explained in part by limited stability in ASD symptoms at the age of assessment. In contrast, the present study included psychiatric symptom levels at a clinically stable outcome age. Contrasting findings in the neurotypical literature (Gardiner et al., 2017), our results indicated no association between increases in IC and older age in the FXS sample; however, these findings are consistent with evidence of more apparent EF deficits with increasing age in children with ASD (Hill, 2004). Although a certain threshold of baseline IC is essential to daily functioning, our results suggest that the attenuated growth of IC in young males with FXS, rather than low levels of IC at 18 months, may contribute to elevated rates of

ASD symptoms in this population. These findings complement existing research indicating that ASD symptoms manifest and intensify in severity with increasing age in children with FXS (Lee et al., 2016). Further, early IC impairment and lack of growth in IC across early childhood likely have implications for the development of other complex, higher-order functions and social behaviors. In the NT group, ASD symptoms were unrelated to IC levels at 18 months or growth in IC with age. Low levels and limited variability of ADOS-2 CSS scores in the NT group may in part explain these null findings. Given children with higher ADOS-2 CSS scores are more likely to be diagnosed with ASD, findings may suggest that IC is a less sensitive predictor of ASD symptoms at subclinical levels.

The present study illustrates the early emergence of IC impairment prior to the average age of diagnosis of ASD or ADHD, implicating the primacy of IC deficits or mechanistic involvement of this neurocognitive ability in the development of these psychiatric features in young males with FXS (Daniels & Mandell, 2014; Visser et al., 2014). It is evident that delayed IC, and particularly blunted trajectories of IC across early childhood, has cascading effects for individuals with FXS including heightened vulnerability for ADHD and ASD, disorders that impair daily functioning and reduce quality of life for these individuals and their families (Hatton et al., 2002). It is important to note that the present study examined ADHD and ASD symptoms continuously and not formal diagnoses. Further work is needed to clarify whether IC is related to the diagnosis of ADHD or ASD for individuals with FXS or may contribute to the differentiation of these psychiatric conditions from the FXS phenotype. Regardless, the knowledge gleaned from the present study may identify IC as a developmentally sensitive target for early and



individualized intervention of these psychiatric symptoms, which we know to be important for ensuring optimal developmental outcomes for these children. Further, the lack of specificity of IC in FXS, as indicated by significant associations between IC and ADHD symptoms in NT children, suggests treatments already developed to address ADHD may have similar effectiveness for children with FXS. Studies implementing motoric stopping and proactive monitoring of contextual cues trainings indicated both strategies successfully improved response inhibition (Chevalier et al., 2014; Traut et al., 2021). Additionally, Traut et al. (2021) determined that children with low proactive control, defined as maintenance of goal-relevant information, benefitted more from monitoring training; this type of training may also be appropriate for children with low cognitive ability or high levels of inattention. A review of executive function (EF) interventions for children determined that children with the lowest initial EF levels evidence the greatest gains following these interventions (Diamond & Lee, 2011), findings which are promising for children with FXS. Interventions that alter deviant IC trajectories may reduce the severity or prevent the development of later psychiatric problems in young males with FXS and ultimately reduce emotional stress and economic burden associated with caring for children with developmental disabilities.

This study is the first longitudinal study of early inhibitory control trajectories in relation to psychiatric features in children with FXS and represents a large sample size relative to most research involving rare genetic disorders. It is possible that shared method invariance partially, but likely not completely, accounts for the association between IC and ADHD (Nigg, Goldsmith, et al., 2004); however, significant relationships between IC and ASD symptoms support the validity of our findings and

disconfirm the likelihood of shared method invariance driving results. The present study leveraged parent-ratings of child IC and demonstrated that IC difficulties are not only early emerging in males with FXS but are also *salient* to parents at an early age despite the complex behavioral phenotype evident in individuals with FXS. This suggests that parent-report measures of IC are sensitive to early group differences. Further, characterization of the centrality of early IC impairment to FXS may prime parents of children with FXS to monitor this ability and to pursue early intervention services specific to regulatory vulnerabilities, which may mitigate the development of maladaptive psychiatric outcomes (i.e., ADHD and ASD symptoms) in children with FXS. Though parent ratings have the benefit of high ecological validity from having observed a child's behaviors across a variety of settings, these ratings may be biased by knowledge of their child's diagnosis or differential expectations for their child's behavior at certain ages. This may be influenced by level of parental education, access to medical and mental health resources, and having older children with developmental disabilities. One limitation of the present study is that the FXS and NT samples are not matched on demographic information (i.e., maternal education, income), and therefore it is possible that these characteristics may impact parent ratings. Currently, few validated IC tasks exist for use with young children and toddlers. The development of behavioral performance measures of IC for use with young children that are sensitive to "extreme" ability levels could improve understanding of developing brain-behavior relationships and facilitate the examination of heterogeneous mechanistic pathways involved in disorders characterized by executive deficits (Blair et al., 2005). Accordingly, next steps of this work should entail inclusion of a matched comparison group of males with another

neurodevelopmental disorder (e.g. Down syndrome, idiopathic autism). One weakness of the present study is the inclusion of only male children. Despite evidence of poorer IC ratings and performance by neurotypical male compared to female children and adolescents and atypical neural activation patterns underlying IC in females with FXS, few if any studies to date have examined IC in females with FXS or sex differences in these abilities in individuals with FXS (Eisenberg et al., 2005; Garon et al., 2016; Menon et al., 2004; Moilanen et al., 2010; Thorell et al., 2004). Though the present study did not examine sex effects given the lack of an adequate sample of young females with FXS, research on IC as an early behavioral marker in females with FXS should also be explored. Finally, examination of IC functioning at multiple levels of analysis (i.e. genetic, neural, physiological, cognitive, behavioral) will provide a more comprehensive understanding of this neurocognitive ability in individuals with FXS.

In conclusion, the present study determined that compared to their neurotypical peers, young males with FXS exhibit IC delays as early as 18 months and flat trajectories of IC through age 5. We also determined that IC levels at 18 months are associated with later ADHD symptoms in young males with FXS. Alternatively, attenuated growth in IC over time was associated with greater risk for ASD symptoms in male children with FXS. Differentiating the mechanisms leading to these psychiatric features may enable implementation of more specific interventions that are effective in promoting optimal outcomes for individuals. Our findings help to refine the early developmental phenotype of FXS and highlight the utility of monitoring change in developmental abilities over time. Finally, the present study points to IC as a potential target for early detection and intervention of ADHD and ASD symptoms in male children with FXS.

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## Appendix A: Tables

Table A.1 Sample 1 Demographic Characteristics by Percent of Group

	FXS	NT
<b>Ethnicity (%)</b>		
<i>n</i>	80	49
Hispanic/Latino	2.5	0
Not Hispanic/Latino	75	63.3
Unknown	22.5	36.7
<b>Race (%)</b>		
<i>n</i>	80	49
White	73.7	91.8
Black	3.7	6.1
Hispanic/Latino	1.3	0
American Indian/Alaska Native	1.3	0
More than one race	15	2.1
Unknown	5	0
<b>Maternal Education (%)</b>		
<i>n</i>	56	31
Less than high school	7.1	3.2
High school degree	8.9	6.5
Associate's degree	7.1	9.7
Some college	17.9	6.5
Bachelor's degree	19.6	25.8
Some graduate work	14.3	6.5
Graduate degree	25	41.9
<b>Income (%)</b>		
<i>n</i>	41	29
\$5,000-\$25,000	7.3	3.4
\$25,001-\$50,000	26.8	31
\$50,001-\$75,000	19.5	20.7
\$75,001-\$100,000	14.6	13.8
\$100,001-\$150,000	12.2	17.2
\$150,000+	19.5	13.8

Table A.2 Sample 1 Inhibitory Control and Participant Characterization by Age

	FXS <i>M (SD)</i>	Neurotypical <i>M (SD)</i>
*		
<i>n</i>	174 observations	112 observations
CA	45.39 (13.91)	42.47 (14.84)
IC	3.11 (0.82)	4.32 (0.97)
18 months		
<i>n</i>	7	13
CA	18.85 (1.34)	18.21 (0.53)
ECBQ IC score	2.89 (0.56)	3.60 (1.02)
24 months		
<i>n</i>	22	12
CA	25.24 (1.09)	24.82 (1.18)
ECBQ IC score	3.68 (0.92)	3.76 (0.90)
36 months		
<i>n</i>	44	28
CA	37.07 (1.96)	36.83 (1.61)
CBQ IC score	2.86 (0.78)	4.34 (0.91)
48 months		
<i>n</i>	55	32
CA	49.00 (3.19)	47.42 (3.31)
CBQ IC score	3.07 (0.81)	4.46 (0.80)
60 months		
<i>n</i>	46	27
CA	62.71 (5.38)	61.97 (5.1)
CBQ IC score	3.17 (0.74)	4.71 (0.98)

\*= Pooled mean and SD across repeated observations

CA= Chronological age in months

ECBQ= Early Childhood Behavior Questionnaire

IC= Inhibitory control

CBQ= Children's Behavior Questionnaire



Table A.3 Sample 1 Linear Mixed Model Results of IC Trajectories in FXS and NT

	Estimate	SE	df	<i>t</i>	<i>p</i>
Intercept	3.13	0.14	91.79	21.89	<.001
Age	-.00058	0.0044	83.35	-0.13	.896
Group	0.69	0.22	76.72	3.15	.002
Age x Group	0.021	0.0069	70.71	3.09	.003

Table A.4 Sample 1 Average IC Trajectory Parameters by Group

	FXS ( <i>n</i> =80) <i>M (SD)</i>	Neurotypical ( <i>n</i> =49) <i>M (SD)</i>	<i>d</i>
IC intercept	3.15 (0.44)	3.82 (0.53)	1.40
IC slope	0.0019 (0.0088)	0.0142 (0.0097)	1.35

*IC intercept*= Inhibitory control at 18 months

*IC slope*= Change in inhibitory control over chronological age

Table A.5 Sample 2 Participant Characterization for IC Trajectories and Age 5 Outcome Data

	FXS ( <i>n</i> =26) <i>M (SD)</i>	Neurotypical ( <i>n</i> =22) <i>M (SD)</i>	<i>d</i>
CA	60.70 (3.52)	59.98 (3.35)	-0.21
IC intercept	3.18 (0.50)	3.86 (0.53)	1.34
IC slope	0.0013 (0.011)	0.0167 (0.012)	1.35
MSEL ELC	50.32 (6.03)	96.55 (18.24)	3.36
MSEL NVDQ	50.35 (15.51)	96.59 (12.36)	3.27
CBCL-ADHD problems	8.17 (2.31)	3.68 (2.93)	-1.71
ADOS-2 CSS	5.73 (2.36)	2.00 (1.51)	-1.85

CA= Chronological age in months

IC intercept= Inhibitory control at 18 months

IC slope= Change in inhibitory control over chronological age

MSEL ELC= Mullen Early Learning Composite standard score

MSEL NVDQ= Mullen Nonverbal Developmental Quotient

CBCL-ADHD= Child Behavior Checklist- Attention Deficit/Hyperactivity Disorder problems subscale raw score

ADOS-2 CSS= Autism Diagnostic Observation Schedule, Second Edition Calibrated Symptom Severity score

Table A.6 Sample 2 FXS Group Bivariate (and Partial) Correlations

	1	2	3	4	5
1. IC intercept	-				
2. IC slope	.17	-			
3. CBCL-ADHD	-.48 <sup>†</sup> (-.46 <sup>†</sup> )	-.43 <sup>†</sup> (-.41)	-		
4. ADOS-2 CSS	-.19 (-.03)	-.66** (-.63*)	.24	-	
5. MSEL NVDQ	.25	.27	-.19	-.47 <sup>†</sup>	-

*IC intercept*= Inhibitory control at 18 months

*IC slope*= Change in inhibitory control over chronological age

*CBCL-ADHD*= Child Behavior Checklist- Attention Deficit/Hyperactivity Disorder problems subscale raw score

*ADOS-2 CSS*= Autism Diagnostic Observation Schedule, Second Edition Calibrated Symptom Severity score

*MSEL NVDQ*= Mullen Nonverbal Developmental Quotient;

Partial correlations, controlling for the other IC parameter, are shown in parentheses;

<sup>†</sup> $p < .05$ , \* $p < .01$ , \*\* $p < .001$

Table A.7 Sample 2 Neurotypical Group Bivariate (and Partial) Correlations

	1	2	3	4	5
1. IC intercept	-				
2. IC slope	.25	-			
3. CBCL-ADHD	-.68** (-.70**)†	-.64* (-.66*)	-		
4. ADOS-2 CSS	.17 (.22)	-.17 (-.22)	-.03	-	
5. MSEL NVDQ	.23	.32	-.16	-.27	-

*IC intercept*= Inhibitory control at 18 months

*IC slope*= Change in inhibitory control over chronological age

*CBCL-ADHD*= Child Behavior Checklist- Attention Deficit/Hyperactivity Disorder problems subscale raw score

*ADOS-2 CSS*= Autism Diagnostic Observation Schedule, Second Edition Calibrated Symptom Severity score

*MSEL NVDQ*= Mullen Nonverbal Developmental Quotient;

Partial correlations, controlling for the other IC parameter, are shown in parentheses;

† $p < .05$ , \* $p < .01$ , \*\* $p < .001$

## Appendix B: Figures

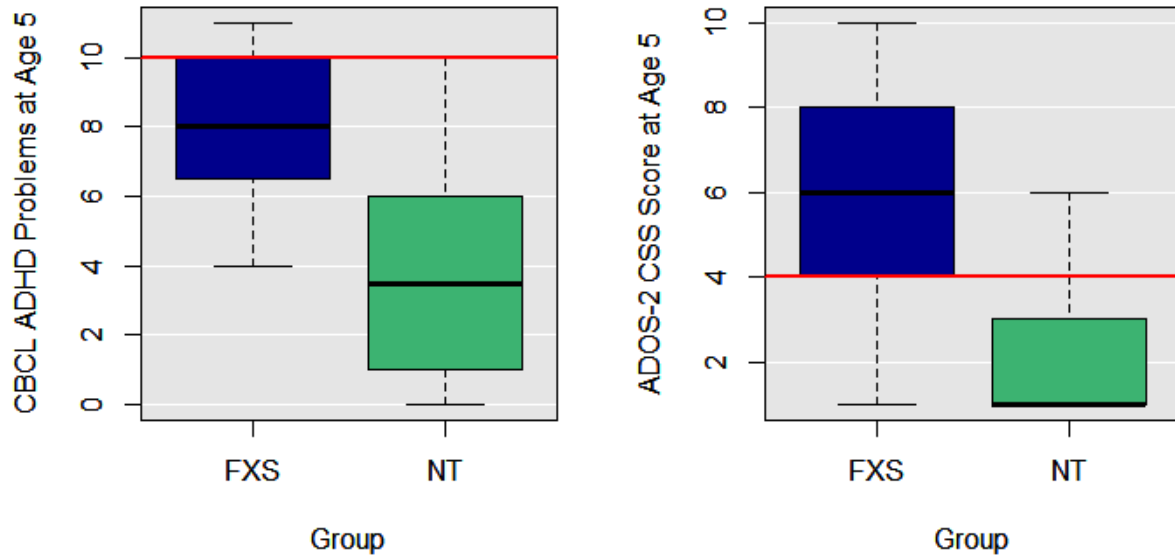


Figure B.1 Variance in Psychiatric Symptom Severity at Age 5 by Group

*Note.* Scores above the red lines fall within the borderline clinical or clinical range for the CBCL, and autism spectrum disorder or autism range for the ADOS-2.

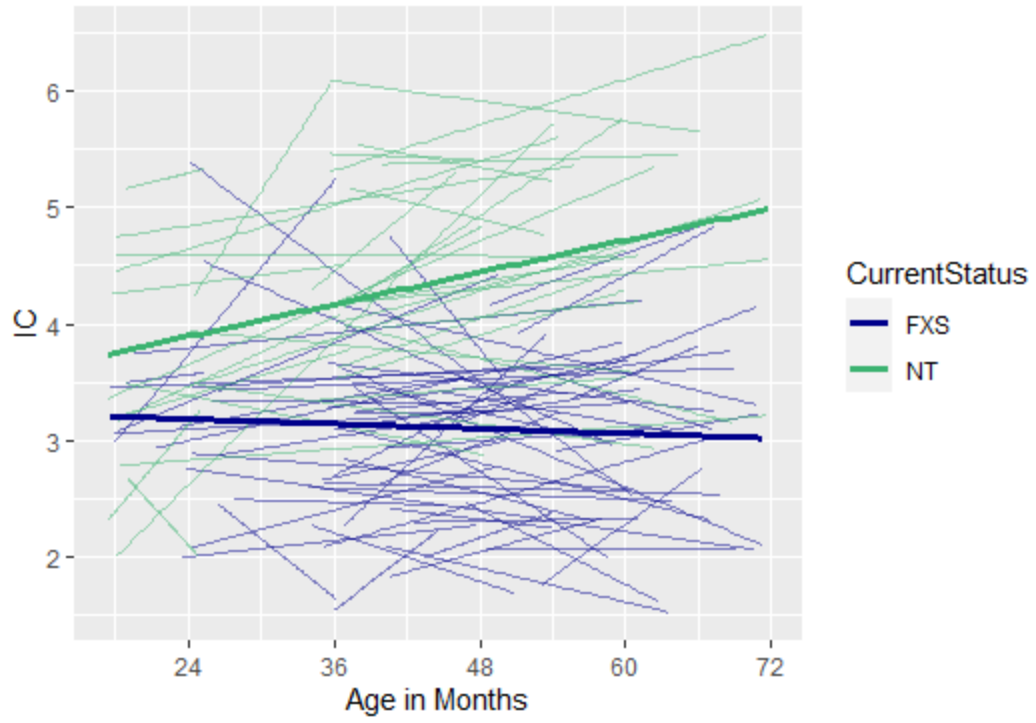


Figure B.2 Comparison of IC Trajectories by Group

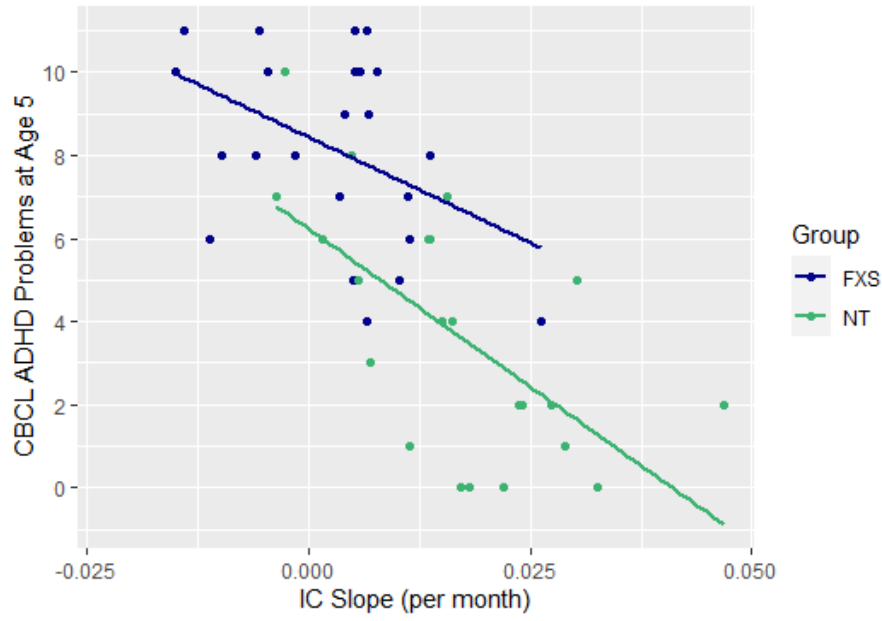


Figure B.3 Comparison of IC Slope Predicting ADHD Symptoms by Group



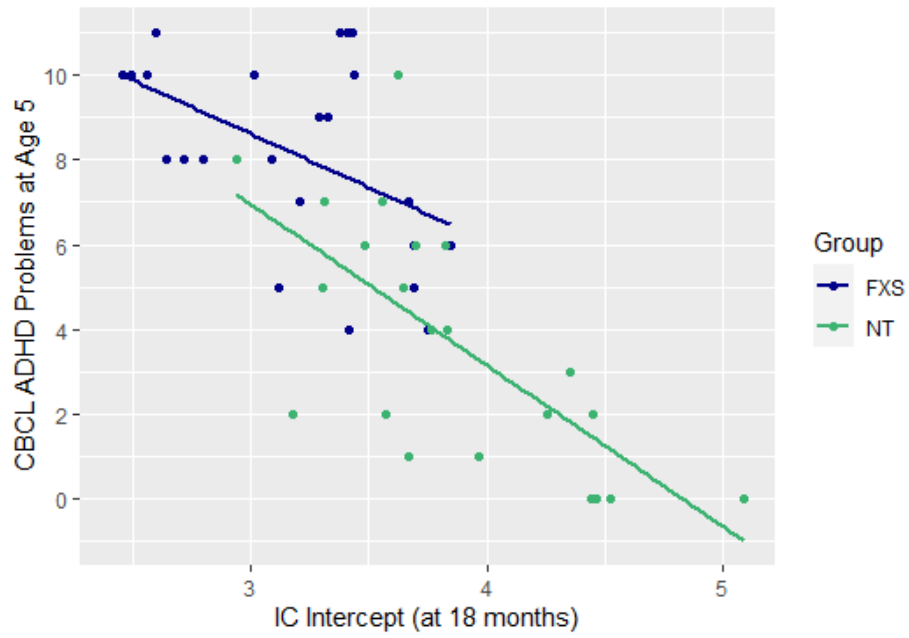


Figure B.4 Comparison of IC Intercept Predicting ADHD Symptoms by Group

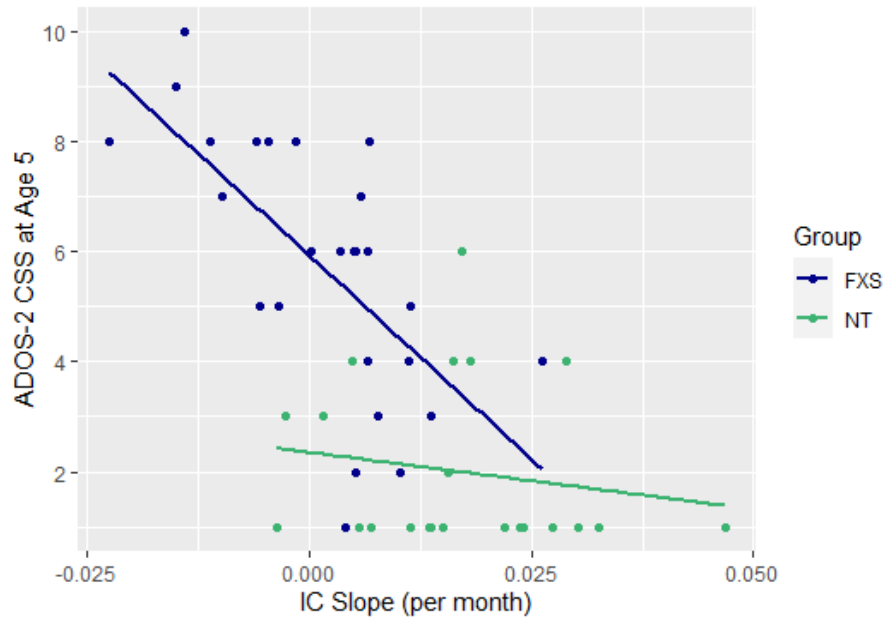


Figure B.5 Comparison of IC Slope Predicting ASD Symptoms by Group

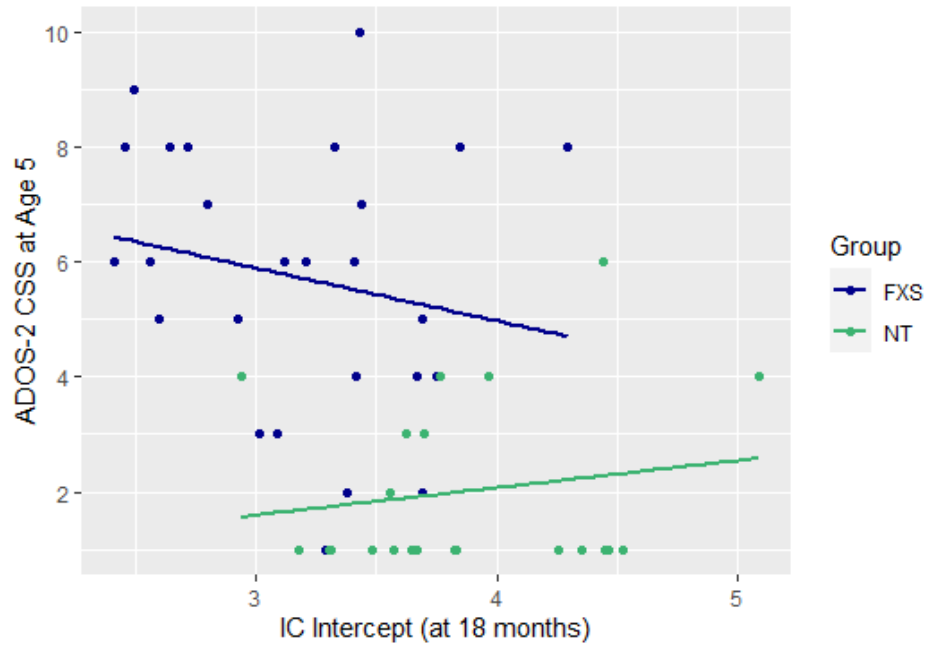


Figure B.6 Comparison of IC Intercept Predicting ASD Symptoms by Group