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The Emergence and Stability of Attention Deficit Hyperactivity Disorder in Boys with Fragile X Syndrome

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Abstract

Background—Children with fragile X syndrome (FXS) are at high risk for developing a range of behavioral disorders, including Attention Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorders (ASD). However, very few studies have investigated the comorbid profile of FXS and ADHD and the possible dissociation from the FXS and ASD profile. The present study examined the relationship of childhood temperament characteristics of the Surgency facet (activity level, impulsivity, approach, shyness, and smiling and laughter) and the severity of ADHD and ASD features at two measurement time points in childhood, preschool (ages 3–4) and at school entry (ages 5–6).

Methods—The study consisted of males with FXS measured at each time point (preschool and school entry), as well as comparison of typically developing (TD) boys at the preschool measurement time point. Parent reported measures of temperament and behavioral symptoms were collected at each time point. Multiple regression analyses were used to analyze obtained data.

Results—Elevated activity level scores are associated with ADHD scores at preschool age and elevated shyness and decreased smiling and laughter is strongly associated with ADHD scores upon school entry. Impulsivity emerges as a strong indicator of elevated ADHD scores around school age, but even preschool impulsivity scores demonstrate some predictive value for higher ADHD scores later in school. Finally, no Surgency characteristic was significantly related to ASD scores at any age.

Conclusions—Impulsivity serves as an indicator of elevated ADHD symptoms across development periods in boys with FXS, while activity level is just indicative of higher ADHD scores at the preschool age. The Surgency facet of temperament at either age does not predict strong relationships of comorbid pathologies of ADHD and ASD in FXS. However, Surgency characteristics may serve as informative discriminative factors when studying behavioral outcomes in boys with FXS.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a persistent pattern of inattention and/or hyperactivity/impulsivity that occurs across settings (American Psychological Association, 2013) and across development. ADHD affects nearly 10% of children throughout the United States (CDC, 2011) with symptoms associated with poor academic performance, challenges within the home setting, and difficulties in peer relationships. While preschool represents a developmental stage during which ADHD symptoms become sufficiently differentiated to support diagnostic decision making, evidence clearly documents that features are present very early in development and that indicators of risk can be observed in the first five years (Armstrong & Nettleton, 2004; Berger & Nevo, 2011; Tandon, Si, & Luby, 2011). Early detection has therefore been a primary focus in this body of work, and accumulating research now indicates that early intervention can alter trajectories not only to ameliorate ADHD symptoms but to potentially prevent or reduce the impact of secondary conditions like conduct disorder or oppositional defiant disorder associated with poor social and school outcomes (Anastopoulos et al., 2010; Brocki et al., 2007; Halperin et al., 2012). While the cause of ADHD is not clearly delineated, evidence indicates multiple mechanisms for the development of ADHD including genetic, environmental, and various biological processes such as physiological arousal (Faraone & Mick, 2010; Hankin, Abela, Auerback, McWhinnie, & Skitch, 2005).

Given the pressing need to identify ‘at-risk’ symptoms of ADHD, recent efforts have focused on early temperament styles as possible predictors of poor behavioral outcomes in children (DePauw & Mervielde, 2011; Gartstein et al., 2012; Nigg, 2004). Temperament is defined as constitutionally-based individual differences in reactivity and regulation which emerge during infancy (Posner & Rothbart, 2000; Rothbart, 1981; Rothbart & Bates, 2006). Temperament characteristics are generally consistent across settings (e.g., home, school, with peers) and across childhood development and, additionally, are postulated as a component for the later development of psychopathology, including ADHD (Nigg, Goldsmith, & Sachek, 2004; Rothbart & Bates, 2006). Thus, given its early developmental emergence, relative stability, and value in identifying risk markers for disorders that may emerge later in development, studies that employ temperament traits to investigate pathways to childhood disruptive behaviors are increasingly recognized (Martel, Pierce et al., 2009).

There are multiple models to help conceptualize temperament. Most of the noted work in temperament characterizes infants or children based on their observed individual differences. Some models simplify temperament in to two domains, such as “Uninhibited” or “Inhibited” (Kagan & Snidman, 1991). Other models account for the multiple characteristics, such as the Chess and Thomas model (1977). This model employs four

classifications, “easy”, “difficult”, “slow-to-warm up” or “inconsistent” that are based on how an individual rates on nine characteristics. Similarly, investigators Buss and Plomin outline a model to describe how individuals fall on four domains, “Emotionality”, “Activity”, “Sociability”, and “Impulsivity” (Buss & Plomin, 1975). According to Rothbart’s model, there are fifteen specific, individual characteristics that load onto three domains: Negative Affect (characterized by fear, distress, and sadness), Effortful Control (characterized by attention and soothability), and Surgency (characterized by impulsivity, activity, and approach). Rothbart’s model has been widely used across populations and ages, including FXS (Roberts et al., 2014; Tonnsen, et al., 2013), making it an ideal model for the present study. Specifically, the domain of *Surgency*, with its traits including activity level, impulsivity, and approach, is strongly associated with ADHD symptoms (DePauw & Mervield, 2011; Rothbart, Ahadi, Hershey, & Fisher, 2001). Investigating the developmental trajectory of Surgency characteristics could provide insight into when and which symptoms of ADHD become elevated over time in both clinical and non-clinical populations.

ADHD in Fragile X Syndrome

Children with identified genetic disorders, such as fragile X syndrome (FXS) are at a disproportionately high risk for developing ADHD. FXS is caused by a trinucleotide (CGG) repeat expansion in the 5 untranslated region of the Fragile X Mental Retardation 1 (FMR1) gene on the X chromosome (Sherman, 2002), and is the most common heritable form of intellectual disability world-wide (approx. 1 in 2500; Hagerman, 2008). Children with FXS, usually boys, present with a number of behavioral and cognitive concerns that are now well-documented and serve to distinguish the fragile X phenotype from those of other neurodevelopmental disorders such as Williams syndrome, Down syndrome, and 22q11 syndrome. Included in the FXS phenotype are a range of comorbid disorders, namely Autism Spectrum Disorder (ASD) (Bailey et al., 2001; Hatton et al., 2006), anxiety disorder (Bailey et al., 2008; Tonnsen, Malone, Hatton, & Roberts, 2013), and ADHD (Cornish & Wilding, 2010). In terms of ADHD comorbidity, an estimated 84% of boys and 67% of girls with FXS display clinical symptoms of inattention and impulsivity, and up to 66% of boys and 30% of girls display abnormally elevated levels of hyperactivity (Bailey et al., 2008; Sullivan et al., 2006). The prevalence of ADHD symptoms in children with FXS is between 54% and 59%, which is higher than rates found in individuals with other neurodevelopmental disorders and in individuals with non-specific intellectual disability (Sullivan, Hatton, & Hammer, 2006).

Exploring deeper than the diagnostic labels of ADHD seen in boys with FXS, deficits with associated ADHD symptoms such as sustained attention and executive functioning are commonly reported in these boys, resulting in pervasive inhibitory control deficits that persist across development into early adulthood (Bailey et al., 2008; Cornish et al., 2013; Farzin et al., 2006; Hatton et al., 2002; Scerif et al., 2004; Scerif et al., 2012; Sullivan et al., 2006). These attention deficits appear to emerge early, becoming pronounced around the age of four (Cornish et al., 2013; Scerif et al., 2012). If intervened upon quickly, expected outcomes include improved attention associated with lower rates of hyperactivity and improved prosocial behaviors (Scerif et al., 2012), along with improved cognitive outcomes such as nonverbal intellectual ability and reduced autism symptoms in young boys with FXS

(Cornish et al., 2012; Cornish et al., 2013). Although these studies provide crucial new information on the cognitive outcomes of poor attention performance in FXS, and provide a much-needed developmental profile, to date no study has examined the emergence and presentation of ADHD as a clinical entity in this population. Being able to capture early symptoms as well as establish how the symptoms are distinct from other comorbidities such as autism will be key to identifying potential risk markers to facilitate early identification and the development of targeted treatments. Treatments, especially those targeted at preschool populations, have increasingly gained credibility and reliability in their findings (Halperin, 2012). An efficient mechanism for early identification, such as temperament, is crucial in getting these interventions implemented during this time of developmental growth and cognitive plasticity (Halperin, 2012).

ADHD and Temperament in FXS

There is an emerging body of research that has sought to define the temperament profiles of children with FXS (Bailey et al., 2000; Hatton et al., 1999; Roberts et al., 2006; Roberts et al., 2014; Shanahan et al., 2008; Tonnsen et al., 2013). The majority of these studies have consistently found boys with FXS to be more active, less adaptable, and less approachable than their typically-developing peers (Bailey et al., 2000; Hatton et al., 1999; Roberts et al., 2006; Shanahan et al., 2008). Recently, the temperament domain of Surgency and specifically impulsivity, have been shown to be especially impaired in FXS (Roberts, et al., 2014). In typically-developing preschool children, surgency characteristics are seen as an early indicator of possible ADHD (Nigg et al., 2004; Rothbart & Bates, 2006). In the case of FXS, as the understanding of profiles of ADHD symptoms in these individuals increases, Surgency may also play a similar predictive role in identifying emergence and severity of these ADHD symptoms. Temperament profiles may also serve as a discriminative factor when studying behavioral outcomes. Temperament profiles could potentially provide insight into the differentiated development of behavioral disorders, such as ADHD and ASD, in children with FXS.

Longitudinal Profiles of Temperament and ADHD

Longitudinal data permit the examination of research changes or stability in variables of interest over time. However, given low incidence and retention rates for populations like fragile X syndrome, it is often a challenge to collect longitudinal data. To date, most studies regarding ADHD symptoms in children with FXS are cross-sectional (Bailey et al., 2008; Sullivan et al., 2006). Those studies that have longitudinal data and predictive information regarding outcome trajectories often focus on one aspect of ADHD, such as attention (Cornish et al., 2013; Scerif et al., 2012). Further, longitudinal research temperament has provided information about the stability of temperament characteristics throughout childhood (Rothbart et al., 2001; Putnam et al., 2008), but there is a lack of longitudinal temperament data informing behavioral outcomes in typically-developing and special populations of children. Longitudinal data depicting both temperament characteristics and behavioral profiles could provide greater, comprehensive understanding of the development of children with FXS.

The Current Study

The overarching aim of the current study was to examine the emergence, stability, and predictors of ADHD in young boys with FXS. Second, we aimed to examine the association of ADHD to temperament reflected in Surgency as a potential risk marker. We asked specifically whether elevated ADHD symptoms were present at preschool or school entry and whether there was a change in symptom emergence across these two key developmental periods. Next, we asked whether there was a relation between Surgency and ADHD symptoms across time and whether early-emerging Surgency predicted later-occurring ADHD symptoms. We included ASD symptoms to enable us to determine the specificity of these relations to ADHD versus to problem behavior more broadly, and we contrasted relations in boys with FXS to those in a typically-developing chronological age-matched comparison group to control, at least partially, for developmental issues. To our knowledge, this is the first longitudinal study of the emergence and stability of ADHD in very young children with FXS, and it is the first to incorporate temperament factors as potential risk markers associated with later-emerging ADHD.

METHODS

Participants

Data for the current study were taken from two completed studies at the University of North Carolina at Chapel Hill targeting the longitudinal development of children with FXS. The first study focused on preschool development and included measures of broad development and behavior for boys 2 to 7 years of age collected at 12 month intervals (FXS $n = 20$). The second study focused on family adaptation and included boys with FXS and typically-developing boys (FXS $n = 13$; TD $n = 17$) from 1 to 14 years of age. The boys with FXS were assessed every eighteen months. Data from participants with FXS across both studies were included if the child had an assessment between 3 to 4 years of age to represent “preschool” and also between 5 to 6 years of age to represent “school entry.” Children were included from both samples to increase the power of the potential findings in the analyses. Of the participants in the FXS group, only participants with data for both preschool and school age assessments were included. The average time span between assessments was 23.70 months (range: 13–35 months; $SD = 7.77$).

The final sample consisted of 33 boys with FXS and a control group of 17 typically-developing boys. FXS status was confirmed through genetic records. Typical development was characterized as no evidence or suspicion of a developmental or intellectual disability. Longitudinal data are not available for the typically developing participants as the study from which they were drawn had only one assessment time point that fit within the time frame of the study, the “preschool” ages (3–4). Thus, our inclusion of the TD group allows a cross-sectional perspective which, while not as valuable as longitudinal data, is important as a reference. The two groups were matched on chronological age. The FXS group at the time of the “preschool” assessment had an average age of 41.09 months (range: 36–59 months; $SD = 6.50$). The boys in the “preschool” control group had an average age of 45.53 months (range: 38–53 months; $SD = 4.26$). At the subsequent “school entry” assessment, the FXS group had an average age of 64.79 months (range: 60–83 months; $SD = 4.46$).

Measures

Attention-deficit/hyperactivity disorder (ADHD)—The Child Behavior Checklist (CBCL; 1.5–5, 6–18; Achenbach, 1991; Achenbach & Rescorla, 2001) was completed by each participant's mother at each assessment. The CBCL is a widely-used, 118-item parent rating scale used to assess the internalizing and externalizing symptoms of children. Items are answered using a 3-point Likert scale of “not true (0),” “somewhat or sometimes true (1),” and “very true (2).” The CBCL consists of individual symptom-specific scales, composite scores (internalizing, externalizing, and total problems), and also scales based on criteria from the Diagnostic and Statistical Manual (DSM-IV). For the DSM-based scales, there are raw scores as well as t-scores indicating severity. The CBCL was normed on a large, representative sample of children and adolescents, yielding high rates of reliability ($r = 0.95$; Nakamura, Ebesutani, Bernstein, & Chorpita, 2009). The ADHD scale of the CBCL has shown consistent reliability, discriminative validity, and convergent validity. Further, inter-rater reliability yielded similarly high consistency ($r = 0.96$; Nakamura et al., 2009). The DSM-ADHD scale had high test-retest reliability ($r = 0.93$; Nakamura et al., 2009). The CBCL has also successfully been used previously with children with FXS (Bargagna, Canepa, & Tinelli, 2002; Hatton, et al., 2002; Hatton, et al., 2006; Farzin, et al., 2006). As recommended by the publisher, the ADHD raw scores were used as a dependent variable across all analyses given that T scores do not drop below 50. The clinical cutoff for ADHD symptoms is indicated by a T score above 70. For the typically-developing boys at the preschool age, no participants met the clinical cutoff for ADHD. For the boys with FXS at the preschool age, 3 participants' scores met the clinical cutoff for ADHD, and 11 were at-risk for elevated ADHD symptoms (scores between 60–69). For boys with FXS at the school age, 4 participants' scores met the clinical cutoff, and 17 were at-risk for elevated ADHD symptoms.

Autistic behavior—Indication of autistic behavior severity was measured using the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1998) at each assessment point. The CARS is an experimenter rating scale of autistic behaviors based on observations made during each assessment. It yields a high internal consistency rate ($r = 0.94$) and is highly correlated with clinical ratings of autism (DiLalla & Rogers, 1994; Eaves & Milner, 1993). The measure is comprised of 15 items that represent a range of autistic behaviors. Each item is rated on a scale from 1 (within normal limits) to 4 (severely abnormal), allowing for a total score between 15 and 60. Scores above 30 indicate a profile of autistic behavior ranging from mild to moderate to severe. Discriminative validity has been demonstrated in the scale's sensitivity in discriminating children with autism from children without autism (DiLalla & Rogers, 1994; Eaves & Milner, 1993). The CARS has been reliably used with children with FXS (e.g., Bailey et al., 2001; Hatton et al., 2002; Hatton et al., 2006). The total raw score scale was used as a dependent variable across all analyses. At the initial preschool assessment, 36% ($n = 12$) of boys with FXS were above the CARS clinical cutoff score for ASD. The mean score was 27.2 (range: 16.5 – 36.0; $SD = 5.27$). At the subsequent school entry assessment, 33% ($n = 11$) of boys with FXS met criteria for an ASD. The mean score was 27.56 (range: 16.5 – 29.0; $SD = 6.02$). At the initial preschool assessment, no TD boys met criteria for an ASD. The mean score was 15.09 (range: 15.00 – 15.50; $SD = 0.20$).

Temperament: Surgency—The Children's Behavior Questionnaire (CBQ) by Rothbart, Ahadi, Hersey, and Fisher (2001) was completed by mothers at each assessment to assess the characteristics of Surgency in children. The CBQ is comprised of 195 items, loading onto 15 scales of children's temperament. These scales are activity level, anger/frustration, attentional focusing, discomfort, fear, high intensity pleasure, impulsivity, inhibitory control, low intensity pleasure, perceptual sensitivity, positive anticipation (approach), sadness, shyness, smiling/laughter, soothability. A principal factor analysis suggested that the 15 scales loaded onto three theoretical constructs of temperament: Negative Affectivity, Surgency (Extraversion), and Effortful Control (Roberts, et al., under review Rothbart, Ahadi, Hershey, and Fischer, 2001;). Each item is answered using a 7-point Likert scale ranging from "extremely untrue of my child" to "extremely true of my child." Internal consistency reliability and test-retest reliability were adequate, and scores ranged from 0.67 to 0.94, with a mean internal consistency score of 0.77 across the 15 scales (Rothbart, Ahadi, Hershey, & Fischer, 2001; Putnam & Rothbart, 2006). Additionally, the inter-rater reliability across the scores ranged from 0.28 to 0.79, with a mean reliability score of 0.51. The raw scores from the five Surgency subscales (activity level, impulsivity, approach, shyness, and smiling and laughter) were used as the independent variables across all analyses.

Procedure

Data Collection—Data were collected as part of a larger assessment battery. Two examiners went to the participants' homes to conduct the assessments. Parent rating scales (CBQ, CBCL) were mailed ahead of the scheduled assessment and then collected on the day of the assessment. Examiners completed the CARS immediately post-assessment. At the initial time point (preschool), scores were obtained from both typically-developing (TD) boys and boys with FXS for the CBQ, for the CBCL, and the CARS. At the subsequent point (school entry), scores from boys with FXS were obtained for Surgency domains using the CBQ, for the CBCL, and for the CARS.

RESULTS

Means and standard deviations for parent-reported Surgency characteristics raw scores are presented in Figure 1. The means and standard deviations of the scores of parent-reported ADHD and experimenter-reported ASD are presented in Table 1. Multiple regression analyses were used to examine differences seen in Surgency (activity level, impulsivity, social approach, shyness, and smiling/laughter) as differential predictors of ADHD and autism severity. Preliminary analysis of behavioral ratings in the FXS group found that preschool and school age ADHD ratings were correlated ($r = .39, p < 0.05$). Also, preschool and school age autistic behavior ratings were correlated ($r = .68, p < 0.05$). Further, it was found that in the FXS group that ADHD ratings and ASD ratings were not correlated, thus independent of each other. ADHD and ASD ratings were found to be uncorrelated and independent in the TD group as well. In assessing the stability of CBCL and CARS scores from preschool to school age, neither CBCL or CARS scores were found to differ; however, there was a trend for an increase in ADHD ($p < .081$). Normality of residuals was found.

Preschool Surgency and Concurrent ADHD and ASD in FXS and TD

Analyses were conducted examining the five Surgency characteristics as predictors of ADHD in the FXS preschool group. The model was significant, $F(5, 25) = 2.50, p < 0.05$. The correlation coefficient was 0.58, indicating the Surgency characteristics accounted for 34% of the variance found in ADHD scores. Activity Level was significantly related to ratings of ADHD symptoms ($\beta = .53, p < 0.01$). No other Surgency characteristics significantly related to ADHD scores in the FXS group. In the control group, the overall model was not significant, $F(5, 11) = 1.5, p = 0.27$. Surgency scores in TD boys had no significant relation to the ADHD raw scores. See Table 2 and Figure 1. Finally, analyses were conducted examining the five Surgency characteristics as predictors of the ASD raw score outcome variable in the FXS group. The model was not significant for the FXS group, $F(5, 25) = 1.0, p = 0.42$, or for the control group, $F(5, 11) = 0.92, p = 0.50$, and no Surgency characteristics significantly related to ASD raw scores.

School Age Surgency and Concurrent ADHD and ASD in FXS

Analyses were conducted examining the five Surgency characteristics as predictors of the ADHD raw score outcome variable. The model was significant, $F(5, 26) = 6.19, p < 0.01$. The Surgency characteristics accounted for 55% of the variance found in ADHD raw scores. Higher impulsivity ($\beta = .87, p < 0.01$) and shyness ($\beta = .67, p < 0.01$) were associated with elevated ADHD scores. See Table 3. Analyses examining the five Surgency characteristics as predictors of ASD raw scores was not significant, $F(5, 26) = 1.10, p = 0.39$.

Preschool Surgency Predicting School Age ADHD and ASD in FXS

Analyses were conducted examining the five Surgency characteristics reported in preschool as predictors of the ADHD raw score outcome variable reported at school entry. The model was significant, $F(5, 25) = 4.00, p < 0.01$. Surgency characteristics accounted for 45% of the variance seen in ADHD scores. Higher impulsivity ($\beta = 0.56, p < 0.02$) and lower smiling and laughter ($\beta = -0.45, p < 0.03$) in preschool were related to higher ADHD scores at school age. See Table 4. Analyses were also conducted examining the five Surgency characteristics reported in preschool as predictors of the ASD raw score outcome variable reported at school entry. The model was not significant, $F(5, 25) = 0.53, p < 0.75$.

DISCUSSION

The current study examined Surgency and its concurrent and predictive association with ADHD behavior in boys with FXS. Data were collected from two time points, preschool and school entry, in an effort to gain insight about the emergence and stability of these problematic behaviors and to examine the predictive value of temperament as a precursor to later emerging ADHD. Detection of early markers of psychopathology permits earlier identification and, subsequently, earlier intervention. This study is the first to demonstrate the potential value of early temperament assessments to detect problem behavior in boys with FXS.

We reported that preschool boys (M 41 months of age) with FXS did not differ from typically-developing controls in mean level of ADHD symptoms; however, none of the

typical controls displayed scores in the clinical range, whereas 42% of boys with FXS displayed scores that fell above the clinical cutoff (9%) or were in the “at risk” range (33%). Both the mean levels and categorical rankings reflect increased ADHD behaviors approximately 2 years later at school age (M 64 months of age) with nearly double the raw score for boys with FXS across this age span. Likewise, 64% of the school age boys with FXS fell in the clinical range with 12% above the clinical cutoff and 52% in the “at risk” range. This represents an increase of 22% of boys with FXS falling outside normative expectations for ADHD behaviors across a 2-year time span. It should be noted that all 3 of the boys who fell above the clinical range at preschool age also fell above the clinical range at school age demonstrating stability for this subgroup at an individual level. While the rates of 9% and 12% did exceed the clinical cutoffs for ADHD symptomology, and are higher than normative samples, they are far lower than the rates of 54 – 59% reported for older aged children with FXS (Sullivan et al., 2006). Given that the majority of individuals with ADHD who do not have FXS are diagnosed by 6 years of age, our data suggest that there may be a more gradual emergence of symptoms and increased symptom severity over time in boys with FXS than other populations.

Autistic behavior, in contrast, did not appear to change over time in our sample, consistent with some existing work (Cornish et al., 2012) but discrepant from other work indicated a slight increase over time (Hatton et al., 2006). These findings are novel with regard to the increased ADHD symptoms over time as previous reports have reported stability of these features using parent (Hatton et al., 2002) and teacher scales (Cornish et al., 2012). We attribute our findings to the fact that our study represents the examination of ADHD features using rating scales during one unique developmental window – the transition from preschool to primary school. Other studies represented older aged children, with means of 8 and 10 years of age, respectively (Hatton et al., 2002; Sullivan et al., 2006). Finally, while previous research has shown a correlation of increased ADHD scores related to increased ASD scores (Farzin et al., 2006; Sullivan et al., 2006), the Surgency domain of temperament at these ages does not predict strong relations of comorbid pathologies. This study demonstrates that Surgency characteristics are indicative of elevated ADHD symptomatology in boys with FXS, but does not appear to be related to autistic behavior.

Temperament ratings of Surgency characteristics show mean levels that are generally similar to typically-developing controls with the exception of shyness, which is elevated for the group with FXS at both preschool and school age. These characteristics also appear to be stable over time, notable given that activity level using temperament scales does not change whereas the ADHD score, of which activity is a primary component, does appear to increase over time. Both the temperament scale and the CBCL scale were completed by the same informant at the same time; thus, it is possible that differences reflect constructs that vary across measures with the temperament facet being a more discreet reflection of a single behavior and the ADHD score representing multiple components including activity, attention, and impulsivity.

Integrating temperament with ADHD ratings, we found that elevated activity level, a single characteristic of Surgency, was associated with elevated ADHD scores at preschool age and at a trend level at school age. This finding of increased activity levels in the preschool and

early childhood years is consistent with previous reports (Sullivan et al, 2006). Of note, the relation between activity level and ADHD scores appears to be unique to boys with FXS and not observed in typically-developing boys suggesting a specific FXS developmental phenotype. In addition to the trend for activity level, we report that elevated shyness and impulsivity were strongly associated with ADHD scores at school age. While we hypothesized that activity level and impulsivity would be associated with ADHD, the emergence of shyness was unanticipated; however, it is consistent with previous findings (Bailey et al., 2008; Sullivan et al., 2006). We interpret this relation to reflect self-regulation more broadly as shyness on the CBQ, which also loads on the Effortful Control factor reflecting difficulties regulating social engagement and is associated with impulsivity. Our finding that impulsivity is associated with ADHD at the school age and not preschool age likely reflects the lack of expected developmental maturity in impulse control in FXS and the increased reliance on impulse control to execute more complex, higher order tasks that are increasingly salient at school age and in classroom settings. Further, this development of impulse control, and any consequential deficits, is unique to elevated levels of ADHD symptoms in boys with FXS, and not of the development of other problematic behaviors, such as autism.

Our examination of the prediction of ADHD features indicated that elevated impulsivity at preschool was the only factor to emerge in predicting ADHD at school entry. While not surprising given that impulsivity is one of the core features of ADHD, it is interesting to note that impulsivity was not associated with ADHD features at the preschool age but emerged as a primary predictor of ADHD at school age and was the only feature to predict the longitudinal outcome of ADHD over time. Also, elevated activity level is a core feature of ADHD, and it was associated with ADHD symptoms at both the preschool and school age periods. However, it was not a predictor of ADHD over time thus suggesting that its association is more generalized and associated with concurrent ADHD symptoms and less critical for discriminating ADHD outcomes over time.

There were several limitations in the study. First, non-diagnostic parent report measures were used to assess the outcome measures of ADHD (the CBCL; Achenbach, 1991; Achenbach & Rescorla, 2001) and ASD (the CARS; Schopler, Reichler, & Renner, 1998). However, our focus was on sub-threshold symptomology as a continuous variable versus diagnostic categorization. Using continuous variables allows a more sensitive representation of symptomology independent of diagnostic category and further describe individuals' functional impairment (Biederman et al., 2010; Willoughby, 2003). Second, our measure of ADHD (the CBCL) was not normed on samples with intellectual disability. However, highly regarded measures used in ADHD diagnostics (i.e., Conners-3; Conners, 2008) have also not been normed on samples with intellectual disability. Similarly, we were limited by the measures employed during data collection, and thus the use of the CARS is a limitation given it is not a gold standard measure like the ADOS. Third, our sample size of boys with FXS is not large (N=33); however, the longitudinal nature and repeated measures help offset the small sample size related to issues of power. Finally, we did not have longitudinal data for the typically-developing group, which limited our comparisons and conclusions.

Future work examining parent-reported temperament in conjunction with experimental and physiological measures, such as variability seen in heart rate activity or cortisol levels would be a good next step. Also, longitudinal research should be conducted to examine the stability of symptoms in the developmental trajectory of individuals that spans beyond the preschool to school age years. Even in the short time from preschool to school entry, there was an observed shift in the saliency of characteristics related to ADHD outcomes. Following participants throughout the remainder of childhood and adolescence would be informative to the presentation of ADHD features and how they may change or stabilize with maturation. Future studies should continue to investigate biological and environmental contributors to the early emergence of ADHD in individuals with FXS. The identification of early-emergent features of ADHD can potentially contribute information for early intervention strategies for children with FXS as well as for the broader non-FXS population.

In conclusion, the current study presents the first examination of the emergence, stability, and predictors of ADHD in preschool-aged boys with FXS. Collectively, our findings suggest a nuanced picture of the emergence and stability of ADHD over time in boys with FXS. We report that ADHD features are raised to the level of clinical concern in approximately 9% of preschool aged boys with FXS with another 33% considered in the elevated “at risk” range. These rates increase to 12% falling in the clinical range and 52% in the “at risk” range. Impulsivity is the primary factor contributing to these increases over time. Identifying elevated impulsive traits early in childhood in FXS can lead to early awareness of the risk for ADHD that is critical to optimize outcomes. Earlier identification will lead to implementation of various interventions targeted at decreasing impulsive behavior; and the earlier these management skills are taught, the more likely children and families will be able to prevent undesirable consequences that result from impulsive behavior, such as poor school performance, ineffective emotional regulation strategies, and poor social relationships. The results of this study provide insight into the possible temperamental indicators associated with the early emergence of ADHD, a critical factor because temperament is an early emerging trait that is generally stable across situations and time.

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Figure 1.
Surgency Characteristic Raw Scores for FXS and TD Boys

Table 1

ADHD and ASD Raw Scores for FXS and TD Boys

	Preschool		School Age
	FXS (n=33)	TD (n=17)	FXS (n= 33)
ADHD (CBCL)			
M	4.52	4.24	8.09
SD	2.23	2.51	1.93
Clinical Cutoff	9%	0%	12%
ASD (CARS)			
M	27.20	15.09	27.60
SD	5.19	0.19	5.93
Clinical Cutoff	36%	0%	33%

Table 2

Regression Results for FXS and TD Boys at Preschool

	ADHD			
	Coefficient	SE	t	p
FXS (n=33)				
Activity Level	1.35	0.50	2.70	0.01
Approach	-0.19	0.50	-0.37	0.72
Impulsivity	0.21	0.70	.30	0.77
Shyness	0.28	0.43	.65	0.52
Smiling & Laughter	0.12	0.60	.21	0.84
TD (n=17)				
Activity Level	0.47	1.44	0.33	0.75
Approach	-0.17	1.20	-0.14	0.89
Impulsivity	2.27	1.47	1.55	0.15
Shyness	0.79	0.75	1.06	0.31
Smiling & Laughter	0.83	1.18	0.70	0.50

Table 3

Regression Results for FXS Boys at School Age

	ADHD			
	Coefficient	SE	t	p
FXS (n=33)				
Activity Level	−0.09	0.54	−0.167	0.09
Approach	0.01	0.37	0.03	0.98
Impulsivity	2.06	0.65	3.19	0.00
Shyness	.99	0.36	2.76	0.01
Smiling & Laughter	−0.15	0.39	−0.38	0.70

Table 4

Regression Results for Preschool Surgency Predicting School Age Raw Scores of ADHD/ASD in Boys with FXS

	ADHD			
	Coefficient	SE	t	p
FXS (n=33)				
Activity Level	0.16	0.42	0.37	0.72
Approach	0.33	0.42	0.78	0.45
Impulsivity	1.42	0.59	2.41	0.02
Shyness	0.56	0.36	1.53	0.14
Smiling & Laughter	-1.14	0.51	-2.24	0.30