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Boys with fragile X syndrome: investigating temperament in early childhood

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Abstract

Background Fragile X syndrome (FXS) is an x-linked genetic disorder that represents the most common hereditary cause of Intellectual Disability (ID). Very specific behavioural features (e.g. attention deficit hyperactivity disorder and stereotyped behaviour) are associated with FXS in adolescents and adults, yet research on temperament and behavioural characteristics in young children with FXS has been more limited and less conclusive.
Method This study investigated temperament differences in young boys (3–7 years old) with FXS ($N = 26$) recruited from a national FXS centre and controls ($N = 26$) matched on age, gender and race.
Results Compared with controls, boys with FXS exhibited less overall surgency/extraversion and effortful control. Boys with FXS also displayed significantly greater activity and shyness and less attentional focusing, inhibitory control, soothability and high intensity pleasure (tendency to enjoy intense/complex activities), relative to comparison children. A significant interaction between age and diagnosis (FXS or control) was observed for negative affectivity only.
Conclusions Attention difficulties commonly found in adolescents and adults with FXS appear to also be characteristic of young boys with FXS, as reflected by lower effortful control. Age-related findings concerning negative affectivity may be particularly significant, leading to improved intervention/preventative efforts.

Keywords behavioural measurement methods, behavioural phenotypes, fragile X, psychiatric disorders

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Fragile X syndrome (FXS), first identified in 1969, is a single-gene, X chromosome-linked disorder that affects approximately 1 in 4000 men and 1 in 8000 women (Turner *et al.* 1998), with some estimates as high as 1 in 2500 children (Fernandez-Carvajal *et al.* 2009). FXS represents the most common hereditary cause of ID, generally in the moderate and severe ranges, frequently comorbid with autism spectrum and anxiety disorders (Cordeiro *et al.* 2010), with associated features including speech/language and motor delays, hand-flapping/hand-biting, poor eye contact and attentional difficulties and intellectual impairment (Hagerman & Cronister 1996).

The majority of research addressing social-emotional functioning of individuals with FXS to date has been conducted with adults and older children, focusing on externalising behaviour problems, such as aggression, inattention and hyperactivity (Hagerman 2002; Hatton *et al.* 2002, 2006; Sullivan *et al.* 2006). A defined pattern of problem behaviour, including hyperactivity, inattention, autistic features and aggression, along with comorbid anxiety, has emerged for this population, estimated to occur in up to 86% of males with FXS (Hagerman 2002; Hatton *et al.* 2002, 2006; Sullivan *et al.* 2006; Cordeiro *et al.* 2010). Smith *et al.* (2012) compared adolescents and adults with FXS only, FXS and autism and autism only. Those dually diagnosed with FXS and autism had higher levels of communication and social reciprocity deficits, as well as the highest levels of repetitive and challenging behaviours, with ID found to be the common covariate for behaviour problems and adaptive functioning.

The study of early temperament manifestations in children with FXS is critical, as it provides information regarding individual differences in emotional processing and behavioural repertoire that set the stage for later-appearing symptoms/behaviour problems (Gartstein *et al.* 2012), as well as cognitive functioning (Wolfe & Bell 2007; Eisenberg *et al.* 2010; Sánchez-Pérez *et al.* 2015). A number of temperament frameworks have been proposed (e.g. Buss & Plomin 1975, 1984; Thomas & Chess 1977), and the psychobiological model (Rothbart & Derryberry, 1981) has gained considerable acceptance. According to this model, temperament represents reactive and regulatory tendencies, working in tandem and 'coming online' within their respective timelines. These reactive and regulatory tendencies are thought to be a product of constitutional factors, along with environmental and maturational influences (Rothbart 2011). *Reactivity* refers to the latency, rise time, intensity, and duration of response to stimulation, with emotional reactivity applying to fear, anger, sadness and positive emotions. *Self-regulation* refers to processes serving to modulate reactivity including behavioural approach, withdrawal, inhibition and importantly attention skills, which provide the foundation for flexible/adaptive regulatory strategies. According to Rothbart (2011), temperament undergoes development, especially rapidly in early childhood, which can be expected to vary for neurotypically developing and non-neurotypically developing children, although the latter's differences in trajectories have not been studied sufficiently to date.

Structurally, the psychobiological model encompasses three factors, often labelled as negative affectivity, extraversion/surgency, and effortful control. *Negative affectivity* involves tendencies to experience and display fear, anger, sadness and physical discomfort and is reminiscent of neuroticism factors that have emerged in analyses of adult personality structure (e.g. Digman 1990). *Extraversion/surgency* is largely manifested through smiling, laughing, activity, appreciation of high intensity stimulation and approaching novel stimuli (Gartstein & Rothbart 2003). The surgency factor label is frequently used interchangeably with the terms positive emotionality and extraversion, including characteristics of enthusiasm, activity, approach tendencies and sociability (Rothbart 2011). *Effortful control* is composed of dimensions involving attention-related abilities (e.g. maintaining attentional focus) and enjoyment of calm activities (e.g. being read to or sung to). Effortful control also includes a dimension referred to as inhibitory control, which reflects one's ability to inhibit a prepotent response in favour of a novel, more adaptive one (Kochanska *et al.* 2000). Temperament development is of particular interest in non-neurotypically developing children at risk for psychopathology. Children with FXS often exhibit a trajectory of mild behaviour problems in infancy/toddlerhood, followed by exacerbating behavioural/emotional difficulties (Hatton *et al.* 1999; Bailey *et al.* 2000; Hepburn & Rogers 2001; Baranek *et al.* 2008), and temperament has been noted to contribute to these escalating problems (e.g. Tonnsen *et al.* 2013; Grefer *et al.* 2016). Developmental changes in effortful control are likely especially consequential to this pattern of escalation, given that executive functions underlying effortful control develop rapidly between 3 and 7 years of age (Posner & Rothbart 2000), and children with FXS would be expected to lag behind, demonstrating less advanced attention-based regulation. This developmental trajectory of effortful control in children with FXS could be responsible for the observed pattern of behaviour problems/symptoms exacerbating later in childhood, as regulatory functioning is closely linked with a range of behavioural/emotional difficulties (Rothbart 2011; Gartstein *et al.* 2012).

Children with FXS have been described as significantly more active (Bailey *et al.* 2000; Roberts *et al.* 2006) and less adaptable, approachable, persistent and intense in terms of their temperament, compared with age-matched controls (Hatton *et al.* 1999; Roberts *et al.* 2006). Hepburn & Rogers (2001) provided support for a possible downward extension of this temperament profile for 1- to 3-year-old children with FXS, reporting significantly less adaptability, persistence and approach, compared with age-matched controls with a developmental delay. Shanahan *et al.* (2008) found that 30- to 37-month-old boys with FXS were rated by their parents as displaying significantly less anger and sadness than typically developing controls, and by trained coders as displaying less facial sadness, with higher mental age and fewer autistic features predicting sadness in boys with FXS. Although the Shanahan *et al.* (2008) findings could be viewed as discrepant from the results reported by Hepburn & Rogers (2001), domains of temperament addressed in these investigations differed conceptually and operationally, with the Hepburn & Rogers (2001) study relying on Thomas & Chess (1977) temperament definitions and Shanahan *et al.* (2008) using temperament constructs consistent with the psychobiological model (Rothbart 2011; Rothbart & Derryberry 1981).

Importantly, temperament attributes distinguish children with FXS and other developmental disabilities. Boys (ages 3–6 years old) with FXS were rated by their mothers as exhibiting increased avoidance of novel objects/situations, and decreased social withdrawal, compared with age/IQ-matched controls with idiopathic developmental delay (Kau *et al.* 2000). Thus, males with FXS were more likely to avoid unfamiliar objects or people but were not more likely to withdraw from familiar people or remain withdrawn, consistent with the Thomas & Chess (1977) 'slow to warm-up' temperament style. In a study conducted by Bailey *et al.* (2000), boys with autism, 36–95 months old, exhibited a more variable developmental profile, relative to males with FXS, demonstrating a relatively flat profile. Males with autism demonstrated more delayed social skills and difficulties with communication, cognitive and social functioning relative to those with FXS. Boys with FXS and those with autism were slower to adapt, less persistent, and more withdrawn, compared with typically developing controls. Additionally, boys with FXS were described as more active relative to comparison peers, whereas males with autism were shown to be less intense, rhythmic, but more distractible, and having a higher response threshold than controls. Thus, significant differences in temperament, developmental status and functional abilities were detected for males with FXS only and boys with autism only, suggesting that these populations are distinct in important ways.

Temperament has been linked with behavioural and mood-related concerns, as fear, anger/frustration, sadness, soothability and approach were associated with the emergence of anxiety symptoms for males with FXS: higher levels of sadness and fear and lower soothability, along with increasing approach over time, predicted anxiety (Tonnsen *et al.* 2013). Importantly, higher levels of negative affectivity across early childhood accounted for subsequent anxiety problems, but not symptoms of autism. Thus, early negative affect is critical to the emergence of anxiety in children with FXS (Tonnsen *et al.* 2013), especially significant because of the high rates of anxiety reported for this population (Cordeiro *et al.* 2010)

In a longitudinal study conducted by Grefer *et al.* (2016), the contribution of surgency and its five fine-grained component scales (i.e. activity level, approach, impulsivity, shyness and smiling/laughter) was examined in relation to the emergence and stability of attentional problems in 3- to 6-year-old boys with FXS. Activity level was associated with preschool ADHD scores, while increased shyness and decreased smiling/laughter were associated with ADHD scores later in elementary school. Preschool impulsivity predicted symptoms of ADHD in the school-aged period; however, impulsivity was a stronger predictor of elevated ADHD scores for older children. Preschool surgency ratings accounted for a significant portion of ADHD scores for the FXS group in the preschool and school-aged periods. Grefer *et al.* (2016) concluded that boys with FXS demonstrate a unique developmental phenotype with respect to the etiology of attentional difficulties, as the same pattern of results was not observed for typically developing boys in this study.

The primary goal of this study was to examine differences in temperament in young boys with FXS and typically developing controls, utilising both the overarching temperament factors and the fine-grained scales. The former aspect of our approach makes a unique contribution to the literature, as prior research addressing temperament in children with FXS has been largely focused at the subscale level. We hypothesised significant differences between children with FXS and controls for multiple temperament attributes: higher scores on activity level, shyness, anger/frustration and fear, along with lower scores on soothability and high intensity pleasure (tendency to enjoy activities that are complex/intense in nature) for children with FXS. We also anticipated that children with FXS would demonstrate lower levels of effortful control compared with typically developing matched controls and hypothesised an age-by-FXS diagnosis interaction, wherein greater differences in Effortful Control are demonstrated in the comparison of older boys with FXS and age-matched controls, relative to their younger counterparts. This expectation is largely based on the Kau *et al.* (2000) findings concerning a 'unique etiological profile for attentional skills in children with FXS', which suggest a developmental trajectory for this regulatory domain of temperament that differs for boys with FXS and comparison children, as components of attention are known to provide the basis for Effortful Control underlying self-regulation. Other age-by-FXS diagnosis interaction analyses (i.e. for negative affectivity and surgency/extraversion) should be considered exploratory in nature.

Method

Participants

Children with fragile X syndrome

Parents of children between the ages of 3 months and 7 years, with an existing diagnosis of FXS, from across the country, were identified at several FXS conferences conducted through the Children's Hospital of Pittsburgh Fragile X Center. Parents were contacted via telephone to inquire about their participation in this study. Families who agreed to participate (N = 40) were mailed temperament measures, consent forms and demographic questionnaires, with completed forms returned by 31 parents. Only three participants under 3 years of age were recruited, and were excluded from analyses because they completed different, age-appropriate temperament questionnaires. Temperament assessments were obtained for two girls, for whom only descriptive data were reported (Table 1). Girls were excluded from analyses because of previous research suggesting significant behavioural differences for boys and girls with FXS (e.g. Freund *et al.* 1993). Most children lived with married parents (85.2%), with approximately 15% living in either single-parent homes or with parents living with a domestic partner. All parents identified their child with FXS as a biological child. Mean years of education for the primary caregiver was 15.96 years, with a modal family income of between $30 001–$50 000/year.

Controls

The comparison sample is made up of typically developing children whose parents participated in temperament research through the Oregon Social Learning Center (OSLC) and the University of Oregon (UO). A subset of these children was selected from each site (OSLC: n = 24; UO: n = 4), matching each child with FXS on the basis of gender, race and closest date of birth.

Measures

The Child Behavior Questionnaire (CBQ; Rothbart *et al.* 2001), a 195-item, parent-report measure designed for children 3–7 years of age and widely used

Table 1 Demographic features of families participating in the study (N = 56)

Variable	M	SD	Min	Max	Range
Age of FXS boys (in months)	68.692	17.481	39	93	54
Age of Control boys (in months)	68.2308	18.296	37	93	56
Variable	Frequency	Percent			
Gender					
Male	52	92.9			
Female	2	7.1			
Child ethnicity					
Caucasian	56	100			

FXS - fragile X syndrome; N = 56, FXS = 28; control = 28; females (N = 2) were not included in further analyses.

in studies of FXS (Roberts *et al.* 2014; Tonnsen *et al.* 2014; Grefer *et al.* 2016). The CBQ consists of 16 scales, contributing to three overarching temperament factors: negative affectivity (NA) – discomfort, sadness, fear, anger/frustration and soothability (negatively loading); surgency/extraversion (SE) – impulsivity, high intensity pleasure, activity level, approach, smiling/laughter and shyness (negatively loading); and effortful control (EC) – low intensity pleasure, inhibitory control, perceptual sensitivity, attentional focusing and attentional shifting. A recent confirmatory factor analysis indicated that the CBQ retains its three-factor structure (e.g. NA, SE and EC) measuring temperament in boys with FXS (Roberts *et al.* 2014), supporting our use of the overarching factors. The CBQ subscales demonstrate good internal consistency (α's 0.67–0.94; mean α = 0.77; Ahadi *et al.* 1993). In this study, internal consistency was satisfactory, with α's: 0.62–0.85 (mean α = 0.72) for children with FXS, and α's: 0.60–0.94 (mean α = .76) for controls; with the exception of the Attention Shifting scale, for which acceptable internal consistency could not be attained with the FXS sample. Thus, comparisons between boys with FXS and control group males were not presented for this CBQ subscale.

Results

Independent sample *t*-tests were performed to identify group differences between children with FXS and controls on the three broadband temperament factors (NA, SE and EC) and 15 fine-grained temperament dimensions of the CBQ (Table 2). Only results significant at the $P \leq 0.005$ are discussed, because of the multiple statistical tests run. Boys with FXS displayed significantly less SE and EC than matched controls, but were not different in NA overall. Children with FXS exhibited significantly greater activity and shyness, along with lower levels of attentional focusing, inhibitory control, soothability and high intensity pleasure. Additionally, there was a

Table 2 Independent samples *t*-tests for temperament measures

	FXS group (*n* = 26)	**Control group (*n* = 26)**				
Variable	**Mean**	**SD**	**Mean**	**SD**	***t*(50)**	***P***
Activity level	5.411	0.709	4.77	0.782	3.092**	0.003
Frustration/anger	4.396	0.724	4.384	0.776	.061	0.952
Attentional focusing	2.682	0.688	4.863	0.688	−11.610**	0.000
Discomfort	4.023	0.749	4.085	0.749	−.292	0.772
Soothability	4.051	0.612	4.871	0.624	−4.783**	0.000
Fear	3.529	0.986	3.605	1.025	−.276	0.784
High intensity pleasure	4.425	0.938	5.117	0.740	−2.955**	0.005
Impulsivity	4.370	0.929	4.621	0.822	−1.034	0.306
Inhibitory control	2.915	0.745	4.955	0.759	−9.775**	0.000
Low intensity pleasure	5.216	0.792	5.689	0.557	−2.489†	0.016
Perceptual sensitivity	4.314	0.847	4.843	1.003	−2.058†	0.045
Sadness	3.650	0.582	4.096	0.905	−2.114†	0.040
Shyness	5.004	1.067	2.934	0.796	7.932**	0.000
Approach	4.942	0.875	5.001	0.703	−.267	0.790
Smiling and laughter	5.689	0.614	5.910	0.489	−1.434	0.158
	FXS group (*n* = 26)	**Control group (*n* = 26)**				
	Mean	**SD**	**Mean**	**SD**	***t*(25)**	***P***
Surgency/extraversion	3.305	.569	3.953	0.800	−3.363**	0.001
Negative affectivity	2.309	0.542	2.506	0.798	−1.039	0.304
Effortful control	4.501	0.457	5.204	0.371	−6.086**	0.000

†$P \leq .05$, *$P \leq .005$, **$P \leq .001$.
FXS - fragile X syndrome; SD - standard deviation.

trend towards boys with FXS displaying less low intensity pleasure ($t(50) = -2.489$, $P = 0.017$), sadness ($t(50) = -2.114$, $P = .040$) and perceptual sensitivity ($t(50) = -2.058$, $P = .045$).

Two-way ANOVAs were conducted to determine if interaction effects between diagnostic status (FXS or control) and age (3–5 years old or 5–7 years old) explain significant variance in the three overarching temperament factors. A statistically significant interaction between age and diagnosis was observed for NA only (partial $\eta^2 = 0.092$), indicating that the differences in NA between children with FXS and controls are dependent on age (Table 3). Whereas younger boys with FXS had lower NA scores relative to the comparison boys, boys with FXS in the older age group received higher ratings of NA than controls. Graphically depicted (Fig. 1), the pattern of age-related changes indicates that whereas neurotypically developing controls score lower on NA at older ages, for children with FXS, NA ratings increase with age.

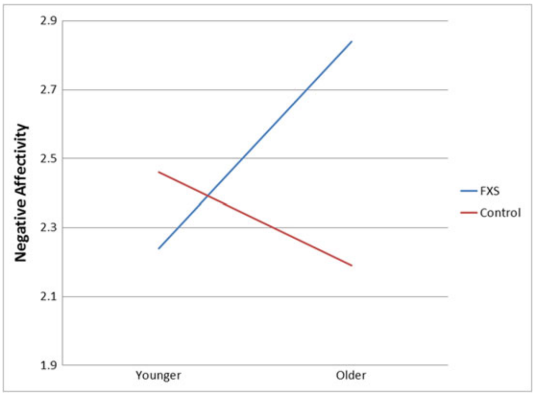

Figure 1 Negative affectivity (NA): diagnostic status (FXS or control) by age (3–5 years old or 5–7 years old) interaction. FXS - fragile X syndrome.

Discussion

In this study, we set out to identify early temperament differences between young boys with FXS and age, gender and race/ethnicity matched comparison peers. In terms of the overarching temperament factors, boys with FXS exhibited less SE and EC in comparison to typically developing controls. Boys with FXS were significantly higher on activity level and shyness and lower on attentional focusing, inhibitory control, soothability, and high intensity pleasure, relative to comparison boys. A significant interaction between age and diagnosis (FXS or control) was observed for negative affectivity only, with higher levels of NA exhibited by older boys with FXS relative to controls and an opposite pattern of differences (relatively lower levels of NA for boys with FXS) emerging for the younger age group.

As hypothesised, for boys with FXS, temperament was characterised by significantly higher levels of activity and shyness, coupled with lower EC, including attentional focusing, inhibitory control and soothability (i.e. ability to calm down with assistance from caregivers) and reduced high intensity pleasure (i.e. enjoyment of intense/complex patterns of stimulation). However, boys with FXS were not rated as higher on anger/frustration or sadness, but rather displayed similar or reduced overall levels of reactivity within these domains of negative affectivity,

Table 3 Two-way ANOVA for fragile X syndrome (FXS) status and age to predict negative affectivity

Source	Sum of squares	Df	Mean square	F	P
Corrected model	2.831	3	0.944	2.185	0.101
Intercept	322.339	1	322.339	746.527	0.000
FXS status	.436	1	0.436	1.010	0.320
Age group	.450	1	0.450	1.041	0.312
FXS*Age group	2.267	1	2.267	5.251	0.026 *
Error	22.453	52	0.432		
Total	352.322	56			
Corrected total	25.283	55			

*$P \leq 0.05$, **$P \leq 0.01$.
FXS status - fragile X or control; age group = 3–5 years old or 5–7 years old; FXS*Age group = interaction term.

compared with typically developing controls. The latter finding is consistent with the pattern of results reported by Shanahan *et al.* (2008), wherein similar or reduced levels of negative reactivity in boys with FXS were observed compared with controls. Additionally, boys with FXS displayed significantly less SE, and high intensity pleasure, when compared with matched controls, indicating that boys with FXS exhibit lower overall levels of enjoyment/positive emotionality, relative to controls, and that these differences are particularly salient for activities high in intensity/complexity/level of stimulation. These SE-related findings are important because the positive affectivity domain of temperament has not been as widely examined as negative emotionality, especially for children representing special populations with developmental and/or medical conditions. Existing studies including children with FXS suggest a mixed picture for SE, with certain aspects (e.g. impulsivity) conferring risk with respect to ADHD, and others, namely, smiling and laughter, buffering the risk for maladaptive behaviour (Grefer *et al.* 2016). Additional research is needed to clarify the role of the different facets of positive emotionality with respect to emerging symptoms of developmental psychopathology for children with FXS and other neurodevelopmental conditions.

Interaction effects of age and FXS status on the three overarching temperament factors were examined via two-way ANOVAs, performed to address the possibility that FXS diagnosis differentially impacts temperament, depending on the specific developmental period. Our findings suggest potentially important developmental changes for children with FXS with respect to negative affectivity, but not effortful control, as hypothesised. Although younger boys with FXS had lower NA scores relative to comparison males, boys with FXS in the older age group exhibited higher levels of NA, compared with controls. These results are consistent with a noted pattern wherein younger children with FXS are characterised as displaying temperaments marked by hyporeactivity (e.g. less anger and sadness; Shanahan *et al.* 2008), and older children tend to display more hyperreactivity in their profiles (e.g. increased aggression and hyperactivity; Hatton *et al.* 2002; Sullivan *et al.* 2006). Results of our analyses, which should be replicated in the future in the context of longitudinal investigations, suggest this shift from a hypo to a hyper-reactive profile likely occurs before 7 years of age.

Although we hypothesised that less rapid advances in EC for children with FXS might contribute to noted increases in emotional/behavioural difficulties over the course of childhood for this population, obtained results suggest higher levels of negative emotionality demonstrated by older boys with FXS relative to controls may be involved. The observed pattern of results is noteworthy in part because higher levels of negative affectivity in early childhood have been linked with anxiety symptoms in children with FXS (e.g. Tonnsen *et al.* 2013), and because anxiety represents a particularly significant concern for this population (Cordeiro *et al.* 2010). Future studies should focus on determining a transition point for the trajectory of NA in children with FXS and its deviation from growth demonstrated by typically developing children. More precise information concerning these developmental parameters could facilitate preventative/intervention efforts, especially important to the well-being of these youngsters and their families.

This study makes several contributions to the still limited existing literature addressing temperament in young children with FXS. First, this study utilised age, gender and race/ethnicity matched comparison children, allowing us to control for these demographic factors by holding them constant across diagnostic status groups. This is in comparison to several other studies (Hatton *et al.* 1999; Bailey *et al.* 2000) in which a temperament instrument normative sample was utilised as a control group. In addition, prior studies utilised control groups significantly larger than the FXS samples (e.g. FXS group, $N = 30$; Control group, $N = 60$), which may have systematically impacted their findings, possibly resulting in a greater likelihood of statistically significant differences (Stevens 2009). Second, to our knowledge, the present study is the first to utilise the complete CBQ temperament assessment protocol, examining all of the structural components, not just selected factors/scales, in identifying differences in profiles for young boys with FXS and matched comparison children. Third, this study demonstrated that attentional difficulties commonly found in older children and adults with FXS (e.g. Sullivan *et al.* 2006) are paralleled by differences in the regulatory domain of temperament for young boys with this condition.

Fourth, we provided evidence of an interaction effect involving FXS diagnosis and age for negative emotionality, likely contributing to the pattern of exacerbating symptoms of developmental psychopathology demonstrated by children with FXS. Finally, the present investigation provided evidence of differences with respect to surgency/extraversion overall, and particularly the fine-grained dimension of high intensity pleasure, which may be important to the emergence of behaviour problems/symptoms as well.

Developmental differences in how FXS impacts NA were suggested by our cross-sectional analyses and should be replicated in future research. These differences are important in their own right and because their identification can facilitate prevention/intervention efforts. Differences in temperament profiles observable prior to symptom onset could signal early intervention/preventative targets, for example, for temperament-based therapeutic strategies (Hepburn 2003). Caregivers of children with FXS could be provided with information regarding their child's unique temperament profile, aspects consistent with profiles demonstrated for others with this diagnosis as well as neurotypically developing comparison children (Carey 1994). The latter can be informative in facilitating an approach to parenting that buffers against risk for subsequent psychopathology (e.g. encouraging appropriate levels of sensitivity for 'slow to warm-up' youngsters; Buss & Kiel 2013).

Several limitations should be noted and addressed in future research. First, the small sample size limited the statistical power of the analyses conducted in the context of this study and our ability to detect significant effects in the small to medium range. Second, our sample was racially homogenous, and more diverse groups should be recruited in future studies in an effort to enhance generalizability. Third, girls with FXS ($n = 2$) were not included in the analyses, and future research should make an effort to specifically recruit families of girls with FXS. Fourth, the current study did not include assessments of autism spectrum disorder symptoms or cognitive functioning, which should be considered in future studies addressing temperament development in this population. Finally, our exclusive reliance on parent-report represents another limitation, which should be addressed in future research. For example, investigators may include laboratory observations and/or physiological indicators of temperament in future studies.

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