TEMPERAMENT IN YOUNG CHILDREN WITH FRAGILE X SYNDROME

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Abstract

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Fragile X Syndrome (FXS) is an x-linked, genetic disorder that represents the most common hereditary cause of mental retardation. While the literature suggests that there are very specific behavioral features associated with FXS in older children and adults, the literature regarding temperament in young children with FXS has been limited and yielded mixed findings. The present study sought to examine early temperament differences between children with FXS (N=28) and normal controls (N=28), matched on age, gender, and race. Child temperament characteristics were assessed via the Child Behavior Questionnaire (CBQ; Putnam & Rothbart, 2006) and behavior problems were evaluated using the age appropriate version of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000, 2001).

Independent samples t-tests were performed to detect group differences on the sixteen fine-grained dimensions and three broadband factors of the CBQ. Children with FXS were rated by their parents as displaying significantly greater activity and shyness and significantly less attentional focusing, inhibitory control, soothability, and high intensity pleasure. Children with FXS were also reported as exhibiting less surgency/extraversion and effortful control. Behaviorally, children with FXS were rated by their parents as having significantly more total problems compared to controls. Correlations between temperament and behavior problem scores revealed that broadband temperament factors were not significantly related to the externalizing,

internalizing, or total problems scales of the CBCL for children with FXS. Two-way ANOVAs were executed for the three broadband temperament factors to determine if temperament changes over time for children for children with FXS and controls (Tables 7,8,9). A significant interaction between age and fragile x diagnosis (FXS or control) was detected for the temperament factor Negative Affectivity.

Our analyses suggest that attentional difficulties commonly found in teens and adults with FXS are also characteristic of young children with this condition. Youngsters with FXS were described as exhibiting lower levels of positive affectivity and greater total problems compared to matched controls. Positive emotionality findings may be of particular significance because this domain of temperament has not been widely examined.

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CHAPTER ONE

INTRODUCTION

Since identification of Fragile X Syndrome (FXS) approximately 40 years ago, a large and highly varied body of research has been conducted with individuals with this disorder. Research focusing on psychological constructs and early behavioral manifestations of this disorder however, has been a relatively recent phenomenon, partly due to earlier and more accurate diagnosis of this disorder. Thanks to earlier diagnosis, research on early childhood temperament has surfaced within the last 10 years, providing valuable information regarding early manifestations of Fragile X Syndrome. While the literature to date suggests that there is a very specific behavioral phenotype associated with older children and adults with FXS, the literature regarding temperament in young children with FXS has been mixed. Some research suggests that children with FXS are more active (Roberts, Boccia, Hatton, Skinner, & Sideris, 2006) less adaptable, less approachable, less persistent, and less intense when compared to normal controls (Hatton et al., 1999; Roberts et al., 2006) while other research suggests that young children with FXS display reduced levels of negative reactivity (e.g., anger and sadness) when compared to normally developing controls (Shanahan et al., 2008). Given the mixed findings regarding temperament in children with FXS, the present study will provide a brief review of the current literature regarding temperament and externalizing difficulties in young children with Fragile X Syndrome as well as address some previous limitations of research.

Fragile X Syndrome (FXS), first identified in 1969, is a single-gene, X-chromosome linked disorder that affects approximately 1 in 4000 males and 1 in 8000 females (Turner et al., 1996). It represents the most common hereditary cause of Mental Retardation and is frequently

comorbid with Autism Spectrum Disorders (ASDs).While it is unclear as to whether FXS is a subtype of a Pervasive Developmental Disorder or a different disorder altogether, some studies estimate that approximately 25% of boys with FXS also meet clinical criteria for ASDs (Bailey, Hatton, & Skinner, 1998). Fragile X Syndrome is caused by an expansion of the CGG trinucleotide sequence (mutation) on the X-chromosome, with individuals with greater than 200 repeats being characterized has having the *full mutation* (CDC, 2006). Individuals with between approximately 55-200 CGG repeats are characterized as having the *premutation* and those with less than 40 repeats are placed in the normal range. Individuals with between 40-55 CGG repeats are placed in the "*grey zone*," as the number of repeats overlap with those in the permutation and normal ranges.

In those with the full mutation of Fragile X Syndrome, there is a mutation of FMR1 gene on the X chromosome that causes a halting or reduction in a protein (FMRP) needed for normal brain growth, development, and functioning (Tassone et al., 1999). This process of "turning off" the FMR1 gene is referred to as methylation and the resulting lack of FMRP causes Fragile X Syndrome. The CDC (2006) estimates that approximately 95% of individuals with Fragile X Syndrome have the full mutation.

Fragile X Syndrome can be accompanied by a variety of physical, behavioral, intellectual, and social characteristics. Physical features include but are not limited to large ears, recurrent ear infections, flexible joints, low muscle tone, flat feet, a long face, macroorchidism (enlarged testicles), and seizure disorders. Behavioral, intellectual, and social characteristics include speech and language delays, motor delays, hand-flapping/hand-biting, poor eye contact, Autism Spectrum Disorders, attentional difficulties, and mental retardation (fragilex.org). Research on cognitive impairment in individuals with Fragile X Syndrome has consistently

shown that this group experiences developmental delays and mental retardation, with impairment being primarily in the moderate and severe ranges (Hagerman & Cronister, 1996).

It is important to note that females with Fragile X often have much less severe manifestations as FXS is an X-linked condition and may have somewhat different symptom profiles. Females with Fragile X Syndrome may have visual-spatial and executive functioning difficulties (Hagerman, 1995, 1996 b; Keysor & Mazzocco, 2002: Lachiewicz, 1995); Lesniak-Karpiak, Mazzocco, & Ross, 2003; Mozzocco, 2001), display shyness, demonstrate poor communication skills, demonstrate difficulties with attention or ADHD (Dyer-Friedman et al., 2002; Freund, Reiss, & Abrams, 1993; Hagerman et al, 1992; Mazzocoo et al, 1997), display autistic behaviors (Clifford et. al., 2006; Hatton et al, 2006) and may be highly anxious. Some studies have also found that approximately fifty percent of females with full mutation Fragile X Syndrome demonstrate intellectual functioning in the borderline or impaired ranges (Keysor & Mazzocco, 2002).

Temperament

One of the earlier definitions of temperament was provided by Gordon Allport (1961), who conceptualized temperament as encompassing individual differences in emotional reactivity, largely determined by heredity. Since the inception of the concept of temperament in the 1960s, and the work conducted by Thomas, Chess, & Birch (1968), so influential in shaping research addressing temperament in childhood, alternative descriptions and definitions of temperament have been offered. Rothbart & Derryberry (1981), for example, defined temperament as "constitutional differences in reactivity and self regulation." In this definition, constitutional refers to an individual's biological makeup, which is shaped over time by heredity, maturation,

and experience. Reactivity refers to an organism's emotional, motor, and attentional reactivity, as indicated by measurements of threshold, latency, intensity, and recovery time of reactions. Self-regulation is defined as encompassing processes that serve to modulate reactivity, thought to have a largely attentional basis, and linked with the development of the executive attention network (Rothbart & Bates, 2006).

Structural definitions of temperament represent hierarchical models that incorporate more fine-grained as well as broadly defined dimensions. For example, within the psychobiological framework of temperament discussed by Rothbart and others, three broader over-arching factors as well as their composites, more fine-grained characteristics, play important roles in childhood. Higher order temperament constructs include negative emotionality/affect, positive emotionality/extraversion, and effortful control/regulatory capacity (Gartstein & Rothbart, 2003; Rothbart & Bates, 1998; Rothbart, 1989). Fine-grained aspects of temperament include activity level, frustration/anger, attentional focusing, attentional shifting, discomfort, soothability, fear, high intensity pleasure, impulsivity, inhibitory control, low intensity pleasure, perceptual sensitivity, sadness, shyness, approach, and smiling and laughter. Rothbart (1989) also described temperament as a product of a developmental process, with new temperament dimensions emerging during the different stages, as a result of maturation of the neurobehavioral systems supporting these domains of temperament. For example, fear, one fine-grained dimension of temperament, does not come "on-line" for normally developing infants until late in the first year of life (Rothbart, 1989).

Parent or caregiver report measures of temperament provide a rich body of information regarding a child's behavior in a variety of contexts over a long period of time. Although questions have been raised regarding the validity of parent report measures, a number of

measures, such as the Child Behavior Questionnaire (CBQ), reflect efforts to minimize potential error/bias by asking about the frequency of commonly observed behaviors over a specified period of time (e.g., past six months; Rothbart, Ahadi, Hershey, & Fisher, 2001). Thus, parent-report measures do not have to require comparative judgments that may be a source of error/bias in some cases, and provide information regarding a child's behavior that may otherwise not be observed in laboratory settings, representing an important method for temperament inquiry (Rothbart & Gartstein, 2008). Further, parent report measures of temperament are commonly used in early childhood investigations of temperament in individuals with FXS (Hatton et al., 1999; Bailey et al., 2000, Kau et al, 2000, Bargagna, Canepa, Marcheschi, & Tinelli, 2001, Roberts et al, 2006; & Shanahan et al, 2008).

Previous research conducted with children and adolescents with FXS clearly demonstrates high rates of externalizing and internalizing difficulties. In one study, between 27-29% of boys with FXS (ages 4-12 years) were found to have internalizing or externalizing difficulties that fell in the clinical or borderline ranges and 17% of boys with FXS displayed clinical or borderline levels of aggressive behavior on the Child Behavior Checklist (Hatton et al., 2002). Girls with FXS, on the other hand, are more likely to display mood and anxiety symptoms, with one study estimating that 38% of females with FXS met criteria for a mood disorder and 50% displayed anxiety symptoms, based on a structured diagnostic interview (Freund et al., 1993).

Early temperament has been shown to reliably predict later behavioral problems including internalizing and externalizing difficulties in normally developing children (Caspi & Silva, 1995; Lemery et al., 2002, Gartstein, Putnam, & Rothbart, 2012). More specifically, early temperament measures of negative emotionality, including anger, sadness, frustration, and fear

are related to child and adolescent externalizing difficulties (Caspi & Silva, 1995; Lemery et al., 2002). Research further suggests that children with the highest externalizing tendencies show high levels of Negative Emotionality (i.e., anger, sadness, frustration, physical discomfort, and fear), high Surgency (i.e., smiling, laughing, displaying pleasure, and approaching novel stimuli), and low Effortful Control (i.e., attentional regulation, inhibitory or attentional control, and low intensity pleasure) (Gartstein & Fagot, 2003; Gartstein, Putnam, & Rothbart, 2012; Muris & Ollendick, 2005; Rothbart & Bates, 2006). Similarly, later internalizing difficulties, such as anxiety or depression, have also been reliability predicted by preschool measures of negative emotionality and the temperament construct of Withdrawal/Avoidance (Ruschena, Prior, Sanson, & Smart, 2005). Whereas, in infancy, research suggests that a mixture of negative emotion and high levels of motor activity places a child at a higher risk for anxiety symptoms during the preschool period. Thus, the domain of negative emotionality becomes an important area of inquiry as it has predictive utility in determining later internalizing and externalizing difficulties. As previous research has demonstrated high rates of externalizing and internalizing difficulties in children with FXS, temperament may represent an ideal area for early identification and intervention for children with FXS and their families. Although this relationship has not yet been extended to children with FXS, it is possible that similar temperament aspects may be associated with both externalizing and internalizing difficulties commonly demonstrated by children with FXS.

Temperament and Fragile X in the Literature

Much of the psychological research conducted with individuals with Fragile X Syndrome has been conducted within the last decade or so. This body of literature has predominantly been

conducted with adults and older children and with a particular focus being specific externalizing type behavioral problems, including aggression, inattention, and hyperactivity (Hagerman 2002; Hatton et al., 2002, 2006; Sullivan et al. 2006). Within this literature, there is little mention of precursors to behavioral problems or other difficulties including internalizing problems, such as anxiety. In adults and older children, research has consistently shown a defined pattern of problem behavior, including hyperactivity, inattention, autistic behaviors, and aggression (Hagerman, 2002; Hatton et al., 2002, 2006; Sullivan et al., 2006; Kau et al., 2000). However, it remains unclear as to how these behavior problems develop in young children and whether or not this same profile of difficulties can be extended to young children, and if so, to what extent. More sophisticated genetic screening has recently allowed for earlier diagnosis of those with FXS, with diagnosis now coming as early as in utero, infancy, or early childhood for those with full mutation FXS. This earlier diagnosis provides a platform for identifying possible early precursors to behavioral problems, including temperament. It is important to identify early precursors for internalizing and externalizing difficulties commonly found in children with FXS as they could provide a point of early intervention and inform treatment as well as serve to aid in diagnosis.

Research examining temperament, especially negative reactivity in young children with Fragile X Syndrome, has yielded mixed results. Some research suggests that children with FXS are rated by their parents as significantly more active (Roberts, Boccia, Hatton, Skinner, Sideris, 2006) less adaptable, less approachable, less persistent, and less intense when compared to normally developing, age matched peers (Hatton et al., 1999; Roberts, Boccia, Hatton, Skinner, Sideris, 2006). While other research suggests that young children with FXS display reduced

levels of negative reactivity (e.g., anger and sadness) when compared to normally developing controls (Shanahan et al., 2008).

To date there have been only a handful of studies examining temperament in individuals with Fragile X Syndrome, with no known prior studies including females in their samples. One study, conducted by Kerby & Dawson (1994) examined temperament in nine adult males (mean age 44.0 years) with Fragile X Syndrome and Mental Retardation and compared them to age and IQ matched peers (mental retardation without FXS). Two caregivers rated each participant on the four scales of the Emotionality, Activity, and Sociability Temperament Scales (EAS) parent-report form, with slightly modified language (changed *child* to *he)*. Caregivers rated males with FXS as significantly more shy, more emotional, less social, and less active than controls. Limitations of this study included a small sample size, the fact that all participants in this study were living in institutions, and the severe level of mental retardation present in the sample that may not be representative of the population of males with FXS.

A longitudinal study conducted in 1999 by Hatton, Bailey, Hargett-Beck, Skinner, & Clark, compared the maternal ratings of temperament of 45 males (ages 47-88 months) with full mutation Fragile X Syndrome to a normal control reference sample (n=350), included in a previous study (Carey & McDevitt, 1978). Researchers collected 102 maternal ratings, utilizing the Behavioral Style Questionnaire (BSQ; Carey & McDevitt, 1978), for 45 males with an average 2.3 assessments per child (range 1 to 4 ratings) and the length of time between assessments ranging from 6 to 18 months. When compared to the control group, mothers of males with FXS rated their sons as significantly more active and less adaptable, approachable, intense, and persistent when compared to controls. Males with FXS did not significantly differ from controls on Rhythmicity, Mood, Distractibility, and Threshold. Using hierarchical linear

modeling, Hatton and colleagues also demonstrated that temperament remained stable across assessments and that temperament ratings were not significantly related to intelligence.

Researchers also examined the temperament cluster categories of each group and found that only 16 of the males with FXS fell into easy, difficult, or slow to warm up categories, first outlined by Thomas & Chess (1963). The remainder of the participants in the FXS group fell into two intermediate categories; intermediate high (i.e., demonstrating scores similar to but not reaching cutoff values for the difficult temperament category), and intermediate low (i.e., demonstrating scores similar to but not reaching cutoff values for the easy temperament category). There were significantly less children with FXS rated as easy by their mothers (i.e., 6.6% of total sample compared to 34.3% of total sample) when compared to controls. In addition, a greater proportion of males with FXS were rated as having difficult temperament than controls, however, this difference did not reach significance. Finally, males with FXS were significantly more likely to be rated as intermediate high than controls.

Hepburn and Rogers (2001) extended these findings and supported the concept of a possible temperament profile for children with FXS by reporting that very young children (ages 1-3 years) with FXS also display significantly less adaptability, persistence, and approach when compared to age-matched controls with a developmental delay utilizing the Toddler Temperament Scale. Limitations of this study include a relatively small sample size and a possibly dissimilar reference group (i.e., control group pulled from previous study conducted in 1978 with participants being primarily white and middle class).

Roberts, Boccia, Hatton, Skinner, & Sideris (2006) examined the relationship between temperament and vagal tone in 29 boys with full mutation Fragile X Syndrome, ages 1-11 years (mean= 4.11 years; SD= 2.07 years) when compared to 31 typically developing controls matched

on chronological age and ethnicity. Vagal tone, "a component of parasympathetic activity of the autonomic nervous system that reflects central nervous system organization and functioning" was hypothesized to play a role in the reactive and regulatory aspects of temperament. Mothers of participants in this study rated their child on the age appropriate form of the Carey Temperament Scales and their vagal tone was measured during a 30 minute, laboratory assessment, that consisted of an adaptation phase, multiple baseline periods, and an experimental phase in which participants were asked to complete cognitive tasks. Males ages 1-3 years (n=10) were rated by their mothers on the Toddler Temperament Scale (TTS; *Fullard, McDevitt* &. Carey, *1984*), males ages 3-7 years (n=38) were rated on the Behavioral Style Questionnaire (BSQ; Carey & McDevitt, 1978), and males ages 7 to 11 years were rated on the Middle Childhood Temperament Questionnaire (MCTQ; Hegvik, McDevitt, & Carey, 1982). Consistent with previous research, Roberts et al. found that boys with FXS were rated by their mothers as being more active, less adaptable, and less persistent and attentive than typically developing peers. Differences in the temperament dimension Intensity were not found in this study. Further, boys with FXS displayed lower baseline and less vagal reactivity in response to the cognitive tasks presented during the experimental phase of heart rate monitoring. However, researchers in this study did not find a relationship between vagal tone and individual temperament dimensions in either the experimental or control groups. Although, baseline measures of vagal tone were found to be correlated with the persistence/attention dimension in both groups, researchers suggested that group differences in temperament did not serve to mediate or moderate measurements of vagal tone. Limitations of this study included a small sample size (n=29), a single observation of temperament and vagal tone, and a wide age range of participants that may

have obscured the relationship between temperament and vagal tone due to changes in temperament as a result of a neurodevelopmental processes.

Kau, Reider, Payne, Meyer, and Freund (2000) conducted a study examining temperament and behavioral difficulties in males, ages 3 to 6 years, with Fragile X Syndrome (n=41) when compared to age-matched controls with an idiopathic developmental delay (n=16). Of note, 25 males in the FXS group had the full mutation of Fragile X Syndrome and 14 were mosaic. Participants in this study were rated by their mothers on the Dimensions of Temperament Scale-Revised (DOTS-R; Windle & Lerner, 1986), Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983; McConaughy & Achenbach, 1988), Abberant Behavior Checklist-Community (ABC; Aman & Singh, 1986, 1994), Preschool Language Scale-Third Edition (Zimmerman, Steiner, & Pond, 1992) or the Clinical Evaluation of Language Fundamentals- Third Edition (Semel, Wiig, & Secord, 1995), and the Vineland Adaptive Behavior Scales-Interview Edition (Sparrow, Balla, & Cicchetti, 1984). Young males with FXS were found to have significant delays in motor skills when compared to controls and motor age, as measured by their scores on the Vineland Adaptive Behavior Scales, was thus used as a covariate in subsequent analyses. When researchers controlled for motor age, boys with FXS were rated by their mothers as exhibiting increased avoidance of novel objects and situations, decreased social withdrawal, and "more positive mood quality" when compared to age and IQ-matched controls with idiopathic developmental delay. 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, which researchers suggested is consistent with the "slow to warm up" temperament style outlined by Thomas & Chess. Contrary to the researchers' hypotheses, boys with FXS were significantly less socially introverted than boys with an idiopathic developmental

delay and both groups were rated similarly on scales of attention, hyperactivity, rigidity, and somatic complaints. Kau et al., suggested that the literature inconsistent and non-significant findings regarding hyperactivity and inattention found in this study may be due to the significant motor delay demonstrated by young males with FXS or because of the possible unknown course of attentional difficulties. It is possible that although both groups demonstrated high levels of inattention and hyperactivity in early childhood, that males with idiopathic developmental delays demonstrate a weakening of these symptoms over time while males with FXS maintain a relatively stable level of inattention and hyperactivity.

Shanahan, Roberts, Hatton, Reznick, & Goldsmith (2008) conducted a recent study investigating the relationship between early temperament and negative reactivity in 25 boys (age 3 years) when compared to 64 typically developing, age matched controls. Information from the control group was gathered via collaboration with a separate ongoing study of twin development and one twin was selected randomly from each pair to be included in the control group. Parent report measures included the Children's Behavior Questionnaire (CBQ; Rothbart, Ahadi, Hershey, & Fisher, 2001), a temperament measure for children ages 3-7 years, and the Childhood Autism Rating Scale (CARS; Schopler et al., 1988), a measure of behaviors associated with the diagnosis of Autism. In addition, participants completed the Mullen Scales of Early Learning (Mullen, 1995), a standardized measure of cognitive and motor development, and the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith & Rothbart, 1999), a laboratory-based, standardized temperament assessment, in either their home or the laboratory. Researchers in this study selected only the anger and sadness scales from the CBQ and the arm restraint task from the Lab-TAB based on their interest in negative reactivity.

Despite several studies suggesting that males with FXS are more active, less adaptable, less intense, less approachable, and less persistent than controls (Hatton et al, 1999; Hepburn & Rogers), Shanahan et al. (2008) found that when compared with age-matched controls, boys with full mutation FXS were rated by their parents as displaying significantly less anger and sadness than typically developing peers. Boys with FXS were also rated by trained coders as having less facial sadness on the Laboratory Temperament Assessment Battery (Lab-Tab) but were not significantly different from controls on facial anger, distress vocalizations, or bodily struggle. Thus, boys with Fragile X actually displayed similar or reduced levels of negative reactivity when compared to typically developing controls, across all measures used. Shanahan et al. (2008), reported that the temperament profile found in boys with FXS in this study (i.e., similar or lower levels of negative reactivity) was similar to that of the temperament profile of young children with Williams Syndrome (Jones et al., 2000). Further, mental age was positively correlated with parent ratings of sadness on the CBQ whereas a higher total score on the CARS was negatively correlated with parent reported sadness on the CBQ for boys with FXS. Thus, higher mental age and lower levels of autistic behavior predicted parent reported sadness on the CBQ in boys with FXS.

The authors of this study suggested that their findings may be inconsistent with previous research on temperament in children with FXS because of the younger age and/or cognitive level of their sample. Shanahan et al. suggested that because their sample was younger than previous samples, it is possible that negative reactivity is expressed in different ways at different ages, with younger children being characterized by under-responsiveness and older child and adults being characterized by over-responsiveness. Researchers also suggest that the reduced levels of anger and sadness may be a reflection of compromised cognitive competence. That is to say,

boys with FXS may have displayed reduced levels of anger and sadness because of a limited understanding of the behaviors of others and other areas important to social and emotional development. Thus, further research must be conducted in order to determine the developmental trajectory of behavioral problems in young children with Fragile X Syndrome as well as their relationship to temperament.

Bailey, Hatton, Mesibov, Ament, & Sinner (2000) investigated the relationship between early development, temperament, and functional impairment in young boys with Autism and Fragile X Syndrome. In this study, researchers compared 31 boys with full mutation FXS and no Autism to 31 boys with Autism and no FXS, matched on chronological age and race, in order to determine whether boys with FXS could be distinguished from boys with Autism on measures of development, functional ability, or behavior. An original sample of 44 boys with FXS was identified, however, 13 of these boys scored above the clinical cutoff on the Childhood Autism Rating Scale (CARS; Schopler, Reichler, Renner, 1988) and thus were excluded from the FXS sample. Each group, FXS no Autism and Autism no FXS, had an age range of 36-95 months (M=64.1 months).

Measures used in this study included the Battelle Developmental Inventory (BDI; Newborg, Stock, Wrek, Guidubald, & Suinicki, 1984), a measure of developmental status in five domains (Personal-Social, Adaptive, Motor, Communication, and Cognitive), the ABILITIES Index (Simeonsson & Bailey, 1988), a knowledgeable informant measure of nine areas of functioning (Audition, Behavior, Intellectual Functioning, Limbs, Intentional Communication, Tonicity, Integrity of Physical Status, Eyes, and Structural Status), and the Behavioral Style Questionnaire (McDevvit & Carey, 1978), a parent reported measure of child temperament.

Bailey et al. (2000), reported significant overall differences on the five domains of the

BDI between boys with FXS and no Autism and boys with Autism and no FXS. Researchers noted that boys with FXS demonstrated a relatively flat profile of development across domains (i.e., little variation in developmental age (DA) across domains; largest difference between any two DA scores was 2.8 months) whereas boys with Autism demonstrated a highly variable developmental profile (i.e., largest difference between any two DA scores was 10.3 months). When each domain was examined separately, only one significant difference remained in the area of Personal-Social development, with boys with FXS scoring significantly higher than boys with Autism. In terms of functional impairment, boys with FXS were rated by their parents or a knowledgeable observer as significantly more impaired in audition, use of limbs, tonicity, integrity of physical health, structural status, and vision when compared to the Autism control group. Contrastingly, boys with Autism were rated as more impaired in behavior, intellectual functioning, and communication when compared to FXS controls.

To compare the temperament of children with FXS and no Autism, Autism and no FXS, and normal controls, Bailey et al. utilized a reference group (n=350) from a previous study (McDevitt & Carey, 1978), considered as the "normative sample" for the Behavioral Style Questionnaire. When compared to the reference group, boys with FXS and boys with Autism were rated by their mothers as significantly slower to adapt, less persistent, and more withdrawing, which is generally consistent with previous literature on temperament in these groups. Boys with Autism were also rated as significantly less intense, less distractible, less rhythmic, and having a higher response threshold than the reference group, whereas boys with FXS were rated as significantly more active than the reference group.

When compared to the Autism no FXS group, significant overall differences in the nine dimensions of temperament were noted between the FXS and Autism groups. Boys with FXS

were also rated by their mothers as significantly more active, intense, and distractible, having a more negative mood quality, and having a lower threshold for change when compared to boys with Autism. However, it is important to note that boys with FXS did not differ from the reference sample (normal controls), on these temperament domains, with the exception of activity.

In a second analysis, a three group design was utilized in which 13 pairs of boys matched on age and race were also matched with a boy with FXS who had exceeded the CARS cutoff score for Autism (FXS and Autism condition). Significant overall differences in developmental status were detected for all groups and significant differences in four out of the five domains (i.e., Personal-Social, Communication, Adaptive, Cognitive but not Motor) were noted for all groups. Boys with Autism again scored significantly lower than boys with FXS on the Personal-Social domain, but the greatest deficits were demonstrated by boys with FXS and Autism. Boys with FXS and Autism scored significantly lower than boys with FXS only and boys with Autism only on the Communication and Adaptive domains. In addition, they scored significantly lower than the Autism only (but not FXS only) group in the Motor domain and significantly lower than the FXS only (but not the Autism only) group in Personal-Social and Cognitive domains. Similarly, boys with FXS and Autism were significantly more intellectually impaired than boys with FXS only and Autism only. Interestingly, no significant differences were found for any of the nine temperament dimensions across the three groups (FXS only, Autism only, FXS and Autism). However, the authors noted that the results produced were in the same direction as the two-group analysis but did not reach significance, possibly due to the small sample size.

Thus, significant differences in temperament, developmental status, and functional abilities were detected for boys with FXS only and boys with Autism only, suggesting that these

two groups may be different in meaningful and significant ways. Bailey et al.'s findings also suggest that having Fragile X Syndrome and Autism produced the lowest levels of functioning and development, working in an additive fashion to produce the most severe outcomes. In terms of temperament, boys with FXS were less adaptable, less persistent, and more withdrawing than normal controls, which is consistent with previous literature.

Girls with Fragile X Syndrome

To date, little psychological research has been conducted with young girls with Fragile X Syndrome. This finding may perhaps be attributed to the differential prevalence rates of the disorder as well as the less severe behavioral manifestation of FXS in girls. Similar to the literature on males with FXS, much of the existing research on females with FXS is conducted with older children and adults. Existing research suggests that approximately 50% of females with full mutation FXS demonstrate intellectual functioning in the borderline or impaired ranges (Keysor & Mazzocco, 2002) and that developmental delays can be detected as early as 9 months of age (Mirrett, Bailey, Roberts, and Hatton, 2004). This is in contrast to the nearly 80% of males with FXS who have mental retardation (Rousseau et al., 1994). Of note, females with mental retardation are often removed from the experimental group in the existing literature, in order to detect less pronounced differences related to the diagnosis of FXS. Of those females with intellectual functioning in the normal range, FXS has been associated with executive functioning, learning, behavioral, and emotional difficulties (Freund, et al, 1993; Hagerman et al., 1992; Hagerman, 1995; 1996b, Keysor & Mazzocco, 2002; Lachiewicz, 1992; Mazzocco et al., 1993, 1997). More specifically, research suggests associations between FXS and autistic behavior, Attentional-Deficit Hyperactivity Disorder (ADHD), difficulties with mathematics, depression,

and anxiety in females. In a study conducted by Freund et al. (1993), researchers reported that 38% of females with FXS met criteria for a mood disorder and 50% displayed anxiety symptoms, based on a structured diagnostic interview (Freund et al., 1993). Thus, the literature suggests that females with FXS as a group display a less severe symptom profile overall, different problem behaviors, and more variability in presentation than males with FXS.

Although the body of literature on individuals with Fragile X Syndrome is vast and wide reaching, the focus on psychological constructs and early behavioral manifestations of this disorder is a relatively recent phenomenon. Even more recent is the research on temperament in young children with Fragile X Syndrome, occurring predominantly within the last 10 years. In addition, particular attention was paid to the relationship between temperament and externalizing behaviors commonly found in children with FXS (i.e., hyperactivity, aggression, etc.), as prior research with typically developing children has demonstrated a significant association between child temperament and later behavior problems. No studies were found examining temperament in young females with FXS, thus a short review of the literature on behavioral manifestations of FXS within this group was presented.

Few studies have been conducted to date, examining temperament in young children with Fragile X Syndrome. The existing literature has yielded mixed findings regarding temperament profiles for these children. Some studies have suggested higher levels of negative reactivity in males with FXS (Merenstein et al, 1996, Kau et al. 2000, Hatton, et al. 2002), while other studies have found similar or reduced levels of negative reactivity in males with FXS, when compared to normal controls (Shanahan et al, 2008).

Several possible explanations could contribute to the inconsistencies found in the literature. One such possibility is that inconsistencies may be due to the fact that multiple

measures of temperament (i.e., Dimensions of Temperament Survey, Child Behavior Questionnaire, Behavioral Style Questionnaire, Toddler Temperament Questionnaire, Middle Childhood Temperament Questionnaire, and the Emotionality, Activity, and Sociability Temperament Scale) were utilized across studies, each with slightly different conceptualizations of temperament. For example, several of the measures are based on the Thomas and Chess nine dimension model of child temperament, while others are based on the Rothbart psychobiological model of temperament. Although there is significant overlap in these models, it is possible that subtle but significant differences in conceptualization of temperament exist that may be producing these mixed findings. In addition, informants varied between studies with parents, researchers, and other knowledgeable caregivers providing ratings across studies.

It is also plausible that there is a developmental trajectory associated with temperament and behavioral problems in children with FXS, in which very young children with FXS display temperaments that could be characterized as hyporeactive (i.e., less anger, less sadness), while older children and adults display more hyperreactive traits (i.e., increased aggression, inattention, and hyperactivity). If in fact a developmental pathway exists, cross sectional research would likely detect differences in temperament when comparing very young children with FXS to older children and adults with FXS, as they may represent age dependent manifestations of the same behavioral problem trajectory. Consistent with this explanation is Shanahan et al.'s findings of reduced levels of negative reactivity in 25 3-year-old males with full mutation FXS. Similarly, a pilot study conducted by the same researchers found reduced or similar levels of reactivity in 12-month-old infants when compared to normal controls, as measured by laboratory based measures of temperament (Roberts, Hatton, & Baranek, 2002). Other studies included in this review that suggest greater levels of reactivity in children with FXS generally included older samples. As no

longitudinal studies of temperament in the first five years of life have been conducted to date, it is unclear as to whether the inconsistencies may be due age-related changes in temperament and negative reactivity.

A final explanation for the inconsistencies in prior research could be the relationship between cognitive ability and the expression of temperament. Shanahan et al. (2008) reported a correlation between increased mental age and increased parent reported sadness in 3-year-old boys with FXS. This finding may suggest that samples that included younger children may be finding reduced levels of negative reactivity, partly due to low cognitive competence. Further, Bailey, Hatton, and Skinner (1998) found that while individuals with FXS demonstrate relatively stable development over time, as measured by the Battelle Developmental Inventory, there is great variability in the developmental level across individuals. Thus, samples across studies may be capturing groups that are not similar in terms of cognitive competence. Further research is needed to identify factors that could help to explain these mixed findings and possibly illuminate a developmental pathway to behavioral difficulties commonly demonstrated by older children and adults with FXS.

The temperament research to date has yielded mixed results regarding a specific temperament profile for children with FXS. Some studies suggest that a distinct temperament profile can be identified in children with Fragile X Syndrome that is significantly different from that of typically developing children, or children with a developmental delay. However, other studies failed to produce results consistent with this conclusion, thus it remains unclear whether children with FXS can be distinguished from typically developing and/or developmentally delayed children with respect to temperament domains. It is possible that a distinct temperament and related behavioral profile exists for young children with FXS that can aid in early diagnosis

and treatment. It is also possible that there is a developmental trajectory for temperament and problem behaviors with negative reactivity emerging early in childhood and becoming exacerbated over time to produce the relatively stable behavioral phenotype in older children and adults. Several recommendations for future research could improve the existing literature on Fragile X Syndrome and temperament and serve to clarify the relationship between early temperament and behavioral problems in children with FXS.

To date there have been no longitudinal studies of temperament in children with FXS between the ages of birth to five years. Longitudinal research could help to clarify the relationship between early childhood temperament and Fragile X as some research suggests a temperament profile including greater activity and less adaptability, approachability, persistence, and intensity (Hatton et al., 1999; Roberts, Bocia, Hatton, Skinner, Sideris, 2006) when compared to typically developing children. However, other research suggests similar or reduced levels of negative reactivity (i.e., anger and sadness) in young children with FXS (Shanahan et al., 2008). These inconsistent findings may be due, in part, to a developmental trajectory of behavioral problems in children with FXS that may be obscured by single assessment research designs that capture only a snapshot of a child's temperament and behavior. Thus, it may be that very young children with FXS demonstrate a temperament profile characterized by under reactivity whereas older children and adults demonstrate a profile characterized by over reactivity. A meta-analysis of existing research on children and adults with Fragile X could also illuminate differences that are obscured by statistical factors such as low power due to small sample sizes. In the present review, the largest sample size included consisted of 45 boys with FXS (Hatton et al., 1999). This relatively small sample size may be hindering researchers' abilities to detect true differences in temperament within this group. Without sufficient power,

statistical analyses may lack the precision needed to detect small or moderate effect sizes and researchers may miss potentially meaningful relationships.

Finally, research on individuals with Fragile X has largely been conducted with males, with no known studies examining temperament in girls with FXS. This finding is most likely due to differential prevalence rates of Fragile X Syndrome in males and females, with some estimates suggesting 1 in 4000 males and 1 in 8000 females being born with the disorder. Research on females with Fragile X is needed because females with Fragile X often have less severe symptomology, may have less pronounced physical attributes associated with FXS, have less cognitive and sensory difficulties, or may not display any of the characteristics seen in males (National Fragile X Foundation, 2011).

The Present Study

The primary goal of this study is to examine differences in temperament in young children with Fragile X Syndrome when compared to normal controls. It is hypothesized that children with FXS will be rated by their parents as displaying significantly more activity, more shyness, more anger/frustration, more fear, less soothability, and less high intensity pleasure than normal controls, which is consistent with findings from previous temperament research conducted with older children and adolescents with Fragile X Syndrome. It is also hypothesized that children with FXS will demonstrate lower scores on Effortful Control broadband temperament factor when compared to normal controls. This factor is composed of Low Intensity Pleasure, Smiling/Laughter, Inhibitory Control, Perceptual Sensitivity, and Attentional Control subscales, which correspond with previous findings in the literature that children with FXS have behavioral problems including hyperactivity and inattention (Hagerman, 2002; Hatton et al.,

2002, 2006; Sullivan et al., 2006; Kau et al, 2000). Because no research to date has focused on the association between early childhood temperament and behavior problems in children with FXS, no apriori hypothesis regarding this relationship could be established. However, we anticipate a trend that is similar to that seen in normal controls (e.g., greater negative reactivity is related to externalizing problems).

Given prior research suggesting that temperament undergoes development, which may be particularly important for children with FXS because their behavioral difficulties tend to become exacerbated over time, researchers will conduct exploratory analyses to examine the influence of age and fragile x diagnosis on temperament. Due to the lack of prior research in this area and the exploratory nature of these analyses, no apriori hypotheses regarding the development of temperament could be established.

CHAPTER TWO

METHODS

Participants

Fragile X Syndrome Participants

Parents of children between the ages of three months and seven years of age, with an existing diagnosis of Fragile X Syndrome, from across the country, were recruited as the primary participants in this study. Families were identified via a sign up sheet presented at several Fragile X Syndrome conferences conducted through the Children's Hospital of Pittsburgh Fragile X Center. Parents were contacted via the telephone to inquire about their participation in this study. After contacting these families, forty families agreed to participate, and were mailed the appropriate temperament measure, based on child age, consent forms, a demographic information form, and a postage paid return envelope. Thirty-one families returned their completed forms and were included in this study (see Table 1). Of the families that could be reached and had children between three months and seven years of age, zero families declined to participate in the study and 9 families did not return their forms, for unknown reasons. Four families had children that were outside of the age ranges included in this study and three families could not be reached.

The FXS sample is composed of 31 children, 29 males and 2 females, from across the continental United States. Most children lived with married parents (85.2%), with approximately 15% of children 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 parent completing the temperament and behavior problems questionnaires was 15.96 years, or approximately the number of years needed to complete a college degree. Mean family income was between $30,001-$50,000 per year.

Follow up data regarding behavioral difficulties were collected for children with Fragile X Syndrome who participated in the original temperament data collection phase between six months to two years after obtaining the initial temperament data. Fifteen families agreed to participate in the follow-up and eleven families returned their behavioral data packets.

After the completion of data collection, 28 out of the 31 temperament data sets collected were for children between the ages of 3-7 years. Thus, 28 out of 31 data sets utilized the Child Behavior Questionnaire to address temperament, whereas only 2 participants responded to the Infant Behavior Questionnaire-Revised and 1 to the Early Childhood Behavior Questionnaire, respectively. Thus, only data from the children ages 3-7 years were utilized for analyses in this study. It should also be noted that temperament data was collected for two girls, whose descriptive data was reported but were excluded for the purposes of the analyses due to the small number of female participants and previous research suggesting significant behavioral differences in boys and girls with FXS. In terms of behavioral data, 11 participants returned their behavioral data packets; however, two of these children were excluded from the temperament investigation because their temperament data was gleaned from the IBQ-R and thus were excluded from the behavioral data analysis. Finally, one female was excluded from the behavioral analysis.

Controls

The comparison sample is made up of typically developing children whose parents have taken part in temperament development research conducted at the Oregon Social Learning Center or the University of Oregon, with collaborators on this project represented at each site. A subset of these children were selected from each site and their data compiled, matching each child to a child with FXS on the basis of gender, race, and closest date of birth. Controls were

selected if their age was the same as the FXS match plus or minus three months. That is, if a child with FXS was 60 months of age, then the matched control child had to be between 57 and 63 months of age. The sample collected from the Oregon Social Learning Center (OSLC) is composed of 159 children, approximately half boys and half girls, which were evaluated at approximately 5 year of age. The families in this study were recruited in the Eugene and Springfield, Oregon areas via newspaper advertisements. Families were included in this study if they had a child that was approximately 5-years old at the time of data collection and had a father in the home. Children included in this sample were mostly Caucasian (92.6%), with other ethnic groups making up approximately 7% of the total sample (e.g., African American (5%); Asian (1.1%), Hispanic (1.6%), Native American (0.5%) and multiracial (3.7%). Families that participated in this study completed a number of assessments including questionnaires, interviews, home visits, and lab interviews. However, only the temperament and behavioral problems questionnaire data was utilized in the present study. Based on age, gender, and race, twenty-four control children were selected from the Oregon Social Learning Center control sample due to the matching criteria outlined above.

The University of Oregon (UO) sample is composed of 361 children from Eugene, Oregon and the surrounding areas, identified on the basis of birth announcements published in the local newspaper, and subsequently contacted by telephone. Researchers reported that nearly all participants were Caucasian (Gartstein, Putnam, & Rothbart, 2012). Participants in this study were asked to complete temperament measures across three time periods: infancy, toddler period, and school-aged. Temperament measures utilized in this study included the Infant Behavior Questionnaire-Revised (IBQ-R; Garstein & Rothbart, 2003), Early Childhood Behavior Questionnaire (ECBQ, Putnam et al., 2006), and the Child Behavior Questionnaire (CBQ,

Rothbart et al., 2001). Child behavior problems were also assessed during the toddler and childhood phases. Of the originally recruited families, 187 families completed all three phases of data collection and the CBQ, thus, control children were selected from theses 187 families. Four children from the UO sample were selected as controls for the present study based on gender, race, and age. Children selected from this sample were used to match children who tended to be at the outer ranges of the selected age groups (e.g., 36-39 months or 90-93 months of age), as this study was longitudinal in nature and captured a wider age range of children.

Measures

Infant temperament

Infant temperament was measured via the Infant Behavior Questionnaire-Revised (IBQ-R) (Gartstein & Rothbart, 2003), a 191 item, parent-report measure designed for infants between three and twelve months of age. Items address infant temperament characteristics on a 7-point Likert scale with responses ranging from "Never" to "Always". The IBQ-R consists of 14 scales which contribute to three overarching temperament factors; Positive Affectivity/Surgency (PAS), Negative Emotionality (NE), and Regulatory Capacity/Orienting (RCO). PAS includes Activity Level, Smiling and Laughter, High-Intensity Pleasure, Perceptual Sensitivity, Approach/Positive Anticipation, and Vocal Reactivity. NE was defined by Distress to Limitations, Fear, Sadness, and, negatively loading, Falling Reactivity. Finally, the third factor, RCO, consists of Duration of Orienting, Low-Intensity Pleasure, Soothability, and Cuddliness (Gartstein & Rothbart, 2003). The 14 subscales of the IBQ-R have previously been demonstrated to have good internal reliability ranging from 0.70 to 0.90 for parent report (Garstein & Rothbart, 2003; Parade & Leerkes, 2008). Inter-rater reliability between mothers and fathers was significant for all subscales except high intensity pleasure, soothability, and cuddliness (Parade & Leerkes, 2008).

Furthermore, Garstein & Rothbart (2003) reported some support for the monomethod discriminant validity of the IBQ-R, with a number of inter-correlations in the low to moderate range.

Early Childhood Temperament

Toddler temperament was measured via the Early Childhood Behavior Questionnaire (ECBQ) (Putnam, Gartstein, & Rothbart, 2006), a 201 item, parent-report measure designed for toddlers between eighteen months and three years of age. Items address toddler temperament characteristics on a 7-point Likert scale with responses ranging from "Never" to "Always". The ECBQ consists of 18 scales, which contribute to three overarching temperament factors: Negative Affectivity (NA), Surgency/Extraversion (SE), and Effortful Control (EC). NA is composed of the Discomfort, Fear, Motor Activation, Sadness, Perceptual Sensitivity, Shyness, Soothability, and Frustration scales. SE is composed of Impulsivity, Activity Level, High-Intensity Pleasure, Sociability, and Positive Anticipation. Finally, the third factor, EC, is composed of Inhibitory Control, Attention Shifting, Low-intensity Pleasure, Cuddliness, and Attention Focusing. The 18 scales of the ECBQ have previously been demonstrated to have good internal reliability ranging from 0.56 to 0.90 for parent report, with the majority of scales demonstrating reliability over 0.80 (Putnam, Gartstein, & Rothbart, 2006). In addition, similar levels of internal consistency were found for secondary caregivers, primarily fathers.

Inter-rater reliability between primary and secondary caregivers was significant for all three factors (NA, SE, EC) and all subscales except for Low-Intensity Pleasure, Attention Shifting, and Attention Focusing (Putnam, Gartstein, & Rothbart, 2006). Of note, Attention Shifting and Attention Focusing approached significance at the 0.05 level and were significant at 0.10.

Child Temperament

Child temperament was measured via the Child Behavior Questionnaire (CBQ) (Rothbart, Ahadi, Hershey, & Fisher, 2001), a 195 item, parent-report measure designed for children between 3 and 7 years of age. Items address child temperament characteristics on a 7-point Likert scale with responses ranging from "Never" to "Always." The CBQ consists of 16 scales, which contribute to three overarching temperament factors: Negative Affectivity (NA), Surgency/Extraversion (SE), and Effortful Control (EC). Negative Affectivity consists of the scales of Discomfort, Sadness, Fear, Anger/Frustration, and Soothability, which loads negatively. Surgency/Extraversion consists of Impulsivity, High Intensity Pleasure, Activity Level, and Shyness, which loads negatively. Also loading on the SE factor are the Positive Anticipation and Smiling/Laughter scales. Effortful Control consists of Low Intensity Pleasure, Smiling/Laughter, Inhibitory Control, Perceptual Sensitivity, Attentional Focusing, and Attentional Shifting (Rothbart, Ahadi, Hershey, & Fisher, 2001).

The 16 subscales of the CBQ have previously been demonstrated to have good internal reliability ranging from .67 to .94 with a mean internal consistency estimate of .77 for all 15 scales (Ahadi, Rothbart, & Ye, 1993). Kochanska et al. (1994) found a mean alpha value of .78 across the 15 scales, with a range of .68 to .93. Rothbart et al. (2001) reported internal consistency estimates for 4 and 5 year old children from .64 to .92, with a mean of .73, and .67 to .92, with a mean of .75, for 6 and 7 year old children. Inter-rater reliability between mothers and fathers was significant for all subscales except Discomfort in 5-year-old children (Rothbart et al, 2001). Furthermore, test-retest data from ages 5 years to 7 years was significant for all subscales for both mothers and fathers.

Child Behavior

Child Behavior was assessed using the Achenbach System of Empirically Based Assessment, Child Behavior Checklist (CBCL) parent report form (Achenbach & Rescorla, 2000, 2001). Depending on the child's age, either the CBCL for ages 1 ½ years to 5 years (Preschool form) or the CBCL for ages 6-18 years (School aged form) was used. The CBCL parent report form is a questionnaire that asks parents to rate their child's behavior problems, along with providing additional information concerning certain areas of competence/impairment for older children.

Child Behavior Checklist for Ages 1 ½ - 5 Years

The Child Behavior Checklist Preschool form, Parent Report Version (CBCL-Preschool) is a 99-item parent-report measure that addresses behavior problems in children ages 1 ½ years to 5 years of age. The Preschool CBCL consists of both the Syndrome and DSM-Oriented Scales. The Syndrome Scales include the Emotionally Reactive, Anxious/Depressed; Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior scales. The DSM-Oriented Scales include the Affective Problems, Anxiety Problems, Pervasive Developmental Problems; Attention Deficit/Hyperactivity Problems, and Oppositional Defiant Problems scales. In addition, a Total Problems score, as well as two broadband scores for Internalizing and Externalizing difficulties, are produced. For each item, parents rated their child on a rating scale of 0 (Not True) to 2 (Very True or Often True). The CBCL has been shown to have satisfactory psychometric properties including a mean test-retest score of r=0.85 for the CBCL scales, a mean inter-rater reliability (between mothers and fathers) of r=0.61, and a mean 12-month stability correlation of r=0.61 (Achenbach & Rescorla, 2000). Alpha values ranged from .66 to .92 for the syndrome scales, .63 to .86 for the DSM-oriented scales, and .89 to .95 for

the composite scales (e.g. Total Problems, Internalizing, and Externalizing scores). In addition, the CBCL preschool version has demonstrated adequate content, construct, and criterion-related validity.

Child Behavior Checklist for Ages 6-18 Years.

The Child Behavior Checklist School Aged form, Parent Report Version (CBCL-School Aged) is a 113-item parent-report measure that addresses behavior problems and competencies in children ages 6 to 18 years of age. In addition to the 113 Likert-rating scale items, there are 7 items that require parents to discuss their child's competencies and 6 items about any other disabilities or problems a child may encounter. For the purposes of this study, only the Likert rating items will be utilized. Similar to the Preschool version, the School-Aged CBCL consists of both the Syndrome and DSM-Oriented Scales. The Syndrome Scales include the Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior subscales. The DSM-Oriented Scales include the Affective Problems, Anxiety Problems; Somatic Problems; Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problem subscales. In addition, a Total Problems score, as well as two broadband scores for Internalizing and Externalizing difficulties, are produced. For each Likert scale item, parents rated their child on a rating scale of 0 (Not True) to 2 (Very True or Often True). The CBCL has been shown to have satisfactory psychometric properties including a mean test-retest value of .88 or better for all scales (Competence & Adaptive Scales r^2=0.90; Syndrome Scales r^2=.90; DSM-Oriented Scales r^2=.88), a mean inter-rater reliability (between mothers and fathers) of .59, a mean 12 month stability correlation of .65, and a mean 24 month stability correlation of .68. (Achenbach & Rescorla, 2001). Achenbach & Rescorla (2001) reported alpha

coefficients ranging from .63 to .79 for the Competence & Adaptive scales, .78 to .97 on the Syndrome Scales, and .72 to .91 for the DSM-Oriented scales of the CBCL. In addition, the CBCL school aged version has demonstrated adequate content, construct, and criterion-related validity.

Procedure

Families were initially recruited by telephone, after determining their child's eligibility (between the age of 3 months and 7 years and a diagnosis of FXS) for the temperament study, using information obtained at several Fragile X Syndrome Conferences conducted by the Children's Hospital of Pittsburg Fragile X Center. Specifically, collaborators at the Children's Hospital of Pittsburg Fragile X Center asked eligible families about their interest in this research, providing contact information to our study group when such interest was expressed by potential participants (i.e., after they have signed a consent form documenting their interest and willingness to share contact information with our study group). Families that agreed to participate in the study were mailed a temperament measure (based on child age; IBQ-R, ECBQ, or CBQ) with instructions, an informed consent form, a demographic questionnaire, and a postage paid, return envelope. All parents were asked to complete the questionnaires and return them in the included envelope. Families who agreed to participate in the initial study were contacted between 6 months to 1.5 years after completion of the initial temperament phase of investigation regarding participation in a follow-up investigation addressing behavioral difficulties in children with FXS. The date of completion of this behavioral data depended primarily on when families could be contacted and how quickly forms were completed and returned. Families who agreed to participate in the follow-up to the temperament study were

mailed a behavior problems rating form (Child Behavior Checklist; Achenbach & Rescorla, 2000, 2001) along with instructions, an informed consent form, and a pre-paid postage return envelope. The informant for the temperament measure also completed the behavior rating scales. Comparison sample families have participated previous temperament related research, understanding that the information they provided about their children would be used in a variety of scientific projects.

Analytic Strategy

In the present study, three related temperament measures (IBQ-R, ECBQ, CBQ) were used across three age groups (3-12 months, 18 months-3 years, 3-7 years respectively) of participants. As 28 of 31 complete data sets contained temperament data from the CBQ, temperament analysis will be conducted for only the children that fell within the age range of this measure, 3 to 7 years of age.

First, descriptive statistics will be computed for all of the variables examined in this study, including skewness and kurtosis to check for normality of data. Second, independent samples t-tests will be computed for age, gender, and race matched participants to determine if children with FXS are statically different from normal controls on the three broadband factors as well as the 16 fine-grained scales identified as variables of interest. As no prior research to date as examined the entire Rothbart Psychobiological model of temperament, the present study aims to investigate these previously unexplored domains.

Similarly, descriptive statistics and independent sample t-tests will also be computed for CBCL data. Researchers will compare age, gender, and race matched participants to determine if children with FXS are statistically different from normal controls per parent report of behavioral

difficulties, including the Total Problems, Externalizing, and Internalizing scores of the CBCL. Then, simple correlations will be computed to determine if the three overarching temperament factors, Extraversion/Surgency (ES), Negative Affectivity (NA), and Effortful Control (EC), are associated with the Total Behavior Problems, Externalizing, and Internalizing scores of the CBCL for both children with FXS and normal controls. In order to minimize Type I error, potentially inflated by multiple statistical tests, further correlations will only be run for fine-grained attributes associated with significantly correlated broadband temperament variables, with the exception of the Activity Level, Soothability, Shyness, High Intensity Pleasure, Anger/Frustration, Fear, and Sadness subscales because of specific apriori hypotheses. That is, if Negative Affectivity is found to be correlated with behavioral problems in children with FXS, then the Discomfort, Sadness, Fear, Anger/Frustration, and Soothability scales would also be tested to see if they correlate with scores from the CBCL.

In order to determine if temperament develops over time, a two way ANOVA will be conducted to determine if there is an interaction effect between fragile x syndrome status (FXS or control) and age how this impacts temperament. Given the range of the Child Behavior Questionnaire, children will be divided into two age groups: those 36-60 months (3-5 years) and 61-93 months (5-7 years). Initially, a two way ANOVA will be conducted for the three broadband temperament factors (Negative Affectivity, Surgency/Extraversion, and Effortful Control). If any of these interactions are significant, then a two way ANOVA will be conducted for the fine-grained scales that make up the significant broadband factor, to determine any further interaction effects. These analyses are exploratory in nature due to the lack of prior research in this area.

CHAPTER THREE

RESULTS

A power analysis was conducted aprori based on previous effect sizes found for temperament differences between children with FXS and controls. A power analysis suggested that a sample size of approximately 40 (20 in each group) would be necessary to detect moderate and larger effect sizes.

Descriptive statistics were computed for the all variables addressed in this study (see Tables 1, 2, & 3). To establish normality of the data, skewness and kurtosis values were reported (Table 2 & 3), with the distributions determined to be approximately normal.

Temperament and Behavioral Differences in Children with FXS

Independent samples t-tests were performed to detect group differences between children with FXS and age, race, and gender matched controls, on the three broadband temperament factors (SE, NA, EC) and 16 fine-grained temperament dimensions of the CBQ (Table 4). As a number of t-tests were run for this particular analysis, broad band and fine-grained temperament results significant at the $p \leq 0.005$ will be discussed. In terms of the broadband temperament factors, children with FXS were rated by their parents as displaying significantly less Surgency/Extraversion ($t(50)=-3.363$, $p=0.002$) and Effortful Control ($t(50)=-6.086$, $p=.000$) than matched controls but were not rated as significantly different in Negative Affectivity ($t(50)=-1.039$, $p=.304$). When examining the fine-grained temperament dimensions, Children with FXS were rated by their parents as displaying significantly greater activity ($t(50)=3.092$, $p=0.003$) and shyness ($t(50)=-7.932$, $p=.000$) relative to controls. Children with FXS were also rated as displaying significantly less attentional focusing ($t(50)=-11.610$, $p=.000$), inhibitory

control (t(50)= -9.775, p=.000), soothability (t(50)=-4.783, p=.000), and high intensity pleasure (t(50)= -2.955, p=.005). Additionally, there was a trend toward children with FXS displaying less low intensity pleasure (t(50)=-2.489, p=.017), sadness (t(50)=-2.114, p=.040) and perceptual sensitivity (t(50)=-2.058, p=.045). No significant group differences were detected for Frustration/Anger (t(50)=.061, p=.952), Attentional Shifting (t(50)=-1.246, p=.220), Discomfort (t(50)=-.292, p=.772), Fear (t(50)=-.276, p=.784), Impulsivity (t(50)=-1.034, p=.306), Approach (t(50)=-.267, p=.790), and Smiling/Laughter (t(50)=-1.434, p=.158).

Independent samples t-tests were also used to detect group differences in problem behaviors as measured by the Internalizing, Externalizing, and Total Problems scales of the Child Behavior Checklist (Table 5). For the purposes of this study, both the raw and t-scores were reported for descriptive purposes and raw scores utilized for analyses. Children with FXS were rated by their parents as having significantly more total problems, as measured by the CBCL Total Problems raw score (t(14)=3.063, p=0.009, than age, gender, and race matched controls. Additionally, 75% of the boys in the FXS group had total behavior problem scores that were at least one standard deviation above the control group mean and 87.5% of the boys in the FXS group had total problems scores above the control group mean. Group differences on the CBCL Externalizing Behavior raw scores approached significance (t(14)=1.918, p=.078), with children with FXS displaying greater externalizing problems than controls. No significant group difference was found for the CBCL Internalizing Behavior raw score (t(14)=1.1438, p=.172) between children with FXS and controls.

The Relationship Between Temperament and Behavioral Difficulties

Correlations between the temperament broadband factors and seven fine-grained dimensions (Activity Level, Frustration/Anger, Soothability, Fear, Sadness, High Intensity Pleasure, Shyness) identified a-priori and CBCL behavior problem scores were also computed (Table 6). Broadband temperament factors were not significantly related to the externalizing, internalizing, or total problems scales of the CBCL for children with FXS. No significant correlations were noted between the seven fine-grained temperament dimensions of interest (e.g., Activity Level, Soothability, Shyness, High Intensity Pleasure, Anger/Frustration, Fear, and Sadness) and behavior variables for children with FXS.

Correlations between temperament broadband factors and the seven fine-grained temperament factors identified as areas of interest were also computed for matched controls. Surgency was found to be positively correlated with the CBCL Externalizing Problems raw score ($r(7)=.719$, $p=0.0045$). Given this significant correlation, the fine-grained temperament variables that make up the Surgency/Extraversion factor (e.g., Impulsivity, High Intensity Pleasure, Activity Level, and Shyness) were also correlated with the problem behavior scales of the CBCL. Impulsivity was positively correlated with the CBCL Externalizing Raw Score ($r(7)=.744$, $p=0.034$). No other significant correlations were detected.

Exploratory Analyses

Given prior research suggesting that temperament undergoes development, two way ANOVAs were conducted to determine if there is an interaction effect between fragile x syndrome status (FXS or control) and age (3-5 years or 5-7 years) and examine how this impacts

temperament (Tables 7,8,9). No interaction effect was detected for the Surgency/Extraversion ($F(1, 52)=1.647$, $p=.205$, partial $\eta^2 = .031$) and Effortful Control ($F(1,52)=.010$, $p=.920$, partial $\eta^2 = .000$) broadband factors. There was a statistically significant interaction between age and fragile x diagnosis on Negative Affectivity, $F(1,52)=5.251$, $p=.026$, partial $\eta^2 = .092$. Two way ANOVAs were then run for the fine-grained dimensions that make up the Negative Affectivity domain (i.e., Discomfort, Sadness, Fear, Anger/Frustration, and Soothability). No significant interaction effects were detected for the Soothability ($F(1,52)=1.001$,$p=.322$, partial $\eta^2 = .019$), Discomfort ($F(1,52)=.365$,$p=.548$, partial $\eta^2 = .007$), Anger/Frustration ($F(1,52)=1.174$, $p=.284$, partial $\eta^2 = .022$), Sadness ($F(1,52)=.344$, $p=.560$, partial $\eta^2 = .007$), or Fear ($F(1,52)=.513$, $p=.477$, partial $\eta^2 = .010$) dimensions.

CHAPTER FOUR

DISCUSSION

Summary of Findings

The present study attempted to identify early temperament and behavioral differences between young children with FXS and age, gender, and race matched controls. Additionally, relationships between temperament characteristics and emerging behavioral problems were also addressed. Children with FXS were rated by their parents as displaying significantly greater activity and shyness and significantly less attentional focusing, inhibitory control, soothability, and high intensity pleasure. Trend level data suggest that children with FXS were also rated as displaying less low intensity pleasure, sadness, and perceptual sensitivity relative to age, gender, and race matched controls. In terms of the broadband temperament factors, children with FXS were reported as exhibiting less surgency/extraversion and effortful control than controls. Children with FXS were also rated by their parents as having significantly more total behavior problems compared to controls. A trend toward greater externalizing behavior in children with FXS was also detected. Correlations between temperament and behavior problem scores were also computed. Broadband temperament factors and fine-grained dimensions identified as areas of interest apriori were not found to be significantly related to externalizing, internalizing, or total problems scales of the CBCL for children with FXS. Correlations between temperament and behavior problems in normal controls revealed that surgency/extraversion was positively correlated with externalizing problems, as was impulsivity, one of the fine-grained attributes that make up the surgency/extraversion factor. Two-way ANOVAs were executed to determine if temperament changes over time for children for children with FXS and controls. A significant interaction between age and fragile x diagnosis (FXS or control) was detected for Negative

Affectivity. An interaction effect was not detected for the Surgency/Extraversion Effortful Control broadband factors or the fine-grained dimensions that make up the Negative Affectivity domain (i.e., Sadness, Discomfort, Fear, Anger/Frustration, Soothability).

As hypothesized, boys with FXS were rated by their parents as displaying significantly more activity and shyness and significantly less effortful control, soothability, and high intensity pleasure. Boys with FXS were not however, rated by their parents as displaying significantly more anger/frustration or sadness than controls as hypothesized. Instead, boys with FXS displayed similar or reduced levels of anger/frustration and sadness when compared to normal controls. This finding is consistent with the results reported by Shanahan et al. (2008), wherein researchers found similar or reduced levels of negative reactivity in boys with FXS when compared to typically developing controls. Additionally, boys with FXS displayed significantly less surgency/extraversion, attentional focusing, and inhibitory control when compared to age, gender, and race matched controls. These results suggest that children with FXS were rated by their parents as displaying less high intensity pleasure and exhibiting lower levels of positive affectivity/surgency overall, relative to matched controls. Children with FXS were also rated as displaying more shyness, consistent with prior research, and less soothability, which represents a regulation-related domain of temperament. These positive emotionality findings may be of particular significance because this domain of temperament has not been widely examined, especially for this special population.

Interestingly, lower levels of positive affectivity were not also accompanied by higher levels of negative affectivity, as boys with FXS had similar or somewhat reduced levels of anger/frustration, sadness, discomfort, and fear when compared to controls. These results could be interpreted to suggest that possible mechanisms for behavioral problems in young boys with

FXS may be somewhat different from those observed for typically developing children. The existing literature in normally developing children suggests that negative emotionality has predictive utility in determining internalizing (Ruschena, Prior, Sanson, & Smart, 2005) and externalizing difficulties (Caspi & Silva, 1995; Lemery et al., 2002). If replicated with larger samples, these results may suggest that temperament based parenting interventions for parents of children with FXS may want to address how parents can respond to lower levels of positive emotionality in contrast to high levels of negative emotionality. It is possible that children who do not respond with positive emotions to their caregivers' bids for attention pose a particular challenge in the socialization efforts, which could be addressed therapeutically for this group. Additionally, temperament based parent-training can help parents of children with FXS with high activity levels and low soothability respond to their children more effectively using a goodness-of-fit parenting model. That is, the goodness-of-fit between parental demands and expectations on one hand, and the child's temperament on the other hand, could be improved through psycho-educational efforts, for example, providing temperament feedback based on parent-report assessments.

In terms of behavioral problems, parents of boys with FXS reported significantly more total problems on the Child Behavior Checklist than age, gender, and race matched controls. Parent reported externalizing behavior problems approached significance, suggesting that with a larger sample size and enhanced power, this difference would have likely reached the criterion typically utilized for judging statistical significance. Thus, children with FXS may actually display more externalizing behaviors when compared to controls, which would be consistent with behavioral problems commonly associated with a diagnosis of FXS (e.g., attentional difficulties and aggression). In addition, our analyses suggest that attentional difficulties

commonly found in older children and adults with FXS (Hagerman, 2011) are also characteristic of young children with this condition. That is, children with FXS were described by their parents as exhibiting less attentional focusing, inhibitory control, and effortful control, than comparison peers, coupled with a relatively greater activity levels.

Correlational analyses revealed that broadband temperament factors and the seven fine-grained temperament dimensions were not related to externalizing, internalizing, or the total problems scales of the CBCL for children with FXS. In control children, Surgency/Extraversion was positively correlated with externalizing problems. Of the fine-grained attributes that make up the Surgency/Extraversion factor (e.g., Impulsivity, High Intensity Pleasure, Activity Level, and Shyness), Impulsivity was also positively correlated with externalizing behavior. These results should be interpreted with caution because of the small behavioral data sample size (N=8) and will need to be replicated.

To examine the possibility that there is a developmental trajectory associated with temperament in children with FXS, two-way ANOVAs were executed examining the effect of age and FXS status on broadband temperament factors. A significant interaction between age and fragile x diagnosis (FXS or control) was detected for Negative Affectivity. That is, the relationship between age and Negative Affectivity depended on whether or not the child had FXS or not. These findings suggest potentially important developmental trends for children with FXS, which should be re-examined utilizing longitudinal designs. Our results could be interpreted as supporting the idea that developmental trajectories for Negative Affectivity may be different for boys with FXS than normal controls. Differences in reactivity/regulation may be of particular importance to children with FXS, wherein very young children with FXS could be characterized as displaying temperaments marked by hyporeactivity (i.e., less anger, less

sadness), while older children and adults display more hyperreactive traits (i.e., increased aggression, inattention, and hyperactivity).

Future research focusing on early temperament differences in children with FXS will need to provide replication of these results because of the small sample size and a number of exploratory analyses. If replicated, these results would indicate that boys with FXS are perceived as displaying significantly less Surgency/Extraversion and Effortful Control than controls, based on the report of their caregivers. Further, boys with FXS were described as displaying significantly more activity and shyness and less attentional focusing, inhibitory control, soothability, and high intensity pleasure. In terms of behavioral problems, boys with FXS were rated by their parents as displaying significantly more total behavior problems than controls. Broadband temperament factors and fine-grained dimensions were not found to be significantly correlated with parent reported behavioral problems for boys with FXS. Overall, boys with FXS were described as displaying lower levels of positive emotionality and similar or reduced levels of negative emotionality when compared to controls. Further, an interaction between a diagnosis of FXS (FXS or control group) and age was detected for the Negative Affectivity domain, where the effect of age on Negative Affectivity depended on whether the child had FXS or not.

This study is likely to make a contribution to the limited number of existing studies addressing temperament in children with FXS, despite its exploratory components. First, this study utilized age, gender, and race matched comparison peers, allowing us to better control for "third variables" related to these demographic factors. This is in comparison to several other studies (Hatton et al., 1999; Bailey et al., 2000) in which a temperament measure's normative sample was utilized as a control group, with data sometimes collected several decades prior to that of the FXS sample. Other studies utilized control groups significantly larger than the

included FXS samples (i.e., FXS group N=30, Control group N=60), which may have systematically impacted their findings (Shanahan et al., 2008). Second, the present study is the first to utilize the entire temperament assessment protocol (i.e., not just selected subscales) from the Rothbart psychobiological measures of temperament (e.g., Infant Behavior Questionnaire-Revised, Early Childhood Behavior Questionnaire, Child Behavior Questionnaire). Previous studies have relied on subsets of scales to test their hypotheses, forgoing the opportunity to examine the entire spectrum of potentially relevant temperament attributes. Third, this study demonstrated that attentional difficulties commonly found in older children and adults with FXS (Hagerman, 2011) are also characteristic of young children with this condition. Fourth, the positive emotionality findings from this study, though exploratory, are likely to stimulate additional research, and may serve as a foundation for temperament-based parent education programs for families of children with a FXS diagnosis, given that these results are replicated in future studies. Several temperament based parenting education outcome studies have lead to positive findings indicating reduced child behavior problems at home (McClowry, Snow, & Tamis-LeMonda 2005), reduced child anxiety disorder rates post intervention (Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005), and increased satisfaction with parent child interactions and perceived parenting competence (Sheeber & Johnson, 1994) in neurotypical children. These interventions are based on the notion of goodness-of-fit parenting, first articulated by Thomas and Chess (1968), and are aimed at improving the match between parental responding and their child's difficult temperament. In a recent study, maternal, self-reported stress was associated with child temperament characterized as detached and hypersensitive/hyperactive in young boys with Fragile X Syndrome and not with degree of disability (Sarimi, 2010). Temperament-based parent education interventions could be especially helpful for young children identified as

displaying detached and hypersensitive/hyper-reactive temperaments and their caregivers as these traits were associated with the highest levels of maternal stress. Although the relevance of a temperament-based intervention for families with children with FXS does not hinge upon a consistent temperament profile for this group, identifying temperament characteristics in young children with FXS could provide a foundation on which to build interventions such as these.

Limitations of the Present Study and Implications for Future Research

Importantly, several limitations should also be noted and addressed in future research. First, the relatively small sample size (N=26) likely limited the statistical power of the analyses conducted in the context of this study, and our ability to detect significant effects in the small/medium range. This limitation is particularly relevant to the analyses addressing behavior problems (N=8). Further research, with larger sample sizes, is necessary to determine whether other important temperament and behavior problem related differences between boys with FXS and controls can be detected. Further, a replication of this study with a larger sample size may reveal other associations between temperament and behavioral problems. A longitudinal study would also help to determine if temperament characteristics are not only associated with, as suggested by this study, but predict later behavior problems. Second, our sample was racially homogenous, and more diverse samples should be recruited in future research in an effort to enhance generalizability, and possibly enhance the ability to detect hypothesized effects/relationships (i.e., because racial heterogeneity may contribute to greater variability in the examined variables). This recruitment may be facilitated by future researchers by collaborating with Fragile X Syndrome Centers located in the same geographical region as the researchers. Third, because of the limited data collected for girls with FXS, likely due to the lower prevalence

rate of FXS in females and possible self-selection bias presented when recruiting from conferences, girls with FXS (N=2) were removed from our analyses. Future research could make efforts to specifically recruit families of girls with FXS in order to determine if and how girls with FXS are temperamentally different from boys with FXS, and from same age, gender, and race/ethnicity matched controls. As girls often have less severe presentations of the disorder and thus may have families that are less active in the conference circuit, it may be beneficial for future researchers to identify families of girls with FXS via another method. Fourth, the current study did not utilize an Autism specific measure or cognitive measure during data collection, due to limited contact with geographically distant participating families. Future research may want to utilize an autism specific measure to determine the presence of a secondary diagnosis of Autism, which may affect findings. However, a study conducted by Bailey et al. (2000) found no significant differences for any of the nine temperament dimensions of the Behavioral Style Questionnaire between boys with FXS only and FXS and Autism, which suggests that this limitation may have a minimal effect on the pattern of results observed in this study. Further, researchers may want to utilize a cognitive measure to determine IQ level and its impact on temperament characteristics, as Shanahan et al. (2008) suggested that the reduced levels of anger and sadness may be a reflection of compromised cognitive competence, with boys with FXS displaying similar or reduced levels of anger and sadness because of a limited understanding of the behaviors of others and other areas important to social and emotional development. Finally, our exclusive reliance on parent-report measures represents another limitation, which should be addressed in the future. For example, laboratory observations of temperament could be utilized to determine how children with FXS are temperamentally different from age, gender, and race

matched controls. This would be especially important for more comprehensive studies examining the contributions of early temperament to behavioral difficulties in children with FXS.

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APPENDIX

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	4	7.1
Child Ethnicity		
Caucasian	56	100
Hispanic	0	0
Asian	0	0
Mixed	0	0

N=56, FXS= 28; Control=28; Females (N=4) were not included in further analyses.

Table 2: Descriptive Statistics for FXS Group

Overarching Factors (N=26)	M	SD	Min	Max	Range	Skewness	Kurtosis
CBQ Surgency/Extraversion	3.305	.569	2.42	4.87	2.45	.475	.954
CBQ Negative Affectivity	2.309	.542	1.21	3.37	2.16	-.138	.112
CBQ Effortful Control	4.501	.457	3.65	5.39	1.74	-.079	-.681
Fine-grained Subscales (N=26)	**M**	**SD**	**Min**	**Max**	**Range**	**Skewness**	**Kurtosis**
Activity Level	5.411	.709	3.85	6.85	3.00	-.021	-.142
Frustration/Anger	4.396	.704	3.08	5.77	2.69	.180	-.919
Attentional Focusing	2.682	.688	1.44	4.22	2.78	.561	-.215
Attentional Shifting	4.051	.612	2.77	5.15	2.38	.008	-.585
Discomfort	4.023	.749	2.42	5.42	3.00	-.246	-.422
Soothability	4.051	.612	2.77	5.15	2.38	.008	-.585
Fear	3.529	.986	1.73	5.70	3.97	.158	.192
High Intensity Pleasure	4.425	.938	2.92	6.77	3.85	-.249	-.047
Impulsivity	4.370	.929	2.92	6.977	3.85	.260	.258
Inhibitory Control	2.915	.745	2.00	4.67	2.67	.601	-.312
Low Intensity Pleasure	5.216	.792	3.42	6.33	2.92	-.503	3.70
Perceptual Sensitivity	4.314	.847	2.67	5.70	3.03	-.001	-1.022
Sadness	3.650	.582	2.50	4.92	2.42	.052	-.029
Shyness	5.004	1.067	2.54	6.67	4.13	.052	-.029
Approach	4.942	.875	3.25	6.44	3.19	-.213	-.477
Smiling & Laughter	5.689	.614	4.58	6.77	2.19	.000	.887
CBCL subscales (N=8)	**M**	**SD**	**Min**	**Max**	**Range**	**Skewness**	**Kurtosis**
Internalizing Problems Raw Score	10.125	4.863	5.00	21.00	16.00	1.798	4.352
Internalizing Problems T-score	60.250	5.751	52.00	71.00	19.00	.459	1.235
Externalizing Problems Raw Score	14.000	8.586	4.00	30.00	26.00	1.018	.454
Externalizing Problems T-score	60.625	8.651	48.00	74.00	26.00	.303	-.462
Total Problems Raw Score	55.250	22.877	24.00	95.00	71.00	.491	-.206
Total Problems T-score	64.875	7.791	52.00	75.00	23.00	-.349	-.771

Note. CBQ-R – Child Behavior Questionnaire (Rothbart, Ahadi, Hershey, & Fisher, 2001), CBCL- Child Behavior Checklist (Achenbach & Rescorla, 2000, 2001).

Table 3: Descriptive Statistics for Control Group

Overarching Factors (N=26)	M	SD	Min	Max	Range	Skewness	Kurtosis
CBQ Surgency/Extraversion	3.953	.800	2.94	6.09	3.15	1.391	1.363
CBQ Negative Affectivity	2.506	.798	1.22	4.18	2.95	.439	-.350
CBQ Effortful Control	5.204	.371	4.68	6.08	1.39	.565	-.303
Fine-grained Subscales (N=26)	**M**	**SD**	**Min**	**Max**	**Range**	**Skewness**	**Kurtosis**
Activity Level	4.771	.781	3.62	6.31	2.69	.403	-.786
Frustration/Anger	4.384	.776	2.75	5.54	2.79	-.461	-.417
Attentional Focusing	4.863	.666	3.56	6.67	3.11	.779	1.157
Attentional Shifting	4.326	.944	1.80	6.08	4.28	-.921	1.362
Discomfort	4.085	.795	2.17	5.33	3.17	-.561	-.026
Soothability	4.871	.624	3.75	6.08	2.33	.062	-.764
Fear	3.605	1.025	1.63	6.25	4.63	.263	.708
High Intensity Pleasure	5.117	.740	3.38	6.38	3.00	-.523	.018
Impulsivity	4.621	.822	3.46	6.08	2.62	.241	-.959
Inhibitory Control	4.955	.759	3.18	6.31	3.13	-.273	-.022
Low Intensity Pleasure	5.689	.557	4.54	6.83	2.29	-.100	-.588
Perceptual Sensitivity	4.843	1.003	2.92	6.33	3.42	-.256	-.992
Sadness	4.096	.905	1.58	5.67	4.08	-.793	1.281
Shyness	2.934	.796	1.23	4.23	3.00	-.280	-.290
Approach	5.001	.703	3.46	6.77	3.31	.061	.827
Smiling & Laughter	5.910	.489	5.15	6.62	1.46	-.200	-1.480
CBCL subscales (N=8)	**M**	**SD**	**Min**	**Max**	**Range**	**Skewness**	**Kurtosis**
Internalizing Problems Raw Score	6.750	4.528	1.00	13.00	12.00	-.239	-1.524
Internalizing Problems T-score	53.250	9.362	41.00	65.00	24.00	-.272	-1.659
Externalizing Problems Raw Score	6.875	6.058	0.00	16.00	16.00	.406	-1.582
Externalizing Problems T-score	49.125	10.120	33.00	64.00	31.00	-.091	-.382
Total Problems Raw Score	25.125	15.824	4.00	46.00	42.00	-.267	-1.583
Total Problems T-score	50.250	9.543	36.00	62.00	26.00	-.366	-1.287

Note. CBQ-R – Child Behavior Questionnaire (Rothbart, Ahadi, Hershey, & Fisher, 2001), CBCL- Child Behavior Checklist (Achenbach & Rescorla, 2000, 2001).

Table 4. 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	.709	4.77	.782	3.092**	.003
Frustration/Anger	4.396	.724	4.384	.776	.061	.952
Attentional Focusing	2.682	.688	4.863	.688	-11.610**	.000
Attentional Shifting	4.051	.612	4.326	.944	-1.246	.219
Discomfort	4.023	.749	4.085	.749	-.292	.772
Soothability	4.051	.612	4.871	.624	-4.783**	.000
Fear	3.529	.986	3.605	1.025	-.276	.784
High Intensity Pleasure	4.425	.938	5.117	.740	-2.955**	.005
Impulsivity	4.370	.929	4.621	.822	-1.034	.306
Inhibitory Control	2.915	.745	4.955	.759	-9.775**	.000
Low Intensity Pleasure	5.216	.792	5.689	.557	-2.489†	.016
Perceptual Sensitivity	4.314	.847	4.843	1.003	-2.058†	.045
Sadness	3.650	.582	4.096	.905	-2.114†	.040
Shyness	5.004	1.067	2.934	.796	7.932**	.000
Approach	4.942	.875	5.001	.703	-.267	.790
Smiling & Laughter	5.689	.614	5.910	.489	-1.434	.158
	FXS Group (n=26)		Control Group (n=26)			
	Mean	SD	Mean	SD	t(25)	*p*
Surgency/Extraversion	3.305	.569	3.953	.800	-3.363**	.001
Negative Affectivity	2.309	.542	2.506	.798	-1.039	.304
Effortful Control	4.501	.457	5.204	.371	-6.086**	.000

Note. †$p \leq .05$; *$p \leq .005$; ** $p \leq .001$,

Table 5. Independent Samples T-Tests for Child Behavior Checklist (CBCL) Scores

	FXS Group (n=8)		Control Group (n=8)			
Variable	Mean	SD	Mean	SD	t(14)	*p*
Int Prob Raw score	10.125	4.853	6.750	4.528	1.438	.172
Ext Prob Raw score	14.000	8.586	6.875	6.058	1.918	.076
Total Prob Raw score	55.250	22.877	25.125	15.824	3.063*	0.008

Note. Int Prob Raw score= CBCL Internalizing Problems Raw score; Int Prob T-score = CBCL Internalizing Problems T-score; Ext Prob Raw score= CBCL Externalizing Problems Raw score; Ext Prob T-score = CBCL Externalizing Problems T-score; Total Prob Raw score= CBCL Total Problems Raw score; Total Prob T-score = CBCL Total Problems T-score. †p ≤ .05; *$p \leq .005$; **$p \leq .001$.

Table 6: Correlation Matrix for Temperament Variables and Behavior Problems

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Act	---	.954**	-.282	.412	.086	085	-.557	6.11	.564	-.214	.372	.593	.602
2. Fru	.735*	---	-.379	.440	.237	-.049	-.345	.506	.669	-.233	.490	.605	.640
3. Sth	-.779*	-.529	---	-.143	.198	.004	-.373	.143	-.255	.556	-.617	-.526	-.694
4. Fea	.557	.310	-.686	---	.374	-.382	.019	.023	.900**	-.165	-.052	.152	.065
5. Sad	.560	.856**	-.147	-.022	---	-.160	.258	.068	.584	.386	-.408	-.496	-.422
6. Hip	.402	.033	-.131	-.334	.176	---	-.480	.665	-.404	.592	-.233	-.213	-.134
7. Shy	-.045	.080	-.198	.727*	-.200	-.796	---	-.839**	.061	-.332	.04`	-.276	-.162
8. Surg	.708*	.431	-.559	-.050	.342	.742*	-.555	---	.130	.569	.024	.206	.189
9. Neg Aff	.743*	.762*	-.795*	.348	.486	.151	.052	.720*	---	-.141	.114	.241	.229
10. Eff Con	-.243	-.068	.603	-.634	.080	.240	-.430	.104	-.263	---	-.501	-.538	-.563
11. Int Raw	.472	.256	-.469	.290	.166	.059	-..217	.292	.216	-.232	---	.895**	.908**
12. Ext Raw	.605	.384	-.389	-.044	.389	.473	-.5996	.719*	.422	.137	.811*	---	.960**
13.Total Raw	.522	.297	-.453	.245	.243	.131	-.286	.372	.258	-.179	.991**	.871**	---

Note. FXS values listed *above* the diagonal *(N=8)* . Control values listed *below* the diagonal *(N=8)* . Act= Activity Level; Sth = Soothability; (Fru) = Frustration; Fea = Fear; Sad = Sadness; HIP = High Intensity Pleasure; Shy = Shyness; Int Raw= CBCL Internalizing Raw Score; Ext Raw = CBCL Externalizing Raw Score; Total Raw = CBCL Total Raw Score. *$p \leq .05$; ** $p \leq .01$.

Table 7: Two-way ANOVA for FXS Status and Age to predict Surgency/Extraversion

Source	Sum of Squares	Df	Mean Square	F	*p*
Corrected Model	7.135	3	2.378	5.413	.003
Intercept	724.980	1	724.980	1649.999	.000
FXS Status	6.530	1	6.530	14.862	.000
Age Group	.588	1	.588	1.337	.253
FXS*Age Group	.724	1	.724	1.647	.205
Error	22.848	52	.439		
Total	770.672	56			
Corrected Total	29.983	55			

Note. FXS Status= Fragile X or Control, Age Group= 3-5 years or 5-7 years, FXS*Age Group= Interaction Term. *$p \leq .05$; ** $p \leq .01$.

Table 8: Two-way ANOVA for FXS Status and Age to predict Effortful Control

Source	Sum of Squares	Df	Mean Square	F	*p*
Corrected Model	7.81	3	2.600	15.003	.000
Intercept	1290.547	1	1290.547	7446.094	.000
FXS Status	7.392	1	7.392	42.652	.000
Age Group	.199	1	.199	1.146	.289
FXS*Age Group	.002	1	.002	.010	.920
Error	9.013	52	.173		
Total	1346.061	56			
Corrected Total	16.813	55			

Note. FXS Status= Fragile X or Control, Age Group= 3-5 years or 5-7 years, FXS*Age Group= Interaction Term. *$p \leq .05$; ** $p \leq .01$.

Table 9: Two-way ANOVA for FXS Status and Age to predict Negative Affectivity

Source	Sum of Squares	Df	Mean Square	F	*p*
Corrected Model	2.831	3	.944	2.185	.101
Intercept	322.339	1	322.339	746.527	.000
FXS Status	.436	1	.436	1.010	.320
Age Group	.450	1	.450	1.041	.312
FXS*Age Group	2.267	1	2.267	5.251	.026 *
Error	22.453	52	.432		
Total	352.322	56			
Corrected Total	25.283	55			

Note. FXS Status= Fragile X or Control, Age Group= 3-5 years or 5-7 years, FXS*Age Group= Interaction Term. *$p \leq .05$; ** $p \leq .01$.