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Infant Temperament in the *FMR1* Premutation and Fragile X Syndrome

Bridgette L. Tonnsen^a, Anne C. Wheeler^b, Lisa Rague^a, Jane E. Roberts^c

^aDepartment of Psychological Sciences, Purdue University

^bRTI International

^cDepartment of Psychology, University of South Carolina

Abstract

Although temperament has been studied for decades as a predictor of psychopathology in the general population, examining temperament in neurogenetic groups has unique potential to inform the genetic and biological factors that may confer risk for psychopathology in later development. The present study examined early temperament in two heritable neurogenetic conditions associated with atypical CGG repeat expansions on the *FMR1* gene: the *FMR1* premutation (FXpm; 55–200 repeats) and fragile X syndrome (FXS; >200 repeats). We focus specifically on the FXpm, as the condition is highly prevalent (1:209 females and 1:430 males) and associated with increased risk for pediatric psychopathology, including attention problems, autism, and anxiety. In contrast, FXS is a low-incidence disorder (1:4,000) often associated with intellectual disability and more severe co-occurring psychosocial conditions. Given information on infant clinical phenotypes in the FXpm and FXS is sparse, we aimed to characterize parent-reported infant temperament in infants with the FXpm (n=22) relative to FXS (n=24) and controls (n=24), assessed on 1–3 occasions each. Results suggested temperament in infants with the FXpm was largely typical, yet also resembled FXS in the negative affect domain, with trends toward suppressed negative affect in younger participants. In contrast, temperament features of infants with FXS consistently deviated from TD controls in both negative affect and surgency domains. These data suggest that *FMR1* gene mutations are associated with atypical temperament that emerges as early as infancy, particularly among infants with FXS, warranting further study of whether temperament may index emergent clinical risks in these populations.

Temperament, often referred to biologically-grounded emotional, attentional, and regulatory processes that guide individual responses to the environment (Rothbart & Derryberry, 1981), has been studied for decades as a salient and stable predictor of personality and psychopathology in typically developing populations. More recently, this work has begun rapidly expanding to subsets of the population with neurogenetic disorders as a means to inform the biological architecture contributing to these individual differences. The present study advances this work by providing an initial characterization of temperament in an understudied neurogenetic population at high-risk for psychopathology: infants with the

FMR1 premutation (FXpm). The FXpm is a genetic abnormality that is highly prevalent – affecting 1:209 females and 1:430 males in the United States – and is caused by an atypical expansion of 55–200 CGG trinucleotide repeats on the promotor region of the *FMR1* gene (Tassone et al., 2012). FXpm “carriers” are at risk for passing an expanded sequence of >200 CGG repeats to offspring, resulting in fragile X syndrome. Fragile X (FXS) is a low incidence disorder (1:4,000; Crawford, Acuña, & Sherman, 2001) that presents more severely in males and is characterized by intellectual disability, anxiety, autism symptoms, and attention problems (Bailey et al., 2008). Although FXpm carriers were initially believed to be unaffected, evidence over the last decade has unveiled a number of clinical and medical features associated with the FXpm. In children, these features include elevated rates of anxiety, attention problems, developmental disabilities, aggression, and autism (Bailey et al., 2008), with atypical nonverbal skills, visual processing, and sensory responsivity more recently reported to emerge as early as infancy (Gallego, Burris, & Rivera, 2014; Wheeler et al., 2016). In adulthood, additional risks include mood and anxiety disorders, reproductive conditions, and neurocognitive and motor disorders (Grigsby et al., 2014; Roberts et al., 2015; Wheeler et al., 2014). Thus, although the FXpm is not associated with a specific profile of intellectual disability or considered a phenotypic “disorder” to date, a subset of FXpm carriers exhibit both psychological and medical risks that emerge as early as infancy and intensify across development.

Given the elevated risk for psychopathology and well-established genetic architecture of *FMR1* mutations, mapping onset of psychopathology in affected individuals has promise for informing biological mechanisms and pathways of psychological disorders. This approach has been applied to identify biological bases of clinical features in infants with FXS, with a number of studies examining the prevalence and emergence of atypical autism symptoms (Roberts, Tonnsen, McCary, Caravella, & Shinkareva, 2016), anxiety (Tonnsen, Malone, Hatton, & Roberts, 2013), and attention problems (Cornish, Scerif, & Karmiloff-Smith, 2007; Tonnsen, Grefer, Hatton, & Roberts, 2014) in young children. In contrast, studies characterizing early development in the FXpm remain sparse, with only one publication to date characterizing general development in infants (Wheeler et al., 2016). This gap likely reflects challenges in recruiting infants with the FXpm in the absence of newborn screening, as most infants with the FXpm do not exhibit severe clinical symptoms (e.g. intellectual disability, medical problems) that would trigger an independent genetic evaluation. Furthermore, infants who are known FXpm carriers, such as those identified through cascade testing after a relative is diagnosed with FXS, often do not participate in routine developmental evaluations that could be aggregated for population surveillance. Thus, despite mounting evidence of enhanced psychological risks in children with the FXpm, little work has been done to characterize the emergence and risk factors associated with psychopathology in this highly prevalent population.

The present study addresses this gap by characterizing temperament in infants with the FXpm in contrast to infants with FXS and low-risk controls. In infancy, three empirically-validated temperament dimensions have been identified as surgency, negative affect, and regulatory capacity (Gartstein & Rothbart, 2003). Although temperament profiles are generally thought to reflect individual differences in personality rather than “good” or “bad” subclinical features, variations in infant temperament have been prospectively mapped onto

later forms of psychopathology, consistent with evidence of shared biological pathways of personality and behavior. For example, elevated negative affect in early childhood has been repeatedly linked to later anxiety symptoms in nonsyndromic samples (Gartstein et al., 2010), with similar findings in young children with FXS (Tonnsen et al., 2013). In non-FXS samples, these associations have been translated to a new wave of preventative efforts whereby infants high in behavioral inhibition – a withdrawn and inhibited behavioral style highly related to negative affect – are routed to preventative treatments prior to the onset of anxiety-related impairment (e.g. Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005). These preventative programs have significantly reduced the onset of anxiety disorders in behaviorally inhibited youth, providing compelling evidence that infant temperament profiles provide clinically meaningful information that may be leveraged to optimize outcomes for children “at risk” for impairment.

Although no studies to date have reported temperament features in infants with the FXpm, the temperament profile in older children with FXS is relatively well-characterized. Studies using the three-factor psychobiological model of temperament employed in the present study (Rothbart & Derryberry, 1981) have reported lower surgency and regulatory capacity in FXS relative to non-FXS controls (Low Kapalu & Gartstein, 2016) and negative affect that is low in early childhood but increases with age (Low Kapalu & Gartstein, 2016; Shanahan, Roberts, Hatton, Reznick, & Goldsmith, 2008). Using other theoretical models of temperament, children with FXS have been reported to display elevated activity and lower adaptability, intensity, persistence, and approach (Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Hatton, Bailey, Hargett-Beck, Skinner, & Clark, 1999; Roberts, Boccia, Hatton, Skinner, & Sideris, 2006). Notably, early childhood temperament in FXS has also been prospectively associated with psychopathology outcomes, with higher negative affect predicting later anxiety symptoms (Tonnsen et al., 2013) and atypical surgency predicting attention deficit hyperactivity disorder (ADHD) features (Grefer, Flory, Cornish, Hatton, & Roberts, 2016). Together, these studies suggest that temperament profiles present atypically in FXS in early development and provide useful clinical information about psychopathology risk in this population. However, no studies have explicitly examined FXS temperament profiles in infancy, nor has temperament been explored in the FXpm at any age. It is also unclear how temperament may differ across sex in the FXpm and FXS, with most studies to date focusing on males. In typically developing samples, sex differences in infants are generally minimal (Gartstein & Rothbart, 2003), with males exhibiting higher surgency and lower effortful control in meta-analyses incorporating wider age ranges, potentially reflecting the enhanced risk for externalizing problems (Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006). Similarly, males with *FMRI* mutations exhibit higher psychosocial risks (Bailey et al., 2008), likely due to the buffering effect of a second, unaffected X chromosome in females. Given the FXpm is a high-incidence disorder with known psychological risks, further characterizing temperament profiles in this population across sexes – particularly in early development – may lay the foundation for earlier detection and prevention of maladaptive outcomes.

The present study aimed to describe group-level temperament profiles in infants with the FXpm relative to FXS and unaffected controls. Our aims were primarily exploratory in nature, as only one study to date has characterized early development in the FXpm (Wheeler

et al., 2016), no studies have explored FXpm-associated temperament, and no studies have focused on FXS-associated temperament in infants. However, we approached this study with two potential outcomes in mind. First, infants with the FXpm could exhibit similar temperament profiles to those observed in older children with FXS, reflecting shared genetic vulnerabilities and qualitatively similar yet less frequent comorbid conditions in the FXpm relative to FXS (Bailey et al., 2008). From this perspective, we would expect infants with the FXpm to exhibit reduced surgency, negative affect, and regulatory capacity, paralleling previous work in older samples with FXS (Low Kapalu & Gartstein, 2016; Shanahan et al., 2008). This outcome would suggest that infants with the FXpm may benefit from similar surveillance and intervention approaches as FXS. Alternatively, profiles in the FXpm could present differently from FXS, reflecting the distinct biological mechanisms sustaining clinical features in the FXpm. Indeed, FXpm symptoms are posited to emerge secondary to toxic effects of *elevated* messenger RNA (mRNA), whereas features in FXS emerge secondary to *reduced* mRNA and fragile X mental retardation protein, a protein necessary for healthy synaptic plasticity (Santoro, Bray, & Warren, 2012). Thus, it is possible that distinct neurobiological pathways sustain psychopathology in the FXpm relative to FXS, as reflected by distinct prodromal temperament profiles in infancy. The later outcome would suggest that translational efforts to monitor and prevent psychopathology in the FXpm and FXS may require distinct approaches, despite both conditions emerging from atypical *FMR1* gene function.

Methods

Participants

Participants were drawn from three longitudinal studies of infant development. Across sites, participants ($n = 70$) included 22 infants with the FXpm (8 male), 24 infants with FXS (12 male), and 24 TD controls (15 male). Participants completed one (FXpm $n = 11$, FXS $n = 8$, TD $n = 12$), two (FXpm $n = 9$, FXS $n = 10$, TD $n = 9$), or three assessments (FXpm $n = 2$, FXS $n = 6$, TD $n = 3$), generating 120 assessments across groups (FXpm $n = 35$, FXS $n = 46$, TD $n = 39$). Assessment ages ranged from 5.26 to 15.19 months. Fifteen infants with the FXpm were enrolled as part of a pilot newborn screening study for FXS (P30HD003110-S1; PI: Bailey). Details on recruitment and screening procedures can be found elsewhere (Skinner et al., 2011). The remaining participants were recruited from two longitudinal studies on FXS and the FXpm (R01MH090194 and R01MH107573; PI: Roberts).

Measures

Temperament.—Infant temperament was assessed using the Infant Behavior Questionnaire-Revised (IBQ-R; Gartstein & Rothbart, 2003), a 191-item measure in which parents rate their child's behavior over the past two weeks on a 7-point Likert-type scale (1=Never, 7=Always). Fourteen subdomains load onto three core domains: surgency, negative affect, and regulatory capacity. Scale and subscale definitions are detailed in Table 1. Internal consistency ranges from .91–.92 for core domains and .70–.90 for subdomains (Gartstein & Rothbart, 2003).

Developmental Abilities.—The Mullen Scales of Early Learning (MSEL; Mullen, 1995) is an examiner-administered developmental assessment that generates an Early Learning Composite (ELC), calculated from the fine motor, expressive language, receptive language, and visual reception domains. Internal consistency is .91 for the ELC (Mullen, 1995). We used participants' oldest available MSEL associated with temperament data due to the increased stability of developmental skill scores at older ages. No infants received standard scores at the measure floor ($SS=49$). Table 2 includes descriptive data.

Analytic Plan

Analyses were conducted using SAS 9.4. We first preliminarily examined sex effects across the sample and within each group using nonparametric Wilcoxon two-sample tests (two-tailed), collapsing across individuals. We next examined whether the FXpm and FXS were associated with atypical age-related patterns of temperament by constructing mixed effects multilevel models predicting each broad domain from group, age, and the interaction of group $\times$ age, controlling for ELC. The FXpm group was coded as the reference group in primary models, which were repeated with the TD group referenced to solicit FXS-TD contrasts. Significant group $\times$ age interactions were probed by contrasting groups separately for observations below and above the median age (10.40 months). In recognition that domain-level temperament dimensions represent subdomains that may contribute meaningful information about within- and between-group differences, as has been demonstrated in FXS (Grefer et al., 2016; Tonnsen et al., 2013), we next examined group differences in fine-grained temperament dimensions. We used pairwise nonparametric Wilcoxon two-sample tests (two-tailed), collapsing across individuals, and corrected for familywise error using the Holm-Bonferroni method. Where reported, we calculated Cohen's d as a measure of effect size using $d=Z/\sqrt{N}$ (Pallant, 2007) with $d=0.2$, 0.5 , and 0.8 representing small, medium, and large effects, respectively (Cohen, 1988).

Power.—Given our complex data structure, with varied number and spacing of assessments across individuals, we conducted an approximated sensitivity analysis in G*Power 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2007) using a series of multiple regression models that paralleled fixed effects in our mixed effects models. We generated a conservative sensitivity calculation by including one observation per participant ($n=70$), which likely underestimates true power afforded by repeated observations, as well as a liberal sensitivity estimate that included all observations without nesting ($n=122$), potentially overestimating power due to unstructured clustering. These analyses revealed 80% power to detect small to medium effects ($n=122$; $f^2=.07$; $n=70$: $f^2=.12$), corresponding to 6–10% variance in temperament outcomes (Cohen, 1988).

Results

Preliminary Analyses and Transformations.

Composite and subdomain scores were relatively normally distributed (skew and kurtosis <1.2) and were therefore not transformed. Temperament and cognitive variables were standardized ($M=0$, $SD=1$) prior to analyses, and age was centered at 10 months. Number of assessments (Kruskal-Wallis $\chi^2(2)=2.11$, $p=.348$), assessment age ($\chi^2(2)=1.82$, $p=.403$),

age at developmental testing ($X^2(2)=0.400$, $p=.819$), and sex (Fisher's $P=.010$, $p=.215$) did not differ across groups. Participants' ELC varied across groups ($X^2(2)=10.75$, $p=.005$), with lower scores in FXS than FXpm and TD groups, which did not differ from each other (Table 1). ELC also correlated with surgency ($r=.23$, $p=.01$; negative affect $r=.09$, $p=.34$; regulatory capacity $r=.07$, $p=.428$), controlling for assessment age, thus was covaried in all models.

Sex Effects.

Males and females did not differ in surgency ($Z=1.21$, $p=.225$), negative affect ($Z=0.94$, $p=.349$) or regulatory capacity ($Z=0.62$, $p=.535$). As detailed in Table 3, this pattern was maintained in FXS and the FXpm. However, males in the TD group exhibited higher surgency than females, with a small to medium effect ($d=.333$).

Model Construction.

Mixed effect models were analyzed in PROC MIXED using the Kenward-Rogers method for degrees of freedom and unstructured covariance matrices. Preliminary fit parameters suggested repeated measures of temperament clustered within individuals (intraclass correlation coefficients: surgency=.70, negative affect=.65, regulatory capacity=.49). Models specifying age as a random effect either did not improve model fit (surgency, negative affect) or failed to produce interpretable covariance estimates for slope (regulatory capacity), likely reflecting variable number of assessments per child. As such, only intercepts were modeled as random effects, and fixed effects of age are best interpreted as age-related patterns that control for nesting within participants rather than individual growth trajectories. Models with and without sex included produced similar results. Given sex effects were minimal, we excluded sex in the final models.

Broad Temperament Domains.

Primary temperament domains differed across genetic groups. Table 3 details fixed effects for each model, and Figure 1 depicts scatterplots of predicted unstandardized domain scores by group across age. The FXS group exhibited lower surgency than both TD and FXpm groups, and lower negative affect than the TD group. The group x age interaction for the FXS and TD groups approached significance ($p=.10$), with lower negative affect in FXS within the youngest half of observations (<10.40 months, Wilcoxon $Z=2.86$, two-tailed $p=.004$) but similar negative affect across FXS and TD groups in the oldest half of observations ($Z=1.28$, $p=.199$). The FXpm group also exhibited marginally lower negative affect than the TD group. Regulatory capacity did not differ across groups.

Temperament Subdomains.

Because temperament trajectories did not significantly vary across age in our primary domain-level models, we analyzed pairwise group differences using nonparametric, rank-based Wilcoxon analyses, collapsing across age and individuals (Table 1). The FXS group was generally rated lower than TD controls in surgency subdomains, with activity level, approach, vocal reactivity, and smiling and laughter retaining statistical significance after family-wise error corrections. The FXS group also exhibited lower perceptual sensitivity

than the FXpm group, with additional trends toward lower activity level, approach, vocal reactivity, and smiling and laughter in FXS. The FXpm group exhibited trends toward lower high-intensity pleasure and vocal reactivity than TD controls. Group differences in negative affect were primarily driven by lower distress to limitations in FXS relative to TD controls. Additional trends included marginally slower recovery from distress and lower fear in FXS relative to TD controls, and lower distress to limitations and sadness in FXpm relative to TD controls. Regulatory capacity subdomains did not differ by group.

Discussion

Although temperament has been studied for decades as a predictor of psychopathology in the general population, examining temperament in neurogenetic groups has unique potential to inform the genetic and biological factors that may confer risk for psychopathology in later development. The FXpm is an ideal genetic subgroup for this type of work: the condition is highly prevalent in the general population (1:209 females and 1:430 males; Tassone et al., 2012), recently has become more detectable in infancy through newborn screening programs (Tassone et al., 2012), and is associated with higher risk for a number of psychopathological outcomes (e.g. attention problems, autism, anxiety; Bailey Jr. et al., 2008) that are highly relevant to the general population. To this end, the present study provided the first known characterization of infant temperament in the FXpm contrasted to FXS and TD controls. Two major findings emerged. First, infants with the FXpm exhibited temperament features that were largely typical, yet also resembled FXS in the negative affect domain. Second, temperament features of infants with FXS consistently deviated from TD controls in both negative affect and surgency domains, even in our very young sample (5–15 months). These data suggest that *FMR1* gene mutations are associated with atypical temperament that emerges as early as infancy, particularly among infants with FXS, warranting further study of whether temperament may index emergent clinical risks in these populations.

Our findings contribute to the sparse information on early development in the FXpm, suggesting generally typical temperament in early development, although a subset of features trend toward those observed in FXS. Specifically, whereas infants with the FXpm exhibited surgency and regulatory capacity that did not statistically differ from the TD group, negative affect was marginally lower than TD controls and did not statistically differ from the FXS group. This trend toward *suppressed* negative affect in the FXpm – particularly in the domains of sadness and distress in response to environmental limitations – deviates from the general population literature, whereby problem behaviors in later development are associated with *enhanced* negative affect in early childhood (Gartstein et al., 2010). Instead, this trend is similar to the non-linear patterns of reactivity associated with maladaptive outcomes in FXS, whereby negative affect is atypically low in early childhood but elevated in school-aged children (Low Kapalu & Gartstein, 2016; Shanahan et al., 2008). Notably, this shift between suppressed and elevated reactivity in FXS is most pronounced in children with higher rates of problem behaviors; for example, children with FXS with elevated autism features have been shown to display enhanced shifts between hypo- and hyper-responsiveness, as measured by heart activity during a toy play task (Roberts, Tonnsen, Robinson, & Shinkareva, 2012). A recent study on sensory sensitivity in infants with the FXpm reported similar shifts in responsiveness (Wheeler et al., 2016), with sensory

hyporesponsivity in early childhood that increased at older ages. These findings raise a possibility that surveillance of psychopathology risk in the FXpm may necessitate a different strategy from children in the general population, as early temperament trajectories associated with psychopathology may instead resemble a similar, albeit less pronounced, non-linear profile to FXS. Further longitudinal work is critical to delineating these trajectories and their implications for clinical screening and treatment procedures.

Our findings also provide one of the first characterizations of temperament in infants with FXS, suggesting that both surgency and negative affect are atypical in infancy. In the surgency domain, infants with FXS were generally rated as less active, less likely to seek novel environmental situations, less vocally reactive, and reduced in indices of positive affect such as smiling and laughter. In the negative affect domain, we replicated previous studies suggesting negative affect is reduced low in early childhood, despite being elevated in school-aged children (Low Kapalu & Gartstein, 2016; Shanahan et al., 2008), with particularly low distress to limitations in our sample. Notably, despite lower overall levels of negative affect in young children with FXS relative to controls, previous within-group studies have reported that higher negative affect is prospectively associated with anxiety in later childhood (Tonnsen et al., 2013). Similarly, despite lower levels of surgency in our sample, higher levels of surgency are associated with attention problems in preschool and school-aged children with FXS (Grefer et al., 2016). These data further support the notion of non-linear developmental trajectories in FXS and warrant further longitudinal studies of temperament profiles in this population, particularly as children transition between infancy and early childhood periods.

Despite offering the first known characterization of temperament across these groups, our study was limited by small sample sizes that are typical to syndromic studies but limit our capacity and power to detect subtle effects that may be emerging early in development. Future studies are critical to replicating our findings in larger, longitudinal samples. It will also be important to continue to monitor the changing landscape of temperament in *FMR1*-associated mutations, with particular attention toward the association between temperament and later problem behaviors such as anxiety, autism features, and attention problems, as well as the integration of biomarkers (e.g. FMRP, CGG repeats) that may further inform mechanisms of these associations. Future work is also needed to explore whether the *lack* of sex effects observed in our FXS and FXpm groups is atypical, as only males in our TD group exhibited higher surgency relative to females, a pattern that is often reported in the literature (Else-Quest et al., 2006).

Although parent-reported temperament has proved useful in characterizing temperament and problem behaviors in FXS and other special populations, future work should also examine behavioral and physiological metrics of temperament, potentially providing more sensitive indices of the manifestation of individual differences in day-to-day life. With further replication and longitudinal extension, further study of temperament in the FXpm and FXS may inform biological mechanisms of individual differences that could be translated to more precise, targeted treatments for psychopathology and improved quality of life for affected individuals.

References

- Bailey DB, Hatton DD, Mesibov G, Ament N, & Skinner M (2000). Early development, temperament, and functional impairment in autism and fragile X syndrome. *Journal of Autism and Developmental Disorders*, 30(1), 49–59. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10819120> [PubMed: 10819120]
- Bailey DB, Raspa M, Olmsted M, Holiday DB, Bailey DB, Raspa M, ... Holiday DB (2008). Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. *American Journal of Medical Genetics. Part A*, 146A(16), 2060–9. 10.1002/ajmg.a.32439 [PubMed: 18570292]
- Cohen J (1988). *Statistical power analysis for the behavioral sciences* (Erlbaum L, Ed.) Statistical Power Analysis for the Behavioral Sciences (Vol. 2nd). Lawrence Erlbaum Associates 10.1234/12345678
- Cornish KM, Scerif G, & Karmiloff-Smith A (2007). Tracing Syndrome-Specific Trajectories of Attention Across the Lifespan. *Cortex*, 43, 672–685. [PubMed: 17710820]
- Crawford DC, Acuña JM, & Sherman SL (2001). FMR1 and the fragile X syndrome: human genome epidemiology review. *Genetics in Medicine Official Journal of the American College of Medical Genetics*, 3(5), 359–371. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11545690> [PubMed: 11545690]
- Else-Quest NM, Hyde JS, Goldsmith HH, & Van Hulle CA (2006). Gender differences in temperament: A meta-analysis. *Psychological Bulletin*, 132(1), 33–72. 10.1037/0033-2909.132.1.33 [PubMed: 16435957]
- Faul F, Erdfelder E, Lang A-G, & Buchner A (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175–191. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17695343> [PubMed: 17695343]
- Gallego PK, Burris JL, & Rivera SM (2014). Visual motion processing deficits in infants with the fragile X premutation. *Journal of Neurodevelopmental Disorders*, 6(1), 29 10.1186/1866-1955-6-29 [PubMed: 25093044]
- Gartstein M. a, Bridgett DJ, Rothbart MK, Robertson C, Iddins E, Ramsay K, & Schlect S (2010). A latent growth examination of fear development in infancy: contributions of maternal depression and the risk for toddler anxiety. *Developmental Psychology*, 46(3), 651–668. 10.1037/a0018898 [PubMed: 20438177]
- Gartstein M. a, & Rothbart M (2003). Studying infant temperament via the revised infant behavior questionnaire. *Infant Behavior and Development*, 26(1), 64–86.
- Grefer M, Flory K, Cornish K, Hatton D, & Roberts J (2016). The emergence and stability of attention deficit hyperactivity disorder in boys with fragile X syndrome. *Journal of Intellectual Disability Research: JIDR*, 60(2), 167–78. 10.1111/jir.12226 [PubMed: 26610738]
- Grigsby J, Cornish K, Hocking D, Kraan C, Olichney JM, Rivera SM, ... Yang J-C (2014). The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. *Journal of Neurodevelopmental Disorders*, 6(1), 28 10.1186/1866-1955-6-28 [PubMed: 25136377]
- Hatton DD, Bailey DB, Hargett-Beck MQ, Skinner M, & Clark RD (1999). Behavioral style of young boys with fragile X syndrome. *Developmental Medicine and Child Neurology*, 41(9), 625–32. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10503921> [PubMed: 10503921]
- Low Kapalu CM, & Gartstein MA (2016). Boys with fragile X syndrome: investigating temperament in early childhood. *Journal of Intellectual Disability Research*, 60(9), 891–900. 10.1111/jir.12304 [PubMed: 27321588]
- Pallant J (2007). *SPSS survival manual: A step-by-step guide to data analysis using SPSS version 15*. New York: McGraw Hill.
- Rapee RM, Kennedy S, Ingram M, Edwards S, & Sweeney L (2005). Prevention and early intervention of anxiety disorders in inhibited preschool children. *Journal of Consulting and Clinical Psychology*, 73(3), 488–97. 10.1037/0022-006X.73.3.488 [PubMed: 15982146]
- Roberts JE, Boccia ML, Hatton DD, Skinner ML, & Sideris J (2006). Temperament and vagal tone in boys with fragile X syndrome. *Journal of Developmental and Behavioral Pediatrics JDBP*, 27(3), 193–201. <http://doi.org/00004703-200606000-00003> [pii] [PubMed: 16775515]

- Roberts JE, Tonnsen BL, McCary LM, Caravella KE, & Shinkareva SV (2016). Brief Report: Autism Symptoms in Infants with Fragile X Syndrome. *Journal of Autism and Developmental Disorders*, 46(12), 3830–3837. 10.1007/s10803-016-2903-5 [PubMed: 27628938]
- Roberts JE, Tonnsen BL, McCary LM, Long ACJ, Golden RN, & Bailey DB (2015). Trajectory and predictors of depression and anxiety disorders in mothers with the FMR1 premutation. *Biological Psychiatry*. 10.1016/j.biopsych.2015.07.015
- Roberts JE, Tonnsen BL, Robinson A, & Shinkareva SV (2012). Heart activity and autistic behavior in infants and toddlers with fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*, 117(2), 90–102. 10.1352/1944-7558-117.2.90 [PubMed: 22515825]
- Rothbart M, & Derryberry D (1981). Development of individual differences in temperament In *Advances in developmental psychology*. (Vol. 1, pp. 37–86). Hillsdale, New Jersey: Erlbaum.
- Santoro MR, Bray SM, & Warren ST (2012). Molecular Mechanisms of Fragile X Syndrome: A Twenty-Year Perspective. *Annual Review of Pathology: Mechanisms of Disease*, 7(1), 219–245. 10.1146/annurev-pathol-011811-132457
- Shanahan M, Roberts JE, Hatton D, Reznick J, & Goldsmith H (2008). Early temperament and negative reactivity in boys with fragile X syndrome. *Journal of Intellectual Disability Research JIDR*, 52(10), 842–854. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18498331> [PubMed: 18498331]
- Tassone F, Iong KP, Tong T-H, Lo J, Gane LW, Berry-Kravis E, ... Hagerman RJ (2012). FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. *Genome Medicine*, 4(12), 100 10.1186/gm401 [PubMed: 23259642]
- Tonnsen BL, Grefer ML, Hatton DD, & Roberts JE (2014). Developmental trajectories of attentional control in preschool males with fragile X syndrome. *Research in Developmental Disabilities*, 36C, 62–71. 10.1016/j.ridd.2014.09.015 [PubMed: 25462466]
- Tonnsen BL, Malone PS, Hatton DD, & Roberts JE (2013). Early negative affect predicts anxiety, not autism, in preschool boys with fragile X syndrome. *Journal of Abnormal Child Psychology*, 41(2), 267–80. 10.1007/s10802-012-9671-2 [PubMed: 23011214]
- Wheeler AC, Bailey DB, Berry-Kravis E, Greenberg J, Losh M, Mailick M, ... Hagerman R (2014). Associated features in females with an FMR1 premutation. *Journal of Neurodevelopmental Disorders*, 6(1), 30 10.1186/1866-1955-6-30 [PubMed: 25097672]
- Wheeler AC, Sideris J, Hagerman R, Berry-Kravis E, Tassone F, Bailey DB Jr. (2016). Developmental profiles of infants with an FMR1 premutation. *Journal of Neurodevelopmental Disorders*, 8, 40 10.1186/s11689-016-9171-8 [PubMed: 27822316]

Figure 1.
Group Differences in Temperament Composites

Table 1.

IBQ-R Core Temperament Domains and Subdomains (Gartstein & Rothbart, 2003)

Domain/Subdomain	Description
Surgency	
Activity Level	Gross motor activity, including movement of arms and legs, squirming and locomotor activity.
High-Intensity Pleasure	Pleasure or enjoyment related to high stimulus intensity, rate, complexity, novelty, and incongruity.
Approach	Rapid approach, excitement, and positive anticipation of pleasurable activities.
Vocal Reactivity	Amount of vocalization exhibited by the baby in daily activities.
Perceptual Sensitivity	Detection of slight, low intensity stimuli from the external environment.
Smiling and Laughter	Smiling or laughter during general caretaking and play.
Negative Affect	
Rate of Recovery from Distress	Rate of recovery from peak distress, excitement, or general arousal; ease of falling asleep.
Fear	Startle or distress to sudden changes in stimulation, novel physical objects or social stimuli; inhibited approach to novelty.
Distress to Limitations	Fussing, crying or showing distress while (a) in a confining place or position; (b) in caretaking activities; (c) unable to perform a desired action.
Sadness	Lowered mood and activity related to personal suffering, physical state, object loss, or inability to perform a desired action; general low mood.
Regulatory Capacity	
Duration of Orienting	Attention to and/or interaction with a single object for extended periods of time.
Low-Intensity Pleasure	Amount of pleasure or enjoyment related to low stimulus intensity, rate, complexity, novelty and incongruity.
Cuddliness	Expression of enjoyment and molding of the body to being held by a caregiver.
Soothability	Reduction of fussing, crying, or distress when soothing techniques are used by the caregiver.

Table 2. Descriptive Statistics and Wilcoxon Pairwise Comparisons for Core Temperament Constructs and Covariates, Collapsing across Individuals

Assessment-Level Variable	FXS (n=46)	FXpm (n=37)	TD (n=39)	Pairwise Wilcoxon Two-Sample Tests									
				FXS vs. FXpm					TD vs. FXpm				
				Z	p	d	Z	p	d	Z	p	d	Z
Surge	4.42 (0.66)	4.86 (0.52)	5.02 (0.59)			.36			.14				
Activity Level	3.68 (0.80)	4.21 (0.92)	4.35 (1.06)	2.50	.013	.28	-0.84	.400	.10	2.89	^a .004	.32	
High-Intensity Pleasure	5.87 (0.77)	6.00 (0.49)	6.24 (0.57)	0.47	.641	.05	-1.99	.047	.23	2.19	.028	.24	
Approach	4.96 (0.94)	5.43 (0.75)	5.73 (0.66)	2.33	.020	.26	-1.75	.080	.20	3.86	^a <.001	.42	
Vocal Reactivity	4.35 (0.91)	4.69 (0.73)	5.06 (0.86)	2.00	.046	.22	-1.85	.064	.21	3.49	^a <.001	.38	
Perceptual Sensitivity	2.93 (1.23)	3.92 (1.33)	3.61 (1.37)	3.16	^a .002	.36	0.97	.332	.11	2.11	.035	.24	
Smiling and Laughter	4.49 (1.04)	4.93 (0.92)	5.07 (0.91)	2.20	.028	.24	-0.53	.596	.06	2.70	^a .007	.29	
Negative Affect	2.85 (0.61)	3.01 (0.61)	3.31 (0.68)			.09			.25			.31	
'Rate of Recovery from Distress	5.33 (0.75)	5.29 (0.77)	4.96 (0.91)	-0.15	.880	.02	1.53	.127	.18	-1.85	.064	.20	
Fear	2.21 (0.70)	2.52 (0.99)	2.63 (1.05)	1.43	.153	.16	-0.46	.645	.05	1.71	.088	.19	
Distress to Limitations	3.31 (0.89)	3.63 (0.79)	4.07 (0.99)	1.54	.124	.17	-1.81	.070	.21	3.18	^a .002	.35	
Sadness	3.20 (0.81)	3.18 (0.73)	3.51 (0.82)	-0.46	.645	.05	-1.74	.081	.20	1.54	.123	.17	
Regulatory Capacity	4.85 (0.63)	4.83 (0.53)	4.78 (0.57)			.06			.02			.09	
Duration of Orienting	3.50 (0.98)	3.14 (1.16)	3.26 (0.95)	-1.75	.081	.19	-0.80	.424	.09	-0.48	.631	.05	
Low-Intensity Pleasure	4.85 (1.06)	5.20 (0.83)	5.15 (0.86)	1.45	.147	.16	0.45	.655	.05	1.13	.258	.12	
Cuddliness	5.68 (0.77)	5.88 (0.69)	5.57 (0.91)	1.32	.187	.15	1.66	.097	.19	-0.44	.662	.05	
Soothability	5.40 (0.85)	5.15 (0.55)	5.10 (0.59)	-1.37	.172	.15	-0.28	.782	.03	-1.54	.124	.17	
Chronological Age	10.47 (2.38)	9.75 (3.19)	10.48 (2.11)	-1.10	.270	.12	-1.25	.212	.14	0.04	.968	.00	
Person-Level Variable													
				FXS vs. FXpm					TD vs. FXpm				
				Z	p	d	Z	p	d	Z	p	d	
Early Learning Composite	79.50 (22.11)	95.45 (15.34)	99.17 (11.22)	2.26	.023	.334	-1.52	.129	.224	-2.93	.003	.423	
Age of Mullen Assessment	12.36 (3.06)	10.97 (3.43)	11.61 (1.72)	-0.54	.590	.079	-0.25	.800	.037	0.47	.635	.068	

Note:

^aRejected null hypothesis of no group difference with Holm-Bonferroni correction to correct for familywise error, using original $\alpha < .05$.

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Rate of Recovery from Distress¹ is reverse-coded in Negative Affect composite.

Domain-level variables statistically compared in mixed effects models that accounted for variable nesting and age, as reported in text. Cohen's d calculated using the formula: $d = Z / (N)$ (Pallant, 2007)

Table 3.

Sex differences by group, collapsed across observations

	Surgency			Negative Affect			Regulatory Capacity								
	Male <i>M</i> (<i>SD</i>)	Female <i>M</i> (<i>SD</i>)	<i>Z</i>	<i>p</i>	<i>d</i>	Male <i>M</i> (<i>SD</i>)	Female <i>M</i> (<i>SD</i>)	<i>Z</i>	<i>p</i>	<i>d</i>					
FXS	4.47 (0.57)	4.36 (0.77)	−0.21	.833	.03	2.91 (0.60)	2.77 (0.62)	−0.81	.419	.12	4.84 (0.61)	4.86 (0.67)	0.43	.666	.06
FXpm	5.00 (0.50)	4.81 (0.53)	0.65	.517	.10	2.98 (0.62)	3.02 (0.62)	−0.55	.583	.09	5.09 (0.48)	4.73 (0.52)	1.74	.081	.29
TD	5.20 (0.52)	4.79 (0.61)	−2.08	.037	.33	3.41 (0.75)	3.18 (0.58)	−1.12	.263	.18	4.76 (0.66)	4.79 (0.42)	−0.01	.989	.00

Note: Cohen's *d* calculated using the formula: $d = Z / (N)$ (Pallant, 2007).

Table 4.

Results of Fixed Effects Models for Group Comparisons

	Surgency		Negative Affect		Regulatory Capacity	
Reference Group: FXpm	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Intercept	0.20 (0.19)	.287	0.05 (0.20)	.801	-0.03 (0.19)	.886
Age	-0.04 (0.04)	.216	0.08 (0.04)	.038	-0.13 (0.04)	.003
Group:						
FXS vs FXpm	-0.60 (0.28)	.034	-0.38 (0.29)	.198	0.26 (0.27)	.354
TD vs FXpm	0.24 (0.26)	.372	0.46 (0.28)	.098	-0.11 (0.26)	.681
Group x Age:						
FXS vs FXpm	0.06 (0.05)	.248	0.03 (0.05)	.551	0.01 (0.06)	.847
TD vs FXpm	0.02 (0.06)	.720	-0.08 (0.06)	.212	0.07 (0.07)	.340
Early Learning Composite	0.12 (0.12)	.330	-0.07 (0.13)	.579	0.19 (0.12)	.122
Reference Group: TD	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Intercept	0.44 (0.19)	.023	0.51 (0.20)	.012	-0.14 (0.19)	.476
Age	-0.02 (0.05)	.698	-0.01 (0.05)	.911	-0.06 (0.06)	.378
Group:						
FXS vs TD	-0.84 (0.28)	.004	-0.84 (0.29)	.006	0.36 (0.28)	.196
FXpm vs TD	-0.24 (0.26)	.372	-0.46 (0.28)	.098	0.11 (0.26)	.681
Group x Age:						
FXS vs TD	0.04 (0.07)	.558	0.11 (0.07)	.098	-0.06 (0.08)	.454
FXpm vs TD	-0.02 (0.06)	.720	0.08 (0.06)	.212	-0.07 (0.07)	.340
Early Learning Composite	0.12 (0.12)	.330	-0.07 (0.13)	.579	0.19 (0.12)	.122