Cynthia S. Keysor
Department of Psychiatry
Kennedy Krieger Institute
Baltimore, MD 21211 and
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
Baltimore, MD 21205

Michéle M. M. Mazzocco
Kennedy Krieger Institute
Baltimore, MD 21205
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
Baltimore, MD 21205 and
Department of Population and Family Health Sciences
Johns Hopkins University School of Public Health
Baltimore, MD 21205

Daniel R. McLeod
Rudolf Hoehn-Saric
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
Baltimore, MD 21205

Physiological Arousal in Females With Fragile X or Turner Syndrome

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ABSTRACT: *Physiological arousal was measured in 12- to 22-year-old females with either fragile X, Turner syndrome, or neither disorder to explore potential differences in the manifestation of arousal and anxiety in adolescents and young women. Physiological arousal was measured at baseline and during performance on mental arithmetic, divided attention, and risk-taking tasks. Contrary to prediction, females with fragile X rarely exhibited higher arousal than females in either the Turner syndrome or comparison groups. On the Divided Attention Task, both the fragile X and Turner syndrome groups exhibited higher arousal relative to one another based on different physiological indices. Relative to the comparison group, the fragile X group presented with a heightened state of arousal at baseline, based on mean skin conductance range, which may account for little increase in arousal on the cognitive tasks for females with fragile X. Females with Turner syndrome exhibited higher arousal relative to the comparison group on all cognitive tasks, but not for*

Correspondence to: Michéle M. M. Mazzocco
E-mail: m4mfour@hotmail.com
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Fragile X and Turner syndromes are distinct disorders with different genotypes, phenotypes, and clinical manifestations. Both involve X chromosome gene function, and there is some similarity between their respective global psychological phenotype descriptions. In particular, social skills difficulties, including heightened anxiety or difficulty dealing with anxiety, have been reported for girls with fragile X and Turner syndrome. In the present study, the nature of anxiety in each disorder is indirectly explored through studies of physiological arousal in 12- to 22-year-old females. Of interest is whether arousal levels differ across these two populations and whether these differences have implications for how anxiety in each disorder is manifested. The rationale for this research approach is discussed following a brief review of each disorder.

FRAGILE X SYNDROME

Fragile X syndrome typically results from a mutation of a single X chromosome gene, referred to as the FMR1 (fragile X mental retardation 1) gene. FMR protein production is disrupted as a consequence of this gene mutation, and it is believed that the diminished FMR protein levels lead to the clinical manifestations of fragile X syndrome (Pieretti et al., 1991). The prevalence of this disorder is approximately 1 in 4,000 males and 1 in 8,000 females (Turner, Webb, Wake, & Robinson, 1996), with males being significantly more impaired than most affected females. The majority of males with fragile X (Bailey, Hatton, & Skinner, 1998) and approximately half of females (Rousseau et al., 1994) have mental retardation. Shyness and social anxiety reported for both males and females may contribute to social skills deficits, such as avoidance of eye contact and difficulty initiating and maintaining conversation (Hagerman, 1996; Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997; Sobesky, Porter, Pennington, & Hagerman, 1995).

Symptoms of shyness and social anxiety have been retrospectively reported in females with fragile X as early as the preschool years (Freund, Reiss, & Abrams, 1993) and also in adulthood (Mazzocco, Baumgardner, Freund, & Reiss, 1998; Sobesky et al., 1995). A review of the recent literature suggests that the prevalence of anxiety disorders in this population has varied partly as a factor of methodological differences in study design (Keysor & Mazzocco, 2002. The reliability of self-report measures, used primarily with adult women with fragile X, has been questioned because high Lie-Scale scores on the Minnesota Multiphasic Personality Inventory–II (Hathaway & McKinley, 1989) suggest a tendency for these women to present themselves in a positive though unrealistic light (Sobesky, Pennington, Porter, Hull, & Hagerman, 1994; Sobesky et al., 1995). Kovar (1995) cautions that underreporting may not represent denial or unawareness of symptoms; instead, women with fragile X may be aware of their deficits without recognizing the magnitude of their impairment. Interestingly, Kovar's hypothesis parallels findings that patients with generalized anxiety disorder accurately report the direction, but not the degree, of changes in skin conductance and heart rate experienced under stress (McLeod, Hoehn-Saric, & Stefan, 1986). Viewed as a potential indicator of anxiety, physiological arousal may be a useful indicator of distress levels in this population, which could aid in identification of situations and factors associated with increased anxiety.

There is evidence that hyperarousal and hypersensitivity characterize the phenotype of fragile X syndrome, particularly for males (reviewed by Hagerman, 1996), which enhances their intolerance of physiological responses to environmental stimuli. In a preliminary study, 5- to 37-year-old males with fragile X ($N = 10$) exhibited higher tonic levels of skin conductance in response to eye contact during conversation than did males with either Down Syndrome or attention deficit hyperactivity disorder (Belser & Sudhalter, 1995). This finding suggests that arousal may underlie the social avoidant behavior of males with fragile X. Electrodermal response (EDR), an alternative measure of sympathetic nervous system (SNS) activity that measures quick, phasic responses to stimuli, was enhanced in 4- to 49-year-old males with fragile X ($N = 15$) relative to age- and gender-matched controls (Miller et al., 1999). The fragile X group exhibited heightened arousal in response to a variety of stimuli and had lower rates of habituation. An association between higher sympathetic arousal and deficient FMR protein also was reported among males

($n = 19$) and females ($n = 6$) with fragile X. This association suggests that FMR protein may affect the balance of sympathetic/parasympathetic systems, leading to an imbalance that favors greater sympathetic activity (Miller et al., 1999). However, in more recent studies involving young boys with fragile X ($N = 29$, range = 1–11 years), no such association was found between FMR protein levels and heart rate measures (Roberts, Boccia, Bailey, Hatton, & Skinner, 2001). Hyperarousal in this population may be explained less by enhanced sympathetic activity and more by decreased parasympathetic activity (Boccia & Roberts, 2000). When heart period measures in young boys with fragile X ($N = 20$, mean = 4.03 years) were recorded during alternating passive or cognitive tasks, boys with fragile X recorded different patterns of arousal regulation across experimental phases, with a shorter heart period (i.e., faster heart rate) but lower vagal tone relative to chronologically age-matched peers. The latter is indicative of a less active parasympathetic system and thus decreased ability to regulate behavior (Boccia & Roberts, 2000). Considered together, these findings suggest that measures of physiological arousal may be useful for understanding autonomic nervous system function and its association with anxiety behaviors in both males and females with fragile X syndrome, possibly including shyness and social anxiety. To date, these associations are unclear.

TURNER SYNDROME

Turner syndrome results from the partial or complete absence of the second X chromosome that is present in normal female development. It occurs predominantly in females, with a prevalence of approximately 1 in 2,000 to 1 in 5,000 live female births (Hook & Warburton, 1983). Its physical phenotype is associated, at least in part, with deficiencies in growth hormone and estrogen (Hall & Gilchrist, 1990), and these deficiencies appear associated with aspects of the psychological phenotype (Ross, Roeltgen, Feuillan, Kushner, & Cutler, 1998, 2000). Turner syndrome leads to a lowering of global intellectual scores, but mental retardation in females with Turner syndrome is no more frequent than in the general population. Social skills deficits have been implicated as a component of the psychological phenotype, particularly with respect to poor peer relationships and low self-esteem (McCauley, Feuillan, Kushner, & Ross, 2001; McCauley, Ross, Kushner, & Cutler, 1995; McCauley, Sybert, & Ehrhardt, 1986; Rovet & Ireland, 1994).

Although significant psychopathology has not been implicated in Turner syndrome, Mambelli et al. (1996) have suggested that girls with Turner syndrome may have difficulty dealing with anxiety. In a recent study using self-report measures (McCauley et al., 2001), 13- to 18-year-old girls with Turner syndrome rated themselves as slightly less anxious on the Revised Children's Manifest Anxiety Scale (Reynolds & Richmond, 1978) than girls in a comparison group, yet they also had higher Lie-Scale scores suggestive of inaccurate self-reporting. This response pattern raises questions about the reliability of self-report based assessments of anxiety in females with Turner syndrome. With no known studies of physiological arousal in females with Turner syndrome, the present research measures arousal as a potential indicator of anxiety in this population.

ANXIETY, AROUSAL, AND PSYCHOPHYSIOLOGY

Anxiety has been defined as "an unpleasant subjective experience of tension, apprehension, or anticipation, imposed by the expectation of danger or distress or the need for a special effort" (Kelly, Brown, & Shaffer, 1970, p. 429). It also has been described as "a complex phenomenon that includes heightened arousal, increased muscular and autonomic tonus, as well as cognitive efforts to conceptualize its apparent cause" (Hoehn-Saric, Hazlett, Pourmotabbed, & McLeod, 1997, p. 49). Physiologically, anxiety is associated with increased blood flow in the muscles and decreased blood flow in the skin (Blair, Glover, Greenfield, & Roddie, 1959), with various stimuli having differential effects on the sympathetic impulses that are discharged in the skin and muscle nerves (Gellhorn, 1965). For example, mental stress such as experienced on a mental arithmetic task results in greater sympathetic activity in the skin than within the muscles (Steptoe, 1987). Heart rate is expected to become higher and more stabile under stress compared to normal resting conditions (Porges & Raskin, 1969).

Nonanxious individuals may experience a heightened physiological response to novel situations, but they generally return to a lower autonomic state earlier, and habituate more quickly, than do individuals with anxiety disorders; variation in this pattern depends on the nature of the stimuli and type of anxiety disorder (Hoehn-Saric & McLeod, 1988). Among individuals with anxiety disorders, heightened physiological arousal is not necessarily associated with self-reports of increased anxiety. This response pattern was found for adult patients with various anxiety disorders when measures were taken at rest (Hofmann, Newman, Ehlers, & Roth, 1995; Kelly et al., 1970; McLeod, Hoehn-Saric, Zimmerli, de Souza, & Oliver, 1990; Tyrer, Lee, & Alexander, 1980) and during performance on a mental arithmetic task (Kelly et al., 1970).

In children, cardiac measures have often been used as indicators of arousal in response to stressful situations. In one longitudinal study, extremely low or high scores on assessment classified 21-month-olds as either inhibited or uninhibited (Garcia-Coll, Kagan, & Reznick, 1984). Inhibited children were consistently shy, quiet, and timid, and compared to uninhibited children, they had higher but more variable heart rates on an information-processing task. Reassessment 1 month later found that 68% of the inhibited children retained this classification; their heart rate remained higher, but became more stabile than that of uninhibited children on the cognitive task. The inhibited children with high and stabile heart rates (vs. high and variable) were those most likely to maintain their inhibited status when reassessed at age 4 years (Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984) and at the final assessment at age 7.5 years (Kagan, Reznick, & Snidman, 1988). The authors hypothesized that the ‘‘stress circuits’’ of inhibited children may be more easily excitable, although it was unclear whether their heightened arousal was a chronic condition or a specific acute response to unfamiliarity, potential harm, or a challenging cognitive task (Reznick et al., 1986).

Others have measured cardiac vagal tone, as indexed by respiratory sinus arrhythmia (RSA), in infants and children, emphasizing the potential impact of parasympathetic nervous system (PNS) function on arousal states. In some individuals, the PNS may be compromised, resulting in disruption of the regulation of homeostatic function. Porges (1992) suggested that cardiac vagal tone may be a reliable indicator of PNS tone, with lower vagal tone reflecting less variability in RSA and thus, less ability for physiologic self-regulation in the event of stress; this in turn negatively impacts one’s ability to organize behavioral responses. Consistent with this model, Porges (1992) found that, as a group, high-risk neonates had significantly lower vagal tone than full-term babies. This also was true in a longitudinal study of very low birth weight (VLBW) neonates for whom lower cardiac vagal tone also predicted poorer social competence at age 3 years (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997). By age 8 years, greater social competence in the VLBW group was best predicted by greater maturation of RSA, measured as the difference in RSA from 33 to 35 weeks’ gestational age. The authors suggest that the degree of RSA maturation may be a useful physiological marker of neural maturation and may be useful in the early identification of children at risk for later social behavior problems (Doussard-Roosevelt, McClenny, & Porges, 2001).

The purpose of the present study was to determine if adolescent and young adult females with fragile X or Turner syndrome differ in level of physiological arousal, and whether these differences have potential implications for how anxiety is manifested in each disorder. Females in either the fragile X or Turner syndrome group, and those with neither disorder in the comparison group, were assessed on several physiological measures of arousal and on the self-report Subjective Units of Distress Scale (SUDS). These assessments occurred following initial and task-interim baseline periods and during performance on each of three cognitive tasks believed to induce stress. It was hypothesized that physiological measures would reflect higher levels of arousal in the fragile X group relative to the Turner Syndrome or comparison groups because the evidence for heightened anxiety is stronger in the fragile X literature than in studies of Turner syndrome. Similarly, higher SUDS ratings also were predicted for the fragile X group relative to the Turner or comparison groups. For both the Turner and fragile X groups, SUDS ratings were not expected to correlate with measures of physiological arousal.

METHOD

Participants

The two primary participant groups included females with fragile X ($n = 13$) or Turner syndrome ($n = 11$). Females with neither disorder comprised the comparison group ($n = 14$). The 38 participants were drawn from a larger study of cognitive and behavioral phenotypes of fragile X and Turner syndrome. Those included in the present study were over 12 years of age because human subjects approval for the procedures described later were approved only for this older age group.

The three groups of females were well matched on age. Those in the fragile X group were 13 to 22 years old (mean $= 16.50 \pm 3.1$ years) who were identified by DNA analysis to have the full mutation. Participants in the Turner syndrome group were 12 to 20 years of age (mean $= 16.70 \pm 3.1$ years), and the comparison group participants ranged from 12 to 17 years of age (mean $= 14.96 \pm 1.7$ years). Scores on a measure of global intelligence differed across the groups, with females in the fragile X group scoring lower than the remaining two groups. Girls with fragile X had IQ scores between 59 and 125 (mean FSIQ $= 88.5 \pm 17.4$), participants in the Turner group had IQ scores between 65 and 126 (mean FSIQ = 96.5 ± 18.0), and the comparison group participants had IQ scores between 79 to 133 (mean FSIQ = 108.9 ± 15.9). These IQ score means and ranges indicate that the participants in the present study were representative of the populations from which they were drawn.

Participants were recruited through fragile X or Turner syndrome newsletters and through pediatric and endocrinology clinics at the Johns Hopkins University School of Medicine, Kennedy Krieger Institute, and Thomas Jefferson University. The comparison group included unaffected siblings of children who participated in other concurrent studies of genetic or behavioral phenotypes that were conducted at the Kennedy Krieger Institute Learning Disabilities Research Center. All participants under the age of 18 years were accompanied by parents who gave informed consent. Participants over 18 years of age gave informed consent, and for lower functioning participants over 18, parental consent also was obtained. Participants who were unable to refrain from taking medications were excluded from the study due to the potential confound with assessing physiological arousal.

Measures

Psychomotor Performance Tasks. Psychomotor performance tasks were chosen to examine physiological changes as a result of engaging in stressful cognitive tasks. All tasks were presented by an Apple II Plus microcomputer. The computer monitor was within a comfortable distance of the subject, and a numeric keypad was placed in the subject's lap. The psychomotor performance battery included the Mental Arithmetic Task, the Divided Attention Task, and the Risk-Taking Task, each of which required approximately 5 minutes to complete.

The Mental Arithmetic Task presented the participant with three one-digit numbers: one on the left, one in the center, and one on the right of the computer monitor screen. The participant's goal was to add the three numbers mentally, without the use of a calculator or pen and paper. To indicate completion of the mental arithmetic task, participants pressed the center key ("2") on a numeric keypad. The participant was then asked to select the correct answer from among three given choices by pressing the left, center, or right key, corresponding to "1," "2," or "3," respectively. For each of the first three correct answers, the participant earned 20 points per answer. The number of points earned after these first three correct trials increased by 10 for every additional two correct answers. All points were lost if four mistakes were made in a row. A message then was displayed informing the participant of this loss and urging the individual to try harder. After each answer, the remaining time was displayed along with the number correct thus far and the point value of the next correct answer. This information remained on the screen until the next answer was chosen. The number of problems attempted, the number correct, and percent accuracy were measured. Individuals whose percent accuracy was the same may have differed in the number of correct responses. This would suggest that participants who achieved a higher number of correct answers worked more quickly than individuals who answered fewer problems correctly.

The Divided Attention Task (McLeod, Hoehn-Saric, Labib, & Greenblatt, 1988) included both divided attention and reaction time components. A sequence of numbers, centrally located, was presented on the monitor screen. When one number left the screen, another number was presented. Following the appearance of the number "5," the participant had to determine whether the number presented immediately afterward was a number greater than five. Additionally, participants were instructed to press a key as soon as possible each time a "0" appeared in the sequence. The number of correct hits (detecting "0"), misses (failing to detect "0"), and percent accuracy were measured.

On the Risk-Taking Task (McLeod et al., 1988), participants could lose or gain points depending on their response. A left-key response ("1") accumulated points and increased the width of a green bar on the computer monitor screen. A right key response ("3") saved trial points to a cumulative task total, thus ending a given trial. With a probability of 0.05, any left-key response could produce a red bar signaling that twice the number of points accumulated from that particular trial would be subtracted from the cumulative task total. To assess risk-taking behavior, the number of left-key presses prior to a right-key press that saved the trial points was measured.

Psychophysiological Measures. The laboratory examinations included measures of skin conductance, gastrocnemius electromyographic (GEMG) activity, heart rate, and cardiac vagal tone. Skin conductance measures of interest were mean skin conductance; skin conductance range, reflecting the difference between the largest and smallest within-subject skin conductance values; and skin conductance fluctuations, which reflect the frequency of change in direction of skin conductance over time. Skin conductance fluctuations provide a good measure of lability. Lader, Gelder, and Marks (1967) found that the number of spontaneous fluctuations in skin conductance differed among patients with different anxiety disorders. All measures were recorded during initial and task-interim periods of rest, and during performance on the Mental Arithmetic, Divided Attention, and Risk-Taking Tasks described previously. With the exception of cardiac vagal tone, all physiological measures were expected to increase in response to heightened arousal.

All measures were recorded, amplified, and converted from analog to digital form for all subjects using a Coulborn Instruments Lablinc Interface System (Lehigh Valley, PA), a Modular Instruments Processing Center (Malvern, PA), and a Zytek 386 Tower Computer (Zytek Engineering, Inc., Baltimore, MD). Skin conductance was recorded by placing electrodes (silver/silver chloride, 1 cm in diameter) on the volar surfaces of the index and middle fingers (middle segments) of the nondominant hand and was monitored by means of a constant voltage electrodermograph. The electrode paste was prepared from a neutral ointment cream (Unibase, Park-Davis Co., Morris Plains, NJ) and saline according to the procedure suggested by Fowles et al. (1981). GEMG activity (in mV) was assessed following standard preparation of the skin and electrode placement (silver/silver chloride, 15 mm in diameter) over the right gastrocnemius muscle. To obtain a measure (in ms) of heart interbeat interval (IBI), disposable electrodes were placed on the right and left chest and on the right and left abdomen. The EKG lead that best displayed the T wave and the onset of the QRS complex was used. All physiological data were sampled at a rate of 350 times per second. Data were collected through the serial interface and stored by the Modular Instruments software for later analysis. All signals were amplified, decoded, and averaged by the microcomputer.

The amplitude of RSA was quantified to assess cardiac vagal tone. RSA reflects the functional effects of the cardiac vagal efferent activity at the level of the heart. To obtain a measure of cardiac vagal tone, each series of sequential IBIs was estimated for successive 500-ms windows and analyzed by computer programs created in accordance with methods developed by Porges (1985). More details on this procedure can be found in McLeod, Hoehn-Saric, Porges, and Zimmerli (1992).

Procedure

Testing was conducted in the morning, beginning at approximately 9:00 a.m., to control for diurnal variations that may have confounded the data. Participants had been advised to have a light breakfast without caffeine-containing beverages. Participants were directed to sit in a comfortable, reclining chair in an air-conditioned room kept in constant dim illumination. Electrodes were then attached in the manner described earlier.

The baseline resting period lasted 15 minutes, with physiological measures recorded during the last 5 minutes. After the initial baseline rest period, participants performed the Mental Arithmetic Task, the Divided Attention Task, and then the Risk-Taking Task. Each task lasted approximately 5 minutes and was preceded by its own 15-minute baseline period. The small sample size of the study prevented systematic variation of task order. For this reason, the order of tasks was held constant for all participants so that order effects would not confound the results of group differences, if found. We chose an order consistent with that used in previous studies of anxiety correlates conducted in our physiological laboratory (D.R.M., R.H.-S.). Physiological measures were recorded throughout the duration of each of the cognitive tasks, but only during the last 5 minutes of each baseline period. Participants were asked to rate themselves on the SUDS, an analog rating scale, at the end of each baseline period and after completion of each of the three cognitive tasks. This scale is a thermometerlike illustration of states ranging from 0 (*fully relaxed*) to 100 (*highly anxious*). On this scale, the participants mark their level of anxiety experienced at a current time.

RESULTS

The primary variables of interest included both performance and physiological outcome variables. These variables were examined for possible main effects of group status (Turner, fragile X, or comparison group). Possible statistical interaction between task order and diagnostic group could not be determined from the present preliminary study. However, main effects that did emerge differentiated physiological response patterns between the three diagnostic groups, as indicated in Table 1. When main effects were indicated for a variable, all three possible pairwise post hoc comparisons were carried out. In view of the small sample sizes, normality of data could be neither assumed nor statistically examined. Therefore, nonparametric comparisons were used. All analyses were unpaired, corresponding to the research design. Thus, Kruskal-Wallis statistics were used to test for possible main effects of group. All Kruskal-Wallis results carried out were based on more than five observations per sample; therefore, post hoc paired comparisons were based on Mann–Whitney U tests. Means and standard deviations for measures associated with performance on the cognitive tasks appear in Table 1; Table 2 presents

Table 1. Mean (+*SD*) Values for Performance Measures on Cognitive Tasks by Group

	Group		
Task	Fragile X Syndrome	Turner Syndrome	Comparison
Mental arithmetic			
# Attempted	30.62 (10.65)	33.82 (8.48)	39.57 (10.11)
# Correct	25.08 (12.71)	28.91 (12.17)	37.29 (10.52)
%Accuracy	0.82 (0.28)[a]	0.83 (0.29)	0.93 (0.07)
Divided attention			
# 0 Hits	6.43 (0.43)	6.42 (0.67)	6.59 (0.39)
# 0 Omissions	0.85 (0.56)	0.84 (0.63)	0.61 (0.31)
%Accuracy	0.89 (0.07)	0.88 (0.09)	0.92 (0.04)
Risk-taking			
Risk escape response	8.50 (7.17)	14.54 (7.70)[a,b]	8.21 (2.88)

[a]Significantly different from comparison group, $p < .02$. [b]Significantly different from fragile X group, $p < .02$.

means and standard deviations for physiological measures.

Kruskal Wallis analyses showed main effects for several physiological and performance variables of interest, during the initial baseline and during administration of all three tasks. For baseline and all experimental tasks, cardiac vagal tone, as reflected by RSA, and the ratings on the SUDS failed to show a main

Table 2. Mean (+*SD*) Values of Physiological Arousal at Initial Baseline and for Each Task

	Group		
Arousal Index	Fragile X Syndrome	Turner Syndrome	Comparison
Mean skin conductance			
Baseline	6.12 (4.57)	6.28 (4.66)	3.95 (4.35)
Mental arithmetic	7.17 (4.17)	10.33 (5.00)[a]	6.08 (4.30)
Divided attention	6.60 (4.14)	11.76 (5.34)[a,b]	6.45 (4.34)
Risk-taking	6.14 (4.54)	9.94 (6.11)	7.29 (4.76)
Skin conductance range			
Baseline	3.59 (3.02)[a]	3.13 (3.97)	0.88 (0.99)
Mental arithmetic	4.08 (1.8–)	4.89 (2.73)	3.60 (2.32)
Divided attention	4.16 (2.09)	4.30 (1.85)	3.48 (2.57)
Risk-taking	3.74 (2.45)	2.96 (1.84)	3.14 (2.00)
Skin conductance fluctuation			
Baseline	21.92 (20.39)	14.00 (12.99)	9.21 (14.25)
Mental arithmetic	31.15 (16.72)	41.36 (20.47)[a]	19.14 (13.76)
Divided attention	26.62 (13.70)	60.46 (22.95)[a,b]	19.93 (11.91)
Risk-taking	22.23 (17.93)	34.09 (23.78)	28.21 (16.78)
Heart IBI			
Baseline	770.95 (110.5)	741.90 (120.3)	855.90 (144.5)
Mental arithmetic	756.39 (114.8)	701.83 (114.4)[a]	805.08 (117.3)
Divided attention	784.30 (112.0)	709.12 (120.1)[a]	840.83 (108.7)
Risk-taking	806.02 (115.2)	727.56 (122.6)[a]	839.94 (100.8)
Gastrocnemius EMG			
Baseline	4.27 (1.83)	3.29 (1.37)	4.64 (2.17)
Mental arithmetic	4.21 (1.31)	3.65 (1.69)	4.43 (2.45)
Divided attention	4.23 (1.28)	3.21 (1.29)[a,b]	4.26 (1.57)
Risk-taking	5.57 (2.39)	3.79 (1.48)	4.95 (2.09)

[a]Significantly different from the Comparison group, $p < .05$. [b]Significantly different from the fragile X group, $p < .05$.

effect of group or any significant pairwise comparison. Therefore, cardiac vagal tone and SUDS ratings are not reported.

Initial Baseline Measures

During initial baseline, skin conductance range differed as a function of group ($H = 6.69$, $p < .04$). Post hoc Mann–Whitney comparisons revealed that girls with fragile X had a significantly higher mean skin conductance range than girls in the comparison group ($U = 42.0$, $p < .02$). Although girls with Turner syndrome also had higher mean skin conductance range scores than girls in the comparison group, this difference was not statistically significant ($U = 42.0$, $p = .055$). Girls with fragile X or Turner syndrome did not differ from each other on this measure ($p = .58$). During baseline, the groups did not differ significantly on any other physiological measures.

Mental Arithmetic Task

On the Mental Arithmetic Task, there was no significant difference across the three groups in the number of problems attempted ($p > .064$) whereas accuracy of problems attempted did differ across groups ($p < .03$). Girls with fragile X had lower accuracy than the control group ($U = 37.0$, $p < .01$); no other significant performance differences were found.

With respect to psychophysiological measures obtained during the Mental Arithmetic Task, there was a significant group difference only for skin conductance fluctuations ($H = 8.23$, $p < .02$). No other main effects were reported for the remaining psychophysiological measures on this task. However, in view of apparent trends noted (see Table 2), additional post hoc analyses were carried out. There were no significant differences between the fragile X and comparison groups on any measures (ps $> .23$). However, relative to girls in the comparison group, girls with Turner syndrome had a shorter heart IBI ($U = 40.0$, $p < .05$), higher mean skin conductance ($U = 36.0$, $p < .03$), and greater skin conductance fluctuations ($U = 28.0$, $p < .01$). There were no significant differences between girls in the fragile X and Turner syndrome groups on these measures.

Divided Attention Task

No significant group differences were found on the Divided Attention Task for the number of hits ($H = .79$, $p = .67$), omissions ($H = 1.45$, $p = .48$), or the percent accuracy ($H = .92$, $p = .63$).

During the Divided Attention Task, there were significant differences among four of the psychophysiological measures. Mean GEMG measures, heart IBI, and skin conductance fluctuations differed as a function of group ($p < .03$), as did mean skin conductance ($p < .001$). No significant differences on these four measures were observed between girls in the fragile X and comparison groups ($p > .30$). When compared to girls in the comparison group, girls with Turner syndrome had significantly lower mean GEMG ratings ($U = 36.5$, $p < .03$), significantly shorter heart IBI ($U = 25.0$, $p < .01$), and markedly higher skin conductance mean and fluctuations ($U = 30$, $p < .02$ and $U = 11.0$, $p < .001$, respectively). Relative to girls with Turner syndrome, girls with fragile X had higher mean GEMG ($U = 33.0$, $p < .03$), markedly fewer skin conductance fluctuations ($U = 14.0$, $p < .001$), and lower mean skin conductance values ($U = 33.0$, $p < .03$).

Risk-Taking Task

The Risk Taking Task yielded several significant main effects, including a significant group difference in the rate of risk escape responses ($H = 9.85$, $p < .01$). The fragile X and comparison groups did not differ on escape response rate ($p = .52$). Girls with Turner syndrome had a significantly higher risk escape mean score than did either the fragile X or comparison groups ($U = 25.0$ and 27.0, respectively, ps $< .01$).

When psychophysiological measures during the risk task were examined, group differences emerged for mean GEMG value ($H = 6.18$, $p < .05$) and heart IBI ($H = 7.49$, $p < .03$). No post hoc comparisons of the fragile X and comparison groups were statistically significant. Girls with Turner syndrome had a shorter mean IBI than those in the comparison group ($U = 27.0$, $p < .01$).

Correlational Analyses

Nonparametric correlations were conducted, within each group, to examine the magnitude and significance of associations between degree of psychophysiological arousal, the SUDS, and performance accuracy (Tables 3 & 4). Only significant correlations at $p < .05$ are reported in the tables due to the large number of correlations performed. For this reason, the correlations reported also should be interpreted with caution, as none were statistically significant when adjusted by a Bonferroni correction. In Table 3, significant correlations at $p < .05$ occurred most frequently for the comparison group. Longer heart IBI was associated with a greater number of correct responses ($\rho = 61$,

Table 3. Spearman Rank Correlations of Cognitive Performance Measures With Physiological Indices of Arousal and the SUDS, by Group and Task

Task	Comparison Group
Mental arithmetic	
	Heart IBI
#Correct	$\rho = .61$
	$p = .028$
Accuracy	$\rho = .55$
	$p = .046$
Risk-taking	
	Heart IBI
Risk escape	$\rho = -.66$
Response	$p = .018$
Mental arithmetic	Turner Syndrome
	Mean Skin Conductance
#Attempted	$\rho = -.67$
	$p = .035$

$p = .028$) and greater accuracy ($\rho = .55$, $p = .046$) on the Mental Arithmetic Task, and with fewer risk escape responses on the Risk-Taking Task ($\rho = -.66$, $p = .018$). For girls with Turner syndrome, heightened mean skin conductance was associated with fewer attempted problems on the Mental Arithmetic Task ($\rho = -.67$, $p = .035$). No significant correlations between the SUDS and performance measures were found for the fragile X group.

Table 4. Spearman Rank Correlations of SUDS With Measures of Physiological Arousal at Initial Baseline and Following Each Cognitive Task

Baseline—significant for girls with Turner syndrome only	
	SUDS
Heart IBI	$\rho = -.66$
	$p = .037$
Mental arithmetic—significant for comparison group only	
	SUDS
Mean skin conductance	$\rho = -.69$
	$p = .013$
Skin conductance fluctuation	$\rho = -.66$
	$p = .018$
Divided attention—significant for comparison group only	
	SUDS
GEMG	$\rho = .56$
	$p = .045$
Risk-taking—significant for girls with fragile X syndrome only	
	SUDS
GEMG	$\rho = -.58$
	$p = .045$

Note. SUDS = Subjective Units of Distress Scale; GEMG = gastrocnemius electromyographic.

In Table 4, correlations between the SUDS ratings and measures of psychophysiological arousal are reported, with no evidence of a consistent pattern for group or task. Again, the reported findings may be spurious and should be interpreted with caution. At initial baseline, only girls with Turner syndrome reported heightened self-perceived distress in association with shorter heart IBI ($\rho = -.66$, $p = .037$). No other associations between the SUDS and physiological arousal were found for girls with Turner syndrome at baseline or for any of the cognitive tasks. On the Mental Arithmetic Task, girls in the comparison group reported *higher* levels of perceived distress in association with *lower* mean skin conductance ($\rho = -.69$, $p = .013$) and *fewer* fluctuations in skin conductance ($\rho = -.66$, $p = .018$). Thus, the SUDS ratings were inconsistent in direction with the level of recorded arousal on the Mental Arithmetic Task. On the Divided Attention Task, girls in the comparison group did report heightened levels of distress in association with increased GEMG activity ($\rho = .56$, $p = .045$). No other significant associations for the comparison group were found. Finally, girls with fragile X reported *greater* distress in relation to *decreased* GEMG activity only on the Risk-Taking Task ($\rho = -.58$, $p = .045$); no other significant associations between the SUDS and measures of arousal were found for this group.

In summary, these findings reveal indicators of higher arousal in girls with fragile X or Turner syndrome, although to varying degrees and different in pattern. Girls with fragile X showed higher arousal at initial baseline, relative to the comparison group, but only with respect to mean range in skin conductance. During the Mental Arithmetic Task, girls with fragile X had lower performance accuracy, but did not manifest more arousal than did girls in the comparison group. In contrast, girls with Turner syndrome manifested signs of higher arousal than did the girls in the comparison group; although not significantly less accurate, their overall accuracy was lower than that seen in the comparison group. Similarly, on the Divided Attention Task, girls with fragile X had poorer performance, but girls with Turner syndrome demonstrated more indices of arousal. On the Risk-Taking Task, girls with Turner syndrome showed the highest degree of risk taking and higher indices of arousal based on heart IBI. Overall, relative to girls in the comparison group, girls with Turner syndrome recorded significantly higher levels of arousal on several different indices while girls with fragile X recorded higher physiological activity only at initial baseline and on a measure that did not indicate heightened arousal for girls with Turner syndrome at any phase of the procedure.

DISCUSSION

The aim of this study was to assess whether there are group differences in levels of psychophysiological arousal recorded for females with fragile X or Turner syndrome, or females with neither disorder, and whether these differences have potential implications for the manifestation of anxiety in each of these X chromosome gene disorders.

Fragile X Versus Turner Syndrome

The hypothesis that physiological arousal would be significantly higher for females with fragile X than those with Turner syndrome received little support. Significantly higher mean GEMG activity on the Divided Attention Task was the only incidence of girls with fragile X recording higher arousal than girls with Turner syndrome. On this same task, measures of mean skin conductance and fluctuations indicated higher arousal levels for girls with Turner syndrome, relative to those with fragile X. Thus, both groups experienced heightened arousal on the Divided Attention Task, although higher arousal was demonstrated by different physiological indices. Given that different regions of the SNS can be stimulated, resulting in potentially different patterns of physiological activity (Gellhorn, 1965), it is possible that either the nature of the stimulus associated with arousal in each group differed, or the nature of the stimulus was the same for both groups but different regions of the SNS were stimulated.

Fragile X Versus Comparison Group

In addition to a lack of difference between the fragile X and Turner syndrome groups, there was little difference in physiological arousal between girls with fragile X and those in the comparison group. *Only at initial baseline did girls with fragile X present with significantly higher arousal than girls in the comparison group, based on the mean skin conductance range.* The heightened state of arousal for females with fragile X at rest may explain why they recorded little increase in arousal on the cognitive tasks, relative to the increase recorded by females in either the Turner syndrome or comparison groups. This result parallels the hypothesis that adult patients with anxiety showed less of an increase in physiological activity on a Mental Arithmetic Task, compared to those in a comparison group, because of their state of heightened arousal at rest (Kelly et al., 1970).

The heightened arousal at baseline in females with fragile X is consistent with several other sets of findings. Preliminary evidence suggests abnormal hypothalamic–pituitary–adrenal (HPA) function in children with fragile X. Normal cortisol diurnal patterns reflect gradual and steady decreases in cortisol levels throughout the day, excepting increases during stressful situations (Stansbury & Gunnar, 1994). In a small sample of 8 males and 7 females with fragile X, cortical levels did decline throughout the day, although mean cortisol levels were higher relative to normative data during the middle and late part of the day (Wisbeck et al., 2000). These data were reported with parametric procedures, and thus may have been subject to outlier effects; regardless, they are consistent with our hypothesis of a higher baseline level of arousal in females with fragile X syndrome. Similarly, heightened arousal, based on mean skin conductance, was found in males with fragile X relative to males with Down Syndrome during conditions that involved participants either having or not having eye contact during a conversation. Although males with fragile X were less aroused during the condition with no eye contact, their heightened state of arousal under both conditions suggests that hyperarousal may be related to fragile X independent of associated developmental delays (Belser & Sudhalter, 1995). Further support of this is found in Cohen (1995), who reported higher arousal and less tolerance to environmental stimuli in males with both fragile X and autism compared to males with autism who do not have fragile X, and in Roberts et al. (2001), who reported a high baseline heart rate among young boys with fragile X.

Turner Syndrome Versus Comparison Group

Contrary to our prediction, girls with Turner syndrome recorded significantly higher levels of arousal than girls in the comparison group during all cognitive tasks, but not consistently on the same physiological indices nor for the initial resting assessment. Differences in arousal levels were found on the Mental Arithmetic and Divided Attention Tasks, on which girls with Turner syndrome recorded significantly higher mean skin conductance and greater skin conductance fluctuations than girls in the comparison group. These differences are not sustained on the Risk-Taking Task; in fact, scores indicate that girls with Turner syndrome experience a decrease in arousal level based on these measures. Although the scores do not return to the initial resting values, the decline may suggest that girls with Turner syndrome were beginning to habituate to the procedure in general.

Heightened arousal in females with Turner syndrome on the cognitive tasks generates interesting questions about the extent to which arousal is moderated by positive or negative self-concept, or associated perhaps with cognitive difficulties such as attention deficits. School problems were reported more frequently in 5- to 14-year-old girls with Turner syndrome than for those in the comparison group (McCauley et al., 1995), with school problems resulting in low self-concept regarding intellectual and school status for both preadolescent and adolescent girls with Turner syndrome (McCauley, Ito, & Kay, 1986). Thus, females with cognitive deficits or low self-concept may perceive themselves to have less ability to perform a task or actually experience greater difficulty while performing a task, resulting in increased distress that is communicated through a state of heightened arousal. Similarly, attention problems also have been reported to occur more frequently in preadolescent and adolescent girls with Turner syndrome than in girls in a comparison group (Lesniak-Karpiak, Mazzocco, & Ross, in press; McCauley et al., 2001; McCauley, Kay, Ito, & Treder, 1987). Perhaps females with Turner syndrome who have attention difficulties feel more anxious on effortful cognitive tasks that require concentration. Although the females with Turner syndrome in the present study did not perform worse than those in either the fragile X or comparison groups, it is possible that their anxiety, reflected by their heightened arousal, was related to their perceived ability to perform, and this may have interfered with a potentially stronger performance. Further research is necessary to better understand the association between arousal, cognitive deficits, and self-concept in this population.

Physiological Measures and Self-Reports

The lack of any group differences on the SUDS suggests that the level of perceived distress was similar for all groups at rest and following completion of each task. Across all groups, few correlations between the SUDS and measures of physiological arousal were significant, consistent with past studies that have found little to no association between some measures of physiological arousal and self-ratings of anxiety (Hofman et al., 1995; Kelly et al., 1970; McLeod et al., 1990; Tyrer et al., 1980). Of the few significant associations to emerge, there were instances when heightened arousal correlated *negatively* with increased levels of distress, similar to the findings of McLeod et al. (1990).

Several possibilities could explain the lack of significant association between the SUDS and the various physiological indices of arousal. First, it may be that girls with fragile X really do not feel particularly distressed, but simply have a higher resting state of arousal by nature. Their sensitivity to feeling distressed is therefore tempered by a chronic state of arousal such that they have a higher threshold before perceiving themselves as feeling distressed. Second, girls in any group may indeed feel distressed, but are unable to accurately convey their level of distress or anxiety on a measure such as the SUDS. Third, physiological measures are objective in nature and thus not influenced by cognitive variables that may be impacting one's ratings on the SUDS. For example, to perceive oneself as anxious or distressed, there is a cognitive component of awareness and labeling that must factor into the equation. Although one may exhibit symptoms of nervousness or distress and thus appear anxious to an observer, the person in question may not acknowledge or be aware of those behaviors, or may simply attribute them to feelings other than anxiety.

Limitations of the Study

The limitations of this study are linked to our sample size, the instruments we used, and the lack of available normative data. The small sample size for each group may have prevented detection of more subtle differences in arousal. Together, the small sample size and wide age range among participants prohibited assessment of potential developmental effects in arousal, within or between the groups examined, and this may have minimized findings that are more pronounced within a narrower age range. Fortunately, the groups were well matched on age, and thus age was unlikely to be a confound in our between-groups findings. The small sample of girls with Turner syndrome prevented examination of whether arousal levels differ as a function of estrogen levels or as a function of age at which hormonal treatments typically administered to girls with Turner syndrome were initiated. Significantly larger groups of participants, within the full age range employed in the present study, are necessary to diminish these limitations. With respect to the measures used in the study, two limitations are noteworthy. Although our participants included children, heart activity for detecting vagal tone was estimated based on an adult range; it was not adjusted for younger-aged participants because this was the first study in our laboratory to include children. In addition, children and adults were both included in the cohort, and we chose to maintain consistent techniques across all participants. In future studies, calculation of more discreet units of measurement may prove useful for detecting differences in regulation in children. The second potentially limiting measure is the SUDS, a nonstandardized instrument that may have prevented participants from adequately reporting subjective states of distress. The SUDS allows a wide range of responses and has a limited structure. Finally, it was not possible to assess performance of the fragile X and Turner samples relative to normal variation in the general population. Although our comparison group addressed this need, it was limited to a small group of females. Currently, there is no published report of normative arousal responses to the tasks used in this study, on the adolescent group we examined, from which to examine Age × Diagnosis interactions. These limitations prevent generalization of the findings, but they do not diminish their importance as preliminary evidence for arousal differences in these disorders. Moreover, the findings to emerge from this study are consistent with other preliminary data on arousal systems in fragile X syndrome and with reports on social characteristics of each disorder.

Conclusions and Future Directions

The results from this study provide a foundation for continued exploration of arousal in fragile X and Turner syndrome populations. The finding that girls with fragile X exhibited heightened arousal at rest provokes the question of whether their arousal is an acute or a chronic state. If chronic, one could predict that girls with fragile X are desensitized to feeling anxious, and that such a feeling would be the "norm" for this group and thus more difficult to self-detect. This would influence their accuracy in self-reports of anxiety, as has been suggested by Sobesky et al. (1994) and Kovar (1995). Alternatively, heightened arousal at rest for females with fragile X may have been impacted by the presence of the examiner, more so than for girls in the other groups. With respect to females with Turner syndrome, the findings reveal a normal state of arousal at rest, and arousal level increases on the first two cognitive tasks which are most pronounced by mean fluctuations in skin conductance. Although decreased arousal is recorded by completion of the final task, the findings suggest that females with Turner syndrome may experience anxiety on cognitive tasks. It is unclear to what extent heightened arousal is associated with the specific tasks or with task order. Heightened arousal in females with Turner syndrome did not differentiate their actual performance level on any tasks, relative to the remaining groups, but the extent to which arousal interfered with a stronger performance remains unknown. It would be interesting to explore the association between arousal on cognitive tasks and degree of poor self-esteem, as has been reported for this syndrome (McCauley et al., 2001).

Continued investigation of arousal, under conditions likely to induce social anxiety, would contribute to our understanding of physiological arousal and anxiety in girls with fragile X or Turner syndrome. Exploring the relation between FMR protein and arousal also may prove helpful in understanding arousal states and their impact on girls with fragile X, as would studies of arousal levels as a function of estrogen treatment in females with Turner syndrome. Finally, arousal level should be systematically examined in relation to social difficulties specific to each disorder, as understanding these potential associations may have important implication for social skills intervention for girls with fragile X or Turner syndrome.

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