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Electrodermal Responses to Sensory Stimuli in Individuals With Fragile X Syndrome: A Preliminary Report

L.J. Miller,[1]* D.N. McIntosh,[2] J. McGrath,[3] V. Shyu,[2] M. Lampe,[4] A.K. Taylor,[5] F. Tassone,[5] K. Neitzel,[4] T. Stackhouse,[2] and R.J. Hagerman[1]

[1]*Department of Pediatrics, University of Colorado Health Sciences Center, Denver, Colorado*
[2]*Department of Psychology, University of Denver, Denver, Colorado*
[3]*The Sensory Integration Research Center, The Children's Hospital, Denver, Colorado*
[4]*The Fragile X Treatment & Research Center, The Children's Hospital, Denver, Colorado*
[5]*Kimball Genetics, Denver, Colorado*

The fragile X mutation and fragile X syndrome are associated with hyperarousal, hyperactivity, aggression, and anxiety. These may be related to strong reactions to auditory, tactile, visual, and olfactory stimuli [Hagerman, 1996b; Hagerman and Cronister, 1996]. However, almost no data exist describing hyperarousal and sensory sensitivity in individuals with the fragile X mutation. This study establishes a reliable laboratory paradigm for examining reactions to sensory stimuli. We found the pattern of electrodermal responses (EDRs) to stimulation in one sensory modality predicted the pattern of EDRs in four other sensory systems. In addition, the EDR pattern of individuals with the fragile X mutation was related to their FMR-protein expression. Finally, EDRs in individuals with fragile X syndrome were significantly different from those of normal controls, demonstrating greater magnitude, more responses per stimulation, responses on a greater proportion of trials, and lower rates of habituation. The findings support the theory that individuals with fragile X syndrome have a physiologically based enhancement of reactions to sensations. Because electrodermal activity indexes sympathetic nervous system activity, the data suggest that the overarousal to sensation may involve the sympathetic system. Am. J. Med. Genet. 83:268–279, 1999. © 1999 Wiley-Liss, Inc.

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INTRODUCTION

The fragile X mutation not only causes mental retardation and learning disabilities, it also causes behavior problems including hyperarousal, hyperactivity, aggression, anxiety, and extreme sensitivity to sensory stimuli [Hagerman, 1996b]. Medications that decrease anxiety and hyperarousal are often useful in the treatment of anxiety and aggression in fragile X syndrome [Hagerman, 1996a]. The shyness and social anxiety seen in females with the full mutation [Freund et al., 1993; Sobesky et al., 1995] may be secondary to hyperarousal.

Hyperarousal may be related to strong reactions to sensory stimuli such as noises, touch, visual, and olfactory stimuli [Hagerman and Cronister, 1996]. Frequently, parents of individuals with fragile X syndrome describe autistic-like behaviors in their children in reaction to sensory stimulation [Hagerman, 1996b]. The approach/withdrawal behaviors seen in fragile X syndrome may occur as a result of sensory reactivity [Cohen, 1995; Cohen et al., 1991].

Sensitivity to visual stimuli or visual avoidance is a problem in over 90% of males with the fragile X mutation, presenting even in high functioning, nonretarded males [Merenstein et al., 1996]. Avoidance is observed in greeting behaviors, such as turning eyes and body away while shaking hands [Wolff et al., 1989]. This visual avoidance is different from the continuous lack of eye contact seen in autistic males and may be a manifestation of sensory sensitivity in response to eye contact [Cohen et al., 1989]. Bregman et al. [1988] suggest that the poor eye contact in fragile X syndrome relates to anxiety, and Belser and Sudhalter [1995] suggest links among poor eye contact, hyperarousal, and anxiety.

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*Correspondence to: Dr. Lucy Jane Miller, UCHSC Research Office, 1901 West Littleton Boulevard, Littleton, CO 80120-2058.

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Scharfenaker et al. [1996] note that individuals with fragile X syndrome display adverse reactions to other sensory stimuli as well. For example, tactile defensiveness, an avoidance or negative response to typically neutral tactile stimuli [Ayres, 1964; Baranek et al., 1997b], is a hallmark feature of fragile X syndrome and is included on the fragile X checklist [Hagerman et al., 1991]. Tactile defensiveness is thought to be a manifestation of general sensory defensiveness [Royeen and Lane, 1991], defined as avoidant, aversive, or negative responses to typically neutral sensory stimuli across modalities [Kinnealey et al., 1995]. Indeed, recent research supports a construct of multi-modal sensory defensiveness [Baranek et al., 1997a].

We believe that the construct of sensory defensiveness is useful in understanding the behaviors of individuals with the fragile X mutation. However, despite the wide acceptance of this construct among occupational therapists and others, theoretical specification and empirical verification is needed to validate the phenomenon. With notable exceptions [Baranek et al., 1997a, 1997b; Kinnealey et al., 1995], previous theory and research on sensory defensiveness has been based on statistical inference from test scores rather than on data from controlled laboratory paradigms. A necessary first step in examining sensory responsiveness in individuals with the fragile X mutation is to establish whether generalized sensory defensiveness (i.e., hyperresponsiveness across sensory modalities) occurs in these individuals.

Hyperarousal, Electrodermal Activity, and Fragile X Syndrome

Although patients with fragile X syndrome clinically demonstrate hyperarousal, little experimental work evaluating and describing the phenomenon exists. Isolating and studying arousal phenomena with a controlled laboratory procedure will assist in understanding their underlying causes. For example, difficulties in modulating arousal could be because of problems associated with the sympathetic nervous system, the parasympathetic nervous system, or both.

One way to quantify individuals' responses to stimuli is assessing electrodermal activity. Eccrine sweat gland activity makes the skin more electrically conductive and results in electrodermal changes. Because these glands are innervated by cholinergic fibers of the sympathetic nervous system (SNS), measuring skin conductance indirectly assesses SNS activity [Andreassi, 1989; Dawson et al., 1990; Fowles, 1986]. Electrodermal activity changes in the presence of startling or threatening stimuli, aggressive or defensive feelings [Fowles, 1986], and during positive or negative emotional events [Andreassi, 1989]. Individuals who have atypical responses to stimuli may demonstrate electrodermal activity that diverges from normal patterns.

Electrodermal activity includes two variables. First is skin conductance level (SCL), the slow, tonic changes measured across many discrete stimuli. Second are electrodermal responses (EDR) related to specific stimuli; these are quick, phasic changes imposed on shifts in tonic level in conductivity [Fowles, 1986].

Atypical electrodermal activity marks unusual responses to stimuli in several clinical groups. Hyporesponsiveness, a decreased amplitude of electrodermal responses (EDR) to stimuli, occurs in individuals with Down syndrome who have lower amplitude EDRs than do controls [Clausen et al., 1976; Martinez-Selva et al., 1995; Wallace and Fehr, 1970]. Many individuals with schizophrenia demonstrate either low responses or nonresponses, with nonresponses more prevalent with greater symptomotology [Kim et al., 1993]. Individuals with ADHD also demonstrate hyporesponsiveness [Fowles and Furuseth, 1994; Satterfield and Dawson, 1971]. Habituation, the reduction or cessation of response with repeated stimulation, is faster than normal in individuals with ADHD [Rosenthal and Allen, 1978] and conduct disorder [Zahn and Kruesi, 1993].

In contrast to the dominant pattern of hypoarousal in many groups, children with autism show evidence of mixed hypoarousal and hyperarousal. They have shown larger initial responses [Bernal and Miller, 1970] and higher arousal [Stevens and Gruzelier, 1984] than is normal. Van Engeland [1984] demonstrated that although individuals with autism were more often nonresponsive than were controls, when they did respond the amplitude in the autistic group exceeded the normal control group.

The dominant pattern among clinical groups is low EDR, with the exception of autism. Only one study has examined reactivity in individuals with fragile X syndrome. In this comparative study, Belser and Sudhalter [1995] found that two males with fragile X syndrome had higher skin conductance levels (SCL) during conversations involving eye contact than did a male with ADHD and a male with Down syndrome [Belser and Sudhalter, 1995]. These data suggest that individuals with fragile X syndrome, like those with autism, will demonstrate hyper-reactivity.

Belser and Sudhalter's [1995] seminal work shows enhanced electrodermal activity and thus heightened sympathetic arousal among individuals with fragile X syndrome. Replication is needed because they measured tonic levels of skin conductance, which may be more influenced by changes in skin hydration than by changes in sympathetic activity [Fowles, 1986]. An alternative index of SNS activity is EDR, the phasic changes in conductance. EDR is less influenced by hydration changes. An additional benefit of measuring EDR is that doing so extends Belser and Sudhalter's work by allowing evaluation of specific responses to each separate stimulus. Measuring only SCL makes such specific reactions unavailable for analysis.

In this study, we explore physiological measurement of responses to a standard presentation of multiple sensations. We examine phasic responses to stimuli (EDR), rather than changes in tonic levels (SCL), and we develop a replicable sensory stimulation paradigm measuring five modalities of sensory stimulation.

We have three research questions. First, what is the relation among reactions to sensory stimuli in different modalities? We hypothesize that there will be high correlations of responses across the sensory systems. Second, is there an association between FMR1 protein (FMRP) expression and EDR after sensory stimula-

tion? Because FMRP expression is related to degree of symptomotology (i.e., IQ) (Tassone F, Hagerman RJ, Ikle D, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK, submitted), we hypothesize that FMRP levels will be related to abnormal EDRs after sensory stimulation. Third, do EDRs after sensation discriminate between males with fragile X syndrome and normal controls? Based on clinical evidence of hyperarousal and sensitivity to sensory stimulation, we hypothesize that individuals with fragile X syndrome will demonstrate higher magnitudes, more responses, and slower habituation to stimulation than normal controls.

MATERIALS AND METHODS

Participants

All participants were seen at The Fragile X Treatment & Research Center and The Sensory Integration Treatment and Research Center at The Children's Hospital in Denver, Colorado. Group A was the clinical sample used to address question 1 (regarding the relation among reactions in various sensory modalities) and question 2 (regarding the association between FMRP and EDR). Group A includes 25 individuals (19 male, 6 female) with the fragile X mutation, the diagnosis of which is confirmed by molecular studies. Table I describes the group A participants. In this sample, 68% were treated with medications (including three on stimulants, 10 on a selective serotonin reuptake inhibitor, and two on anticonvulsants).

Group B was the clinical sample used for the third question (whether males with fragile X syndrome and normal controls show differing EDRs). It included only the 15 males with fragile X syndrome. Four males were removed from the larger group A clinical sample because they had the fragile X mutation but did not have fragile X syndrome. None of the four had the physical phenotype. Two had the premutation, one had greater than 80% of the gene unmethylated, and one had the premutation in greater than 80% of cells. Seventy-three percent of participants in this subsample were on medications. Table II describes the group B clinical sample.

The control participants (n = 25 for group A and a subset, n = 15 for group B) were referred by staff and faculty at The Children's Hospital and the University of Colorado Health Sciences Center in Denver, Colorado. Participants were screened for developmental normality based on parent report and were excluded if they had significant birth risk factors or any educational or medical disorders. All controls had normal intelligence and demonstrated age-appropriate behavior. They were age- and gender- matched to participants with the fragile X mutation.

Procedures

Sensory challenge protocol. To gauge individuals' responses to sensory stimulation, we created a laboratory paradigm, the Sensory Challenge Protocol, during which experimenters presented sensory stimulation while electrodermal activity was recorded continuously. Experimenters were blind to the condition of the participants, including their cytogenetic and DNA results, except as they might surmise from observation. The instructions below are written as if a child were being tested. For adults, the instructions are similar, although caretakers rather than their parents usually accompanied adults with developmental disabilities. Normal control adults were usually unaccompanied.

Introduction. The experimenter greeted the child in the waiting room and told the child that she/he is going to go on a pretend "space ship" trip. (Parents were told on the phone to prepare the child for this "fun time.") The child was slowly and gently moved to the laboratory that is set up to represent a space ship. The setting for the protocol resembles a spaceship to improve motivation and decrease anxiety in the participants. The lights are low in the room, and we have painted two rolling shades to look like three dimensional control panels for a space ship; they are pulled down to hide two of the walls. On a third wall is a one-way mirror through which the computer operator

TABLE I. Samples for Group A: Participants With the Fragile X Mutation

	Fragile X groups				
	Males				Females
	Full mutation-full methylation	Full mutation-partial methyl.	Mosaic	Premutation	Full mutation
N	11	3	3	2	6
Age mean	21	22	22	10	12
Range	4–44	8–49	9–45	7–12	5–24
IQ mean (SD[a])	49 (14)	45	57	98	76 (17)
Range	31–74	23–63	20–103	92–104	51–95
Gene functioning	N/A[b]	36%[c]	45%[d]	N/A[e]	65%[f]
Mean range		0.04–0.81	0.19–0.84		0.40–0.79
FMRP mean	4%	21%	35%	76%	52%
Range	0–13%	12–39%	13–70%	69–83%	24–67%

[a]Standard deviation.
[b]Not applicable: all subjects fully methylated.
[c]Percent cells with an unmethylated mutation.
[d]Percent cells with a premutation.
[e]Not applicable: all subjects unmethylated.
[f]The percent of cells with the normal *FMRI* gene on the active X chromosome (activation ratio).

TABLE II. Sample for Group B: Participants With Fragile X Syndrome

	Full mutation-full methylation	Full mutation-partial methylation	Mosaic
N	11	2	2
Age mean	21	29	27
Range	4–44	8–49	9–45
IQ mean (SD[a])	49 (14)	36	34
Range	31–74	23–48	20–49
Gene functioning mean	N/A[b]	14%[c]	25%[d]
Range		0.04–0.24	0.19–0.31
FMRP mean	4%	12%	17%
Range	0–13%	12–12%	13–21%

[a]Standard deviation.
[b]Not applicable: all subjects fully methylated.
[c]Percent cell unmethylated.
[d]Percent cells with a premutation.

can observe the session and make appropriate adjustments in marking events or annotations to the record, if needed. A small wooden console painted to look like a control panel for a space ship is centered approximately 60 cm in front of the child's eyes. A hole in the console enables the child to see the screen of a 13" video monitor and the strobe light. The setting and procedures seemed quite effective in eliciting cooperation and relaxation among participants.

The experimenter showed the child into the room and asked the child to seat herself/himself in a sturdy armchair placed on a 71-cm square tilt board anchored firmly on four 10-cm wooden cubes. The ambient light in the room was set at a low level throughout the sensory challenge protocol. As the experimenter attached electrodes to the child, the child watched on the monitor a section of the movie Apollo 13 depicting astronauts with electrodes attached to them. The segment is nonstimulating yet still entertaining. In addition, the segment helped the participants become involved in, interested in, and comfortable with the application of the electrodes.

Our electrodes produced minimal discomfort as they are attached with Velcro straps. The effect of placing and maintaining these electrodes on participants was minimal. During the protocol, the participants' arms rested gently on the armrests of the chair. At times, individuals with fragile X syndrome expressed concerns (e.g., excessive talking, pointing, or moving). In these instances, the administration of sensory stimuli was paused, the experimenter reiterated the need to hold still, and the computer operator inserted a comment in the data file. Most individuals complied easily; in only one instance, a three-year-old boy with fragile X syndrome, was the session terminated because of noncompliance with standard procedures.

The computer operator and experimenter communicated through headsets. If either needed to halt the proceedings or make adjustments it could be done with a minimum of disruption to the laboratory session. When the equipment had been tested and computer operator had set the child's baseline, the experimenter was signaled to begin the protocol.

There were 10 contiguous trials in each of five sensory systems administered in the following order: olfactory, auditory, visual, tactile, and vestibular. The stimuli were presented for 3 seconds each and were administered on a standard, pseudorandom schedule 15 or 19 seconds apart, with 20 seconds between each sensory modality. Presentation of all stimuli was controlled by a recorded set of instructions given to both the experimenter and the computer operator simultaneously through earphones.

The experimenter said to the child: "Now we are going to go on a pretend space ship trip. You are going to smell some funny things, hear and see some funny things, and feel some funny things. Here we go! The first thing is a smell. Can you take a big breath and smell in now?" The word "now" is timed to correspond with the first olfactory trial.

Olfactory. The olfactory stimulus is wintergreen oil, contained in a small vial with a cotton ball. The wintergreen is commercially available in the extract section of the grocery store; we used Walgreen's wintergreen oil (synthetic methyl salicylate n.f.). It was kept about 1.25 cm deep in the small vial. The experimenter wore a sterile glove and timed her movements so that as the tape said "Ready, set, go . . . " she was ready to take her thumb off the vial, and place it about 2.5 cm from the participant's nose, centered between nose and lips. Experimenter then moved the vial in a 2.5-cm path from the left to right to left (as the tape said "1 . . . 2 . . . 3 . . . " with 1 second for each excursion from side to side), and experimenter said "Smell in." She then placed her thumb over the top of the vial to try to trap any lingering odors in the bottle, and dropped the vial to her side. At the conclusion of the 10 olfactory stimuli, the experimenter turned the glove inside out to trap odors and then discarded it.

Auditory. After the 20-second wait period following olfactory stimulation, the experimenter said, "Now we are going to hear some funny things," and started a tape recorder to begin the series of presentations. A professionally recorded fire engine siren plays at 90 decibels. As with the olfactory stimuli, there were 10 stimulation events each 15 or 19 seconds from the beginning of the preceding stimulation event.

Visual. After the 20-second wait period following auditory stimulation, the experimenter said, "Now we are going to see some funny things." A commercially available 20-watt strobe light was set at 10 flashes per second and built into the space ship console slightly

below eye level. The strobe was attached to an Able-Net Incorporated power link to enable the experimenter to turn the strobe on and off as directed by the audiotape using a foot pedal. The strobe is on for 3 seconds and then remains off until the next trial.

Tactile. After the 20-second wait period following visual stimulation, the experimenter said, "Now we are going to feel some funny things." The "Mr. Thumbuddy," a cloth finger puppet with a 5-cm feather attached to his hat, from the Miller Assessment for Preschoolers [Miller, 1988, 1982] was used as the tactile stimulus. The experimenter gently placed the feather on the participant's right ear canal, then gently drew the feather along chin line to bottom of chin, and finally raised the feather to the child's left ear. Each movement was timed to correspond with the "1 . . . 2 . . . 3" on the audio-tape.

Vestibular. After the 20-second wait period following tactile stimulation, the experimenter said, "Now we are going to feel some different funny things." The participant's chair was resting on the top surface of a "tilt board" supported by a 10-cm cube at each corner. The platform is a 71-cm square of plywood attached to a rotation platform (62.5 cm) available from Achievement Products, Inc. (Canton, OH). Before administering the movement stimuli, the experimenter removed the two blocks located behind the participant's seat while holding the platform steady. Then the experimenter smoothly and slowly tipped the child backwards to a 30-degree angle.

If at any point the child experienced severe discomfort or verbally indicates that she/he would not continue, the session was terminated. We made every reasonable effort to coax the child to complete the session, if possible. At the end of the session, the experimenter thanked the child and parent for participating, and the child chose a gift. The parent received a small stipend for participating.

Measurement of electrodermal responses. We recorded electrodermal activity continuously throughout the presentation of stimuli. The method generally followed procedures recommended by Fowles et al. [1981]. Autogenics 5-mm diameter electrodes were applied to the palmar surface of the distal phalanges of the second and third fingers of the right hand [Scerbo et al., 1992]. Electrodes were secured using a 0.7-cm 5-cm Velcro band. Repeated efforts by a lab assistant to create artifactual EDR readings by moving, shaking, and pressing her fingers and right hand and arm were largely ineffective. Artifacts occurred only when leads were pulled directly. As described below, in the rare cases when participant movement generated a response, a data analyst individually removed the response during the computer-aided scoring procedure. Further, to evaluate the potential frequency of movement artifact from our finger electrodes, we recorded electrodermal activity simultaneously from two sites on 10 sensory defensive participants (not used in the present study) during the sensory protocol. In addition to the site used in this study, we attached electrodes to the thenar and hypothenar surfaces of the participants' left hands. The latter were attached with adhesive collars and filled with electrode gel [Fowles et al., 1981]. The tracings were parallel, suggesting that neither our methods (finger placement, Velcro strip, and no gel) nor movement of the hand or fingers contributed to the pattern of data in the present study.

We attached the electrodes to a Coulbourn Isolated Skin Conductance Coupler (S71-23). The unit applies a constant 0.5-volt potential across each electrode pair and conditions the skin conductance signal. Because we were interested in responses to each stimulus (EDR), not in changes in the slower fluctuating tonic SCL, we used AC coupling. AC coupling automatically corrects for drifts in baseline conductance level over the extended time of the presentation of stimuli [Boucsein, 1992]. We used a low-cut filter set to 0.2 Hz; signals >0.2 Hz are passed without distortion respecting amplitude. The signals were sampled at a rate of 50 Hz, digitized, and stored on a microcomputer.

We scored the resultant data using KIDCal, a custom-written computer program. The program first establishes baseline skin conductance by examining the electrodermal readings before any stimulus presentation. It searches for the longest segment meeting three criteria. The segment must be: 1) 30 seconds long; 2) with an end-to-end slope of less than 0.01 micromhos; and 3) with no peak greater than 0.05 micromhos. If KIDCal does not find such a 30-second segment, it reduces the length of the segment by one second, in iterative runs, to a minimum baseline period of five seconds, until criteria 2 and 3 are met. Mean conductance for the data contained within that line was considered baseline for that participant. Although this results in a baseline that may be different from the zero point provided by AC coupling, in practice, there is seldom any difference between these two lines. In 12 cases, eight with the fragile X mutation and five comparisons, KIDCal was unable to locate a baseline because of variability in responsivity during collection of baseline information. For these, the analyst set the baseline to the point at which most responses bottomed out over the entire data collection period. For all participants, the analyst reviewed the entire tracing to evaluate the position of the baseline. For 3 of 25 participants with the fragile X mutation and one comparison participant, the analyst adjusted the baseline because it appeared affected by artifact within the prestimulus period. The analyst was blind to participants' group memberships.

The program then marked and recorded as EDRs peaks in electrodermal activity that were: 1) at least 0.05 micromhos in amplitude above the KIDCal baseline; 2) occurred at least 1 second after each stimulus; 3) occurred at least 0.6 seconds after a previous peak; and 4) occurred at least 0.6 seconds prior to the subsequent stimulus. Responses of less than 0.05 micromhos were not considered valid responses [Boucsein, 1992; Dawson et al., 1990].

After the program had marked all peaks meeting the above criteria, the data analyst reviewed the electrodermal tracing for the entire stimulation period. During the data collection, the computer operator had noted any unusual events in the session or dramatic movement or attempted removal of electrodes by the participants. These comments are automatically time marked and embedded in the electrodermal data file.

The data analyst compared the tracing with the comments by the computer operator. If any event or behavior resulted in artifactual responses, the analyst removed the invalid peak from the file. Five fragile X participants and one comparison participant showed artifacts in the electrodermal tracings that required removal before data analysis. The analyst coded four participants' data as errors related to removal of electrodes. We excluded from analyses any sensory domain in which responses to more than three stimuli were unsound.

We used three variables to describe electrodermal responses. We evaluated the differences in overall size and differences in changes in size over trials. Decrements in size of the variables over trials show habituation of responses with repeated stimulation. The first variable was the mean magnitude of response to each stimulus. When computing this average, we included cases of nonresponse when a response was possible (i.e., after presentation of a stimulus); therefore, we use the term magnitude to refer to this mean score [Boucsein, 1992]. When there were multiple responses to a single stimulus, we used only the amplitude of the main (largest) peak. As is usually found in skin conductance responses, our magnitude data were positively skewed and therefore required logarithmic transformation before analysis [Dawson et al., 1990; Kirk, 1982; Venables and Christie, 1980]. Because the log of 0 (a nonresponse) is undefined, we added 1 to the magnitude score before the transformation was performed.

The second variable was the number of responses to each stimulus. The number of responses was the sum of peaks 0.05 micromhos over baseline between 1 second post-stimulus and 0.6 seconds prior to the presentation of the next stimulus. We did not count peaks occurring less than 0.6 seconds after a previous peak.

The third variable was the individual's probability of responding to stimuli at each trial. We computed this variable by taking the proportion of sensory domains to which the person responded at each trail. For example, if a participant responded to the first olfactory, auditory, and visual stimuli, but not to the first tactile and vestibular stimuli, that person's proportion at trial 1 would be 0.60 (3 in 5).

We estimated the stability of the EDR data based on test-retest consistency after a one-week interval. One-tailed Pearson correlations were conducted on a subset of six participants (four participants with fragile X syndrome and two controls). All dependent measures yielded strong significant positive correlations: magnitude of responses ($r(5) = 0.94$, $P < 0.01$); number of peaks ($r(5) = 0.96$, $P < 0.001$); proportion of stimuli to which the person responded ($r(5) = 0.88$, $P < 0.01$).

Genetic studies. Molecular studies and *FMR1* studies were conducted at Kimball Genetics, Denver, Colorado to confirm the diagnosis of the fragile X mutation. FMRP immuno-cytochemistry was performed so that the relation of FMRP expression to EDR could be analyzed.

FMR1 ***DNA studies.*** DNA studies were performed on genomic DNA isolated from 5 ml of peripheral blood samples. Southern blot and polymerase chain reaction (PCR) analysis were performed on each sample [Taylor et al., 1994]. Southern blots were hybridized with the *FMR1*-specific probe, StB12.3 [Oberle et al., 1991]. PCR analysis was performed using primers 1 and 3 described by Brown [1993]. PCR products were separated by 6% denaturing polyacrylamide gel electrophoresis, transferred to nylon membrane, and hybridized with an oligonucleotide probe, (CGG)5.

A phosphorimager (Molecular Dynamics Inc.) was used to accurately quantitate the following, using ratios of the computer-quantitated signal intensity of appropriate bands from Southern blots: 1) for mosaic males with a full mutation and premutation, the percent of cells containing a premutation (termed the "percent premutation"); 2) for males with a partially methylated full mutation, the percent of cells with an unmethylated mutation; 3) for females with a full mutation, the percent of cells with the normal *FMR1* gene on the active X chromosome (termed the "activation ratio" or "AR"). These measures reflect the degree of gene functioning and they correlate strongly ($r(23) = 0.97$) with the percentage of lymphocytes expressing FMRP in this study as well as in previous research [Tassone F, Hagerman RJ, Ikle D, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK, submitted]. The means of these data for each group are described in Tables I and II.

FMRP immunocytochemistry. Immunocytochemistry was performed on blood smears made using 20 μl of peripheral blood on each microscope slide. FMRP-specific monoclonal antibody from hybridoma clone 1C3-1a [Devys et al., 1993] was used in an indirect alkaline phosphatase approach according to Willemsen [1995] and Tassone F, Hagerman RJ, Ikle D, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK, [submitted]. Slides were analyzed under the microscope, and lymphocytes were distinguished from other blood cells types by morphology. The cytoplasm appears red for FMRP-positive lymphocytes and colorless for FMRP-negative lymphocytes. For each slide, 200 lymphocytes were scored and the percent of lymphocytes expressing FMRP was determined.

RESULTS

Consistency of Responses Across Stimulus Modalities

Based on theories of sensory defensiveness, we expected participants' responses to be interrelated across stimuli modalities. To evaluate this, we computed intercorrelations and Cronbach's alpha for both the log transformed EDR magnitude and the number of EDR responses for all individuals with the fragile X mutation and normal controls ($n = 50$).

For the five sensory domains, mean EDR magnitudes were highly intercorrelated (0.69 to 0.94) as were mean number of peaks per stimulus (0.64 to 0.89). To further investigate the degree to which all sensory measures could be combined into one generalized sensory score, data from the five sensory systems were combined into a single variable for which internal consistency was evaluated (i.e., Cronbach's alpha = 0.94. and 0.92, for magnitude and number of peaks, respectively). Be-

cause the internal reliability was high, we averaged data from olfactory, auditory, visual, tactile, and vestibular domains for analyses of questions 2 (whether there is an association between FMRP and EDR after stimulation) and 3 (whether EDRs after sensation discriminate between males with fragile X syndrome and normal controls).

Relation of EDR to FMRP Expression

We hypothesize that among individuals with the fragile X mutation (n = 25), FMRP expression (percent FMRP-positive lymphocytes) would negatively correlate with each EDR variable. Because the EDR variables were moderately negatively correlated with age, we used partial correlations to control for age in these tests.

FMRP expression was significantly negatively correlated with magnitude of responses ($r(20) = -0.37$, $P < .05$, one-tailed), mean number of peaks after each stimulus ($r(21) = -0.54$, $P < 0.005$), and mean proportion of stimuli to which individuals responded ($r(21) = -0.47$, $P < 0.01$). Thus, the more FMRP expression, the more normal the EDR. We found the same pattern of correlations for the three molecular variables: percent lack of methylation, percent of cells with the premutation, and activation ratio.

Group Differences in EDR

We hypothesize that males with fragile X syndrome would demonstrate more electrodermal activity than would matched normal controls. As described above, we used a subset of the sample (15 males with fragile X syndrome and their age- and gender-matched normal controls; see Table II for sample description) to evaluate this question.

The electrodermal tracings appear different for each group. Figure 1A presents a representative graphic EDR profile of an individual from the control group following each of seven vestibular stimuli (a dark vertical line represents each stimulus). Figure 1B presents a representative EDR profile after the same number of olfactory stimuli for an individual with fragile X syndrome. In Figure 1A, lower amplitudes of EDR, one peak after each stimulus, and definite habituation (a decrease in the response to the same stimuli over time) are seen. By contrast, Figure 1B demonstrates larger amplitude of EDRs, the presence of multiple peaks, and the absence of habituation.

We used analyses of variance (ANOVAs, group by trials) to evaluate the statistical significance of group differences. Table III displays the statistical tests for each EDR variable. Figure 2A displays the mean magnitude of EDR across trials by group. The two groups differed significantly in magnitude of responses with individuals with fragile X syndrome showing larger main peaks (M = 0.09 log micromhos, SD = 0.09) than did controls (M = 0.02, SD = 0.02). There was a significant trials effect that follow-up orthogonal contrasts demonstrated was related to significant linear ($F(1, 28) = 5.0$, $P < 0.05$), and third-order ($F(1, 28) = 7.5$, $P < 0.01$) polynomial trends. Thus, the change in responses across repeated stimulation appears to include both linear and curvilinear changes. The group-by-trials interaction was not significant; thus, the repetition of stimuli affected changes in magnitude similarly in both groups.

Figure 2B displays the mean number of responses to each stimulus across trials by group. As noted in Table III, the groups differed significantly in how many EDRs were displayed after each stimulus, with the fragile X syndrome group demonstrating more responses (M = 1.7, SD = 1.0) than did the control group (M = 0.58, SD = 0.43). There was a significant effect for trials; follow-up contrasts show that the differences are described by significant linear ($F(1, 25) = 27.6$, $P < 0.001$), quadratic ($F(1, 25) = 16.3$, $P < 0.001$), third-order ($F(1, 25) = 14.0$, $P = 0.001$), and fourth-order ($F(1, 25) = 12.1$, $P < 0.01$) polynomials. The nonsignificant interaction on this variable suggests that repetition of stimuli affects changes in the number of responses similarly for the two groups.

Figure 2C displays the mean proportion of stimuli to which participants responded across trials and by group. This variable depicts the proportion of the five sensory domains to which the individuals responded at each trial. On average, controls responded to 70% of the stimuli at trial 1, whereas individuals with fragile X syndrome responded to 85% of stimuli on trial 1. By trial 8, controls responded to an average of only 25% of stimuli, whereas those with fragile X syndrome responded to 70% of the stimuli.

Table III shows that individuals with fragile X syndrome responded to a greater proportion of the stimuli (M = 0.75, SD = 0.28) than did individuals without fragile X syndrome (M = 0.38, SD = 0.26). Although repetition of stimuli had an aggregate effect on whether people responded, the significant groups-by-trials interaction modifies the main effects. People with fragile X syndrome and controls did not respond the same to repetition of stimulation. Follow-up orthogonal contrasts indicate that the pattern of differences in their responses followed significant linear ($F(1, 28) = 19.0$, $P < 0.001$), and quadratic ($F(1, 28) = 4.4$, $P < 0.05$) trends. Whereas controls decreased responding after repeated stimulation, individuals with fragile X syndrome did not cease responding to stimuli with repetition. Controls habituated more than did individuals with fragile X syndrome.

DISCUSSION

We addressed three research questions. The pattern of EDR to stimulation in one sensory modality predicted the pattern of EDR to stimulation in the other sensory systems. Males with fragile X syndrome differed significantly from controls in their pattern of EDR. Among individuals with the fragile X mutation, EDR was related to their lymphocyte levels of FMRP expression. We discuss the implications of these findings below.

Interrelation of Sensory Modalities

The strong relation among responses across sensory modalities has implications for understanding sensory processing disorders. Our data are consistent with

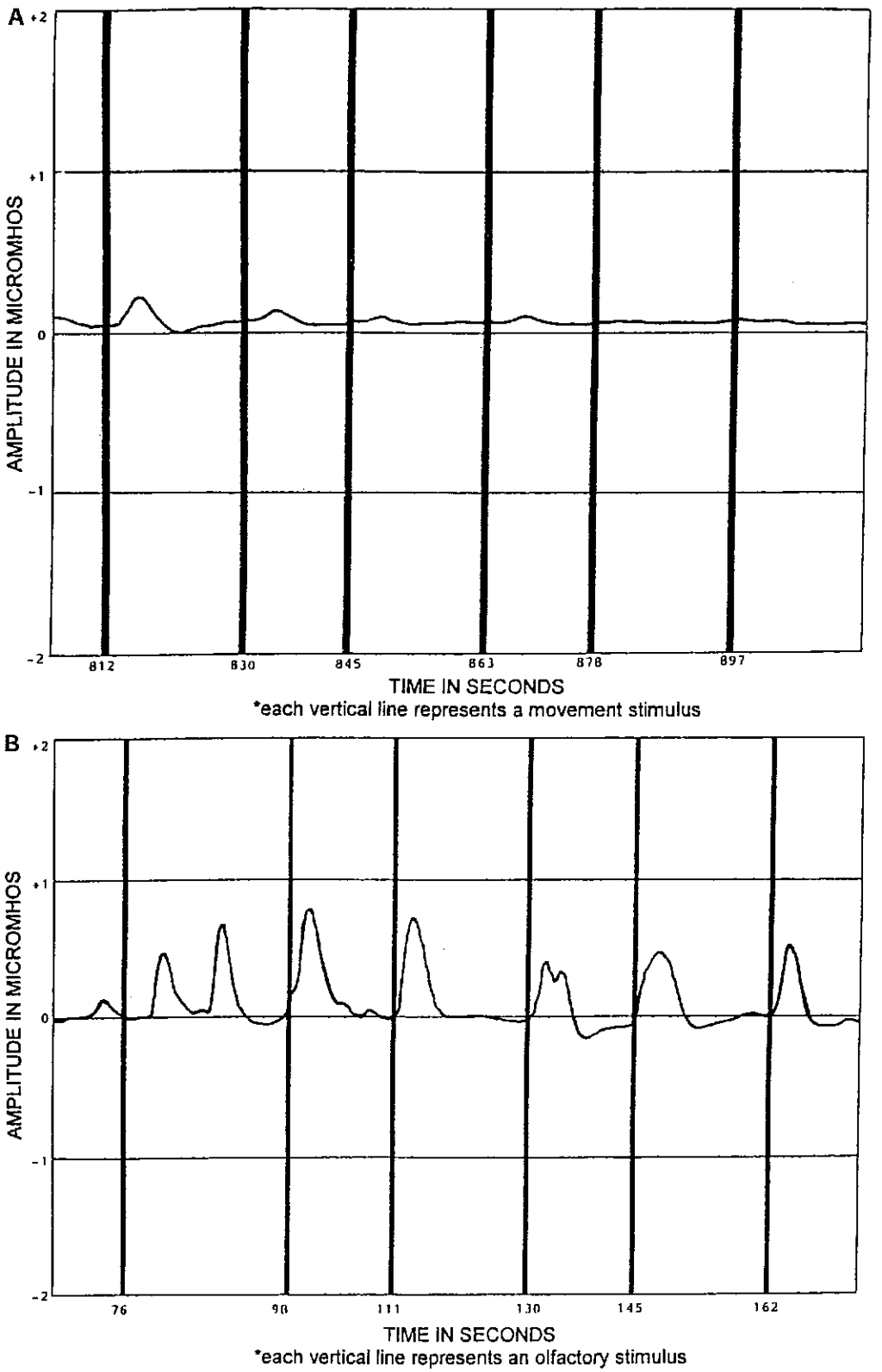

Fig. 1. Graphic profiles of responses to sensation. Amplitude is in micromhos. Black lines indicate stimulus presentation. A: Response to vestibular stimuli of a representative individual from the control group. B: Responses to olfactory stimuli of a representative individual with fragile X syndrome.

TABLE III. Results of Analysis of Variance Tests of Group by Trial Differences in Electrodermal Responses

Outcome variable	Group[a] F[b] (df[c]) P[d]	Trial F (df) P	Group by trial F (df) P
Magnitude of main peak	6.8 (1,28)*	4.5 (7,22)**	1.6 (7,22)
Number of peaks per stimulus	10.3 (1,25)**	3.6 (7,19)*	1.5 (7,22)
Proportion of trials with EDR	8.3 (1,28)***	6.1 (7.22)***	2.9 (7,22)*

[a]Group is a between-subjects variable (n = 15/group).
[b]F statistic from the Analysis of variance.
[c]Degrees of freedom used to calculate the significance of the F statistic.
[d]Statistical significance: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

theoretical work in the occupational therapy literature [Fisher and Murray, 1991] that discusses the phenomenon of multi-modal sensory defensiveness [Baranek et al., 1997a]. One of the clusters of behaviors included in the broad category of sensory integration disorders is sensory modulation disorder (SMD). Ayres [1979] theorized that modulation disorders are disruptions in the ability of the central nervous system to regulate activity. Parham and Mailloux [1996] have defined SMD as an inability to grade responses to sensation. Either over- or under-arousal related to a generalized reactivity to sensation in all sensory systems may underlie poorly regulated reactions to sensation seen in individuals with fragile X syndrome. We believe that future work specifying the sensory phenomena in fragile X syndrome will uncover valuable information about the underlying link between sensation and arousal in a variety of clinical groups (e.g., individuals with autism, ADHD).

Group Differences in Responses to Sensory Stimulation

In response to stimulation, males with fragile X syndrome displayed greater magnitude of EDR, more EDRs per stimulation, and EDRs on a greater proportion of trials than did age and gender-matched normal controls. In addition, those with fragile X syndrome showed less habituation as measured by the proportion of stimuli to which they respond. There is evidence that a lack of habituation is related to defensive reactions to stimuli, as opposed to orienting responses [Boucsein, 1992]. Thus, the lower rates of habituation among the fragile X group may indicate relatively more defensive reactions as compared with normal controls.

Our overall findings of heightened electrodermal activity agree with the findings of Belser and Sudhalter [1995]. Our findings of high levels of phasic changes in response to stimuli are consistent with and extend their data showing higher levels of tonic skin conductance in arousing situations. Given that Belser and Sudhalter [1995] evaluated only tonic levels and we tested only phasic changes, future work evaluating tonic levels and phasic reactions together would help clarify the relation between these variables in this population.

Because individuals with Down syndrome show lower than normal electrodermal activity [Clausen et al., 1976; Martinez-Selva et al., 1995; Wallace and Fehr, 1970], it is unlikely that the high levels of activity among people with fragile X syndrome is caused by mental retardation per se [Belser and Sudhalter, 1995]. The hyporesponsiveness seen in cases of ADHD [Fowles and Furuseth, 1994; Satterfield and Dawson, 1971] and schizophrenia [Kim et al., 1993] and the faster habituation seen in individuals with ADHD [Rosenthal and Allen, 1978] and conduct disorder [Zahn and Kruesi, 1993] also suggest that the hyperresponsiveness is not caused by attention or behavior problems. To confirm this distinction, we are currently examining individuals with ADHD, anxiety disorders, and mental retardation because of various causes.

Individuals with autism show EDR patterns potentially similar to those we demonstrated [Bernal and Miller, 1970; Stevens and Gruzelier, 1984; van Engeland, 1984]. Individuals with fragile X syndrome and autism may be members of a higher-order group whose clinical disorders include hyperarousal, sensory hyperreactivity, or both. Possibly, there is common dysfunction of SNS activation or sensory modulation in these two groups.

FMRP Expression and EDR

Within the group demonstrating the fragile X mutation, having higher lymphocyte FMRP levels is associated with more normal patterns of EDR. This is consistent with studies showing FMRP expression to be important in understanding fragile X syndrome [e.g., Comery et al., 1997; Tassone F, Hagerman RJ, Ikle D, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK, submitted]. Neuroanatomical studies in fragile X syndrome and neurochemical studies of the FMR1 protein (FMRP) provide hints regarding the cause of the atypical EDRs. Arbitol et al. [1993] found that FMRP is highly transcribed during fetal development in the nucleus basalis magnocellularis, which is the source of cholinergic neurons to the limbic system. A deficiency or absence of FMRP therefore may lead to an imbalance of sympathetic/parasympathetic systems with an over-responsiveness of sympathetic systems as reflected in electrodermal response.

Future Directions

Our data point to avenues of future research that could clarify and expand our findings. First, some of the patterns among individuals with fragile X syndrome were quite unusual. We were unable to tie these patterns to any particular source of artifact, and removal of participants with extreme patterns did not change the overall pattern of our results. Nonetheless, replication and extension of these findings would be

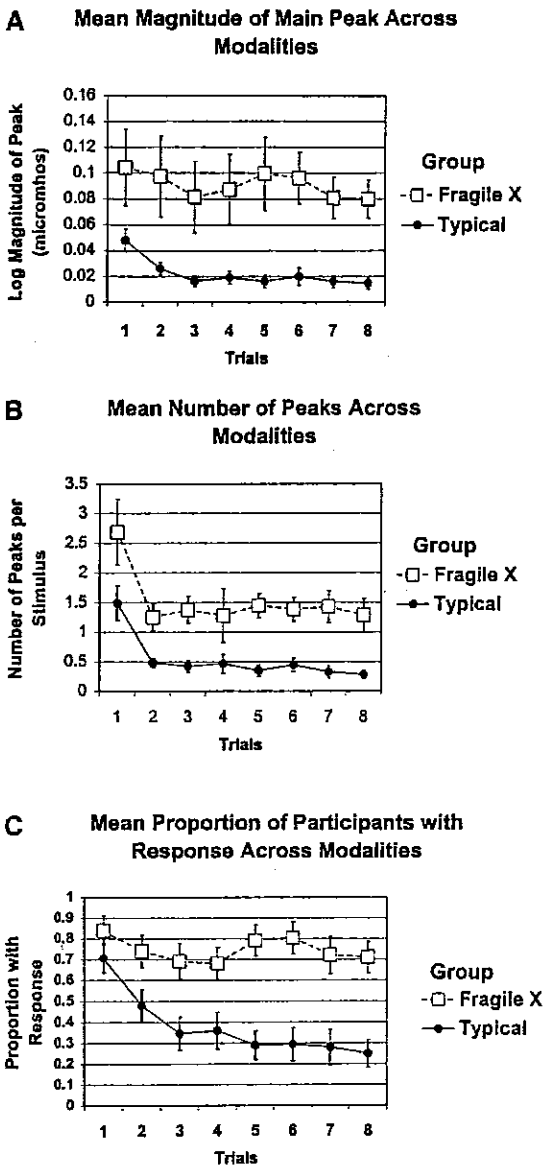

Fig. 2. Electrodermal variables describing responses to stimulation at each trial, averaged across stimulus modalities. Data are presented separately for fragile X (n = 15) and control (n = 15) participants. Bars represent plus and minus one standard error. A: Mean magnitude in $\log_{10}$ (micromhos) of responses to each trial. B: Mean number of responses to each trial. C: Mean proportion of stimuli to which participants responded at each trial.

useful. Because our window of assessment of EDR extended to 0.6 seconds before the subsequent stimulus, some of the responses among those with fragile X syndrome may be anticipatory responses to the next stimulus. However, this is not likely to explain our results for three reasons: 1) the varied interstimulus interval makes it difficult for participants to predict onset of the next stimulus; 2) the high correlation among stimulus modalities suggests that the anticipation possible with the olfactory and tactile procedures did not have a large effect; and 3) we did not count peaks from 0.6 seconds before the stimulus to 0.8 seconds after. Because there is an approximate 1-second lag between a stimulus and the resultant EDR peak, the stimulus generating the anticipatory response would have to have occurred approximately 1.5 seconds prior to the next stimulus.

The second issue to address in future work is the role of medications. Visual inspection of the data from individuals with fragile X syndrome suggests higher EDRs among of those not on medications. Subsequent research needs to examine the effects of medications directly, particularly whether specific medications alter the responses to sensory stimulation.

Third, our findings support an intrinsic and physiologically based enhancement of reactions to sensations in males with fragile X syndrome. Because electrodermal activity indexes SNS activity [Andreassi, 1989; Dawson et al., 1990; Fowles, 1986], the present data suggest that the SNS may be affected in fragile X syndrome. This information should inform future research focusing on physiological and anatomical underpinnings of abnormal responses to sensory stimulation. Early work on the anatomical substrate of EDR in the central nervous system (CNS) emphasized three central pathways: a pre-motor cortical-spinal system, a limbo-hypothalamic system, and the reticular formation [Edelberg, 1972; Fowles, 1986]. Recent investigation of the anatomical substrate in fragile X syndrome has documented enlargement of the caudate, hippocampus, and thalamus [Reiss et al., 1994, 1995]. Comery et al. [1997] study enhanced dendritic branching in *Fmr1* knockout mice, so it appears that the lack of FMR1 protein may interfere with the normal pruning process of neural connections during development. Therefore, patients with fragile X syndrome may have enhanced neuronal connectedness, and the hippocampus, which is important for behavioral arousal and inhibition, is particularly large in these patients. Perhaps the hippocampus is the main generator of hyperarousal in patients with fragile X syndrome.

Fourth, the role of anxiety needs to be examined. Clinically, increased sensory responsiveness appears to relate to the anxiety and aversive responses that occur with direct eye contact, light touch, or loud sounds. Anxiety, a core feature of fragile X syndrome, is intrinsically tied to hyperarousal [Hagerman, 1996b]. People with various types of anxiety show abnormal electrodermal activity, often including failure to habituate to stimuli [Boucsein, 1992]. Future research should explore the relations among hyperarousal, sensory sensitivity, and anxiety.

Finally, consistent with focusing on the sensory aspects of fragile X syndrome, EDRs could be used in studies of the effectiveness of sensory integration intervention, an expansion of the methods suggested by Reisman and Gross [1992].

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