Influence of Stimulants on Electrodermal Studies in Fragile X Syndrome

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ABSTRACT   Attention Deficit Hyperactivity Disorder (ADHD) is seen in the majority of children with Fragile X Syndrome (FraX). Previous work has documented an enhanced sweat response to stimuli in children with FraX compared to controls utilizing electrodermal response (EDR) measures. The present study assesses the EDRs both on and off stimulants in 19 children with ADHD and FraX compared to 17 age- and IQ-matched control patients with ADHD and developmental delays. Although the baseline EDRs were comparable between FraX patients and controls, the patients with FraX had a significant decrease in EDR amplitude and number of peaks when treated with stimulants compared to controls. This suggests that patients with FraX are more responsive to the enhancement of inhibitory systems that occur with stimulant use for ADHD. The use of a quantifiable measure, such as EDR, is recommended in future studies of treatment efficacy. *Microsc. Res. Tech. 57:168–173, 2002.*   © 2002 Wiley-Liss, Inc.

INTRODUCTION

The majority of children with fragile X syndrome (FraX) have attentional problems and hyperactivity. Hyperactivity or Attention Deficit Hyperactivity Disorder (ADHD) in boys with FraX has ranged from 70 to 100% in various studies (Baumgardner et al., 1995; Borghgraef et al., 1987; Bregman et al., 1988; Hagerman, 1996b; Turk, 1992). Girls with FraX, in contrast to boys, are less frequently hyperactive but often impulsive and inattentive. Approximately 30 to 50% of girls with FraX have ADHD (Freund et al., 1993; Hagerman et al., 1992). Approximately 65% of children with FraX and ADHD show improvement with stimulant medication (Hagerman et al., 1988), although other medications such as clonidine or even risperidone can be helpful for treatment of ADHD (Hagerman, 1996a; Hagerman et al., 1995). The cause of ADHD in FraX is unknown, but it is presumed to be related to the *FMR1* protein (FMRP) deficit causing dysfunction in dopamine or norepinephrine pathways that are important for processing information and inhibition. In children with ADHD without FraX, dysfunction of frontal and basal ganglia areas can be improved with stimulant medication that enhances neurotransmission in both dopaminergic and norepinephrine pathways (Barkley, 1997).

The FMRP deficit also causes neuroanatomical changes that lead to the behavioral and cognitive problems in FraX. Neuroanatomical studies of FraX knockout mice and patients with FraX have demonstrated enhanced dendritic branching and immature dendritic spines compared to controls (Comery et al., 1997; Greenough et al., 1999; Weiler and Greenough, 1999).

These findings suggest that FMRP is important for dendritic spine maturation, and for the normal pruning process of dendritic connections in development. Enlargement of the brain and particularly the caudate and hippocampus in patients with FraX may be related to the enhanced dendritic connections (Reiss et al., 1995; Schapiro et al., 1995).

Sensory hyperarousal is also a common behavioral feature of patients with FraX (Cohen, 1995), and it is often associated with hyperactivity and/or anxiety (Belser and Sudhalter, 1995; Cohen et al., 1989; Hagerman, 1996b). Behavior problems thought to be associated with sensory hyperarousal include avoidance behavior such as poor eye contact, turning away with greeting, tactile defensiveness or avoidance of touch, tantrum behavior, and autistic-like mannerisms such as hand flapping and hand biting when overexcited (Belser and Sudhalter, 1995; Hagerman, 1999; Wolff et al., 1989). A recent study by Miller et al. (1999) has demonstrated enhanced electrodermal responses (EDR) to sensory stimuli in boys with FraX compared to normal controls. EDR measures eccrine sweat gland activity, which makes the skin more electrically con-

TABLE 1. Fragile X Group[1]

DNA	Sex	Age	IQ-Test	Medication
Premutation	M	15	59-WISC III	Methylphenidate
Mosaic	M	5.5	79-KABC	Methylphenidate, folic acid
Mosaic	M	6.1	61-Leiter R	Methylphenidate
Mosaic	M	9	62-KABC	Methylphenidate
Mosaic	M	9.1	69-KABC	Methylphenidate, clonidine
Mosaic	M	12	66-KABC	Methylphenidate, clonidine, tegretol
Mosaic	M	15	58-WISC III	Adderall, paroxetine
Full	M	6.5	54-VIN	Adderall, clonidine
Full	M	7	64 KABC	Adderall
Full	M	7	66-KABC	Methylphenidate
Full	M	8	61-KABC	Methylphenidate
Full	M	8.5	61-VIN	Dextroamphetamine
Full	M	12	42-VIN	Methylphenidate, folic acid
Full	M	14	42-WISC III	Methylphenidate
Full	M	16	64-WISC III	Methylphenidate
Full	M	16	40-WISC III	Methylphenidate
Full	F	5.8	67-KABC	Methylphenidate, sertraline
Full	F	15	64-KABC	Dextroamphetamine, fluoxetine
Full	F	16	48-WISC III	Methylphenidate

[1]KABC, Kaufman Assessment Battery for Children; Leiter R, Leiter International Performance Scale, Revised; WISC III, Wechsler Intelligence Scales for Children, 3rd ed.; VIN, Vineland Adaptive Behavior Scales.

ductive. EDR represents quick, phasic changes that are imposed on shifts in the tonic level of conductivity (Fowles, 1986). The EDR changes reflect sympathetic activity through cholinergic fibers that innervate the eccrine sweat glands. In a group of 25 males and females with FraX, the percentage of lymphocytes that were positive for FMRP correlated inversely with the degree of abnormality in the EDR, including the amplitude and the number of peaks after each stimulus (Miller et al., 1999). These results suggest enhanced sympathetic activity in individuals with FraX compared to normal controls without FraX. A subgroup of individuals with ADHD has been hypothesized to have enhanced sympathetic or norepinephrine activity, particularly those who respond well to clonidine (Hunt et al., 1995). However, previous EDR studies in the ADHD population have demonstrated hyporesponsiveness (Fowles and Furuseth, 1994; Satterfield and Dawson, 1971) although habituation, the reduction or cessation of response with repeated stimulation, is faster than normal in ADHD (Rosenthal and Allen, 1978). Clonidine is an α_2-adrenergic presynaptic agonist that lowers norepinephrine levels at the synapse. This decreases sympathetic activity, and clonidine is used for the treatment of high blood pressure in addition to the treatment of ADHD. Approximately 80% of boys with FraX respond well to clonidine, with a decrease in hyperactivity and hyperarousal (Hagerman et al., 1995), which is consistent with the hypothesis that boys with FraX have enhanced sympathetic activity.

Studies of EDR in FraX represent an easily quantifiable measure of hyperarousal and medication effects. There is a significant need in treatment studies to have a quantifiable physiological measure of treatment effects in addition to subjective questionnaires to document behavioral improvements. Stimulants are the most common medications used to treat ADHD in children with FraX. Here, we report the effects of stimulants on EDR activity in a sample of individuals with FraX, and a matched group of control children with mental retardation and/or developmental delay.

MATERIALS AND METHODS
Subjects

There were 36 children and adolescents with ADHD ages 5–16 who participated in the study. All study participants met DSM-IV criteria for the diagnosis of ADHD (American Psychiatric Association, 1994). Our subjects were 19 individuals with ADHD and FraX (diagnosed with *FMR1* DNA testing), and 17 control individuals with ADHD and developmental delays of a variety of etiologies but negative for FraX. Individuals with developmental problems were used as controls because matching simply for ADHD would be insufficient to control for the cognitive deficit seen in individuals with FraX, which could influence EDR. Subjects were administered appropriate IQ measures for their ages and functioning levels including the Leiter International Performance Scale-Revised (Roid and Miller, 1997), the Kaufman Assessment Battery for Children (KABC) (Kaufman and Kaufman, 1983), and the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1991). For those individuals for whom a standardized intelligence scale was not available, the Vineland Adaptive Behavior Scales (Sparrow et al., 1984) composite score was used (see Table 1). A variety of IQ measures were used for data analysis as preexisting information was used from the subjects' charts. The subjects enrolled in the study were currently taking stimulant medication for attention and impulsivity problems. Methylphenidate was the most common medication with 76% use across both groups. Other medications that the subjects were taking prior to enrolling in the study were continued during the baseline and stimulant intervals. The subjects were recruited from patients seen at the Child Development Unit at The Children's Hospital in Denver, Colorado, and were enrolled in the study after informed consent was obtained from the parents and patients. The ethnic composition of the subjects was 83% Caucasian, 11% Hispanic, 3% African American, and 3% Middle Eastern.

TABLE 2. Control Group[1]

Diagnosis	Sex	Age	IQ test	Medication
Asperger	M	7.75	84-KABC	Methylphenidate
ARND	M	7	83-WISC III	Detroamphetamine
FAS	M	9	80-KABC	Methylphenidate, depakote
FAS	F	9.5	81-WISC III	Adderall, fluoxetine
Down syndrome	M	9.9	40-WISC III	Methylphenidate
Down syndrome	M	15	43-WISC III	Methylphenidate
18p partial trisomy 8	M	12	42-KABC	Methylphenidate, fluoxetine
Developmental delays	M	5	55-WPPSI-R	Methylphenidate
Developmental delays	M	6	74-WPPSI-R	Methylphenidate
Developmental delays	M	8	69-WPPSI	Adderall, fluvoxamine
Developmental delays	M	10	68-WISC III	Methylphenidate
Developmental delays	M	11	48-WISC III	Methylphenidate
Developmental delays	M	11	59-WISC III	Adderall, sertraline
Developmental delays	F	11.5	53-WISC III	Methylphenidate
Developmental delays	F	13	49-VIN	Methylphenidate, fluoxetine
Motor and language delays	M	6.5	71-Bayley	Methylphenidate
Learning disability	F	7.5	79-Binet	Dexadrine, clonidine

[1]KABC, Kaufman Assessment Battery for Children; WISC III, Wechsler Intelligence Scales for Children, 3rd ed; VIN, Vineland Adaptive Behavior Scales; Bayley, Bayley Scales of Infant Development; Binet, Stanford-Binet Intelligence Scale.

The FraX group had an age range of 5.5 to 15 years with a mean of 11.3 (SD = 4.2), and IQ scores ranging from 40 to 79 with a mean of 59.3 (SD = 10.1). Information on age, IQ, gender, DNA testing, and medications for this group is provided in Table 1. Three different stimulants were used in this study: 14 participants had methylphenidate, 2 participants had dextroamphetamine, and 3 participants had Adderall. Additional medications were used in 42% of the subjects with FraX (see Table 1).

The control group of 5 females and 12 males ranged in age from 5 to 15 years with a mean of 9.4 (SD = 2.6). The subjects within this group included 3 with fetal alcohol syndrome, 2 with Down syndrome, one with Asperger syndrome, and one with partial trisomy of chromosome 8. The remaining subjects in the control group had developmental delays or non-specific mental retardation in addition to ADHD. All of the control subjects, with one exception, were administered a standardized IQ test (KABC, WISC III, Stanford-Binet IV) with scores ranging from 40 to 84 with a mean IQ of 64.31 (SD = 15.71) (see Table 2). The two groups did not differ significantly in age or IQ ($P = .12$; $P = .26$). Methylphenidate was used by 12 of the subjects in the control group; 3 used Adderall and 2 used dextroamphetamine. Additional medications including valproate, fluoxetine, fluoxamine, and sertraline were used during the baseline and stimulant phases of the study for 35% of the control subjects.

Procedures

We used the Sensory Challenge Protocol, in which experimenters presented sensory stimuli (olfactory, auditory, visual, tactile, and vestibular), while electrodermal activity was recorded continuously (for a full description, see McIntosh et al., 1999). This protocol was developed, and has been used successfully, in individuals with FraX (Miller et al., 1999). Each stimulus was presented for 3 seconds and then repeated 10 times, 15 to 19 seconds apart in a pseudo random schedule. There was a 20-second break 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 olfactory stimulus was wintergreen oil, the auditory stimulus was a recorded fire engine siren played at 90 decibels, the visual stimulus was a 20-watt strobe light set at 10 flashes per second, the tactile stimulus was a feather attached to the cap of a finger puppet placed in the right ear canal and gently moved along the jaw and chin line, stopping in the left ear canal, and the vestibular stimulus was the tipping back of the child's chair to a 30-degree angle.

The measurement of the EDR followed procedures recommended by Fowles et al. (1981), and used previously (McIntosh et al., 1999; Miller et al., 1999). Two 5-mm diameter electrodes were applied to the thenar and hypothenar eminence of the palm of the left hand and secured with a sticky collar. The electrodes were attached to a Coulbourn Isolated Skin Conductance Coupler (S71-23). This unit applies a constant 0.5-volt potential across each electrode pair and conditions the skin's conduction signal. We used AC coupling because we were interested in the response to each stimulus (EDR), and not in the changes in the slower fluctuating tonic skin conductance level. AC coupling automatically corrects for drifts in baseline conductance level over the extended time of the presentation of stimuli (Boucsein, 1992). A low cut filter set at 0.2 Hz was utilized, and signals greater than 0.2 Hz were passed without distortion respecting amplitude. The signals were sampled at a rate of 250 Hz, digitized, and stored on a microcomputer. Next, a data analyst, blind to group membership or condition, checked the electrodermal record for movement artifact. Questionable responses were then eliminated. We utilized a refined version of a custom-written computer program that has been previously reported (McIntosh et al., 1999; Miller et al., 1999) to score the cleaned EDR records. The amplitude of the peaks was measured from the point at which the skin conductance increases sharply (i.e., baseline) to the point at which the conductance begins to fall (i.e., peak). Only peaks greater than 0.05 micromhos were considered valid (Dawson et al., 1990). Furthermore, only peaks for which the onset was between .8 and 5 seconds post-stimulus were considered valid EDR to the stimulus.

As in our previous work (McIntosh et al, 1999; Miller et al., 1999), we used three variables to describe EDR. First, we counted the number of responses to each stimulus (i.e., the sum of peaks 0.05 micromhos over baseline during the response window). Second, we evaluated the mean magnitude of the largest response to each stimulus. Third, we calculated each 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 trial (e.g., responses in 5 of the 6 = .83). The EDRs to the sensory protocol were recorded before initiating stimulant medication (baseline session), and were then repeated one hour after an oral dose of stimulant. In 32 patients, recording of EDR was done without stimulants first, and then the patient was given the stimulant medication, and the EDR was studied 1 hour after the stimulant dose was taken orally. In 4 patients, the EDR was studied first on stimulant medication 1 hour after oral dose, and the EDR without stimulants was studied the subsequent morning. The dose of stimulant medication was appropriate for weight, and was approximately 0.3 mg/Kg/dose for methylphenidate, and 0.2 mg/Kg/dose for dextroamphetamine or Adderall. Adderall is a mixture of 4 different dextro and levo amphetamine salts, which is commonly used to treat ADHD (Hagerman, 1999). See Figure 1 for a case example of EDR measures on methylphenidate.

RESULTS

First, we evaluated the degree of association among the dependent variables across subjects both on and off the target medication. The EDR variables were highly intercorrelated, with r's ranging from .71–.98. However, we report analyses for all three outcomes here, as despite their high intercorrelations, differences in results were noted.

For each outcome variable, we conducted 2 (group: FraX vs. MR control) × 2 (medications: on vs. off, within subjects) × 8 (trials: repeated measure, first through 8th presentation of stimulus) repeated measures analyses of variance (ANOVAs). Only the first 8 trials were used because our previous studies demonstrated that an increase in arousal on trials 9 and 10 related to movement of the examiner to prepare for the next sensory stimulus (Miller et al., 1999). We also conducted simple main effects analyses of the influence of medication on EDR for each group individually.

For mean number of responses to each stimulus, there was no main effect for Group or Trial, nor any significant interactions involving Trial. A main effect for medication occurred, indicating that combining across the FraX and MR control samples, medications reduced the number of responses, $F(1, 33) = 10.46, P < .005$. This effect was modified by a significant group by medication interaction, $F(1, 33) = 4.65, P < .05$. As displayed in Figure 2, this interaction suggests that medication influenced only the EDR of individuals with FraX. Indeed, follow-up simple effects analyses demonstrated that for individuals with FraX, the number of responses was significantly lower when they were on the medication than when they were not, $F(1, 17) = 12.60, P < .005$. This was not the case for the MR control group, $F(1, 16) = 0.70, P = .41$.

Male, 7 years old. Diagnosis: Fragile X Syndrome
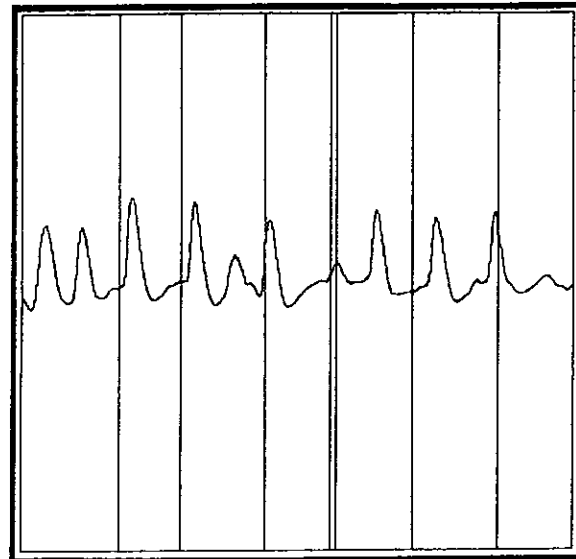
Baseline
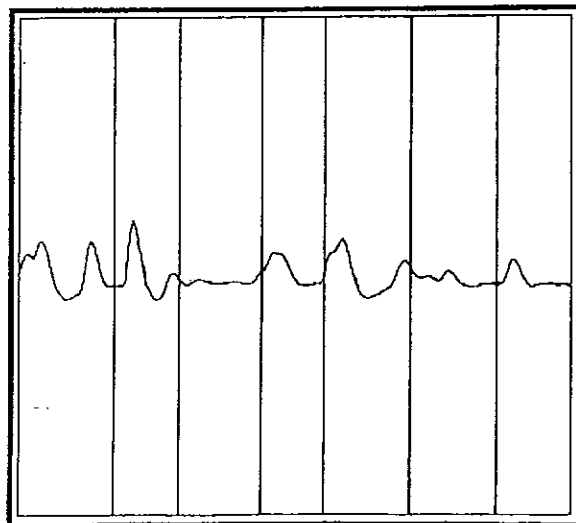
On methylphenidate

Fig. 1. The vertical lines represent a visual stimulus, and the waves represent the electrodermal response (EDR) to the stimuli. The top box is the EDR without medication, and the bottom box is the EDR 1 hour after taking oral methylphenidate, 5 mg. The patient is a 7-year-old boy with fragile X syndrome.

For magnitude of EDR, there was also a main effect for medication. This indicates that medications reduced mean magnitude of responses across the entire sample (FraX and MR control combined), $F(1, 33) = 5.28, P < .05$. There was also a main effect for Trial, indicating that responses of the combined groups changed with repetition of stimulation, $F(7, 231) = 4.92, P < .001$. No main effect of Group, or any significant interactions were displayed by the data. However, as displayed in Figure 3, a simple-effects analysis

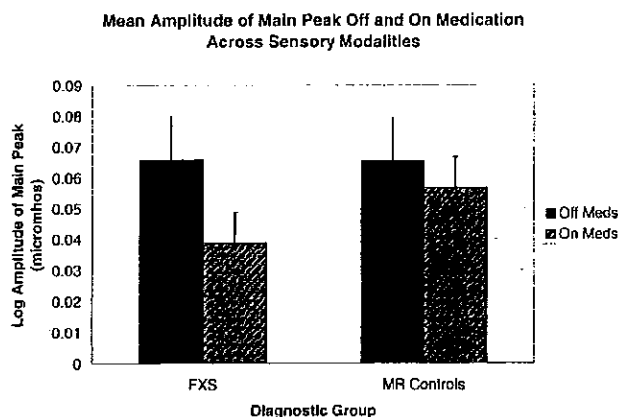**Mean Amplitude of Main Peak Off and On Medication Across Sensory Modalities**

Fig. 2. Graph of mean amplitude of main peak off and on stimulus in patients with fragile X syndrome (FXS) and controls with mental retardation (MR).

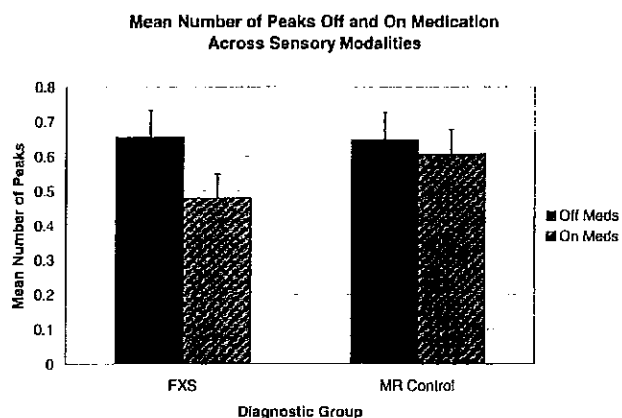**Mean Number of Peaks Off and On Medication Across Sensory Modalities**

Fig. 3. Graph of mean number of peaks off and on stimulants in patients with fragile X syndrome (FXS) and controls with mental retardation (MR).

shows that for individuals with FraX, the magnitude of responses was significantly lower when they were on the medication than when they were not on medication, $F(1, 17) = 9.36$, $P < .01$. This was not the case for the MR control group, $F(1, 16) = 0.52$, $P = .48$. For proportion of responses, none of the combined analyses were significant (Group by medication, $F(1, 34) = .67$, $P < .42$), nor were the effects of medication within Groups significant.

DISCUSSION

Previous research and clinical experience have demonstrated that stimulant medication is helpful in treating ADHD in approximately two-thirds of children with FraX (Hagerman, 1999). Both the FraX and control subjects in this study were clinical responders to stimulants. We were interested in evaluating the changes in EDR that occurred with the use of stimulants in order to find a physiological measure reflective of sympathetic activity. Patients with FraX have been found to have enhanced EDR to stimuli compared to normal controls (Miller et al., 1999); but in this study there

were no significant differences between patients with FraX and developmentally disabled controls group-matched on age and IQ on EDR reactivity after sensation. This suggests that some of the developmentally delayed controls also demonstrated hyperarousal similarly to patients with FraX, which is different from the normal controls in the Miller et al. (1999) study. The hyperarousal of the controls with ADHD and developmental delays reported here is also different from the hyporesponsiveness of ADHD patients reported in previous studies (Fowles and Furuseth, 1994; Lazzaro et al., 1999; Satterfield and Dawson, 1971). It is likely that the etiology of the developmental delay such as fetal alcohol syndrome or autism spectrum disorder contributed to the hyperarousal reported here. However, stimulant medication caused a significant decrease in the mean number of peaks and in the amplitude of the main peak in patients with FraX but not in the developmentally delayed controls reported here. On visual inspection, all of the stimulants (methylphenidate, dextroamphetamine or Adderall) appear to have the same effect on the EDR (see Fig. 1).

It appears that the enhanced electrodermal responsiveness to sensory stimuli in FraX is reduced by stimulant medication, perhaps through the stimulant's enhancement of inhibitory systems. Why this occurs more dramatically in individuals with FraX than controls is unclear. Perhaps FraX has a more dramatic dopamine deficit than controls, so that the relative effect of stimulants is more marked as dopamine neurotransmission is enhanced. Perhaps the enhancement in dendritic connections in patients with FraX compared to controls leads to a more dramatic effect of stimulants on EDR. Future studies should assess the relationship between behavioral measures and the changes in EDR with stimulants. In our anecdotal clinical experience, a negative clinical response to stimulants is associated with a lack of improvement or increased hyperactivity as measured by EDR. Future studies should also assess the effect of other medications including clonidine, selective serotonin reuptake inhibitors, and risperidone, which are commonly used in the treatment of individuals with FraX (Hagerman, 1999).

Our study is only a preliminary assessment of the effects of stimulant medication on patients with FraX and developmentally disabled controls, using EDR as an outcome variable. The sample size is small and heterogeneous and includes wide variability on EDR. Some of the controls were overreactive to stimuli without medication and others were not. Further research involving larger sample size in specific conditions, such as Down syndrome or fetal alcohol syndrome, would clarify whether consistent EDR findings are seen in specific disorders. In FraX, there is also significant variability in the magnitude of the EDR response. In general, patients with FraX tend to be more hyperreactive than controls, although this difference was not statistically significant here. Molecular variations at the FMR1 gene leading to variable levels of FMRP and background gene effects may influence the EDR response (Miller et al., 1999). Larger numbers of patients must be studied to sort out the molecular correlates of medication effects in the EDR response. Occasionally, we have tried to evaluate a patient with FraX that was so anxious and severely reactive to sensory stimuli that

they refused to enter the laboratory. Therefore, the patients assessed here may not represent the severe end of the spectrum for sensory reactivity and behavior problems in FraX.

Approximately one third of the study patients and controls were also treated with other medications, including serotonin agents, risperidone, or clonidine. Since the patients were on these medications in both phases of the EDR study (i.e., on and off stimulants), their effect on the EDR was controlled. Further research is needed to evaluate the effects of each of the medications separately on the EDR.

The purpose of this study was to document that there are stimulant effects on the sympathetic system that can be studied through the use of EDR. Although most studies of medication efficacy use behavioral rating scales, there are significant benefits of having a quantifiable physiological measure to assess medication effects. These physiological measures increase reliability because they are less reliant on subjective assessments. They also may give us insight into the underlying neural mechanisms influencing the response to medication. Future studies can utilize this methodology in the study of the efficacy of a variety of medications and therapy interventions in the treatment of special populations including those with FraX.

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