Physiological Correlates of Social Avoidance Behavior in Children and Adolescents With Fragile X Syndrome

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ABSTRACT

Objective: To investigate whether eye-gaze avoidance, a striking phenotypic feature in fragile X syndrome (FXS), is associated with high levels of "hyperarousal" during social interactions with others. To date, almost all studies in this area have been confounded by inclusion of task demands in addition to social demands. **Method:** We monitored the cardiovascular activity and eye-gaze avoidance of 50 boys and girls with FXS aged 5 to 20 years during a 25-minute intensive social interaction session with an unfamiliar experimenter. To control for possible family and genetic factors in cardiovascular activity, we compared each child with FXS with their same-sex typically developing biological sibling. **Results:** Participants with FXS obtained significantly higher heart rates, lower vagal tone, and lower heart rate variability estimates both at baseline and during the social interaction session compared with their typically developing siblings. Although eye-gaze avoidance occurred at significantly higher levels in the children with FXS, this behavior decreased slightly over the course of the session (a "warm-up" effect) and did not seem to be associated with cardiovascular activity. In the girls with FXS, higher levels of the fragile X mental retardation protein were associated with higher (and more typical) heart rate variability. **Conclusions:** These data suggest that both sympathetic and parasympathetic nervous systems are dysregulated in FXS. However, given that prolonged exposure to social demands does not inevitably lead to increased anxiety or "hyperarousal," professionals should not be deterred from providing much needed social skills interventions for individuals with FXS. *J. Am. Acad. Child. Adolsc. Psychiatry,* 2009;48(3):320–329. **Key Words:** fragile X syndrome, hyperarousal, eye-gaze avoidance, vagal tone, heart rate.

Fragile X syndrome (FXS) is the most common inherited known cause of intellectual disability occurring in as many as 1 in 4,000 male subjects and 1 in 8,000 female subjects.[1] The syndrome results from a mutation to an unstable sequence of CGG nucleotides within the *FMR1* gene, which is located on the long arm of the X chromosome.[2] This critical sequence of CGG nucleotides within *FMR1* repeats approximately 5 to 45 times in unaffected individuals; if the sequence expands to more than 200 repeats, hypermethylation of the promoter region of the gene is highly probable, and production of the "fragile X mental retardation protein" (FMRP), the protein product of the *FMR1* gene, ceases to occur. The FMRP participates in the translational machinery that converts messenger RNA into protein, and thus, it is the lack of FMRP that seems to give rise to the cascade of physical, cognitive, and behavioral manifestations of the disorder.[3] Given that FXS is an X-linked disorder, women are less affected by the syndrome and usually have higher levels of FMRP.

One of the most striking phenotypic features commonly seen in people with FXS is the propensity to avoid social situations, often manifested by severe eye-gaze avoidance and anxiety during social interactions, particularly in male.[4–6] It has been suggested that eye-gaze avoidance displayed in people with FXS often follows a predictable pattern that is different from the eye-gaze avoidance commonly shown by children diagnosed with autism. For example, Cohen and

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coworkers[6] observed 12 young male subjects with FXS while interacting with their mothers for 10 minutes and then while interacting with a stranger for 10 minutes. Results showed that children with FXS engaged in significantly higher levels of social avoidance behaviors compared with patients with Down syndrome and autism or with typically developing children. A further study conducted by Cohen and coworkers[7] indicated that the manner in which children established eye contact with their parents differed between children with FXS and those diagnosed with autism. Specifically, children with FXS seemed to establish eye contact with the parent only when the parent was looking elsewhere, suggesting some kind of approach-avoidance conflict.[8]

The approach-avoidance hypothesis has been tested to some extent in a recent study in which pairs of FXS-affected and -unaffected siblings were exposed to conditions in which an experimenter sat face to face with the participant and delivered different levels of social and performance demands.[5] Results showed that escape behaviors (including eye-gaze avoidance) were more likely to occur during conditions that involved high levels of social demands but not task demands. In the high social demand condition, eye-gaze avoidance occurred approximately 80% of the time in boys with FXS, and approximately 40% of the time in girls with FXS, despite repeated prompts for eye contact being made throughout the condition. More detailed analysis of the data indicated that prompts for eye contact from the experimenter were followed by a significant elevation in the probability of child eye contact, suggesting that the children were, in fact, responsive to the prompts for eye contact but that, once eye contact was established, it was maintained for only 1 or 2 seconds on average.

Murphy and coworkers[9] have suggested that the cognitive processing demands typically associated with social interactions may contribute to increased eye-gaze avoidance in FXS. To test this theory, they experimentally manipulated levels of antecedent social and task demands while male participants with FXS were required to work on a computer task. In two of the conditions, the experimenter sat directly opposite the participant and delivered the task demands, whereas in two other conditions, the experimenter sat at the back of the room, and the task demands were delivered by the computer. In this study, however, eye-gaze avoidance was coded not only when the subject looked away from the experimenter (i.e., social avoidance) but also when the subject looked away from the computer screen (i.e., task avoidance), thus confounding task avoidance with social avoidance. Although Murphy et al.[9] found that eye-gaze avoidance occurred in both sets of conditions, given their definition of eye-gaze avoidance, it seems that they were primarily studying task avoidance rather than social avoidance per se.

To further understand eye-gaze avoidance in FXS, several researchers have suggested that social avoidance behavior in FXS may result from a form of "hyperarousal" in which the sympathetic and parasympathetic nervous systems of people with FXS are dysregulated.[10,11] This hyperarousal hypothesis may help to explain why people with FXS often seem overly anxious or agitated during social interactions. In the first of these studies, Belser and Sudhalter[12] reported that the tonic skin conductance of several male subjects with FXS was significantly elevated during conversations involving direct gaze from others. Miller and coworkers[13] also found that electrodermal responses were elevated in a group of 15 male subjects with FXS during auditory, tactile, visual, and olfactory stimulation compared with a group of age- and sex-matched typically developing controls. Interestingly, Miller et al.[13] also found that levels of FMRP were associated with electrodermal activity, such that people with higher levels of FMRP evidenced a more typical electrodermal response.

Several studies have since monitored physiological arousal during cognitively demanding tasks, as opposed to social tasks. For example, Roberts and coworkers[10] monitored cardiovascular activity in 29 boys with FXS, aged 1 to 11 years, while they alternated between a baseline task (watching a video) and performed a series of challenging cognitive tasks (subtests from the Stanford-Binet IV). Results showed that boys with FXS had significantly elevated heart rates (a measure of sympathetic nervous system activity) and significantly lower vagal tone (a measure of parasympathetic nervous system activity) both at baseline and during completion of the cognitive tasks, in comparison to a group of age-matched typically developing children. However, in this study, no relation was found between levels of FMRP and the cardiovascular indices.

In the study by Keysor and coworkers,[11] skin conductance, heart rate, vagal tone, and electromyographic activity were monitored in 13 girls with FXS aged 13 to 22 years while they performed a series of mental