Title: A Novel Eye Tracking Paradigm for Indexing Core Social Phenotypes of Fragile X Syndrome

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Introduction: Fragile X syndrome is characterized by hallmark features of gaze avoidance, reduced social approach, and social anxiety. Yet, measurement of these core phenotypic features is challenging, as they are often captured using behavioral rating scales that are subject to rater biases and lack of sensitivity to subtle behavioral differences. The lack of sensitive, quantifiable, and accessible outcome measures has been a significant challenge to clinical trials in fragile X syndrome (e.g., Jacquemont et al., 2014). This study investigated the utility of an experimental eye tracking paradigm for indexing social-related phenotypes in adolescents and young adult males with fragile X syndrome. Specifically, we indexed gaze behavior in response to direct and averted social gaze. Preferential attention to direct gaze is an innate skill that is thought to have evolutionary significance, as direct gaze represents a primary communicative channel by which humans exchange social-cognitive information, facilitating adaptive social engagement (Baron-Cohen & Ring, 1994).

Methods: Participants were 24 males with fragile X syndrome, aged 16-26 years (M=19). Nonverbal IQ ranged from 36-56 (M=39). Participants completed a series of behavioral assessments, which included measures of nonverbal IQ (Leiter-R), autism symptom severity (ADOS-2), and examiner-rated social approach (Social Approach Scale; Roberts et al., 2007). Social avoidance symptoms were indexed via maternal report using the Social Avoidance subscale of the Anxiety Depression and Mood Scale (ADAMS). Participants completed an eye tracking paradigm adapted from Wieser et al. (2009) in which they see a series of 32 neutral female faces display either direct gaze or averted gaze. Faces were initially presented with eyes closed for at least 1200 ms, and after the participant looked directly at the eye region for 300 ms, the eyes of the face opened to display direct or averted gaze. Participants’ eye movements were recorded with an Eyelink 1000 Plus eye tracker, in monocular remote mode. The average first fixation duration within the eye area of interest for each condition was extracted; this index reflects stimulus saliency (Liversedge et al., 1998). An advantage of this index is that it does not require sustained attention to the stimulus, which is important given the low functioning level of the participants. The design of the eye gaze paradigm, which checked the participant’s eye position online to ensure that they were fixating within the eye region of the face when stimulus gaze was initiated, ensured that the first fixation captured the initial viewing response to direct or averted gaze. All participants had >80% usable trials.

Results: Nonverbal IQ and autism symptom severity were covaried in all analyses. A mixed effects model testing condition effects (i.e., direct, averted) indicated longer first fixation duration in response to averted gaze ($F[1, 21] = 86689.70, p < .001$). A second mixed effects model tested social avoidance symptoms as a predictor of eye gaze behavior; a significant social avoidance-by-condition effect was detected, with parent-reported social avoidance being strongly associated with longer first fixation duration in the averted gaze condition; this relationship was weaker in the direct gaze condition ($F[1, 20] =5.71, p = .024$). Next, we tested the first fixation duration in response to direct and averted gaze as predictors of social approach. After correcting for multiple comparisons, first fixation duration in response to averted gaze was a significant predictor of social approach, with a large effect size ($F[1, 20] = 7.87, p = .011; \eta^2_p = 0.28$). To shed light on the value of eye tracking measures relative to traditional behavioral rating scales, we followed our previous model with a parallel analysis testing parent-reported social avoidance symptoms as a predictor of social approach. The ADAMS social avoidance subscale was not a significant predictor of social approach ($F[1, 22] = 1.38, p = .254$), although the effect size was consistent with a medium effect ($\eta^2_p = .06$).
Discussion: Longer first fixation duration in the averted gaze condition suggests that males with fragile X perceived averted gaze as having increased saliency relative to direct gaze. Time fixating on the averted gaze stimuli was highly predictive of examiner ratings of participants' social approach behavior, suggesting that the eye tracking paradigm was successful in tapping behaviors linked with meaningful phenotypic variation. Notably, gaze behavior during the experimental eye tracking paradigm was a stronger predictor of social approach behavior than parent-reported social avoidance symptoms. This eye tracking paradigm may represent a useful outcome measure for clinical trials; it provides a quantitative index that is closely tied with core features of the fragile X phenotype, can be completed in ~20 minutes, and can be used successfully with individuals with low IQ.

References/Citations: