

Social Approach and Autistic Behavior in Children with Fragile X Syndrome

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Abstract Social avoidance is a core phenotypic characteristic of fragile X syndrome (FXS) that has critical cognitive and social consequences. However, no study has examined modulation of multiple social avoidant behaviors in children with FXS. In the current study, we introduce the *Social Approach Scale* (SAS), an observation scale that includes physical movement, facial expression, and eye contact approach behaviors collected across multiple time points. Our findings suggested that social approach behaviors in children with FXS were affected by age, gender, setting, and time spent with an examiner. Selected social approach behaviors were related to autistic behavior. Increased eye contact over the course of a research assessment, in particular, was found to be a strong predictor of lower autistic behavior.

Keywords Fragile X · Autism · Social approach

Introduction

Fragile X syndrome (FXS), the most common known inherited cause of developmental disability, is a single-gene disorder associated with the amplification of a

CGG repeat on the *FMRI* gene. The estimated prevalence of FXS is 1:4,000 males and 1:8,000 females (Sherman, 2002). Individuals with the full mutation (>200 CGG repeats) typically have hypermethylation of the promoter region of the *FMRI* gene (Oberle et al., 1991), leading to transcriptional silencing and a reduction in the levels of the fragile X mental retardation protein (FMRP). Reduction or absence of FMRP is associated with clinical involvement in FXS (Kaufmann, Abrams, Chen, & Reiss, 1999; Tassone et al., 2000; Hatton et al., 2006; Sullivan et al., 2006). FXS affects both males and females; however, males are typically more severely affected. The majority of males with FXS have an IQ in the mild to moderate mental retardation range, and virtually all have learning difficulties (Bennetto & Pennington, 2002).

Social avoidance, or social withdrawal, is one of the most frequent and disabling behavioral abnormalities in individuals with FXS (Hagerman, 2002; Kau et al., 2004; Kaufmann et al., 2004). According to Merenstein et al. (1996), 75% of young males with the full mutation display excessive levels of shyness and anxiety with ~50% reporting an occurrence of panic attacks. Similarly, females with the full mutation are described as shy and socially anxious (Hagerman, 2002) and nearly two-thirds may meet DSM-IV criteria for Avoidant Personality Disorder (Freund, Reiss, & Abrams, 1993). These significant reactions to social interactions do not appear to be a generalized response across people and settings. In fact, evidence suggests that persons with FXS are generally interested in social interaction but often display anxiety and social withdrawal in response to initial interactions with unfamiliar people or when placed in novel settings (Cohen et al., 1988; Bailey et al., 1998). Illustration of the

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simultaneous social approach–withdrawal behavior is reflected in the greeting behavior of males with FXS who withdraw by avoiding eye contact and turning their body away from the person they are greeting while physically approaching them and voluntarily shaking their hand (Wolff, Gardner, Paccla, & Lappen, 1989).

These social behavioral abnormalities and other aspects of atypical social interaction observed in FXS have stimulated a great deal of controversy regarding the association of FXS and autism (Hagerman, 1992; Bailey et al., 1998; Kaufmann et al., 2004). Approximately 25–33% of children with FXS meet diagnostic criteria for autism (Bailey et al., 1998; Rogers, Wehner, & Hagerman, 2001; Kaufmann et al., 2004). However, up to 90% display one or more autistic features including perseveration, self-injury, hand flapping, poor eye contact, and social avoidance (Merenstein et al., 1996; Hagerman, 2002).

The underlying mechanisms associated with autistic behavior in FXS are not known; however, evidence exists that social anxiety and associated arousal dysregulation are related to specific aspects of autistic behavior (Cohen, 1995; Miller et al., 1999; Hessel et al., 2001; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001; Budimirovic et al., 2006). Recent research has focused on identifying specific factors and behaviors in children with FXS that confer “high risk” for an autism diagnosis, determining whether autistic behavior in FXS exists along a continuum, and identifying if sub-phenotypes within FXS exist based on autism status (Kaufmann et al., 2004). Given findings that persons with FXS and autism have poorer outcomes than those with FXS who do not have autism (Bailey et al., 1998; Rogers et al., 2001), this work is critical to guide identification and treatment efforts.

In terms of specific predictors of autism in FXS, a number of studies have shown that lower IQ/developmental skills (Cohen, 1995; Bailey et al., 1998; Rogers et al., 2001; Kau et al., 2004), increased age (Hatton et al., 2006), lower FMRP (Hatton et al., 2006), more problem behavior (Hatton et al., 2002; Kau et al., 2004), and lower adaptive behavior (Hatton et al., 2003; Kau et al., 2004), particularly adaptive socialization skills (Kaufmann et al., 2004) are associated with increased autistic behavior in FXS. Regarding factors that distinguish FXS individuals with and without autism, several studies have shown differentiated patterns across specific cognitive and social-behavioral domains. Bailey et al. (2001) reported that FXS children with autism displayed a pattern (greater delays in language and social domains) similar to children with autism (non-FXS) and lower levels of

development than those with FXS without autism. Similarly, Rogers and colleagues reported that FXS children with autism performed similarly to children with autism (non-FXS), while children with FXS without autism performed similarly to children with developmental delays on imitation tasks, sensory processing patterns, and ADI-R profiles (Rogers et al., 2001; Rogers, Hepburn, Stackhouse, & Wehner, 2003; Rogers, Hepburn, & Wehner, 2003). Consistent with these findings, Kau and colleagues found that FXS boys with autism were distinguishable from FXS boys without autism and comparable to boys with autism (non-FXS) in several measures of social interaction (Kau et al., 2004). Interestingly, their data suggest that a distinct social behavioral profile, characterized by poor socialization skills and withdrawn behavior, is a distinct sub-phenotype associated with autism within FXS (Kau et al., 2004).

In similar work examining specific behaviors that confer high risk for autism spectrum disorders (ASDs) within FXS, Kaufmann and colleagues completed a series of studies. In the first one (Kaufmann et al., 2004), they reported that most boys with FXS displayed one or more autistic behaviors. However, the severity and profile of autistic behaviors allowed differentiation into three groups: (1) FXS boys without an autistic disorder ($n = 32$, 57%), (2) FXS boys with a pervasive developmental disorder ($n = 10$, 18%), and (3) FXS boys with autism ($n = 14$, 25%). While impairment in social interaction was expressed with variable severity across the three groups, severe social deficits, particularly difficulty with complex social interaction, was the primary predictor of ASD diagnoses (Kaufmann et al., 2004). In a subsequent study, adaptive socialization and social withdrawal measures predicted distinct FXS subgroups based on autism diagnoses (Budimirovic et al., 2006). Furthermore, their findings suggested that two distinct but interrelated social behavior abnormalities contributed to autism diagnoses in boys with FXS: adaptive socialization associated with cognitive processing, and social avoidance associated with anxiety and arousal dysfunction (Budimirovic et al., 2006).

In preliminary work using the *Social Approach Scale* (SAS), a measure modified by our group to sensitively reflect multiple forms of social approach behavior in FXS, we (Weisenfeld & Roberts, 2005) reported that young boys with FXS displayed significantly increased social approach behaviors with more time spent with the assessor ($t = 7.17$, $p < 0.01$). Additionally, we found that the SAS was positively correlated to Childhood Autism Rating Scale (CARS) scores. The correlation between scores of the SAS and CARS after

an extended period of social interaction was stronger ($r = 0.56$) than after a short-period of initial social interaction ($r = 0.32$). This suggests that difficulties with social approach during initial interaction with an examiner is moderately related to autistic behavior in boys with FXS. However, a failure to “warm up” or modulate and increase social approach over time may be a specific behavior that differentiates FXS boys with and without elevated autistic behaviors.

These findings suggest that specific FXS profiles associated with ASD diagnoses should be examined in more detail. For example, the question of whether these social-behavioral abnormalities exist along a continuum or represent distinct subphenotypes within FXS is critical to guide diagnostic and treatment efforts. While highly speculative, three potential sub-phenotypes within FXS are described here. The “low-social withdrawal” group is characterized as having good social interactions with others, mild social fear, occasional withdrawal in response to novelty, and a low probability of an autism diagnosis. The “high-social withdrawal-anxiety” group is characterized as having generally good social interactions with others, high-social fear, frequent social withdrawal in response to novel persons and environments, with elevated risk of being on the autism spectrum (e.g., PDD) but low likelihood of an actual autism diagnosis. The “high-social withdrawal-autism” group is characterized as having abnormal sociability with minimal interest in others, high-social fear, generalized social withdrawal across multiple settings, and a high likelihood of an autism diagnosis. As noted, delineation of these groups is speculative and largely based on preliminary evidence and the theory that a small percentage of persons with FXS truly meet diagnostic criteria for autism, and these individuals can be differentiated from those who do not meet based on their generalized lack of interest in others in contrast to those who are avoidant to novelty.

Taken together, there has been a great deal of work describing social behaviors and autism in FXS that has clearly shown that this relationship involves multiple aspects of social behavior, including basic non-verbal interactions, complex socialization, and approach-withdrawal in a complex and interactive manner. Despite existing work in this area, no studies have examined the effect of setting and duration of social interaction or included multiple measures of social approach that differentiated behaviors during initial versus more sustained interactions. This lack of information is likely due, in large part, to the availability of appropriate measurement tools. Most scales document global ratings of behavior across contexts or collapse initial response behaviors with more static behaviors,

rather than sensitively measuring social behaviors within and across contexts over time.

This study is an extension of our previous work designed to provide a detailed examination of social approach behaviors in male and female children with FXS. To accomplish this, we introduce the SAS, a new measure designed to sensitively measure changes over time across multiple forms of social approach behavior including physical movement, facial expression, and eye contact. These three behaviors are measured at the immediate onset of social interaction and at the end of a prolonged social interaction. In addition, the SAS includes location and duration of interaction as factors that potentially affect social interaction in FXS, and allows examination of the relation of social approach to autism and related behaviors in FXS. The goals of the present study are to:

1. Describe the profile of social approach, including measures of physical movement, facial expression, and eye contact, in boys and girls with FXS. Examine variables that predict social approach including gender, age, adaptive function, setting, and duration of interaction across time. We hypothesize that low levels of social approach behavior will be associated with male gender, older ages, lower adaptive function, less familiar settings, and shorter-duration of interaction.
2. Examine the relationship between social approach parameters of physical movement, facial expression, and eye contact across time and their association with other measures of social avoidance in FXS. We hypothesize that low levels of social approach behavior at the end of an assessment day will represent impaired behavioral regulation and will be linked to other measures of avoidant or withdrawn behavior.
3. Evaluate the relationship between social approach parameters of physical movement, facial expression, and eye contact across time and autistic behavior in FXS. We hypothesize that low levels of social approach behavior at the end of an assessment day will be associated with the presence and severity of autistic behavior.

Method

Participants

Participants in this study were recruited from a series of longitudinal studies of the Carolina Fragile X Project. All children have the full mutation of FXS

based on DNA results. The sample consisted of 92 males and 20 females. As expected, the IQ of the females was typically higher than for the males (see Table 1 for a description of the subject characteristics).

Measures

Social approach

The (SAS) scale is based on work by Goldsmith and Lemery (1993, unpublished manuscript) who found a strong correlation ($r = 0.44, p < 0.01$) between the SAS and the Shyness subscale of the Rothbart Children’s Behavior Questionnaire in typically developing children (Locke et al., 2003). We modified the SAS to reflect factors believed to be important in describing social approach behaviors in FXS. These modifications included the addition of an eye contact scale, documentation of the duration of time spent interacting with the participant and location, and repeated measures of social approach at multiple time points in an assessment to reflect the variance in social approach in FXS observed during initial versus more sustained interactions. The SAS contains three scales that reflect physical movement (MO, e.g., walks away), social shyness/facial expression (FA, e.g., fearful facial expression), and eye contact (EC, e.g., avoids eye contact). Higher numerical ratings reflect less approaching behavior.

In the current study, examiners assigned SAS scores at different times over the course of a research assessment. For children completing a 1-day assessment (20 males, six females), SAS ratings were completed at the beginning of the day, rating 1 day 1 (r1d1) and at the end of the day, rating 2 day 1 (r2d1). For children completing a 2-day assessment

(72 males, 14 females), they received the day 1 ratings as just described in addition to at the beginning of day 2, rating 1 day 2 (r1d2), and at the end of the day, rating 2 day 2 (r2d2). Although two examiners were present for most of the assessments, one examiner was assigned to work primarily with the child and the other examiner worked primarily with the mother. Thus, the two examiners experienced different types of interactions with the children and for differing amounts of time. Therefore, the SAS was rated by consensus across the two examiners to take these factors into account.

Withdrawn and attention problem behavior

The Withdrawn and Attention Problems subscales of the Child Behavior Check List (CBCL), Parent Form, were used to assess these targeted problem behaviors in relation to the SAS. The CBCL reflects standardized descriptions of children’s behavioral and emotional characteristics (Achenbach & Rescorla, 2000, 2001). There are two versions of the CBCL, administered according to age: 1½–5 years or 6–18 years. Both age versions include a Withdrawn scale (Withdrawn and Withdrawn/Depressed, respectively). Similarly, both age versions include an Attention scale (Attention in both scales). The *t* scores are generated for each syndrome scale. The *t* scores between 66 and 69 are considered to be in the borderline clinical range, while *t* scores above 70 are considered to be clinically significant. Additionally, the CBCL is normed on a national sample and has very high test–retest reliability ($r = 0.95$) and acceptable criterion-related validity making it a widely used instrument for measuring behavioral and emotional problems in childhood.

Table 1 Characteristics of the FXS cohort

Variable	Males		Females	
	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>
Chronological age (in months)**	79.4 (52.11)	92	49.6 (40.73)	20
Mullen scales of early development#*	53.15 (7.68)	46	72.21 (13.44)	14
Leiter-R non-verbal IQ##*	53.37 (11.62)	41	84.5 (13.58)	6
Vineland adaptive behavior composite*	52.46 (17.08)	89	76.0 (15.75)	19
CBCL Withdrawn scale	60.88 (7.84)	85	57.44 (7.69)	16
CBCL Attention scale*	63.67 (7.96)	85	57.94 (8.53)	16
CTS Approach scale	3.62 (0.94)	87	3.77 (1.13)	19
CTS Persistence scale	3.99 (3.99)	84	3.72 (0.744)	19
Childhood autism rating scale*	27.63 (5.5)	86	21.08 (5.41)	18

Mullen mean age for boys: 32.9 months; ## Leiter mean age for boys: 128.2 months *CBCL* child behavior checklist, *CTS* Carey temperament scales

* Significant differences between FXS males and females, $p < 0.001$

** Significant differences between FXS males and females, $p < 0.02$

Temperament

Three Carey Temperament Scales (CTS), the Toddler Temperament Scale (Fullard, McDevitt, & Cary, 1995), the Behavioral Style Questionnaire (McDevitt & Carey, 1995), and the Middle Childhood Temperament Questionnaire (Hegvik, McDevitt, & Carey, 1995), were used in this study. The CTS are rating scales used to measure behavioral style (McDevitt & Carey, 1995). The forms consist of ~100 items that parents rate on a 6-point scale. These ratings then yield a score for each of the nine temperament dimensions: Activity, Rhythmicity, Approach, Adaptability, Intensity, Mood, Persistence, Distractibility, and Threshold. Only the Approach (the nature of responses to new stimuli) and Persistence (the length of time certain activities are pursued by the child, with or without obstacles and interruptions) subscales were used because of the focus on these dimensions of behavior. Raw scores were converted to *z*-scores based on a reference sample. For these subscales, higher scores indicate less approaching and less persistent behavior. The CTS have test–retest reliabilities ranging from 0.81 to 0.88 and are widely used to describe childhood temperament.

Autistic behavior

The CARS (Schopler, Reichler, & Renner, 1988) is an examiner rating of a child's behavior utilized as a way to describe autistic behavior. The CARS consists of 15 items and a total score, with the latter following a continuum of autistic behaviors from non-autistic (total score between 15 and 29.5), mildly/moderately autistic (score between 30 and 36.5), to severely autistic (score of 37 or more). The CARS is widely used and has been found to be both reliable ($r = 0.88$) and valid ($r = 0.84$, $p < 0.001$) when compared to criterion clinical ratings. Consistent with our previous and current studies using the CARS (Bailey et al., 1998; Hatton et al., 2006), CARS ratings in this study are used to *describe autistic behavior rather than to diagnose autism* which is beyond the scope of training and measurement for the current study. For ease of discussion and comparability to other studies, children with a total CARS score of 30 and above are described as being on the autism spectrum (ASD), a general term used to describe persons with mild to severe symptoms of autism. The CARS was completed after each child was assessed with the standard protocol for their study. Per administration guidelines (Schopler et al., 1988), ratings were based on direct observation of the child,

parent interview, and review of parent rating scales. As in our previous studies (Bailey et al., 1998; Bailey, Hatton, Skinner, & Mesibov, 2001), examiners came to consensus before assigning a numerical rating for each CARS item.

Adaptive behavior

The *Vineland Adaptive Behavior Scales* (VABS) is a widely used assessment tool used to measure the adaptive behavior abilities of individuals from birth to 90 years of age (Sparrow, Balla, & Cicchetti, 1984). The VABS produces an Adaptive Behavior Composite (ABC) standard score (mean of 100, standard deviation of 15). The VABS has test–retest reliability ($r = 0.88$) as well as acceptable content and criterion-related validity. In this study, the mother of each participant was interviewed using the VABS.

Cognition

Due to the wide age range of the subjects in this study and the use of the SAS in multiple studies with different foci, two cognitive measures were administered for participants in the current study. The Mullen Scales of Early Learning (MSEL), a standardized, individually administered test that is designed to measure the developmental level of children from birth to 68 months (Mullen, 1995), was used to assess children 5 years of age and younger. An Early Learning Composite standard score is computed (mean of 100, standard deviation of 15). The test–retest reliability of the Mullen ranges from 0.71 to 0.96 and it has been found to be correlated to the Bayley Scales of Infant Development (range of 0.30–0.70). The Leiter-R, a non-verbal measure used to assess cognitive function in children and adolescents aged 2–20 years (Roid & Miller, 1995, 1997), was used for children 5 years of age and older. The Brief IQ measure was used in this study (Mean of 100, standard deviation of 15). The Brief IQ measure of the Leiter-R has reliabilities ranging from 0.88 to 0.90 and is correlated to the WISC-III ($r = 0.85$). Examination of the comparability of these two very different cognitive measures, one a measure of broad developmental skills and the other a brief measure of non-verbal IQ, with two different age groups strongly suggested that they were not comparable measures across our sample. Thus, we include the cognitive data for subject descriptives only and did not use these data in analyses. While not a perfect substitute, we used the VABS, which is comparable across our sample, as a general indicator of functioning level which is impor-

tant given the relationship of autism to adaptive behavior (Hatton et al., 2003; Kaufmann et al., 2004).

Procedure

Although participants were recruited from an ongoing series of longitudinal research studies, each subject was assessed in a similar manner using a standard protocol of cognitive and behavioral assessments for each study. Prior to conducting any assessments, each examiner was trained on the protocols for each study. Training included thorough review of standard procedures and training manuals, viewing of videotaped training sessions, and mock assessments. Two examiners were present for most assessments thereby facilitating ongoing consistency of administration and scoring for the various measures. Variation within and between the studies included the length of the assessment (1 or 2 days), duration of interaction with the examiner on each assessment day(s), and location (typically home or school). The effect of these variables was examined.

Data analysis

Considering that the goals of the present study were to delineate the basic features of the SAS as well as the relationship between the SAS and social avoidance and autistic behavior, we used several statistical approaches and tests in this study. Descriptive statistics were used to characterize the FXS cohort under study, determine the relative distribution of SAS and related values, and as an aid for the interpretation of our regression models. Different regression models, including univariate, multivariate, and ordered logistic regression models, were used to characterize the FXS subgroups and to examine the relationship between measures of social avoidance and autistic behavior. Similar regression models were used for evaluating the relationship between SAS parameters and cognitive function, social avoidance, and autistic behavior. These models were applied by two complementary strategies: unbiased analyses corrected for multiple comparisons (Bonferroni correction) and hypothesis-driven analyses without corrections. The latter tested the hypothesis that *elevated* second daily measures for each SAS scale (i.e., r2 measures), in particular for the second day (i.e., r2d2 values), would reflect inadequate behavioral regulation that is correlated with social avoidance and severity of autistic behavior in FXS. Regardless of approach, age and adaptive behavior were incorporated as co-variables in the models. When appropriate, we applied post hoc

analyses that minimized the effects of variance heterogeneity, non-Gaussian distribution, and unequal N values (Scheffe, 1953). In our logistic models, we used the p - and Chi-square values corresponding to logistic likelihood ratio tests to determine the relative contribution of each variable. These tests assessed the deviance of a fitted model including each variable against a model not including each variable, and were in general agreement with p - and Chi-square values obtained from the Wald test. In addition to absolute scores for each SAS measure, we also examined differences/change scores between first and second evaluations for each day (r1d1-r2d1, r1d2-r2d2) and each SAS scale. The latter measures were analyzed as simple differences as well as scaled differences [i.e., divided by the first measure: (r1d1-r2d1)/r1d1 and (r1d2-r2d2)/r1d2], in order to control for variability in magnitude of initial (r1) responses. Converging significant results obtained through unbiased and targeted approaches were considered as the most psychobiologically relevant.

Results

Characteristics of FXS Cohort

There were significant differences between boys and girls with FXS (Table 1) and between boys with ASD and those without (Table 2). The male subcohort was older and had a lower level of cognitive performance than the females. The VABS scores were significantly higher in the younger male group, when compared with older boys.

SAS profiles: relationship with duration, setting, gender, age, and adaptive function

Scores for the three SAS scales showed a distinctive profile, indicating that children with FXS displayed more social approach behavior (physical movement, facial expression, and eye contact) as time spent with the examiner increased. In general, the difference in scores between first and second evaluations, for each day, was less pronounced for EC indicating that eye contact was less improved by time spent with the examiner than physical movement and facial expression. Several factors influenced this general SAS profile. Time spent with the examiner, which was on average 3.5 h for each day of evaluation, did not influence any of the SAS parameters. On the other hand, physical movement ratings at the end of each day

Table 2 Characteristics of the males FXS+ASD cohort

Variable	FXS with ASD		FXS without ASD	
	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>
Chronological age (months)	80.57 (47.34)	28	77.09 (54.52)	58
Mullen scales of early development ^{#,*}	49.23 (0.59)	13	54.45 (8.49)	31
Leiter-R non-verbal IQ ^{##}	49.87 (12.68)	15	56.52 (10.56)	25
Vineland adaptive behavior composite ^{**}	44.58 (14.83)	26	55.76 (17.09)	58
CBCL Withdrawn scale [*]	63.78 (7.32)	27	59.35 (7.8)	55
CBCL Attention scale [*]	66.48 (8.7)	27	62.31 (7.32)	55
CTS Approach scale	3.79 (1.01)	25	3.55 (0.91)	57
CTS Persistence scale ^{**}	4.35 (0.70)	23	3.84 (0.69)	56
Childhood autism rating scale ^{**}	33.93 (3.69)	28	24.59 (3.13)	58

Mullen mean age for boys: 32.9 months; ## Leiter mean age for boys: 128.2 months *CBCL* child behavior checklist, *CTS* Carey temperament scales

* Significant differences between FXS males with and without ASD, $p < 0.03$

** Significant differences between FXS males with and without ASD, $p < 0.007$

(*r2d1MO* and *r2d2MO*, respectively) at school ($n = 30$) were higher than at home ($n = 46$). Scores for the end of day ratings on the second day for the eye contact scale (*r2d2EC*) also approached trend level, again with higher values at school than at home.

Males had a less marked difference between the beginning and end of day measures (Fig. 1a, b). This flattened trajectory was particularly obvious for the eye contact scale; values for the end of day ratings on both days were significantly higher for males, even after correcting for cognitive function. This suggests that poor eye contact may be more problematic for males and less influenced by familiarity of the person with whom they are interacting. However, the difference in eye contact between boys and girls was no longer significant when age was included as a co-variate. The latter could be explained by the fact that the male group was older and that older FXS boys tended to have higher scores at the end of the assessment days (see Fig. 1c, d). In addition, after correcting for multiple comparisons, results suggest that older males are less physically approaching and have poorer eye

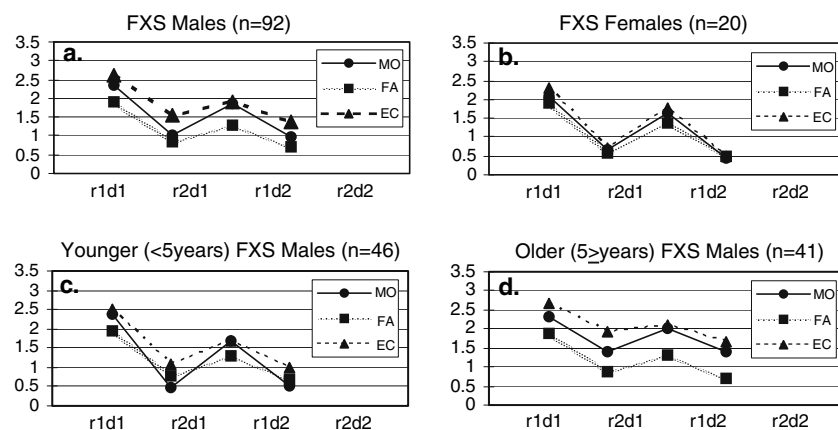
contact at the end of both assessment days than younger males.

Global adaptive function, the VABS composite score, showed a weak association with SAS parameters. We found an inverse association such that boys with lower VABS scores displayed less eye contact at the end of the first assessment day and less physical approach at the end of the second assessment day. However, when age was introduced as a co-variate, due to the lower VABS scores in the older boys, only eye contact appeared correlated, though at a trend level. In younger FXS boys, there also was a significant correlation indicating that young boys with lower VABS scores showed less eye contact at the beginning of both assessment days.

Social avoidance and autistic behavior profiles of FXS cohort

In order to interpret the relationship between SAS ratings and other social behavior variables, we also examined the social avoidance and autistic behavior

Fig. 1 SAS profiles: effects of gender and age. The relatively more pronounced differences between *r1* and *r2* measures for every SAS scale in females and younger males. *r1d1* first evaluation of the first day, *r2d1* second evaluation of the first day, *r1d2* first evaluation of the second day, *r2d2* second evaluation of the second day, *MO* physical movement, *FA* facial expression, *EC* eye contact



profiles of the male FXS cohort (Tables 1, 2). Due to the small sample, we were unable to conduct similar analyses in the female cohort. Regarding social avoidance, males with FXS had relatively high scores on the Withdrawn scale of the CBCL (CBCLw) and the Approach subscale of the CTS (CTSapr). As postulated, CBCLw scores were significantly correlated with CTSapr, even after co-varying for age and/or VABS scores. Nonetheless, the relationship between CBCLw and CTSapr was not specific since CBCLw was also correlated with the Persistence subscale of CTS (CTSper). On the other hand, the selectivity of the CBCLw–CTSapr association was suggested by the lack of correlation between CTSapr and CBCL Attention (CBCLatt), a CBCL scale with distinctively high scores in FXS (Hatton et al., 2002; Kau et al., 2004). The relevance to ASD of the CBCLw–CTSapr correlation was underscored by the fact that this association was driven by CBCLw items predictive of ASD status (Budimirovic et al., 2006). In particular, items 75 and 111 that represent shy and withdrawn behaviors, respectively, were significantly correlated with CTSapr scores.

Similar to our previous reports (Bailey et al., 1998; Kaufmann et al., 2004), autistic behavior was distributed in a continuum of CARS score severity throughout the FXS male group (range: 17.5–45.5). Boys with FXS and ASD, as defined by the CARS cut-off (≥ 30), had lower IQ (mean IQ: 49.6 vs. 55.2 for those without ASD) and VABS standard scores (mean VABS: 44.6 vs. 55.1 for those without ASD) although they did not differ in terms of age. As we reported (Kau et al., 2004; Kaufmann et al., 2004), CBCLw scores were higher in the FXS + ASD group. Furthermore, logistic regression models confirmed our earlier observations using DSM-IV diagnoses that CBCLw scores and items

representing “true” social avoidance were selectively predictive of autism status (Budimirovic et al., 2006). CBCL items 42, 75, and 111, and not CBCL Attention, were significantly correlated with ASD diagnosis (greater prediction of the No ASD status). Unexpectedly, the CTSapr subscale was not correlated with ASD diagnosis.

Relationship between SAS and social avoidance

There were no correlations between total scores on CBCLw and SAS parameters. CBCLw items were weakly associated with SAS. Specifically, r1d1EC, r1d2MO, r1d2FA, and r2d2FA were significantly correlated with specific CBCLw items, representing both social avoidance (i.e., items 65 and 75) and social indifference (i.e., items 80 and 88), though these associations did not consider the effect of multiple comparisons. Scores on CTSapr showed a stronger relationship with the SAS; CTSapr was correlated at a trend level, after stringent corrections for multiple comparisons (p -value set at 0.004–0.01 for trend), with several parameters of facial expression: r1d1FA, r2d1FA, and r1d2FA (stronger for the initial daily measures). These associations took into consideration age and/or VABS scores as co-variables and are summarized in Table 3. SAS parameters were not correlated with other examined CBCL (i.e., CBCL Attention) or CTS (i.e., CTS Persistence) scales.

Relationship between SAS and autistic behavior

We evaluated the relationship between SAS and autistic behavior, in terms of the continuum of CARS scores and as CARS-based ASD categories (Yes versus No). There were multiple SAS parameters significantly

Table 3 Correlations between SAS and social withdrawn measures (p -values)

Variable	r1d1FA	r1d1EC	r2d1MO	r2d1FA	r1d2MO	r1d2FA	r2d2fFA
CBCLw	–	–	–	–	–	–	–
CBCLw65	–	–	0.049*	–	–	–	–
CBCLw75	–	–	–	–	0.031*	0.043*	–
CBCLw80	–	–	–	–	–	0.034*	–
CBCLw88	–	–	–	–	0.029*	0.023*	–
CTSapr	0.007*	0.009*	–	–	–	0.008*	–
CTSapr	0.007**	0.023**	–	0.01**	–	0.008	–
CTSapr	0.017#	0.038#	–	0.04#	–	0.026#	–

CBCLw CBCL Withdrawn, CTSapr CTS Approach, VABS composite scores

* Items showing differences by regression (co-varied for age) between SAS and CBCLw or SAS and CTSapr

** Items showing differences by regression (co-varied for VABS) between SAS and CTSapr

Items showing differences by regression (co-varied for age + VABS) between SAS and CTSapr

Significance using Bonferroni correction ($p < 0.004$), Trend level ($p = 0.004–0.01$), and not using Bonferroni correction ($p < 0.05$)

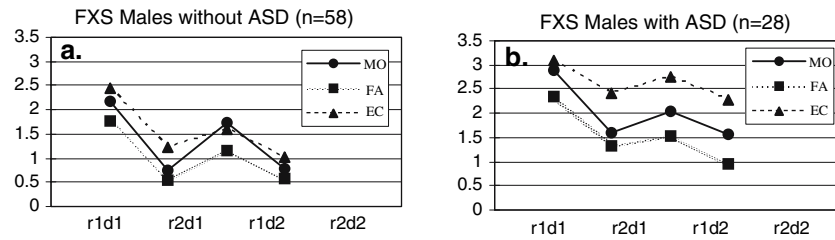


Fig. 2 SAS profiles in boys with FXS: effects of autistic behavior. Males with FXS and severe autistic behavior (ASD category) showed higher SAS scores, particularly on Eye Contact, and less marked differences between r1 and r2. *r1d1*

first evaluation of the first day, *r2d1* second evaluation of the first day, *r1d2* first evaluation of the second day, *r2d2* second evaluation of the second day, *MO* physical movement, *FA* facial expression, *EC* eye contact

correlated with CARS, even after correcting for multiple comparisons and co-varying for age and/or VABS. When co-factors were introduced to the models, only end of day measures remained significant whether using continuous or categorical CARS measures. Specifically, four SAS parameters were significant in models with age + VABS: *r2d1MO*, *r2d1FA*, *r2d1EC*, and *r2d2EC*. This indicates that physical movement and facial expression at the end of the first assessment day and eye contact at the end of both days were associated with autistic behavior. Overall, boys with FXS + ASD had flatter SAS profiles in particular for EC (Fig. 2). Table 4 depicts the significant data for CARS categories. This suggests that a subset of SAS parameters (physical movement and facial expression at the end of the first assessment day and eye contact at the end of the first and second day) is not only associated with the spectrum of autistic behavior in boys with FXS, but also with its severity.

Secondary SAS parameters

We postulated that SAS is an instrument that can assess behavioral regulatory responses to social

Table 4 Relationship between SAS change scores and autistic behavior (*p*-values)

Variable	r2d1MO	r2d1FA	r2d1EC	r2d2EC
ASD	0.002	0.0006	0.0002	0.0004
ASD	0.003*	0.0006*	0.0003*	0.0006*
ASD	–	0.0014**	0.0044**	0.0052**
ASD	0.04#	0.0032#	0.0023#	0.0041#

ASD: CARS as categories (cut off ≥ 30)

* Items showing differences by regression (co-varied for age) between SAS and ASD

** Items showing differences by regression (co-varied for VABS) between SAS and ASD

Items showing differences by regression (co-varied for age + VABS) between SAS and ASD

Significance using Bonferroni correction (*p* < 0.004), Trend level (*p* = 0.004–0.01), and not using Bonferroni correction (*p* < 0.05)

approach. Specifically, we hypothesized that measures at the end of assessment days would be indicators of the ability to adapt to the presence of a novel examiner. Impairment in behavioral regulation in FXS, more severe in those individuals with FXS and autism, would be manifested by higher end of day values and by smaller change scores from the initial to the end of day measures (*r1*–*r2*). Accordingly, we examined the profile of individuals with “normal” or good approach at the end of the day (i.e., scores of 0 on *r2*). Fifty-six boys with FXS had one or more zero scores at the end of day ratings, while 31 had three or more zero scores at the end of day ratings. The latter group had higher VABS scores (mean VABS 55.9 vs. 52.5 in entire cohort) and lower proportion of subjects with ASD (~10%) than the entire cohort (~32%). Considering the association between social avoidance parameters and facial expression and between eye contact and autistic behavior, we evaluated subjects with zero values for either *r2d1FA* and *r2d2FA* or *r2d1EC* and *r2d2EC*. The former group (*n* = 44), linked to facial expression, did not have a distinguishable profile but a rather high-ASD proportion (~21%). Confirming the association between eye contact and autistic behavior, only one of the 26 subjects (~4%) with zero scores on eye contact at both days was labeled as ASD, and the group had an overall higher function profile (mean VABS 57.4 vs. 52.5 in entire cohort).

Data on SAS change scores was in general agreement with the aforementioned results. Change scores for facial expression on the first day and eye contact on the second day (i.e., *r1d1FA*–*r2d1FA*, *r1d2EC*–*r2d2EC*) were inversely correlated with CARS scores, even after controlling for differences in age and VABS scores. These co-variables were introduced because of the influence of gender on the change in eye contact on the second day (lower in males), age on the change in physical movement on the first day (inverse correlation in boys), and VABS on the change in physical

movement on both days, and the change in eye contact on the second day (also inversely correlated in males). As for the primary SAS measures, data on CARS as a categorical variable were in general consistent with analyses of CARS as continuous scores. Boys in the “Yes ASD” category had significantly lower modulation or improvement in facial expression of avoidance across the first day than those in the “No ASD” category. Similarly, boys in the “Yes ASD” category had less modulation or improvement in eye contact across the first day at a trend level. SAS change scores were not related to any social avoidance parameter.

Discussion

The primary purpose of this study was to examine social approach behaviors and their relationship to social avoidance and autistic behavior in children with FXS in order to further delineate the spectrum of social behavior abnormalities in children with FXS and autism. Secondly, we introduce the SAS, a new behavioral scale that measures multiple social approach behaviors including physical movement, facial expression, and eye contact. The SAS also examines the effect that time spent with a person and location has upon these multiple social approach behaviors. Our findings suggest a complex relationship involving gender, age, location, and duration of interaction to social approach and autistic behavior in children with FXS. We found an association between initial facial expression and avoidant temperament and withdrawn behaviors. Moreover, modulated eye contact, corresponding to increases at the end of assessment days, was a stronger as well distinctive and specific correlate of severity of autistic behavior in boys with FXS despite being influenced by a variety of factors (i.e., location, age).

Our data support the notion that children with FXS display a specific profile of social approach behaviors as reflected on the SAS. As expected, individuals with FXS were the least socially approaching at the onset of the assessment day and the most socially approaching at the end of the assessment days. This pattern was observed across all FXS subgroups; however, we could not clearly differentiate the effect of gender and cognitive function upon social approach behavior because of the interaction between younger age and female gender and between older age, male gender, and lower cognitive function. Girls and younger (<5 years) boys with FXS displayed a more variable profile reflected in greater change in social approach over time, “warming up” more easily after exposure to unfamiliar examiners, than older boys with FXS.

Location, or evaluation setting, influenced the second daily measures of eye contact approach, the most sensitive SAS parameter, as well as second daily measures of physical approach behavior. Boys with FXS showed higher scores (i.e., less approach) for both eye contact and physical approach at school than in the familiar home setting. Similar to our recent findings of a significant, albeit small, increase in CARS scores over time in children 1–14 years of age (Hatton et al., 2006), our SAS data also suggest an increase in social avoidant behaviors in older boys with FXS. These effects were not found on the facial expression (FA) scale but were observed on both the physical movement (MO) and eye contact (EC) scales for the end of day ratings. Thus, older boys with FXS displayed similar approach behavior to young boys upon initial interaction with the examiner; however, older boys did not “warm up” over time as observed in the younger boys. One possible explanation for this finding is that boys with FXS learn or are reinforced for displaying socially avoidant behaviors resulting in an increase of these behaviors over time (Hall, DeBernardis, & Reiss, 2006). For example, if a young boy with FXS finds some aspects of social interaction difficult and avoids eye contact and moves away from people as a way to cope with this difficulty and is allowed to react this way or reinforced for acting this way (e.g., social demands are removed), then an increase in his avoidance behavior is likely given standard behavioral conditioning theory. An alternative explanation for this age effect is that boys with FXS become more aware of their social challenges as they age resulting in increased social avoidance.

Analyses of the relationship of social approach behaviors on the SAS to social avoidance on parent ratings of problem behavior and temperament highlighted the importance of differentiating between a general style of poor approach across time and settings versus a pattern of poor approach primarily as a response to unfamiliar places or people in boys with FXS. When taking broad measures of social withdrawn behavior (CBCLw total score), there was no relationship to any SAS parameter. However, a focus on specific behaviors (CBCLw items) supported relationships, though weak, between increased social avoidance and less physical approach as well as social indifference and more fearful facial expression particularly during initial interaction on the SAS. A stronger relationship was shown with temperament ratings of low-approach behavior related to high-facial fear and poor eye contact during initial interaction on the SAS. Taken altogether, facial expression during initial interaction on the SAS is related to both

specific behaviors on the CBCLw and to general ratings of approach on the CTS. The discrepancy in relationship between total scores on CBCLw, specific items on CBCLw, and general ratings on the temperament scales (CTS_{apr}) is likely due to different conceptualizations of approach and withdrawn behavior across these measures. Specifically, the CBCLw scale reflects a combination of social avoidance and social indifference behaviors (Budimirovic et al., 2006) that are static across time (e.g., is *generally* withdrawn and uninvolved with others), whereas the CTS reflect approach as a response to *new* persons, places, and events. On the other hand, the SAS allows ratings of both initial approach and approach with increased familiarity. The closer association between social avoidant behaviors and SAS measures of facial expression approach, in contrast with the relationship between SAS measures of eye contact and a variety of factors including autistic behaviors (see next section), emphasizes the relative specificity of SAS measures.

A strong relationship between the SAS and autistic behaviors in boys with FXS was demonstrated by a series of analyses using the CARS scores on a continuum and as a categorical variable (CARS ≥ 30 = ASD behavior), and either primary or secondary (i.e., change scores) SAS measures. Analyses examining SAS profiles suggest that the relationship between ASD and SAS is primarily driven by the degree to which the boys with FXS “warm up” or increase social approach over time regardless of using CARS scores as a continuum or as a categorical variable. Boys with FXS and ASD display similar levels of initial approach to boys with FXS without ASD; however, boys with FXS and ASD display a flatter SAS profile characterized with little modulation over time. Eye contact, in particular, appears to differentiate boys with FXS and ASD from those with FXS alone in that boys with FXS and ASD continue to display poor eye contact over time while boys with FXS alone increase eye contact over time. The relationship between poor modulation of SAS and autistic behaviors in FXS was confirmed by calculating change scores for modulation of social approach, controlling for initial responses, across both evaluation days. In addition to describing the relationship of SAS to autistic behavior, we tested our hypothesis of abnormal regulation of social approach in boys with FXS and ASD. Examination of the predictive value of second (“modulated responses”) daily SAS parameters for CARS scores and ASD status demonstrated that age-appropriate eye contact approach (zero scores), but not facial expression or physical approach (also

zero scores), was significantly correlated with higher cognitive function and less severe autistic behavior.

Our results that autism status is associated with less social approach behavior within our sample of boys with FXS are consistent with studies of children with autism (non-FXS). This work has shown that children with autism (non-FXS) often do not respond to social stimuli in general (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998), and display less positive responses and more “no responses” than verbal-matched children with mental retardation (Jackson et al., 2003). In addition, our findings that social approach behaviors are associated with autistic behavior in boys with FXS are consistent with other reports (Hatton, Bailey, Hargett-Beck, Skinner, & Clark, 1999; Kaufmann et al., 2004). However, to our knowledge, this is the first study to report a relationship between *modulation* of social approach behaviors over time to autistic behavior in boys with FXS.

While we did not include physiological or imaging measures in the current study, the recent demonstration of an association between decreased cortisol reactivity and increased autistic behavior in males and females with FXS (Hessl & Cohen, 2005) may be explained by limbic dysfunction. In relationship with our data on the SAS, disturbed behavioral regulation of limbic origin as well as involvement of other brain regions implicated in social cognition (e.g., superior temporal sulcus) are potential mechanisms for abnormal social approach in FXS.

This study has a number of limitations such as failure to include the ADOS-G or ADI-R as measures of autistic behavior, lack of a consistent IQ measure, and a small sample of females. However, our findings increase knowledge on the relationship of social approach to social withdrawal and autistic behavior in children with FXS in several important ways. First, we documented a distinctive profile of social approach behaviors in FXS that vary over time and are influenced by gender and setting. While numerous clinical reports have described approach-withdrawal behavior and increased social avoidance to unfamiliar people in persons with FXS (Cohen et al., 1988; Hagerman, 2002), this is the first study to document this phenomenon using multiple markers across time in a relatively large sample. Second, we found that less social approach characterizes older boys with FXS. In particular, our data show that these difficulties are specific to poor modulation of social approach over time with older boys displaying less “warming up” to unfamiliar people over time. Third, a relationship between the SAS and autistic behavior was supported. This relationship seems to be primarily driven by

whether or not boys with FXS increase their social approach behaviors over time. Improved eye contact, in particular, was found to be a very strong predictor of lower autistic behavior in this sample. Thus, these data suggest that modulation of social approach behaviors, particularly eye contact, may differentiate subgroups of boys with FXS based on their autism status. Fourth, social approach behaviors characterized by SAS that consistently correlated with measures of social avoidance (i.e., facial expression) were different from those associated with autistic behavior (i.e., eye contact), supporting the notion that social avoidance and autistic behavior are related but distinct behaviors. Finally, we introduce the SAS, a new measure that appears to be a sensitive and valid measure of social approach behaviors in children with FXS. We are currently examining the relationship of the SAS to social approach and autistic behaviors in a longitudinal sample. In addition, we have collected salivary cortisol and will evaluate the relationship of this biomarker to the SAS and other relevant behavioral measures.

Taken together, these findings suggest a complex relationship between social approach, social withdrawal, and autistic behavior in boys with FXS. Given the high estimates of autistic behavior and elevated level of autism diagnoses in FXS, it is critical that we have a clear understanding of these behaviors to guide diagnostic and treatment efforts. For example, knowing that improvement in social approach behaviors may distinguish boys with FXS from those with FXS and ASD, clinicians should gather parental or teacher information via rating scales to reflect social interaction with familiar people, and/or schedule an adequate amount of time to interact with the child to allow direct observations of this phenomenon. Similarly, the development of individual education programs can be more highly targeted if parents and professional differentiate between social approach problems that are chronic across multiple settings over time versus those that are situation or time specific.

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