Symposium Title: Improving Measurement of Behavioral Constructs in Neurodevelopmental Disorders: Graduate Student Research Symposium

Chair: Kathryn Unruh¹

Discussant: Sigan Hartley²

Overview: The purpose of this symposium is to highlight the research of graduate students contributing to the area of measurement in neurodevelopmental disorders. This symposium features work in a variety of neurodevelopmental disorders (e.g., ASD, FXS, IDD), in addition to a range of ages, verbal ability levels, and behavioral domains. The first set of presentations will detail methods for measuring anxiety in males with FXS and males with ASD, using both parent report and cortisol measurements to differentiate groups. The second set of presentations will explore the measurement of language abilities in school-aged children with FXS and ASD. Authors will address the differences in play-based and standardized measurement of expressive language as well as potential targets for assessing language-based treatment effects. The final presentation will demonstrate the construction and feasibility of a measure of social motivation in adolescents with ASD who have minimal verbal ability / IDD and postulate on the effectiveness and future use of similar measures for capturing this construct. The role of the discussant will be two-fold. First, to provide an overview of the unique challenges that researchers face when attempting to appropriately measure behaviors in the populations of interest in neurodevelopmental disorders, including adequate phenotypic classification and sensitive treatment outcome measurement. Second, the discussant will highlight the importance of the Gatlinburg conference in the development of student trainees.

Paper 1 of 5

Paper Title: Prevalence and Correlates of Anxiety Disorders in Adolescent and Adult Males with Fragile X Syndrome and Autism Spectrum Disorder

Authors: Jordan Ezell³, Sara Matherly³, Leonard Abbeduto⁴, Jane E. Roberts³

Introduction: Fragile X syndrome (FXS) is a monogenetic disorder characterized by abnormal social behavior and intellectual disability. FXS is also the most frequent inherited cause of autism spectrum disorder (ASD). Additionally, high rates of anxiety symptomatology have been reported in FXS and ASD. Yet, few studies have examined rates of anxiety using a DSM-IV based measure in adolescents and adults with FXS compared to those in ASD, or the relationship of anxiety symptoms to autism severity, age, and nonverbal cognitive ability. In fact, Cordeiro, et al (2011) is the only study to examine anxiety in FXS using a DSM-IV based measure; however, this study included both males and females across a wide range of ages (5-33) and did not directly compare FXS to ASD or use mechanistic factors such as biomarkers. Since nearly 70% of males with FXS meet criteria for ASD with considerable overlap with ASD and anxiety features, disentangling the relationship of these features in FXS is critical to direct targeted treatments and can contribute to the latent heterogeneity in ASD. The purpose of this study is to advance our understanding of the nature of anxiety disorders in adolescent males with FXS through comparison to those with idiopathic, non-syndromic ASD by examining the prevalence of anxiety disorders and the relationship of anxiety disorders to autism severity, age, and nonverbal cognitive ability, as well as biomarkers.

Methods: Participants included males with FXS (n=31) or ASD (n=20) from 16 to 24 years of age from an ongoing longitudinal study. Measures included the Children’s Interview for Psychiatric Symptoms-Parent Version (P-ChIPS); a semi-structured, DSM-IV (adapted for DSM-V) interview with mothers, that measured diagnosis of anxiety disorders including Specific and Social Phobias and Generalized Anxiety Disorder (GAD). The Autism Diagnostic Observation Schedule-2 (ADOS-2) was used to document autism severity, and the Leiter International Performance Scale-Revised (Leiter-R) measured nonverbal IQ. Additionally baseline cortisol levels and change in cortisol levels over the first day of assessment were analyzed in the FXS group.

---

¹ Vanderbilt Brain Institute, Vanderbilt University
² Waisman Center, University of Wisconsin-Madison
³ University of South Carolina
⁴ MIND Institute, University of California, Davis
**Results:** Nonparametric analyses were used to compare the FXS and idiopathic ASD groups because of the small sample size. Findings indicate that 51% of the FXS adolescents met criteria for an anxiety disorder compared with 50% in ASD. Across the FXS and ASD groups 35% versus 15% met for Specific Phobia, 12% versus 30% met for Social Phobia and 33% versus 40% met for GAD, respectively. Although there are differences in the rates of specific anxiety disorders between etiologic groups, the Pearson’s Chi-squared test revealed that these differences are not significant for Specific Phobia ($\chi^2(1, N = 51) = 1.4, p = .24$), Social Phobia ($\chi^2(1, N = 51) = 1.5, p = .22$), or GAD ($\chi^2(1, N = 51) = 2.9, p = 0.09$). Odds Ratios analysis did show that the FXS group is 2.9 times more likely to have a specific Phobia than the ASD group. Using the Mann-Whitney-Wilcoxon Test, analyses showed that the FXS anxious and non-anxious groups had no differences in ADOS-2 severity scores, nonverbal intellectual ability, and age. Further analysis showed the same results for the ASD anxious and non-anxious groups. Exploratory analysis in the FXS group indicated that baseline cortisol and change in cortisol over the assessment day were not significantly different between the anxious and non-anxious groups.

**Discussion:** Our primary finding is that approximately half of the FXS and ASD sample met for an anxiety disorder based on DSM-V criteria. This study is generally consistent with previous work indicating high prevalence of anxiety disorders in FXS and ASD; however, lower rates were found for both the presence of any and specific anxiety diagnoses across both groups. Even though the rates of anxiety disorders were nearly identical across genetic etiologies there were clear differences within specific disorders. This is consistent with the Cordeiro, et al (2011) study which also found the most common anxiety disorder in FXS to be specific phobia. Studies in idiopathic ASD indicate varied rates of anxiety disorders, which is thought to reflect heterogeneity within sampling due to wide ranges of age, autism severity, and intellectual functioning. Further, no significant relationship was found between cortisol regulation and DSM-V anxiety disorders within the FXS group. This might be related to previous studies indicating that physiological dysregulation patterns in FXS may not be directly related to presence of anxiety disorders, but rather to the presence of ASD symptoms. Thus, our measurement of cortisol regulation may be confounded with other features of the FXS phenotype which includes ASD symptoms. This study is the first that directly compares rates of anxiety disorders across adolescents and adults with FXS and idiopathic ASD within a small range of ages, intellectual ability, and autism severity. Reduced rates of anxiety disorders may be indicative of adolescent or young adult males with lower intellectual functioning who have FXS or ASD.

**References:**

**Paper Title:** Cortisol Profiles Differentiate Young Adult Males with Autism Spectrum Disorder from Fragile X Syndrome

**Authors:** Sara Matherly, Jessica Klusek, Angela John Thurman, Andrea McDuffie, Jane E. Roberts, Leonard Abbeduto

**Introduction:** Fragile X syndrome (FXS) is the most common known single-gene cause of autism spectrum disorder (ASD) and is characterized by problems modulating social and emotional behaviors, particularly during stress. Anxiety and atypical arousal modulation are also hypothesized to underlie behavioral attributes seen in idiopathic ASD (iASD), such as the need for consistency and sameness. However, self-report and parental-reports can be limited in these populations due to difficulties verbalizing experiences and conceptualizing normative social frameworks. Thus, salivary cortisol, a stress response hormone secreted by the hypothalamus-pituitary-adrenal (HPA) axis, provides a promising index of anxiety and arousal modulation particularly in populations with intellectual disabilities. Elevated baseline and suppressed HPA axis regulation have been found in FXS. In contrast, hypo-responsiveness to social stimuli has been reported in iASD; however, no direct comparisons exist between responses in FXS to iASD. This study sought to delineate the interaction between genetic etiology and autism symptomatology on
HPA axis regulatory subsystems in adolescent males with FXS and iASD, which has implications for education, assessment, and interventions to promote positive outcomes in adulthood.

**Methods:** Participants included adolescent males with iASD (n=15) and FXS (n=54). The FXS group did not differ in age (M=18.3, SD=2.3) to the iASD group (M=18.0, SD=2.4). Salivary cortisol was measured in two conditions: pre-assessment and reactivity post-assessment following a day of standardized and experimental assessments of language and cognition at two study sites; UC Davis MIND Institute and University of South Carolina. Modulation of stress response was computed as the reactivity subtracting pre-assessment level. Cortisol was analyzed by radioimmunoassay and values were natural-log transformed for normality. Autism severity scores based on overall behaviors from the ADOS-2 were used as a continuous index of autism symptomatology. Nonverbal intellectual ability was measured using growth composite scores from the Leiter-R.

**Results:** Nonverbal IQ was not related to cortisol modulation in either group so was not included in the models. Results of an ANOVA testing the effects of group (FXS versus iASD) and autism severity and the interaction of group with autism severity indicated an interaction effect (F[1, 64]=4.517, p=.037). Post-hoc interaction contrasts indicated that the effect of autism symptoms on modulation of cortisol differed by group. Autism symptoms in FXS were not associated with modulation of cortisol (F[1, 64] = .230, p = .636, = .003); however, an association between autism symptoms and modulation of cortisol was found in iASD with increased autism features related to greater modulation reflected in higher cortisol levels at the end of the day (F[1, 64] = 5.760, p = .019, = .081).

**Discussion:** Salivary cortisol was examined as a biomarker of stress in males with FXS contrasted to those with iASD due to the complex phenotypic overlap in both of these populations. Results illustrate greater autism symptomatology was associated with greater modulation and higher stress response levels post-assessment in males with iASD, but not FXS. These findings support etiology specific physiological dysregulation patterns in FXS contrasted to iASD with autism symptomatology negatively influencing stress responses in males with iASD only. Future work will compare HPA axis stress responses to anxiety and other behavioral attributes in FXS.

**References:**


**Supported by:** NIH 2R01HD024356-20

**Paper Title:** Comparison of Methods for Assessing Spoken Language in Young Children with FXS or ASD

**Authors:** Lauren Bullard4 5, Robyn Tempero Feigles4, Stephanie Summers4, Andrea McDuffie4, Angela John Thurman4, & Leonard Abbeduto4

---

5 Human Development Graduate Group, University of California, Davis
Introduction: The ability to use spoken language for communication is substantially impaired in individuals with fragile X syndrome (FXS) or autism spectrum disorder (ASD). At the same time, however, the patterns of language impairment may differ across these two conditions. When considering language differences, it is important to acknowledge that the context used for measuring language may impact the profiles obtained for children with neurodevelopmental disorders. This is especially important to consider when assessing developmentally young children or children with high levels of challenging behaviors as the demands associated with testing may negatively impact results. The present study sought to characterize spoken language in children with FXS and ASD using both standardized and naturalistic approaches as well to examine the associations between the two approaches.

Research Questions:
1. Are there between group differences in child expressive vocabulary and grammar as measured by widely used standardized language measures?
2. Are there between-group differences in child expressive vocabulary and grammar as measured during a semi-structured naturalistic play-based language sample?
3. Are there concurrent associations between child language sampled during play and measured using standardized assessments of vocabulary and grammar?

Methods: The present study is part of a larger longitudinal study of children with FXS or idiopathic ASD. Participants were 14 children with ASD and 14 with FXS, ages 4 to 10 years, matched on chronological age, nonverbal IQ, and autism symptom severity. A comparison group of 14 typically developing 2- to 5-year-olds, matched on nonverbal cognitive ability level was also included. Language was assessed in two contexts: (1) commonly used standardized assessments and (2) a semi-structured parent-child play sample measuring expressive vocabulary and grammar. The Expressive Vocabulary Test, Second Edition (EVT-2; Williams, 2007) was administered as was the syntax construction subtest of the Comprehensive Assessment of Spoken Language (CASL; Carrow-Woolfolk, 1999). During the semi-structured parent-child play sample, the mother and child were given a standardized set of developmentally appropriate toys and instructed to play as they usually would for approximately 15 minutes. Play samples were video-recorded and a 10-min segment was transcribed using Systematic Analysis of Language Transcripts (SALT; Miller & Iglesias, 2008) to obtain measures of vocabulary (i.e., number of different words; NDW) and syntax (i.e., mean length of utterance in morphemes; MLU).

Results: A series of one-way ANOVAs were conducted to compare measures of child spoken language across the three participant groups. Within the standardized contexts, there was a significant effect of group \( (p < .05) \) for expressive vocabulary as measured by the EVT and expressive syntax as measured by the CASL. Post hoc comparisons revealed that children with ASD performed significantly lower on the EVT \( (M = 35.14, SD = 27.11) \) and CASL \( (M = 4.50, SD = 6.44) \) when compared to children with typical development, \( (M = 63.79, SD = 17.43) \) and \( (M = 13.77, SD = 7.51) \). Within the naturalistic context, there was a significant effect of group \( (p < .05) \) for NDW and MLU. Post hoc comparisons revealed that children with ASD used significantly fewer different words \( (M = 53.21, SD = 51.39) \) and had a shorter utterance length \( (M = 2.24, SD = .90) \) during parent-child play compared to typically developing participants, \( (M = 100.21, SD = 34.49) \) and \( (M = 3.28, SD = 1.02) \). The difference in MLU between children with FXS \( (M = 2.36, SD = 1.07) \) and typically developing children was marginally significant \( (p = .057) \). For all three groups, there were significant concurrent associations between the two assessment contexts. For the typically developing group, NDW during the play sample was significantly associated \( (p < .05) \) with performance on the EVT. For the FXS and ASD groups, NDW during the play sample was significantly correlated with performance on the EVT and MLU was significantly correlated with performance on the CASL.

Discussion: Consistent differences in vocabulary and grammar were observed for children with ASD and typically developing children matched on developmental level regardless of the assessment measure used. Data from the FXS group suggests that results from the naturalistic context may be more sensitive to between-group differences in grammar than typical standardized tests. There were robust relationships between expressive language as measured during naturalistic play-based interactions with a caregiver and results of standardized language testing. These results suggest that more naturalistic interactions may provide a useful alternative to standardized assessments, especially given the lower burden of the former (e.g., testing time and demands on the child). This finding has a range of implications for providing assessment at a distance using telehealth technology.
References:


Supported by: NICHD R01 HD054764

Paper 4 of 5

Title: Inferential Language Use by School-Aged Boys with Fragile X Syndrome: Effects of a Parent-Implemented Spoken Language Intervention

Authors: Sarah Nelson*, Amy Banasik*, Robyn Tempero Feigles*, Andrea McDuffie*, Leonard Abbeduto*

Introduction: School-aged boys with fragile X syndrome, the leading inherited cause of intellectual disability, have difficulty using spoken language to engage in sustained back-and-forth interactions with a conversational partner. Narrative story-telling, in which the use of both literal and inferential language (i.e., language that goes beyond describing concrete events depicted in story illustrations; van Kleeck, Vander Woude, & Hammett, 2006) is necessary to effectively describe a sequence of events in a coherent manner, is one aspect of spoken language that is important for a range of developmental and academic outcomes. The current study examines the impact of a distance-delivered, narrative-based, parent-implemented spoken language intervention (McDuffie et al., under review) on the use of inferential language. The intervention was designed to lead to more sustained conversational interactions and enhanced vocabulary and syntax, and inferential language was not explicitly targeted; however, previous research with other populations suggests that the maternal behaviors targeted in this intervention as well as the shared story-telling context in which parent training was embedded could promote the use of inferential language. Expressive language samples are recommended as an outcome measure for individuals with FXS (Berry-Kravis et al., 2013), and coding inferential language use during narrative expressive language samples could be a useful approach for characterizing spoken language beyond the common measures of vocabulary and syntax.

Research Questions

1. Does participation in a parent-implemented spoken language intervention result in changes in the frequency of children’s use of common categories of inferential language during shared story-telling interactions with the mother? Do these gains generalize to a clinic-based narrative language sample with the mother?
2. Does participation in a parent-implemented spoken language intervention result in changes in the frequency of children’s prompted and spontaneous use of inferential language during shared story-telling interactions with the mother? Do these gains generalize to a clinic-based narrative language sample with the mother?

Methods: Twenty mother-child dyads were randomly assigned to either an active treatment group or a treatment-as-usual control group following a pre-treatment assessment visit. Three shared story-telling interactions between mother and child were recorded in the home via distance video teleconferencing during the two weeks prior to, and following, the 12-week intervention. Dyads also completed a narrative language sample at the pre- and post-intervention assessment visits. Video recordings of these language samples were transcribed and coded for the presence of prompted and spontaneous inferential language in the categories of character goal-related actions, character actions not related to a goal, causal antecedents and consequences, character state, character emotion, character dialogue, story setting, and evaluations (Tompkins, Guo, & Justice, 2013).

Results: Two-way mixed ANOVAs with Time (Pre/Post) as the repeated measure and Group (Treatment/Comparison) as the between-participants factor were used to examine treatment gains. For child use of common categories of inferential language in the home-based distance sessions, the analysis yielded significant Time x Group interactions (p<.02) for character goal and non-goal related actions, character state, dialogue, and setting, and a marginally significant interaction for causal inferences.
Furthermore, for the clinic-based generalization context, the analysis yielded a significant Time x Group interaction for character state inferences (p=.018), and marginally significant interactions for causal (p=.089) and setting (p=.052) inferences. For child use of prompted and spontaneous inferential language, the analysis yielded a significant Time x Group interaction for prompted inferences (p=.001) in the home-based distance sessions as well as a significant Time x Group interaction for prompted inferences (p=.002) in the clinic-based generalization context. In all comparisons, inferential language use was greater in the treatment group. There were no significant differences between groups for use of spontaneous inferential language.

**Discussion:** These results suggest that participation in an intervention embedded in the context of shared story-telling can lead to increases in frequency of child use of common categories of inferential language. These gains were observed despite the fact that inferential language was not directly targeted in the intervention; we expect that this was likely due to mother’s use of the targeted language facilitation strategies. Although there were significant gains in treatment group in the frequency of use of prompted inferences, no differences emerged between groups in the use of spontaneous inferential language, suggesting that the children were relying largely upon maternal scaffolding to engage in inference generation. Because inferential language is important for both narrative and reading comprehension, gains in inferential language could potentially lead to positive functional and academic outcomes for school-aged boys with fragile X syndrome. Furthermore, these results provide preliminary evidence for the utility of using inferential language as coded from narrative expressive language samples as a sensitive outcome measure in treatment studies.

**References**


**Supported by:** NICHD U54 HD079125-02
**Methods:** Visual attention to paired stimuli is a well-documented, robust measure of preference. Our preferential viewing (eye-tracking) task measures patterns of visual attention to social and nonsocial content. Social images (SOC) are paired with one of two types of objects: images previously found to be of high interest to individuals with ASD (Sasson, et al., 2012; HAI images; e.g. trains, electronics) and images previously found to be of low interest to individuals with ASD (Sasson, et al., 2012; LAI images; e.g. clothing, furniture). Stimuli were presented in a passive manner (no instructions) for 5 seconds each, with a variable 2-6 second interstimulus interval. Variables of interest included: latency (duration to first fixation on each discrete image in an array), preference (total viewing time to a discrete image, controlling for total look time), fixation count (number of discrete fixations on an image) and average fixation duration (average length of fixations to an image). Participants with ASD were classified as either MVA (Verbal IQ < 70; N = 15; mean age = 11.9 years) or AVA (Verbal IQ > 90; N = 48; mean age = 13.9 years); our sample also included typically developing peers (TYP; N = 31, mean age = 13.8 years).

**Results:** Task completion rate was similar across ASD groups (67% of MVA, 69% of AVA). Repeated measures ANOVA revealed that both MVA and AVA subgroups were slower than the TYP group to orient to faces (latency), only when paired with HAI images ($F(2,71) = 6.59, p = .002$) but not LAI images ($F(2, 71)= .457, p = .635$). Latency to face did not differ between ASD subgroups for either array type ($t = -1.6, p = .22$). Interestingly, preference for faces was reduced in AVA participants compared to TYP for both array types ($F(1, 72) = 7.67, p = .001$); this difference was not observed for MVA participants ($p = .920$). Number of discrete fixations in MVA participants was greater than both TYP and AVA participants ($F(2,59) = 11.2, p < .001$); however, these fixations were shorter in their average duration ($F(2,59) = 17.18, p < .001$).

**Conclusions:** Here we demonstrate that minimally verbal children with ASD can successfully complete a passive eye-tracking task at rates that are comparable to those of verbal ASD peers. Both MVA and AVA children were significantly slower to look to faces when paired with an HAI image relative to TYP, providing evidence that social motivation deficits may manifest similarly in both ASD subgroups. Domain general attentional parameters (e.g., fixation duration) were similar in AVA and TYP but altered in MVA suggesting that MVA children may have a unique attentional impairment relative to their verbal peers with ASD.

**References:**


**Supported by:** NIH R01MH07 may play an important role in idiopathic primary ovarian insufficiency or neurodegenerative disorders.