Symposium Title: Anxiety in Autism and Fragile X Syndrome

Chair: Jane E. Roberts¹

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Overview: Anxiety disorders constitute the most common and debilitating mental health problem in childhood. Neurodevelopmental subgroups such as autism spectrum disorder (ASD) and fragile X syndrome (FXS) are at even greater risk, with 65% and 87% meeting criteria for an anxiety disorder respectively (Cordeiro et al., 2011; Salazar et al., 2015). Recognition of anxiety in individuals with ASD or FXS is quite complex, however, given overlapping features. Also, assessment of anxiety in these populations is fraught with challenges due to a paucity of standardized measures designed for neurodevelopmental populations and the presence of cognitive and language impairments that typically preclude accurate self-report. Despite these challenges, accurate and early recognition of anxiety in neurodevelopmental disorders is critical to direct treatment aimed to reduce impairment or even prevent the occurrence of anxiety in high-risk populations. Furthermore, risk markers of anxiety, particularly those that are objectively and quantitatively measured, may be promising biomarkers for anxiety in high-risk populations, and may also be utilized as outcome measures in anxiety interventions. In this series of talks, we will present data on the presence of anxiety across the spectrum of development from infancy through adulthood utilizing multiple measures including eye-tracking, diagnostic interviews, rating scales, direct observation and biomarkers.

References/Citations:

Paper 1 of 4

Paper Title: Early Risk Markers of Anxiety in Infant Siblings of Children with Autism Spectrum Disorder

Authors: Abigail L. Hogan¹, Shannon L. O’Connor¹, Nicolas Poupore¹, Bridgette Tonnsen³, Jane Roberts¹

Introduction: Siblings of children with autism spectrum disorder (ASD) are at elevated risk for anxiety, which can have debilitating effects on both social and academic functioning (Shivers et al., 2013). However, very few studies have focused on the early risk markers of anxiety in these children. Prospective studies of later-born siblings of children with ASD (ASIBs) provide a unique opportunity to examine early predictors of anxiety from a developmental perspective. A better understanding of early anxiety risk markers is of critical importance, as it enables the early identification of children at elevated risk for anxiety, thus providing an opportunity for early intervention and the optimization of anxiety-related outcomes. In typically-developing infants, heightened fear responses and atypical heart activity (e.g., respiratory sinus arrhythmia, RSA) have been identified as early markers of the later emergence of anxiety (Brooker et al., 2013). Additionally, increased attention to potentially threatening targets is commonly observed in children with anxiety. The present study investigated multiple indices of fear and baseline RSA in 12-month-old ASIBs and low-risk controls (LRCs) to determine if early risk markers of anxiety are present. Both social fear and object fear were investigated, as previous work has suggested that social fear may be a more salient marker of anxiety risk during infancy (Brooker et al., 2013).

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Methods: Participants included 28 ASIBs (chronological age $M = 12.94$ months, $SD = 1.33$ months) and 19 low-risk typically developing controls (chronological age $M = 12.34$ months, $SD = 0.72$ months). The proportion of males was similar across both groups (ASIB: $n = 21, 75%$; LRC: $n = 14, 74%$). Parent-reported fear was measured via the Fear Subscale from the Infant Behavior Questionnaire-Revised (IBQ-R; Gartstein & Rothbart, 2003), which includes fear responses to both social and non-social stimuli. Observed social fear was measured by gaze elicited during a Stranger Approach paradigm, and observed object fear was measured by gaze during a “Scary Spider” paradigm. For each paradigm, the proportion of time spent directing gaze toward the fear-inducing target (i.e., stranger or spider) served as an index of attention to threat. The proportion of time spent directing gaze to the parent was also calculated to reflect the amount of social referencing to a caregiver. Additionally, the proportion of time averting gaze (i.e., looking away from both the target and the parent) was computed. Heart activity was recorded during a baseline period, and RSA was derived.

Results: Independent samples t-tests were used to examine group differences in parent-reported fear, observed behavioral social and object fear (i.e., gaze behavior), and RSA. While the ASIB group had elevated parent-reported fear ($M = 3.06, SD = 1.22$) compared to LRCs ($M = 2.49, SD = 0.98$), the difference was not significant but a medium effect size is suggested, $t(45) = -1.71, p = .09, Cohen’s d = .52$. In both the social and object fear paradigms, ASIBs and LRCs demonstrated similar gaze behavior for looking at the parent and fear target, $t < ±1.32, ps > .20$. However, the ASIB group spent more time averting gaze away from both the target and the parent in the object fear paradigm; while this was not significant, a medium effect size was indicated $t(45) = -1.77, p = .08, Cohen’s d = .52$. Groups did not differ on baseline RSA, $t(31) = .85, p = .40$. Pearson correlations between all measures of fear and RSA were investigated. In the ASIB group, elevated parent-reported fear was correlated with more time looking at the parent during the object fear paradigm, $r = .51, p = .006$. Additionally, reduced RSA was correlated with increased time averting gaze from the target and the parent during the social fear paradigm, $r = -.51, p = .04$. No significant correlations between fear and baseline RSA were observed in the LRCs, all $rs < ±.44, ps > .20$.

Discussion: To date, it is unclear whether early risk markers of anxiety can be reliably identified in ASIBs during infancy. Such information could provide critical insight into the emergence of anxiety in this high-risk cohort and provide valuable opportunities for intervention and optimization of outcomes, as evidence has shown that intervention during the preschool years can have a protective effect on anxiety and internalizing symptoms through adolescence in community samples. Results from the present study suggest that risk markers shown to be predictive of anxiety in community samples, such as heightened fear responses and reduced RSA, may not distinguish ASIBs at 12 months of age. However, parents of ASIBs did rate their children marginally more fearful than did parents of LRCs, and ASIBs tended to spend more time averting their gaze during an object fear paradigm. Though these results were marginally significant, the medium effect sizes suggest that these differences likely exist, but the statistical power to detect may have been limited by the small sample. Additionally, interesting correlations were observed in the ASIBs, but not the LRCs. For example, elevated parent-reported fear in ASIBs was related to increased time spent looking at the parent during the object fear paradigm. Thus, children whose parents perceive them as more prone to fearful responses in novel situations may reference their parents more often in an effort to determine how to respond in those situations. Finally, decreased baseline RSA in ASIBs was associated with more gaze aversion during the social fear paradigm, supporting theories that reduced RSA contributes to poorer modulation of attention. In all, these findings suggest that individual differences in physiology and fear may be interacting in ASIBs to confer later risk for anxiety. Future studies should examine the longitudinal effects of such factors as they relate to anxiety outcomes in ASIBs.

References/Citations:
Paper Title: Anxiety Disorders in Preschool Children with Fragile X Syndrome

Authors: Kelly E. Caravella1, Jane E. Roberts1

Introduction: Individuals with fragile X syndrome (FXS) are at high risk for comorbid disorders with reported rates of up to 86% meeting criteria for anxiety disorders (Cordeiro, Ballinger, Hagerman, & Hessl, 2011). To date, no research has been conducted that examines the prevalence of these disorders in preschool years for children with FXS. Other preschool populations with disabilities, such as those with autism spectrum disorders (ASD), have also evidenced elevated rates of generalized anxiety disorder (66%), specific phobia (53%) and social anxiety (15%; Salazar et al., 2015). Co-morbid anxiety symptomatology causes significant impairment in individuals with FXS and their families; therefore, identifying the onset and presentation of these disorders can lead to more precise treatment and interventions.

Methods: The mothers of 22 participants with FXS (15 Male, 7 Female) ages 3-6 years were administered the Preschool Age Psychiatric Assessment (PAPA; Egger & Angold, 2004) at a single time point. The PAPA is a semi-structured diagnostic interview that measures symptoms consistent with DSM-IV childhood disorders and requires in-depth research training. The anxiety disorders domain was used in the analysis, which includes the following subdomains: Separation Anxiety Disorder, Specific Phobia, Generalized Anxiety Disorder and Social Phobia. PAPA algorithms provide a dichotomous output representing whether symptoms did or did not meet criteria for each disorder.

Results: The majority of males (93%) and one female (14%) met criteria for at least 1 anxiety disorder. The female met criteria for Social Phobia and Generalized Anxiety Disorder. Anxiety diagnoses in the sample of males were present at the following rates: Specific Phobia (93%), Separation Anxiety Disorder (7%), Generalized Anxiety Disorder (27%) and Social Phobia (40%). When Specific Phobia was present, 57% endorsed more than 1 phobia. Phobias that were endorsed by more than one participant included: animals (n = 6), doctors/dentists (n = 4), injections (n=5), loud sounds (n = 3) and costumed characters (n=2). At least 7 additional participants with FXS will be added to the sample prior to conference presentation.

Discussion: These findings indicate that impairing anxiety symptomatology is present in preschool age children with FXS, and is occurring at higher rates in males than females. The occurrence of anxiety co-morbidities was also common with 60% of those who met for an anxiety disorder meeting for 2 or more disorders. Rates of males in our sample with anxiety disorders are comparable to work with older persons (Cordeiro et al., 2011) suggesting an early onset and persistence of symptoms beginning in the preschool years. However the rates of anxiety disorders in females with FXS in our sample is much lower than previous work (14% vs. 77%; Cordeiro et al., 2011). This may represent a later onset of impairing anxiety symptomatology in females with FXS. The near universality of specific phobia across all males with FXS is noteworthy and higher than rates found in older individuals suggesting developmental effects reflecting elevated prevalence in young children that may wane over time compared to other anxiety disorders.

References/Citations:
Paper Title: Characterizing Anxiety through Eye Tracking: Attentional Bias toward Threat in Fragile X Syndrome

Authors: Bridgette L. Tonnsen, Abigail L. Hogan, Jordan A. Ezell, Kelly E. Caravella, Jane E. Roberts

Introduction: Anxiety is one of the most common and debilitating comorbidity among individuals with fragile X syndrome (FXS), affecting over 85% of males (Cordeiro et al., 2011). However, efforts to assess anxiety in this population are challenged by language and cognitive impairments that often compromise the utility of traditional self-report measures. Bias toward threatening stimuli is a consistent marker of anxiety in non-FXS samples but has yet to be explored as a marker of anxiety in FXS. The present study explored bias to threat in FXS by (1) comparing threat bias in adolescents with FXS to typically developing controls (TD), thus establishing syndrome-specific patterns relevant to FXS, and (2) examining whether within-group variability in threat bias predicts anxiety in FXS. We hypothesized that adolescents with FXS would exhibit increased bias to threat relative to controls, with the greatest bias among individuals with FXS and comorbid anxiety disorders.

Methods: Participants included 25 males with FXS and 10 TD controls assessed between 15 and 23 years of age. We employed a chronological rather than mental age match group to maximize similarities in biological maturation and exposure to social experiences. Eye tracking was conducted using the SR Research EyeLink 1000 Plus system. We adapted task procedures and stimuli from Mogg et al., 2007. During each trial, participants were presented with pairs of faces that varied by facial expression (fearful, neutral) and intensity of the fearful facial expression (mild fear, full fear). For each participant, we calculated average proportion trials oriented toward fear (bias score) for each trial type (mild, full) and the difference in bias scores across trial types [(bias on full trials) – (bias on mild trials)]. Anxiety diagnoses were measured using the Children’s Interview for Psychiatric Syndromes – Parent Version (P-Chips; Weller et al., 1999), a semi-structured diagnostic parent interview of anxiety symptoms consistent with DSM-V. We used Wilcoxon two-sample tests to test group differences and used one-sample median test to determine whether observed biases were greater than expected by chance.

Results: Cross-group analyses indicate similar attentional biases across FXS and TD groups on full-intensity trials (Z=.18, p=.86), with both groups displaying significant biases toward fear (TD S=21.5, p=.008; FXS S=100, p<.001). However, groups displayed different patterns of orienting on partial intensity trials (Z=-3.51, p<.001), with the FXS group failing to show orienting bias (S=47.5, p=.13) and the TD group orienting away from fear (S=-27.5, p=.002).

Within the FXS group, 13 of 23 individuals met criteria for an anxiety disorder. Individuals with FXS+Anxiety exhibited statistically similar response biases on full versus partial intensity trials (S=13.5, p=.13), whereas those without anxiety exhibited greater fear bias on full intensity trials relative to partial intensity trials (S=26, p=.04), similar to patterns observed in the TD group (S=27.5, p=.002).

Discussion: Our data suggest visual threat bias presents abnormally in FXS and may offer an objective measure of anxiety that circumvents traditional limitations of self- and parent-report in this population. With further study, it is possible that eye tracking measures may improve characterization of anxiety in FXS and offer a sensitive metric for monitoring change over time, such as during the course of behavioral or psychopharmacological treatments.
References/Citations:


Paper Title: Differential Effects of Anxiety and Autism on Social Scene Scanning in Males with Fragile X Syndrome

Authors: Hayley Crawford^4,5, Joanna Moss^5,6, Chris Oliver^5, Deborah Riby^7

Introduction: Existing literature draws links between social attention and socio-behavioural profiles in neurodevelopmental disorders. Research has primarily identified atypically reduced social attention in autism spectrum disorder (ASD), which is behaviourally associated with social withdrawal, and atypically prolonged social attention in Williams syndrome, which is behaviourally associated with hyper-sociability (Riby & Hancock, 2008). Fragile X syndrome (FXS) is associated with a known socio-behavioural phenotype that includes being motivated to interact with others and interested in the social world. However, these features co-occur with heightened anxieties and social communication impairments. Previous studies investigating social attention in FXS have largely focussed on dwell time to the eye region of static isolated faces. However, studies investigating social attention to more naturalistic scenes in FXS are scarce. There is a need to utilise ecologically valid social scene stimuli to understand the social attention of individuals with FXS. Furthermore, given the socio-behavioural profile of the disorder, preliminary insight into the role of anxiety and autistic features is important to understand the potential mechanisms underlying social attention in this group. Using eye-tracking, this study addresses the following research aims: 1) to compare and contrast social attention in males with FXS compared to typically developing (TD) children matched on gender and receptive language ability, 2) to investigate the relationship between social attention and anxiety in males with FXS, and 3) to investigate the relationship between ASD symptomatology and social attention in males with FXS.

Methods: Participants were 11 males with FXS (M\text{age} = 26.29) and 11 TD children who were matched on gender, and receptive language ability (M\text{age} = 6.28). For the eye-tracking task, participants were presented with 20 colour photographs of naturalistic social scenes including human actors engaged in natural activities. Participants also saw 5 filler photographs of landscapes with no actor. The stimuli used were identical to those used in Riby and Hancock (2008). Firstly, we compared dwell times to the background, body, and face regions of the naturalistic social scenes in participants with FXS and TD participants. We then investigated the relationships between a) social scene scanning and anxiety using the Spence Child Anxiety Scale-Parent Version (Spence, 1999), and b) social scene scanning and autism symptomatology using the Social Communication Questionnaire (Rutter, Bailey & Lord, 2003).

Results: Data were presented as the total time, in milliseconds, that fixations were within each area of interest (background, body, face). Between-group comparisons of social attention were analysed using an ANOVA. The relationships between social scene scanning with anxiety and autism were assessed using Pearson’s and Spearman’s correlations. There was no difference in the overall amount of time participants spent viewing stimuli indicating comparable task engagement across the groups. Males with FXS did not differ to TD children on overall dwell time to the background, body or face regions of the naturalistic social

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scenes. Whilst males with FXS displayed 'typical' social attention, increased looking at faces was associated with both heightened anxiety and fewer social communication impairments in this group. This pattern of results was not observed in the TD group.

**Discussion:** Together, these results suggest that whilst social attention to naturalistic social scenes may be developmentally 'typical' in males with FXS, anxiety and autism symptomatology are differentially related to social attention in this population. These results offer novel insights into the mechanisms associated with social attention in FXS. This research paves the way for future investigations of the relationship between clinically-relevant, socio-behavioural phenotypes and social attention in theories of social attention in neurodevelopmental disorders.

**References/Citations:**