Symposium Title: Brain, Behavior and Treatments in Fragile X Syndrome

Chair: Jennifer L. Bruno

Discussant: Heather C. Hazlett

Overview: Fragile X syndrome (FXS), the most common known cause of inherited intellectual disability, is characterized by deficient production of the fragile X mental retardation gene protein (FMRP) (Swanger & Bassell, 2011), resulting in neurological and cognitive deficits. Previous research has described altered patterns of neurobiology present from early in development (Hoeft et al., 2010) and relationships between brain structure and behavior present in early childhood (Wolff, Hazlett, Lightbody, Reiss, & Piven, 2013). This symposium will focus on middle childhood/early adolescence, a critical time for brain and behavioral development. The first symposium will discuss FXS-specific differences in subcortical structure volume and patterns of restricted/repetitive behaviors. The second symposium addresses variation within males with FXS presenting evidence for subgroups defined by early structural brain growth and the clinically significant differences between these groups into middle childhood/early adolescence. The third symposium discusses the application of a novel treatment targeting problem behaviors in boys with FXS. Collectively, these presentations address behavior challenges that are unique to individuals with FXS including discussion of their variability, neurobiological underpinnings and response to treatment.

References/Citations:

Paper 1 of 3

Paper Title: Brain and Behavior Patterns In Fragile X Syndrome

Authors: Amy A. Lightbody1, Heather C. Hazlett2, Jennifer L. Bruno1, Joseph Piven2, Allan L. Reiss1

Introduction: Fragile X syndrome (FXS) remains the most common inherited cause of intellectual disability occurring in ~1 in 4,000 males and ~1 in 8000 females (Crawford, et al. 2001). The disorder impacts brain development and the phenotype includes cognitive impairment, aberrant behaviors, and social deficits. Individuals with FXS, particularly boys, often meet criteria for autism. However, studies suggest that repetitive behaviors may drive that diagnosis (Hall, et al, 2010) rather than the more salient social feature typically associated with autism. This study aims to understand differences in brain anatomy and the manifestation of repetitive behavior using a unique control group that accounts for gender, age, and level of autism symptomatology in an idiopathic group of individuals with developmental delay. In this way, we intend to elucidate how the brain and specific behaviors are developing irrespective of a clinical diagnosis of autism.

Methods: Participants included 44 boys with FXS and a control group of 57 boys matched on age (4-14 years) and symptoms of autism who participated in a longitudinal study of brain development in FXS. As part of a larger battery, participants completed the Differential Ability Scales (second edition) to evaluate IQ and the Autism Diagnostic Observation Schedule (ADOS) to assess autism symptomatology. Parents filled out the Repetitive Behavior Scale-Revised (RBS-R) addressing the frequency and severity of repetitive behaviors. Participants also underwent a structural MRI scan of their brain. Differences in brain region volumes and repetitive behaviors were analyzed using multi-variate analysis of covariance.

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Results: Controlling for total brain tissue volume, boys with FXS differed from the control group on all subcortical brain volume comparisons. The FXS group demonstrated larger volumes for bilateral thalamus, caudate, putamen, pallidum, and accumbens and bilaterally smaller volumes for the hippocampus and amygdala (all $p<0.001$). These findings are consistent with previous literature describing volumetric differences in children ages 1-5 years (Hoeft, et al, 2010). In examining differences in repetitive behavior between the two groups, children with FXS demonstrated overall higher levels of repetitive behaviors as measured by the RBS-R ($p<0.03$). For subdomains of the RBS-R, the types of behaviors demonstrated across the two groups differed. Parents of children with FXS endorsed more stereotyped ($p<0.003$) and restricted ($p<0.02$) behaviors than those in the control group, but fewer compulsive behaviors ($p<0.04$). There were no differences between the two groups on the self-injury, ritualistic, and sameness subdomains.

Discussion: These findings provide further evidence of the brain anatomy differences found in FXS from an early age and suggest that these differences are unique to FXS despite similar behavior manifestations in children of the same age and gender who do not have FXS. In addition, the types of repetitive behaviors (hallmark symptoms in both FXS and autism) demonstrated across the two groups are not the same despite similar overall levels of autism symptoms in both groups. This may indicate different mechanisms for repetitive behavior in FXS versus other conditions. Further brain-behavior connections and treatment implications will be discussed.

References/Citations:

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function remained stable at the third time point but the autism severity scores were only significantly different for the restrictive and repetitive behavior subscale (p's<0.05). Group differences were also significant for measures of expressive and receptive vocabulary (p<0.05), which were included at the third time point.

**Conclusions:** These results confirm the presence of two longitudinally defined, neuranatomically distinct and clinically relevant phenotypes among individuals with FXS. The stability of these groups into middle childhood/early adolescence indicates that subgroups based on early brain growth are relevant for later developmental outcomes. This information may be used to predict outcomes and guide design of targeted therapies. Furthermore, TDA of longitudinal anatomical MRI data may represent a useful method for reliably and objectively defining subtypes within other neuropsychiatric disorders.

**References/Citations:**

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**Paper 3 of 3**

**Paper Title:** Telehealth Delivery of Function-Based Behavioral Treatment for Problem Behaviors in Boys with Fragile X Syndrome

**Authors:** Scott S. Hall¹, Joy S. Pollard³, Katerina Monlux¹, Arlette Bujanda³

**Introduction:** Boys with fragile X syndrome (FXS) are at increased risk for exhibiting severe problem behaviors such as self-injury and aggression (Hall et al., 2016). These behaviors can be extremely distressing to families and can severely impact the child’s quality of life. However, interventions to decrease these behaviors in the long-term have met with limited success. In this study, we examined whether function-based behavioral treatments, delivered via telehealth, could reduce problem behaviors in boys with FXS.

**Methods:** Participants included 10 boys with FXS, aged 3 to 10 years, who were reported to exhibit problem behavior on at least a daily basis. For each participant, a Board Certified Behavior Analyst conducted an in-home functional analysis of the child’s problem behavior to identify the function(s) of the child’s problem behavior (Beavers et al., 2013). Based on this information, the child’s primary caregiver received coaching to implement function-based behavioral treatment with their child via telehealth over 12 weeks. In each case, telehealth sessions were initially implemented for 5 days per week, and were subsequently faded down to once per week, depending on progress.

**Results:** Significant reductions in the frequency of problem behavior were observed for 8 of the 10 boys with FXS over the 12-week treatment period. For the remaining two boys, one caregiver was unable to continue with the treatment due to work scheduling conflicts and another caregiver requested to be withdrawn due to illness. Across all caregivers, scores obtained on the Treatment Acceptability Rating Form - Revised (Reimers et al., 1992) indicated that treatment acceptability remained high during the 12 week period and at a 4-week follow-up.

**Discussion:** These data suggest that function-based behavioral treatments delivered via telehealth can be an acceptable, efficient and cost-effective method for reducing problem behaviors in children with FXS. The advantages and disadvantages of implementing behavioral treatments via telehealth for children with FXS will be discussed.

**References/Citations:**

³ Behavior Change Institute


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