Symposium Title: Early Phenotypic Profiles in Neurogenetic Syndromes

Chair: Deborah J. Fidler, Ph.D., Colorado State University

Discussant: Nancy R. Lee, Ph.D., Drexel University

Overview: In recent years, researchers have increasingly emphasized the role of developmental processes in the formation of behavioral phenotypes in young children with neurogenetic disorders (Edgin et al., 2015; Fidler, 2005; Fidler, Lunkenheimer & Hahn, 2011; Karmiloff-Smith, 2011). From this perspective, early developmental profiles may facilitate or constrain a child’s development, and can become magnified into pronounced areas of strength and weakness throughout the lifespan (Karmiloff-Smith, 2011). This symposium will focus on new empirical examinations of phenotypic profiles in Down syndrome and fragile X syndrome during the early childhood years. Topics include early neuropsychological correlates of cognitive development in infants with Down syndrome, early self-regulatory aspects of temperament in infants with Down syndrome, and motor and physiological influences on early development in fragile X syndrome. The work presented will help identify very early targets for intervention and facilitate the development of treatment approaches to strengthen areas of potential vulnerability.


Paper 1 of 4

Title: Cognition and Neuropsychological Function in Infants with Down Syndrome

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Introduction: Cognitive delays associated with Down syndrome (DS), the most prevalent chromosomal cause of intellectual disability (ID), can be detected early in development (Fidler, 2005). While difficulties with attention and memory are core aspects of the cognitive phenotype associated with Down syndrome throughout childhood and into adulthood (Lanfranchi et al., 2009; Oxelgren et al., 2017), the underlying neuropsychological factors that contribute to slower rates of early cognitive development remain poorly understood. Several candidate information processing dimensions are likely to have an important impact on cognitive development during the first year of life, including the ability to sustain attention, the ability to shift attention, and the ability store and retrieve information temporarily in short-term memory (e.g. Petersen & Posner, 2012; Reynolds & Romano, 2016). This study aimed to characterize the nature of early cognitive functioning in infants with DS and to identify neuropsychological sources of within-syndrome variability in cognitive skill development.

Methods: Participants were 38 infants with Down syndrome (Mean chronological age (CA) = 9.65 months; SD = 3.64). Infants were assessed using the Bayley Scales of Infant Development- III (Bayley, 2006) and a set of laboratory tasks that measured sustained attention (duration of visual attention during a 2-minute object exploration task), attention shifting (mean latency to shift attention on an alternating object presentation task), and visual short-term memory (dishabituation to a novel object on a change preference task). Approximately 30% of administrations were coded for inter-rater agreement, with all kappas > .86.

Results: Participant scaled scores were compared across the BSID III domains (Mental scales, Expressive Language, Receptive Language, Gross Motor, Fine Motor) using a Repeated Measures-ANOVA to identify subtle areas of emerging strength and challenge. Using scaled scores, infants demonstrated specific, but subtle areas of strength and challenge across Bayley domains, F (2.95, 109.315) = 5.79, p = .001. The strongest performances were observed on the language subscales (Expressive Language M = 5.84, SD = 2.91; Receptive Language M = 5.26, SD = 2.76), and the weakest performances were observed on the motor scales (Gross motor M = 4.00, SD = 2.89; Fine motor M = 4.97, SD = 2.86), with mean scores on the Cognitive scale falling in between (M = 5.29, SD = 2.80). In addition, latency to shift attention was negatively associated with performance on the Bayley Cognitive Scale raw scores (r (35) = -.54, p = .001), however, no meaningful associations with cognitive performance were observed for the other two neuropsychological dimensions (visual memory, sustained visual attention). To control for chronological age effects, Bayley Cognitive Scale scores were regressed on attention shifting performance and chronological age.
The resulting regression equation was significant (F (2,33) = 35.52, p = .0001), with an $R^2$ of .82. Mean latency to shift attention explained a significant amount of variance in Bayley Mental Scale score even when controlling for the effects of chronological age.

**Discussion:** This study is among the first to examine the neuropsychological correlates of the acquisition of cognitive skills in infants with DS. Given that there is a great deal of variability in cognitive outcomes in this population, with severity of intellectual disability ranging from mild to severe/profound, identifying a key early source of within-group variability may offer important guidance regarding how best to identify those individuals with DS who are most at risk for severe impairments. Future research should seek to track these findings longitudinally in order to clarify whether early attention shifting predicts more adaptive outcomes over time as individuals progress through childhood.

**References**


**Paper 2 of 4**

**Title:** Goal-directed and Social Temperament Profiles in Infants with Down Syndrome

**Authors:** Emily Schworer, M.S., Deborah Fidler, Ph.D., & Lisa Daunhauer, Sc.D.

**Affiliation:** Human Development and Family Studies, Colorado State University

**Introduction:** Down syndrome (DS) is a neurodevelopmental disorder that affects approximately 1 in every 691 live births and is the most common chromosomal cause of intellectual disability (Parker et al., 2010). DS is associated with a distinct behavioral phenotype, including relative competencies in early social relatedness and relative challenges in aspects of executive function (EF), the cognitive underpinnings of goal-directed behavior (Fidler, 2006). Pronounced difficulties with EF have been shown to negatively impact critical outcomes in DS, including adaptive behavior, academic achievement, and functional performance (Fidler et al., 2005; Will et al., 2016; Daunhauer, Fidler, & Will, 2014). Self-regulation in infancy has been identified as a precursor and predictor of EF (Hendry, Jones, & Charman, 2016). Therefore, given the later developmental challenges with EF, it is critical to have a more complete understanding of the profiles of early self-regulatory behavior in infants with DS to facilitate greater EF competence across the lifespan in DS.

**Methods:** Participants were 25 infants ranging from 4 to 16 months old with DS, mean mental age (MA) = 6.2 months, $SD = 2.8$; mean chronological age (CA) = 8.5 months, $SD = 3.4$, and a primary caregiver. Infants completed the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley, 2006) to assess approximate developmental age. Parents completed the Infant Behavior Questionnaire-Revised (IBQ-R; Gartstein & Rothbart, 2003), a parent report questionnaire used to measure 14 different characteristics of infant temperament. Questions were answered on a 7-point Likert scale ranging from never to always, and scores indicate the average rating on each characteristic of temperament. The broad dimensions of Surgency/Extraversion, Negative Affectivity, and Orienting/Regulation were examined. In addition, using a theoretically based approach, characteristics were sorted into two categories for additional analysis: social-emotional regulation dimensions (Fear, Smiling and Laughter, Vocal Reactivity, Sadness, High Intensity Pleasure, Low Intensity Pleasure, Cuddliness, and Soothability) and goal-directed regulation dimensions (Activity Level, Distress to Limitations, Approach, Duration of Orienting, Perceptual Sensitivity and Falling Reactivity/Rate of Recovery from Distress).

**Results:** A repeated measures ANOVA was completed using existing broad dimensions of Surgency/Extraversion, Negative Affectivity, and Orienting/Regulation, $F(1.6, 44.3)= 70.3, p < .001$. Mean inspection indicated that infants had high scores on the Orienting/Regulation dimension, $M = 5.3, SD = 0.7$ and low scores on the Negative Affectivity dimension, $M = 2.9, SD = 0.6$. The
Surgency/Extraversion dimension fell into the middle range, $M = 4.3$, $SD = 0.9$. In addition, separate repeated measures ANOVAs were used to examine patterns of scores among the socially-oriented and goal-directed dimensions. A mix of scores was observed on the social-emotional regulation dimensions, $F (3.7, 89.4) = 45.8$, $p < .001$, with lower average item scores on Fear, $M = 2.5$ ($SD = 1.3$), and higher average item scores on Cuddliness, $M = 5.9$ ($SD = 0.8$), Low Intensity Pleasure, $M = 5.7$ ($SD = 0.9$), High Intensity Pleasure, $M = 5.1$ ($SD = 1.2$), and Soothability, $M = 5.7$ ($SD = 0.7$). Differences were also observed among the more goal-directed domains, $F (3.4, 77.0) = 13.1$, $p < .001$. Mean inspection indicated that infants had higher scores on one goal-directed dimension, Falling Reactivity/Rate of Recovery from Distress, $M = 5.5$ $SD = 0.7$, or the ability to recover from peak arousal states. All other scores on socially-oriented and goal-directed dimension fell into a middle range of average item scores (between 3.2 and 4.9).

**Discussion:** Although temperament has been examined in DS previously, earlier studies used older measures that are not as rooted in the early measurement of self-regulation. Overall, infants with DS showed a general trend toward low negativity and moderately high positive affect. The current results also suggest that infants with DS demonstrate under-responsivity to fearful situations and higher ratings for pleasure, cuddliness, and soothability. Infants also showed a high level of ease in recovery when in distress, which may suggest under-responsivity in this domain. All other means were in the mid-range of the scale, indicating infants did not have relatively high or low levels of activity level, distress, approach to objects, or sustained attention. Improving our understanding of the nuances in child behavior is critical for the identification of risk factors among early infant behavior in DS. Defining early self-regulation in DS is an important first step for future targeted early intervention to improve the lives of young children with DS and their families.

**References**


**Paper Title:** Object Exploration in Infants with Fragile X: Contrasts to High-Risk for Autism and Typical Development

**Authors:** Elizabeth A. Will, Ph.D., Jane E. Roberts, PhD

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**Introduction:** Early object exploration in infancy promotes optimal cognitive, perceptual, and social outcomes in typically developing (TD) children (Bornstein et al., 2013; Libertus & Hauf, 2017). Infants with fragile X syndrome (FXS) experience salient developmental liabilities, including impaired motor skills and dysregulated physiological arousal that have been linked to a number of poor outcomes including severity of autism symptomatology in this high-risk population (Roberts et al., 2012). Motor proficiency and physiological arousal are mechanistic underpinnings of attention and object-manipulation in TD infants (Richards, 2011; Libertus & Hauf, 2017); therefore, impairments in these domains may have implications for early object exploration in
infants with FXS. The primary objectives of this study are 1) to examine group differences in object-attention and manipulation in 12-month olds with FXS compared to age-matched TD and at-risk siblings of children with autism (ASIB) infants, and 2) to determine the relationship of motor and arousal to object-attention and manipulation outcomes as foundational mechanisms.

**Method:** This study design included 20 infants with FXS (mean chronological age (CA) =12.6 months), 38 ASIBs (M CA =12.74 months), and 37 TD infants (M CA=12.39 months), matched on CA. Measures included the Mullen Scales of Early Learning (MSEL, Mullen, 1995) as an indicator of fine and gross motor skills, a 3-minute object exploration task, and heart activity during a baseline video. In the object exploration task, infants were presented with age-appropriate toy keys. This task was coded for object-attention, total duration (seconds) of time spent gazing at the keys; and for manipulation, total duration (seconds) of time spent holding, mouthing, or touching the keys with high reliability across 20% of the sample (kappas=.88 for gaze; .98 for manipulation). Physiological arousal was measured during a 5-minute neutral video as an indicator of baseline arousal. Group differences between FXS, ASIBs and TD infants, as well as differential contributions of arousal and motor, were examined using multiple regression models.

**Results:** Results indicated no group differences or significant associations between arousal or motor skills and attention outcomes. Results from the manipulation models indicated that groups significantly differed on total duration of manipulation, such that FXS infants spent approximately 45 seconds longer in object-manipulation than TD (b=-44.79; p<.005) infants, and approximately 40 seconds longer than ASIB infants (b=-39.44; p=.010). Results also indicated that regardless of group, gross motor skills, but not fine motor skills were significantly associated with object-manipulation (b=-5.32; p=.020). Physiological arousal was not significantly associated with object-manipulation outcomes. Corrected post-hoc bivariate correlations were examined to further delineate why FXS infants demonstrated similar object attention but longer manipulation. Correlations indicated that object attention and manipulation were significantly associated in the FXS group (r=.74; p<.001), but not the TD or ASIB group.

**Discussion:** Collectively, results provide insight into early developmental foundations for infants with FXS. Findings demonstrate the general importance of early gross motor skills in object exploration outcomes, regardless of early delays. Further, infants with FXS, who experience motor delays, appear to rely on concurrent visual attention and manual exploration to a significantly greater extent than TD and ASIB infants in order to obtain object information. This suggests that infants with FXS experience greater challenges obtaining object-knowledge through integrated attention and manual exploration, potentially due to early motor impairments. Findings also suggest that factors other than early motor skills and arousal influence object manipulation for infants with FXS which should be the target of future research. Given the impact of early object knowledge on cognitive and social development, these findings have critical implications for outcomes in FXS.

**References**
Given that children with FXS demonstrate dysregulated heart activity compared to typically developing (TD) children (Klusek et al, 2015; Roberts et al, 2012), cardiac reactivity to an auditory startle could provide insight into anxiety features in children with FXS. The relationship between Negative Affect and auditory startle in children with FXS has not been investigated but would contribute to the characterization of early anxiety features in FXS. The purpose of this study is to advance our understanding of the nature of anxiety disorders in young males with FXS by examining cardiac reactivity to an auditory startle task and the predictive relationship between infant Negative Affect to auditory startle in children with FXS contrasted to TD children.

**Methods:** Participants included 25 children with FXS and 21 TD children drawn from an ongoing longitudinal study at the University of South Carolina. Negative affect was measured using the Infant Behavior Questionnaire (IBQ; Rothbart, 1981) when the participants were 24 months old (Time 1) The auditory startle data were collected when these participants were between 3-6 years of age (Time 2). The auditory startle task takes place in the context of a silent children’s movie and is comprised of three phases, 1) pre-startle (30 seconds), 2) 100-decibel white noise startle (1 second), and 3) post-startle (60 seconds).

**Results:** First, we used a multi-level model to test the difference in reactivity to startle in children with FXS and TD contrasting their pre-startle and post-startle heart rate levels. The interaction term testing the difference between TDs and FXS was significant $B=.50(.19), t=2.51$ indicating that the FXS group showed increased heart rate in response to the startle whereas the TD group showed a decrease (see figure). Second, a multiple linear regression found that Negative Affect was predictive of post-startle heart activity with age at startle covaried ($R^2 = .23, F(3, 36) = 3.53, p = .024$). A moderate correlation was found between Negative Affect and post-startle heart activity in the FXS group ($r = -.451, p = 0.052$) but not in the TD group ($r = -.227, p = 0.322$), suggesting the model was driven by the FXS group. However, when a group by negative affect interaction was added to the regression model, negative affect was not significant in predicting post-startle heart activity. Thus, post-startle heart activity and negative affect differ by group but not as an interaction, suggesting that other variables may be contributing.

**Discussion:** The preliminary results of this study are consistent with previous research showing altered physiological reactivity in clinical samples with FXS compared to TD children. This study supports that autonomic reactivity, indexed by heart rate, may represent a mechanistic vulnerability to anxiety in FXS. Elevated Negative Affect and exaggerated heart rate in response to a startle might be early features or contributing factors to the onset of anxiety in young children with FXS. Thus, features indicative of anxiety might be detectable as young as 24 months in children with FXS.

**References/Citations**
