**Symposium Title:** Risk and Resilience in Infant Siblings of Children with Autism Spectrum Disorder

**Chair:** Abigail Hogan¹ & Bridgette L. Tonnsen²

**Discussant:** Leslie Carver³

**Overview:** Prospective studies of infants at risk for autism spectrum disorder (ASD) have expanded over the last decade, painting a rich developmental picture of early risk and resilience in children with a family history of ASD. Notably, although ASD outcomes are present in approximately 1 in 5 infant siblings of children of autism (ASIBs; Ozonoff et al., 2011), recent work suggests that ASIBs who are not later diagnosed with ASD still face a multitude of developmental risks distinct from ASD, including elevated attention problems, anxiety, learning and language deficits, and sleep disruptions. Indeed, those ASIBs who were once thought to be “unaffected” exhibit subtle neurobiological and behavioral differences early in life that can provide insight into the trajectories of both typical and atypical development. In this early career symposium, investigators will present cutting-edge findings related to risk and resilience associated with developmental profiles in high-risk ASIBs across multiple outcomes (ASD, anxiety, developmental skills) and assessment methods (clinical, behavioral, psychophysiological). This work represents critical steps toward characterizing the early developmental profiles of high-risk infants. We also highlight the importance of tracking high-risk development prospectively as it relates not only to ASD, but also to other neurodevelopmental outcomes. Finally, given the focus of these studies, this symposium is in direct alignment with this year’s conference theme by recognizing the critical role of familial and biological factors that impact development in high-risk infants.

**Paper 1 of 3**

**Paper Title:** Behavioral and Physiological Social Anxiety Risk Factors across the First Two Years of Life in Siblings of Children with Autism Spectrum Disorder

**Authors:** Abigail Hogan¹, PhD, Nicolas Poupore¹, BS, & Jane Roberts¹, PhD

**Background:** Siblings (ASIBs) of children with autism spectrum disorder (ASD), even those who are not later diagnosed with ASD themselves, are at elevated risk for a variety of suboptimal developmental outcomes, including anxiety disorders¹. Childhood anxiety can have detrimental long-term effects that carry into adulthood and impact quality of life. However, early intervention for anxiety has been shown to ameliorate these long-term impacts. In neurotypical infants and toddlers, several early risk markers for social anxiety have been identified. These include high and stable expression of behavioral inhibition, a temperament profile characterized by excessive fear in response to novelty, and reduced physiological reactivity, as indexed by blunted respiratory sinus arrhythmia (RSA) responses²–⁴. Identifying early risk markers of social anxiety in ASIBs can provide important insight into the emergence and trajectories of prodromal anxiety features in this high-risk population. The objective of the present study is to examine the developmental trajectory of several early social anxiety risk markers in ASIBs not diagnosed with ASD (non-ASD ASIBs) and low-risk controls (LRCs) in the first two years of life using a multiple measures approach that includes parent report, observed behavior, physiological indices.

**Methods:** Participants included 32 later-born siblings of children with ASD who were not diagnosed themselves with ASD at >=24 months (non-ASD ASIBs) utilizing standard clinical best estimate procedures including the ADOS-2 and clinical review. Low-risk controls (n=42) with no personal or family history of ASD or related disorders were also included. Participants were assessed at

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several timepoints from 7 to 28 months of age, for a total of 214 observations (ASIB: n = 90; LRC: n = 124). Parent-reported behavioral inhibition was measured via the Fear subscales from the IBQ-R\(^t\) (<18 months) and ECBQ\(^t\) (>=18 months). The Stranger Approach Task\(^t\) was used to elicit observed behaviors consistent with behavioral inhibition (e.g., escape behavior, distress vocalizations, bodily fear) during a novel social scenario. A composite behavioral inhibition score was computed by averaging the fear scores for each fear behavior\(^8\). Physiological reactivity was measured through heart activity recorded during a baseline period and the Stranger Approach paradigm. Reactivity was defined as Baseline RSA minus Stranger RSA.

**Results:** Multi-level growth models were employed, with age, group, and age by group interaction entered as predictors. For parent-rated behavioral inhibition, significant main effects of age \((b = -0.03, p < .01)\) and group \((b = 0.39, p < .05)\) were revealed, with a non-significant interaction effect \((b = -0.03, p = .11)\), suggesting that parent-reported behavioral inhibition was higher in ASIBs but decreased in both groups with age. For the behavioral inhibition composite score, a significant main effect of group emerged \((b = 0.16, p < .05)\), in that the ASIBs exhibited higher behavioral inhibition across age. For physiological reactivity, the age by group interaction was significant \((b = -0.07, p < .05)\), indicating that physiological reactivity in ASIBs becomes more blunted with age.

**Conclusions:** This is the first study to examine early risk markers for social anxiety in infants with familial risk to ASD. Results suggest that non-ASD ASIBs exhibit elevated behavioral inhibition throughout the first two years of life, as indicated by both higher parent-reported behavioral inhibition and higher observed behavioral inhibition in response to a novel adult. Interestingly, physiological reactivity in response to a novel adult becomes more atypical as non-ASD ASIBs age. These patterns of behavioral inhibition and blunted physiological reactivity are early risk markers for social anxiety in neurotypical infants. Thus, it appears that even ASIBs without ASD themselves are showing atypical social responsivity and may be at elevated risk for later social anxiety symptoms and diagnoses.

**References/Citations:**


*Figure 1. Physiological reactivity across the first two years of life in non-ASD ASIBs and Low-Risk Controls (LRCs).*
Introduction: Aberrant attention orienting is one of the earliest identified predictors of autism and may play an integral role in developmental cascades that contribute to impairments. For example, a number of studies have described “sticky attention” in infant siblings of children with autism (ASIBs) within the first year of life, whereby infants have difficulty disengaging attention from a primary stimulus to orient to a peripheral stimulus (e.g. Elsabbag et al., 2013; Zwaigenbaum et al., 2005). However, the stability, biological signature, and developmental consequences of atypical attention in ASIBs is poorly understood. Examining these points of ambiguity is an important next step to informing translational efforts that may facilitate earlier identification and treatments, potentially minimizing maladaptive outcomes associated with ASD (Dawson, 2008). The present study investigated early attentional processes in infants at high familial risk for autism (ASIBs) and low familial risk (LR) controls using an attentional cueing paradigm that measures flexibility of attention orienting. In addition to measuring behavioral orienting, we also measured decelerations in heart rate that index attention orienting (Richards & Casey, 1991), informing whether atypical orienting patterns in ASIBs may be related to atypical physiological engagement. Our primary question was whether behavioral and heart-defined markers of attention orienting differ across ASIB and LR infants across 6-12 months of age. We hypothesized that consistent with previous literature, ASIBs would exhibit atypically long saccade latencies when required to disengage attention between competing stimuli, and these longer saccade latencies would also be indexed by greater heart rate decelerations. We expected these atypical profiles to become more robust with age.

Methods: Forty-six infants (23 ASIB, 23 LR) were assessed on 1-3 occasions each for a total of 99 assessments (ASIB one assessment n=7, two n=5, three n=11; LR one n=6, two n=8, three n=9). Infants were administered the gap-overlap task, a commonly used paradigm to measure flexibility of attention orienting. For each trial type, the primary variable of interest was the latency to look from a central to a peripheral stimulus. Three trial types were presented. During baseline trials, the peripheral stimulus appears as the central stimulus disappears. During gap trials, the peripheral stimulus appeared following a 200ms gap, which generally facilitates a more rapid saccade. During overlap trials, the peripheral stimulus appears while the central stimulus remains presented, generally resulting in a slower saccade due to the child’s need to disengage attention from the central stimulus prior to looking toward the peripheral stimulus. During the behavioral cueing task, we simultaneously measured heart rate deceleration responses, a robust metric of attentional engagement in infants (Richards & Casey, 1991). Group differences in saccade latencies were analyzed using nested mixed effects models with random intercepts. Final models will also examine associations between infant attention and later attention orienting and autism outcomes in the preschool period.

Results: Multilevel models revealed group differences in both behavioral and physiological variables. Groups differed in trajectories of saccade latencies for each trial type. These differences are depicted in Figure 1 which displays individual trajectories (light gray lines) as well as average trajectories by group (thick black lines) for each group across baseline and overlap trial types. As depicted in this graph, ASIBs demonstrated initially slower baseline latencies that improved more rapidly with age, controlling for developmental abilities. Post-hoc analyses indicated significant group differences in the youngest age group only (<8 months; $Z = -2.36, p = .009$). Age related patterns of overlap and gap latencies also differed by group, controlling for baseline latencies and developmental abilities. As a group, ASIBs demonstrated initially similar overlap latencies that improved less rapidly with age, compared to accelerated improvements in overlap latencies in the LR group. This pattern was distinct from gap
trials, in which the ASIB group demonstrated initially slower gap latencies that improved with age, whereas the LR group exhibited relatively stable gap latencies over time. Post-hoc cross sectional analyses generally corroborated these trends, with longer gap latencies in the youngest group only ($Z = 2.47, p = .007$) but non-distinct overlap latencies ($p$’s > .15). Interestingly, mean latencies generally shortened over time in all groups and trial types, with the exception of overlap latencies among ASIBs, which decreased between 5-8 and 8-11 months ($Z = 2.41, p = .02$) but then remained relatively stable, with a slight but nonsignificant increase between 8-11 and 11-14 months ($Z = 1.00, p = .32$). Groups did not differ in behavioral attentiveness or proportion of stuck trials. Developmental ability did not relate to behavioral attention variables. Group differences in physiological variables were less robust. Across the sample, lower developmental abilities were associated with greater proportion of time in a period of decelerated heart rate. In addition, ASIBs exhibited initially longer interbeat intervals (slower heart rate) that generally became more typical with age. Post-hoc Wilcoxon analyses indicated significantly longer IBI in ASIBs in the youngest age group ($Z = -1.86, p = .03$). However, heart rate decelerations did not differ across groups.

**Discussion:** The present study identified abnormal visual orienting and co-occurring physiological functioning within the first year of life in infant siblings of children with ASD. Importantly, our longitudinal models suggest that commonly reported “disengagement deficits” observed among ASIBs may emerge due to initially abnormal patterns of general orienting (across trial types) that improves at varied rates over time. This interpretation, supported by aberrant heart activity observed at younger ages among ASIBs, suggests persistent orienting deficits that are present, rather than beginning to emerge, around 6 months of age. Although additional work is needed to clarify the long-term clinical implications of these findings, our results suggest that abnormal orienting is apparent within the infant ASD phenotype and may co-occur with aberrant physiological functioning early in development.

**References/Citations:**

Paper Title: A Longitudinal Examination of Onset Patterns and Developmental Trajectories among Infant Siblings with Autism Spectrum Disorder

Authors: Chandni Parikh\(^4\), PhD, Ana-Maria Iosi\(^5\), PhD, and Sally Ozonoff\(^6\), PhD

Introduction: Although heterogeneous in the timing of symptom emergence, Autism Spectrum Disorder (ASD) has an early onset, with signs first appearing between 9 and 18 months (Ozonoff et al., 2011). Parents often report having concerns as early as the first birthday, attesting that parental observations can be a valuable resource for identifying possible “red flags” (Al-Qabandi et al., 2011). The American Academy of Pediatrics (AAP) recommends the use of an ASD-specific standardized screening instrument at the 18- and 24-month well child visits (Johnson & Myers, 2007). Despite significant progress, there are still major challenges in the early detection of ASD, with a mean age of diagnosis in the United States of 4 years (CDC, 2016). The Infant Toddler Checklist (ITC), a parent report instrument, was originally developed as a broadband screener for communication delays, but was later also validated as a narrow-band screener for autism (Wetherby et al., 2008). However, no studies to date have shown validation on children younger than 18 months or in high-risk samples (e.g., infant siblings of children with autism). Previous prospective studies have indicated that infants developing ASD show declining developmental trajectories across the first years of life (Jones & Klin, 2013; Landa et al., 2013; Ozonoff et al., 2010). The current methods used for ASD screening at the standard 18- and 24-month visits may not be sufficient in capturing individual differences in infant/toddler early developmental trajectories. The objectives of the current study were to: 1) examine the screening properties of the ITC in a high-risk sample at the recommended ages of 18 and 24 months; and 2) examine whether similar declining growth trajectories are evident on the ITC in a high-risk sample.

Methods: Using a prospective infant sibling design, infants with typically developing siblings and infants with a family history of ASD were examined for up to seven visits (6, 9, 12, 15, 18, 24 and 36 months) in the first three years of life. Three outcome groups were classified at the 36-month visit based on meeting the DSM-5 criteria for ASD and obtaining scores above the ASD cutoff on the ADOS-2: an ASD group \((n = 30)\), a typically developing group \((n = 125)\), and an atypical group \((n = 80)\) that demonstrated delayed development but did not meet criteria for autism. The ITC was used to assess social communication from 6 to 24 months of age.

Results: We calculated the sensitivity, specificity, and positive predictive value for the ITC at the AAP recommended ages of 18 and 24 months. First, we used the broadband screener cutoff recommended by Wetherby et al., (2008) in which a positive screen was defined as a score in the bottom 10\(^{th}\) percentile on the social scale, symbolic scale, or total score. The results indicated low to moderate psychometric properties, as can be seen in Table 1. Next, we used Wetherby et al.’s (2008) narrow-band cutoff for ASD, defined as a score in the bottom 10\(^{th}\) percentile on the social scale alone. The results are provided in Table 1. Finally, we created a composite score (range 0 to 6) by summing three items from the ITC: item 2 (“when your child plays with toys, does he/she look at you to see if you are watching”), item 3 (“does your child smile or laugh while looking at you”), and item 19 (“when you call your child’s name, does he/she respond by looking or turning toward you”). The items in the composite measure were chosen because these behaviors are reliably present in the first year of life in typically developing children (Inada, Kamio, & Koyama, 2011), and thus have the capacity to decline in frequency as ASD emerges. We examined growth trajectories to see whether scores on this 3-item composite showed a decline over time (i.e. a regressive pattern) in the ASD group. We used

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multilevel models and included fixed effects for group (ASD, typical, and atypical), linear and quadratic effects of age (centered at 6 months), and interactions between group and age. The results indicated no overall group differences ($F(2, 221) = 0.13, p = .88$) at 6 months of age; however, over time, the ASD group showed a decline in social-communication scores, while the typical and atypical groups demonstrated similar gains over time (see Figure 1). This resulted in the ASD group having significant lower scores at 24 months than both the typical and atypical groups (both $p$'s < .001).

**Discussion:** Early recognition of ASD-related risk behaviors and timely interventions can have cascading effects that improve adaptive, cognitive, and social development (Zwaigenbaum et al., 2015). A promising screening approach may be to look at children’s developmental change over time, rather than focusing on a screening score at a single age. The current results demonstrate that the ITC at 18 and 24 months has relatively low sensitivity and positive predictive value in high-risk infants. However, growth trajectories indicate that parents are able to report prospectively and longitudinally about their child’s development and can identify a declining course of development that could be beneficial in earlier identification. These investigations further emphasize the importance of the parental role in the early identification of ASD.

**References/Citations:**


Table 1. Sensitivity, specificity, and positive predictive value with the Infant-Toddler Checklist for 18 and 24 months

<table>
<thead>
<tr>
<th>Age</th>
<th>Broadband Screener</th>
<th>Narrow-band ASD Screener</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity (CI)</td>
<td>Specificity (CI)</td>
</tr>
<tr>
<td>18 months</td>
<td>64% (43% - 82%)</td>
<td>79% (72% - 85%)</td>
</tr>
<tr>
<td>24 months</td>
<td>78% (56% - 93%)</td>
<td>80% (74% - 86%)</td>
</tr>
<tr>
<td>18 months</td>
<td>56% (37% - 75%)</td>
<td>85% (79% - 90%)</td>
</tr>
<tr>
<td>24 months</td>
<td>55% (32% - 76%)</td>
<td>89% (83% - 93%)</td>
</tr>
</tbody>
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*Note. CI = confidence interval: 95%