Symposium Title: Mechanisms and Functional Consequences of Motor Impairments across Down Syndrome, Fragile X, Autism, and Single Gene Mutations

Chair: Elizabeth Will

Discussant: Brittany Travers

Overview: Motor impairments are a common feature across multiple neurodevelopmental disorders and are often associated with poor functional outcomes and underlying genetic risk (Bishop et al., 2018; Buja et al., 2018). Motor skills are associated with the rate of language acquisition (Leonard et al., 2015) and with social cognition (Leonard et al., 2014) in autism spectrum disorder (ASD), as well as autism symptom severity in certain genetic conditions (Roberts et al., 2009; 2016). The degree of motor impairment can vary as a function of specific genetic etiology (Bishop et al., 2017; Will et al., 2018). For instance, children with intellectual disability (ID) demonstrate more significant delays than children with non-syndromic autism with ID (Bishop et al., 2017), and age-related differences in motor skills emerge between children with Down syndrome relative to fragile X syndrome (Will et al., 2018). Yet, the syndrome-specific features of motor impairments, their underlying mechanisms, and functional consequences remain poorly understood. As such, the three presentations in this symposium aim to identify motor phenotypes, their functional impact on communication, and underlying neural mechanisms in neurogenetic and ASD-risk populations. The first presentation examines syndrome-specific patterns of motor impairments and their impact on communication across infants and toddlers with Down syndrome compared to fragile X syndrome. The second presentation examines the influence of motor trajectories on social communication outcomes in infants at high-risk for ASD. The third presentation examines how neural mechanisms in school-age children are associated with early motor development as a function of genetic etiology in ASD. Collectively, these presentations highlight the role of motor impairments and their underlying mechanisms and functional impact as shared and unique features across neurodevelopmental risk populations.

Paper 1 of 3

Paper Title: Motor Impairments in Infants and Toddlers with Down syndrome: Implications for Language and Cross-Syndrome Comparisons to Fragile X Syndrome

Authors: Elizabeth Will & Jane Roberts

Introduction: Infants and toddlers with Down syndrome (DS) experience significant motor impairments, such as delayed milestones and poor motor control (de Campos et al., 2013; Pieria et al., 2013), that may hinder important developmental outcomes, such as language (LeBarton & Iverson, 2016; Libertus & Violi, 2014). Although growing evidence suggests the importance of motor skills on language outcomes for children with ASD, implications for motor impairments in DS remain unclear. Fragile X syndrome (FXS) is another neurogenetic condition associated with ID. FXS affects 1 in 5,000 males and 1 in 8,000 females (Coffee et al., 2009). Although infants and toddlers with DS and FXS demonstrate relatively unique developmental profiles in specific domains (Will et al., 2018), motor impairments are a shared feature across these neurogenetic disorders and one that may have unique implications for communication outcomes (LeBarton & Iverson, 2016). Identifying the syndrome-specific nature of motor impairments and their influence on communication in DS relative to other neurogenetic conditions with ID is important for phenotypic characterization and targeted intervention. Accordingly, we aimed to identify the association between fine and gross motor skills and receptive and expressive communication in infants and toddlers with DS (Study 1) and identify the phenotypic specificity of these associations through cross-syndrome comparisons between matched samples of infants and toddlers with DS and FXS (Study 2).

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Methods: Participants for Study 1 included infants and toddlers with DS (n=41) between 10 and 45 months-old. Participants for Study 2 included infants and toddlers with DS (n=37) as well as infants and toddlers with FXS (n=38). DS and FXS groups were well matched on chronological age (CA; t=.23; p=.823) and nonverbal mental age (NVMA; t=.40; p=.689). All participants completed the Mullen Scales of Early Learning (MSEL; Mullen, 1995), a comprehensive developmental assessment that measures Fine Motor, Gross Motor, Visual Reception, Expressive Language, and Receptive Language. Additionally, their parents completed the Vineland Adaptive Behavior Scales (VABS-II; Sparrow, Cicchetti, & Balla, 2005), a comprehensive and structured caregiver interview that measures Motor, Socialization, Communication, and Daily Living adaptive behavior skills. Because subscales of the MSEL and VABS-II are closely related with one another, we used MSEL motor (fine and gross) as predictors of VABS-II communication (expressive and receptive).

Results: In Study 1, we used a multivariate multiple regression approach to test the unique association between fine and gross motor skills on receptive and expressive communication skills in infants and toddlers with DS. Study 1 results indicated that for infants and toddlers with DS, gross motor was significantly associated with both receptive ($b=.83; p<.001; \eta^2=.49$), as well as expressive ($b=.52; p=.005; \eta^2=0.19$) communication, even when controlling for visual reception (i.e., cognition). Fine motor was also significantly associated with both receptive ($b=1.22; p<.001; \eta^2=0.63$) and expressive ($b=.76; p=.001; \eta^2=.25$) communication, controlling for visual reception. Effect size estimates indicate that receptive language was more strongly predicted by motor skills for infants and toddlers with DS, with large effects for both gross motor ($\eta^2=.49$) and fine motor ($\eta^2=.63$). Study 2 tested cross-syndrome comparisons between MA and CA-matched samples of infants and toddlers with DS and FXS using an independent samples t-test and a moderated multiple regression approach. Results from preliminary t-tests on motor skills identified significant group differences on gross motor ($t=-2.32; p=.023$), such that the DS group had lower gross motor skills, but no group differences on fine motor. Moderated regression model results indicated that although the DS group had significantly lower gross motor skills than the matched FXS group, there was no significant difference in the association of gross motor skills on either receptive ($b=-0.28; p=0.197$) or expressive ($b=0.20; p=0.063$) communication as a function of neurogenetic condition. Interestingly, although DS and FXS groups did not significantly differ on fine motor skills, there was a significant difference in the effect of fine motor on receptive communication ($b=-0.54; p=0.024$) as a function of neurogenetic condition with FXS demonstrating a weaker relationship. There was no such difference in the effect of fine motor on expressive communication ($b=0.67; p=0.87$).

Discussion: To our knowledge, these are among the first studies to investigate the influence of motor development on communication in infants and toddlers with DS, as well as to draw cross-syndrome comparisons to FXS. Results from Study 1 indicate significant and unique contributions of both fine and gross motor to receptive and expressive communication outcomes for infants and toddlers with DS. Furthermore, these results suggest a unique influence of motor beyond that of co-occurring intellectual disability or developmental delay. Study 2 results demonstrate syndrome-specific developmental influences of fine motor on receptive communication for infants and toddlers with DS compared to those with FXS at the same chronological age and developmental level. Collectively, these findings highlight the importance of early motor development for children with DS and also those with FXS, which to date, has been vastly understudied. Findings also suggest that motor-based interventions may improve communication for young children with neurogenetic conditions, and this may especially be the case for fine motor and receptive communication in young children with DS. Variations in early motor delays between DS and FXS may contribute to differential cascading influences on communication development across these neurogenetic conditions. Future work is necessary to disentangle syndrome-specific motor impairments and their developmental pathways to inform targeted and early intervention efforts.

References/Citations:


**Paper 2 of 3**

**Paper Title:** The Pull to Sit Task: Examining the Role of Early Motor Development in the Emergence of Social-Communication Abilities in High-Risk Infants

**Authors:** Jessica Bradshaw¹, Dexin Shi², Ami Klin², Warren Jones², Cheryl Klaiman²

**Introduction:** Motor deficits are not a diagnostic or cardinal feature of autism spectrum disorder (ASD), but many toddlers with ASD show atypical motor development alongside their social and communication impairments (Lloyd, MacDonald, & Lord, 2013). The role of motor milestone achievement (e.g., crawling and walking) and social development has been established in both typically developing and at-risk (infant siblings of children with ASD) populations (e.g., Bradshaw et al., 2018; West et al., 2017; Walle & Campos, 2014). These studies suggest that motor abilities afford increased opportunities for social interaction and social learning, which allow for rapid acquisition of social and language skills. In the first year of life, weaknesses in head, neck, and trunk control have been documented in high-risk infants (Flanagan et al., 2012), but the impact of this potential deficit on later social-communication development is not known. The current study compares early trajectories of motor development from 1-6 months of age for infants who are at high and low risk for ASD and evaluates the association between motor development and acquisition of social-communication skills at 1 year.

**Methods:** An assessment of motor and neurological functioning, modified from the NICU Network Neurobehavioral Scales (NNNS) was administered to 100 infants four times between 1-week and 6-months of age. Infants were either high-risk (HR) infant siblings of children with ASD (N=51) or low-risk (LR) infants with no family history of ASD (N=49). The Pull to Sit item from the NNNS is the focus of the current analysis. This item evaluates the infant’s response to being pulled from a supine to sitting position in regard to: increase in shoulder and body tone, muscular resistance to stretching the neck and lower musculature, and infant’s attempts at righting head when in an upright position. This item is scored on a scale from 1-9, with higher scores indicating excellent shoulder/body tone and independent head righting without a head lag. Infants were seen again at 12 months and administered the Communication and Symbolic Behavior Scales (CSBS), which provides standard scores in the areas of Social, Speech, and Symbolic skills, as well as a total score. Multiple group latent growth curve models were used to explore the growth trajectories of performance on the Pull to Sit task from 1-week to 6-months of age and to compare trajectories between risk groups. The effects of growth trajectory on later social-communication outcomes were investigated.
Results: Results from multiple group latent growth curve model indicated linear growth for both groups and significant individual differences in trajectory (slope and intercept) that were not explained by risk status. That is, high-risk and low-risk infants exhibited similar growth trajectories. However, there was a significant effect of growth trajectory on later social-communication outcome. When combining both high-risk and low-risk infants, the slope of their motor development trajectory significantly predicted the CSBS Social and Symbolic composites at 12 months, with faster growth associated with higher scores at outcome. When the groups were analyzed separately, this finding held only for the high-risk group. High-risk infant motor trajectories significantly predicted their CSBS Symbolic Composite (β = .493, p < .05) and CSBS Social Composite (β = .346; p < .10) at 12 months. There was no evidence of this association for low-risk infants. These findings were not accounted for by infants with global motor delays, as only 3 infants (1 LR and 2 HR) were delayed in motor skills at 12 months.

Discussion: These findings suggest that for infants who are at increased risk for developing ASD and social-communication impairments, motor development in the first six months of life may be critical. Adequate muscle tone development leads to independent, volitional control of actions. Good head, neck, and trunk control and freedom of movement allow for independent, visual exploration of the environment. A 3-month-old infant who can hold her head up in a sitting position and volitionally turn to sights and sounds of interest may experience more social interaction with caregivers, which afford increased learning opportunities. Elucidating the role of early motor skills in the emergence of social-communication skills and the development of ASD can inform early detection and novel intervention strategies for infants at an age that comes well before a diagnosis of ASD is possible.

References/Citations:
1 University of South Carolina
2 Marcus Autism Center

Paper 3 of 3

Paper Title: Motor development, the brain, and genetics: Is there a converging biological pathway in ASD?

Authors: Caitlin M. Hudac1, Monique Mahony1, Anne Arnett1, Arianne S. Wallace1, Jennifer Gerdts1, Evan Eichler2, Sara Jane Webb3, and Raphael Bernier1

Introduction: Children with ASD and an identifiable likely gene disrupting (LGD) genetic mutation demonstrate more extended motor deficits than those without a genetic abnormality (Bishop et al., 2017). Further, the severity and functional consequence of the specific genetic event is meaningful – for instance, children with an LGD regulated by CHD8 demonstrate slower motor development (Buja et al., 2018). Recent work supports CHD8 regulation of other ASD risk genes such that genes targeted by CHD8 exhibit shared features as children with a CHD8 LGD (Cotney et al., 2015). Yet despite the critical role in brain development (e.g., chromatin modification) for CHD8 (Sutterlin et al., 2018), it is unclear how motor skills relate to core symptoms at a brain level, due in part to the difficulty testing this population with traditional behavioral measures (e.g., IQ testing). Here, we explore
associations between brain markers (P3a component) and motor development (age of walking unassisted) in children with an LGD targeted or not target by CHD8.

Methods: As part of our ongoing genetics-first characterization studies, we focus on a subset of 41 children with ASD with an identified LGD that either is CHD8 (n = 6), targets CHD8 (n = 18), or does not target CHD8 (n = 14). A comparison group included an ASD group without a known LGD (Idiopathic group, n = 57). All participants completed a comprehensive battery of laboratory clinical and behavioral assessments, as well as a passive auditory oddball EEG experiment that measured brain activity as reflected by the central P3a component (180-350 ms). A larger P3a effect corresponds to a larger domain-general brain response. Bonferroni correction is applied for tests of multiple comparisons.

Results: Characterization of brain markers and age walking for each group are provided in Table 1. Consistent with prior work (Bishop et al., 2017; Buja et al., 2018), children with an LGD began walking later (M = 18.2 months) than the Idiopathic group (M = 12.8 months). Critically, the Target group started walking earlier in development compared to the CHD8 group, p = .035. There are no significant group differences on brain markers, including P3a amplitude or P3a response. However, partial Pearson correlations (correcting for nonverbal IQ) indicated that age of walking unassisted was related to P3a condition effect, r(92) = - .21, p = .045. As illustrated in Figure 1, the effect was unique to genetic group. There was no association in the Idiopathic group. Late Nontarget walkers exhibited a very small brain response, whereas both late CHD8 and Target walkers exhibited larger brain responses.

Discussion: These results provide new evidence linking a developmental motor milestone (the age of walking unassisted) to the brain response later in life. Specifically, we note distinct patterns based upon genetic etiology, such that children with a CHD8 LGD or a CHD8 target LGD exhibit a larger response. We will discuss possible biological connections to better understand the implications of how motor development may affect brain development.

References/Citations:

2 Department of Psychiatry, University of Washington
2 Department of Genome Sciences, University of Washington
Table 1: Subject characterization

<table>
<thead>
<tr>
<th>Measure</th>
<th>CHD8</th>
<th>Target</th>
<th>Nontarget</th>
<th>Idiopathic</th>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>6</td>
<td>18</td>
<td>14</td>
<td>57</td>
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<tr>
<td>Age in years</td>
<td>10.6 (4.9)</td>
<td>13.8 (4.5)</td>
<td>11.4 (4.2)</td>
<td>12.5 (2.5)</td>
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<td>Female : Male (% male)</td>
<td>2:4 (85.7)</td>
<td>3:15 (83.3)</td>
<td>2:12 (85.7)</td>
<td>11:46 (80.7)</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>55.5 (31.1)</td>
<td>78.8 (26.8)</td>
<td>64.4 (32.4)</td>
<td>91.9 (25.8)</td>
</tr>
<tr>
<td>Nonverbal IQ range</td>
<td>20-100</td>
<td>32-137</td>
<td>19-120</td>
<td>30-154</td>
</tr>
<tr>
<td>Walking unassisted in months¹</td>
<td>20.67 (4.2)</td>
<td>15.11 (4.8)</td>
<td>18.71 (7.3)</td>
<td>12.79 (2.7)</td>
</tr>
<tr>
<td>P3a amplitude in µV</td>
<td>13.82 (3)</td>
<td>15.16 (6.1)</td>
<td>13.05 (4.1)</td>
<td>14.59 (5)</td>
</tr>
<tr>
<td>P3a condition effect in µV</td>
<td>6.07 (4.3)</td>
<td>9.11 (4.2)</td>
<td>6.44 (3.8)</td>
<td>9.09 (4.4)</td>
</tr>
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</table>

¹ From Autism Diagnostic Interview-Revised, Question 14

Note: Mean (Standard deviation) reported unless otherwise described.