**Symposium Title:** Insights from Infants: Charting Early Brain and Behavior across Neurodevelopmental Disorders

**Chairs:** Jason Wolff¹

**Discussant:** Carissa Cascio²

**Overview:** A child’s brain and behavior undergo unique and rapid changes during the first years of life, and it is no coincidence that many developmental disorders first become evident during this time. Understanding how children transition from appearing typical across multiple domains to manifesting deficits and delays offers the possibility of identifying specific targets and optimal timing for early screening and intervention/prevention efforts. In this symposium, we will present new findings from ongoing longitudinal studies of children with autism spectrum disorder (ASD), fragile X syndrome, and Angelman syndrome in order to highlight the essential role of early neural circuitry in relation to developmental outcomes. The first presentation will describe the development of structural connectivity (measured by diffusion tensor magnetic resonance imaging) and its relation to social communication and repetitive behavior symptom severity in high-familial risk infants later diagnosed with ASD. The second presentation will concern the development of neural circuitry and cognition in infants with fragile X syndrome, describing how such development differs from that observed in non-syndromic ASD. The third presentation will share new data on neural circuitry in young children with Angelman syndrome and detail its relevance to early emerging motor deficits. The final presentation will demonstrate how the development of neural circuitry, as characterized by EEG, may be used to predict diagnostic and cognitive outcomes in infants at-risk for ASD as young as age 3 months. Finally, our discussant will synthesize these data and address clinical relevance as it pertains to key continuities and discontinuities observed across our four featured studies.

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**Paper 1 of 4**

**Paper Title:** Development of Structural Connectivity Linked To Symptom Severity in Infants with ASD

**Authors:** Jason J. Wolff¹, Meghan R. Swanson³, Yadira Peralta¹, Martin A. Styner³, Kelly N. Botteron⁴, Stephen R. Dager⁵, Jed T. Elison¹, Annette M. Estes⁵, Heather C. Hazlett³, Robert T. Schultz⁶, Joseph Piven³, and the IBIS Network

**Introduction:** Diffusion tensor imaging (DTI) is a specialized modality of magnetic resonance imaging that may be used to characterize the properties of white matter structural connectivity. Through DTI, we have previously identified differences in white matter development between high familial risk infants who went on to develop ASD versus those who did not (Wolff et al. 2012). These developmental differences were characterized by crossing trajectories wherein infants who later developed ASD had initially higher fractional anisotropy (FA; a measure reflecting structural coherence based on magnitude of directional diffusion) followed by slower development into toddlerhood. Similar findings of initially high FA followed by slower development have been reported by other research groups (e.g. Solso et al. 2016). To build upon this existing body of work, our present study goals included: 1) examine the development of white matter circuitry in HR infants with ASD (HR-ASD) relative to a low-risk control group, and 2) examine the relation of early white matter development to measures of later symptom severity.

**Methods:** The present study included longitudinal DTI data collected at 6, 12, and 24 months of age for 54 high-risk siblings who received a clinical best-estimate diagnosis of ASD at age 2 years and 114 low-risk control infants without ASD. DTI data were collected on identical 3T scanners during natural sleep as part of an ongoing longitudinal study. White matter pathways of interest were deterministically segmented (7 bilateral projection and association pathways and 3 divisions of the corpus callosum). Symptom severity scores were derived from the ADOS at age 2 years (Hus et al. 2014). Developmental trajectories

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between outcome groups were examined using linear mixed effects models, while relations of white matter development to behavior were examined through ordinal regression. Brain-behavior analyses were limited to pathways showing an effect for group or group X age.

Results: There were significant main effects for the anterior internal capsule, genu and body of the corpus callosum, corticospinal tracts, and superior cerebellar peduncles (all \( p < .015 \)). For growth trajectories (group X age), HR-ASD differed from LR controls on all pathways showing a main effect with the addition of the pontine crossing tract (all \( p < .04 \)). Growth trajectories for HR-ASD relative to LR controls were uniformly characterized higher FA at age 6 months followed by slower growth thereafter. Among the HR-ASD group, FA development from 6 to 24 months (rate of change) was significantly associated with ADOS severity scores at age 24 months in 4 of 8 pathways examined. These included the genu (\( \chi^2 = 9.3, \ p = 0.002, \ OR = 4.6, \ 95\% \ CI[1.7-12.4] \)) and body of the corpus callosum (\( \chi^2 = 6.2, \ p = 0.013, \ OR = 4.5, \ 95\% \ CI[1.4-14.9] \)); left ALIC (\( \chi^2 = 4.8, \ p = 0.029, \ OR = 3.4, \ 95\% \ CI[1.1-10.2] \)); and PCT (\( \chi^2 = 4.4, \ p = 0.037, \ OR = 2.0, \ 95\% \ CI[1.0-4.0] \)). These relationships were uniformly characterized by faster growth rate associated with more severe ASD at age 24 months.

Discussion: Early development of white matter circuitry is rapid in pace and includes both exuberant growth (myelination, arborization) and regressive events (axon elimination). The present results further support that these developmental processes may be significantly altered in infants who develop ASD. This work also provides new evidence that a faster rate of change in structural connectivity is associated with more severe impairment by toddlerhood, a result consistent with reports identifying that “more” is not necessarily better early in the development of ASD (Hazlett et al. 2012; Wolff et al. 2017).

References/Citations:

Paper 2 of 4

Paper Title: Development of White Matter Circuitry Is Diminished In Infants with Fragile X Syndrome

Authors: Meghan R. Swanson\(^3\), Jason J. Wolff\(^1\), Mark D. Shen\(^3\), Martin A. Styner\(^3\), Annette M. Estes\(^5\), Guido Gerig\(^7\), Kelly N. Botteron\(^4\), Joseph Piven\(^6\), Heather C. Hazlett\(^3\), for the IBIS Network

Introduction: Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability in males and is a single gene disorder frequently associated with autism spectrum disorder. However, there are no data on the brain development of children with FXS during infancy. The aims of the current study were to 1) characterize the development of white matter across ages 6, 12, and 24 months in infants with FXS in relation to typically developing controls and 2) examine relations of white matter development to verbal and nonverbal skills.

Methods: Longitudinal behavioral and brain imaging data were collected at two academic medical centers between August, 2008 and June, 2016. Twenty-seven infants with FXS and 63 typically developing controls contributing brain imaging and

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behavioral assessment data at one or more time point (possible timepoints - 6, 12, and 24 months). Nineteen major white matter pathways were defined in common atlas space based on anatomically informed methods. Trajectories of diffusion parameters, including fractional anisotropy (FA), were compared between groups using linear mixed modeling. Fiber pathways showing group differences were subsequently examined in relation to direct measures of verbal and nonverbal cognitive development. These analyses focused on 12-month brain and behavior data as this was the time point with the most infant FXS data (n= 18).

**Results:** There were significant differences in the development of 12 of 19 fiber tracts, including the left and right anterior limb of the internal capsule, inferior longitudinal fasciculus, uncinate fasciculus, superior cerebellar peduncles, and sections I-III and Va of the corpus callosum (sections project to the prefrontal, premotor, primary motor, and parietal cortical regions, respectively). For all 12 of these pathways, there were significant main effects between groups (FDR correct p-values ranged from .038 - .001) but not for the interaction of age x group, indicating that lower FA was present and stable from 6 months of age in infants with FXS. Compared to controls, infants with FXS had lower FA by an average of 3.5 – 7.9% across these tracts. There were no significant effects for the middle cerebellar peduncles, posterior limb of the internal capsule, anterior thalamic radiations, and sections IV (somatosensory) and Vb (occipital) of the corpus callosum. Lower FA values in the uncinate fasciculi were correlated with lower nonverbal developmental quotient in the FXS group.

**Discussion:** Results substantiate in human infants the essential role of fragile X gene expression on the early development of white matter (e.g., Pacey et al., 2013). Findings also suggest that the neurodevelopmental effects of FXS are well established at 6 months of age. The patterns of white matter trajectories in infants with FXS were distinct from patterns reported in previous studies of infants and toddlers with autism spectrum disorder (e.g., Wolff et al., 2012).

**References/Citations:**
Results: Children with AS were observed to have significantly smaller brain tissue volume when compared to TD controls, with 29% smaller WM volume ($p < .0001$; Cohen’s $d = 3.66$) and disproportionately less white matter than gray matter ($p < .0001$, $d = 1.43$). Examination of WM properties from DTI found a strong positive correlation between FA measured a major motor pathway (the internal capsule) and motor skills ($r = .64$, $p = .01$), indicating that poorer WM integrity in a key motor tract was related to poorer motor functioning.

Discussion: Animal models for AS have clearly demonstrated early-emerging WM deficits related to microcephaly that is part of the clinical phenotype of AS. Here we find initial face validity and support for decreased WM volume in children with AS, and find a significant positive relationship between the integrity of WM circuitry and motor functioning. It raises the potential that WM deficits may underlay initial symptoms of AS and potentially offer the sensitivity and specificity necessary to serve as a biomarker and outcome measure in upcoming clinical trials that aim to target brain development in AS.

References/Citations:

Paper Title: Circuit Level Brain Activity Changes in Infants at High Risk for ASD

Authors: Abigail Dickinson, Andrew Marin, Yin-Ying Lin, Aaron Scheffler, Damla Senturk & Shafali Jeste.

Introduction: Heterogeneous genetic and environmental etiologies of ASD converge upon circuit level brain disruption well before behavioral symptoms and developmental delays emerge (ASD; (Geschwind, 2009; Port et al., 2014). The dynamics of neural oscillations in the alpha range (6-12 Hz) are exquisitely sensitive to typical circuit level developmental changes and can therefore be used to detect atypical development. Robust developmental measures include peak alpha frequency and alpha band connectivity (Dickinson et al., 2017), and these are easily measured through quantitative electroencephalography (EEG). In order to quantify EEG patterns that may relate to atypical development, we can prospectively study infants who are at high risk for neurodevelopmental disorders, with risk conferred by having an older sibling with ASD. These infants develop ASD at a rate of 15-20% and broader neurodevelopmental conditions (global delay or language delay) at a rate of 11% (Charman et al., 2017). Here we study infant EEG, with focus on alpha oscillations, in order to: 1) characterize trajectories of brain development in infants who develop ASD, and 2) determine if the earliest collected early EEG measures predicts later cognitive function and social communication skills.

Method: Longitudinal EEG data were collected during the first year of life (3, 6, 9 & 12 month) from high and low risk infants at “rest,” a condition created by bubbles being blown into the testing booth from behind a curtain. Data were pre-processed according to previously published lab protocols. We examined EEG spectral power and coherence in the alpha band and peak alpha frequency 59 participants (28 high risk) contributed usable EEG data at 3 months of age. As data collection is ongoing, 36 month outcomes are not yet available on most infants, therefore we anchored our findings in 18 month assessments. Of the 59

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participants studied here, 49 completed the ADOS toddler module at 18 months. Infants were grouped into ‘ASD’ (ADOS-t CSS ≥ 4, N=9) and ‘typically developing’ (CSS<4, N=40) groups based on the presence of social communication impairments and restricted and repetitive behaviors at 18 months. The Mullen scales of early learning were used to assess overall development at 18 months. Alpha phase coherence was used to establish connectivity between every possible electrode pair, and a robust curve fitting procedure was used to quantify peak alpha frequency.

**Results:** (1) FDR corrected analyses reveal that alpha phase coherence was increased at 3 months in the group of infants who demonstrate ASD behaviors at 18 months. These group differences were evident in one left hemisphere frontal electrode pair (ASD: M=0.37; typical: M=0.28; P<.001), and one right hemisphere parietal electrode pair (ASD: M=0.35; typical: M=0.28; P<.001). (2) Across all high and low risk participants, occipital peak alpha frequency at 3 months was inversely correlated with non-verbal IQ at 18 months (R=-.56, P=.02).

**Conclusion:** The present data suggest that the dynamics of circuit level activity are altered as early as 3 months of age in participants who later demonstrate developmental delays associated with ASD. These measures are also associated with nonverbal cognitive function. The early hyperconnectivity demonstrated here is consistent with previous reports of increased frontal lobe intrahemispheric connections during infancy in ASD, and may be driven by early cortical overgrowth (Courchesne & Pierce, 2005). Future analyses will explore how trajectories of circuit development manifest over the entirety of the first year. In this presentation, we will discuss the potential utility of scalable electrophysiological markers of circuit development to 1) objectively identify children who show ASD-related neurodevelopmental disruptions during the first year of life, 2) support individualized prognoses, and 3) inform neurobiological targets of early intervention.

**References/Citations:**