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Technology and Innovation Laboratory (TIL)
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Early Head and Body Overgrowth in Boys and Girls with ASD: Prevalence Rate and Clinical Outcomes

D. J. Campbell, J. Chang and K. Chawarska, (1)Child Study Center, Yale University School of Medicine, New Haven, CT, (2)Statistics, Yale University, New Haven, CT

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Abstract #16304  

The Use of Mobile Technology in the Treatment of Prosodic Deficits in Autism Spectrum Disorders

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Abstract Text:

Background: Language deficits in ASD are both highly prevalent and have significant impact on adaptive functioning. For 80% of individuals with ASDs who acquire spoken language, deficits in prosody are among the most chronic impairments. Prosodic speech deficits impede social interaction and limit participation in daily activities. Despite the handicapping nature of prosodic disorders, there are few interventions to treat these deficits.

Objectives: The purpose of this study is to assess the feasibility and preliminary utility of an application, SpeechPrompts, for iOS devices in the treatment of prosodic disorders in school-age children with ASD.

Methods: Students, 5-19 years of age with a diagnosis of ASD and prosody deficits, were enrolled in the study (N=40). These students were recruited from the caseloads of school-based speech-language pathologists (SLPs; N=10) in an educational setting. SLPs recorded speech samples for each student pre and post intervention. These samples were rated by an SLP unfamiliar with the students using a Likert scale for each of the following prosodic features: Rate, Rhythm, Intensity, Stress, Global Intonation. SpeechPrompts is an iOS application whose main function is to provide a visual representation of the prosodic features of speech. The application provides both real-time feedback and opportunities for the student to match their speech to an adult or peer target. Each SLP received an iPad with the SpeechPrompts application. A brief tutorial was provided to each SLP and included instruction on the use of the main features of the application. The application was presented to the enrolled students as part of their speech and language services. The SLPs were instructed to use the application as them deemed fit using clinical judgment. Intervention duration was ten weeks. SLPs completed weekly engagement questionnaires for each of their students which rated the students’ and SLPs’ experiences with SpeechPrompts. SLPs also completed end-of-study surveys.

Results: Usage data collected revealed SLPs accessed the application daily during the school week with a median frequency of 2.5 sessions per day. Post-treatment prosody ratings based on speech samples obtained at end of treatment indicated improvements in prosodic functioning with greatest improvements observed in vocal intensity and stress patterns. Engagement measures indicated that students enjoyed the sessions (88%), did not engage in disruptive behavior while using the application (88%) and looked forward to using the application again (96%). All SLPs enrolled in the study reported that they felt comfortable recommending SpeechPrompts to colleagues in end-of-study surveys.

Conclusions: Results of this study suggest that SpeechPrompts has the potential to be a useful tool in the treatment of prosodic disorders as seen by improvement in prosodic functioning in this small group of students. Moreover, the application appears to maintain the student’s attention and engagement over the course of treatment. In conclusion, SpeechPrompts provides SLPs with an additional tool in their repertoire to address these difficult to treat set of speech difficulties commonly observed in children with ASDs.
Abstract # 16518

High-Risk Siblings with Atypical Developmental Trajectories: Clinical Outcomes at Early School Age

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Background: Prospective studies of siblings of children with ASD (high risk (HR)) indicate highly variable and vulnerable developmental trajectories in the first 3 years of life but little is known beyond this age.

Objectives: To examine clinical outcomes in a group of complex cases ascertained through the prospective longitudinal HR sibling study from 6 to 36 months.

Methods: Six HR siblings with complex clinical presentations in the first 3 years of life (i.e., borderline and fluctuating ASD symptoms) were comprehensively assessed at the age of 4-6 years, using a battery comprised of cognitive, neuropsychological, language, adaptive, social and emotional functioning measures.

Results: Clinician Best Estimate. Four of the six children continued to evidence social pragmatic difficulties at follow-up, but were subthreshold for ASD. One child met criteria for ADHD and Anxiety-NOS. Of the two children who previously received a PDD-NOS diagnosis, one met criteria for ASD and the other showed no evidence of ASD. ASD Symptom Severity. In all but one case, ASD symptom severity declined or remained stable between 3 and 6 years. Level of ASD related symptoms on the ADOS ranged from ‘minimal’ to ‘low’. Infrequently observed were unusual sensory interests, or restricted, repetitive patterns of behavior or interests. Comorbid symptoms. The Early Childhood Inventory-4 revealed clinical or borderline range scores for Generalized Anxiety Disorder, Social Phobia, or ADHD. Two children had elevated global scores on the BRIEF suggesting the presence of executive functioning vulnerabilities. No children had a significant elevation on the Shift scale (assessing flexibility/adaptability), a scale that typically distinguishes children with ASD from other clinical groups. Cognitive functioning. All children were functioning in the average to above average range; in two cases verbal IQ scores exceeded nonverbal IQ scores by at least 1 standard deviation (SD). Language. All children’s core language fell in the average to above average range. In four out of six cases, narrative skills fell at least 1SD below their formal language production. Adaptive Functioning. All but one child had a Socialization score in the ‘Adequate’ range on the Vineland-II. However, examining interpersonal skills, three of the six were functioning below age-based expectations. Social Perception: Scores on measures of affect recognition, memory for faces, and memory for names were lower than cognitive ability by at least 1SD in 50-75% of children.

Conclusions: These preliminary data underscore the complexity of long-term outcomes in HR siblings. A common theme suggests that variability is a defining feature of their presentation as these children evidenced variable developmental trajectories and variable diagnostic outcomes; a co-occurring vulnerability for both ASD symptomatology and other disorders exists on a clinical and also on a subclinical level. This variability highlights the danger of an “averaging artifact” where the pattern detected at a group level does not describe well any single member of the group. Understanding the full range of outcomes among HR siblings in future research, in terms of categorical presentation and functioning along specific dimensions, will be crucial for understanding the risk factors and clinical needs of this unique population.
Abstract #16617

Components of Limited Activity Monitoring in Toddlers and Children with ASD

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Abstract Text:

Background: Our previous work with eye tracking has shown that 20 month old toddlers with ASD monitor the activities of others to a lesser extent than both developmentally delayed and typically developing peers. However, it is unclear whether the gaze cues of others, the presence of distractors, or motion cues were responsible for the differences between groups. Furthermore, it is unclear whether diminished activity monitoring is only present in the toddler years, resolving as the children grow older, or whether these deficits persist.

Objectives: To use eye tracking to examine activity monitoring in toddlers and children with ASD and to decompose factors that impact activity monitoring.

Methods: Toddlers with ASD (N=10; Age: M=23, SD=3 months) and typical development (TD; N=23; Age: M=21, SD=3 months) and children with ASD (N=17; Age: M=37, SD=1 month) and TD (N=9; Age: M=38, SD=3 months) were shown 16 20s video clips and 16 10s static images depicting two female adults interacting over a shared activity. Stimuli varied along 3 dimensions: (1) Gaze: mutual towards each other or towards the activity; (2) Distractors: many distractors or no distractors, where distractors were colorful toys; and (3) Motion: static image or video clip. Stimuli were counterbalanced across and within participants and eye tracking was used to evaluate patterns of attention. A 2nd order linear mixed model approach was used to examine attention to the scene, activities, people, and background elements.

Results: Decreased looking at the scene overall was associated with ASD (p<.01), fewer distractors (p<.05), and no motion (p<.01). TD participants looked more at the scene when motion was present (Group x motion interaction, p<.01). Decreased looking at activities was associated with ASD (p<.01), being in the younger age group (p<.01), the presence of more distractors (p<.01), and the lack of motion (p<.01). Older TD children looked more at activities than other groups (Group x age interaction, p<.01). Increased looking at the background was associated with ASD (p<.01), being younger (p<.05), more distractors (p<.01), and no motion (p<.01). Decreased looking at the people in the scene was associated with ASD (p<.01), being older (p<.01), more distractors (p<.01), and presence of motion (p<.01). Younger TD toddlers looked more at people than all other groups (Group x age interaction, p<.01). Eye tracking outcome measure associations with clinical characterization in ASD replicated previously observed findings.

Conclusions: Our results suggest that toddlers and children with ASD show a general pattern of diminished attention towards people and their activities. In typical development but not ASD, transitions consistent with a sharpening of attention towards the activities of others appear between 2 and 3 years of age. Interestingly, an effect of gaze direction was not present in the results of any outcome measures, suggesting that dynamic and complexity cues may play a greater role in shaping attention to scene-relevant context at these ages.
Abstract #16669
A Preliminary Head-Mounted Eye-Tracking Study of Individuals with ASD Touring a Museum of Art

S. J. Wallace1, G. Vaccarino Gearty2, E. S. Kim1, M. Perlmutter1, Q. Wang1, C. A. Wall1, J. S. Kowitt3, L. Friedlaender4 and F. Shic1, (1)Child Study Center, Yale University School of Medicine, New Haven, CT, (2)University of Chicago, Chicago, IL, (3)Educational Psychology, University of Connecticut, Storrs, CT, (4)Yale Center for British Art, Yale University, New Haven, CT

Abstract Text:

**Background:** Eye tracking is a powerful tool for studying attention patterns, revealing differences in attention to people’s mouths, eyes, and activities among individuals with typical development (TD) and autism spectrum disorders (ASD). Many current eye tracking studies have used table-mounted devices to examine pre-recorded video stimuli. However, commercial head-mounted eye trackers can be expensive, limiting accessibility. Gaze tracking in real world situations may offer insight into the difficulties individuals with ASD experience in authentic social interactions.

**Objectives:** 1) To construct an untethered head-mounted eye-tracking device; 2) To contrast patterns of attention in individuals with ASD and TD towards people in paintings and social situations.

**Methods:** We used inexpensive electronic components to construct untethered head-mounted eye trackers. A tour guide escorted pairs of participants (n = 9, ASD; n = 13, TD) through an art museum to view four paintings featuring a variety of social content. For each painting, participants completed three tasks: (1) silently observing the painting, (2) listening while the guide spoke, and (3) answering open-ended and rating questions asked by the guide (QA). Behavioral coding was completed on all participants. Eye-tracking data has been analyzed for (n = 5, ASD; n = 3, TD). To track gaze, we detected the pupil centroid and estimated a map from its position to calibration targets in scene videos.

**Results:** Linear mixed model analyses revealed a task x group interaction for within-painting regions of interest (p < .01). During the QA task, participants with ASD looked more at the painting background than did TD individuals (p < .05). This effect was absent in the silent observation task, and marginally significant (p = .080) during the listening task. While looking at the guide or the other participant, participants with ASD looked less at people’s eyes than did TD participants (p < .05). There also was a task x group interaction for duration spent looking at real world versus the paintings (p < .05), with ASD and TD participants showing opposite patterns of attentional allocation. Behavioral coding showed a higher number of shifts of attention to the guide (p < .05) and to the painting (p < .05) by participants with ASD than by TD participants. Participants with ASD gestured more than TD participants (p < .05).

**Conclusions:** High-functioning adults with ASD show similar gaze patterns towards paintings as do TD adults during silent viewing. These patterns become more atypical as the social demands imposed by the guide increase. During real-world social interactions, individuals with ASD showed decreased attention towards the eyes of others. Individuals with ASD tended to monitor the real world more than typical individuals, and engaged in more discrete shifts of attention during social interaction, suggesting either executive function or social information processing deficits. More prototypical patterns of attention towards paintings in the absence of communicative processing demands may be due to an equalizing effect of art on attention, or the static nature of the painting compared with the dynamic, social nature of interaction with the guide.
Abstract #16675

The Relationship Between Autism Symptoms and Arousal Level in Toddlers with ASD, As Measured By Electrodermal Activity

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Abstract Text:

Background:
Electrodermal activity (EDA) is a measure of skin conductance and is often used to determine the level of emotional arousal in children and adults (Dawson, 2000). Previous studies have examined EDA in the context of face recognition, gaze direction and eye contact in children and adults with Autism Spectrum Disorders (ASD) using EEG and eye-tracking protocols (Joseph, Ehrman, McNally, & Keehn, 2008; Kylliainen & Hietanen, 2006; Kylliainen et al., 2011). However, little is known about EDA in toddlers with ASD and even less is known about it during real-world behavioral assessments.

Objectives:
To use EDA measurements to examine differences in reactivity between toddlers with ASD and their typically developing (TD) peers during a behavioral assessment of social communication.

Methods:
21 toddlers (10 TD, 11 ASD; mean age=22 months) received the Communication and Symbolic Behavior Scale (CSBS) as part of a comprehensive assessment of social functioning, communication skills, and development. The CSBS comprises a number of activities designed to elicit social and communicative behaviors in toddlers. These include interaction with animal figurines, toy cars, books, wind-up toys, bubbles, balloons, and a snack session. The activities were grouped into four categories: books, animals, mechanical toys, and temptation episodes. During the 30 minute session, participants wore a sensor on their ankle (Affectiva Q-Sensor) that measured EDA in microsiemens at 8 Hz. The first second of each activity was used as a baseline measure. We used the largest absolute change to identify the magnitude of change from baseline during each activity.

Results:
We used a 2 (diagnosis) by 4 (activity) mixed factorial design and ran a linear mixed models ANOVA. Because the children were likely to vary in verbal abilities based on diagnostic group, we controlled for Verbal DQ scores as measured on the Mullen Scales of Early Learning. In TD toddlers, there was a significant difference in the absolute change in EDA between the animal toys and the temptation tasks (p<0.05). However, this was not the case in children with ASD. For these children, there was a significant difference in EDA between the animal toys and the mechanical category which includes cars, helicopters, spinning and wind-up toys (p<0.01).

Conclusions:
Children with ASD have a dissimilar reaction to activities on the CSBS as compared to their typically developing peers. Both groups responded similarly to the animal toys, which are generally the least exciting and interactive items. However, while TD children showed a greater change in EDA during the "temptation" toys which require them to interact with the examiner in order to operate the object, those with ASD showed a heightened response to mechanical toys. These results are consistent with previous findings demonstrating that children with ASD are more likely than TD children to have a circumscribed interest in mechanical systems (Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011). These preliminary results offer physiological evidence of arousal differences between toddlers with ASD and their typical peers upon presentation of specific stimuli.
Abstract # 16939

Parsing Heterogeneity of Early ASD Phenotype: Stability and Change

S. H. Kim¹, S. Macari², C. A. Saulnier³, A. M. Steiner⁴, T. R. Goldsmith⁵, J. Koller⁶, K. D. Tsatsanis² and K. Chawarska², (1)40 Temple St., Suite 7D, Yale University School of Medicine, New Haven, CT, (2)Child Study Center, Yale University School of Medicine, New Haven, CT, (3)Marcus Autism Center, Children’s Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA, (4)Yale University, New Haven, CT, (5)Department of Pediatrics, University of New Mexico, Albuquerque, NM, (6)The Hebrew University of Jerusalem, Jerusalem, Israel

Background: Past studies have consistently found high stability in the diagnosis of Autism Spectrum Disorders (ASD) during toddler years. However, diagnostic stability has not been examined in current cohorts of toddlers for whom intensive interventions are readily accessible. Moreover, due to tremendous heterogeneity observed within ASD early on, knowledge of short-term outcomes is still limited.

Objectives: (1) To replicate and extend previous findings on stability of early diagnosis using toddlers from a large clinic-referred sample (born between 2006-2012); (2) To identify more homogeneous subgroups within ASD based on a constellation of key clinical features in the second year of life; (3) To examine short-term outcomes in the identified subgroups at 1-2-year follow-up.

Methods: One hundred toddlers referred for a differential diagnosis of ASD at 14-27 months (Time 1) and followed until 30-49 months (Time 2) were evaluated with regard to autism symptoms, verbal and nonverbal skills, and adaptive functioning. At Time 1, we identified homogeneous subgroups within ASD using Hierarchical Clustering (HC) analysis. Developmental outcomes of the identified clusters were compared using generalized linear mixed models. All but one child received early intervention (Mean=16.9 hours/week; SD=9.16).

Results: 94% of children given an ASD diagnosis at Time 1 maintained the ASD diagnosis at Time 2. HC analysis identified 4 clusters at Time 1. Toddlers in clusters 1 and 2 had higher nonverbal and verbal skills and adaptive communication, daily living, and social functioning than toddlers in clusters 3 and 4. Clusters 1 and 2 differed from one another by levels of autism symptoms and nonverbal skills. Clusters 3 and 4 differed in nonverbal, verbal, adaptive social, and daily living skills. Within each cluster, toddlers demonstrated high stability of nonverbal and daily living skills over time. However, changes over time were found within clusters in severity of autism symptoms, verbal, communication, and socialization skills. Specifically, autism severity in cluster 2 increased over time (Cohen’s $d$=-1.1) whereas in the three remaining clusters, it remained stable. Verbal and communication skills significantly improved in three clusters ($d$’s=1-1.8). However, cluster 4 showed only a modest increase in verbal skills ($d$=0.5) and a decrease ($d$=-0.6) in adaptive communication skills. Finally, cluster 1 showed improvement ($d$=0.6) in adaptive social skills, whereas cluster 4 showed worsening of skills ($d$=-1.4); adaptive socialization for the other two clusters remained stable over time. The clusters differed in the amount of intervention they received between Time 1 and Time 2 with cluster 4 showing the most hours of intervention.

Conclusions: High stability of early ASD diagnosis was replicated with the current cohort of toddlers. However, considerable heterogeneity in clinical presentation at 14-27 months resulted in four subgroups whose short-term outcomes also varied. Short-term prognosis was better for children with intact cognitive and adaptive skills early on despite pronounced autism symptoms, especially in terms of progress in verbal and adaptive communication functioning. Identifying subgroups within ASD during toddler years based on multiple clinical features will be crucial for predicting outcomes and programming treatment.
Abstract # 16992

The Utility of the First Year Inventory in Evaluating Autism Symptoms at 12 Months in Infants at High Risk for ASD

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Background: Younger siblings of children with autism spectrum disorder (ASD) (high-risk siblings, HR) are at higher risk of developing ASD and other developmental problems than those in the general population. Research has suggested that some symptoms of ASD are present in HR siblings at 12 months of age. Screening at this age, however, is complicated by variable autism symptom onset patterns, and especially complex in HR populations because of the substantial numbers of HR infants who do not develop ASD but present with similar symptoms over the second year of life.

Objectives: We examined the utility of information gathered at 12 months via parental questionnaire (First Year Inventory; FYI; Baranek et al., 2003) for predicting a later diagnosis of ASD in HR infants at the domain and construct level as well as at the item level.

Methods: Participants included 96 families of 12-month-old infants: 71 at HR and 25 at low risk (LR) for ASD. The 61 questions on the FYI comprise two domains (Social Communication and Sensory-Regulatory), each domain consisting of four constructs. At 36 months, the infants were extensively assessed (Mullen, ADOS, Reynell, Vineland) by a team of expert clinicians and classified as having ASD (n=16); other delays, subclinical autism symptoms, or a history of either (HR-ATYP; N=36); or typical development (HR-TYP, n=19; LR-TYP, n=25). Analysis consisted of between-group ANOVAs followed by post-hoc tests and classification tree (CART) analysis of FYI items.

Results: The four groups differed on the Social Communication domain (F(3,92)=5.2, p=.002) and two of its four constructs: Social Orienting and Receptive Communication (F(3,92)=3.0, p=.021) and Imitation (F(3,92)=6.0, p=.001). Post-hoc analyses showed that infants with ASD had significantly higher (worse) scores on the Social Communication domain compared to HR-ATYP (p=.025, d=.75) and LR-TYP (p=.001, d=1.18) but not HR-TYP infants. The ASD group had significantly higher scores on the Social Orienting/Receptive Communication construct than the LR-TYP (p=.021, d=.91) group, but not the other HR groups. The ASD group had higher scores on the Imitation construct than the HR-ATYP (p=.004, d=.94), HR-TYP (p=.002, d=1.17), and LR-TYP (p=.002, d=1.10) groups, with large effect sizes for each comparison. There were no between-group differences for the Sensory-Regulatory domain or any of its constructs. The CART analysis revealed that a combination of questions related to recent declines in play and communication and to lack of imitation of vocal sounds correctly predicted almost 2/3 of the children with ASD and 93% of the children without ASD.

Conclusions: Our results suggest that parent-reported information about social communication and imitation in 12-month-old infants helps identify infants at highest risk for an ASD among HR siblings. We will also discuss concordance between parent report and clinician observation as a critical issue in the development of screening tools.
Abstract # 17033
Early Head and Body Overgrowth in Boys and Girls with ASD: Prevalence Rate and Clinical Outcomes

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Background:
Brain enlargement in infancy, recently reported to occur in association with an generalized overgrowth in physical stature, is one of the best-replicated biological findings in ASD. It is not clear whether generalized overgrowth is also present in girls, what its prevalence is, and whether it is associated with clinical outcomes in childhood.

Objectives:
To examine: somatic growth in boys and girls with ASD compared to a community sample of typically developing (TD) children; prevalence of generalized overgrowth in ASD and TD infants; and predictive association between generalized overgrowth and clinical phenotype at 4 years.

Methods:
Head circumference (HC) as an indirect measure of brain size in infancy, height, and weight measurements were collected retrospectively from 200 children (161M/39F) with ASD and 147 typically-developing (TD) controls (98M/49F) between birth and 24 months of age. Growth curves for each measure were modeled using splines. The three measures were combined using principal components analysis to obtain a generalized overgrowth component (PC1). Prevalence rates of macrocephaly were estimated by the proportion of children with HC scores 2 SD above/below the TD mean; macrosomy rates were estimated similarly using PC1 scores. Extreme generalized and HC growth rates were estimated by the proportion exceeding 2 SD above the mean in change between birth and 24 months in TD group. Social, developmental, and adaptive functioning was measured at 2 and 4 years.

Results:
Generalized overgrowth was more pronounced in boys than in girls with ASD. Extreme overgrowth from birth to 2 years was present in 16% of the ASD toddlers as compared to 3.4% in TD controls ($p<.001$); at 2 years. Corresponding estimates were similar when only HC growth was considered: extreme HC overgrowth was noted in 15.0% of toddlers with ASD but only 3.4% of TD controls ($p < .001$). At 24 month 6.5% of toddlers with ASD had macrocephaly compared with 4.1% of TD controls ($p=.47$). Within ASD group, larger body size at birth predicted lower verbal ($p=.01$), nonverbal ($p=.005$), and adaptive communication ($p=.02$) skills and higher autism severity ($p=.02$) at 4 years. Accelerated somatic postnatal growth contributed to poorer verbal ($p=.005$), nonverbal ($p=.01$), adaptive communication ($p=.007$), and repetitive behavior ($p=.002$) scores at 4 years after controlling for body size at birth.

Conclusions:
Co-occurrence of accelerated skeletal and HC growth in ASD suggests a common mechanism, potentially constraining the search for underlying biological factors. Girls are less likely to exhibit overgrowth than boys, though factors related to such dimorphism remain unknown. Although early growth abnormalities in ASD are less common than previously thought, their presence is predictive of clinical outcome at 4 years. Future studies will elucidate pre- and postnatal factors affecting growth in ASD and determine whether the generalized overgrowth endophenotype plays a role in etiology of the disorder and reveals novel treatment targets.
Abstract #17053
Dimensionality of Gaze Patterns Towards Faces and Objects in Toddlers with ASD

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Abstract Text:

Background: Eye-tracking is a prominent tool in psychological and cognitive research. However, the analysis of eye-tracking data is confounded by choices in how fixations should be defined, i.e. how densely packed points must be in order to be considered a fixation. Our previous work (Shic, Scassellati, & Chawarska, 2008), has shown that by manipulating fixation parameters, the fixation statistics between ASD and TD toddlers can reversed. There exists evidence that scale-free fractal structure may derive from gaze patterns of viewing naturalistic stimuli.

Objectives: (1) To explore the nature of toddlers’ scanning patterns during complex scene viewing, independent of fixation parameters. (2) To apply this technique to examine scale-free gaze behaviors in toddlers with Autism Spectrum Disorders (ASD) and typical development (TD) when looking at faces and blocks.

Methods: We presented 6 trials (10s/trial) with pictures of faces and 6 trials with block designs to TD toddlers ($n=12$, Mean age=23.8(±2.8) months) and toddlers with ASD ($n=10$, Mean age=22.7 (±3.7) months). We examined the log of the number of fixations (n) as a function of the log of box size (s) ranging from .1 deg. to 10 deg. This is a greedy box-counting algorithm for fractal dimensionality, equivalent to an adaptation of fixation identification algorithms at multiple distance scales.

Results: The smallest $R^2$ in our linear regression is $R^2=.944$, with an average of $R^2=.992$, suggesting that the scanning patterns were strongly self-similar and that measures of gaze pattern fractal dimensionality through box counting is robust. A mixed linear model on the box count dimensionality of our eye tracking data revealed a main effect of stimulus class (p<.01) with a higher dimensionality for blocks than faces. An interaction was found for group and stimulus class (p<.05) driven by a lower dimensionality for faces than blocks in TD toddlers, but no such effect for toddlers with ASD. There was a trend for toddlers with ASD to exhibit higher dimensionalities for scanning faces (p=.08). Our results are consistent with lower dimensionalities being associated with more directed patterns of scanning.

Conclusions: Our use of fractal dimensionality may offer a route to more robust, more informative, and less biased approaches towards eye-tracking analysis. Consistent with previous experiments, our study, which reports on box counting fractal dimensionality, suggests that TD toddlers use different basic attentional strategies to process faces and blocks, whereas toddlers with ASD may be employing similar distributional strategies for both stimuli classes.
Abstract #17177

Early Intervention in Autism: Wide-Locus GWAS Leading to Novel Treatment Options

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Abstract Text:

Background:
The prevalence of autism spectrum disorders (ASD) has increased 20-fold over the past 50 years to >1% of U.S. children. Although twin studies attest to a high degree of heritability, the genetic risk factors are still poorly understood.

Objectives:
From recent results in a comorbid disease, childhood absence epilepsy, we had hypothesized that axonal guidance and calcium signaling are involved in autism as well. Our study aimed at identifying overlapping genetic risk factors for both neurodevelopmental diseases as well as indications for differences in the etiology to guide with developing novel autism-specific pharmacological interventions.

Methods:
We analyzed data from the two stages of the Autism Genome Projects as independent populations using u-statistics for genetically structured wide-locus data and added data from unrelated controls to explore epistasis. To account for systematic, but disease-unrelated differences in (non-randomized) genome-wide association studies (GWAS) and for conducting multiple tests in overlapping genetic regions, we present a novel study-specific criterion for ‘genome-wide significance’.

Results:
Enrichment of the results in both studies with related genes confirms this hypothesis. Additional ASD-specific variations identified in this study suggest protracted growth factor signaling as causing more severe forms of ASD. Another cluster of related genes suggests a novel class of ion channels as additional, ASD-specific drug targets. The involvement of growth factors suggests the time of accelerated neuronal growth and pruning at 9–24 months of age as the period where treatment with a novel class of ion channel modulators would be most effective in preventing progression to more severe forms of autism.

Conclusions:
These results are the first to suggest a pharmacological intervention in autism based directly on observations in patients with autism. The major difference for this novel approach to identify ASD-specific risk factors and drug targets and previous statistical approaches is that genetic risk factors are assumed to be epistatic (within several neighboring SNPs) and in linkage disequilibrium with more than a single SNP. By extension, the same computational biostatistics approach could yield profound insights into the etiology of many common diseases from the genetic data collected over the last decade.
Abstract # 17427

Biochemical Assessment of Circadian Processes in ASD

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Background: The pineal hormone melatonin (MEL) is secreted with a marked day-night rhythm and it plays a crucial role in circadian rhythms. MEL also has powerful antioxidant properties. Studies in school-age children, adolescents and young adults have reported lower group mean production of melatonin in ASD.

Objectives: We wished to examine daytime and nighttime production of MEL, as well as other diurnally varying neurohormones, in younger ASD and typically developing individuals in order to understand better this apparent deficit and to assess the potential utility of the measure in screening.

Methods: Melatonin sulfate, norepinephrine, epinephrine, cortisol and creatinine were measured in methanolic extracts of daytime and overnight diapers obtained from toddlers ages 18-36 months. ASD subjects received an extensive behavioral assessment and caregivers completed a questionnaire asking about sleep and gastrointestinal related behaviors and problems.

Results: Diapers have been obtained from 53 typically individuals and a similar number of ASD subjects. Analysis of diaper extracts for the neurohormones has been successful and data analysis is ongoing.

Conclusions: Collection and extraction of daytime and overnight diapers obtained from toddlers with ASD provides a feasible approach to the study of circadian rhythms in younger individuals with ASD. The completed data analysis will indicate whether lower production of melatonin is also found in younger individuals with ASD and will examine the specificity of potential alterations in diurnally vary neurohormones.
The Effects of a Novel Vasopressin V1a Antagonist on Orienting to Biological Motion


Abstract #17479

Abstract Text:

Background: Eye tracking has become an increasingly prominent tool in the study of ASDs. However, to date, only a few studies have used eye tracking to monitor the effects of potential interventions and no studies have used eye tracking to systematically evaluate the effects of novel pharmacological agents.

Objectives: To explore the impact of a novel V1a antagonist, RG4914, on the social attention of high-functioning adults with autism through eye-tracking tasks including biological motion preference.

Methods: High-functioning adults (M=23.4 years, range=18 to 40 years) with autism (n=19) participated in a multi-center (3-site), randomized, double-blind, placebo-controlled, cross-over study of the effects of RG4914. Each participant was seen on two separate days for dosing. On the first dosing day, participants completed (1) predose assessments including eye tracking; (2) a 2 hour infusion of RG4914 or placebo; and (3) a postinfusion assessment battery including eye tracking. The second dosing day was similar to the first dosing day, with the exception of a crossover for the IV compound (RG4914 or placebo). Administered eye-tracking tasks included biological motion preference (based on work similar to Annaz et al., 2012). In this preference task, outcome variables included %Looking time towards the biological/social stimulus, %Orienting (% of trials where the first attended to stimulus was the more social target), and Latency (response time to attend to either the social or control stimulus).

Results: Linear mixed model analyses conducted over data aggregated for each eye-tracking task revealed a significant effect of RG4914 vs. placebo on %Orienting in biological motion preference tasks (p<.05, ES=0.8), with participants administered RG4914 directing their first gaze shift more often to biological motion targets. While similar analyses for Latency were not significant (p>.05), the effect size was moderate (ES=-.4) with trends suggesting that participants administered RG4914 orient more quickly as well as more often to biological information. Primary hypotheses on %Looking for biological motion preference were also not significant; however, an exploratory analysis revealed a significant interaction (p=.05) between the day of dosing and changes between pre- and post-infusion performance, with participants administered a placebo on day 1 showing greater decreases in looking at biological motion as compared to participants administered the active compound.

Conclusions: This study provides preliminary evidence of the ability of a novel V1a antagonist, RG4914, to affect behaviorally primitive and evolutionarily preserved attentional responses to biological motion. Furthermore, this study suggests that eye tracking may be useful not only for monitoring the effects of treatments for individuals with ASD, but may also serve as a valuable tool in the development of new interventions, behavioral, pharmacological, or otherwise. Because of the small sample sizes of this study, and the exploratory nature of both the analyses and the designed experiments, these results should be taken as preliminary.
Abstract #17577

Performance on a Novel Kinect Emotional Choice Game Correlates with Broader Autism Phenotype Characteristics in Typically Developing Adults

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Abstract Text:

Background: While video game overuse has caused difficulties in the lives of some individuals with autism spectrum disorders (ASD) (Mazurek et al., 2011), video gameplay may provide a useful way to measure social cognition. We designed a video game that physically engages participants in a fun, unstructured task that implicitly measures emotion processing, using the Microsoft Kinect platform. Difficulties in emotion processing and other autistic-like traits have been shown to vary beyond populations with ASD diagnoses, with ASD representing extrema (Lundstrom et al., 2012).

Objectives: To examine relationships among preferences for emotional information expressed through whole-body, volitional actions, the ability to recognize emotional information, and traits associated with the broader autism phenotype.

Methods: TD adults (N = 19; 5 females; age M = 22.7 years, SD = 6.1 years; FSIQ M = 111, SD = 21.85) played a video game on the Kinect platform using the custom-built Yale Interactive Kinect Environment Software (YIKES). Live video images of each participant were integrated in the game environment, which was projected on to a wall. The participants were asked to move left and right to position their images to catch emotional (fearful, happy, and neutral) faces “falling” from the top of the screen. A total of 280 face images were presented, divided over eight rounds of gameplay. Outcome variables were ratios of number of emotional (fearful or happy) faces, to total number of faces caught, in each of round. Given the large number of variables associated with gameplay dynamics and high levels of correlations among variables, we used principal component analysis (PCA) for dimensionality reduction. We examined correlations (Pearson’s) between the identified principal components (PCs) and performance on the Developmental Neuropsychological Assessment (NEPSY-II) Affect Recognition subtask, the Broader Autism Phenotype Questionnaire (BAPQ), and IQ (measured using the Wechsler Abbreviated Scale of Intelligence; WASI).

Results: PCA revealed 3 factors accounting for 83% of all variance: principal component 1 (PC1: 51% of variance) represents diminished selection of negative (fear) content and increased selection of positive (happy) content; PC2 (21%) represents increased selection of any emotional content; and PC3 (11%) represents avoidance of negative content and selection of positive content specifically in mood-negative contexts. PC1 showed no correlations with any examined phenotypic characteristic. PC2 was associated with lower BAPQ scores (r = -.47, p < .05) and with higher Affect Recognition scores (r = .47, p < .05). PC3 correlated with performance IQ (r = .46, p < .05).

Conclusions: Performance on a simple, emotional-choice, whole-body-movement video game can provide information about phenotypic characteristics of typical adults. Correlations between PC2 and BAPQ or AR scores suggest that preferential orienting towards emotional information is related to the ability to identify emotions in pictures of faces, and to fewer broader autism features in TD adults. These results provide evidence that video games may be used as an appealing platform for understanding cognitive ability, emotional processing, and social capabilities. Future directions include extension to children and to individuals with ASD, and exploration of therapeutic applications.
Background: Given the current emphasis on early screening for autism spectrum disorders (ASD), it is crucial to examine the efficacy of screening tools and understand the potential vulnerabilities associated with utilizing parent reports. Although parents have an optimal perspective from which to observe and engage with their infants across diverse contexts, utility of parent ratings in a high-risk population is unclear, given contrast effects based on an older sibling with ASD along with other limitations of informant reporting. To further the development of ASD screening tools for infants, it is critical to evaluate concordance between parent report and clinical observation.

Objectives: To investigate agreement across parental and clinician ratings, we compared similar items on the First Year Inventory (FYI; Baranek et al., 2003) a parent questionnaire designed to screen for ASD at 12 months, and the ADOS-Toddler (ADOS-T; Lord et al., 2013), a standardized ASD diagnostic tool, administered concurrently to 12-month-olds at high and low risk for ASD.

Methods: 161 (high-risk(HR)=95, low-risk(LR)=66) infants were evaluated with the ADOS-T at 12 months by clinicians blind to their risk status. Prior to the ADOS-T assessment, parents completed the FYI. Nine items describing comparable behaviors were identified across the instruments, including social, communication, and repetitive behavior. Each measure rates behaviors on a 0 to 3 scale. Items were compared using paired-samples t-tests with Bonferroni correction for multiple comparisons.

Results: Regardless of risk status, parents rated three speech and communication-related items (amount of babbling, directed vocalizations, and gestures) and object imitation as more typical compared to the clinical assessment ($p<.005$). Clinicians and parents in both risk groups agreed on items assessing response to name, response to joint attention, showing, and repetitive behaviors. Interestingly, response to name appeared twice on the FYI in slightly different formats. When the question was phrased globally (i.e., “Does your child answer to his name?”), both HR and LR parents rated the infant’s behavior as more typical than the clinician ($p<.001$); however, when the same question was presented in a multiple-choice format (“What do you typically have to do to get your baby to turn towards you?”), parent and clinician ratings were more similar in both risk groups.

Conclusions: Parents of high- and low-risk infants rated their children’s behaviors similarly to clinicians on a number of items tapping into social and repetitive behavior, but discrepancies between expert clinicians and parent ratings on speech and communication items were common in both risk groups and may reflect the effect of unfamiliar context on child’s behavior during direct assessment. Wording of questions appeared to affect the degree of discrepancy between clinician and parent report. These findings suggest a further need to examine the sources of disagreement between parental report and clinician rating of key behaviors as well as the impact of design features on screening instruments’ ability to capture behavior most accurately. In addition to these issues, our discussion will also include preliminary results of the FYI’s utility in identifying those with a later ASD diagnosis in a high-risk sample.
Abstract # 17830

Interest in Potential Reinforcers in the Second Year of Life Predicts Outcome of Behavioral Intervention in Toddlers with ASD

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Background: There is substantial variation in language and intellectual outcomes in children with ASD. A recent study suggests that the number of stimuli that children find reinforcing may constitute a predictor of response to behavioral treatment in preschool-aged children with ASD (Klintwall & Eikeseth, 2012). However, very little is known if a similar effect can be found in children presenting for a differential diagnosis of ASD in the second year of life. Advancing our understanding of factors that affect amenability to treatment at the very early stages of ASD emergence would improve our ability to individualize treatments very early on and to enhance outcome in the affected children. Moreover, in contrast with our original work, which was based on informant report, in this study we intended to design and test a coding system based on children’s responses to play probes in the context of semi-structured interaction with an examiner.

Objectives: To address this gap we investigated child interest in objects and activities during the Autism Diagnostic Observation Schedule-Toddler Module (ADOS-T; Lord et al, 2000) assessment as a predictor of subsequent development measured by adaptive behavior and verbal and non-verbal developmental quotient (DQ) at ages 2-4 years.

Methods: Reinforcing function of stimuli can be approximated from exhibited affect and attention towards the object or activity. Based on our previous work (Klintwall & Eikeseth, 2012), we developed a novel scoring system for capturing toddlers’ interest in potential reinforcers (e.g. edibles, toys): the Assessment of Volition and Object Curiosity (AVOC). The scoring system yields a mean interest score. AVOC was used to score video recordings of 70 toddlers with ASD who underwent assessment between 14 and 32 months (Time 1). Developmental (Mullen Scales of Early Learning; Mullen, 1995) and adaptive skills (Vineland Adaptive Behaviors Scales-II; Sparrow, et al., 2005) were measured concurrently and then again when the children were 21 to 49 months old (Time 2). Between measurements, the children received a variety of community-based behavioral and developmental interventions.

Results: The AVOC scoring system exhibited acceptable levels of test-retest (0.80) and inter-rater reliability (0.90). AVOC score, ADOS-T total score, Mullen verbal and nonverbal DQ, and Vineland adaptive full scale score (Adaptive Behavior Composite; VABC) was entered into linear regression models at Time 1 to predict outcome at Time 2 defined as VABC, verbal DQ and non-verbal DQ. The AVOC score was the only significant predictor of Time 2 adaptive behavior (p=.001, R²=.394) as well as non-verbal DQ (p=.024, R²=.277), outperforming Time 1 verbal DQ (p=.216 and p=.226, respectively), non-verbal DQ (p=.652 and p=.856) and ADOS-T scores (p=.305 and p=.285). AVOC score at Time 1 also contributed, along with non-verbal DQ, to variance in verbal DQ at Time 2 (p=.009, R²=.318).

Conclusions: Interest in potential reinforcers was a powerful predictor of subsequent development for toddlers with ASD. Future studies should aim to evaluate and develop techniques for identifying and expanding the repertoire of stimuli functioning as reinforcers for children who score low on the AVOC, thus possibly improving their outcomes.
Clinical and Biomarker Effects of a Novel Vasopressin 1a Receptor Antagonist Vs Placebo in High Functioning Adult Autism

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Abstract Text:

Background: Oxytocin and vasopressin play a critical role in social cognition and social signalling deficits of ASD. Experimental therapeutic interventions to enhance oxytocin or block Va1A receptor signalling may modulate these domains in ASD.

Objectives: To explore the impact of a novel V1a antagonist R050288442 vs placebo on core social cognition measures, exploratory biomarkers, and safety/tolerability measures in adult high functioning ASD.

Methods: High-functioning adults (M=23.4 years, range=18 to 40 years) with autism (n=19) participated in a multi-center (3-site), randomized, double-blind, placebo-controlled, cross-over study of the effects of novel vasopressin 1a receptor antagonist R050288442. Each participant was seen on two separate days (1 week apart) for dosing a 2 hour infusion of R050288442 or placebo. Safety/tolerability, PK, PD, core social cognition, olfaction, language sampling and AVPR1A polymorphisms measures were collected.

Results: At baseline, the Affective Speech Recognition (ASR), Reading the Mind in the Eyes (RMET) and olfaction measures correlated with measures of functioning on the Vineland and ADOS as well as IQ. The Va1 antagonist showed evidence of anxiolysis. The Va1 antagonist showed effects on olfaction, RMET and scripted interaction in the predicted direction of modest effect sizes. There were large negative effect sizes of the Va1 antagonist vs placebo on the social cognition ASR measure Lust and Fearful subscales, and there appeared to be carryover effects from infusion 1 to infusion 2 that may influence these findings.

Conclusions: This study provides preliminary evidence of the ability of a novel V1a antagonist R050288442 to affect core symptoms of social cognition and olfaction. Effects on the laying down of social memory and social learning may persist well past the pharmacokinetic effects of the compound. These results should be taken as preliminary but may help to guide the development of new oral vasopressin antagonist interventions in ASD.