Symposium Title: From Brain to Cognition to Health: A Translational Approach to Understand and Improve Health and Behavioral Outcomes in Developmental Disabilities

Chair: Gregory Wallace\(^1\) and Nancy Raitano Lee\(^2\)

Discussant: Sigan Hartley\(^3\)

Overview: Individuals with developmental disabilities have poor health-related outcomes compared to their typically developing peers. For example, adults with ASD present with higher than expected rates of hypertension and obesity, both of which represent risk factors for subsequent medical conditions, such as cardiovascular disease and diabetes (Croen et al., 2015). Similarly, individuals with Down syndrome (DS) present with heightened rates of obesity and cardiopulmonary disease as well as numerous other health conditions (Colvin & Yeager, 2017). Additionally, both disorders are associated with elevated rates of sleep disturbances (Esbensen & Schwichtenberg, 2016) which are becoming increasingly recognized as a significant risk factor for poor health and behavioral outcomes. Nevertheless, the etiological underpinnings as well as the cognitive-behavioral correlates of sleep quality and congenital heart defects in DS and eating habits in ASD. Additionally, a novel intervention program that has employed cognitive-behavioral strategies (i.e., targeting executive function challenges) to address food selectivity in neurodevelopmental disorders will be presented and the implications for improving health outcomes will be discussed.

References/Citations:


Paper 1 of 4

Paper Title: Health and Academic Achievement in Youth with Down Syndrome: Evidence For Poorer Reading Outcomes in Those with Parent-Reported Sleep Disturbance but Not Congenital Heart Defects

Authors: Megan Perez\(^4\), Moshe Maiman\(^4\), Mary Godfrey\(^4\), Manisha Udhnani\(^2\), Taralee Hamner\(^3\), Catherine Stephan\(^2\), Rebecca LaQuaglia\(^2\), Nancy Raitano Lee\(^2\)

Introduction: Down syndrome (DS), the most common genetic cause of intellectual disability, is a multisystem disorder characterized by high rates of sleep-related breathing disorders and cardiopulmonary abnormalities (Colvin & Yaeger, 2017). In the past decade, increased attention has been paid to the cognitive-behavioral correlates of congenital heart defects (Visootsak et al., 2011) and sleep disturbance (Chen et al., 2013; Esbensen & Hoffman, 2018) in this group. However, less is known about relations among sleep, congenital heart defects, and academic achievement in school age children with DS, despite ties among these variables in children without identified chromosomal abnormalities (Galland et al., 2015; Oster et al., 2017). Thus, the current research aimed to examine these relations.

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**Methods:** The sample included 31 children with DS (mean age: 11.47±3.13; Males: n=13). As a part of a larger study of reading development, children completed the Word Reading and Pseudoword Decoding subtests of Wechsler Individual Achievement Test – Third Edition (WIAT-III) as well as Kaufman Brief Intelligence Test- Second Edition. Parents completed a medical history questionnaire in which they were asked to report on whether they suspected that their child had difficulties sleeping (Sleep difficulties: n=13) and if their child had a congenital heart defect (CHD; n=17). To quantify parental concerns about sleep-related breathing disorders (SRBD) continuously, parents completed the Pediatric Sleep Questionnaire (Chervin et al. 2000) and a score was calculated for SRBD symptoms.

Multiple linear regression analyses were run with the two WIAT-III reading subtests as the dependent variables and the following as the independent variables: step 1: age and sex; step 2: parent report of CHD and sleep disturbance. Follow-up partial correlation analyses were also completed in which relations among the two reading subtests and a continuous measure of SRBD symptoms were examined after controlling for the effects of age, sex, and intellectual ability.

**Results:** Multiple linear regression results are as follows. After accounting for the effects of age and sex in step 1, the two regression models were significant in step 2 (Word reading: \( R^2 \Delta: = .17; F \Delta [2,26] = 3.40, p=.049 \); Pseudoword Decoding: \( R^2 \Delta: = .27; F \Delta [2,24]=3.75, p=.04 \). However, an examination of the individual contributions of sleep disturbance and CHD status to academic achievement revealed significant effects of sleep (Word reading: \( \beta =-.47; t=-2.60, p=.015 \); Pseudoword Reading: \( \beta =-.55; t=-2.70, p=.013 \)) but not CHD (Word reading: \( \beta =.25; \) n.s.; Pseudoword Reading: \( \beta =.12; \) n.s) status for all three dependent variables. Partial correlations analyses examining relations between reading achievement and sleep disturbance continuously (when controlling for age, sex, and intellectual ability) revealed a significant inverse relationship between SRBD symptoms and reading achievement: Word reading: \( r=-.51, p=.006 \); Pseudoword Decoding: \( r=-.58, p=.003 \).

**Discussion:** The results of the current study provide additional support for the importance of identifying SRBD in youth with DS. Like their peers without DS, sleep difficulties are associated with lower levels of academic achievement even after accounting for the effects of overall intellectual ability. In contrast, a history of CHD was not significantly related to reading abilities in this sample. The clinical implications of these findings will be discussed both within context of the early identification of children who may be at additional risk for academic difficulties due to sleep disturbance as well as the need to evaluate the effects of sleep treatments on cognitive outcomes in DS.

**References/Citations:**

Paper Title: Neuroanatomic Correlates of Poor Sleep in Youth with Down syndrome: Regionally Specific Differences in Brain Morphometry Differentiate Youth with DS with and without Suspected Sleep Disturbance

Authors: Nancy Raitano Lee2, Elizabeth Adeyemi3, Liv S. Clasen5, Jay N. Giedd6

Introduction: Over the past several years, there has been an increased interest in identifying factors that contribute to individual differences among individuals with Down syndrome (DS) and other neurodevelopmental disorders (Karmiloff-Smith et al., 2016). One factor that has been the focus of several recent investigations is sleep disturbance. Poor sleep has been linked to behavior problems and executive dysfunction in youth with DS (Chen et al., 2013; Esbensen et al., 2018). Moreover, sleep difficulties have been linked to a number of health-related outcomes in the general population, including obesity, cardiovascular disease, and dementia (for reviews, see Linz et al., 2015; Shi et al., 2017; St-Onge, 2017). Given heightened rates of early onset dementia in adults with DS (Hartley et al., 2015), it has been proposed that poor sleep could be a factor that precipitates dementia onset (Fernandez & Edgin, 2013). However, little is known about the neuroanatomical correlates of sleep difficulties in individuals with DS. Thus, the current research sought to examine brain morphometry among youth with DS with and without parent reported sleep difficulties and to compare findings with that found among typically developing peers.

Method: Participants included 30 youth with DS (mean age: 15.5±5.5; 13 males) and 26 typically developing (TD) peers (mean age: 15.8±5.4; 10 males) matched groupwise on chronological age and sex who were a part of a study on the developing brain conducted at the National Institute of Mental Health (Lee et al., 2016). Participants with DS were stratified based on parent report of suspected sleep difficulties (SD) – 17 youth were in DS+SD group and 13 were in the DS only group. T1-weighted scans were gathered on a 3-T magnetic resonance imaging scanner. Cortical lobar (frontal, temporal, parietal, occipital), cingulate, cerebellar, and hippocampal morphometry was processed with FreeSurfer imaging software. One-way ANOVA was used to evaluate differences among the three groups (DS+SD, DS only, TD). Post hoc comparisons were completed to evaluate between group differences and a false discovery rate (FDR) adjustment (for all 21 pairwise comparisons) was applied to control for the experiment-wise error-rate.

Results: As expected, ANOVA results revealed significant differences among the three groups for all regions examined (ps<.03). Post hoc, FDR-adjusted group comparisons revealed that many of the differences were between the DS+SD and DS only groups. Specifically, the DS+SD group had significantly smaller regional brain volumes for all cortical lobar measurements (qs <.05) compared to peers with DS only. Moreover, for the frontal and parietal lobes, only the DS+SD group evidenced significantly smaller regional volumes than the TD group (qs <.05); these regions did not differ significantly for the DS only and TD groups. In contrast, hippocampal, cerebellar, and cingulate volumes did not differ between the DS and DS+SD groups; these regions did, however, differ between both the DS only and DS+SD groups and TD peers (qs<.05).

Discussion: Suspected sleep difficulties in youth with DS are associated with regionally-specific differences in brain morphometry. In particular, cortical lobar volumes were found to be significantly reduced in youth with DS+SD compared not only to TD peers but also peers with DS only. In contrast, hippocampal, cerebellar, and cingulate volumes did not differ significantly between the DS and DS+SD groups but did differ from TD peers. Implications of these findings for understanding the morphometric underpinnings of the cognitive and behavioral correlates of poor sleep as well as potential ties to risk for developing other health-related conditions, including dementia, will be discussed.

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References/Citations:


**Paper 3 of 4**

**Paper Title:** Eating Habits and their Cognitive, Neural, and Health Correlates in Autism

**Authors:** Gregory L. Wallace, Emily Richard, Anna Schnizler, Jason Crutcher, Kelsey Csumitta, Jason Avery, Lauren Kenworthy, & Alex Martin

**Introduction:** Evidence continues to mount across clinic-referred and epidemiologic samples that individuals with Autism Spectrum Disorder (ASD) are at significantly increased risk of becoming overweight or obese when compared to the general population as a whole (e.g., Must et al., 2017) or to individuals with other developmental disabilities (e.g., Phillips et al., 2014). Nevertheless, the mechanisms underlying this risk in ASD remain largely unknown or, at best, poorly understood. Aberrant eating behaviors are common in people with Autism Spectrum Disorder (ASD). While prior research focused on selective eating, little is known about overeating and its possible cognitive (including executive function, e.g., flexibility, inhibition), neural, and health-related correlates, in ASD.

**Methods:** Participants were derived from two independent samples. Study 1 included 158 children with ASD (n=99) and typically developing controls (n=59). In study 1, one item assessing overeating (0=not true, 1=somewhat or sometimes true, 2=very true or often true) was taken from the Child Behavior Checklist, height and weight were assessed using a well-calibrated stadiometer and scale, respectively, and executive function was assessed using the Behavior Rating Inventory of Executive Function. Study 2 included 213 children with ASD (n=130) and typically developing controls (n=83). In study 2, the emotional overeating scale from the Children’s Eating Behavior Questionnaire was used to assess overeating, height and weight were assessed using parent report, and executive function was assessed using the Flexibility Scale. Study 3 involved an overlapping sample of participants from Study 1 (ASD n=21; TD n=21) who also completed a taste perception task administered via gustometer while in the functional magnetic resonance (fMRI) environment. These participants also completed the Adolescent/Adult Sensory Profile, a

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Children’s National Health System
self-rating of sensory processing, including items focusing on taste and smell, and the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA-24) assessing dietary intake.

Results: In both studies 1 and 2, parents reported that their children with ASD exhibited more frequent overeating than their same-age TD peers, even after controlling for psychotropic medication usage (ts>2, ps<.05). Furthermore, as overeating frequency increased in children with ASD so did: a) the likelihood of being overweight or obese (χ²s>13, ps<.05), and b) parent-reported inflexibility (rs>.26, ps<.05). In study 3, neural responses to taste perception did not differ between the ASD and TD groups; however, neural activity in gustatory cortex (i.e., left anterior and mid-dorsal insula) and reward-based regions (e.g., striatum) were positively associated with self-ratings of taste and smell reactivity on the AASP (rs>.50, ps<.01). These taste and smell sensitivities from the AASP were also negatively correlated with the Healthy Eating Index from the ASA-24 (r=-.42, p<.01) revealing more taste and smell sensitivities associated with a poorer diet.

Discussion: These findings across multiple studies and samples suggest that eating habits in ASD include not only increased selective eating, but also increased overeating, compared to the neurotypical population. Moreover, these eating habits in ASD are likely risk factors for suboptimal health outcomes (e.g., overweight/obesity) that in turn increase risk for downstream health concerns (e.g., cardiovascular risks). Moreover, cognitive correlates (e.g., flexibility and set-shifting) of these eating behaviors (i.e., overeating) might provide another avenue through which to develop interventions, akin to other recent efforts, as discussed in the final talk of this symposium (Kuschner et al., 2017). Finally, neural activity appears to mediate the association between taste/smell sensitivities and eating habits in ASD. More work is needed to extend this line of inquiry in an effort to improve health-related outcomes in ASD through a greater understanding of mechanistic underpinnings of eating habits and their consequences so that identification of potential treatment targets for future intervention development can be accelerated.

References/Citations:


Paper 4 of 4

Paper Title: The BUFFET Program: A Cognitive Behavior Therapy Approach to Food Selectivity in School-Age Children with ASD

Authors: Emily S. Kuschner8,9, Ashley deMarchena10, Brenna Maddox9, Hannah Morton11, Laura Anthony12, Judy Reaven12, Elizabeth Parks Prout8,9

Introduction: Food selectivity is a well-documented, critical concern for individuals with autism spectrum disorder (ASD). Far surpassing “pickiness” common in early neurotypical development, food selectivity intensity and duration in people with ASD are pervasive into later childhood, adolescence, and adulthood (Bandini et al., 2017; Kuschner et al., 2015). Despite daily impact and

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risk for poor health outcomes like obesity (for review see Sharp et al., 2013), effective food selectivity treatment options for people with ASD older than ~8 years are limited and nonspecific. The Building Up Food Flexibility and Exposure Treatment (BUFFET) program (Kuschner et al., 2017) aims to begin to fill this gap. BUFFET was created as the first outpatient intervention to address the unique challenges of school-age youth with ASD and food selectivity. BUFFET was designed to uniquely leverage emerging cognitive skills in later childhood to shift inflexibility and maladaptive thoughts about food while also bolstering autonomy and self-determination in treatment change; the rationale is that these cognitive skills are needed for sustainable gains.

Objectives: The goal of this study was to conduct an open pilot trial to examine the feasibility and acceptability of BUFFET in youth with ASD (8-12 years). A secondary proof-of-concept goal was to examine change following treatment in outcome measures related to willingness to try to new foods, daily impact on the family, and nutrition profiles.

Methods: Eleven food selective children with ASD (mean age=9.9yrs, range 8.5-11.9; mean FSIQ=109, range 91-132) and their parent(s) participated in BUFFET across 14 weekly, 90-minute sessions; children were assigned to one of three groups. The program provides seven weeks of skill building (e.g., coping strategy identification, cognitive restructuring of “Food Foe Thoughts” into “Food Friend Thoughts”, food psychoeducation and problem solving skill development), followed by seven weeks of exposure practice (termed “BUFFET Building”).

Results: Findings suggest that the BUFFET Program is feasible and acceptable. There was a high attendance rate (91%) with no attrition. Parents reported a high level of satisfaction with the treatment. All reporting families indicated that the BUFFET Program provided an excellent quality of service and helped them deal more effectively with problems. Willingness to eat foods (Would you eat this food if someone asked you to?) increased following treatment. Children rated a standardized set of over 200 foods on a Food Frequency Questionnaire as “YES”, “NO” or “MAYBE” foods. The number of “YES” foods significantly increased from pre- to post-treatment, p=.006, η²=0.54. Following the BUFFET Program, parents reported a statistically significant decrease in the overall impact of their child’s food selectivity, p=.03, η²=0.40. Finally, results showed increases in Vitamin D and calcium intake (all p<0.03, η²>0.2, Cohen’s d>1.0).

Discussion: Pilot study findings suggest feasibility and acceptability of BUFFET. Proof-of-concept results show improvement in the number of foods children are willing to eat, daily impact, and aspects of the child’s nutritional profile. The innovative approach used in BUFFET offers promise for a research-proven treatment for improving daily life and mitigating health risks in an underserved group of older youth with ASD and pervasive food selectivity.

References/Citations: