Early classroom exposure to expository passages predicts neurodevelopmental trajectory of comprehension networks

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Introduction: Successful language comprehension in elementary school is a key predictor of long-term educational outcomes, and requires adequate skill in both narrative and expository genres (e.g. stories versus science/history material). Historically, expository comprehension has received lower attention in the classroom, resulting in a performance gap between expository and narrative in grade school. In response, the Common Core State Standards of education now encourage earlier to expository comprehension (5-7 years old). However, very little is known of the neural substrates of genre, or how/whether genre-specific brain networks are influenced by early exposure. Previous neuroimaging work in our own lab has found that appropriate expository comprehension requires recruitment of restricted comprehension regions within the default mode network (DMN), and this specialization is facilitated by goal-oriented areas in the frontoparietal control network (FPN). No studies to date have tracked the development of these systems, or how they are influenced by early classroom experiences. In the current study, we used functional magnetic resonance imaging (fMRI) to identify (1.) the neurodevelopmental trajectory of expository comprehension, and (2.) whether greater exposure to exposition in the first-grade classroom interacts with this neural trajectory.

Methods: As part of a larger longitudinal study (n = 140), we used fMRI and a longitudinal design to examine 18 children in the summers after second and third grade (time 1 age = 8.54 +/- .28, time 2 age = 9.52 +/- .31, 10 females). All subjects had typical IQ and word reading ability as they listened to scientific passages in the scanner. First-grade teacher reports on the number of minutes per day spent on expository comprehension and total comprehension were also collected.

Results: We found that during expository comprehension, third graders showed greater recruitment of DMN and FPN areas than second graders, suggesting increased engagement in building a situation model of the stimuli with increased age. Interestingly, children who had a higher percentage of first grade expository exposure in the classroom, showed more mature activation patterns. Specifically, exposure correlated with increased DMN recruitment in second grade, and increased left angular gyrus (AG; the primary higher-order area recruited in adult expository comprehension) in third grade. Exposure also corresponded with increased growth in left AG activation from second to third grade, emphasizing the importance of this region in genre-based brain specialization.

Discussion: These results indicate that greater early exposure to exposition in the classroom corresponds with earlier specialization of ideal expository neural networks in children. These findings have important implications for early classroom practice, and pave the way towards future examinations of how these trends vary among different learner subpopulations.
Stability and Validity of Parent-Child Engagement in Infants and Toddlers at High Risk of Autism Spectrum Disorder

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Introduction: Infant siblings of children who are diagnosed with autism spectrum disorder (ASD) are at heightened risk (HR) for ASD and other communication impairments. Past work in our laboratory has shown that early differences in sensory responsiveness are useful for predicting future communication outcomes in this at-risk population. We hypothesize that differences in sensory responsiveness may influence communication development by impacting the extent to which infants can effectively engage with their adult communication partners. To test this hypothesis, we must have a stable measure of parent-child engagement. This study explores the stability of metrics of parent-child engagement derived from repeated measures of parent-child free play (PCFP) samples collected in infants who are at HR and relatively lower, general population level risk (LR) for ASD.

Methods: Ten infants between 6 and 18 months of age at either HR or LR for ASD and their primary caregivers were recruited from a larger longitudinal study of sensory responsiveness. Two 15-minute PCFP procedures around a standard set of toys were collected for each parent-infant dyad within a two-week timeframe. PCFP samples were videotaped and coded for parent-child engagement with an established coding system (Bottema-Beutel, 2014) by two blinded coders. Two metrics of engagement hypothesized to mediate sensory responsiveness and future communication skill were derived across each PCFP: total time spent in higher order supported joint engagement (HSJE; caregiver influences child play, child acknowledges caregiver by engaging in reciprocal play) and total time spent in lower order supported joint engagement (LSJE; caregiver appears to influence child play, but child does not actively acknowledge caregiver by engaging in reciprocal play). Generalizability (G) and Decision (D) studies (Sandbank & Yoder, 2014) were carried out to evaluate the stability of metrics for LSJE and HSJE. The a priori threshold for acceptable stability was g > 0.6.

Results: Preliminary analyses were carried out using PCFP data from 8 infants. These analyses indicate that HSJE is acceptably stable with a single sample and single coder (g = 0.64), but that LSJE is not (g = 0.34). Three samples and two coders or four samples and a single coder would be required to achieve acceptable stability for this lower level engagement state (g = 0.61 or 0.64, respectively). Final analyses will be presented at Science Day.

Discussion: Findings suggest that we can derive acceptably stable estimates of parent-child engagement in infants, though the feasibility of doing so depends on the engagement state of interest. These results provide much-needed information on minimizing measurement error in engagement metrics for our ongoing longitudinal study. Broader implications and future directions will also be discussed.

References


Psychosocial Parent Characteristics in a Sample of Pediatric Patients with Functional Abdominal Pain

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Introduction: Functional abdominal pain (FAP) is abdominal pain with no significant organic pathology. Approximately 2-4 percent of primary care diagnoses are related to abdominal pain (Starfield, et al., 1980). Parents' emotions, behaviors, and health status impact how children experience pain (Palermo, Valrie, & Karlson, 2014). For example, Campo, et al. (2007) found that mothers of children with functional abdominal pain are more likely to experience depression and anxiety. The purpose of the current study was to further characterize previously established pediatric FAP profiles (Walker et al. 2012) by examining parents' psychosocial characteristics. Pediatric measures assessing abdominal pain severity, gastrointestinal symptoms, non-gastrointestinal symptoms, pain threat appraisal, pain coping efficacy, pain catastrophizing, negative affect, and disability were used to categorize patients into three distinct FAP profiles: High Pain Dysfunctional (HPD), High Pain Adaptive (HPA), and Low Pain Adaptive (LPA). We hypothesized that three parental characteristics previously associated with greater pain and disability in their children (i.e., parent anxiety, depression, and catastrophizing about their child's pain) would be highest for parents of youth in the HPD group.

Methods: Pediatric patients (N = 284, ages 11-17) and their parents were recruited from a pediatric gastroenterology clinic during an initial evaluation for FAP. Thirteen patients were excluded from analysis due to significant organic pathology related to abdominal pain. Adolescents completed measures assessing pain, coping, and functioning and were classified into the three FAP profiles. Parents completed measures assessing their own anxiety, depression, and catastrophizing about their child's pain.

Results: Pediatric FAP profiles differed significantly regarding age (p<.01) and gender (p<.001). Therefore, these variables were included as covariates in subsequent ANCOVA analyses. ANCOVA results indicated significant differences between FAP profiles for parental anxiety, F(2, 261) = 6.267, p = .002, and catastrophizing about their child's pain, F(2, 265) = 8.57, p < .001. Specifically, parents of patients in the HPD profile reported significantly higher levels of anxiety (p<.01) and pain catastrophizing (p<.01) compared with parents of patients in the HPA and LPA profiles. Parental depression did not significantly differ by FAP profile.

Discussion: Parental anxiety and catastrophizing about children's pain were highest for pediatric patients in the profile characterized by high pain, functional impairment, and low coping efficacy. The study provides additional support for examining pediatric FAP patients using pain profiles by demonstrating these profiles correspond with parental characteristics generally regarded as predictors of poorer child outcomes. Future studies may examine parental anxiety and parental pain catastrophizing as mediators of the effects of treatment in pediatric FAP patients.

References


Eye Gaze Patterns Correlate with Vocal Complexity and Language Development in Infants at High- and Low-Risk for Autism Spectrum Disorder

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Introduction: Theory and recent research suggest that linguistic development relies on attention to audiovisual speech cues. Specifically, typically developing infants shift their gaze from the eyes to the mouth of a speaker in the second half of the first year of life and again in the second year of life, presumably to facilitate integration of the auditory and visual elements of speech. These shifts appear to correspond with the timing of qualitative changes in prelinguistic and linguistic development, such as onset of canonical babbling and vocabulary burst. Gaze patterns to audiovisual speech differ in children diagnosed with or at heightened risk for autism spectrum disorder (ASD) relative to their typically developing (TD) or lower risk peers. The present project is evaluating whether individual differences in gaze to audiovisual speech are related to differences in vocal complexity and vocabulary in infants at high risk (i.e., siblings of children with ASD) and relatively low risk (i.e., siblings of TD children) for ASD.

Methods: For each participant, gaze patterns to eye versus mouth regions of the face were measured as infants viewed videos of a woman speaking in infant-directed speech in their native language (English). Concurrent vocal complexity was measured with two consecutive, full-day audio recordings using LENA digital language processors and in the context of the Communication and Symbolic Behavior Scales (CSBS). Concurrent word use and understanding was measured with the MacArthur-Bates Communication Development Inventories (MB-CDI).

Results: Preliminary results from our pilot sample of 13 low risk infants, aged 5-25 months (Mage = 14.4 months, 6 males) indicate that eye gaze patterns to audiovisual speech is associated with several indices of vocal complexity and vocabulary, with large effects. Time looking to mouth correlated with canonical syllabic communication (i.e., the proportion of intentional communication acts that include a canonical syllable; r (12) = 0.60, p = 0.040), consonant inventory (r (12) = 0.62, p = 0.031), receptive vocabulary (r (13) = 0.73, p = 0.005), and expressive vocabulary (r (13) = 0.62, p = 0.023). Data collection on low and high-risk infants is ongoing.

Discussion: Preliminary findings suggest that eye gaze patterns to audiovisual speech hold some promise for predicting prelinguistic and linguistic development. We hypothesize that a greater amount of time looking to the mouth region will additionally be associated with greater vocal complexity and a larger vocabulary in infants at high risk for ASD. If our hypotheses are born out, we will have identified a novel measure that may facilitate earlier identification of language impairments in infants at heightened risk for ASD.

References:


Perceptual Auditory Filters in Noise Exposed Macaque Monkeys with Permanent Hearing Loss

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Introduction: Sensorineural hearing loss (SNHL) is known to impair auditory processing, causing difficulties in many listening environments including speech in background noise. Loss of spectral resolution abilities has been associated with SNHL and is thought to contribute to these deficits. We previously established a nonhuman primate model of noise-induced SNHL, which was validated with physiological (auditory brainstem response), histological (inner/outer hair cell and ribbon synapse counts), and behavioral (tone detection in quiet, steady state noise, and modulated noise) measures. Building off additional prior work in our lab investigating perceptual auditory filters of normal hearing macaques, the aim of this study was to measure spectral resolution in macaque monkeys with noise-induced SNHL.

Methods: Two monkeys (one Macaca mulatta and one Macaca radiata) were trained in a Go/No-Go lever release task to detect pure tone signals (0.5-32 kHz) in quiet and in noise maskers. Spectral resolution was measured based on responses to noises that were spectrally notched around the tone frequency. Tone thresholds in quiet were used to construct an audiogram for each subject. Tone thresholds in notched-noise were used to derive perceptual auditory filters using the rounded exponential fit. Filter widths were characterized using the half power bandwidth (BW3dB), equivalent rectangular bandwidth (ERB), and a quality factor (qERB). Behavioral data were obtained at baseline and following exposure to a 50 Hz bandwidth of noise centered at 2 kHz of 141 or 146 dB SPL for four hours.

Results: Compared to baseline, post-exposure tone alone thresholds were higher and auditory filters were broader for both subjects in a frequency-specific manner. Greater changes were observed i) at and above 2 kHz for both macaques and ii) overall for the 146-dB-exposed macaque. Filter broadening was similar to that reported for humans with similar degrees of SNHL. Ratios of post-exposure to baseline BW3dB, ERB, and qERB values correlated with changes in the audiogram.

Discussion: These findings provide evidence for a relationship between degree of SNHL and severity of spectral resolution impairment. These findings also serve as the basis for ongoing investigations of the neural correlates of spectral resolution as well as changes in perceptual and neural spectral resolution following noise-induced SNHL.
Tailored Therapeutic Strategies for Genetic Epilepsies with Impaired GABAergic Signaling in Pre-Clinical Mouse Models

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Introduction: Mutations in GABAA receptor subunit genes are frequently associated with epilepsy including the severe epileptic encephalopathies. These epilepsy syndromes are often not responsive to existing antiepileptic drugs (AEDs) and the patients thus have poor neurodevelopmental outcome with intractable seizures and impaired cognition at least partially due to the poor seizure management. Thus, identification of the correct AEDs is essential for effective treatment.

Methods: We have substantially characterized the molecular mechanisms underlying GABAA receptor gene mutations and developed multiple genetically modified mouse models of genetic epilepsy. In this study, we screened multiple existing anti-epileptic drugs in an epilepsy mouse model Gabra1+/-/Gabrg2+/- mice, which is associated with intractable seizures and optical atrophy. Several major categories of anti-epileptic drugs were tested in the treatment of seizures induced by pentylenetetrazole (PTZ) (30mg/kg, ip) in wild type and Gabra1+/-/Gabrg2+/- mice including diazepam(0.3mg/kg, ip), levetiracetam (Kappra)(10mg/kg, ip), phenobarbital (50mg/kg, ip), vigabatrin (50mg/kg, ip), and cannabidiol (10mg/kg, ip). The surgery to implant the EEG headmount and the video-monitoring synchronized EEG recordings were conducted as previously described.

Results: We found that the double knockout mice demonstrated less spike-wave discharge (SWD), myoclonic jerk and duration of SWD in EEG after pretreatment of Phenobarbital.

Discussion: Phenobarbital is the most effective in reducing seizures both at behavioral and EEG levels compared with other compounds in Gabra1+/-/Gabrg2+/- mice. This study could provide therapeutic clues for epilepsy patients with similar mutations based on the findings from the disease representative pre-clinical mouse models.
Here-to-There: Correlates and Factors of Adult Siblings’ Preparation for Caregiving Roles

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Introduction: This study examined the correlates and predictors of future planning activities to prepare adult siblings for future caregiving of their brother-sister with intellectual and developmental disabilities (IDD). Participants included 521 adult siblings of individuals with disabilities who responded to a national survey gathering information about family characteristics, current caregiving roles, and future planning activities. Results indicated that future planning activities can be considered as three domains: legal activities, residential activities; and conversations with the brother-sister about the future. Our findings indicate that both parent and brother-sister characteristics predict which activities are completed in the legal and residential future planning domains. Such predictors include: parent’s ability to care; brother-sister’s current residential status; presence of an intellectual disability; and, whether or not the brother-sister receives Medicaid waiver benefits. This study adds to the research concerning the preparation of adult siblings of individuals with disabilities for future caregiving roles.
Individual Differences in Bodily Mapping of Emotions: The Exceptional Case of Athletes

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Introduction: This study examines the emotional intelligence and awareness of college student-athletes in comparison to non-athlete, college students. College student-athletes practice several performance strategies such as self-talk, imagery, and activation in both practices and competition (Lane et al., 2009). These psychological skills are designed to enhance mind-body connection and are associated with improved emotional intelligence. We examine embodied emotions in athletes to see if those individuals who consistently train to increase the mind-body connection and emotional intelligence show enhanced capacity to embody emotions.

Methods: Twenty-eight collegiate athletes and one hundred forty two regular college students enrolled at Vanderbilt University participated in this experiment. Questionnaires were administered to determine scores for alexithymia, loneliness, schizotypal personality, empathy, stress, and childhood trauma for each participant. The questionnaires were followed by the test section of the study, mapping of bodily emotion. The participants were presented with pictures of two blank human bodies and the name of one emotion, such as happiness or sadness. Their task was to color the bodily regions in which they felt a change in activity. The participants were instructed to color in the bodily regions they felt were activated during the corresponding emotion in the first body and the regions they felt were deactivated during the emotion in the second body. Each participant completed 28 bodies, two bodies for the fourteen emotions.

Results: The average body maps for each emotion by data from group A, the athletes, did not show an increase in embodiment but did indicate that the embodiment was more clear and concise rather than spread out throughout the regions. In areas of high embodiment, the body maps showed heavily concentrated activation and deactivation alike in the athletes. The general activation and deactivation patterns for each emotion did not differ significantly between the two groups, but for the emotions ‘anger,’ ‘sadness,’ ‘happiness,’ ‘love,’ ‘depression,’ and ‘anxiety,’ there was more definition and concentration in the activated or deactivated area in the maps generated by the athletes’ data.

Discussion: The results from the athlete population group can be placed on a spectrum involving regular college students as well as individuals who should lay on the opposite side of the spectrum from those of athletes, for their embodiment skills are often poor because of their deficits in social cognition and function. These individuals include the schizophrenic patient population. With the differences in the detection and mapping of emotion between athletes and non-athletes, there is the implication that neural plasticity for emotional intelligence is plausible.

References:


Repetition Does Not Improve Pronoun Comprehension in Amnesia

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Introduction: Establishing reference is a central component of language comprehension, requiring maintenance of unfolding discourse history as well as integration of multiple sources of information in speech. To interpret pronouns, listeners must relate features of the pronoun (gender, animacy) with existing representations of potential discourse referents. Successful referential processing and resolution of referential ambiguity seems to place high demands on memory. In a previous study, eye-movements of patients with hippocampal amnesia and healthy participants were monitored while listening to short stories. In interpreting ambiguous pronouns, healthy participants demonstrate order-of-mention effects, whereby ambiguous pronouns are interpreted as referring to the first-mentioned referent in the story. By contrast, hippocampal patients exhibited significant disruptions in their ability to use information about which character had been mentioned first to interpret pronouns.

Methods: The present study seeks to determine whether pronoun resolution performance of the hippocampal patients can be 'rescued' by repetition of the target referent, increasing its salience. Participants engaged in a visual world eyetracking paradigm while listening to short stories that contained ambiguous pronouns. The primary manipulation was a repetition of the target referent, prior to the critical pronoun. Participants' eye movements were monitored during comprehension and looks to the target and competitor referents were compared across groups.

Results: Results indicate that patients with hippocampal damage demonstrate disrupted processing of pronouns, even when salience of the target referent is increased via repetition. In contrast, healthy comparison participants demonstrated a large repetition effect.

Discussion: These results have implications for recommended communication strategies in memory-disordered populations. Repeating information (verbatim or paraphrase) is a frequently recommended strategy for communicating with patients with Alzheimer's Dementia. Here, we find empirical evidence that repetition does not improve comprehension of ambiguous pronouns, suggesting that these oft-cited clinical recommendations be empirically evaluated.

References
An Exploratory Analysis of the Relationship Between Parent Verb Input and Verb Expressive Vocabulary in Children with Autism Spectrum Disorder

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Introduction: Little is known about the type of linguistic input that children with autism spectrum disorder (ASD) use to learn verbs, despite the importance of verb acquisition for grammatical development (Tomasello & Kruger, 1992). The purpose of this study was to evaluate if quantity and quality of verb input in parent utterances that follow the child’s attentional lead were significantly related to later child expressive verb vocabulary, and if that relationship might vary as a function of child object interest in children with ASD.

Methods: We conducted a longitudinal correlational design using thirty-one toddlers with ASD and their parents. From videos of initial parent-child free play sessions, trained observers coded parent linguistic responses to child attentional leads for presence of verbs, diversity of verbs, and presence of verb phrase elaborations. Component variables for these aspects of verb input were z-score transformed and averaged to derive an aggregate measure of parental verb input. Object interest was the number of different toys used in differentiated play in a developmental play assessment at the initial measurement period. Child expressive verb vocabulary was the number of action words said as reported by the parent at the initial measurement period and eight months later.

Results: Early parent verb input accounted for a large amount of variance in later child expressive verb vocabulary, even after controlling for early child expressive verb vocabulary, R-square change = .17, p=.005. Early parent linguistic responses without verbs was not significantly correlated with later child verb vocabulary (r=.03). A significant interaction between object interest and parent verb input predicted later child verb vocabulary, p<.05, R-square change =.13. The association between input and verb vocabulary size was stronger in the subgroup of participants with object interest scores .24 standard deviations above the sample mean and below.

Discussion: This exploratory study revealed a significant relationship between quantity and quality parent verb input in follow in utterances and later child expressive verb vocabulary; this relationship was stronger in a sub-group of children with lower object interest. There is a clear need for more research on supporting relevant stakeholders in this important, and often over-looked, part of language development in children with ASD. Developing a knowledge base for how a strong verb vocabulary might be facilitated is an important goal for clinicians and parents alike to consider.

References:

Comparison Of Measurement Systems For Collecting Teacher Language Data In Inclusive Early Childhood Settings

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**Introduction:** Teacher language input plays an important role in children's language development (Dickinson & Porche, 2011; Pentimonti et al., 2017). Enhancing teacher language input is of particular concern in classrooms serving children with or at-risk for language impairments (Justice, Bowles, Turnbull, & Skibbe, 2009; Rescorla, 2009). A critical decision in designing research on training teachers to support children's language is determining how to measure teacher language input in complex classroom environments. Researchers often rely on discontinuous measurement to estimate the frequency of behaviors in classrooms (Lane & Ledford, 2014). Though these measurement systems are often selected for their efficiency, the accuracy of these procedures can be limited (Ledford, Ayres, Lane, & Lam, 2015). The literature examining the efficacy and efficiency of discontinuous measurement systems in classroom research is largely limited to behaviors and participant populations that are outside the area of early childhood special education (Lane & Ledford, 2014). Additional information is needed to determine the extent to which measurement procedures are valid, reliable, and efficient for estimating teacher language. The goal of this study was to compare the accuracy and efficiency of three approaches to measuring teacher language in inclusive preschool classrooms: Momentary Time Sampling (MTS), Partial Interval Recording (PIR), and Continuous Recording (CR).

**Methods:** Sixteen 20-minute video samples of teacher-child interactions were collected in inclusive classrooms serving children with or at-risk for language delays. Each sample was coded for teacher talk using MTS, PIR, and CR. Every recorded teacher utterance was classified by language function (i.e. expansion, positive feedback, etc.) using behavior definitions from Atwater et al., (2014). The frequency of teacher talk and the proportion of utterances coded as language stimulating based on the language function code were compared using summary data from the three measurement systems.

**Results:** MTS and PIR were less accurate than CR in estimating teacher talk. MTS underestimated frequency of teacher talk, capturing, on average, only 30.7% of teacher utterances. PIR overestimated talk, identifying 117% more utterances than TER. MTS also overestimated the percentage of utterances coded as language stimulating compared to TER. MTS was the most time efficient, however there was not a substantial time advantage of MTS over TER (59 vs. 63 minutes respectively).

**Discussion:** Measurement affects estimated outcomes when observing teacher behavior; researchers need to know which types of measures of adult language provide the most representative estimates in classroom settings, and the amount of time required for each type of measurement. The current results indicate that CR provides the most accurate measurement of teacher language, and did not take considerably more time to complete than discontinuous measurement systems.

**References:**
Parents' Support of Early Numeracy and Patterning Skills

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**Introduction:** Children's numeracy and patterning skills vary before school entry (1) and predict later mathematics achievement (1-2). Parents can support their preschoolers' math skills by talking to them about numbers during play (3-5). However, little is known about parent-child talk about patterning or how it compares to number talk in frequency and complexity.

**Methods:** Participants were twenty preschoolers (45% females, 75% White) and a parent (80% mothers). Dyads were videotaped playing with three activities: beads and laces, playing cards, and Lego blocks for 5-minutes each. Parent and child number and patterning talk were separately coded in 10-second intervals.

**Results:** Across activities, parents talked about numbers in 34% of the intervals, while children talked about numbers for 26% of the intervals. Both parents and children discussed patterns for 13% of intervals. Parents talked about numbers (M = 38.89, SD = 6.87) more than they talked about patterns (M = 12.66, SD = 5.01), t(19)=11.19, p<.001, as did children (M numbers = 26.2 SD = 8.84, M patterns = 12.98, SD = 4.13, t(19)=5.83, p<.001). Next we examined the complexity of this talk. Parents talked about foundational (labeling quantities, naming numerals, counting, and ordinal relations; M= 18.94, SD =8.72) more than advanced number concepts (arithmetic and magnitude comparison; M= 10.04, SD =6.34), t(19)=2.92, p<.01). The same trend was found for children (M foundational= 15.78, SD =9.57; M advanced= 7.53, SD =6.35; t(19)=2.65, p<.05). Parents provided foundational patterning input (e.g., gesturing to patterns, discussing similarities and differences; M= 12.15, SD =14.08) more often than advanced patterning input (linking and identifying patterns and their unit of repeat, M= 9.46, SD =6.79, t(19)=3.85, p=.001). Children discussed advanced (M= 4.73, SD =3.08) more than foundational patterning topics (M = .76, SD = 1.28), t(19)=4.95, p<.001.

Partial correlations, controlling for children's age and vocabulary, indicated that parents' advanced and foundational number talk related to children's advanced, r(16) =.53, p=.03, and foundational number talk, r(16) = .6, p=.01, respectively. Parents' and children's advanced and foundational patterning talk were not significantly correlated, r advanced=.39, p=.11 and r foundational=.11, p=.68.

**Discussion:** Findings suggest that both parents and children tend to talk more about numbers than patterns. Further, their number talk tends to focus on foundational more than challenging number topics for preschoolers. Parents also show this trend for patterning, though children displayed interest and ability in focusing on more challenging patterning concepts. Research is needed to determine how this talk varies by toy type, how we might promote the frequency and complexity of this talk, and how parent patterning and number inputs predict children's later numeracy, patterning, and general math skills.

**References:**


Methods of Infant Eye Gaze Analysis and Predicting Language and Sensory Development

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Introduction: Literature and prior work suggest that infant eye gaze patterns may be useful for predicting social and language development and distinguish children at risk for developmental disabilities from typically developing children. There are currently several methods for measuring eye gaze; however, it is unclear which methods yield the most reliable and valid metrics of infant eye gaze. This proposed study will analyze the reliability and validity of eye gaze metrics from three common methods represented in the literature: desk mounted eye trackers, point of view glasses, and head mounted cameras. Desk mounted eye trackers have successfully demonstrated that infant gaze patterns during videos of human speech and non-human speech-sounds change over development (Lewkowicz & Ghazanfar, 2006; Lewkowicz & Hansen-Tift, 2011). Point of view glasses worn by the examiner have been used to measure gaze patterns during live interactions (e.g., Jones et al., 2017). Head mounted cameras, worn by the infants, are a relatively new method for measuring eye gaze and have also been used to measure eye gaze patterns during live interactions (Franchak et al. 2011). To date, no one has compared the validity of all three methods or the stability of these measures across multiple observations. The proposed study will analyze gaze patterns to eyes, mouth, and referent objects to determine how these patterns relate to language development, and which methodology is the most reliable and valid predictor.

Methods: An SMI REDn Scientific Eye Tracking system will monitor eye gaze while infants watch videos of typical and infant-directed speech. Infants will also complete the Brief Observation of Social and Communication Change (BOSCC; Grzadzinski et al., 2016), during which Pivothead SMART point of view glasses will be worn by the experimenter to capture infants’ eye gaze. Finally, infants will wear a Positive Science head mounted camera while participating in the Communication and Symbolic Behavior Scales (CSBS; Weatherby & Prizant, 2003) and a parent-child free-play interaction.

Results: We hypothesize that, in consensus with the literature, infants will demonstrate gaze patterns to the eyes and the mouth throughout development, with various methods having different reliability and validity with identifying such patterns. We also hypothesize that the point of view glasses and head mounted cameras may correlate with joint attention to referent objects, a known predictor of later communication ability.

Discussion: The study will be ongoing at the time of this presentation; preliminary data collected will be included. Should our hypotheses be born out, further work exploring new metrics for joint attention and attention to eyes and mouth in infancy and later risk for autism spectrum disorder (ASD) would be warranted.

References:


**Lifetime dietary antioxidant status and disease drive post mortem changes in neural antioxidant and oxidative stress levels**

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**Faculty Advisor:** Fiona E. Harrison

**Introduction:** Oxidative stress is associated with a number of developmental and neurodegenerative disorders, and investigating these changes in human tissue may yield valuable insight into pathogenic changes in these disorders. Currently, there is no definitive understanding of how post mortem elapsed time affects oxidative stress in human brains, representing a critical gap in knowledge that has broad implications for interpretation of data from human tissue and clinical studies. The current study seeks to determine how time elapsed between death and removal of brain tissue, and subsequent tissue processing for analysis, affect markers of oxidative stress. We further investigated how these changes are impacted by disease status.

**Methods:** Three lines of mice were used (gulo-/-, wild-type, and 5XFAD) for this study. Gulo-/- mice are unable to produce L-gulonolactone oxidase, the enzyme that synthesizes endogenous vitamin C in wild-type rodents. These mice are dependent on diet as a source for vitamin C, mimicking the human state, and serve as an excellent model for deficiency in this vital antioxidant. 5XFAD mice carry five mutations associated with early onset, or familial Alzheimer’s disease, and were chosen as a model for an oxidative stress-related disease. Brains were removed and dissected immediately after sacrifice, after 2 hours, or after 24 hours.

**Results:** Multiple assays were used to assess markers for oxidative stress and antioxidant level within cortical tissue in each of the mouse models. Time post mortem had a significant effect on antioxidant levels (ascorbic acid, vitamin C) in all groups, although this was more severe in brains that were already low in ascorbate. Oxidative stress (malondialdehyde, lipid peroxidation) also increased in the brain post mortem, although only in mice that were low in ascorbate.

**Discussion:** Together, these data help to elucidate how oxidative stress in the brain is intensified by dietary status and post-mortem processing time, and suggests more consideration should be given to how handling of human brain tissue could be optimized in biomedical research to limit confounding factors. This information is indispensable for studying how oxidative stress relates to neurological disease. The results of this inquiry could also better inform future methods of assessing oxidative stress in the brain, indicate the best means of handling brain tissue, and consequently influence understandings of how neurological disorders are impacted by oxidative stress.
Neural correlates of interoception in autism spectrum disorder

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Introduction: Aberrant responses to sensory stimuli are a core feature of autism spectrum disorders (ASD). While most research focuses on sensory signals arising externally, little is known about how individuals with ASD process internal sensory cues. Interoceptive signals are tightly linked to emotional responses, which are also affected in ASD. Neural networks for interoception include insula, cingulate and other medial frontal regions, and somatomotor cortex (Critchley et al., 2004, Pollatos et al., 2007). We asked whether neural response to an interoception task (heartbeat counting) differed in ASD relative to a typically developing comparison (TC) group, and how response to heartbeat counting differs from counting an external (visual) stimulus.

Methods: Participants were 31 individuals with ASD and 54 TC individuals. The session consisted of 4 runs, each with 6-8 randomized blocks of either counting one’s own heartbeats or counting a difficult-to-detect flashing visual stimulus presented at a rate similar to average resting heart rate. Data were processed using FSL’s FEAT tool (Beckmann et al., 2003; Woolrich, 2008). As groups included children and adults, age was added as a covariate in the GLM. Within each group, three contrasts were considered: interoceptive task>rest, visual task>rest, interoceptive task>visual task. Group comparisons of ASD>TD and TD>ASD were computed for each contrast.

Results: Heartbeat counting versus rest: Whole brain analysis within groups indicated that both ASD and TC groups showed significantly increased BOLD signal in bilateral insula, secondary somatosensory, primary motor, premotor, and visual cortex. However, only the TC group had significant BOLD increases BOLD in the bilateral middle frontal gyrus (MFG), left putamen, and left anterior cingulate. Relative to the ASD group, the TC group had significantly greater BOLD response in right lateral occipital cortex and left primary visual cortex. Visual counting versus rest: Both groups had significantly increased BOLD response in bilateral visual cortex, cerebellum, hippocampus, and posterior insula, motor and premotor cortex; only the TC group exhibited response in MFG and anterior cingulate. In group contrasts, the TC group showed greater response in a network of visual areas relative to the ASD group. Heartbeat counting versus visual counting: For both groups, interoception-specific BOLD response was observed in bilateral insula, anterior cingulate, secondary somatosensory cortex, and lingual cortex. The TC group also had increased BOLD signal in MFG, basal ganglia, brainstem, and cerebellum that was absent in the ASD group. Group comparisons showed higher BOLD response in the TC versus ASD group in bilateral lingual cortex and precuneus.

Discussion: This work demonstrates significant differences in neural responses to both interoceptive and exteroceptive processing in individuals with ASD compared to a typical comparison group. While individuals with ASD did show BOLD response in many posterior regions associated with interoceptive processing (insula, somatosensory areas), they did not recruit more frontal regions (MFG, anterior cingulate) recruited in the TC group during the heartbeat task. However, this was also true during the visual counting condition, suggesting these frontal regions may be more associated with counting or tracking of sensory signals more generally (Piazza et al., 2006). These data suggest that aberrant neural response to sensory cues in ASD is not limited to external cues, but also extends to internal cues.

References:


Leading focus groups with children and adolescents: An investigation of effective methods

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Introduction: When a child is diagnosed with cancer, healthcare providers and parents may fail to communicate effectively with the child. Asking children’s communication perceptions and preferences through focus groups is one method that may be helpful in learning more about current practices. Better understanding of beneficial strategies to elicit openness in focus groups with children is needed as children are often reticent to share their feelings. Some researchers recommend splitting focus groups based on gender while others recommend segmenting children by grade level. There are mixed recommendations about the ideal length of a focus group conversation for children of different ages. This study has the potential to identify strategies that create positive outcomes for children. This study addresses the criteria of clinical, behavioral, and intervention research through protocols for focus group facilitators that enable children to feel at ease and willing to disclose useful information. The study used innovative strategies to encourage children to discuss feelings. This study investigates how children ages 7-12 and 13-18 prefer to engage in communication about life-threatening conditions.

Methods: Seven children ages 7-16 participated in focus groups in which they commented on how they preferred communication regarding diagnoses and prognoses of life-threatening conditions. This study used techniques such as having children give themselves pseudonyms and discussing hypothetical medical situations in an effort to create distance between their illness and the conversation, thereby eliciting more accurate and truthful answers. Each focus group was recorded, transcribed, and analyzed to identify how children of different ages reacted to various methods employed during focus group sessions.

Discussion: More research is needed to improve evidence-based practice focusing on communication with children. Researchers are confident substantial progress can be made in the use of effective strategies to conduct focus groups that facilitate expression of children and adolescents.
Audiovisual Multisensory Integration in Individuals with Autism Spectrum Disorder: A Meta-Analysis

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Introduction: Differences in sensory perception are now considered diagnostically significant for autism spectrum disorder (ASD). Researchers have begun to describe how children with ASD differ from their typically developing peers on measures of multisensory integration [MSI]; three non-systematic reviews of this literature have been published. None of the prior reviews, however, have aggregated results in a meta-analysis or synthesized the evidence on correlations between MSI and autism symptomatology. The purpose of the present study was to conduct a systematic review and meta-analysis of the literature on MSI, specifically audiovisual integration, in children with ASD to evaluate the (a) group differences between children with ASD and TD peers and (b) relations between multisensory integration and measures of communication and autism symptom severity.

Methods: To identify eligible studies, a comprehensive search strategy was devised using the ProQuest search engine and the PubMed database. Eligibility criteria for studies were (a) confirmation of ASD diagnosis via standardized measure and (b) inclusion of behavioral or neural measure of audiovisual integration. Grey literature searches are ongoing. Data were extracted from all studies that reported a correlation coefficient (r) of interest or group difference (Hedge’s d); Fisher transformations were then used to transform rs to zs (for variance stabilization). Effect sizes were analyzed using a separate robust variance estimation model to answer each research question; thus, three meta-analytic models were evaluated.

Results: The electronic search yielded 783 records (662 unique). Preliminary analyses included 67 records across all three models. The first model contained 76 effect sizes of group differences between individuals with ASD and TD peers. A significant overall group difference was found, $g = -0.36$, $p = 0.003$, with individuals with ASD demonstrating worse audiovisual integration compared to TD peers. Seventeen correlations were reported between MSI and autism symptom severity; the meta-analysis showed no significant correlation between MSI and autism symptom severity were evident in the literature, $z = -0.09$, $p = 0.328$. Ten correlations were reported between MSI and communication; the meta-analysis showed no significant correlation between MSI and communication were evident in the literature, $z = 0.20$, $p = 0.116$.

Discussion: Preliminary results indicate that children with ASD demonstrate significantly worse audiovisual integration than their TD peers. However, these skills are not related to features of autism, specifically autism symptom severity and communication. Limitations and directions for future primary and meta-analytic research will be discussed.

References:


mGlu7 dysfunction in neurodevelopmental disorders

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Introduction: The metabotropic glutamate receptor 7 is a G-protein coupled receptor that is expressed widely throughout the brain and is highly conserved across species, yet its precise role in brain function remains poorly understood. In recent years, the Vanderbilt Center of Neuroscience Drug Discover (VCNDD) has developed small molecule allosteric modulators that have facilitated further study of mGlu7 biology and evaluation of mGlu7 as a novel therapeutic target. Excitingly, we have found that mGlu7 protein levels are reduced in samples from patients with Rett syndrome, a debilitating neurodevelopmental disorder. Furthermore, positive allosteric modulators with activity at mGlu7 can restore deficits in synaptic plasticity, cognition, social interaction and respiration in Rett syndrome model mice. In patients, Rett syndrome is characterized by a host of symptoms that include repetitive hand wringing, limited speech, intellectual disability, gait abnormalities and seizures. Mutations in the gene for Methyl CpG Binding Protein 2 (MECP2) have been identified to cause 95% of Rett syndrome cases. Recently, six patients with mutations in GRM7, the gene for mGlu7, have been identified [1,2]. These patients suffer from neurological symptoms that appear to overlap significantly with Rett syndrome; specifically, they display intellectual disability and epilepsy. This led us to test the hypothesis that a primary loss of mGlu7 activity could lead to a neurological syndrome.

Results: Our data show that a clinical GRM7 mutation disrupts receptor function in vitro, and that decreased function can be boosted by a positive allosteric modulator. Furthermore, mice lacking mGlu7 altogether recapitulate many symptoms observed in neurodevelopmental syndromes as assessed by paradigms of learning and memory, anxiety, social interaction, and motor control. Mice lacking mGlu7 also exhibit robust seizures at 12 weeks of age.

Discussion: These findings highlight the importance of mGlu7 for proper brain function, and provide further rationale for the development of small molecule activators of mGlu7 activity as a potential therapeutic for Rett syndrome and other neurodevelopmental disorders.

References:

Reuter et al. Diagnostic Yield and Novel Candidate Genes by Exome Sequencing in 152 Consanguineous Families with Neurodevelopmental Disorders. JAMA Psychiatry. 2017 Mar 1;74(3):293-299
Deletion of p75 neurotrophin receptor in Schwann cells results in peripheral neurodegeneration

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Introduction: During nervous system development, neurotrophins and their receptors play a key role in regulating neuronal growth and survival. Consequently, global knockout of p75NTR (p75 neurotrophin receptor) in mice results in a ~50% decrease in the peripheral sensory neurons of the dorsal root ganglia (DRG) as well as pronounced sensory deficits. Previously, this loss was accredited to decreased trophic signaling in neurons. However, p75NTR also functions to regulate Schwann cell (SC) development and recovery after injury. To explore the role of p75NTR in these glia, we generated a SC targeted p75NTR (Dhh-p75Δ) knockout model using Desert hedgehog-Cre mice. Surprisingly, while myelin in the Dhh-p75Δ was largely unaffected, the mice displayed a 30% decrease in DRG neurons as well as markedly reduced heat sensitivity. In contrast, neuron loss was not observed in a neuron specific p75NTR knockout model, Thy1-p75Δ. Additionally, we found that cholesterol biosynthesis was disrupted in Dhh-p75Δ SCs, leading to the accumulation of oxysterols, which are highly oxidizable, neurotoxic lipid precursors. Indeed, we found that treatment of cultured DRG neurons with 10μM 7-deoxysterol killed 45% of the neurons. Therefore, we hypothesize that p75NTR has a key role in regulation of cholesterol synthesis in developing Schwann cells, and disruption of that metabolism in p75 null Schwann cells results in the production of neurotoxic lipid species, which contribute to peripheral neurodegeneration.
The Effects of Word Repetition and Word Diversity on Language Production for Children with Profound Language Impairments

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Introduction: Many children with profound expressive and receptive language delays show deficits in verbal working memory (Acheson & MacDonald, 2009) and require more targeted language exposure compared to typically developing children to achieve word learning (Rice et al., 1994). A common strategy of early language interventions is using short, repetitive phrases that are salient and relevant to the child’s actions to reduce the demand on verbal working memory and facilitate word learning by increasing verbal imitation. This strategy may be at odds with the importance of diversity of language exposure; long-term language and literacy delays are related to lessened exposure to frequency, diversity, and complexity of language (Hart & Risley, 2003). Understanding the necessary balance needed to optimize language learning by balancing word repetition and word diversity for children with language delay will aid parents and practitioners in delivering effective language intervention. The purpose of this study is to understand how adults’ use of word repetition and word diversity contributes to word learning for children with profound language impairments.

Methods: Data were selected from a larger randomized control trial examining the effects of Enhanced Milieu Teaching (EMT) on language learning for children with language delays (Roberts & Kaiser, 2015). Forty-four children (24-42 months) with expressive language delays were included. Children randomly assigned to the intervention group received 24 1-hour sessions of EMT. Ten-minute segments of video-recorded intervention sessions were transcribed and coded. Hierarchical linear modeling was used to measure the relationship between the adult’s use of language and the child’s production of imitated language. To measure the immediate effect of adult language modeling on child language, the total number of words the child imitated was selected as the dependent variable. A lag variable of the child’s imitated language in the prior session was used to account for child language growth during the intervention period. Child IQ, age, gender, race, and initial language level were included as control variables.

Results: Increased adult language was related to an increase in children’s imitated language ($\beta=0.007$, $p<0.01$), while an increase in adult language diversity was related to a decrease in children’s imitated language ($\beta=-0.011$, $p<0.01$).

Discussion: Increasing total adult language while decreasing the diversity of adult language had a positive effect on child imitated language during an early language intervention. Using an intervention model with targeted vocabulary that uses repetitive and somewhat constrained diversity of language models may have a positive benefit on child language learning for children with early language delays.

References:
Language Sample Analysis: Identifying and Addressing the Research to Practice Gap

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Introduction: Despite evidence supporting the value of language sample analysis (LSA) for purposes including eligibility and progress monitoring, speech-language pathologists (SLPs) continue to conduct LSA infrequently and typically without standardized measures [1]. Little is known regarding SLPs’ perspectives on ideal LSA. Such knowledge is essential to identifying and addressing barriers of evidence-based LSA use, which could increase the quality of services provided to children with language disorders. RQ1: Do SLPs report using LSA during the 2016-2017 school year? If so, for what purposes? RQ2: For SLPs who report using LSA, what are the characteristics of the language samples they elicit? RQ3: What barriers might affect the frequency and quality of LSA use?

Methods: Participants were recruited through a local SLP conference; they completed an online REDCap survey. We analyzed responses from 79 employed SLPs. The mean age of participants was 38.13 years (SD=10.85). The mean years of experience was 11.95 years (SD=9.14). The mean caseload was 57 students (SD=31).

Results: RQ1: Sixty-six of the 79 participants (84%) reported using LSA for initial evaluations (53/66=80%), goal selection (58%), treatment planning (58%), re-evaluations (48%), progress monitoring (44%), and screening (38%). Approximately half (41%) reported collecting <6 language samples the previous school year. RQ2: Most participants reported online transcription of samples with pen and paper (n=50); 31 and 11 participants reported using audio recording and video recording respectively. Only 15 participants reported using specific language sample protocols. Frequently derived variables included mean length of utterance (n=55) and Brown’s stages (n=32). Most participants (64%) reported collecting language samples <11 minutes in length. Samples were reportedly short in utterance length as well (<26 utterances: 38%; 26-50 utterances: 32%). RQ3: Commonly reported reasons for not using LSA included limited time (80%), standardized language assessment(s) providing sufficient information (39%), and limited resources (23%). Most participants reported that SLPs should collect 2-4 samples per student each year (63%). No participants reported samples of <25 utterances as ideal; most reported 51-100 utterances as ideal (51%). They indicated that language samples should be 6-10 (33%) or 11-15 (40%) minutes in length. Only 5% reported language samples should be <6 minutes. The majority of participants reported ideally transcribing language samples from audio (23%) and video recordings (72%).

Discussion: Consistent with previous findings, participants reported using LSA infrequently [1]. Reported practices include brief samples, real-time transcription, and limited analysis. In contrast, SLPs reported ideal practices include longer samples, transcription from audio or video recordings, and use for multiple purposes. Identified barriers to evidence-based LSA suggest that SLPs would benefit from training in efficient LSA practices and varied analytic approaches.

References:

Targeted Early Intervention on Sensory Function in High Risk Infants: A Proposed Study Utilizing Single Case Research Design

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Introduction: The presence and intensity of early sensory seeking behaviors, behaviors that suggest an unusual fascination with or craving of certain sensory stimuli (e.g., extended visual inspection, repeated rubbing or banging, smelling, or licking of objects), in early infancy are associated with future symptoms of autism spectrum disorder (ASD). It has been hypothesized that these behaviors produce cascading effects on social development through reduced social orienting (Baranek et al., 2017; Damiano-Goodwin et al., 2017). Findings from studies involving infants at high risk for ASD (i.e., infants who have an older sibling diagnosed with ASD) suggest that early interventions that reduce sensory seeking behavior and/or increase social orienting may mitigate the effects of early sensory differences and yield more optimal social outcomes for this high-risk population. However, at present there is not a high level of evidence that any interventions have the potential to normalize sensory responsiveness (let alone translate to effects on more distal social skills) in children who are diagnosed with or at-risk for autism (Cascio, Woynaroski, Baranek & Wallace, 2016). The proposed targeted intervention is specifically designed to decrease sensory seeking behaviors, with the goal of improving social orienting and/or engagement, and other aspects of social communication, as well as more distal outcomes related to ASD.

Methods: The proposed study will utilize single case research design, which document causal/functional relations between independent and dependent variables (IV and DV) via continuous measurement of dependent variables (Horner et al., 2005). This study will utilize an alternating treatment single-case design across 4 participants aged 18 - 36 months at high risk for ASD who demonstrate high levels of sensory seeking behavior, as indexed by the Sensory Processing Assessment. The intervention procedures will target the following elements over 15 sessions:

1. Using strategies such as following the child’s lead, imitation, playful obstruction, and/or communicative temptations to engage the child in functional and/or cooperative play around the object of the sensory seeking behavior
2. Increasing the salience of social orienting bids to achieve joint engagement with the child
3. Removing the object of child sensory seeking behavior if necessary
4. Attempting to reengage a child with an item or activity which is less likely to elicit sensory seeking behavior and more likely to promote social behavior, such as a social game The primary dependent variable for this project will be sensory seeking behaviors as measured during the intervention session.

We anticipate that there will be a functional relation, as evidenced by a drop in the amount of sensory seeking behaviors coinciding with the use of key intervention strategies as delineated above.

Results: Anticipated results will be discussed.

Discussion: The implications of the proposed study will be discussed. If evidence supports the hypothesis that targeted early intervention may lead to reduced sensory seeking behaviors, increased social orientating and/or engagement, and collateral effects on more distal skills, a treatment study utilizing group research design will be warranted.

References:
Social anhedonia as a vulnerability factor for depression in adults with autism spectrum disorder

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Introduction: Deficits in social reward processing have been associated with the onset, severity, and maintenance of depressive symptoms in the general literature. Social anhedonia, or reduced interest or pleasure in social stimuli, may represent a similar vulnerability factor for co-occurring depressive symptoms in individuals with ASD. In the typically developing (TD) population, lack of motivation to engage in rewarding experiences - or disrupted anticipatory ('wanting') pleasure - has been associated with increased distress due to perceived social isolation, or loneliness. In ASD, a less established body of work has suggested both decreased social anticipatory ('wanting') and consummatory ('liking') pleasure compared to TD counterparts, with some studies suggesting a particular deficit in social 'wanting' that is related to ASD symptom severity. The objective of the current study was to examine anticipatory and consummatory social and non-social pleasure as contributors to loneliness and depressed mood in adults with ASD compared to typically developing adults with depressive disorders (TD-dep) and never-depressed controls (TD-con).

Methods: A total of n=101 adults aged 18-35 with verbal IQ>80 were recruited from the three cohorts (ASD, n=44; TD-dep, n=28; TD-con, n=29). All participants completed diagnostic screening and testing, as well as self-report measures of capacity to experience social pleasure (Anticipatory and Consummatory Interpersonal Pleasure Scale; ACIPS), non-social pleasure (Temporal Experience of Pleasure Scale; TES), autism spectrum traits (Social Responsiveness Scale; SRS), loneliness (Loneliness in Context Questionnaire; LiCQ), and depressive symptoms (Beck Depression Inventory-II; BDI).

Results: The ASD and TD-dep groups did not differ significantly on measures of social and non-social pleasure, for both anticipatory and consummatory dimensions. However, both ASD and TD-dep groups showed decreased capacity for social and non-social pleasure compared to TD-con. The ASD cohort reported greater loneliness and depressive symptoms than TD-con, but less than TD-dep. In the whole sample (and replicated in ASD alone), there was a significant cross-over interaction between capacity for social pleasure and ASD traits on loneliness (t(98)=-2.36, p=0.02): individuals with greater capacity for social pleasure demonstrated a positive relation between ASD traits and loneliness, whereas individuals with decreased capacity for social pleasure exhibited the opposite effect (Figure 1). This moderation effect was not present for the measure of non-social pleasure. Finally, the ASD and TD-dep groups were combined to examine predictors of depressive symptoms trans-diagnostically. When controlling for social and non-social pleasure, loneliness, and ASD traits as predictors of depressive symptoms in a multiple regression framework, only loneliness was a significant predictor of BDI-II scores.

Discussion: Results indicate that individuals with ASD exhibit a similar profile of capacity for social and non-social pleasure compared to TD-dep, in which 'liking' and 'wanting' components are both diminished compared to TD-con. In our transdiagnostic sample, increased ASD traits were associated with greater loneliness for individuals with greater capacity for social pleasure. Interestingly, the opposite effect occurred for individuals with decreased capacity for social pleasure. These findings suggest that social anhedonia may be a shared mechanism across autism and depression populations which may partially explain the experience of loneliness and prevalence of co-occurring mood disorders in ASD.
Examining Expressive Language Benchmarks in Young Minimally Verbal Children with Autism

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Introduction: Despite accessing early intervention, up to 30% of children diagnosed with ASD are classified as nonverbal or minimally verbal at age five (Anderson, 2007). Within the minimally verbal population of children with ASD, there is high variability in both speech and language abilities, without a single identified pattern of characteristics (Tager-Flusberg & Kasari, 2013). Identifying children in this population according to characteristics of their development has important implications for guiding intervention research. The purpose of this study was to classify young minimally verbal children according to expressive language benchmarks proposed by Tager-Flusberg et al. (2009), and to examine the relationship between language measures and autism symptom severity.

Methods: Data were analyzed from pre-intervention assessments of participants in an ongoing intervention study (HRSA grant #R40MC27707). Sixty-three minimally verbal children with autism between 36 and 54 months of age (mean age=48.1 months) participated in this study. A measure of phonology (consonant inventory) was derived from the Profiles of Early Expressive Phonology (Williams & Stoel-Gammon, 2014). Language samples were transcribed and coded to derive measures of vocabulary (number of different words) and pragmatics (number of different communicative functions). The percentage of children in the sample who met benchmarks for each language stage was then calculated for each domain. Additionally, correlations were calculated to examine the relationship between language measures and autism symptom severity as measured by the Autism Diagnostic Observation Schedule (Lord, et al., 2008).

Results: For the domain of phonology, 41.6% of the sample met criteria for pre-verbal status, 13.1% of the sample met criteria first words, 27.9% of the sample met criteria for word combinations, and 16.5% of the sample met criteria for sentences. For the domain of vocabulary, 43.8% of the sample met criteria for pre-verbal status, 56.4% of the sample met criteria first words, and none of the participants met criteria for word combinations or sentences. For the domain of pragmatics, 44.8% of the sample met criteria for pre-verbal status, 31% of the sample met criteria first words, 24.1% of the sample met criteria for word combinations, and none of the participants met criteria for sentences. None of the measures of language correlated with autism symptom severity.

Discussion: While the 63 children were dispersed across all developmental phases for phonology, most children remained in early phases of vocabulary and pragmatic development. None of the measures were significantly correlated with autism severity, suggesting that specific assessments of early language development are needed to determine intervention targets. Future research should focus on individualizing interventions to better target specific language weaknesses highlighted in these language profiles for individuals with ASD.

References:


Williams & Stoel-Gammon (2014), PEEPS: Profiles of Early Expressive Phonology.
Introduction: Children with Down syndrome (DS) exhibit below average nonverbal intelligence and impaired language skills; however, their spoken narrative production is a relative strength (e.g., Finestack, Palmer, & Abbeduto, 2012; Miles & Chapman, 2002). We examined spoken fictional narrative retells and examined how retell skills contribute to literacy skills of children with DS.

Methods: Fifteen, 8- to 18-year old children with DS produced spoken fictional narratives following a clinician model using a wordless picture book. Spoken fictional narratives following a modeled story were analyzed at the microstructure and macrostructure level. Receptive vocabulary, word-level reading, and reading comprehension also were measured.

Results: Children with DS produced limited syntactic (MLU-M: M = 6.59, SD = 2.50) and semantic diversity (NDW: M = 54.53, SD = 24.17). Further analyses using the Narrative Assessment Protocol (NAP; Justice, Bowles, Pence & Gosse, 2010) revealed that the spoken narratives of children with DS rarely contained compound or complex sentences; however, prepositional phrases were used frequently. In addition, participants used verbs more often than nouns and modifiers. At the macrostructure level, children with DS included essential story grammar components (e.g., main characters, conflict/resolution pairings) but did not provide sufficient detail (e.g., modifiers, elaborated noun phrases). Results reflect mastery over concrete ideas but a diminished ability to produce abstract concepts (e.g., characters' thoughts, emotions). A series of regression analyses were completed. Macrostructure was the only variable that contributed unique variance to reading comprehension after controlling for word level reading and receptive vocabulary, F(1,11) = 5.79, p = .035. We then considered that word level reading, instead of reading comprehension, may be more sensitive to variation in performance among participants. After controlling for receptive vocabulary, all narrative measures contributed unique variance to word level reading. Additionally, strong correlations (range: r = .63-.97) were found between narrative microstructure and macrostructure skills and literacy skills.

Discussion: The majority of research on literacy skills of children with DS has focused on identifying how receptive language skills and not expressive language skills are related to reading (e.g., Laws, Brown, & Main, 2016). We found that expressive narrative skills, are related to word-level reading and reading comprehension for children with DS. Narrative analysis using the NAP provided detailed analysis of the sentence structure of spoken narrative retells. Findings from this study support the use of narrative analyses as a valuable assessment tool for educators. Future studies should consider the efficacy of intervention strategies to improve the narrative skills of children with DS and determine whether improvement of narrative skills increases word-level reading and reading comprehension.

References


**Effects of a Virtual Reality Social Training Intervention on Loneliness and Social Cognition in Patients with Schizophrenia**

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**Introduction:** Deficits in social cognition and on social perception tasks are well studied and widely found in populations with schizophrenia. In addition, our work consistently replicates findings that individuals with schizophrenia report severe loneliness, significantly higher than healthy matches. Loneliness is a chronic, gnawing condition that induces distress and impedes life satisfaction and function across the spectrum of mental health. We also find social isolation impedes interpretation of social information and may lead to socio-perceptual deficits. The present study examines the effectiveness of a novel, adaptive virtual reality simulated social exposure training intervention (see Bekele et al, 2016) in both decreasing feelings of loneliness and improving social cognitive function in individuals with schizophrenia. We investigate baseline relationships between social isolation, loneliness and social cognition abilities, as well as pre to post intervention changes in function and subjective social well-being.

**Methods:** Fifteen medicated SZ outpatients completed 10 virtual reality social skills training sessions over the course of 5 weeks. Training sessions depicted three naturalistic social scenarios in which participants were instructed to complete 12 total social missions to obtain information from VR avatar characters. Prior to training and following the final training session, participants were assessed using the CogState Brief Schizophrenia Battery Social Emotional cognition task and rated loneliness using the UCLA Loneliness Scale. Independent raters conducted pre- and post-training clinical interviews to assess changes in participants' levels of positive, negative, and overall psychiatric symptoms.

**Results**  
Greater overall psychiatric symptoms were significantly correlated with higher levels of experienced loneliness (r= 0.60, p< 0.05), consistent with previous findings. There was a significant improvement in social emotional cognition accuracy from pre-training (M= 1.03.5, SD= 0.18) to post-testing (M= 1.12, SD= 0.19) following social VR training (t(26)=1.18, p<0.05). However, loneliness decreased non-significantly from pre-training (M= 50.5, SD= 17.7) to post-testing (M= 45.2, SD= 15.1) after social skills training (t(26)=0.85, p=0.07).

**Discussion:** Previous research indicates that individuals higher on the psychosis spectrum perform worse at social cognition and social perception tasks. Our own research indicates that individuals higher on the psychosis spectrum also endorse higher levels of social distress via social isolation and loneliness. The present study attempts to enhance social cognitive and interpersonal abilities of individuals with schizophrenia while decreasing loneliness by strengthening social bonds and skills using a virtual reality training game. We find that following 10 sessions of VR social training, accuracy on measures of social cognition is improved significantly, however loneliness is reduced non-significantly. These initial results demonstrate potential feasibility of a novel VR social skills training game for improving social experience for patients with schizophrenia.

**References:**  
Functional consequences of RNA editing on mGlu4 dimerization

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**Introduction:** Group III metabotropic glutamate receptors (mGlu4, mGlu6, mGlu7 and mGlu8) are members of the G-protein coupled receptor superfamily and have been implicated in numerous neurological disorders including addiction, depression, anxiety, and neuroblastoma. Positive allosteric modulators (PAMs) highly selective for mGlu4 show potent antiparkinsonian effects in rodent models and knockout mice appear resistant to alcohol addiction. The mGlu4 receptor is localized to the presynaptic membrane where it functions as an autoreceptor controlling synaptic release of neurotransmitter. Though initially thought to exist exclusively as a homodimer, recent studies have shown that mGlu4 also can exist as a heterodimer with mGlu2, and that these different dimer pairs are synapse-specific. The sequence of pre-mRNA transcripts encoding mGlu4 can be modified by adenosine-to-inosine (A-to-I) RNA editing events at up to 4 sites to generate as many as 8 receptor isoforms. These editing events result in non-synonymous amino acid alterations in a region of the receptor proposed to represent the interface at which mGlu receptors dimerize. While it is now known that mGlu4/mGlu2 heterodimers exist, it remains to be determined whether RNA editing can affect mGlu4 homo- or heterodimerization. Using high throughput sequencing, 4 editing sites have been validated within the region of mRNA encoding the ligand binding domain of the mGlu4 receptor and determined the most frequently expressed transcript isoforms. Current studies in the lab focus on determining the extended duplex structures required for editing at each site. Functional studies in this project will involve distinguishing edited receptor isoform stability, signaling, and formation of homo- or heterodimers between these edited receptors and other mGlu receptors. It is anticipated that these studies will provide insights regarding the functional importance of editing events in mGlu4 mRNAs for disorders in which this receptor has been implicated including Parkinson’s disease and anxiety.
The Structure of Embodied Emotions in Schizophrenia

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Introduction: Past research suggests a disconnection between experienced emotions and bodily sensations in individuals with schizophrenia (SZ), but mechanisms underlying abnormal embodiment of emotions in SZ are unknown. There might be an overall reduction of emotion-related bodily sensations, but it is also possible that the spatial distribution of bodily sensations associated with emotions may be altered in SZ. We hypothesized the presence of a more coherent underlying structure giving rise to embodied emotions in healthy controls (HC) compared to SZ.

Methods: Twenty-six SZ and twenty-six demographically matched HC were asked to complete the emBODY task (Nummenmaa et al., 2014). In the emBODY task, participants were asked to shade in where they felt sensations (activation and deactivation) on the outline of a human body when presented with an emotion word. Fourteen emotion words were presented sequentially. From activation and deactivation data, body maps of emotions were generated through nonparametric analyses and two separate principal components analyses (PCA) were conducted, one for each group to determine the multivariate structure of embodied emotions.

Results: The pattern of principal components for HC were similar to that of the SZ group. However, SZ showed components with lesser magnitude than the HC. Moreover, the variance that accounts for these dimensions was slightly reduced for SZ. This suggests similar but weaker embodied emotion in SZ. In this PCA framework, a particular set of innate constructs is thought to yield the activation and deactivation maps of emotions on the body. Our results imply that the complexity of this set in SZ is similar to that of the HC, but the dimensions were able to capture the embodied emotions better for the HC. That is, there is more agreement in the HC population about how embodied emotions are experienced, whereas SZ were not as consistent.

Discussion: Quantitative modeling of the underlying structure of self-reported embodied emotion provided novel insight into altered emotional experience in SZ. Our findings illustrate similar but weaker bodily maps of emotions in SZ compared to HC. Bodily sensations are very different in intensity and captured less effectively for SZ, as seen by the PCA. While an important first step, our analysis was exploratory and limited by the small sample size. Future direction includes probing the specific contents of the underlying dimensions that give rise to embodied emotions.

References:
Emotion recognition improvements in schizophrenia following a novel computerized social-training intervention

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Introduction: Social impairment in schizophrenia (SZ) is considered a core feature of the disorder contributing to poor long-term outcomes. While psychosocial treatments for SZ show some ability to improve social cognition and functioning, such interventions are typically costly and time-intensive, resulting in low engagement and compliance. Virtual reality (VR) is a promising technology for social training by providing the opportunity for content personalization, simulation in a controlled environment, and adaptive feedback ideal for learning. The current study tested the feasibility and effectiveness of a novel, adaptive VR computer intervention for improving social cognitive deficits and associated clinical outcomes in SZ.

Methods: Fifteen medicated SZ outpatients completed a social skills computer game intervention involving 10 training sessions in the laboratory scheduled approximately twice/week (days until completion: M=38.8, SD=16). During each session, participants played an adaptive VR computer game developed in-house with Autodesk Maya 3D animation software and Unity (unity3d.com). The game was structured as a series of 'social missions' to determine information about various Avatars, achieved through selecting appropriate conversation prompts and responses. Characters' speech was lip-synched and customized with scripts from pre-recorded audio files. Independent raters conducted pre- and post-training clinical interviews to assess changes in participants' levels of positive, negative, and overall psychiatric symptoms. Social cognition was measured at pre- and post-training with the Bell Lysaker Emotion Recognition Task (BLERT), a validated assessment of emotion perception predictive of community functioning in SZ.

Results: Level of overall psychiatric symptoms significantly decreased following the social skills computer training (F(1,14)=10.5, p<.01). Negative, but not positive, symptoms also demonstrated significant reduction following training (F(1,14)=8.0, p<.05). Finally, emotion recognition accuracy on the BLERT improved post-training (F(1,14)=4.38, p<.05). On an acceptability survey following study completion, all participants rated the computer training as either 'helpful' (80%) or 'maybe helpful' (20%), and no participants were dissatisfied with the training (80% 'extremely satisfied').

Discussion: Individuals with SZ demonstrated improvement in their level of overall psychiatric symptoms, negative symptoms, and emotion perception accuracy following 10 sessions of a novel, VR computer game involving simulation and practice of interactive, adaptive social conversations. Beyond objective improvements in clinical and social cognitive measures, participants found the computer game training to be subjectively helpful and agreeable. Though much work remains in probing the exact nature of treatment mechanism and durability of these improvements, these promising initial results demonstrate the feasibility and effectiveness of an adaptive VR computer game for improving core social cognitive and clinical features of schizophrenia.
The Physiological Role of CAPS1 RNA Editing

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Introduction: Docking and priming of secretory vesicles at the plasma membrane is a key step in regulated exocytosis and is modulated by a multitude of lipid and protein interactions. Calcium-dependent activator protein for secretion 1 (CAPS1) is a nervous system- and endocrine-specific protein that mediates docking and priming of secretory vesicles and large dense-core secretory granules, primarily through interactions of its Munc-homology domain (MHD) with the SNARE protein syntaxin-1. Ablation of CAPS1 decreases the size of the readily releasable pool of vesicles, thereby reducing the amount of neurotransmitter, neuropeptide or peptide hormone released from cells. Transcripts encoding CAPS1 are modified by an adenosine-to-inosine (A-to-I) RNA editing event in which a genomically-encoded glutamate (GAG) is converted to a glycine (GIG) codon, resulting in a nonsynonymous amino acid change in the MHD. Recent work from our laboratory has demonstrated significant functional consequences for CAPS1 editing, including differences in the rate of vesicular release and mode of exocytosis. To further investigate the physiological role of CAPS1 editing, we will develop and characterize mouse models solely expressing either the non-edited or edited CAPS1 isoforms to study basal and evoked exocytosis events using in vivo microdialysis, and SynpHTomato and FM dye tracking in primary neurons. We also will explore behavioral phenotypes exhibited by these animals, including assessment of locomotor activity as CAPS1 editing has been shown to play an important role in this circuitry. Additionally, we will examine CAPS1 interactions with syntaxin-1, assessing potential editing-dependent differences in binding. It is anticipated that these studies will provide further insights into the physiologic role(s) for CAPS1 editing and how such an RNA modification can affect both nervous system and endocrine function.
Modulation of mGlu3 function in a rodent model of Major depressive disorder

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Faculty Advisor: Conn, Jeff

Introduction: Current first-line medications for Major depressive disorder (MDD) exhibit an undesirable delay in onset and poor efficacy in the general population: three or more weeks of treatment is required to initiate symptomatic improvement, one-third of patients relapse within 6 months, and another one-third never respond whatsoever. Thus, there remains a great unmet need for novel fast-acting antidepressant medications that retain efficacy in treatment-resistant populations. The rapid reversal of depressive-like symptoms by ketamine and related antidepressants is thought to be mediated by glutamate signaling within the prefrontal cortex (PFC). We have recently shown that metabotropic glutamate receptor subtype 3 (mGlu3) induces profound changes in PFC synaptic physiology and is involved in the response to acute stress, however the effects of mGlu3 modulation in a chronic stress model of MDD have yet to be reported. We hypothesize that negative allosteric modulators (NAMs) of mGlu3 will exhibit rapid antidepressant efficacy in rodent models of depressive-like behavior and PFC dysfunction.

Methods: We modeled MDD symptomology in adult C57Bl/6J mice through chronic (4-week) treatment with the stress hormone corticosterone (CORT). Anxiogenic, anhedonic, and depressive outcomes were assessed using a battery of behavioral assays. To interrogate the effects of CORT treatment on PFC function, we evaluated basal membrane and synaptic properties of layer 5 pyramidal neurons. Furthermore, pyramidal neurons were classified by their projection targets using retroviral expression of a fluorescent marker in PFC target structures. Finally, mGlu3 function was assessed using the mGlu2/3 agonist LY379268.

Results: Chronic CORT treatment induced anhedonic- and depressive-like behaviors in adult male mice while no effects on anxiety-like behavior were observed. Additionally, these changes occurred alongside concomitant impairments to fast glutamatergic function in the PFC. CORT treatment was associated with decreased amplitude of miniature excitatory postsynaptic currents, a measure of AMPA receptor function. Synaptic plasticity mediated by mGlu3 was also impaired, consistent with decreased AMPA receptor function and/or a loss of mGlu3 function.

Discussion: We have validated that chronic CORT treatment induces several behavioral and synaptic changes consistent with a depressive-like phenotype. We are continuing to explore the specific neurocircuits affected by CORT exposure, as well as whether novel mGlu3 NAMs will display fast-acting antidepressant efficacy in this model. The results from this project will enhance our understanding of how PFC function is impaired in MDD and will inform efforts to develop novel antidepressants targeting the glutamate system.
An Evaluation of Phonological Awareness Intervention with Down Syndrome Children

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Introduction: Phonological awareness, the ability to analyze the sound structure of a language separate from its meaning, is a metalinguistic skill that contributes to young children's early reading success (Mattingly, 1972; van Kleeck, 1994; O'Connor, Jenkins, Leicester & Slocum, 1993). Phonological awareness skills are strong predictors of reading acquisition. Although there is a large majority of evidence focusing on phonological awareness, little of this literature focuses on children with intellectual disability (Bridges & Catts, 2011; Spector, 1992; Cunningham, 1990; Kennedy & Flynn, 2003). This study explores whether a functional relation exists between an adapted version of the Intensive Phonological Awareness Program (IPA Program; Schuele & Murphy, 2014) and increases in phonological awareness skills in children with Down syndrome.

Methods: A single case, multiple baseline design across participants measured the impact of the IPA Program on phonological awareness skills. Three participants with Down syndrome (entering Kindergarten - 3rd grade) and three typically developing peer group members participated in intervention. For each group, interventionists led three weekly IPA Program lessons. Lessons followed a developmental progression employing multi-sensory methods for the target phonological awareness skills. The Measure of Phonological Awareness (MOPA, researcher-developed tool), with a dynamic assessment protocol, was used as the dependent variable to measure progress during baseline, intervention, and maintenance conditions.

Results: After five weeks of intervention, all participants demonstrated increasing therapeutic trends as functionally related to the intervention. Two weeks post intervention, two participants maintained the phonological awareness skill taught.

Discussion: This study indicates that children with Down syndrome benefit from systematic, focused phonological awareness intervention. Although inconsistency in the data were observed, the participants demonstrated increases in phonological awareness. Findings from this study support small group instruction including typically developing, same level peers as a motivating educational experience for children with intellectual disabilities.

References
Cognitive and linguistic predictors of reading comprehension in elementary grades

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Introduction: The purpose of this study was to identify cognitive and linguistic predictors of later reading comprehension (RC) of struggling readers in elementary grades, in an effort to broaden the understanding of the impact of cognitive variables.

Methods: 426 1st grade students were tested on predictor measures at the beginning of 1st grade and their RC scores were followed for 4 years till the end of 4th grade. Cognitive predictors included nonverbal reasoning, working memory, rapid automatized naming (RAN), and phonological awareness; and linguistic predictors included non-word reading, word reading, listening comprehension, and vocabulary skills. Two-level growth curve modeling was used to examine the relationship between cognitive and linguistic variables and students' RC achievement status and their growth rates.

Results: Overall results of this study were fairly consistent with prior research regarding the relationships between RC and each variable. Significant predictors of end-of-1st-grade RC scores were nonverbal reasoning, phonological awareness, non-word reading, and word reading. Predictors of the growth rate over 4 years were nonverbal reasoning, RAN, listening comprehension, and vocabulary.

Discussion: Nonverbal reasoning was the only predictor out of eight cognitive and linguistic variables for both the proximate achievement status and the growth rate. This finding suggests this nonverbal measure of core cognitive process needs more attention in identifying reading difficulties in intermediate grade students, considering few empirical studies that explored the role of nonverbal reasoning. Nonverbal reasoning has a potential to be a good proxy of reasoning ability that is strongly associated with inference making skills, while partialing out the effect of verbal ability on RC (McCardle et al., 2001). Even though phonological awareness was even a stronger predictor of proximate outcome than nonverbal reasoning with respect to effect size, it was no longer a significant predictor of the growth rate. RAN was found to be a predictor only for the growth rate over time, showing the opposite predictive validity to phonological awareness. Regarding linguistic predictors, non-word and word reading were significant predictors of RC at the end of 1st grade, but failed to predict the growth rate. Instead, listening comprehension and vocabulary, which were not significant for the end-of-1st-grade RC, emerged to be significant predictors of the RC development over 4 years. This shows that 'a developmental asymmetry (Vellutino et al., 2004)' in RC development also takes place in the development of struggling readers, where word reading explains more variance of RC at early stages of reading development, and language comprehension carries greater weight as determinants of RC at later stages of reading development. Findings are discussed more and implications for research and practice are provided.

References:


Patterns of Reading Impairments in Children with SLI

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Introduction: Children with specific language impairment (SLI) are at elevated risk for reading disabilities. Current theoretical models conceptualize reading as a multifactorial skill that involves word-level skills (i.e., decoding) and text-level skills (i.e., reading comprehension). This conceptualization suggests four possible reading outcomes: typical reading, isolated word-level deficit, isolated text-level deficit, and concomitant word-level and text-level deficits. Although on average children with SLI struggle with reading, we know of no study that has examined the specific nature of reading outcomes among children with SLI. Because reading disabilities that involve word-level and/or text-level skills may require different intervention approaches, the purpose of this study was to explore the pattern of reading outcomes among children with SLI compared to that of children with typical language.

Methods: Participants were 32 children with SLI and 39 children with typical language in grades 2 through 4. Each child was classified into one of the four outcomes based on their performance on the Test of Word Reading Efficiency, 2nd edition and the passage comprehension subtest of the Woodcock Reading Mastery Test-III. We used logistic regression to determine the effect of group on reading outcome.

Results: In each logistic regression, a reading outcome (e.g., isolated word-level deficit), scored dichotomously for each participant, served as the dependent variable. Group served as the independent variable. The typical language group was the reference group. We used a Bonferroni correction for multiple comparisons (alpha = .016 for three comparisons; no regression analysis was conducted for isolated text-level deficit). The likelihood of typical word- and text-level reading skills was significantly lower in the SLI group (beta = -2.38, p < .001, odds ratio = 0.09). The likelihood of isolated word-level deficits was approximately equal across the two groups (beta = -0.03, p = .95, odds ratio = 0.97). The likelihood of concomitant word-level and text-level deficits was significantly higher in the SLI group, and the increased likelihood is clinically meaningful (beta = 2.92, p < .001, odds ratio = 18.50). We did not conduct a regression analysis on isolated text-level deficits due to the low occurrence of this outcome: 9% of children with SLI and 3% of children with typical language.

Discussion: Children with SLI are at elevated risk for reading impairments. Relative to children with typical language, they are particularly susceptible to concomitant word-level and text-level reading deficits. Educators working with children with SLI, including classroom teachers, special education teachers, and speech-language pathologists, need to identify reading deficits in children with SLI and intervene appropriately.
Inclusive STEM Classroom Experiences for Students with Autism and Other Developmental Disabilities

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Faculty Advisor: Carter, Erik

Introduction: The proposed study focuses on the use of an observation system to measure the dimensions between teachers in inclusive STEM (science, technology, engineering, math) settings and students with and without moderate and severe disabilities (MSD) including intellectual disabilities (ID) and autism spectrum disorder (ASD). These dimensions include (a) the alignment of classroom activities and arrangements for the student with MSD to the general education class and (b) interactions between students with MSD and their peers, general education teachers, and support personnel (e.g., paraeducators, special education teacher, and related services provider). Research to date is limited in the area of teaching STEM content and process skills to students with disabilities, including students with MSD in various contexts and grade levels (typically middle school).

Methods: Participants are recruited from a large, public school district and meet the following inclusion criteria. The inclusion criteria for students with MSD (including ID and ASD) is that they (a) have a medical and/or educational diagnosis of a MSD (such as ID and/or ASD) as indicated on their Individualized Education Plan (IEP), (b) are determined eligible to participate in the state’s alternative assessment by their IEP team, (c) participate in at least 30-min of STEM instruction in the general education setting each day, (d) communicate and understand using English, and (e) be between the ages of 10 and 22 year old. Students with MSD will be excluded from this study if they (a) do not have a medical and/or educational diagnosis of a MSD, (b) do not have an IEP, (c) do not participate in at least 30-min of STEM instruction in the general education setting each day, or (d) do not communicate using English. Twelve middle or high school students with MSD participated in this study. Researchers observed each participant 3-5 times for approximately 30 minutes each observation. Using an interval recording system, researchers collected data on class tasks, physical arrangements, instructional groupings, social interactions, academic engagement, content alignment, and task alignment for students with MSD and typically developing peers. Data were collected during live observations using pencil-paper recording.

Results: Preliminary results will be presented comparing the experiences of students with MSD with an average peer in the same class. Comparisons will be made regarding the students’ physical arrangement, instructional grouping, social interactions, academic engagement, content alignment, and task alignment.

Discussion: Similarities and differences in experiences of general education STEM instructions will be examined for participants in this study. Limitations will be discussed, and implications for practice and research will be noted.
**M4 Receptor Activation Normalizes Dopaminergic Signaling In Huntington's Disease Mouse Models**

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**Faculty Advisor:** Conn, P. Jeffrey

**Introduction:** Huntington's Disease (HD) is a genetic and neurodegenerative disease characterized by multiple symptom stages resulting in motor and cognitive deficits. Currently, the treatments for HD only address late-stage symptom management and do not provide any efficacy in delaying or preventing disease progression. The goal of these studies is to further our understanding of the HD disease progression with the hopes of identifying novel strategies with which to alleviate early-stage symptoms and prevent disease progression. While the exact causes behind the neurodegeneration observed in HD are not clear, there are several circuit level changes that precede motor symptoms including hyperactive glutamatergic in the striatum. Here, we assess dopaminergic signaling in HD mouse models at a developmental stage that precedes motor symptoms and examine how the M4 muscarinic receptor can modulate this neurotransmission.

**Methods:** Here, we report studies using fast-scan cyclic voltammetry (FSCV) to assess dopaminergic signaling in two animal models of HD (BACHD and YAC128HD). Dopamine release was elicited by electrical or optical stimulation and the peak of the induced dopamine transients was determined. Animals were assessed at 10 weeks of age, a developmental stage that precedes the onset of motor symptoms. In order to assess if M4 receptor expression is altered in HD mice we also performed radioligand binding experiments in striatal membranes.

**Results:** We found that both mouse models displayed a hyperdopaminergic phenotype compared to wild-type littermates at young ages prior to the onset of motor phenotypes. Both electrical stimulation, as well as optical stimulation in mice expressing channel rhodopsin 2 in dopamine neurons, induced larger dopamine transients in ex vivo brain slices of HD mice. In addition, in vivo voltammetry recordings made from anesthetized HD mice demonstrated larger electrically evoked dopamine transients than littermate controls. The increased striatal dopamine release in HD mice did not correlate with changes in motor function when tested in an open field paradigm. In addition, we found that activation of the M4 muscarinic receptor using a positive allosteric modulator (PAM) was able to normalize excessive striatal dopamine release in HD mice.

**Discussion:** Previous studies have demonstrated that chronic administration of M4 PAMs can delay the onset of motor deficits in these mouse models. Here, we report that HD mice display excessive dopamine transmission in the striatum at ages prior to the onset of motor symptoms. Furthermore, we found that activation of the M4 receptor could normalize this excessive dopamine transmission suggesting that this receptor may be a novel therapeutic target with which to normalize neurotransmission in early disease stages.
Examining the relationship between motor abilities and prelinguistic vocalizations in preverbal children with autism

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Faculty Advisor: Bodfish, Jim

Introduction: Up to 30 percent of children with ASD do not develop spoken language. The acquisition of motor skills can influence how children interact with objects and people to support language development. Although previous studies have examined the relationship between motor and language development in ASD, none have focused on the earliest emerging form of prelinguistic vocalizations. Protophones are early developing vocalizations that are present in children as young as three months and are thought to be among the earliest forms of intentional communication. The purpose of this study was to determine the association between both typical and atypical motor behaviors and prelinguistic vocalizations in a sample of preverbal children with ASD.

Methods: This study includes data from The Useful Speech Project (Yoder, Watson, & Lambert, 2015). Participants included 20 children with ASD who were between 20-48 months at baseline with fewer than 20 reported words. Multimedia recordings were used to code motor behaviors and vocalizations using a partial-interval scheme. Motor behaviors were classified into three categories: body postures, motor movements, object-related movements. Prelinguistic vocalizations were classified into five categories: protophones (squeal [high pitch], vocants [mid-range], and growl [low pitch], and fixed signals [cry, laugh]).

Results: Analyses of data to date have focused on the psychometric characteristics of the coding procedure. The coding scheme developed for this project was found to be reliable for both motor codes (mean = 0.80, range= 0.79-1.0) and vocalization codes (mean: 0.88 and range: 0.80-0.98). The coding scheme was also found to be stable across two different assessment periods (r= 0.97). The majority of participants demonstrated the full range of pre-linguistic vocalization types and the full range of motor behaviors indicating that the coding scheme is sensitive to the detection of both motor behaviors and prelinguistic vocalizations in preverbal children with ASD. Data coding on the full sample is ongoing and will be completed by the time of this meeting. Additional analyses will be done using an Operant Contingency Value approach that quantifies the association between motor behaviors and concurrent vocalizations.

Discussion: Results from this study will contribute to the understanding of the relation between motor and language development in ASD and move this area of research to an earlier period of language development than has been investigated previously in ASD.

References:
Early Emerging, Slow Mapping? Comprehension of Conjunction Clauses that Involve Unfamiliar Event Ordering in Different Types of Readers

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Faculty Advisor: Schuele, C. Melanie

Introduction: To comprehend text, multiple operations must be performed simultaneously for readers to construct a situation model that represents what they are reading. Some students struggle with comprehension due to poor word-level reading. Other students have no or relatively mild difficulties with word-level reading yet struggle to comprehend what they read. Students with this pattern typically have language deficiency that affects both oral and written language comprehension. Milder cases of language difficulties often go unrecognized in the classroom (Kilpatrick, 2015). We examined child comprehension of subordinate and coordinate clauses that involved unfamiliar event ordering. We hypothesize that readers with stronger language skills are more likely to form an accurate mapping between the event representation and syntactic structure.

Methods: Thirty-two first to third graders completed a conjunction clause comprehension task, two word-level reading tests (Word Identification and Word Attack of the WRMT-III), and two reading comprehension tests (Passage Comprehension of the WRMT-III and Reading Comprehension of the WIAT-III). The conjunction clause comprehension task included 18 mini-stories (each three to four sentences long). Sixteen mini-stories contained a subordinate conjunction marker (i.e., because, before, after, if), which denoted a causal, temporal, or conditional relation, and two mini-stories described a contrastive relation (i.e., but). Half of the test items involved arbitrary event orders; the other half involved event orders that violated child general event knowledge. Two statements followed the presentation of each mini-story with each statement containing a coordinate or subordinate clause. We asked the child to identify which statement best described the story.

Results: The data of 24 participants were currently entered and analyzed. Child conjunction clause comprehension performances yielded a strong correlation with reading comprehension scores (r = .73, p < .05). We further divided children into the upper third (n = 8) and the lower third (n = 8) based on reading comprehension performance. Children in the upper third scored significantly higher on conjunction clause comprehension (percent correct: M = 90.97, SD = 6.60) than children in the lower third (M = 75, SD = 7.86). We noted that the lower third were mostly children whose parents reported at least one risk factor or more (e.g., family history of learning difficulties or language impairments, receiving services, parent expressed concerns).

Discussion: Conjunction clauses are typically acquired early in child language development. This study demonstrated that some children at greater risk for reading comprehension difficulties might still experience difficulty integrating independent utterances that are pragmatically combined in the discourse into a specific grammatical unit (i.e., conjunction). Addressing the pragmatic use of conjunction clauses may have educational implications.
Abnormal craniofacial and neural development in glycosyltransferase mutant zebrafish recapitulates CDG-ij patient phenotypes

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Introduction: Glycosylation is an important co-translational and post-translational modification required for protein function, such as recognition by ER quality control machinery, binding, structural and metabolic activity. Due to the prevalence and necessity of glycoproteins for normal cellular function, defects within the N-glycosylation pathway result in disruptions in development and function of multiple organ systems, including the nervous, skeletomuscular, respiratory and visual systems. Mutations in over 30 genes involved in N-glycosylation of proteins have been identified as genetic causes of a group of diseases known as congenital disorders of glycosylation (CDG). CDG-ij is caused by mutations within the DPAGT1 gene encoding the first glycosyltransferase (GlcNAc-1-P transferase) of the N-glycosylation pathway. CDG-ij patient symptoms include microcephaly, dysmorphic face, hypotonia, mental retardation, seizures, and exotropia. Recently, clinical studies on CDG-ij patients have added new phenotypes to the disease spectrum to include neuromuscular phenotypes, although additional studies are needed to understand the full pathology of the disease. Prior work in our laboratory identified a mutant zebrafish line, stumpf (stpm365), that carries a point mutation in a highly-conserved domain of Dpagt1. Zebrafish stumpf mutant phenotype includes malformed craniofacial skeleton and defects in neural tissue development, similar CDG-ij patient phenotypes. Using both molecular and imaging techniques, the stumpf zebrafish mutant provides a unique vertebrate model system to study the mechanism of CDG-ij and the disease phenotypic spectrum.
**Region Specific Dysregulation of Dopaminergic Signaling in SAPAP3 Knock out Mice Displaying Excessive Over-Grooming**

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**Faculty Advisor:** Conn, Jeffrey

**Introduction:** Converging clinical and preclinical data suggest that striatal circuitry plays a key role in modulating repetitive behaviors and indicate that aberrant signaling in specific striatal pathways may represent a common mechanistic underpinning of numerous diseases including Obsessive Compulsive Disorder (OCD). Imaging studies have found reduced striatal dopamine (DA) receptor binding in OCD patients compared to healthy controls, an indication that dopaminergic signaling may be hyperactive in these individuals. Consistent with this hypothesis, blockade of dopaminergic signaling by administration of atypical antipsychotics can effectively treat some OCD patients that are refractory to serotonin selective reuptake inhibitors (SSRIs). Furthermore, experimentally mimicking or augmenting DA signaling in rodents can induce repetitive behaviors. However, the precise role of DA in regulating repetitive behaviors is poorly understood. The purpose of this study was to determine if dopamine signaling is altered in a mouse model displaying excessive self-grooming and further elucidate the potential utility of compounds targeting the striatal DA system in modulating repetitive behaviors.

**Methods:** Here, we report studies using fast-scan cyclic voltammetry (FSCV) in mice lacking the postsynaptic protein SAP90/PSD95-associated protein (SAPAP3 KO mice) as well as control littermates. Rodent self-grooming provides a behavioral output with which one can monitor repetitive, self-directed, patterned behavior that has great translational value to OCD-like disorders. Total time spent grooming was monitored in SAPAP3KO mice and control littermates. To further examine the role of DA in regulating repetitive grooming behaviors the magnitude and kinetics of DA transients were assessed using FSCV in ex vivo slice preparations as well as in anesthetized mice in vivo. DA transients were elicited in the dorsolateral striatum (DLS), dorsomedial striatum (DMS); and nucleus accumbens core (NAcc). In some experiments mice were crossed with DAT-Cre animals and channelrhodopsin 2 (ChR2) was virally expressed in DA neurons to allow optical stimulation of DA transients.

**Results:** As previously reported, SAPAP3 KO mice showed excessive grooming compared to control littermates at the age assessed (4-5 months). DA transients evoked by a single electrical pulse in slices from SAPAP3 KO mice were not significantly different from those observed in slices from control littermates in any of the regions tested including the DLS, DMS and NAcc. However, when four electrical pulses were applied at a frequency of 10Hz to mimic DA neuron bursting, the magnitude of DA transients observed in the DMS and NAcc of SAPAP3 mice were greater than those evoked in control littermates. Interestingly, phasic stimulation produced similar DA transients in the DLS of both genotypes suggesting that phasic DA signaling was not globally altered. To confirm this finding we crossed SAPAP3 KO mice with DAT-Cre animals and injected ChR2 containing virus into the midbrain to selectively express ChR2 in DA neurons. Transients were then optically evoked resulting in selective activation of DA neurons. Optical stimulation produced a pronounced enhancement of DA release in SAPAP3 KO mice specifically in the DMS and only following phasic-like stimulation.

**Discussion:** These exciting findings suggest that DA signaling in SAPAP3KO mice is dysregulated in a very precise manner that is sub-region specific as well as dependent on the pattern of stimulation. These results suggest that targeted therapies that can modulate these specific modes of dopaminergic signaling in these distinct striatal subregions could provide improved efficacy in OCD patients that are resistant to SSRI treatment.
Microglial pruning of synapses in the prefrontal cortex during adolescence

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Introduction: Aberrant synaptic elimination during postnatal development has been suggested to contribute to the pathophysiology of neurodevelopmental disorders including schizophrenia and autism spectrum disorder. Recent data point to microglial (MG) involvement in the sculpting of synapses and refinement of neuronal circuitry during early postnatal periods. However, the role of MG in the structural and functional maturation of the PFC, which is delayed and protracted relative to other cortices, has not been examined. We therefore determined if MG contribute to PFC PC synapse elimination during the periaadolescent period.

Methods: Layer 5 (L5) PCs from the PFC of one hemisphere were intracellularly filled with the fluorescent dye Lucifer Yellow for dendritic spine density measurements in Sprague-Dawley rats sacrificed on P24, P30, P35, P39, and P50. In the contralateral hemisphere we assessed colocalization of MG (defined by Iba1 expression) and dendritic spines (revealed by PSD-95 immunoreactivity [-ir]) or presynaptic elements (defined by VGluT1-ir) on PFC PCs. As a prelude to future experiments that will assess the consequences of disrupting adolescent MG pruning on adult PFC PC structure and function, we treated mice that express diphtheria toxin (DT) receptor on MG with DT to establish the extent of PFC MG depletion and the recovery rate of PFC MG following DT administration.

Results: We observed a significant increase in Iba1 and PSD-95 colocalization in the PFC at P39 relative to P24, which subsided and was reversed by P50, suggesting that there is a tight temporal window during which MG prune dendritic spines of PFC PCs during adolescence. MG engulfment of glutamatergic presynaptic elements (VGluT1-ir) significantly increased at P39 and P50. We observed an 87% decrease in the number of PFC microglia 2d after injecting DT to ablate microglia. MG began to recover by 4d and 6d (~45%), with nearly complete recovery seen 10d after DT treatment.

Discussion: Our data points to a critical role for microglia in the pruning of PFC PC dendritic spines during adolescence. This is substantially later than has been observed in other brain areas, consistent with the late maturation of the PFC. MG also engulfed the glutamatergic presynaptic partners of spines when MG engulfment of spine occurred and continued after MG spine pruning had ceased, supporting a model of synapse development in which spine growth precedes synapse formation. Our initial data suggest that DT can ablate microglia over a relatively short time period. We will exploit the short duration of microglial ablation in experiments assessing in the adult the morphological and functional consequences of ablation of MG during critical developmental windows. Understanding developmental pruning processes may lead to the development of new MG-based pharmacotherapies to mitigate structural and functional cortical changes in schizophrenia, including cognitive dysfunctions, and other 'spinopathies.'
The Role of CaMKII in mGlu5 Signaling

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Introduction: Ca2+/calmodulin (CaM)-dependent protein kinase II (CaMKII) is a serine/threonine kinase that accounts for ~1% of total protein in forebrain. Interactions of CaMKII with CaMKII associated proteins (CaMKAPs) and roles of CaMKII in modulating ionotropic glutamate receptors and voltage-gated ion channels have been studied intensively, but the role of CaMKII in G protein coupled receptor (GPCR) regulation is less well understood. There is evidence that the metabotropic glutamate receptor 5 (mGlu5) and CaMKII are functionally linked, although this interaction has not been well characterized. CaMKII is necessary for some mGlu5-stimulated changes in synaptic strength including hippocampal long-term depression (LTD). Recent studies implicate mGlu5 and CaMKII in several neuropsychiatric disorders, including autism spectrum disorder, Alzheimer’s disease, schizophrenia, drug addiction, and Parkinson’s disease.

Methods: These studies have utilized a number of different techniques including in vitro binding assays using purified constructs of the mGlu5-CT and CaMKII. Heterologous cells have been used for binding studies of full-length mGlu5 and CaMKII. Live cell calcium imaging has been performed in heterologous cells and neurons to determine the effect of CaMKII on mGlu5 calcium signaling.

Results: Here, we confirmed a previous report that CaMKII interacts with mGlu5, a Gq coupled receptor. We found that both active and inactive conformations of CaMKII are capable of interacting with the mGlu5 in vitro, in HEK293 cells, and in mouse forebrain lysates. Using a CaMKII autophosphorylation protocol that leads to Thr286-autophosphorylation, we found that autophosphorylated CaMKII binds to mGlu5 much more strongly than inactive kinase. The interaction between mGlu5 and both active and inactive CaMKII is disrupted by Ca2+/CaM apparently by binding to the mGlu5 confirming previously reported results. We identified a tribasic residue on the mGlu5 C-terminus that is capable of disrupting binding between mGlu5 and CaMKII. Co-expression of constitutively-active CaMKII enhances mGlu5 signaling in a heterologous cell system by prolonging Ca2+ oscillations, but reducing peak responses and increasing basal mGlu5 surface expression.

Discussion: Understanding the interplay between these key synaptic regulators may provide mechanistic insights into their role in the modulation of synaptic transmission.
Optimization of Laser-Capture Microdissection for Isolation of Enteric Ganglia from Fresh-Frozen Human Tissue

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Introduction: Gastrointestinal and gut motility disorders affect one of every four people in the United States. The enteric nervous system (ENS), also referred to as the 'second brain,' is often at the center of these disorders, as it plays a crucial role in gut homeostasis and motility. Due to the limitations of current medications, we aim to obtain the full transcriptome of the adult ENS and identify molecules within the ENS that can be targeted pharmaceutically or utilized in stem cell therapies.

Methods: We have begun collecting samples of enteric ganglia from normal human intestinal tissue using laser-capture microdissection (LCM). We have optimized tissue preparation, staining, LCM, and RNA isolation in order to obtain RNA samples with sufficient quality and quantity for RNA-Seq.

Results: When flash-freezing intestinal tissue, flatten samples in large base molds and freeze atop of a 2-MB dry-ice slurry. Preparing sagittal intestinal sections in the plane of the myenteric plexus offers the largest payload of enteric ganglia. PEN-membrane slides offer the greatest speed and precision when collecting enteric ganglia with LCM. Ethanol-compatible dyes offer greater preservation of RNA integrity than aqueous dyes. The RNAeasy Micro kit offers superior RNA quantity and quality, while eliminating DNA contamination. Optimization of these factors offers the quickest workflow and yields exceptional RNA quality that has yielded successful results from RNA-Seq.

Discussion: The data generated using the approach outlined here is being used to develop a global gene atlas of human enteric ganglia. Generation of high-quality RNA is of upmost importance during this process. In conclusion, we have found that RNA with sufficient quality for RNA-Seq can be obtained from enteric ganglia collected from fresh-frozen human intestinal tissue, even when the tissue has a cold ischemic time of 24 hours. This method is poised to generate important findings in enteric neurobiology and gastrointestinal disorders.
Can an Automated Measure - Child Reciprocal Vocal Contingency - Predict Language Outcomes for Young Children with Autism Spectrum Disorder?

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Introduction: Child reciprocal vocal contingency (CRVC) is a new measure of a child's participation in reciprocal vocal interactions in natural settings[1]. Participating in reciprocal vocal interactions could facilitate speech and language development in children with autism spectrum disorder (ASD)[2]. Thus, evaluating correlations between CRVC and language development might inform CRVC's use as an early indicator of treatment response. Although concurrent convergent validity and stability of CRVC have been documented, CRVC's sensitivity to change, predictive convergent validity, and divergent validity have not been evaluated. We address four research questions: (1) Is the mean CRVC value greater than zero? (2) What is the sensitivity to change of CRVC across 12 months in a preverbal subgroup? (3) Does CRVC correlate with expressive vocabulary at four time points spanning 24 months? (4) As a test of divergent validity, is CRVC uncorrelated with problem solving?

Methods: Participants include 68 children with ASD aged 13 to 30 months at study entry. Using a specially designed computer program, we calculated CRVC from daylong vocal samples[3] at study initiation (Time 1) and 12 months later (Time 3). Using a three-event sequential analysis we calculated the operant contingency value, which provides a contingency index independent of chance sequencing [4,5]. The MacArthur-Bates Communicative Development Inventories[6] measured expressive vocabulary at study entry and 6, 12, and 24 months later (Times 1-4). The Early Problem Solving Indicator[7] quantified problem solving at study initiation and 12 months later.

Results: The mean CRVC value differed from zero at Time 1 (M=0.21, SD=0.070, p<.001, d=2.95) and Time 3 (M=0.23, SD=0.065, p<.001, d=3.59). Change in CRVC values across 12 months was small (n=27, M=0.031, SD=0.081, 95% CI [.002, .062], d=0.45, p=.06) for preverbal participants. Time 1 CRVC correlated significantly with expressive vocabulary at Times 2 and 4. CRVC at Time 3 did not correlate with expressive vocabulary concurrently, but did 6 months later (Time 4). As predicted, correlations between CRVC and problem solving were non-significant.

Discussion: Findings suggest continued development of CRVC is warranted, despite mixed results. Positive indicators of CRVC's potential clinical utility include sensitivity to change, correlation with expressive vocabulary but not problem solving at two time points, and derivation using computer analysis of acoustic events without human coding. The lack of correlation between CRVC and expressive vocabulary at some time points suggests that CRVC's utility may be restricted to a particular language level or time span. Pending further evaluation, CRVC may be a useful measure for identifying early response to treatment by signaling upcoming gains in speech-likeness of vocal communication and expressive language and for indicating when intervention changes are needed.

References:


Characterization of seizure activity and sleep-wake architecture in mGlu7 knockout mice by Electroencephalography (EEG)

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Introduction: Rett syndrome is a severe neurodevelopmental disorder caused by loss-of-function mutations in methyl-CpG-binding protein 2 (MeCP2), a transcription factor involved in brain function. There is no cure and very limited clinical treatments are available for this disorder. It has been shown that metabotropic glutamate receptors (mGlus) may serve as potential novel targets for the treatment of Rett syndrome. mGlu7, a specific type of class III mGlu receptor, is of particular interest, due to its important role in controlling neurotransmitter release and because it has been shown to be decreased in autopsy samples from Rett Syndrome patients. Potentiation of mGlu7 activity can rescue cognitive impairment, abnormal social interactions, and apneas in Rett Syndrome model mice, but it has yet to be tested whether mGlu7 potentiation can reduce seizure activity. mGlu7 knockout (KO) mice share similar phenotypes with Rett syndrome model mice, such as impairments in contextual fear and social interaction paradigms, along with limb clamping behavior and seizures. This project aims to characterize and compare seizures observed in mGlu7 KO mice with those present in mice lacking MeCP2 to better understand the brain areas involved and to potentially develop an mGlu7 PAM as a treatment for seizures in Rett syndrome. We describe a series of experiments to analyze seizure activity in mGlu7 KO mice, such as post-seizure quantification of immediate early gene expression along EEG studies study to analyze frequency rhythms and sleep-wake patterns. It is anticipated that this project will identify activation patterns in the brain that are sensitive to mGlu7 modulation, which may have value as a translational biomarker.
Spectrum Pathways Goal Attainment Program: Relationships between Identity and Self-Efficacy, Problem Solving, and Psychological Health

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Introduction: The overarching goal of this project is to increase health and wellbeing for young adults with autism spectrum disorder (ASD) through a community-based intervention focused on increasing self-determination with coaching support. There is an urgent need to prepare for the escalating number of individuals with ASD who are, and will continue to be, transitioning from high school into adulthood. Their outcomes in employment, education, and physical and mental health are highly inter-correlated, although autism identity and self-efficacy in relation to these outcomes have been understudied. As a group, these adults share challenges in core characteristics, yet they vary widely in specific challenges, capabilities, and skills making a one-size-fits-all approach to intervention difficult. The current intervention study addresses this difficulty with an individualized program to help adults select and attain their own goals.

Methods: In this repeated measures design, 16 adults with ASD (ages 18 - 35) are participating in a three-month program providing weekly peer telecoaching. Peer coaches receive training on neurodiversity, coaching skills and goal attainment interventions. Prior to the coaching sessions, all participants receive instruction on the process of goal attainment and goal progress tracking. Additionally, all participants wear actigraphy watches to measure sleep and activity and complete pre-intervention surveys measuring autism identity (ASIS), self-efficacy, problem-solving approaches, and physical and mental health. Some participants also receive an immersive program at a variety of community locations, one week prior to coaching, with curriculum on topics such as self-determination, self-advocacy, and stress reduction. Pre-intervention measures are repeated at the end of the study.

Results: Collection of end of study measures is in progress, so data presented here are pre-intervention. As predicted, autism identity, self-efficacy, and anxiety were interrelated. Scores on the ASIS Positive Difference, Changeability and Spectrum Abilities domains correlated positively with self-efficacy ($r = .530$, $p = .035$; $r = .774$, $p < .001$; $r = .655$, $p = .006$, respectively). Positive Difference and Spectrum Abilities also positively related to the Hope Scale Pathways domain which measures problem-solving style ($r = .574$, $p = .020$; $r = .712$, $p = .002$, respectively). Positive Difference, Spectrum Abilities, and Changeability were negatively correlated with anxiety, ($r = .569$, $p = .021$; $r = .524$, $p = .037$; $r = .563$, $p = .023$, respectively). Additionally, Changeability related negatively to depression ($r = .533$, $p = .034$).

Discussion: These pre-intervention measures demonstrate interrelationships between autism identity and mental health found in previous literature and add self-efficacy and problem-solving to the list of factors relating to autism identity and psychological health. Self-efficacy and problem-solving may be critical factors for successful employment. Future research in this program will examine the effect of the Spectrum Pathways Program on physical and mental health, self-efficacy, autism identity, and problem-solving.
Statewide Implementation of an Experiential Training Paradigm to Support Educators through In-Person and Teleconferenced Training, Coaching, and Mentorship

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Introduction: Federal legislation calls for educators serving students with autism spectrum disorder (ASD) to use evidence-based practices (EBPs). Feedback from educators indicates that correctly identifying and realistically implementing EBPs has become increasingly challenging for educators in recent years. In addition to this, the amount of pre-service information educators receive regarding EBPs and ASD varies greatly by program focus and the time period when they received their degree. Therefore, preparation and training in EBPs for educators is a pressing national need. Vanderbilt Kennedy Center’s Treatment and Research Institute for Autism Spectrum Disorders (TRIAD) ‘Foundations of Autism Workshop’ focuses on the characteristics of ASD and its impact on learning, an introduction to Applied Behavior Analysis (ABA) and EBPs for teaching students with ASD, and strategies to most feasibly and successfully implement EBPs in optimizing learning for all students.

Methods: TRIAD uses a unique three step training paradigm. Educators would attend a 3-day workshop in teams of 2. There, they would participate in large group instruction, modeling, and discussion; small group application and role play activities; demonstration and hands on-practice with students with ASD; planning and coaching with TRIAD Educational Consultants; and individualized goals and action plans. They would then have three hour in person classroom visit by a TRIAD Education Consultant, followed by up to 1 hour of consultation and coaching sessions provided through a teleconference platform by a TRIAD Educational Consultant monthly for the remainder of the school year provided.

Results: An increase in correct responding was noted across 91% of questions (10/11) and a statistically significant increase (p<0.05) was noted for 64% of the questions (7/11). Reported implementation frequency 2 months post-workshop for all strategies were at least weekly or daily.

Discussion: Data indicate this training paradigm results in increased knowledge of evidence-based practices (EBP’s) for educating students with ASD, high reported frequency of implementation, and observed moderate levels of fidelity of implementation shortly following the live workshop. This structure was seen as socially valid by participants regarding feasibility and utility of implementing these strategies in an academic setting. These data are of great value in developing the most effective and efficient forms of professional development to support the critical need for educator training in the provision of EBPs in working with students with ASD. The goal of this paradigm is two-fold: to assist participating school districts statewide in moving towards more inclusive and evidence-based practices and to develop nationally replicable models of high-quality educator professional development. These goals are rooted in an effort to advance policies and practices educating students with neurodevelopmental disabilities.
Cognitive-enhancing effects in PTHS mice. Excitingly, in addition to our results in a rodent model of PTHS, M4 potentiation has also shown efficacy in models of other neurodevelopmental disorders, such as Rett syndrome and Fragile X syndrome, where it has recently been shown that enhancement of M4 receptor signaling can normalize cognitive phenotypes. These data suggest that regulation of M4 signaling in the hippocampus is important for cognitive function in multiple neurodevelopmental disorders. The current study aims to validate potentiation of M4 receptor signaling as a therapeutic strategy for the treatment of PTHS.

**Methods:** Mice Heterozygous male B6;129-Tcf4tm1Zhu/J mice were purchased (The Jackson Laboratory, stock #013598) and bred with female B6129SF1/J mice (stock #101043) to produce Tcf4+/− and WT littermates. Male and female mice aged 7-12 weeks were used for all studies. Experiments were performed with Institutional Animal Care and Use Committee (IACUC)-approved protocols and conducted in full compliance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). Whole Body Plethysmography Mice were placed in a WBP recording chamber (Buxco, two-site system) with a continuous inflow of air (1 liter/min). After a habituation period of 30 min, a baseline recording was established for 30 min. VU0467154 (VU154) treated animals were injected before a 1 hour acclimation period then a 30 min recording was taken. Analysis was performed using FinePointe Research Suite (version 2.3.1.9). Visual Pairwise Discrimination Touchscreen Task Tcf4+/− and WT mice were food deprived to decrease body weight to 85-90% free feeding weight before training to nosepeck stimuli on a touchscreen. A mask was present in front of the screen providing two boxes for stimulus presentation. Once mice completed pretraining, they moved to the pairwise visual discrimination task in which two images were presented (star, S- and marbles, S+) and a liquid reward (30μl 33% ensure) was given for correct (S+) responses. Open Field Mice were injected i.p. with vehicle (10% Tween 80), 0.3 or 1mg/kg VU154 solubilized in vehicle solution. 60 minutes later, locomotor activity was examined for 60 minutes using the infrared photobeam Med Associates system. Conditioned Freeze Mice were injected i.p. with vehicle (10% Tween 80) or 1mg/kg VU154. 60 minutes later, mice were placed in a fear conditioning chamber (Med Associates Inc.) with a vanilla scent. After a 2 minute habituation period, an 80dB auditory cue was played for 30 seconds and co-terminated with a 1 second, 0.75mA foot shock. 24 hours later, mice were placed back in the same chambers with vanilla scent for contextual testing and freezing was quantified using Med Associates software. More than one hour later, cued testing was performed. Mice were placed in boxes with wall inserts to change the shape and color of the box. This test was run under infrared light with an almond scent in the chamber. After a 2 minute habituation, a 60 second auditory tone was played and freezing was quantified. Novel Object Recognition On day 1, mice were habituated to the testing box for 10 minutes. The next day, mice were injected with either vehicle or 1mg/kg VU154. 60 minutes later, mice were trained with two identical objects (orange or lego box) in the arena for 10 minutes. 3 hours later, mice were placed in the same arena with one of each object and recorded for 10 minutes. A blinded investigator scored interactions and data was analyzed in Prism. Expression Studies: Brains were dissected from 2 month old mice and the cerebellum was sub-dissected. Tissue was homogenized in Trizol and RNA was extracted using chloroform, precipitated with isopropanol and washed with ethanol. RNA was then treated with Dnase and processed with Rneasy plus, QIAGEN. Tagman qRT-PCR primers and primers were used to quantify Hprt and Chrmd transcripts. Kennedy et al. 2016: For RNA sequencing, the hippocampus was extracted from 2-month-old mice (four animals per genotype) and the CA1 region was dissected. Total mRNA was extracted (Rneasy, QIAIEN), quality controlled (Bioanalyzer, Agilent), and poly(A) selected and sequenced (HudsonAlpha) on the Illumina platform (HiSeq v.4, paired end, 50 bp, 50 million reads). Statistics Statistical analyses were performed with two-way ANOVA, followed by Tukey's post hoc analyses, or unpaired Student's t test using GraphPad Prism v.6. All data are represented as mean ± SEM. Statistical significance was set at p < 0.05.

**Results:** Figure 1. Gross Brain Weight - Tcf4+/− mice (N=8) have significantly decreased brain weight relative to littermate controls (N=9). Brain weight was normalized to body weight. Micro computed tomography is performed in some PTHS patients, and this symptom is recapitulated in our mouse model. Mice were 20 ± 1 weeks old at time of sacrifice. An unpaired, parametric t-test was used to determine significance (p<0.01). Figure 2. Whole Body Plethysmography - A) Tcf4+/− mice show a significantly increased respiratory rate compared to WT littermates when assessed by whole body plethysmography (p<0.016). B) PTHS model mice have a significantly decreased end expiratory pause, the pause after exhale and before inhale, consistent with the increase in overall breath rate. An unpaired, parametric t-test was used to determine significance (p<0.01). Figure 3. Visual Pairwise Discrimination - Tcf4+/− and WT mice show similar accuracy in a pairwise discrimination touchscreen task, suggesting corticostriatal cognition is not significantly affected in our PTHS model. Figure 4. mRNA Quantification - A) Tcf4+/− mice have significantly fewer Tcf4 RNA transcripts in the cerebellum, verifying the relative amount of Tcf4 expression in PTHS model mice (p=0.037). B) PTHS model mice have significantly increased Chrmd transcripts in the CA1 area of the hippocampus (p<0.01). Figure 6. Fear Conditioning Assay - A) Tcf4+/− mice show a significant deficit in cued fear conditioning 24 hours after training (p<0.04), and this deficit is rescued by administration of the M4 positive allosteric modulator VU0467154 (VU154) prior to training (p<0.04). B) Although Tcf4+/− mice do not show significant differences from WT littermates in contextual fear conditioning, treatment with VU0467154 significantly enhanced performance of both Tcf4+/− and WT (p<0.0001) mice when given before the training session. Figure 8. Open Field Assay - Tcf4+/− mice are hyperlocomotor compared to WT mice (p<0.01), and this locomotor activity is normalized as a result of 1mg/kg VU0467154 (p<0.0001) as well as 0.3mg/kg VU04671541 (p<0.001). Figure 9. Whole Body Plethysmography - VU0467154 treatment normalizes the increased breathing frequency of Tcf4+/− mice (p<0.01).

**Discussion:** VU0467154 (VU154), the positive allosteric modulator (PAM) of the M4 receptor, normalizes the cognitive, locomotor and respiratory phenotypes of our PTHS mouse model which suggests the M4 receptor could represent a novel target for this disorder. Future studies will determine effects of VU154 in additional cognitive assays as well as the social domain of PTHS.

**References:**

Characterization of afferents to the orbitofrontal cortex in the rat

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Introduction: The prefrontal cortex is often defined as the cortical area receiving a mediodorsal thalamic (MD) innervation, although subsequent definitions emphasized overlapping inputs from several areas. In the frontal lobe of the rat, there are two spatially distinct areas innervated by the MD: the medial prefrontal cortex (mPFC), which has been intensely studied over the past century, and a ventrolateral territory, the orbitofrontal cortex (OFC), which has received relatively little attention. Both the mPFC and the OFC are comprised of several distinct cytoarchitectonic regions, some of which receive a dopamine innervation.

Methods: Using retrograde and anterograde tract tracing methods, we examined the sources of afferents to different areas of the OFC, with a particular focus on the dorsal agranular insular cortex, ventral part (Ald2), which receives a dopamine innervation from the midbrain.

Results: The dopamine innervation of the OFC, as visualized by immunohistochemistry for tyrosine hydroxylase (TH), streams from the ventrolateral border of the forceps to the pial surface, fanning out from a narrow band in the deep layers of Ald2 to a broader area in superficial layers, invading, but not filling, lateral OFC medially and dorsal agranular insular cortex, dorsal part (Ald1) laterally. There were several differences in afferents to different OFC regions. OFC projections originating in the thalamus, amygdala, or midbrain did not collateralize to innervate both the mPFC and OFC. Anterograde studies revealed that the amygdala, mediodorsal thalamus, and ventral midbrain dopamine inputs to the OFC were largely spatially segregated, but were all present within Ald2.

Discussion: The concentration of dopamine in the OFC appears comparable to that of the mPFC. However, the density of the dopamine innervation, visualized by tyrosine hydroxylase immunohistochemistry, appears considerably lower in the OFC than the mPFC. Our analysis, however, was not based on phosphorylation-state specific tyrosine hydroxylase staining, which can impact dopamine synthesis and may help resolve this discrepancy. The afferents to the OFC arise from a large number of cortical and subcortical sites. There were several notable differences in nuclei that innervated the dopamine-innervated OFC (Ald2) compared to other orbitofrontal regions. Among these are afferents to Ald2 originating in the auditory cortex and globus pallidus, which did not innervate other areas within the OFC to the same extent. Within the OFC, Ald2 is the only area that receives projections from the thalamus, amygdala, and dopaminergic midbrain, suggesting that it may be defined as prefrontal area based on convergent afferents, despite the fact that these inputs do not directly overlap. These findings highlight the heterogeneity of the OFC, and suggest possible functional attributes of Ald2 and other OFC areas.
Autonomic nervous system dysregulation during social interaction in children with autism spectrum disorder

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Introduction: Children with ASD often show difficulties in social interaction, as well as high rates of anxiety and depression. The autonomic nervous system (ANS) may be crucial in shaping behavior, including social engagement and emotion regulation. Noninvasive cardiac measures of autonomic regulation, including respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP), serve as indicators of parasympathetic and sympathetic arousal, respectively. These measures may be useful in examining ANS dysregulation in children with ASD and its possible negative effects on social behavior and emotion regulation.

Methods: The study investigated children with ASD and typical development (TD). The sample currently includes 13 children with ASD and 4 children with TD; however, data collection is ongoing. All children participated in a modified version of the Trier Social Stress Test (TSST), the TSST-Friendly. The TSST-F involves a conversation with a friendly, engaged peer. RSA and PEP were collected at baseline and throughout the social interaction. Parents reported on child’s anxiety, while children self-reported symptoms of anxiety and depression. Between-group analyses to assess differences in RSA and PEP between children with ASD and TD, as well as within group correlations between physiological response and internalizing symptoms, were conducted.

Results: Findings suggest the TSST-F produces a change in arousal from baseline in the ASD group. Paired sample t-tests show a significant difference between RSA during the interaction and RSA at baseline (t(12) = 2.70, p = 0.02). Early comparisons of 4 age- and gender-matched children with ASD and TD did not show group differences in either RSA or PEP at any time point (p > 0.05); however, results may change with a larger and more representative sample. Additionally, blunted RSA response in the ASD group was associated with more self-reported anxiety (r = 0.74, p = 0.004), and a larger decrease in PEP (more sympathetic activation) was correlated with greater parent-reported anxiety (r = -0.58, p = 0.05).

Discussion: Dysregulated physiological arousal has been associated with risk for psychiatric comorbidities, which is further supported by the findings that a maladaptive blunted parasympathetic response, along with an increased sympathetic response, were both related to more anxiety in these children with ASD. Ongoing analyses of an expanded sample of children with ASD and TD may reveal whether the children with ASD show an atypical physiological response, which may provide insight into the complex relationship between social communication, physiological stress, and internalizing symptoms in individuals with ASD.
Quantitative Measurement of Social Motivation in Adults with Autism Spectrum Disorder using Electroencephalogram

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Introduction: The Social Motivation Theory of Autism suggests that the social-specific reward deficits in Autism Spectrum Disorder (ASD) result from a lack of motivation toward social information. While this theory has been influential in studying ASD-specific social deficits, few measures have been developed to directly quantify social motivation or salience network activity in response to social information. A previous study from our lab demonstrated that individuals with ASD showed a preference for non-social objects over social images in a paired-preference picture viewing task using eye-tracking techniques. The same study showed differences in arousal as measured by pupil dilation in response to social and non-social images. These results suggest that in ASD, social information processing deficits may be context-dependent, rather than a fixed core feature of the disorder. In this model, social inattention may occur as a secondary byproduct of a positive attention bias to nonsocial information. To test this model, electroencephalogram (EEG) can be used to study the correlates of motivation and attention in the form of brain responses. We have developed a novel task that incorporates viewing social and non-social images with EEG to quantify brain responses with differential saliency for and arousal to social and nonsocial stimuli.

Methods: The late positive potential (LPP) is an event related potential (ERP) that indexes motivational salience. The LPP is modulated by the affective content of a stimulus, showing larger responses to positive and negative information, compared to neutral. Joint ERP-fMRI suggest the neural generators of the LPP are regions relevant primarily for anticipatory aspects of reward, including the left orbitofrontal cortex, bilateral amygdala, and insular cortex. Previous studies have also used EEG microstates as a proxy for salience network activity. The purpose of the current study was to measure the salience network activity in response to social and non-social information in the form of LPP as well as EEG microstates in individuals with ASD. Briefly, two groups of adults - ASD and a typical group (TD) - between the ages of 18 and 35 were recruited and matched on gender and IQ. The study employed a passive viewing task, comprised 60 static, high quality color images from three stimulus categories: social (SOC), high autism interest (HAI) and neutral (NEU). Continuous EEG was collected from these participants while viewing the images and analyzed for attention and motivation in the form of LPP and EEG microstates.

Results: Preliminary analyses reveal differences in LPP between the ASD and TD group in response to HAI and SOC images. We will present the results of more detailed analyses, including microstates analyses, and discuss whether specific patterns of spontaneous EEG activity may serve as a biomarker associated with ASD.
Introduction: Socioeconomic status (SES), which includes household income and parental educational and occupational status, predicts children’s academic outcome and cognitive abilities [1]. In addition to SES, home and school literacy environments (together as LE) also shape the trajectory of children’s academic success [2,3]. One way that SES disparity may influence children’s cognitive and academic trajectory is through cortical development [4]. Whether the LE-cognition relationship is linked to brain structural development and whether it is independent from SES remain unknown. Furthermore, LE may not, however, follow a linear relationship with SES, as studies highlight significant variation of LE within lower-income households2. These environmental differences contribute to variability in children’s academic achievement within this lower-income group. As such, LE may differentially influence cortical development in across and between SES groups.

Methods: During the summer following first grade, 102 children completed cognitive assessments for intelligence and reading- and language-related skills and underwent T1-weighted MR imaging. Participants’ parents completed questionnaires regarding their child’s SES (Hollingshead’s Four-Factor Index of Social Status) [5] and LE (e.g., if the child was taught with phonics instruction, how often s/he was read to, or if s/he received tutoring). Children’s cortical structure was reconstructed through an integrated FreeSurfer and MATLAB pipeline. To capture the unique relationship between cortical thickness and LE, multiple regression analyses were applied for within-group (i.e., SES as a continuous distribution) and between-group differences (i.e., higher- v. lower-SES), after controlling for possible confounding factors (e.g., gender, intelligence, and reading ability).

Results: Neither SES or LE was uniquely related to cortical thickness within the whole cohort. However, when the group was divided into low- versus high-SES, LE was linked to cortical differences in children in the lower-SES group. LE was especially linked to frontal regions, which support executive function, and language processing in lower-SES children.

Discussion: Together, these findings highlight the relationship between LE and cortical development in lower-SES children in areas that support reading- and language-related skills and executive functioning. Findings have important implications for informing early home- and school-based literacy practices especially in lower-SES populations.

References:
Audiovisual stimulus correlation drives multisensory perceptual decisions via changes in evidence accumulation

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Faculty Advisor: Wallace, Mark

Introduction: Sensory signals originating from the same event, such as the vocal signals and mouth movements of a speaker, are often temporally correlated. It is hypothesized that the brain evaluates these correlations to facilitate integration and binding across the different sensory modalities. Previous studies have shown that temporal correlation across different sensory modalities can facilitate behavior, whereas uncorrelated signals do not. In the current study, we sought to further illuminate the nature of this relationship, hypothesizing that multisensory behavior will vary not only with the presence of absence of correlation, but also with its strength.

Methods: To this end, we presented participants with sinusoidally amplitude modulated auditory and visual stimuli at modulation depth thresholds. Participants were asked to report the presence or absence of modulation in the stimulus. On a given trial, modulation could be present in auditory, visual, both, or neither modality. Modulation frequency and phase of visual stimuli remained constant while those of auditory stimuli were varied to generate stimulus pairs with a range of temporal correlations.

Results: After accounting for individualized phase shifts which could represent relative temporal processing abilities of the auditory and visual systems, stimulus pairs with higher temporal correlation bestowed better discrimination in all participants. Accuracy and reaction time data were fit to a diffusion model where drift rate was constrained by stimulus correlation given a phase shift. The model searched for each participant’s optimal phase shift parameter. The phase shift that was returned by the model corresponded well to phase shifts measured in discriminability data. The model showed that multisensory behavior is well predicted by a diffusion process in line with theories of decision making.

Discussion: These results suggest that the brain may compute temporal correlations and that the results of such computations is supplied to the decisional system as sensory evidence. Further, they suggest that the strength of the evidence depends on the strength of the correlation.
**Increased Neural Strength and Reliability to Audiovisual Stimuli at the Boundary of Peri-Personal Space**

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**Faculty Advisor:** Wallace, Mark

**Introduction:** The actionable space surrounding the body, referred to as peripersonal space (PPS), has been the subject of significant interest of late within the broader framework of embodied cognition. Neurophysiological and neuroimaging studies have shown the representation of PPS to be built from multisensory neurons within a fronto-parietal network, and whose activity is modulated by the presence of stimuli in close proximity to the body. An area of inquiry that has nonetheless received little to no attention relates to the global characterization of neural dynamics associated with the representation of PPS. Further, although PPS is encoded by multisensory neurons, to date there has been no EEG characterization of the transition of unisensory as well as multisensory stimuli from within to beyond PPS. Similarly, it remains poorly understood whether the PPS constitutes a privileged zone of multisensory integration beyond its association with the tactile modality and the de facto role of the spatial principle of multisensory integration in PPS encoding.

**Methods:** In the current study, to examine the neural dynamics of multisensory processing within and beyond the PPS, we present auditory, visual, and audio-visual stimuli both within and beyond a participant's reaching limit while recording continuous high-density EEG.

**Results:** Results demonstrate a significant increase of global field power (GFP; i.e., overall strength of response across the entire electrode montage) near the PPS boundary - an increase that is largest under multisensory conditions. Source localization of the major contributors to this GFP difference point to neural generators in the intraparietal sulcus (IPS) and insular cortex, a major hub for visuo- and audio-tactile PPS neurons. Furthermore, when neural dynamics are examined in more detail, changes in the reliability of evoked potentials localized to the IPS are predictive on a subject-by-subject basis of the later changes in GFP amplitude linked to stimulus proximity to the PPS boundary.

**Discussion:** Together, these results provide a previously unrealized view into the neural dynamics and temporal code associated with the encoding of non-tactile multisensory stimuli within the PPS.
A Pilot Model for Increasing Access to Services: Embedding ASD Diagnosis within the Medical Home

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Introduction: Early accurate diagnosis of Autism Spectrum Disorder (ASD) currently represents a challenging public health and clinical practice issue. Despite the wide-scale availability of effective screening tools for young children, waits for diagnostic assessment are still often quite lengthy and impede access of appropriate early intervention services. Embedded processes for effective triage and diagnosis of children at-risk for ASD within the medical home may be a viable mechanism for reducing age of detection and initiation of services.

Methods: We tested the impact of embedding a behavioral health provider within the primary care setting with an explicit focus on rapid ASD identification. We hypothesized that embedding a behavioral health provider with specific skills and training related to ASD diagnostic consultation could help accurately and rapidly identify many cases of ASD and potentially represent a more realistic model for advancing ASD identification particularly with reference to underserved populations. We developed explicit ASD diagnostic consultation and support clinics embedded across two Vanderbilt University Medical Center affiliated pediatric primary care programs. A psychologist was physically embedded in the clinic one day per week and available solely for providing follow-up for ASD-related concerns (e.g., failed screenings, diagnostic referrals, behavioral consultation). Data about referral types, show rates, and latency to consultation and diagnosis were used to assess feasibility and impact. Specific data regarding time, cost, and resources associated with implementation of the embedded service model were also collected via electronic medical records.

Results: The embedded psychologist saw over 200 children and adolescents over 14 months, 119 children were referred due to concerns for ASD. Of those children, 50 (42%) received formal diagnoses of ASD. It was possible to determine diagnostic clarity (i.e., ASD vs. no ASD) within the initial consult session for 59% of the children; further testing was required for the remaining children. The latency to evaluation and diagnosis for referred children was less than two months, compared with a minimum of 6-7 months for specialty clinic assessment. Similarly, the median age at diagnosis (32 months) was considerably lower than the national average of approximately 50 months. This study extends support for the value of embedding behavioral health services for children with ASD within pediatric primary care settings.

Discussion: This study extends support for the value of embedding behavioral health services for children with ASD within pediatric primary care settings.
Investigating moderators of working memory performance for struggling readers in elementary grades

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Faculty Advisor: Fuchs, Douglas

Introduction: For this study, I conducted moderator analyses on the working memory (WM) performance of students in 3rd and 4th grades who received one of three interventions: either a reading comprehension (RC) intervention with or without 'domain-specific' embedded WM activities or a 'domain-general' WM intervention without RC components. Overall, no students assigned to one of the treatment groups significantly outperformed their counterparts in the control group on three WM measures that were collapsed into a single factor score (Hedges' g = -0.17-0.33). However, this investigation sought to provide a more nuanced interpretation of these findings by identifying which, if any, of the student characteristics under consideration may have provided a differential impact on the interventions' effects on WM performance.

Methods: The analyses were conducted on data collected as part of the ongoing Accelerating Academic Achievement research center. Two cohorts of students from 2014-16, consisting of 198 students from 85 classrooms in 19 Nashville public schools, were included. All participating students were screened in the fall of their participating year on multiple measures of word reading, nonword reading, listening comprehension, and IQ. Students meeting the eligibility criteria were randomly assigned within schools to one of four groups: RC alone, RC+WM, WM alone, and business-as-usual Control. Students assigned to one of the three treatment groups received 42 25-minute sessions of 1:1 intervention three times per week for 14 weeks.

Results: The interaction between pretest short-term memory (STM) and WM group membership for 4th graders was significant (b = -.392, SEb = .046, p = .046), suggesting that students in 4th grade with relatively higher pretest STM who received WM tutoring performed worse on WM at posttest. Simple slopes for the association between posttest WM and treatment status were tested for low (factor score of -2.0), average (0), and high (2.0) levels of pretest STM. The region of significance for the cross-level interaction includes STM factor scores of 0.82 and above.

Discussion: While this investigation yielded a significant interaction, the results should be interpreted cautiously. Performance on WM and STM tasks tends to be highly positively correlated, so it seems surprising to find a negative interaction between relatively high pretest STM and the completion of 14 weeks of WM training among 4th grade students in this sample. This interaction was not found at grade 3, which had roughly 2.5 times the number of students as did grade 4, rendering the finding potentially spurious. However, the finding may also be attributable to other factors, such as test fatigue (given the large batteries of tests administered) or regression to the mean.
Direct interaction between ASD-linked proteins Shank3 and CaMKII

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Introduction: Shank3 is a postsynaptic scaffolding protein that is important for organizing neurotransmitter receptor signaling complexes at excitatory synapses. Mutations or deletions in the SHANK3 gene are associated with neuropsychiatric disorders, such as autism spectrum disorder (ASD). Shank3 contains several protein-protein interaction domains that link postsynaptic receptors to downstream signaling proteins and the actin cytoskeleton. Calcium/calmodulin-dependent protein kinase II (CaMKII) is a signaling protein that is activated by calcium influx through postsynaptic receptors, and recent proteomics data from our lab found that Shank3 is abundant in CaMKII immune complexes. Therefore, we hypothesized that CaMKII can directly bind to Shank3.

Methods: Immunoprecipitation assays were performed with a GFP antibody from HEK293 cells co-expressing GFP-Shank3 and CaMKII. GST-Shank3 fragments spanning the entire Shank3 protein were incubated with purified CaMKII for GST pull-down assays. Primary hippocampal neurons were generated from embryonic rat brains. Neurons were transfected at DIV 8 and assayed at DIV 13.

Results: We identified a novel direct interaction between Shank3 and CaMKII. Shank3 associates with CaMKII immune complexes isolated from synaptic fractions of mouse forebrain and from co-transfected heterologous cells. Activated, T286 phosphorylated CaMKII can directly interact with a GST fusion protein containing residues 829-1130 of Shank3, and mutation of residues 949-951 (RRK) to alanine essentially abolishes binding in vitro and in heterologous cells. We also found that knockdown of Shank3 in primary hippocampal neurons significantly disrupts CaMKII-dependent CREB phosphorylation in the nucleus.

Discussion: The interaction of Shank3 with CaMKII may play an important role in functionally regulating Shank3. Ongoing studies are examining the impact of CaMKII on Shank3 localization in neurons, scaffolding interactions with other synaptic proteins, and on synaptic signaling to the nucleus.
Alterations in Arginine and Cholesterol Metabolism are rescued with Manganese exposure in a Mouse Model of Huntington’s Disease

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Faculty Advisor: Bowman, Aaron

Introduction: The molecular mechanisms by which mutant Huntingtin (HTT) results in neurodegeneration of striatal medium spiny neurons and the development of Huntington’s disease (HD) remains unclear. There is recent evidence that alterations in arginine and cholesterol metabolism are present in the brain of HD patients. There is also disrupted manganese (Mn) transport and aberrant Mn-dependent biology in the striatum of multiple HD mouse models. Therefore, we investigated the potential for Mn to correct alterations in these metabolic pathways.

Methods: We utilized WT and HD (FVB-YAC128 (FVB-128); C57BL6-YAC128(C57-128)) male and female mice at 12- and 52-weeks of age, exposed to subcutaneous injections of 13.88 mg/kg Mn or vehicle on day 0, 3, and 6 of a 7-day exposure. Animals were weighed prior to each injection. Animals were sacrificed on day 7 (at 13 weeks of age) and the striatum removed, flash frozen in liquid nitrogen and stored at -80°C. One half of the striatum was used to measure the urea cycle metabolites citrulline, ornithine, and arginine with Mass Spectrometry. The other half of the striatum was used to measure cholesterol precursors and total cholesterol including: Lanosterol (LAN), Desmosterol (DES), 7-dehydrocholesterol (7DHC) and 8-dehydrocholesterol (8DHC) with HPLC.

Results: Both HD mouse models have significantly increased body weight compared to WT mice. In C57-128 mice, Mn exposure reduces the elevation in body weight associated with HD while it has no effect on weight in WT animals. FVB-128 mice have a 1.7-fold increase in arginine, 3.7-fold increase in citrulline, and 3.2-fold increase in ornithine in the striatum compared to WT mice (p<0.05). After Mn exposure, the observed elevation in metabolites in FVB-128 were returned to WT levels. Secondly, cholesterol metabolism is selectively altered in the striatum of young and aged HD mice -with no changes observed in the cortex or cerebellum. Young HD mice had approximately 30% greater striatal cholesterol compared to WT; however, aged HD mice have reduced cholesterol levels compared to WT. HD mice also have significantly altered levels of cholesterol precursors including LAN, DES, 7DHC and 8DHC (p<0.05). Mn exposure significantly modifies the relationship between striatal LAN and HD. Alterations in LAN in HD are modified by Mn exposure.

Discussion: These findings provide support for the critical role of Mn-dependent biology in HD pathophysiology. More specifically, the possibility that Mn exposure and Mn-dependent biology may correct known metabolic deficits in the urea cycle and cholesterol synthesis in HD has direct clinical therapeutic implications.
Assessing the Differential Effects of Known and Mystery Rewards in a Preschool-based Group Contingency

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Faculty Advisor: Barton, Erin  

Introduction: Group contingencies are behavioral contracts applied to whole groups. They require all group members to work toward a common criterion-through emitting pre-determined behaviors-and receive a common reward once criterion is met. Group contingencies have been used successfully to modify a variety of behaviors for children with diverse characteristics across multiple settings (Little et al., 2015). However, these interventions have not been applied specifically to increase appropriate social interactions between typically-developing children and those with multiple or severe disabilities (MSD). Further, little research has been conducted to examine if differential outcomes are associated with the type of reward used (known or mystery). While these reward types operate on different principles of reinforcement, they appear equally successful in motivating behavior change within the context of a group contingency (Pokorski, Barton, & Ledford, 2016). For this reason, further exploration into the comparative effects of each is warranted.

Methods: The study was conducted across two inclusive preschool classrooms using a single case research design (i.e., alternating treatments design with a control condition) designed to meet contemporary research standards (Kratochwill et al., 2013). Study participants included typically-developing children (i.e., target children) and children with MSD. The primary dependent variable was appropriate social interactions; challenging behavior was measured as a secondary variable. Data were collected via video and sessions were coded using timed event sampling. Interobserver agreement and procedural fidelity were assessed for at least 30% of sessions across participants, conditions, and dependent variables; means of each exceeded standards.

Results: Data indicate that both reward types produced substantial improvements when compared to no reward, but that neither reward type was notably more efficient or effective in altering the behavior of participants. No changes were demonstrated for children with MSD, nor were any changes in levels of challenging behavior identified for any children.

Discussion: This research is significant for two reasons. First, it represents a methodically rigorous evaluation of the effects of an independent group contingency focused on increasing social skills in a preschool setting, which the literature shows is wanting. Second, no studies to date have directly compared the effects of both reward types on behavior within the context of a single experimental intervention, which might have important implications on behavior. The results of this study provide insight into the effectiveness of various reward types on increasing the social skills of preschool children specifically towards children with MSD, which can be used to guide practice and research for this population.

References:


Neurocognitive mechanisms of digit processing and their relationship with mathematics competence

Author: Pollack, Courtney
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Faculty Advisor: Price, Gavin

Introduction: The dominant neural model of number processing suggests a specific region in the inferior temporal gyrus (ITG) that supports processing digits as visual symbols (1). Yet, prior research has shown evidence both for (2) and against (3) digit related ITG activity, and inconsistent laterality (2, 4). Further, it is unknown whether brain activity related to processing digits as visual symbols predicts mathematical competence. The current study investigated these two issues through a functional magnetic resonance imaging (fMRI) study of digit and letter processing in typically developing adults.

Methods: Thirty-two adults completed a one-hour scanning session during which they performed digit and letter detection tasks. During digit detection, participants viewed symbol strings and determined whether digits were present (e.g., AH3NR) or absent (e.g., AHTNR). Similarly, during letter detection, participants determined whether letters were either present (e.g., 93R78) or absent (e.g., 93478). After scanning, participants completed mathematics and reading subtests of the Woodcock-Johnson III. To analyze the data, we first conducted a whole brain random effects analysis with first level contrasts (voxelwise p < .005 uncorrected, clusterwise p < .05 corrected). Second, we correlated digit related activity separately with calculation skills and with word reading skills, at the whole brain level.

Results: Our first analysis revealed four clusters in frontal, occipital, and temporal regions associated with digit detection, including a cluster in the left ITG. There were five clusters of activation in frontal, parietal, occipital, and temporal regions associated with letter detection, including a cluster in left ITG. Digit and letter related ITG activity appeared to be non-overlapping. However, a direct contrast of digit and letter processing did not reveal a cluster in the left ITG region that was more active for digit detection than letter detection. These analyses suggest the existence of a left ITG region with activity preferential for, but not specific to, digits. Whole brain correlations showed that greater digit related activity in the right ITG was associated with higher calculation skills. In contrast, there was no correlation between letter activity and calculation skills.

Discussion: Results suggest that a region of the left ITG supports processing digits as visual symbols. Moreover, results provide first evidence of a positive relationship between calculation skills and digit processing as visual symbols in the right ITG, a region recently identified as supporting digit processing (4). Taken together, these results illuminate the neurocognitive mechanisms that support digit processing independent of semantic processing, and show this processing is related to mathematics competence.

References:


Respiratory sinus arrhythmia and developmental stuttering

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Introduction: Developmental stuttering is a speech disorder that typically begins in early childhood at approximately age three and is characterized by syllable and word repetitions and prolongations (Yairi & Ambrose, 2013). Despite a growing empirical knowledge base on factors that contribute to the development of stuttering, there is a need for a greater understanding of the exacerbating factors of childhood stuttering. One theoretical account of childhood stuttering suggests that emotional reactivity and emotion regulation are associated with the onset and the development of childhood stuttering (Walden & Conture et al., 2012). Respiratory sinus arrhythmia (RSA) has been used in both biological and psychological studies in children, and can be used as an index of emotion regulation (Porges, 2007). By using physiological correlates of autonomic processes, measures of RSA can provide information about internal temperamental and emotional states that can be difficult to assess exclusively via observation. The purpose of this study is to investigate potential early differences in respiratory sinus arrhythmia between preschool-age children who stutter and persist (CWSP), children who stutter and recover (CWSR), and children who do not stutter (CWNS).

Methods: Participants were 10 preschool-age children who stutter and persist (CWSP), 20 preschool-age children who stutter and recover (CWSR), and 36 children who do not stutter (CWNS). Participants were exposed to two emotion inducing video clips (negative and positive) with neutral clips used to establish pre- and post-arousal baselines. Video clips and baselines were followed by age-appropriate speaking tasks. Respiratory sinus arrhythmia (RSA), used as an index of parasympathetic activity, was measured while participants watched the video clips and performed the speaking task. Participants completed 3 to 5 visits over the course of 24 to 32 months.

Results: Preliminary results indicate that preschool-age children who stutter and persist exhibit higher RSA during the neutral speaking task, possibly indicating lack on engagement in the task. Contrary to predictions, no differences in baseline RSA were seen between the groups. Final results are in preparation.

Discussion: Findings will be taken to assess the role of emotion regulation, indexed physiologically by RSA, in the developmental trajectory of childhood stuttering.

References:


Using Aided Augmentative and Alternative Communication (AAC) Modeling During Small Group Instruction for Young Children with Down Syndrome

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Introduction: Few studies have adapted empirically supported language and communication interventions to address the behavioral phenotype of children with Down syndrome (DS; Abbeduto, McDuffie, Thurman & Kover, 2016; Lemons et al., 2015; McDaniel & Yoder, 2016). Designing interventions to mitigate the language and communication deficits associated with DS may be critically important for improving long-term communication development. Aided augmentative and alternative communication (AAC) modeling interventions are recommended for children with DS, because these interventions leverage the phenotypic strengths of children with DS such as receptive language and social skills while addressing their phenotypic weaknesses including limited speech intelligibility and verbal working memory (Abbeduto et al., 2016; Abbeduto, Warren, & Conners, 2007; Chapman, & Hesketh, 2000; Fidler, 2007; Kent & Vorperian, 2013; Kumin, 1994). The purpose of this study was to evaluate the efficacy of an aided AAC modeling intervention on the communication skills of preschool-aged children with DS during small group instruction.

Methods: Four preschoolers with DS between 3;1 and 5;3 years (Mean = 4;5) and five typically developing peers between 3;5 and 5;9 years (Mean = 4;3) participated in the small group instruction. A multiple probe across behaviors (target vocabulary) design replicated across four preschool aged-children with DS was used to evaluate the efficacy of an aided AAC modeling intervention. A systematic dialogic reading strategy called Read, Ask, Answer, Prompt (RAAP; Binger, Kent-Walsh, Ewing & Taylor, 2010) was applied during the baseline sessions to simulate typical dialogic reading routines in inclusive classrooms. During the intervention sessions, the interventionist used the RAAP strategy and provided aided AAC modeling. Child performance for all dependent variables including: (a) percentage of correctly identified symbols, (b) rate of symbolic communication, (c) number of different words, and (d) number of multiple word combinations were graphed and visually analyzed. Statistical analyses were conducted to complement visual analysis and to quantify the results of visual analysis across participants. Specifically, we calculated the non-overlap of all pairs (NAP; Parker & Vannest, 2009) to examine overlap between baseline and intervention phases and calculated the within-case standardized mean difference (WC-SMD) with a Hedge’s g small sample correction to provide an estimate of the magnitude of aided AAC modeling intervention effects, (Pustejovsky, 2015; Pustejovsky & Ferron, 2017)

Results: For all children with DS the percentage of correctly identified symbols and rate of symbolic communication increased following the aided AAC modeling intervention. We observed 13 out of 16 potential demonstrations of effect regarding the percentage of correctly identified symbols and 11 out of 16 potential demonstrations of effect regarding the rate of symbolic communication. Visual analysis suggested a functional relation between the intervention and the percentage of correctly identified symbols for three of four participants with DS. Visual analysis also revealed a functional relation between the intervention and the rate of symbolic communication for two of four participants with DS. Effects for number of different words and number of multiple word combinations varied for children with different expressive communication skills prior to treatment. Visual analysis revealed there was a functional relation between the aided AAC modeling intervention and number of different words for two of four participants with DS and a functional relation between the intervention and number of multiple word combinations for one participant with DS. Conducting non-overlap and mean-based estimates of effect size complemented the results of the visual analysis and revealed that the change from the baseline to the intervention phase was statically significant for percentage of correctly identified symbols and rate of symbolic communication across metrics (e.g., NAP and WC-SMD) for three of the four participants with DS. All children maintained their percentage of correctly identified symbols from the intervention sessions during the maintenance probes. Increases in rate of symbolic communication did not generalize to thematic play contexts, a distal measure of response generalization.

Discussion: The results of this study indicate that an aided AAC modeling intervention which includes RAAP, a systematic dialogic reading strategy, is an effective intervention to teach target vocabulary and increase rate of symbolic communication to young children with DS. During the baseline and intervention sessions typically developing peers used AAC to respond to questions and share comments about the story. Children with DS increased their percentage of correctly identified symbols, and rate of symbolic communication. For some participants, changes in number of different words and number of multiple word combinations were also observed. Replications of this intervention are needed to determine if these effects are robust for children with DS. Future research is needed to explore the application of similar interventions by typical classroom teachers and school-based speech-language pathologists within inclusive classroom settings.

References:
New Version available at: https://osf.io/pw2z4/
Impact of Prosocial Media on Children's Socio-Emotional Development

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Faculty Advisor: Troseth, Georgene

Introduction: Extensive research, including studies by Calvert and Bryant, has consistently supported that watching educational programming promotes improvements in education-related skills such as comprehension (Calvert, 2001) and problem solving in children (Bryant et al., 1999). However, there has been much less research into how educational, prosocial media affects young children's social and emotional development.

Methods: This study uses the show Daniel Tiger's Neighborhood and its corresponding tablet app to examine three research focuses:
1. How Daniel Tiger influences preschoolers' social and emotional development
2. Parenting Outcomes
3. How are participants' outcomes influenced by exposure to the app vs. the show, parental mediation, and demographic variables.

120 children were put into three conditions:
Condition 1: Watching Daniel Tiger's Neighborhood and playing the Daniel Tiger app
Condition 2: Watching a Control program and playing the Daniel Tiger app
Condition 3: Watching the Control program and playing the corresponding Control app

Results:
1. Exposure to the show and app resulted in an increased use of emotion regulation strategies, as reported by parents, and better performance on theory of mind tasks
2. Parent of children in Condition 1 reported having higher parental affect
3. Parents of children in Conditions 1 and 3 reported a greater awareness of parenting tools. Parents of children in Condition 2 reported much lower awareness of parenting tools. (Rasmussen et al., 2017)

Discussion: This is the first study (that we know of) that shows that children exposed to Daniel Tiger's Neighborhood displayed advanced theory of mind. Development of theory of mind is essential to social development because it is the understanding that other people may think differently from oneself. This also appears to be the first study showing that children exposed to Daniel Tiger's Neighborhood used emotional regulation strategies taught by Daniel Tiger in everyday situations. Participants not only learned the strategies, but applied them in novel situations, displaying a retention of learning and deeper understanding. Importantly, parents also benefitted from exposure to this show, perceiving that they had more tools for effective parenting.

References:


**Introduction:** Executive function (EF) has been found to relate to both word recognition and reading comprehension (RC), but findings have been inconsistent as to which components of EF are related to word- versus listening comprehension-level processing. We hypothesized that a more basic component of EF (inhibition; EF-I) would relate to word-level processes, while EF-I plus a higher-level component EF (shifting; EF-S) would relate to RC, but only for expository RC (as compared to narrative RC).

**Methods:** 1st grade children (n=80) with varying reading ability, were administered behavioral tests of reading and executive functioning.

**Results:** Hierarchical regression analyses revealed that EF-I accounted for a unique proportion of variance in the word-level measures after accounting for vocabulary (R2 change=11% for TOWRE & R2 change =13% for WJ Basic Reading), but EF-S contributed no additional significant unique variance for either word-level measure (R2 change=0% for TOWRE & R2 change=.4% for WJ Basic Reading). In contrast, both EF measures added statistically significant unique variance in predicting expository text (R2 change=6% for EF-I and R2 change=7% for EF-S) after controlling for word recognition and vocabulary.

**Discussion:** Consistent with previous findings, EF-I and EF-S did not add any additional unique variance to the prediction of narrative RC text. Findings thus replicate previous findings that narrative RC does not draw upon EF as much as expository RC, and additionally provide some clarification as to which EF skills are recruited for word- versus comprehension-level processes.
Association Between Vocal Communication with Canonical Syllables and Expressive Language in Young Children with ASD

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Faculty Advisor: Yoder, Paul

Introduction: The onset of canonical babbling is a critical milestone for language development that is often delayed in children with ASD[1-6]. Use of canonical syllables correlates with expressive language skills in children with ASD[7-11]. However, whether these associations are due to their covariation with communication acts or use in words warrants further examination. If vocal communication with canonical syllables predicts later language even after controlling for the number of communication acts and word use, then targeting this predictor may improve the language trajectory of children with ASD.

RQ1: Is vocal communication with canonical syllables correlated with expressive language concurrently and up to 12 months later in initially preverbal children with ASD? RQ2: Do identified associations between canonical syllables in communication acts and expressive language remain significant when excluding canonical syllables in identifiable words and controlling for the number of communication acts?

Methods: Sixty-eight initially preverbal children with ASD from a larger, longitudinal correlational study participated[11]. They used less than 21 spoken words per parent report and less than six spoken words during a language sample. Participants had a mean chronological age of 35.26 months (SD = 7.16) and mental age of 12.59 months (SD = 5.11). Vocal communication with canonical syllables with and without words was measured at Time 1 and 8 months later (Time 3) during the Communication and Symbolic Behavior Scales Behavior Sample[12]. Words were required to meet criteria for pronunciation, referential use, and analyzable content. To increase stability of the expressive language variable, we aggregated data from a semi-structured communication sample and two standardized procedures[12-13] collected at Times 1 through 4, each 4 months apart. The number of communication acts during two procedures at Time 1 was used to control for a generalized tendency to communicate.

Results: For RQ1, we examined correlations of the number of vocal communication acts with canonical syllables in communication acts and expressive language concurrently and up to 12 months later (p<.001). Correlations were moderately strong to very strong (r =.36-.84). For RQ2, concurrent and longitudinal correlations between canonical syllables and expressive language remained significant, even when excluding identifiable words and controlling for the number of communication acts at Time 1 (change in R-squared = .06-.32, p<.05).

Discussion: The results bolster prior conclusions from a recent meta-analysis that indicated strong correlations between vocalizations and expressive language[7], support the construct validity of measuring vocal communication with canonical syllables in children with ASD who are not yet speaking or in the early stages of word learning, and further support investigating interventions targeting prelinguistic vocalizations in this population.

References:


Asynchronous Audiovisual Speech Requires Greater Neural Processing

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Introduction: Speech comprehension is an ecologically important perceptual process involving the convergence of auditory and visual information. A decrease in neural processing effort has been proposed as an important mechanism by which visual speech enhances neural representations of auditory speech. This processing effort can be measured using event-related potentials (ERPs) for speech stimuli, which are smaller in magnitude for audiovisual speech than for auditory speech alone. We tested the dependence of this reduction in processing effort on temporal alignment between the auditory and visual inputs. We anticipated that audiovisual integration would manifest as a reduction in response magnitude when events co-occurred in time. Participants viewed movies of a woman articulating the audiovisual syllable ‘BA’ while undergoing electroencephalography (EEG). As in natural speech, the auditory stimulus (the speech sound) occurred at the same time as the visual stimulus (the mouth moving) on some trials. On other trials, the stimuli were adjusted such that the auditory and visual stimuli were temporally misaligned to varying degrees. Participants were asked to determine whether the auditory and visual stimuli occurred at exactly the same time (synchronously) or at different times (asynchronously) as quickly and as accurately as possible. As anticipated, reductions in ERP amplitude were seen in response to stimuli in which the auditory and visual stimuli occurred simultaneously, confirming that less effort is required to process synchronous audiovisual speech. Furthermore, stimuli with an intermediate level of asynchrony showed partial reduction in ERP magnitude, while stimuli with large asynchronies showed no reduction in ERP amplitude. These results indicate that asynchronous audiovisual speech requires greater neural processing effort than synchronous audiovisual speech.
Psychophysiologic responses to unpredictable verses predictable threat in PTSD

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Introduction: Post-traumatic stress disorder (PTSD) affects more than 30% of Veterans returning from Afghanistan and Iraq. Individuals with PTSD show alterations in many amygdala-mediated fear processes including fear conditioning, fear extinction, and fear potentiated startle. Emerging evidence suggests that PTSD and anxiety disorders may also involve alterations in anxiety processes, such as anticipatory anxiety and hypervigilance, which are mediated by the bed nucleus of the stria terminalis (BNST). In the present study, we examined psychophysiological responses to predictable threat (fear) and unpredictable threat (anxiety) in combat-related PTSD.

Methods: Fifty medication-free adults (15 Combat Veterans with PTSD, 20 combat controls, and 15 Healthy Controls) completed a cued anticipation task with three conditions: unpredictable threat, predictable threat and predictable safe. Skin conductance response (SCR) was measured and analyzed using an event-related analysis. Initial response (SCR amplitude) and sustained response (SCR area under the curve) were computed for each response to cues or images. Repeated measures ANOVAs were performed to test for group differences on cues and on images.

Results: Across all cues and images, the PTSD group had heightened initial SCRs and greater sustained SCRs (p < .05). There was a significant group x cue interaction for initial response (p < .05), which reflected a significant difference between initial SCR to predictable vs unpredictable threat in the two combat groups. The combat control group had significantly elevated SCRs to the unpredictable threat cues whereas the combat PTSD group showed a significantly blunted SCR to unpredictable threat. When viewing the predictable threat images, the combat PTSD group had significantly greater initial SCRs and more sustained SCRs relative to combat controls.

Discussion: Combat Veterans with PTSD Combat Veterans with PTSD showed distinct psychophysiological responses to unpredictable vs. predictable threat cues. Combat exposure was associated with hyper-responsivity to unpredictable cues and PTSD was associated with hypo-responsivity to the unpredictable cues, providing initial evidence for a dissociation in responses to fear vs anxiety cues. PTSD was also associated with heightened skin conductance responses to threat, consistent with previous findings of altered fear processing.
Architectonic feature and relative locations of primary sensory and related areas of neocortex in mouse lemurs

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Introduction: Mouse lemurs are the smallest of the living primates, and they are members of the understudied radiation of strepsirrhine primates, and the lemurs of Madagascar. Overall, they are thought to closely resemble the ancestral primates.

Methods: We used histological and immunochemical methods to identify and characterize sensory areas of neocortex in four brains from lemurs obtained from a licensed breeding colony.

Results: The use of multiple procedures allowed cortical areas to be identified more accurately than was possible in earlier studies. We describe the laminar features of visual areas V1, V2, MT and Prostriata, somatosensory areas 3b, 3a, and 1, adjoining motor cortex, M1, and primary auditory cortex.

Discussion: V1 has 'blobs' with 'non-blobs' surrounds, providing further evidence that this type of molecular organization evolved with the first primates and was retained in all extant primates. The laminar organization of V1 supports the view that sublayers of layer 3 are commonly misidentified as sublayers of 4. S1 (area 3b) is proportionately wider than the elongated area in anthropoid primates, and has disruptions that may separate representations of the hand, face, teeth and tongue. Primary auditory cortex located in the upper temporal cortex, and may include a rostral area, R, as well as A1. Brain sections processed for glutamate transporter - VGLUT2, were most useful as this transporter is present in the terminal axons of thalamic projections to primary sensory areas. The resulting architectonic maps of cortical areas in mouse lemurs can usefully guide future studies of cortical organization and function.

References:


Concurrent changes in behavioral and neural complexity associated with sensorimotor integration: Implications for understanding stereotyped behaviors in autism

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Introduction: Unusual sensory symptoms and motor deficits are highly prevalent in autism spectrum disorder (ASD). Their prevalence suggests that deficits in sensorimotor integration may contribute to characteristic features of ASD. Sensorimotor integration is brain’s process of using continuous sensory information to produce flexible behavior that supports adaptation to one’s surroundings. Thus, impairments in sensorimotor integration may contribute to the development of inflexible social and nonsocial behavior that characterizes ASD. We currently lack techniques to precisely measure sensorimotor integration in ASD limiting our understanding of the role it may play in ASD. Our study aimed to (1) develop methods to simultaneously assess neural and behavioral function during a sensorimotor task, (2) develop measures of the adaptability of neural and behavioral output during the task, and (3) examine differences in neural and behavioral adaptability in persons with ASD.

Methods: We designed a stimulus-tracking task with simultaneous recording of high density EEG. Participants controlled an on-screen cursor with a computer mouse. They were instructed to keep the cursor inside of a target that moved across the screen in a series of unpredictable patterns. The task consisted of two sensory conditions: (1) Visual Feedback: target and cursor were visible on the screen for the duration of the trial, (2) No Visual Feedback: target and cursor were visible initially, but disappeared mid-trial, and participants were instructed to continue moving as if the target and cursor were still visible. Participants included right-handed adults with ASD (N=20) and an age- and gender-matched typically developing group (N=18). We analyzed group and visual feedback effects on motor performance, motor complexity, and neural complexity.

Results: Participants show greater error in task performance when visual feedback is not available (t=10.39, p<0.001). Consistent with this finding, motor complexity is significantly reduced in the absence of visual feedback (t=23.59, p<0.001). Participants also demonstrate lower neural complexity when feedback is withheld (Frontal: t=3.29, p=0.006; Occipital: t=3.07, p=0.009), paralleling the patterns of motor complexity.

Discussion: Our results indicate that reliable sensorimotor integration and the availability of sensory feedback provide the brain with rich information with which to generate complex, adaptive motor output. In the absence of sensory feedback, the neural signal contains less information and correspondingly, the motor signal is more inflexible and stereotyped, thus this task provides a standardized, objective measure of inflexible, stereotyped behavior. Sensorimotor integration is likely disrupted in individuals with ASD resulting in less complex neural signals and consequently less complex, less adaptive behavior. Our ongoing work involves adapting our sensorimotor task for assessment at earlier developmental periods by integrating it into a 'game-like' virtual reality environment.
Developing and Implementing Case-Based Telehealth Training for Primary Care Providers of Adults with IDD

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Introduction: Research and anecdotal evidence finds that adults with intellectual and developmental disabilities often face difficulties in accessing appropriate and timely health care. Medical professionals who serve adults rarely have training in the health care needs of adults with IDD. The Vanderbilt Kennedy UCEDD and its partners, including the Tennessee Department of Intellectual and Developmental Disabilities, selected live videoconferencing with community physicians, advanced practices nurses and physician's assistants as a method of building capacity across Tennessee for clinicians to better serve adults with IDD. We offered free CME credit through both the American Medical Association and the American Academy of Family Physicians. Our Advisory Council, which provided guidance for our telehealth project, included people with disabilities, family members, staff, and faculty. The monthly trainings, which included both case presentations and a didactic, built on information in the IDD Toolkit, www.iddtoolkit.org, an online resource that addresses the specialized health care needs of adults with IDD. Community medical providers were able to present cases to a panel of clinicians in internal and family medicine, psychiatry, neurology, psychology/behavioral health, occupational therapy, and nursing to obtain practical advice on managing health concerns in people with IDD. We also provided education on such topics as common physical health issues, common psychiatric disorders, psychotropic medication use, dealing with challenging behavior, and dementia. The one-hour trainings, conducted once a month during lunchtime, allowed physicians and advanced practice nurses to join the live videoconference from their desks or smart phones, which they found to be very convenient. Our hope was to create a community of practice in which not only the providers on the 'hub team' would share information and suggestions, but also the clinicians out in the field would weigh in on the cases presented.

Methods: We measured outcomes with pre- and post-intervention surveys and plan to examine claims data on patients' emergency department usage, medical hospitalizations and psychiatric hospitalizations.

Results: Surveys indicated significant improvements in several areas, including clinicians feeling more comfortable in gaining informed consent from patients with IDD, gaining a better understanding of people-first language, recognizing the etiologies and specific health concerns of patients with IDD, and having a greater knowledge of community resources for their patients with IDD.

Discussion: We encountered a number of barriers in our efforts. The first barrier was recruiting the clinicians. We had great difficulty getting 20 clinicians to consent to participate. Of those 20, only 15 participated in at least one session of 10 sessions. Of those who did participate, most said they would participate again, if given the opportunity. We found that the cross-interaction that we had hoped to foster among the participants really began in the second half of the 10 sessions. We also found that participants were initially reluctant to make case presentations, but by the end, they were eager to do so. We also learned some valuable lessons about how to collect the outcomes data we were seeking.
RNA Editing-Mediated Regulation of Serotonin 2C Receptor Expression

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Introduction: Pre-mRNA transcripts encoding the 2C subtype of the serotonin receptor (5HT2C) can be differentially modified at five closely spaced adenosine residues within exon 5. These adenosine-to-inosine (A-to-I) editing events can generate as many as 24 protein isoforms that differ by up to three amino acids within the predicted second intracellular loop of the receptor, a region essential for G protein coupling. Functionally, the highly edited 5HT2C isoforms (e.g. 5HT2C-VSV and 5HT2C-VGV) exhibit reduced constitutive activity and altered subcellular localization in comparison to the genomically-encoded isoform (5HT2C-INI). Recent work in our lab has shown that genetically-modified mice solely expressing the fully edited 5HT2C receptor isoform (5HT2C-VGV) present phenotypic characteristics of Prader-Willi Syndrome (PWS) including a failure to thrive, decreased somatic growth, neonatal muscular hypotonia, and reduced food consumption followed by post-weaning hyperphagia. Furthermore, these animals show an anomalous 40- to 70-fold increase in receptor density without a concurrent change in 5HT2C mRNA levels. The molecular mechanism(s) underlying this novel disparity between mRNA and protein isoform expression have yet to be elucidated.

Methods: To assess whether such a disparity exists between edited 5HT2C transcripts and their encoded protein products in wild-type mice, affinity purification methods to isolate 5HT2C receptors will be used, followed by mass spectrometry-based proteomic analysis to quantify the relative expression levels of 5HT2C protein isoforms. Due to the low expression of this G-protein coupled receptor in most regions of the mouse brain, we have employed a CRISPR/Cas9-based approach to generate mutant mice in which hexahistidine- and Strep-II® affinity tags have been 'knocked-in' to the endogenous 5HT2C locus.

Results: Deep sequencing has confirmed that insertion of the twin epitope tag does not alter normal patterns of RNA editing and splicing of 5HT2C transcripts. Purification efficacy has also been validated in a heterologous system (HEK 293) expressing this affinity-tagged 5-HT2C receptor, and subsequent mass spectrometric analysis has detected the desired chymotryptic peptide of interest.

Discussion: Current work is focused on isolating sufficient quantities of the receptor from whole brain and dissected regions for quantitative analysis. Identification of disparities between 5HT2C RNA and protein isoform expression will have important implications for human studies of disease-related alterations in 5HT2C RNA editing, in which inferences about receptor isoform expression and function have been based solely upon edited mRNA distribution profiles.
Theta Power and Phase Coherence Support Multisensory Temporal Processing

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Introduction: Environmental events emanating from a common source frequently generate sensory inputs in more than one sensory modality. The temporal concordance between these inputs serves as an important cue for the nervous system to appropriately integrate sensory information and form coherent perceptual representations. Multisensory integration is highly flexible and dependent upon contextual cues and task demands, but the neurophysiological basis of this flexibility, particularly in the temporal domain, has not been fully explored. In the current study, we investigated the degree to which top down task demands affect physiological measures of multisensory integration. To do so, we employed a combination of electroencephalography (EEG) and a pair of psychophysical tasks in which participants directly attended or ignored the temporal relationship between the auditory and visual portions of audiovisual speech stimuli. Consistent with previous work, our results indicate that oscillatory power in the lower portion of the theta band (3.5-5 Hz) is sensitive to the temporal concordance of audiovisual speech events. Importantly, however, this is only the case when temporal relationships are directly attended by participants. We further demonstrate that phase synchronization differs based on task demands. This suggests that selective oscillatory synchronization in the theta band plays an important role in top down regulation of multisensory temporal processing. Our findings thus indicate that low frequency oscillations may encode multisensory temporal information during deliberate processing of temporal structure.
The development of speech-language dissociations and stuttering chronicity

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Introduction: Cross-sectional studies have found that preschool-age children who stutter are more likely to exhibit variability between speech-language skills than children who do not stutter (e.g., Anderson, Pellowski, & Conture, 2005; Clark, Conture, Walden, & Lambert, 2015). Researchers have speculated that these imbalances contribute to stuttering persistence. An alternate hypothesis supports a framework in which imbalances are characteristic of transient stuttering (i.e., children who stuttered and recovered). It may be the case that children who exhibit speech-language imbalances drop below the diagnostic criteria of stuttering when dyssynchronies in speech-language skills decrease. The purpose of this study is to evaluate the development of speech-language imbalances in children who stutter and are persisting, children who stuttered and recovered and children who do not stutter. The longitudinal study design allows us to determine, for the first time, whether these imbalances might be more characteristic of chronic or transient stuttering. We will explore imbalances using correlation-based dissociations. Based on the current literature, we hypothesize that children who persist will (a) be more likely to exhibit speech-language dissociations and (b) exhibit different speech-language dissociation profiles (i.e., language only or speech and language dissociation) than children who recover and children who do not stutter.

Methods: Participants, aged 3;0-4;11 at an initial visit, were classified as persisting (n = 10), recovered (n = 27), and non-stuttering (n = 24). They completed a speech-language evaluation 3-5 times across two years, which included assessments of articulation, receptive and expressive vocabulary, and receptive and expressive language. Speech-language dissociations will be identified using five norm-referenced assessments: Peabody Picture Vocabulary Test - Fourth Edition, Expressive Vocabulary Test - Second Edition, the expressive and receptive subtests from the Test of Elementary Language Development, - Third Edition, and the Goldman-Fristoe Test of Articulation - Second Edition. Dissociations between pairs of assessments will be measured using a correlation methodology (e.g., Anderson, Pellowski, & Conture, 2005); ten dissociations will be calculated at three time points. Analyses will investigate between-group differences in dissociations across two years of development.

Results: The number of speech-language dissociations exhibited by a child and the standard deviation of a child's test scores are correlated, but only speech-language dissociations appear to differentiate children who persist and recover. Children who persist are more likely to exhibit a specific profile of imbalances between speech and language abilities later in development than children who recover.

Discussion: Measures of speech-language dissociations differentiate stuttering vs. non-stuttering, however, based on present results they do not appear to serve as a risk indicator of chronicity close to stuttering onset. Further, present preliminary results indicate that children who persist are more likely to exhibit dissociations between the speech-language domain compared to children who recover further in development (post recovery). Further development of methodological approaches to specify the nature of the complex interplay between the development of speech-language abilities for children who persist and the role in chronicity is warranted.

References
**Determining How Preverbal Children with Autism Spectrum Disorder Combine Facial Affect and Prelinguistic Vocalizations**

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**Faculty Advisor:** Bodfish, James

**Introduction:** Prior to first words, children with Autism Spectrum Disorder (ASD) produce atypical prelinguistic vocalizations. Differences in prelinguistic behaviors help predict the extent preverbal children with ASD will develop spoken language. A foundational behavior that has been shown in typically developing (TD) infants is the ability to combine early developing vocalizations, called protophones, with different types of facial affect flexibly. Communication partners adapt responses based on these combinations affect and vocalizations.1 However, no study has investigated this behavior in children with ASD.

**Methods:** Twenty children with ASD between 20-48 months and twenty TD children between 8-17 months were selected from existing data sets (2,3). Participants were matched on expressive vocabulary (4) and gender. Vocalizations and facial affect were coded using multimedia recordings of a structured assessment (5) using a partial interval coding scheme. Protophones were classified based on pitch and phonation: squeal (high), vocant (mid-range), and growl (low). Cries and laughter were identified. Affect was categorized as positive, negative or neutral.

**Results:** Six participants with ASD (30%) and three TD participants (15%) did not demonstrate the full range of protophones. Five participants (25%) with ASD did not demonstrate the full range of affect, but all of the TD participants demonstrated the full range of affect. Children with ASD produced more laughs (p<.001), more positive affect (p<.0007), fewer growls (p<.01) and less neutral affect (p<.002) than TD controls. Using operant contingency values to quantify the degree of association between protophones and affect, TD were shown to be more likely to produce protophones in the presence of negative affect compared to the group with ASD (p<.05), and children with ASD were more likely to produce protophones in the presence of positive affect compared to the TD group (p<.02).

**Discussion:** The distributions of protophones and affect differ in children with ASD from TD children, suggesting that children with ASD diverge from the typical development earlier than previously thought. In addition, differences in the strength of association of the production of protophones with affect between children with TD and ASD could suggest that children with ASD have limited vocalization flexibility, because children with ASD are not as likely to communicate negative affective messages with protophones as peers are. If replicated, flexible combination of affect and vocalizations could be an early marker of ASD.

**References**


Early Intervention and Affect in Children with Autism

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Introduction: Early intervention is currently a major focus of autism spectrum disorder (ASD) research, as psychologists, parents, and educators are exploring the most effective ways to help children with ASD learn skills including joint attention, symbolic play, and communication. There are two main intervention frameworks: discrete-trial training (DTT) and play-based intervention (PB). Discrete-trial training involves a structured series of steps to teach a target behavior. In contrast, play-based intervention occurs in a more naturalistic setting and focuses on child-initiated interaction. The purpose of this study is to examine which type of early intervention framework and time intensity produces the most positive affect in young children with autism, to understand which type of intervention and time intensity of intervention young children with ASD enjoy the most.

Methods: This experimental method involves a 2x2 between-subjects design, where children with ASD are randomly assigned to one of four intervention conditions: 15 hours per week of DTT, 25 hours per week of DDT, 15 hours per week of PB, or 25 hours per week of PB intervention. The investigator codes recorded videos of the intervention sessions for instances of positive, negative, and neutral affect. We used four 8-minute video clips per participant to increase the stability (Sandbank & Yoder 2014). Video coding was done using Procoder software, with a 5-second partial interval coding system. A secondary coder codes at least 20% of included videos without the primary coder knowing which will be coded.

Results: We will conduct t-tests to compare the intervention framework (DTT vs. PB) on number of instances of positive affect, negative affect, and neutral affect. We will also conduct t-tests to compare the time intensity of intervention (15 hours per week vs. 25 hours per week) on number of instances of positive affect, negative affect, and neutral affect. We predict that the results of this study will demonstrate that children randomly assigned to 15 hours per week of PB intervention condition will produce the most instances of positive affect.

Discussion: This study is designed to contribute important new information to the field of early intervention research. The findings could be useful for researchers, clinicians, and caregivers when considering or developing interventions for a child with autism. Because early intervention programs for children with ASD can be so time intensive, their level of enjoyment could be an important factor to include when considering different framework options.

References:

Parent and Child Preferences and Styles of Communication about Cancer Diagnoses and Treatment

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Faculty Advisor: Gilmer, Mary Jo

Introduction: Communication challenges frequently occur among families and healthcare providers of children with life-threatening conditions. These obstacles compound concerns related to children's diagnoses and treatment, the family's quality of life, and delivery of care. Despite the prevalence of these barriers in pediatric palliative care, little is understood or being explored around how, when, and what to communicate with diverse families. This study explored 1) perceptions of children with cancer and their parents related to information exchange and 2) wishes of children with cancer and their parents related to communication across the illness trajectory.

Methods: Participants in 6 semi-structured focus groups included children ages 7-17 years at least 6 months post cancer diagnosis (N=7) and their parents (N=9). School-age children, adolescents, and parents were in separate focus groups which were facilitated and audio-recorded by experts in child development and medical ethics. Recordings were transcribed and three researchers used qualitative concept analysis.

Results: Researchers reached consensus on the following themes among children: How to tell, who should tell, when to tell, what to tell, changes in prognosis, side effects of treatment, coping and emotions, and who should be included. Similar parent perceptions also included the theme: Talking with the whole family.

Discussion: Data reveal communication-related difficulties children with cancer and their parents encounter across the disease trajectory. Study findings specifically call attention to challenges experienced by families in obtaining and assimilating information from the healthcare team. Additionally, most families wished to gradually acquire details about the child's disease and prognosis. Quality communication during cancer diagnosis and treatment requires healthcare providers' knowledge of children's developmental needs and family preferences. Results of this study reveal a need for developmentally appropriate, evidence-based education to best inform parents on how, what, and when to communicate information concerning their child's disease, as well as instructions around facilitating those discussions.

References:


An iPSC-Derived GABAergic Interneuron Model for Investigating ATP1A3 Mutations in Alternating Hemiplegia of Childhood

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Introduction: Alternating Hemiplegia of Childhood (AHC) is a rare genetic neurodevelopmental disease caused by heterozygous missense mutations in the ATP1A3 gene, encoding the neuronal specific alpha-3 subunit of the Na,K-ATPase pump. This complex is crucial for many cellular functions including setting the resting membrane potential and regulating ion homeostasis. AHC patients display unique symptoms beginning in early childhood, including episodes of weakness or paralysis often triggered by stress, abnormal eye movements, seizures, painful dystonia, developmental delay, and intellectual disability. It is known that the majority of AHC patients possess one of three mutations in the ATP1A3 gene, resulting in D801N, E815K, or G947R mutants of the alpha-3 Na,K-ATPase subunit. Importantly, emerging data and new reports suggest that the alpha-3 subunit is preferentially expressed on cortical GABAergic interneurons, and that GABAergic cells may have an important role in AHC. We hypothesize that mutant alpha-3 protein perturbs normal neurodevelopment and results in neuronal depolarization that is exacerbated during cellular stress.

Methods: For our studies, we have generated iPSCs from patients with the three most common mutations in AHC. These iPSCs are differentiated into cortical neurons to test the hypothesis that mutant α3 decreases Na,K-ATPase function in a dominant-negative manner. Recent advances in iPSC differentiation techniques have allowed us to use both small molecules and lentivirally-introduced transcription factors to induce GABAergic cell fates in iPSCs for use in this research. Data collection methods include immunoblotting, immunofluorescent staining, fluorescent indicators of ion status, single-cell electrophysiology, and multielectrode array analysis.

Results: Initial studies have characterized Na,K-ATPase subunit expression in developing cortical neurons. Results indicate that neurons derived from all three major ATP1A3 mutations show increased levels of alpha-3 protein and decreased levels of the alpha-1 subunit compared to iPSCs. Expression of the alpha-3 subunit during neuronal differentiation has similar temporal dynamics to control cells. Fluorescent indicators of sodium and calcium concentration in patient-specific iPSC-derived cortical neurons are being used to investigate ion homeostasis in the presence of ATP1A3 mutations. Patch clamping demonstrates that these iPSC-derived neurons are electrically active. Current studies involve multielectrode array analyses, along with testing for lineage-specific consequences of mutant alpha-3 expression in GABAergic iPSC-derived neurons. We are increasing the potential impact of our findings by using CRISPR/Cas9 techniques to create isogenic controls by correcting ATP1A3 mutations in AHC patient-derived iPSC lines.

Discussion: Mechanisms underlying symptoms in AHC patients remain poorly understood and there are no empirically proven treatments for AHC. The impact of the proposed research may be profound for AHC patients and their families by providing fundamental knowledge of the disease and creating routes to future therapeutic discovery.
Meta-modulation of mGlu5 by mGlu3 during hippocampal dependent synaptic plasticity and behavior

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Faculty Advisor: Conn, Jeff

Introduction: The group II metabotropic glutamate receptor 3 (mGlu3) is an emerging therapeutic target for neurological disorders, as preclinical research has demonstrated cognitive enhancing aspects of mGlu3 activation. Additionally, the group I mGlu receptor, mGlu5, has been shown to enhance a form of long-term synaptic plasticity termed long-term potentiation (LTP), which is believed to be the neural correlate of memory formation during learning. In light of recent evidence that mGlu3 and mGlu5 can act as signaling partners to modulate synaptic plasticity in the prefrontal cortex, we hypothesized that mGlu3 may subserve similar functions to those of mGlu5 during hippocampal synaptic plasticity and hippocampal-dependent behaviors.

Methods: We directly tested this hypothesis using acute slice electrophysiology and associative fear learning behavior in mice.

Results: Results demonstrate that mGlu3 activation pharmacologically using the group II mGlu agonist LY379268 enhances the acquisition of trace fear conditioning, and this enhancement is prevented by genetic ablation of mGlu5 using knockout mice. Furthermore, in acute slices, agonism of mGlu3 with LY379268 significantly enhances LTP induced by theta-burst stimulation compared to vehicle controls. Pharmacological antagonism studies show mGlu3 potentiation of LTP to be mGlu5-, NMDA-, and Cannabinoid type 1 (CB1)-receptor dependent. Conversely, mGlu3-LTP was enhanced by bolstering mGlu5 or cannabinoid signaling via the mGlu5 positive allosteric modulator VU0099273 or the monoacylglycerol lipase inhibitor JZL184, respectively.

Discussion: These results taken together demonstrate mGlu3 enhances hippocampal LTP and hippocampal-dependent learning through mechanisms that involve mGlu5 and CB1 receptor activation. This work provides a basic biological mechanism and preclinical therapeutic validation for mGlu3 as a target for neurological disorders in which cognition is disrupted.
Naturalistic Interventions for Children with Autism Spectrum Disorder: A Meta-Analysis

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Faculty Advisor: Stephen Camarata

Introduction: Intervention is important to improve the long-term outcomes of children with ASD and, it is critical to continue searching for effective early interventions for ASD. However, current literature lacks meta-analysis of naturalistic interventions that combines both parent and clinician-implemented treatments. This study evaluated two research questions not previously addressed in the literature: 1. Is naturalistic intervention effective for children with ASD on communication outcomes, particularly prelinguistic outcomes? 2. Is the treatment effect of naturalistic intervention on child communication outcomes moderated by implementation agent (parent vs. clinician) or treatment intensity?

Methods: Databases within ProQuest, PubMed, and dissertation databases were searched, yielding 5,521 studies. The two primary authors screened full-text articles with an agreement of 94%. The search yielded 43 reports and 29 studies. Studies included at the full-text level were randomized controlled trials and quasi-experimental designs of naturalistic interventions for participants with ASD. Out of the 29 studies included, 21 reported prelinguistic outcome measures, which are reported in the current analysis.

Results: A random-effects meta-analysis of prelinguistic outcomes yielded a summary effect size of g = 0.42, 95% CI [0.22, 0.62], which indicates that naturalistic intervention for children with ASD is associated with significantly better prelinguistic outcomes than alternative or no treatment. This finding translates to approximately 6 more measures produced on the MCDI and 3 more instances of child initiations of joint attention on the ESCS. Neither implementer of the intervention nor treatment length in weeks were significant moderators of treatment outcome. Within the parent-implemented treatment, intensity in total hours of parent training was a significant moderator of treatment outcome after controlling for treatment length in weeks.

Discussion: The positive effect size (g = 0.42) indicates that naturalistic interventions demonstrated a positive impact on the prelinguistic skills of children with ASD in comparison to other conditions. Findings also support the number of treatment hours in parent-mediated naturalistic interventions as a potential moderator of treatment outcome. This finding was robust after accounting for length of treatment in weeks, suggesting that the total number of hours may be more important than the treatment length in studies with parent training. Differences between control groups was a limitation of this study. Control conditions in the primary studies vary and the amount and type of intervention provided within treatment-as-usual conditions were not thoroughly reported. Despite this limitation, naturalistic interventions maintained a significant positive effect compared to other conditions. Furthermore, the significant moderating influence of treatment in hours beyond that of treatment in weeks suggests that treatment intensity may be an area of continued research to improve cost-effectiveness and impact of treatment.

References:
Preschoolers with and without a History of Language Delay: Complex Syntax in Maternal Language Input at Home

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Introduction: Children with specific language impairment are less proficient in complex syntax production (i.e., multiclausal utterances) than children with typical language development (e.g., Owen & Leonard, 2006). Parent input is associated with children’s acquisition of complex syntax (e.g., Huttenlocher, Vasilyeva, Cymerman, & Levine 2002). However, the literature on parent complex syntax input to children with low language skills is quite limited. Newhoff (1977) reported that mothers speaking to unfamiliar children produced less complex syntax input in an experimental setting with children with advanced linguistic skills as compared to age-matched children with below age-level language skills. The mothers produced fewer subordinating segments (e.g., infinitives, relative clauses) with the children with low language skills. The current study compared complex syntax input to children with and without a history of language delay in the home environment. Two research questions were addressed.
1. Do children with a history of language delay receive less complex syntax input from mothers than peers with a history of typical language development?
2. Does proportion of complex syntax in parental input predict preschoolers’ performance on a concurrent, norm-referenced omnibus language measure?

Methods: The study involved a secondary analysis of 18 home audio recordings from the Working on Rapid Language Development project (Kaiser, 2009). Participants included mother-son dyads, with 9 boys having a history of receptive-expressive language delay (RE Group, Mean age = 49.9 months) and 9 boys having a history of typical language development (TL Group; Mean age = 49.7 months). For each dyad, we transcribed 200 clausal-level, child-related, maternal utterances and coded utterances for complex syntax.

Results: TL mothers produced a higher proportion of complex syntax input compared to RE mothers (d = 1.19). Examination of subtypes of complex syntax indicated group differences on infinitive clauses and conjunction clauses, but not clausal complements or relative clauses. The latter types were infrequent in both groups. Proportion of complex syntax in maternal input explained a large proportion of variance in preschoolers’ concurrent Preschool Language Scale, Fourth Edition (Zimmerman, Steiner, & Pond, 2002) composite (R-squared = .51).

Discussion: Deficits in complex syntax acquisition for children with language impairments may be compounded by reduced maternal input in addition to language learning difficulties. In the home, mothers appear to align their complex syntax input to child language proficiency. Future studies may evaluate the potential benefit of increased quantity and diversity of complex syntax input to increase child proficiency with these structures. This descriptive study adds to a line of research with the ultimate goal of improving intervention for children with syntactic vulnerabilities.

References:
Remote Microphone Use in the Homes of Children with Hearing Loss: Impact on Child-Directed Speech

Author: Thompson, Emily
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Faculty Advisor: Tharpe, Anne Marie

Introduction: Remote microphone systems (RMSs) have been shown to enhance speech perception for children in school settings but have not been widely utilized in home environments, where background noise and distance can also be problematic for listening (Moeller et al., 1996). This study aimed to explore the amount of child-directed talk produced by caregivers when using and not using RMSs. Specifically, our research questions included: (1) How much child-directed speech (CDS) produced by a caregiver is not accessible by children with hearing loss when not using an RMS during a typical weekend while at home?; (2) Do caregivers produce more CDS when using an RMS versus not using a RMS?; and (3) Do caregivers produce more CDS from a distance when using an RMS versus not using an RMS?

Methods: Participants represent nine families, each having a child with bilateral, permanent hearing loss ranging from moderate to profound in degree, with a mean age of 4.1 years old. All subjects were primarily English or Spanish speakers, and full-time users of either hearing aids or cochlear implants. Language Environmental Analysis™ (LENA) recorders were used to record speech from the key caregiver and input received by the child during two consecutive weekends, including one weekend with and one weekend without use of the RMS (Phonak ROGER™ technology). Prior to the RMS weekend, all families used the RMS during a 3-day acclimatization period to control for a potential novelty effect caused by introduction of the RMS at home. Subsequently, speech samples from the caregivers’ and children's recordings were selected for analyses. Further analyses compared amount of child-directed speech (CDS) produced by the caregiver when close to the child (approximately < 8 feet from the child) and speech produced by the caregiver when farther away from the child.

Results: On average, preliminary results indicate that children are unable to access a significant amount of CDS during a typical weekend at home without RMS use. In addition, caregivers talk significantly more from a far distance when wearing an RMS than when not wearing an RMS, with at least part of that speech being child-directed, thus potentially enhancing communication in the family home. Data collection is ongoing.

Discussion: It is speculated that caregivers are aware of the improved auditory connection with their children when using RMSs, which might promote increased conversations from a distance. Collectively, these findings suggest that the use of an RMS in the homes of children with hearing loss might be an effective intervention for promoting incidental language learning.

References:
Context dependencies in word learning?

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Introduction: Context dependencies in memory have been widely studied, with the general consensus being that matching contexts between learning and test results in the best performance. Matching learning and test contexts has been shown to improve memory for object labels in toddlers (Goldenberg & Sandhofer, 2013; Vlach & Sandhofer, 2011).

Methods: We investigated the effects of matching contexts on retention of labels after a delay. 2.5-year-olds (n=24) were presented with novel labels in matching or mismatching contexts. Across four trials, children revealed above chance and equivalent learning in matching and mismatching contexts immediately and after a 10 minute delay (see Figure).

Results: Children in the both conditions exhibited learning immediately and after a delay. There were no differences in learning between conditions.

Discussion: Our task included half as many trials as previous work. One possibility is that children become more sensitive to context dependencies as task demands increase.

References:


Stress and embodied emotions along the schizophrenia spectrum

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Faculty Advisor: Park, Sohee

Introduction: Severe levels of stress have been linked to the onset of psychosis (Walker et al., 2008). Importantly, stress has immediate effects on the autonomic nervous system, directly impacting emotional and bodily states via musculoskeletal, respiratory, cardiovascular, gastrointestinal and endocrine systems. Although bodily self-disturbances and impaired emotional experience may be central to schizophrenia (Stanghellini et al., 2014), the impact of stress on embodied emotion in this population is unknown. This gap in the literature reflects difficulties in measuring the subjective phenomenology of self-disturbances. Recent progress in cognitive and affective neuroscience has led to the development of objective methods to probe the nature of self-disturbances. One of these innovative techniques, EmBODY, involves visuospatial mapping of physiological sensations of emotional experiences (Nummenmaa et al., 2014).

Methods: Individuals with schizophrenia (SZ), demographically matched controls (CO) and a developmental sample were recruited. We used the EmBODY tool to generate spatial maps corresponding to the bodily activation and deactivation experienced during 14 emotions categories. The Perceived Stress Scale (PSS; Cohen & Williamson 1988) was used to assess self-reported stress. Symptoms were measured with SANS and SAPS (Andreasen, 1983; Andreasen 1984). Schizotypy in healthy participants was assessed with the SPQ-B (Raine & Benishay, 1995).

Results: The body maps obtained show overall reduced embodiment of emotions in SZ as compared to CO. Statistical pattern recognition with linear discriminant analysis revealed less unique bodily sensations of emotions in SZ. Similarity scores between the maps of CO and SZ revealed a specific deficit in embodiment of low-arousal emotions in SZ. Using Spearman rank correlations, we found a linear development of embodied emotions across our developmental sample. We also found that stress positively correlated with embodiment. However, this correlation between perceived stress and emotional embodiment became weaker as age increased.

Discussion: The anomalous physiological experience of emotions observed in our patients could be linked to the social and functional deficits of this population and is a potential target for intervention. We also found that the ability to embody emotions develops linearly and that the impact of stress on embodied emotions decreases with age. This suggests that typically developing adolescents learn to cope with stress so that its effects on affective experiences are less pronounced. Future work will investigate the developmental trajectory of embodied emotions in adolescents at clinical risk for psychosis to elucidate the etiology of the self-disturbances in schizophrenia.

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Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, University of Iowa, 1984
Andreasen NC: Scale for the Assessment of Negative Symptoms (SANS). Iowa City, University of Iowa, 1983
The role of Jedi in the development and function of the somatosensory nervous system

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**Faculty Advisor:** Carter, Bruce

**Introduction:** The dorsal root ganglia (DRG) contain the primary afferent neurons responsible for somatosensation. We previously identified Jedi (PEAR1/MEGF12) as a phagocytic receptor involved in clearing apoptotic neurons generated during normal development. To further investigate the function of Jedi in vivo, we analyzed jedi-/- mice. In the DRG, Jedi is expressed in satellite glial cells, endothelial cells, and perineurial cells; however, it is not expressed in the sensory neurons. Surprisingly, we observed early onset neurodegeneration in jedi-/- DRG. The remaining neurons exhibit hyperexcitability and increased expression of the capsaicin receptor TrpV1. Correspondingly, the jedi-/- mice have exacerbated capsaicin-induced alldynia. The increased excitability correlates with an increase in the expression of Nav1.9, a downstream transducer of TrpV1-initiated cellular depolarizations. Based on these findings, we hypothesize that the absence of Jedi in non-neuronal, supportive cells in the DRG causes an increase in the expression of excitatory ion channels in sensory neurons, leading to excitotoxicity and neurodegeneration of DRG somatosensory neurons.
Metabotropic glutamate receptor 3 as a therapeutic target for MECP2-associated disorders

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Faculty Advisor: Niswender, Colleen M.

Introduction: Abnormal expression and/or function of the Methyl-CpG-binding protein 2 (MeCP2) protein results in a spectrum of phenotypes characterized as MECP2-associated disorders. In particular, loss- and gain-of-function mutations in MeCP2 are associated with the intellectual disability disorders, Rett syndrome (RTT) and MECP2 Duplication syndrome (MDS), respectively. Despite their opposing molecular origins, some acquired phenotypes of RTT and MDS are similar, spanning deficits in motor, social abilities and cognition. These phenotypes are recapitulated in mouse models, and rescued through genetic normalization of MeCP2. This indicates that the neurodevelopmental components of RTT and MDS are not static, but rather responsive to interventions that target the pathophysiology of the disease. Our therapeutic approach focuses on MeCP2-regulated genes that are involved in neurotransmission, such as the metabotropic glutamate receptors. Specifically, we are evaluating metabotropic glutamate receptor 3 (mGlu3), which our preliminary data indicate is decreased in the brains of RTT patients, and has previously been linked to cognitive deficits in other neurological disorders. We hypothesize that modulating mGlu3 function using allosteric modulators will validate mGlu3 as a potential therapeutic target for cognitive phenotypes in MECP2-associated disorders.

Methods: To study these disorders, we will utilize mouse models of RTT and MDS and evaluate the activity of an mGlu2/3 agonist and/or the mGlu3 negative allosteric modulator (NAM, VU0650786) to test the hypothesis that modulating mGlu3 will rescue deficits in synaptic plasticity and behavioral phenotypes of cognition.

Results: Analogous to our data from human RTT samples, we find that mGlu3 expression is decreased in RTT mice. We also demonstrate an mGlu3-mediated long-term potentiation (LTP) at the hippocampal Schaffer collateral-CA1 synapse, as VU0650786 inhibits an mGlu2/3 agonist-induced LTP in wild-type animals. Conversely, we have also found that mGlu3 is increased in MDS mice, and that mGlu3 inhibition using VU0650786 normalizes impairments in long-term depression. Additionally, impaired recognition memory in MDS model mice in the novel object recognition task can be improved by VU0650786 treatment. In summary, our initial data suggest that decreased mGlu3 expression contributes to cognitive deficits in RTT patients, and potentiating mGlu3 may correct these impairments. On the other hand, negatively modulating mGlu3 may be a potential therapeutic strategy for MDS.

Discussion: Our most up to date findings exploring the role of mGlu3 in each disorder reveal that although RTT and MDS share phenotypes, the opposing molecular origins of these disorders appear to correlate with alterations in mGlu3 expression and signaling. Specifically, attenuated mGlu3 signaling may contribute to RTT phenotypes, whereas excessive mGlu3 signaling may underlie MDS phenotypes. Overall, allosterically modulating mGlu3 may be a therapeutic strategy for combating cognitive phenotypes in RTT and MDS.
Developing a Comprehension Interventions for Struggling 3rd Grade Readers: A Pilot Study

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Faculty Advisor: Fuchs, Douglas

Introduction: This pilot project was part of a much larger study to develop an effective RC intervention for struggling readers in the intermediate grades. However, during the first 3 years of that intervention study, 3rd graders had consistently demonstrated minimal benefit from tutoring. Thus, a pilot study was conducted to identify how the intervention might best be adapted to improve the performance of 3rd grade students. The purpose of this poster is to present the results of this pilot, explore the pattern of results, and report on how this data will be used to inform future ideations of the project.

Methods: Students were selected from 8 Metro Nashville public schools. Students chosen for the study were nominated by teachers because they felt they would benefit from tutoring in RC. Students selected for the study needed to demonstrate risk for developing deficits in RC (Gates MacGinitie Reading Comprehension normal curve equivalent < 50th percentile). Students who met inclusion criteria were pre-tested using WIAT-III Reading Comprehension and randomly assigned to treatment and control. 56 third grade students completed the study (27-control; 29-treatment). Students in the treatment condition were tutored in pairs for 48 sessions. All tutoring sessions were 50 minutes and conducted by trained graduate assistants. During sessions students were explicitly taught strategies for comprehending non-fiction text. After completing tutoring, students were assessed using a near transfer reading-comp measure and a knowledge measure developed by the research team. These measures were only administered at post. Students were also assessed at pre- and post on two far transfer RC measures.

Results: Data were analyzed using cross-classified hierarchical linear models with random effects for pair assignment. All models controlled for pretreatment ability and used the Kroger method for calculating degrees of freedom. Effect sizes were calculated using Hedge’s g with an adjustment for small sample size. Students in the treatment group significantly outperformed students in the control condition on the near transfer knowledge test (g=3.06). While not significant, effect sizes on the Gates and Near Transfer RC measure were promising (g=.26 and g=.29 respectively). However, results on the WIAT were not as promising (g=-.58).

Discussion: The mixed results of this pilot study have several implications. First, the intervention continues to need work. Second, the differential results on the two widely-accepted far transfer measures highlight the difficulty of measuring the RC construct. Furthermore, utilizing only one of these measures to determine student need for RC intervention proved insufficient. Thus, in future studies we feel it is necessary to adjust selection criteria.
Reading skill affects the specialization of left ventral occipitotemporal cortex during phonological awareness task in 5-6-year-old children

Author: Wang, Jin
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Faculty Advisor: James Booth

Introduction: The left ventral occipitotemporal cortex (vOT) is important in visual word recognition. Studies have shown that the left vOT is generally observed to be involved in spoken language processing in skilled readers, suggesting automatic access to orthographic information. However, little is known about where and how the left vOT is involved in the spoken language processing of young children with emerging reading ability.

Methods: In order to answer this question, we examined the relation of reading ability in 5-6-year-old kindergarteners to the activation of vOT during an auditory phonological awareness task. Two experimental conditions, onset word pairs that shared the first phoneme and rhyme word pairs that shared the final biphone/triphone, were compared to allow a measurement of vOT's activation to small (i.e., onset condition) and large grain sizes (i.e., rhyme condition).

Results: We found that higher reading ability was associated with better accuracy of the onset, but not the rhyme, condition. In addition, higher reading ability was only associated with greater sensitivity in the posterior left vOT for the contrast of the onset versus rhyme condition.

Discussion: These results suggest that acquisition of reading results in greater specialization of the posterior vOT to smaller, rather than larger grain sizes, in young children.
Investigating Neural Bias to Speech Using Auditory Event-Related Potentials in Children

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Faculty Advisor: Bodfish, James

Introduction: Several previous studies have found that infants and children exhibit a preference for listening to speech over other types of sounds using behavioral paradigms (1-3). The precise temporal resolution of event-related potentials (ERPs) offers the opportunity to pinpoint when in time the potential bias to speech occurs at either the sensory (within 200 ms) or attentional level (~300 ms), however, previous ERP studies have not found evidence for a bias to speech. One crucial difference is that behavioral paradigms have used natural speech, while ERP studies have used synthetic speech. The purpose of the present study was to compare the cortical auditory ERPs (reflecting sensory encoding) and P3a component (reflecting involuntary attention) to both synthetic and natural speech to assess if and when the brain prioritizes processing of speech.

Methods: Twenty-two typically developing children (mean age: 9.5 years, range: 8-11 years) participated in two passive auditory oddball tasks. In the synthetic speech oddball, synthetic vowels (/i/ and /a/) were matched on complexity to complex tones. In the natural speech oddball, natural vowels (/i/ and /a/) were matched on complexity to two cow utterances. Latency and mean amplitude measures of the sensory auditory ERPs were analyzed separately in children who displayed either the P1-N2 waveform characteristic of auditory ERPs in children or the mature, adult-like N1-P2 waveforms.

Results: In the synthetic speech oddball, no evidence for prioritization of the speech signal over the complex tone was found; instead, faster processing was found to the complex tone for N1 and P2 (p < .001 for both contrasts). In contrast, natural speech elicited significantly shorter latencies of the P1, N1, P2, and P3a ERPs compared to the complexity-matched cow utterance (p < .05 for all contrasts). Furthermore, a novel finding was that 7 children showed the adult-like N1-P2 to the simpler synthetic speech and tone stimuli, but showed the child-like P1-N2 to the natural stimuli, indicating that in some children the auditory cortex matures at different rates for simple vs. complex stimuli.

Discussion: Our results provide neural evidence for a bias to natural speech, but not synthetic speech, that begins in the earliest stages of cortical auditory processing. These results are the first to replicate behavioral findings, and suggest that the speech bias is driven by the acoustic properties of the human voice, rather than the linguistic content of the signal. Furthermore, this paradigm could be applied to children with autism spectrum disorder (ASD) who have not been found to show a preference for speech (2-3) and could have strong implications for delayed or impaired language that is often characteristic of children with ASD.

References:
Vouloumanos & Werker, 2007
Klin, 1991
Kuhl, Coffey-Corina, Padden, & Dawson, 2005
Effects of Sticky Mittens Training on Infants' Exploration Behaviors in Various Postures

Author: Wiesen, Sarah
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Faculty Advisor: Needham, Amy W.

Introduction: Through object exploration, infants can learn how to interact efficiently and effectively with their surroundings as well as learn about causality, the contingency between their actions and the outcomes of their actions, and object properties. Early motor interventions, such as sticky mittens training, have the potential to encourage 3-month-old infants to begin reaching for and exploring objects (ex. Needham, Barrett, & Peterman, 2002). During sticky mittens training, infants sit on a parent’s lap, and they wear custom mittens with the palms covered in Velcro loop. Infants are presented with lightweight toys covered in Velcro hook. By swatting to make contact with the toys, infants can obtain toys and move them through their visual fields. The current study tests whether sticky mittens training affects three-month-old infants’ exploration behaviors across different postures.

Methods: Forty-six infants participated in two laboratory visits two weeks apart. Between visits, one group of infants completed sticky mittens training at home with their parents. A second group completed no training between visits. At each visit, an Oball was presented to infants for 60 seconds in each of the following postures: lying supine, reclining, or sitting upright with the Oball suspended near the infant, and sitting upright with the Oball resting on the tabletop. Differences in infants’ manual contact with Oballs across the four postures are compared.

Results: We used a repeated-measures MANOVA to test for changes in touching durations from visit 1 to visit 2 between the two groups of infants across the 4 postures. Our analysis revealed a marginally significant interaction between visit and condition when infants were seated upright with the Oball resting on the tabletop, F(1,44) = 3.07, p = .087, ηp² = .065. Infants in the sticky mittens training condition significantly increased their touching durations in this posture (MV2-V1 = 16.69; SD V2-V1 = 22.12; t(23) = 3.70, p = .001, d = 1.61)), whereas this increase was non-significant for infants without training (MV2-V1 = 5.36, SD V2-V1 = 21.64; ; t(21) = 1.16, p = .26, d = .51.

Discussion: Our findings indicate that there is specificity between training postures and increases in object exploration. Infants with sticky mittens training performed similarly to infants without training in three of the four postures in this study. The posture where we saw group differences is most similar to the posture that infants experience during sticky mittens training. More diverse training experiences might better encourage infants to generalize their learning to various postures.

References:

Needham, Barrett, & Peterman, 2002
Using Robotics to Increase Academic & Social Skills of Students with Autism

Author: Wright, John
Co-authors: John Wright, Dr. Victoria Knight
Faculty Advisor: Knight, Victoria

Introduction: Teaching science based on inquiry methodology is not only recommended by the NGSS (2013), but has also been shown to be beneficial for students with Autism Spectrum Disorder (ASD) and related disabilities (Browder, Trela, Courtade, Jimenez, Knight, & Flowers, 2012; Schenning, Knight, & Spooner, 2013). To engage in the practice of scientific inquiry, students need to participate in scientific discourse, including question-asking (NGSS, 2013). Inquiry-based models of science instruction provide the ideal forum for students to practice communication, social, and academic skills simultaneously.

Methods: Research Design: Multiple probe across participants Students with ASD worked with a facilitating teacher to learn to code & program robots. Using single case research design, we examined the most salient features of a model-lead-test direct instruction for acquiring STEM/robotics skills for students with ASD and increasing inquiry activities. Further, we analyzed the role of creativity and generativity for this population.

Results: All three participants quickly acquired coding skills upon introduction of the independent variable (model-lead-test instruction) and maintained these skills 4-6 weeks after the intervention. Troubleshooting technology, question-asking, and persistence were all collateral benefits of this approach to STEM instruction.

Discussion: Students with ASD have the capacity to embrace complex academic work. This work can then generate self-directed learning. Novel technology can be used to engage students in academic work that is maintained over time. The often innate interest in technology and its ability to generate inquiry based questions that are testable, provides a concrete platform upon which to foster engagement, creativity, and generativity.

References:


The Transcriptional Profile of Prodromal HD Mice Exposed to Manganese: A Bioinformatics Approach

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Faculty Advisor: Bowman, Aaron

Introduction: Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease caused by an expanded CAG repeat of the Huntingtin gene and results in dramatic loss of medium spiny neurons in the striatum. Age of onset is largely dictated by number of CAG repeats; however, environmental factors such as manganese (Mn) exposure may alter symptom onset. Interestingly, both in vivo and in vitro HD models show decreased sensitivity to Mn in the striatum following Mn exposure. Impairments in Mn biology are particularly detrimental to the brain, as Mn is an essential cofactor for several enzymes, regulating urea cycle metabolism, oxidative stress, mitochondrial function, and glutamine synthesis. Understanding Mn biology, therefore, may be critical in determining molecular aspects of HD pathophysiology.

Methods: To study the transcriptional impact of Mn in HD pathology, we utilized a prodromal HD mouse model (YAC128Q). Twelve-week-old male HD and WT littermates were randomized to receive three subcutaneous injections of vehicle (H2O) or 50mg/kg body weight MnCl2 over one week (Day 0, 3 and 6). Animals were sacrificed 24 hours following their last exposure. At sacrifice, striatum was collected. RNA was isolated and sequenced using a standard 100-bp read Illumina platform. We performed quality control using FastQC and TrimGalore!, aligned with STAR, checked post-alignment quality with Qualimap2 and RSeQC, and searched for batch effects and clustering using the plotPCA function of DESeq2. We then determined differential expression (DE) with DESeq2. Select DE genes were chosen for validation using q-RT-PCR.

Results: We found 526 DE genes between HD and WT striatum. Gene ontology analysis indicated ion transport genes were enriched in this geneset. Specifically, HD downregulates ADAM7, ADAM28, and Adamdec1, which are disintegrins and metalloproteases. Furthermore, we found WT mice had 5 DE genes after Mn exposure, whereas HD mice had no DE genes after Mn exposure. A principal component analysis (PCA) revealed a definitive genotype effect, but no clear effect of Mn. Exposure to Mn still does, however, have an effect: five times more genes are DE between WTH2O and 128Mn compared to WTH2O and 128H2O.

Discussion: Our results show that Mn differentially alters the WT striatal transcriptome, while no genes are DE in HD. This supports the hypothesis that HD mice have decreased Mn sensitivity. Comparisons between WTH2O mice and 128H2O/Mn reveal that ion transport genes are dysregulated, suggesting Mn transport may be disrupted in HD. Our PCA shows a large variance unaccounted for by experimental design. One explanation for the variance is differences in neuron and glia composition in our samples. Future studies with larger sample sizes and homogeneous sample types may ameliorate this variance.
Excitatory to Inhibitory Transition in GABAergic Currents Guides Circuit Formation of Cortical Interneurons

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Faculty Advisor: Lagrange, Andre

Introduction: Excitatory GABA is a crucial developmental cue that guides perinatal neuronal migration, synaptogenesis, and circuit formation. The switch from embryonic depolarizing GABA to mature hyperpolarizing responses is mainly determined by the onset of KCC2 expression. Previous work has found that upregulated KCC2 function produces dramatic abnormalities in brain development, especially in GABAergic cortical interneurons. We hypothesize that the timing of this depolarizing/hyperpolarizing GABA switch is critical to timing the end of interneuronal development.

Methods: To test our hypothesis in vivo, we created a conditional DLX5:cre-IRES-eGFP;KCC2flox knockout (KO) mouse to cause indefinitely prolonged depolarizing GABA responses in interneurons. We use ex vivo acute brain slice whole cell patch clamp for measuring the electrophysiological functionality of cortical GABAergic circuits. Seizure susceptibility was measured by latency to onset of fluorothyl-induced seizure. Histology/immunohistochemistry and epifluorescence/confocal imaging was used to measure GFP+ interneuron distribution, vGAT+ puncta, and expression of KCC2, vGlut2, and GABAAR α1, α3, α5 subunits.

Results: Immunostaining shows early onset perisomatic KCC2 expression in interneurons starting from late embryonic development. We confirmed the interneuron-specific lack of KCC2 in our KO by loss of KCC2 in DLX5-lineage rich GCL of the olfactory bulb. Indeed, KO mice have a failure to thrive phenotype with late postnatal mortality, reduced body size and weight, and spontaneous seizures. Moreover, the KO mice exhibit a 45% faster latency onset of fluorothyl-induced seizures. Intriguingly, the distribution of GFP+ cortical interneurons at P12-P14 remains unchanged. Spontaneous IPSCs from layer 5 pyramidal neurons exhibit a non-significant trend towards lower inter-event interval. In preliminary data, we observed a similar density of KO presynaptic GABAergic terminals (vGAT puncta), while thalamocortical projections (vGlut2 marker) and GABAAR α subunit composition are normal.

Discussion: KCC2 in interneurons is expressed embryonically, relating to its regulation of multiple developmental processes of interneurons. As we hypothesized, loss of KCC2 in interneurons has a dramatic systemic effect on mice with reduced weight, seizures, and early mortality. We believe this effect to have neurological origin - KO mice have a low seizure tolerance, and pathology core found no tissue or organ malformation. Nonetheless, we did not find an underlying defective distribution of interneurons nor significant differences in GABAergic input to pyramidal neurons, though a trend suggests a difference in frequency that needs further examination. Preliminary data also suggests normal synaptic composition. Thus, we believe that a significant defect in GABAergic circuitry underlies the phenotype of our mice in an area that we have not yet examined. We hypothesize this to be the aberrant electrophysiology and excitability of KO interneurons, which is the focus of our current investigation.
Investigating the Effectiveness of Social Stories and Visual Supports Interventions for Children At-risk for Emotional and Behavioral Disorders

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Faculty Advisor: Ledford, Jennifer

Introduction: Children who exhibit problem behavior are at-risk for poor academic and social engagement (Bulotsky-Shearer et al., 2012). Early intervention to support children’s engagement in classroom activities is particularly important for children exhibiting persistent problem behavior, as these children are at-risk for disabilities such as emotional and behavioral disorders (EBD; Searle et al., 2014). However, in a recent survey teachers reported they were unfamiliar with 90% of interventions for children with EBD (Stormont et al., 2011) and lacked the knowledge to select evidence-based practices for children with or at-risk for EBD. Consequently, teachers selected strategies based on convenience or familiarity rather than evidence of effectiveness (Gable et al., 2014). Few studies have investigated low-effort interventions for children at-risk for EBD (Kern et al., 2006), thus more studies are needed to identify low-effort interventions that are feasible in general education classrooms. The objective of this study is to evaluate the effectiveness of two commonly used, low-effort interventions for children at-risk for EBD in primary elementary school classrooms: social stories and visual supports. This study is the first to compare these two commonly-used antecedent interventions and the first to evaluate preference regarding format of social stories and visual supports.

Methods: An alternating treatments single case research design (Barlow & Hayes, 1979) was used to compare the effectiveness of social stories and visual supports interventions to each other and a no-intervention condition. Social story intervention variations assessed included stories with and without comprehension questions and a non-social book reading activity. Visual supports variations were chosen based on activity type (e.g., schedule or work boxes). Child engagement was estimated using momentary time sampling procedures. Normative peer comparisons were used to evaluate the social validity of outcomes; surveys were used to evaluate the preference and feasibility of interventions as rated by general education teachers.

Results: Preliminary data indicate engagement in instructional activities did not improve with the use of social stories. Visual supports resulted in modest improvements in engagement. Data collection is still ongoing for remaining participants and should be complete prior to Science Day.

Discussion: Outcomes can better assist practitioners in making decisions regarding intervention components for children at-risk for EBD. Although commonly recommended for use, social stories may not result in meaningful changes in engagement. Visual supports may result in less variable engagement during ongoing classroom routines that matches the level of engagement of peers. Future studies investigating the effectiveness of visual supports during group and individual instructional activities may assist practitioners in selecting the appropriate type of visual support for their students.

References:
More than just numbers: Examining how pattern and spatial skills predict preschoolers’ math knowledge

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Faculty Advisor: Bethany-Rittle-Johnson

Introduction: Preschoolers’ math skills predict later math achievement. While the contribution of number skills is typically studied, pattern and spatial skills also independently predict concurrent and later math knowledge. Little is known, however, about the relations between pattern and spatial skills, nor how both predict math knowledge. We predicted:
Hypothesis 1: Pattern and spatial skills should moderately correlate.
Hypothesis 2: Pattern and spatial skills should each predict math knowledge, over and above the influence of the other.

Methods: Seventy-three 4- to 5-year-olds were assessed at the beginning and end of the school year. At time 1 (T1), spatial skills were assessed including form perception, spatial visualization, and visual-spatial working memory, as well as a novel and validated repeating pattern measure. At time 1 and 2 (T2), math skills were assessed.

Results: Supporting hypothesis 1, composites of pattern and spatial measures moderately correlated r(73)=.36, p<.01, controlling for age, verbal ability, and verbal working memory. In support of Hypothesis 2, pattern and spatial composites predicted mathematics knowledge at both T1 b(pattern)=.35, t(73)=3.25, p<.01, b(spatial)=.23, t(73)=2.22, p<.05, and T2 b(pattern)=.27, t(73)=2.30, p<.05, b(spatial)=.30, t(73)=2.75, p < .01. Controlling for T1 math, only the spatial composite measure predicted T2 math knowledge, b(spatial) = .25, t(73) = 1.95, p <.055. However, in analyses with individual measures, the novel pattern measure was the only unique predictor of later math skill controlling for T1 math and all other skills b(pattern)=.26, t(73)=2.58, p<.05.

Discussion: Thus, while moderately correlated, preschoolers’ pattern and spatial skills each serve as unique predictors of children’s concurrent and later math knowledge over and above general cognitive ability. Thus, curriculum and theory should emphasize the role of pattern and spatial skills in early math development.
Differences in temporal profile of brain responses by pleasantness of somatosensory stimulation in individuals with ASD

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Introduction: Individuals with autism spectrum disorders (ASD) show varied behavioral responses to somatosensory stimuli, including hyper-reactivity to light touch and hypo-reactivity to pain. Previous fMRI studies of sustained painful stimuli have isolated three distinct phases of pain processing that differentially relate to perceptual versus cognitive-emotional aspects of the pain response[1]. Individuals with ASD show diminished response in the two later phases of this triphasic pattern[2], suggesting differences in pain evaluation but not sensation or perception. Investigating whether a similar triphasic pattern applies to non-painful stimuli may further clarify the neural mechanisms underlying somatosensory processing differences in individuals with ASD.

Methods: Twenty-eight adults (ASD=14, typically developing (TD)=14) underwent functional magnetic resonance imaging (fMRI) in a block design using 3 textures with normed pleasantness ratings in the general population[3]: soft brush (pleasant), burlap (neutral), and plastic mesh (unpleasant). On each trial, a texture was stroked along the right forearm with moderate speed and pressure for 30 seconds. Changes in blood oxygenation level-dependent (BOLD) signal were analyzed during three phases (early, intermediate, and late). Results were cluster-corrected, thresholding at Z>2.3 and p<.05.

Results: Between groups, we found significant differences (TD>ASD) in BOLD signal change for pleasant (brush) and neutral (burlap) textures. For the brush, the TD group had greater response in left postcentral gyrus and right superior parietal lobule during the early and intermediate phases (all peak Zs>4.0, all pcorr<.0001). For the burlap, group differences were only significant during the early phase and occurred in the paracingulate gyrus (Zpeak=4.16, pcorr<.005) and right angular gyrus (Zpeak=4.01, pcorr<.05). There were no group differences for the plastic mesh texture. Within groups, the TD group showed significant early and intermediate phase responses to all stimuli. The ASD group had a more limited pattern of response, with increased BOLD signal during the late phase for the burlap texture (Left Central Operculum/Insular Cortex, Zpeak=3.64, pcorr<.005) and during the early phase for the mesh texture (Right Parietal Operculum, Zpeak=3.64, pcorr<.0001 and Left Insula, Zpeak=3.87, pcorr<.0001).

Discussion: Group differences for the more pleasant textures seemed driven by limited responding in the ASD group, who showed more reliable responses to more aversive stimuli. However, an extended late phase response to the neutral burlap in the ASD group may reflect difficulty evaluating affectively ambiguous (neutral) sensory stimuli. Additionally, the finding of an intact early but not intermediate and late phase response by the ASD group to the mildly aversive mesh texture extends the finding in pain processing[2], suggesting a continuum of aversive sensation for which cognitive-affective evaluative processes may be affected in ASD.

References:

