**Symposium Title:** Psychophysiological Biomarkers: Expanding Assessment Options in IDD Research

**Chair:** Alexandra P. Key

**Discussant:** Alexandra P. Key (panel discussion leader)

**Overview:** Individuals with intellectual and developmental disabilities (IDDs) commonly present a complex profile of strengths and weaknesses. Yet, evaluating it is often challenging due to the limited number of standardized behavioral measures optimized for use in persons with IDDs. Recent advancements in the development of noninvasive, low-cost measures of physiological processes, such as eye movements, heart rate and brain activity, offer a novel, objective approach to investigate sensory, cognitive and affective processes in persons with IDDs while placing minimal, if any, demands on compliance or voluntary overt behaviors. This symposium presents findings from four studies demonstrating applications of novel biomarkers in three different IDDs. The first presentation describes the results of a study in children with autism and demonstrates that deficits in the social-communicative domain are associated with alterations in the neural mechanisms of auditory temporal processing (gap detection). Presentations 2 and 3 demonstrate how autonomic (skin conductance, respiratory sinus arrhythmia) and cortical (event-related potentials, ERP) measures provide new insights regarding the role of emotional reactivity and regulation in childhood stuttering. The last presentation reports findings from a study using eye tracking and ERP measures to expand information available from the caregiver reports in order to better understand food-related interests in individuals with Prader-Willi syndrome. The symposium concludes with a panel discussion of the practical issues involved in the selection of the potential biomarkers and their integration in the context of behavioral research, including future treatment studies.

**Paper 1 of 4**

**Paper Title:** Biomarker Development in ASD: Electrophysiological Response during Auditory Gap Detection is Associated with Symptom Severity

**Authors:** Jennifer H. Foss-Feig, Katherine K.M. Stavropoulos, Emily Isenstein, James C. McPartland, Mark T. Wallace, Wendy L. Stone, Alexandra P. Key

**Introduction:** Treatment development in autism spectrum disorder (ASD) is hindered by the lack of robust outcome measures for detecting change as a function of intervention. In recent years, there has been increased focus on developing biomarkers that are objective, quantifiable, reliable, and sensitive, and may serve as markers of physiological changes associated with clinical improvement. Auditory temporal processing, including the ability to detect rapid silent gaps within stimuli, is impaired in ASD. It is also impaired in other language-based developmental disorders, highlighting its importance as a low-level mechanism associated with a key clinical feature of ASD. Whether neural response during auditory gap detection may be a viable biomarker in ASD is yet unknown.

**Objectives:** To explore the brain basis of auditory temporal processing deficits in ASD using electrophysiology and to examine whether neural signatures of auditory temporal processing relate to clinical features in ASD.

**Methods:** EEG data was recorded in an EGI system from 10-13 year old children (15 ASD; 17 typically developing [TD]) using a 128-channel net. Groups were matched for age, gender, and IQ. Participants heard: 1) 1000ms continuous white noise, and 2) the same stimuli interrupted by silent gaps near perceptual threshold (i.e., 3ms). Participants indicated via button-press whether

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2. Seaver Autism Center at Mount Sinai Hospital Icahn School of Medicine
3. Yale University School of Medicine Child Study Center,
4. University of California - Riverside
5. University of Washington
or not each stimulus contained a gap. Amplitude and latency of N1 and P2 event-related potentials were evaluated for near-threshold (3ms) gaps as a function of whether or not children reported detecting the gaps. Repeated measures ANOVAs were conducted (within-subjects factor: Detection Accuracy, Site; between-subjects factor: Group). Children with ASD were administered the Autism Diagnostic Observation Schedule (ADOS) and the Clinical Evaluation of Language Fundamentals (CELF) was administered in both ASD and TD. Parents of children with ASD completed the Autism Diagnostic Interview-Revised (ADI-R), and parents of all children completed the Social Responsiveness Scale (SRS) to report on their ASD symptoms across settings and development. Correlations were computed between ERP variables and clinical symptoms.

**Results:** For N1 amplitude, there was a trend for a Group X Site X Accuracy interaction (p=.07); central N1 was larger for TD than ASD for undetected gaps (p<.05). For P2 amplitude, a significant Group X Site interaction was observed (p<.05); central P2 was larger for ASD than TD regardless of detection accuracy. Across groups, attenuated P2 to behaviorally detected gaps related to worse social (SRS: r=-.408, p=.038) and receptive language (CELF: r=.402, p=.052) skills. In ASD, attenuated P2 related to greater ASD language/communication symptomatology (ADI-R: r=-.547, p=.035; ADOS: r=-.533, p=.034).

**Discussion:** Atypical neural responses during an auditory gap detection task were found for children with ASD, confirming that EEG is sensitive to alterations in auditory temporal processing that differentiate ASD from TD. More importantly, markers of atypical auditory processing that best differentiated ASD from TD were associated with clinical characteristics. In particular, a smaller P2 response, suggestive of poorer neural classification of stimuli, was associated with weaker social and language skills across ASD and TD, as well as greater communication-related symptomatology within ASD. This research suggests that aberrant neural response to low-level auditory information could offer an objective biomarker associated with differences in key phenotypic traits.

**References/Citations:**

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**Paper 2 of 4**

**Paper Title:** Skin Conductance and Respiratory Sinus Arrhythmia: Autonomic Markers of Emotion in Childhood Stuttering

**Authors:** Robin Jones¹, Hatun Zengin-Bolatkale¹, Edward G. Conture¹, Tedra Walden⁶

**Introduction:** Recently, several empirical investigations have studied differences in temperament and emotions between children who stutter (CWS) and children who do not stutter (CWNS), as well as the impact of emotional processes on stuttering frequency (for review, see Jones, Choi, Conture, & Walden, 2014). Findings suggest that there is an association between aspects of emotion and childhood stuttering. To date, physiological measures of sympathetic and parasympathetic nervous system activity, the two branches of the autonomic nervous system, have received less empirical attention compared to caregiver report and behavioral observation. This is unfortunate as physiological activity provides insights into covert processes of emotional reactivity (as indexed by sympathetic activity) and regulation (as indexed by parasympathetic activity), thereby augmenting the larger body of empirical evidence on more overt expressions of emotion. To address this gap in our knowledge, the present

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studies investigated sympathetic and parasympathetic nervous system activity in young CWS and CWNS. Study 1 investigated between group differences in physiological activity, and study 2 investigated the association between stuttering frequency and physiological activity.

**Methods:** Participants were 20 CWS and 21 CWNS for study 1 and 36 CWS and 36 CWNS for study 2. All participants were between 3 years 0 months to 5 years 11 months of age. Participants were exposed to neutral, negative and positive emotion-inducing video clips followed by age-appropriate speaking tasks. During each of the aforementioned tasks the physiological measures of: 1) skin conductance level (SCL)—an index of sympathetic activity (Boucsein et al., 2012), and 2) respiratory sinus arrhythmia (RSA)—an index of parasympathetic activity (Berntson et al., 1997), were used to index emotion reactivity and regulation (Kreiberg, 2010), respectively. Study 1 determined differences in SCL and RSA between CWS and CWNS. Study 2 determined the association between frequency of stuttered disfluencies and RSA, as well as the impact of caregiver reported executive function (composite of inhibitory control and attentional focusing subscales on Children’s Behavior Questionnaire [CBQ], Rothbart, Ahadi, Hershey & Fisher, 2001) on this association.

**Results:** Main findings of study 1 indicated that young CWS, when compared to their CWNS peers, exhibited significantly lower RSA at baseline, and higher SCL during the positive, compared to negative condition. During speaking, only CWS exhibited a significant positive relation between RSA and SCL. Main findings of study 2 indicated that decreases in RSA were significantly associated with increased stuttering frequency for both groups. Further, executive functions differentially impacted this association for CWS compared to CWNS. Specifically, CWS with lower executive functioning exhibited a significant association between RSA during narrative tasks and stuttering, whereas CWNS with higher executive functioning exhibited a significant association between RSA during narrative tasks and stuttering.

**Discussion:** Results were taken to suggest that CWS, when compared to CWNS, exhibit a physiological state characterized by a greater vulnerability to emotion reactivity (i.e., lower baseline RSA), and greater reactivity during positive conditions. Further, decreases in emotion regulation (indexed by decreases in RSA) were associated with increased stuttering, and executive functions impact this association. Present findings provide physiological evidence that emotion importantly contributes to childhood stuttering.

**References/Citations:**
Paper Title: Cortical Markers of Emotion Reactivity and Regulation in Childhood Stuttering

Authors: Hatun Zengin-Bolatkale¹, Edward G. Conture¹, Alexandra P. Key¹, Tedra Walden⁶, Robin Jones¹

Introduction: Developmental stuttering is prevalent in 1% of preschool- and school age children and often negatively impacts their academic, emotional, social, and vocational well-being. These manifold deleterious influences of stuttering on children’s lives suggest a strong need to identify variables associated with the onset, development and maintenance of childhood stuttering. Emotional processes, for example, have been shown to be associated with the onset and development of childhood stuttering (Conture & Walden, 2012). Although increasingly more is known about the behavioral and physiological aspects of such emotional development, far less is known about the cortical processes associated with emotion in children who stutter. To address this gap in our knowledge, the present study investigated cortical associates of emotional reactivity and emotion regulation in young children who stutter (CWS) and young children who do not stutter (CWNS).

Methods: Participants were 17 CWS and 19 CWNS between 4 years 0 months to 6 years 11 months of age. Participants engaged in an Emotional Reactivity and Emotion Regulation tasks. During Emotional Reactivity task, participants passively viewed age-appropriate pleasant, unpleasant, and neutral pictures selected from the International Affective Picture System (IAPS) database (Lang, Bradley, Cuthbert, 2005). During Emotion Regulation task, participants viewed the unpleasant pictures as they listened to pleasant and neutral reappraisal stories about these pictures. The dependent measures were (1) mean amplitude of late positive potential (LPP, an evoked response potential (ERP) sensitive to emotional stimuli) during Emotional Reactivity and Emotion Regulation tasks, and (2) emotional reactivity and regulation related scores on caregiver reports of young children’s temperament (Children’s Behavior Questionnaire [CBQ] Rothbart, Ahadi, Hershey & Fisher, 2001).

Results: Main findings indicated that young CWS, when compared to their CWNS peers, exhibited significantly greater LPP amplitudes to the unpleasant pictures. Further, for only CWS, there were significant correlations between cortical measures of emotional reactivity and aspects of their temperament; also, only for CWS there were significant correlations between cortical measures of emotion regulation and temperamentally related measures of emotion.

Discussion: Results were taken to suggest that CWS, when compared to CWNS, are more emotionally reactive to negatively valenced stimuli (as indicated by cortical measures of emotional reactivity). Present findings provide support for how converging lines of evidence (e.g., cortical and parent indices of emotion) may broaden our understanding of the relation between emotion and childhood stuttering, if not childhood stuttering itself. Specifically, significant correlations between parental reports of temperament and CWS’s LPP amplitude suggest that aspects of CWS’s temperament play a contributing (although not necessarily singular) role in cortical reactivity to emotional stimuli. Thus, the innate emotional processes and proclivities that CWS exhibit should be considered in any truly comprehensive theoretical account of childhood stuttering.

References/Citations:
**Paper Title:** Eye Tracking and ERP Measures as Objective Markers of Hyperphagia in Prader-Willi Syndrome

**Authors:** Alexandra P. Key¹, Dorita Jones¹, Elizabeth Roof¹, Hailee Hunt-Hawkins¹, Elisabeth Dykens⁶

**Introduction:** Hyperphagia, or intense hunger, is one of the distinctive features of Prader-Willi syndrome (PWS). Increased interest in food emerges in early childhood (Miller et al., 2011), and in combination with food-seeking behaviors, remains a lifelong concern for individuals with PWS and their caregivers. Current measures of hyperphagia rely mainly on questionnaires (Dykens et al., 2007). While specifically targeting hyperphagia symptoms, such measures are indirect and suffer from a number of challenges including socially desirable answers and respondent bias. Psychophysiological measures, such as eye tracking and event-related potentials (ERP), do not require active behavioral responses and impose minimal cognitive demands. Therefore, they could provide more objective and direct measures of food-related interest in PWS and be used across the lifespan.

**Methods:** Eye-tracking (Study 1, n=42, 6-35 years) and ERPs (Study 2, n=32, 7-27 years) data were recorded in individuals with PWS in order to identify novel biomarkers of food interest and hyperphagia. Eye gaze fixations were recorded using a tabletop device (Tobii x50) during the spontaneous visual exploration paradigm (modeled after Sasson et al., 2008) using complex arrays of food and nonfood items. Eye tracking data quantified attention to the stimuli (number of fixations) and perseveration (duration of fixations and number of gaze returns). ERPs were recorded during passive viewing of food and non-food images presented one at a time. These data were used to assess perceptual and affective responses indexing stimulus salience.

**Results:** Eye tracking data revealed that participants with PWS explored food pictures more than nonfood images, as evident in the greater number and duration of fixations and more frequent gaze returns to the already-seen foods. Similarly, ERPs noted greater affective response (LPP amplitude) to food than household objects. Both eye tracking and ERP biomarkers of food interest correlated with the caregiver reports on the hyperphagia questionnaire (r’s=.33-.56). Analysis of the subset of participants who provided both eye tracking and ERP data (n=22) indicated that the average duration of fixations on food was associated with the ERP responses indexing perceptual processing, while the number of fixations and gaze returns correlated with the affective ERP responses (r’s=.31-.36).

**Discussion:** Our findings demonstrate that the eye tracking and ERP measures offer feasible new opportunities to characterize food-related interest in PWS. These brief, non-verbal measures provided direct, objective indices of stimulus salience and attention patterns across a wide age and ability range. The results also suggest that hyperphagia may include both attentional and affective components. This information is important for the development of new intervention approaches.

**References/Citations:**