**Symposium Title:** Electrophysiological Biomarkers of Risk Prediction and Outcome in Neurodevelopmental Disorders: Methodological Considerations and Insights Gained from Studies in ASD, ID and ADHD

**Discussant:** Shafali Jeste
Speaker 1: Charlotte Distefano (overview of EEG methods)
Speaker 2: Abby Dickinson (EEG in ASD)
Speaker 3: Caitlin Hudac (EEG in genetic syndromes associated with ASD/ID)
Speaker 4: Sandra Loo (EEG in ADHD)

**Overview:** In neurodevelopmental disorders, such as autism spectrum disorder (ASD), intellectual disability (ID) or Attention Deficit Hyperactivity Disorder (ADHD), the tremendous heterogeneity in etiology and clinical presentation can undermine our ability to effectively stratify patients, target interventions, and predict outcomes from those interventions. Research to improve stratification and outcome measurement in ASD has become increasingly focused on the identification of putative biomarkers, from genetic variants to electrophysiological and imaging characteristics, that may help to define more homogeneous, biologically based subgroups within the spectrum. Electrophysiology (EEG) holds particular promise as a biomarker in neurodevelopmental disorders for both practical and scientific reasons. From a practical standpoint, EEG data acquisition is more feasible than other imaging modalities due to its motion tolerance. Scientifically, EEG measures basic neural processes that are disrupted in neurodevelopmental disorders, such as neural connectivity, circuit formation, and neural synchrony. However, many challenges exist in the development of EEG biomarkers, such as the stability of measures, particularly over developmentally dynamic periods, sensitivity to change, specificity of measures to diagnostic domains and core deficits, and a biomarker’s ability to stratify individuals based on clinical features or likelihood of response to treatment. In this symposium, we will begin with an overview of methodological considerations in EEG studies in neurodevelopmental disorders (Distefano). We then will present data from studies that have taken innovative approaches to identify EEG biomarkers in neurodevelopmental disorders, from ASD (Dickinson) to rare genetic variants (Hudac) to ADHD (Loo). We will discuss common themes across these syndromes that will have relevance to the identification of biomarkers in neurodevelopmental disorders.

**Clinical Relevance:** While behavioral intervention is the mainstay of treatment for neurodevelopmental disorders such as ASD, their clinical heterogeneity precludes a “one size fits all” treatment approach and, in turn, renders the prediction of response to treatment challenging. In that context, necessary efforts are being made in genetics, electrophysiology (event related and resting state), and neuroimaging to quantify biomarkers that may inform treatment targets and outcomes in children with neurodevelopmental disorders.

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**Paper 1 of 4**

**Paper Title:** EEG Data Collection Strategies for Children with ASD: The Role of State in Data Quality and Spectral Power

**Authors:** Charlotte DiStefano, Ph.D.¹, Shafali Jeste, M.D.²

**Background:** Resting state EEG is commonly recorded during eyes open and eyes closed conditions, with eyes closed providing the best proxy of a true “resting state”, free of sensory stimuli. In studies of young children or children with limited cognitive ability, this pure “resting state” is challenging to consistently capture. These children may be unable to understand and follow directions to sit still with closed eyes, and they may require some stimulus in order to remain engaged and calm. This additional stimulus likely introduces more variability in state which, in turn, may influence the success of data acquisition and the actual EEG variables of interest (particularly certain oscillatory bands) (Webb et al., 2015). In order for EEG variables to be reliably related to clinical relevant traits, the distinction between state and trait must be elucidated.

¹ UCLA, Department of Psychiatry and Biobehavioral Sciences
² UCLA, Department of Psychiatry and Biobehavioral Sciences
Objectives: We will review methodological guidelines for collecting EEG data in challenging populations, namely infants, young children, or individuals with neurodevelopmental disorders. We then will present data from a recent study in which we quantified the “state” of participants (ASD and TD) during the EEG recording session. We examined how state related to: (1) child characteristics (age, IQ, diagnosis), (2) EEG data quality (percent of data retained), and (3) EEG power, particularly focusing on alpha due to its documented relationship with the resting state, attention and emotion regulation.

Methods: Participants included a heterogeneous group of children with ASD (N=39) ages 5-10, as well as an age-matched TD group (N=16). The ASD group spanned a wide range of cognitive and language levels. Specific strategies were used to acclimate participants to the EEG testing environment, including modeling, incremental practice and positive reinforcement (Tager-Flusberg et al., 2016). Resting EEG was recorded while participants watched a video of bouncing soap bubbles on a monitor. The state of the participant during the EEG recording was rated using a 5-point likert scale (Perceived State Rating; PSR), where higher scores correspond to higher levels of perceived anxiety/agitation.

Results: EEG data were successfully collected 85% of participants with ASD. In both TD and ASD participants, data retention was not related to chronological age, verbal IQ or non-verbal IQ. Participants with ASD were significantly more likely to have Perceived State Ratings above 1 (more agitated) than TD participants (p=0.002). In the ASD group, significantly less data was retained in participants with PSR 2-5 compared with PSR 1 (t=3.22, p=0.003). PSR groups did not differ on chronological age (t=0.46, p=0.65) or NVIQ (t=1.84, p=0.08). There was a trend toward lower VIQ in the higher PSR group (t=2.10, p=.05). Children in the TD group had significantly higher alpha power compared with children in the ASD group (p-values 0.003-0.036). Within the ASD group, participants with high PSR had the lowest frontal alpha (t=2.49, p=0.02).

Conclusions: Our results suggest that given appropriate supportive strategies, EEG data can be successfully collected from children with ASD, regardless of degree of cognitive and language impairment. The child’s state during the EEG recording was significantly related to both the amount of EEG data retained, and alpha spectral power. Alpha suppression has been consistently linked to attention and vigilance (Boiten, Sergeant, & Geuze, 1992; Klimesch, 1999), suggesting that our finding of reduced alpha power in children with an elevated state rating may reflect that these participants were less “at rest” during the EEG recording. These data highlight the importance of quantifying and addressing state when conducting EEG studies with developmental populations, both to increase data retention rates and to reduce the influence of state on EEG variables of interest.

References/Citations:
Paper Title: Spontaneous EEG Oscillations Relate to Cognitive Function in Autism Spectrum Disorder

Authors: Abby Dickinson, Ph.D.3, and Shafali Jeste, M.D.4

Background: The heterogeneous nature of autism spectrum disorders (ASD) makes the pursuit of a single diagnostic biomarker of ASD impractical. One way to capture the biological heterogeneity of ASD is to stratify children into clinically relevant and physiologically meaningful subgroups. Electroencephalography (EEG) has proven to be a particularly informative assay of neural function in ASD, as it serves as a measure of neural connectivity and synchrony, fundamental processes in brain function known to be disrupted in the condition. Therefore, considerable effort has been placed over the last several years on the quantification of spontaneous EEG activity in children and adults with ASD. However, reports of alterations in EEG oscillations in ASD are far from consistent, mostly due to the variability in the sample characteristics being studied (e.g. Edgar et al., 2015, Chan et al., 2007). For instance, the majority of studies quantifying EEG in ASD have focused on “high functioning” individuals, thus excluding a large proportion of the autism spectrum in which comorbid intellectual disability occurs.

Objectives: Several reports have identified higher spontaneous delta (1-4Hz), and lower alpha (8-12Hz) power in ASD, which has previously been interpreted to reflect increased neural excitation (Wang, 2013). Here we examine whether increased delta and decreased alpha power are present across high- and low-IQ individuals with ASD, or whether this pattern of EEG oscillations defines a specific sub-group within the spectrum.

Method: Fifty-four children with an ASD diagnosis, representing a wide range of ages (2 -12 years) and level of intellectual functioning (IQ ranging from 11 – 126), took part in the current study. The ASD children were split into ‘High IQ’ (N=27) and ‘Low IQ’ (N=27) groups, depending on whether their IQ fell above or below a cut-off of 70. Forty age-matched typically developing (TD) children (IQ ranging from 95-148) served as a control group. High-density EEG was recorded under task-free conditions while children watched bouncing bubbles on a computer screen. EEG data were then analyzed in the frequency domain, with relative spectral power calculated for the delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-20Hz) and gamma (>30Hz) frequency bands.

Results: Low-IQ children with ASD showed both higher relative delta (p=<.01) and lower alpha (p=<.01) power across the scalp compared to TD participants. High IQ children with ASD were found to have similar levels of both delta (p=.57) and alpha (p=.52) power to control participants. No group differences in spectral power were found in any other frequency band.

Conclusions: Our results suggest that the pattern of increased delta and decreased alpha power previously described in ASD is only present in children with ASD who have low IQ. These findings support that discrepancies in the reported EEG profiles of ASD may be partly-driven by between-study differences in the cognitive abilities of ASD participants. In this presentation, we report these findings and then place them into a larger context of EEG studies in ASD. I particular we will discuss how the neurophysiological differences reported here implicate alterations in specific neurobiological processes in individuals with ASD with comorbid intellectual disability.

References/Citations:

3 UCLA, Department of Psychiatry and Biobehavioral Sciences
4 Affiliation: UCLA, Department of Psychiatry and Biobehavioral Sciences
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Paper Title: EEG Biomarkers of Attention and Learning Associated with Rare Genetic Variants

Authors: Caitlin M. Hudac5, and Raphael A. Bernier6

Background: Between 25-50% of cases of Intellectual Disability (ID) are associated with genetic factors (Rauch et al., 2006; McLaren and Bryson, 1987) and similar rates are observed for autism spectrum disorder (ASD; Iossifov et al, 2014; Sanders et al, 2015). The behavioral challenge of accurately assessing performance in individuals with neurodevelopmental disorders is an obstacle to elucidating how genetic factors impact cognitive abilities at a systems level. In order to better capture domain-general aspects of cognition, we explore the neural correlates of attention and learning at a trial level to track ongoing novelty detection (i.e., attention to a novel infrequent sound) across individuals with LGDMs from modular networks associated with ID or ASD (Hormozdiari et al., 2015). These EEG biomarkers may provide critical insight regarding genetic contributions of neurodevelopmental disorders.

Objectives: We will review existing literature characterizing neurodevelopmental disorders associated with rare genetic variants. We will describe a dynamic approach for measuring biomarkers of attention and learning and present data from EEG studies of children with LGDMs from modular networks associated with ASD or with ID.

Methods: In an ongoing study, children age 5-18 (N = 85) with a LGDM completed a phenotype battery that consisted of clinical, behavioral, physical/medical, and electrophysiological assessments. In an auditory oddball EEG paradigm, children watched a video of a trip to the zoo while passively listening to frequent tones (70%, e.g., 1000 Hz), infrequent tones (15%, e.g., 750 Hz), and novel sounds (15%, e.g., chime, creak). Peak amplitude was extracted for the central P3a (180-350 ms) components to measure novelty detection. P3a outcomes are compared to a typical group of children (n = 22) that exhibited larger P3a amplitudes and patterns of habituation (i.e., P3a signal reduction over time) for novel relative to frequent condition.

Results: Per the modular network established by Hormozdiari et al., (2015; Module 1), a posthoc clustering strategy tested P3a responses for genes associated with ASD without ID (n = 1; CHD1) and a variable group of genes whose phenotype is associated with both ID and ASD without ID (n = 8; CHD8, DRYK1A). Consistent with the phenotype, the one child with CHD1 did not have ID and exhibited typical patterns of novelty detection and habituation. Within the variable phenotype group, children without ID (n = 2, CHD8; n = 1, DRYK1A) or with mild ID (n = 2, DRYK1A) exhibited slightly increased patterns of novelty detection and habituation. Children with moderate ID (n = 1, CHD8, n = 1, DRYK1A) did not exhibit novelty detection and a child with profound ID (n = 1, CHD8) exhibited an atypical P3a (frequent > novel). None of these children exhibited patterns of habituation, which is in contrast to other children with moderate to severe ID with a LGDM outside of the modular network (n = 1, SCN2A; n = 1, SUV420H1; n = 1, ADNP) who exhibit typical habituation patterns.

Conclusions: These results indicate specific mechanisms of attention are associated with children with a genetic variant and ID. This strategy highlights the sensitivity of EEG to characterize dynamic features of cognition and learning in low-functioning individuals that may improve assessment and treatment for individuals with ID.

5 University of Washington, Department of Psychiatry and Behavioral Sciences
6 University of Washington, Department of Psychiatry and Behavioral Sciences
References:


Paper Title: Refining EEG Biomarkers in ADHD for Diagnosis and Treatment Response Monitoring

Author: Sandra Loo, Ph.D.7

Background: There is marked heterogeneity in the behavioral, cognitive, and neural presentations of children diagnosed with attention-deficit/hyperactivity disorder (ADHD). This heterogeneity presents research and clinical challenges when trying to identify putative risk genes, define core deficits and recommend optimal treatment interventions for children with ADHD. Electroencephalography (EEG) is a strong candidate biomarker due to its high heritability and strong familial clustering, diagnostic utility, and sensitivity to treatment response. In addition, the first EEG biomarker for ADHD diagnosis was recently approved by the US Food and Drug Administration (FDA). While this diagnostic advancement may represent a milestone in general acceptance of using EEG as a quantitative assessment of brain function, further refinement of EEG biomarkers that better account for clinical heterogeneity and neurodevelopmental changes need to be developed.

Objectives: We will review the vast EEG literature in ADHD leading to the development of the FDA approved EEG biomarker as well as subsequent literature suggesting further refinement is needed. We will then present data from EEG studies of children with and without ADHD as well as EEG correlates of medication response among children with ADHD.

Methods: The sample consisted of 179 participants with ADHD and 93 non-clinical, healthy comparison children, aged 7- to 14-years old. All children received a baseline assessment consisting of semi-structured diagnostic interviews, comprehensive neurocognitive testing and EEG recording. Children with ADHD were then randomized to one of three medication conditions: d-methylphenidate, guanfacine, or their combination. Behavior, cognitive function and EEG during resting state and cognitive activation were measured at baseline and optimal dose for each medication group. Separate analyses for EEG markers that accurately identify children with ADHD diagnosis and that are associated with treatment response were conducted.

Results: First, we tested the FDA approved EEG biomarker (i.e., theta/beta ratio; THBR) for accuracy in ADHD diagnosis. The THBR did not differ significantly between children with ADHD and healthy comparison children. ADHD subtype and psychiatric comorbidities such as disruptive behavior disorders and depression have opposing and significant mediating effects on the THBR. Next, we tested multiple EEG features measured during a working memory task for association with ADHD diagnosis. This data yielded information about cortical mechanisms underlying working memory deficit and developmental course of these mechanisms in ADHD. Prediction of ADHD using multiple EEG measures was moderately high and suggested this may be a promising direction. Finally, we analyzed medication effects on EEG measures for the three medication groups and identified several markers for positive medication treatment response.

7 UCLA, Department of Psychiatry and Biobehavioral Sciences
Conclusions: The data presented suggest that multivariate EEG biomarkers may be useful indices of ADHD diagnosis, developmental course of disorder, and treatment response. Although the clinical utility of EEG measures is promising, the data suggest that caution is warranted when using them in clinical practice.