Promises & Practicalities of Neurophysiology in Clinical Trials in Rare Diseases

Chairs:
Kemi Olugemo, MD, FAAN
Uma Vaidyanathan, PhD

Speakers:

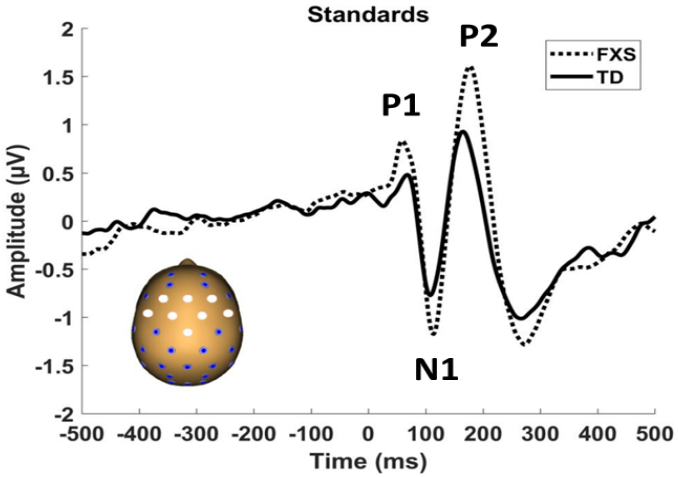
Allyson: Insights from patient journey in drug development, mouse-human models of disease, and consortium for biomarkers

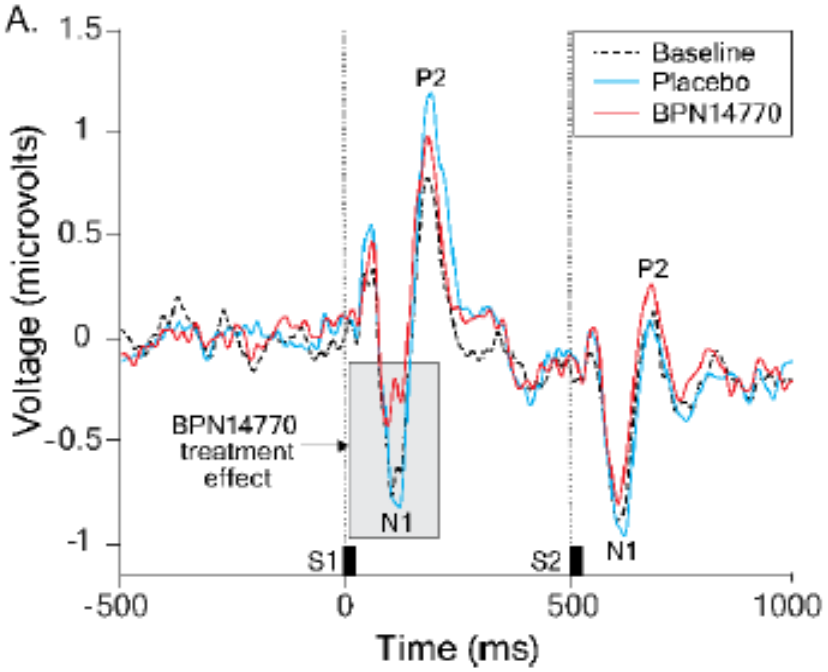
fast

Focus Domain	Measures to consider	Measures specifically assessed for AS
Communication	• ORCA • BSID-3, BSID-4 • VABS-2, VABS-3 • Communication Matrix • ASVA • CGI-AS	• ORCA • BSID-3, BSID-4 • VABS-2, VABS-3 • Communication Matrix • CGI-AS
Fine Motor	• BSID-3, BSID-4 • VABS-2, VABS-3 • ASVA • CGI-AS	• BSID-3, BSID-4 • VABS-2, VABS-3 • CGI-AS
Gross Motor	• BSID-3, BSID-4 • VABS-2, VABS-3 • Actimyo • GMFM • ASVA • CGI-AS	• BSID-3, BSID-4 • VABS-2, VABS-3 • Actimyo • CGI-AS
Global	• CGI-S-AS, CGI-I-AS • Caregiver CGI-AS	• CGI-S-AS, CGI-I-AS
ADL	• VABS-2, VABS-3 • ASVA	• VABS-2, VABS-3
QOL	• QOL Inventory • Caregiver Burden Inventory • Parent Adjustment Questionnaire • EQ-5D-Y • Quality of Life Disability Measure	
Cognition	• BSID-3, BSID-4 • VABS-2, VABS-3 • EEG	• BSID-3, BSID-4 • VABS-2, VABS-3 • EEG
Sleep	• Sleep Diary • Wearables • EEG • Sleep Mats • CGI-AS	• EEG • Sleep Diary • CGI-AS
Seizure	• Seizure Diary • EEG • CGI-AS	• Seizure Diary • EEG • CGI-AS
Behavior	• VABS-2, VABS-3 • ABC-C • BIAPAS	• ABC-C
Biomarkers	• EEG • AERP • APP (plasma) • CSF: UBE3A others	• EEG

a-bom ANGELMAN SYNDROME BIOMARKER & OUTCOME CONSORTIUM

Liz: EEG biomarkers to bridge mouse-human models of neurodevelopmental disorders



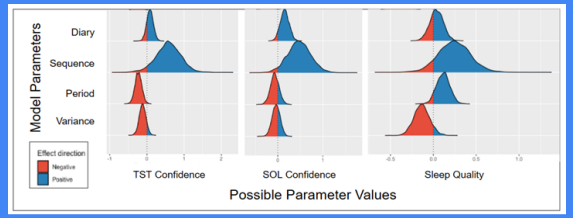


Justin: Considerations in assessing sleep via PSG, EEG

Consideration 1 – Signal Averaging

- In signal processing, it is mathematically guaranteed that averaging two signals in the time domain that have uncorrelated sources of noise will lead to a better underlying estimate
- In terms of sleep we can think about the human and device as two ‘sensors’ of sleep
- By combining them we can have a better estimate of the underlying ‘true’ value

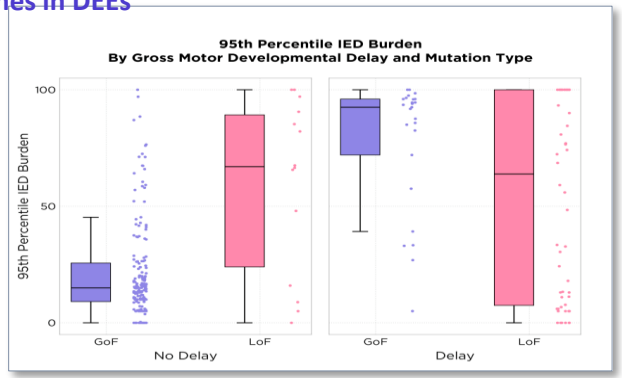
$$\sigma_{n,avg}{}^2 = \frac{1}{M^2}\sum_{j=1}^{M}\sum_{j=1}^{M} E\left(n_j(p)n_j(p)\right) = \frac{1}{M^2}M\sigma_n{}^2 = \frac{\sigma_n{}^2}{M}$$

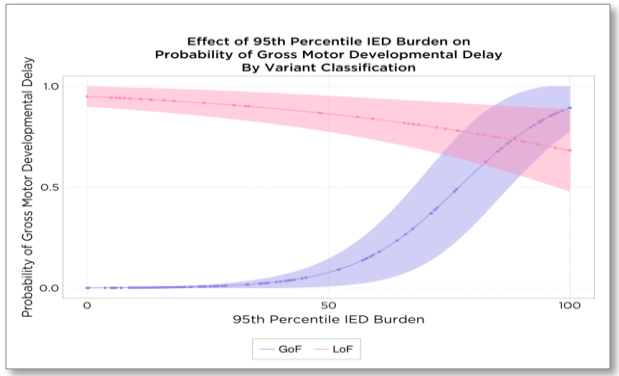


Conklin et al 2024

Dave: Computational approaches to EEG & PSG biomarkers

Machine learning-based analysis of EEG data can be used to identify novel biomarkers predicting developmental outcomes in DEEs





Methods

- A machine learning model trained and evaluated on EEG segments labeled by 8 epileptologists was used to identify 1 second windows containing IEDs, and IED burden; or percent time containing IEDs, was computed using a 20 second rolling window.
- 197 recordings collected from 7 GoF subjects
- 70 recordings collected from 11 LoF subjects
- Subject age range: 1 day – 16 years

Conclusions

- Recurrent epileptiform activity appears to precede developmental delay in SCN2A subjects with GoF variants.
- These findings demonstrate that EEG contains critical biomarkers of DEE- especially for SCN2A GoF subjects, and IED burden could aid in patient selection when therapy carries significant risk.
- Treatments aimed at controlling epileptic activity may be particularly effective in improving developmental outcomes in subjects with GoF mutations.

Why neurophysiology?

- Time scale of phenomena down to ms
- Cost-effective (e.g., vs MRI, DTI, etc.)
- Scalable (wearables, at home EEG)
- Can be real-time
- Large and growing body of research

Next Steps/Further Considerations:

(1) Plethora of endpoints: Need larger datasets and standardization. Note Society for Psychophysiological Research Guidelines

Picton, T. w., Bentin, S., Berg, P., Donchin, E., Hillyard, S. a., Johnson, R., ... Taylor, M. j. (2000). **Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria.** *Psychophysiology*, 37(2), 127-152. https://doi.org/10.1111/1469-8986.3720127

(2) Reliability of signal: how to define? What is alignment?

(3) FDA's 2019 Enrichment for Clinical Trials strategies:

- (a) Enrichment via decreasing variability
- (b) Prognostic enrichment
- (c) Predictive enrichment

PANEL DISCUSSION