Resting-State EEG Asymmetry and Irritability in Children with ASD:
The Autism Biomarkers Consortium for Clinical Trials

J. Benton[1], M. Santhosh[1], H. Borland[1], R. Bernier, G. Dawson, J. Dziura, S. Faja, A. Levin, A. Naples, E. Neuhaus[1], F. Shic, C[1]. Sugar, J. McPartland, & S. J. Webb[1] and the ABC-CT Consortium
[1]Center for Child Health, Behavior and Development, Seattle Children's Research Institute

Background

- **Autism Spectrum Disorder (ASD)** is a neurodevelopmental disorder characterized by social communication and behavioral impairments.
- **Irritability**, or a *proneness to experience negative affective states like anger or frustration,* is associated with several mental health disorders and is an important target of clinical trials for ASD (Barata et al., 2016; Brotman et al., 2017; Elbe & Lalani, 2012).
- **Electroencephalography (EEG)** measures neural activity and has been discussed as a potential biomarker in several mental health disorders. EEG is particularly important in ASD research due to its non-invasive protocol and flexibility (Webb et al., 2015).
- Acquired during resting state EEG, **Alpha power,** represents frequency in the 6 to 12Hz and has been shown to be increased in ASD (representing decreased activity), although findings are mixed (Wang et al., 2013). **Right Frontal Alpha-Asymmetry (FAA)** may index behaviors associated with withdrawal and other negative temperament characteristics. Additionally, infants at higher risk for ASD begin with a relative left frontal asymmetry that shifts toward the right as they develop (Gabard-Durnham et al., 2015; Sutton et al., 2005).

This study...
- Investigates the relationship between frontal alpha asymmetry and irritability in ASD children.
- **Hypothesis 1:** Compared to TD, ASD children will show both higher parent-reported irritability and greater alpha power in the right than left frontal lobe (Right FAA).
- **Hypothesis 2:** Children with ASD who score clinically high in irritability will show Right FAA compared to ASD children with low irritability.

Methods

The Autism Biomarkers Consortium for Clinical trials (ABC-CT) is a NIH-funded five-site longitudinal study investigating potential biomarkers in children ages 6–11.5 with ASD compared to typically developing peers. Data collected includes clinical/social functioning, eye-tracking, and EEG.

Measures
- Autism Diagnostic Observation Schedule (ADOS) for ASD severity
- Differential Ability Scale (DAS) for IQ
- Aberrant Behavior Checklist – Irritability Scale
- Resting-state EEG data – High and Low Alpha Power

Resting-State EEG Collection & Processing
- EEG System: EGI 128 Channel Hydrocel Geodesic Sensor Net, with either 300 or 400 amps, at a 1000 Hz sampling rate, with a 0.1-200Hz filter, and a 0.1Hz digital high pass filter post-acquisition.
- Resting-state EEG stimuli consisted of 180 seconds of non-social abstract images presented as 6 videos divided into 3 blocks. Participants were reminded to sit still and watch the videos without talking.
- Logs, videos, and EEG files were reviewed for protocol fidelity, child compliance, and file integrity.
- Resting-state data was processed through the Batch EEG Automated Processing Platform (BEAPP; Levin et al., 2018) to derive the power within the chosen frequency bands–this study uses high alpha (6-8.99Hz) and low alpha (9-12.99Hz).

Methods

Participants
- 399 (280 ASD) were enrolled in the study
  - 368 (252 ASD) provided ≥20 seconds of attended, artifact free EEG data.
- Using a raw irritability score clinical cutoff of ≥18, participants with ASD were divided into high (H=69) and low (L=183) irritability groups (Brinkley et al., 2007).
- There were no participants in the TD group that met the threshold for high irritability, and therefore were not analyzed by High and Low Irritability.

Analysis
- FAA was calculated using mean Alpha Power as described in Sun, Pferäkylä, & Hartikainen (2017) for:
  - Left Frontal (E20, E23, E24, E27, E28) and
  - Right Frontal (E3, E117, E118, E123, E124)
  - FAA = Right Frontal Power − Left Frontal Power
    - A score >0 reflects Right FAA
- Analyses utilized ANOVAs and correlations.

Resting - 109 electrodes
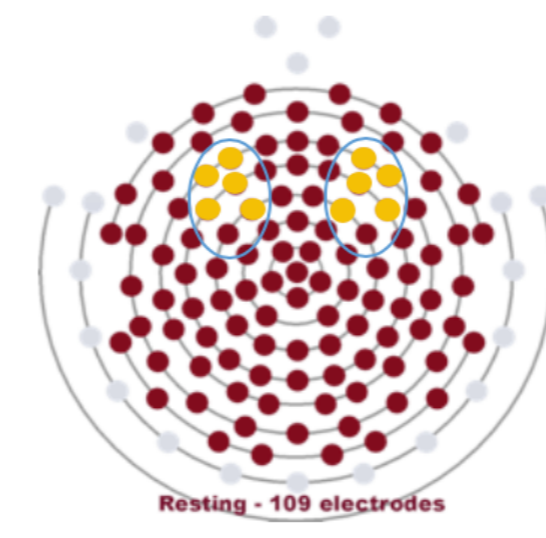
	TD	**ASD**	**ASD Only**	
	All	**All**	**Irritability (H)**	**Irritability (L)**
Total N / %	116	252	69	183
Female N / %	36 / 31.03%	61 / 24.21%	11 / 15.94%	50 / 27.32%
Age in years	8.49 (1.61)	8.58 (1.64)	8.67 (1.75)	8.55 (1.59)
DAS Full Scale IQ	115.22 (12.32)	96.65 (20.97)	98.51 (21.01)	96.67 (17.10)
ADOS CSS	1.59 (0.875)	7.58 (1.787)	7.39 (1.89)	7.65 (1.75)
ABC Irritability	1.23 (2.04)	12.49(9.29)	24.93 (6.02)	7.80 (4.97)
High FAA (9-12.99Hz)	-0.011 (0.274)	0.016 (0.259)	0.036 (0.264)	0.009 (0.257)
Low FAA (6-8.99Hz)	-0.053 (0.276)	-0.013 (0.262)	0.005 (0.273)	-0.019 (0.258)

Table 1. Mean and (SD) for TD and ASD participants at T1.

Results

Hypothesis 1.
There was a significant difference between groups in irritability symptoms, with less irritability reported in the TD group than the ASD group, $F_{(1, 366)}=166.371$, $p<0.001$.
- See the graph to the right.
- There were no differences between diagnostic groups in:
  - High FAA, $F_{(1,366)}=0.84$, $p=0.36$
  - Low FAA, $F_{(1,366)}=1.806$, $p=0.18$.

ASD vs TD Irritability
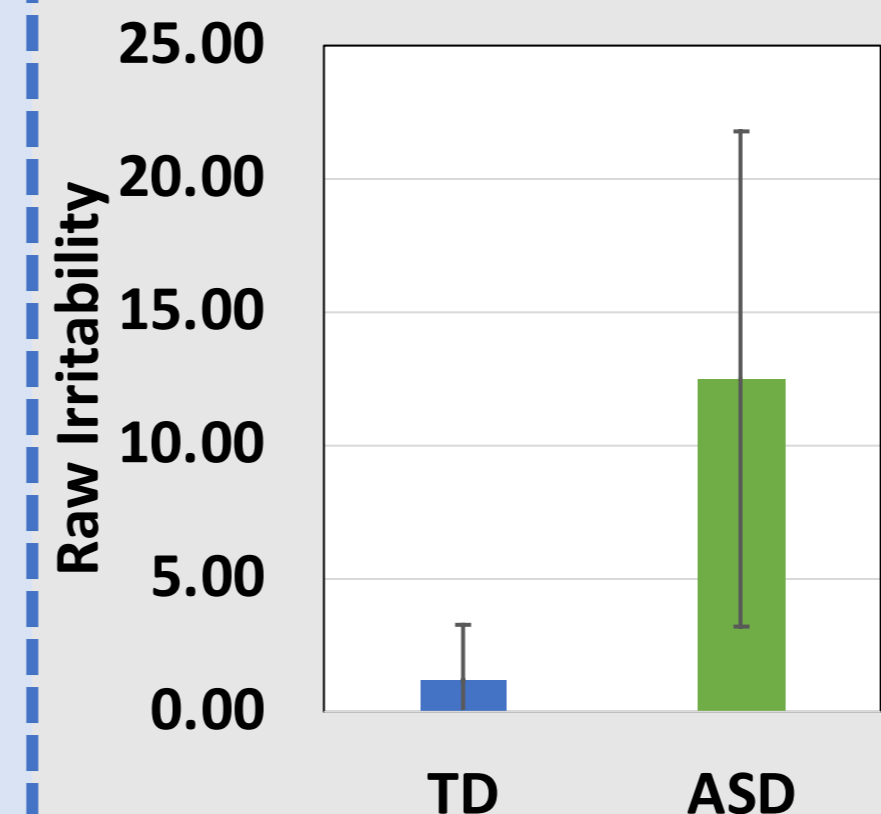
Results

H2a. Correlations within ASD
- No relationships between High FAA or Low FAA and IQ, ASD severity, or parent-reported irritability.

H2b. ANOVAs within ASD
- There was no significant difference between (H) and (L) Irritability ASD groups in either High FAA, $F_{(1,250)}=0.011$ or Low FAA, $F_{(1,250)}=0.677$) as shown in the graph below.

	Low FAA	High FAA	Irritability
Verbal IQ	-0.067	0.06	0.026
Non-Verbal IQ	-0.023	0.096	0.016
Full Scale IQ	-0.041	0.091	0.028
ADOS CSS	0.029	0.035	-0.008
Irritability	0.063	0.043	–

Table 2. Irritability and FAA Correlations in ASD at T1

Frontal Alpha Asymmetry by Low and High Irritability in ASD (N=252)
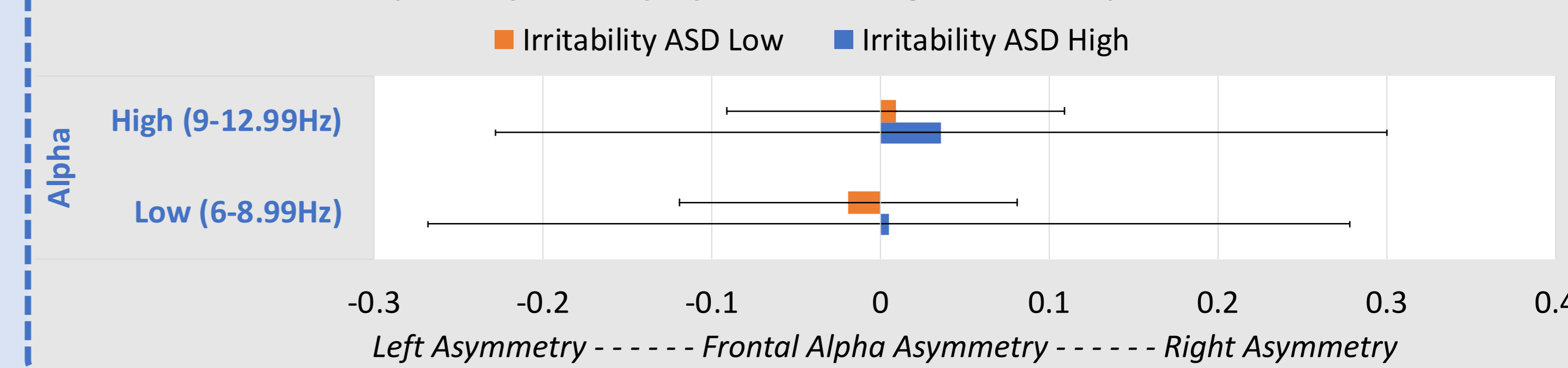
Discussion

- Irritability is a transdiagnostic characteristic and is found across childhood neurodevelopmental disorders and childhood mental health disorders. Irritability is a target of treatment for ASD. Our goal was to examine if frontal asymmetry in the alpha band was related to irritability in children with ASD.

Conclusion
- Children with ASD compared to children with TD were reported as having more behaviors that were characterized as reflecting "irritability" by their parents.
- However, we neither found differences in FAA in children with ASD and TD, nor within children with ASD who had High or Low Irritability scores on the ABC.
- Additionally, there were no relationships between ASD severity, IQ, Irritability, and High or Low FAA.

Future Steps
- It may be that FAA in a child is not related to parent report of irritability or that child mood (state) during the EEG may influence FAA activity. As a follow up, we will be able to look at mood ratings taken by the experimenter during acquisition.

References
- Barata, P. C., Holtzman, S., Cunningham, S., O'Connor, B. P., & Stewart, D. E. (2016). Building a Definition of Irritability From Academic Definitions and Lay Descriptions. *Emotion review: Journal of the International Society for Research on Emotion, 8*(2), 164–172.
- Brinkley, J., Nations, L., Abramson, R. K., Hall, A., Wright, H. H., Gabriels, R., Gilbert, J. R., Pericak-Vance, M. A., & Cuccaro, M. L. (2007). Factor analysis of the aberrant behavior checklist in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 37*(10), 1949–1959.
- Brotman, M. A., Kircanski, K., & Leibenluft, E. (2017). Irritability in Children and Adolescents. *Annual Review of Clinical Psychology, 13*(1), 317–341.
- Elbe, D., & Lalani, Z. (2012). Review of the pharmacotherapy of irritability of autism. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 21*(2), 130–146.
- Gabard-Durnam, L., Tierney, A. L., Vogel-Farley, V., Tager-Flusberg, H., & Nelson, C. A. (2015). Alpha asymmetry in infants at risk for autism spectrum disorders. *Journal of Autism and Developmental Disorders, 45*(2), 473–480.
- Levin, A. R., Méndez Leal, A.S., Gabard-Durnam, L. J., and O'Leary, H.M. BEAPP: The Batch Electroencephalography Automated Processing Platform. *Frontiers in Neuroscience* (2018).
- Sun, L., Peräkylä, J., & Hartikainen, K. M. (2017). Frontal alpha asymmetry, a potential biomarker for the effect of neuromodulation on brain's affective circuitry—Preliminary evidence from a deep brain stimulation study. *Frontiers in Human Neuroscience, 11.*
- Sutton, S. K., Burnette, C. P., Mundy, P. C., Meyer, J., Vaughan, A., Sanders, C., & Yale, M. (2005). Resting cortical brain activity and social behavior in higher functioning children with autism. *Journal of child psychology and psychiatry, and allied disciplines, 46*(2), 211–222. https://doi.org/10.1111/j.1469-7610.2004.00341.x
- Wang, J., Barstein, J., Ethridge, L. E., Mosconi, M. W., Takarae, Y., & Sweeney, J. A. (2013). Resting state EEG abnormalities in autism spectrum disorders. *Journal of neurodevelopmental disorders, 5*(1), 24.
- Webb, S. J., Bernier, R., Henderson, H. A., Johnson, M. H., Jones, E. J. H., Lerner, M. D., McPartland, J. C., Nelson, C. A., Rojas, D. C., Townsend, J., & Westerfield, M. (2015). Guidelines and best practices for electrophysiological data collection, analysis and reporting in autism. *Journal of Autism and Developmental Disorders, 45*(2), 425–443.