EEG and Pupillary Response in Children with Autism: Results from the ABC-CT Feasibility Study

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Background

- Dysregulated attention and arousal are comorbid features of autism spectrum disorder (ASD). These symptoms are associated with differences in noradrenergic and cholinergic activity.
- Pupil diameter (PD) is a marker of noradrenergic and cholinergic (neuromodulatory) activity and indexes brain network dynamics.
- Prior work has established that individuals with ASD exhibit attenuated pupil response to light, suggesting altered neuromodulatory activity.
- However, there have been no studies in humans linking the dynamics of the pupillary light reflex (PLR) to EEG features.
- Understanding the relationship between PD and EEG may help to parse heterogeneity among individuals with ASD.

Method

Sample

Group	n (n males)	Mean Age (Y)	Min. Age (Y)	Max. Age (Y)
ASD	25 (20)	7.77	4.42	11.3
TD	26 (17)	6.59	4.01	11.4

- EEG and eye-tracking (ET) data were collected from 51 participants recruited from the New Haven, CT, Boston, MA, Los Angeles, CA, Durham, NC, and Seattle, WA metropolitan areas as a part of the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) feasibility study.

EEG Processing:

- EEG was recorded at 1000 Hz with a 128-channel Hydrocel Geodesic Sensor net.
- Resting data were collected while participants sat quietly watching an abstract video on a computer screen.
- Data were cleaned utilizing the HAPPE[3] pipeline with line noise removal, a high-pass filter, and rereferencing to an average reference.
- Data were filtered from 0.1-100 Hz.
- Participants were included in the EEG sample if they had at least 40 seconds of artifact-free resting data.
- Multitaper Fourier transforms were used to estimate band-specific power.
- EEG slope and peaks were measured using the FOOOF[4] pipeline and customized MATLAB scripts.
- EEG power was averaged over 125 electrodes.

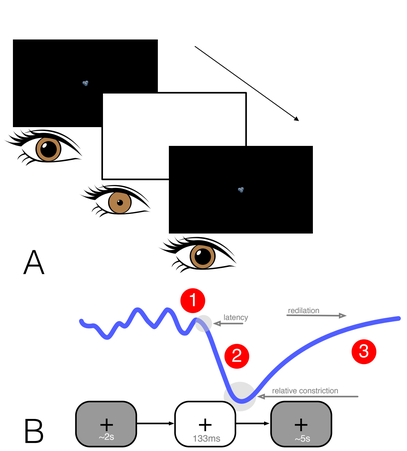
Pupil Analysis:

- Pupil dilation data were collected using an SR Eyelink-1000 + binocular remote camera system at 500 Hz.
- The PLR was calculated in response to a 133ms white flash followed by a black screen.
- PLR dynamics examined included relative constriction, latency of constriction, and redilation and constriction velocities.

Behavioral Data:

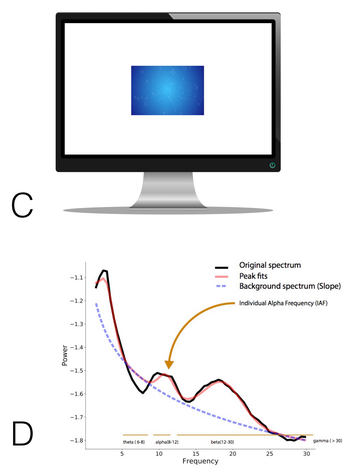
- Diagnosis was confirmed via the Autism Diagnostic Observation Schedule 2nd edition (ADOS), the Autism Diagnostic Interview (ADI), and clinician confirmation of meeting DSM-5 criteria for ASD.
- Vineland Adaptive Behavior Scales 3rd edition (VAB-III)
- Social Responsiveness Scale 2nd edition (SRS)

Method



A. A black screen for ~ 2 seconds was followed by a white screen for 133ms and a black screen for ~5 seconds.

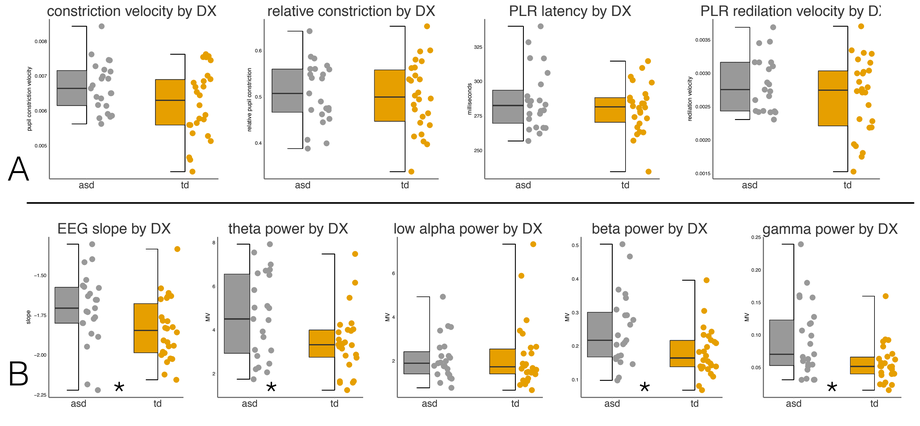
B. The canonical pupillary light response showing (1) latency to constrict, (2) relative constriction, and (3) redilation.



C. Resting EEG was recorded while participants watched a two minute video on a computer screen.

D. Resting EEG power spectra depicting slope, Individual Alpha Frequency (IAF), and band-specific power ranges.

Results

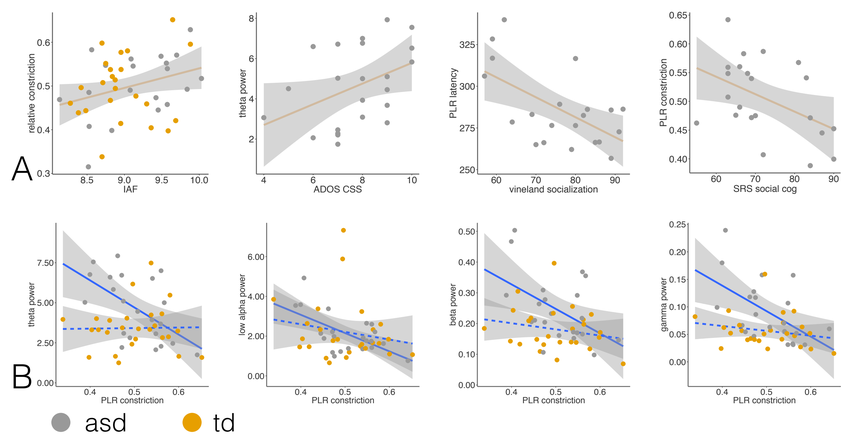


- PLR comparisons revealed marginal differences in constriction velocity (t=1.941, p=.**058**), such that constriction velocity, but not latency, was faster in individuals with ASD than in controls. [Panel A]
- EEG analyses revealed individuals with ASD exhibited an atypical power spectrum featuring a less steep slope (t=2.184, p=.**034***). [Panel B]
- Individuals with ASD exhibited higher power in theta (t=2.5, p=.**017***), beta (t=2.638, p=.**011***), and gamma (t=2.91, p=.**005***) bands compared to controls. [Panel B]

- Across groups PLR latency correlated with:
  - Theta power (r=.374, p=.**009***),
  - Beta power (r=.473, p<.**001***),
  - Gamma power (r=.312, p=.**031***),
- IAF correlated with PLR constriction (r=.295, p=.**051**) and constriction velocity (r=.326, p=.**031***) such that faster IAF predicted increased constriction and constriction velocity.

Results

Neural Response, Pupillary Dilation, and Clinical Characterization



Correlations with PLR constriction and EEG power

Group	r (theta)	p (theta)	r (alpha)	p (alpha)	r (beta)	p (beta)	r (gamma)	p (gamma)
ASD	-.558	**.007***	-.603	**.003***	-.490	**.021***	-.550	**.008***
TD	.018	.931	-.189	.356	-.213	.297	-.220	.281

A. Among children with ASD:
- ADOS calibrated severity score correlated with theta (r=.473. p=.**023***) and PLR latency (r=.359, p=.093). [Panel A]
- PLR latency correlated with the socialization domain of the Vineland (r=-.586, p=.**005***).
- PLR constriction correlated with the Social Responsiveness Scale Cognition Subscale (r=-.459, p=.**003***). [Panel A]

B. PLR constriction displayed strong relationships with EEG power among individuals with ASD but not among TD controls, such that decreased power was associated with reduced constriction. [Panel B]

Conclusions

- These are the first data to examine relationships between EEG and PLR in individuals with ASD, revealing potential relationships between brainstem nuclei, cortical activity, and clinical symptomology.
- The relationship among the PLR and ASD symptomology suggests increased noradrenergic activity, indicated by increased PLR latency and attenuated constriction. These PLR features also predict atypical EEG profile and increased symptomology.
- The relationships between PLR and IAF suggest that, across groups, cortical network activity and neuromodulatory systems exhibit stable relationships.
- The strong relationship between PLR constriction and EEG in ASD suggest that variability in brain activity in ASD is more tightly tied to neuromodulatory function or increased variability in neuromodulatory function in ASD results in more variable EEG activity.
- These findings, showing linkages among brain markers and with clinical symptomology, show promise for these biomarkers as indicators of treatment response and as potential targets for treatment development.

References

1. Nyström, P., Gredebäck, G., Bölte, S., & Falck-Ytter, T. (2015). Hypersensitive pupillary light reflex in infants at risk for autism. Molecular autism, 6(1), 10.
   The PLR paradigm was adapted from this paper.
2. Loth, E., Charman, T., Mason, L., Tillmann, J., Jones, E. J., Wooldridge, C., ... & Banaschewski, T. (2017). The EU-AIMS Longitudinal European Autism Project (LEAP): design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. Molecular autism, 8(1), 24.
   The PLR paradigm was originally part of the EU-AIMS protocol which is described in this paper
3. Gabard-Durnam, L. J., Mendez Leal, A. S., Wilkinson, C. L., & Levin, A. R. (2018). The Harvard Automated Processing Pipeline for Electroencephalography (HAPPE): standardized processing software for developmental and high-artifact data. Frontiers in neuroscience, 12, 97.
4. Haller, M., Donoghue, T., Peterson, E., Varma, P., Sebastian, P., Gao, R., ... & Voytek, B. (2018). Parameterizing neural power spectra. bioRxiv, 299859.

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