Sex differences in the relationship between depressive symptoms and pupillary light reflex in children with ASD: Results from the ABC-CT Phase One Study

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Background

- Children with autism spectrum disorder (ASD) have high rates of unrecognized and untreated co-occurring depression.[1]
- Depression and restricted and repetitive behaviors (RRBs) show sex differences across age, with depression being higher in non-ASD females and RRBs being higher in ASD males.[2,3]
- Both are hypothesized to associate with function of the autonomic nervous system (ANS). [2,3]
- Based on findings from the pupillary light response (PLR), a putative biomarker for ANS function, the ANS may function differently in ASD and typically developing individuals with depression. This variability has been characterized by PLR latency and relative pupil constriction (RPC).[3]
- Sex differences in the relationship between depressive and RRB characteristics and the PLR response have not been investigated in children with ASD.

Objective:
Examine the relationship between (a) depressive and (b) RRB features and PLR latency and RPC across sex.

Methods

ABC-CT Study Details:
- Multi-site, longitudinal study aimed with developing objective and reliable biomarkers of social functioning in ASD.
- A large sample (N = 399) of children with and without ASD was evaluated across 6 months through clinical assessments, electroencephalogram (EEG), and eye-tracking.

Inclusion/Exclusion Criteria:
- Age 6-11.
- ASD diagnoses confirmed via Autism Diagnostic Observation Schedule (ADOS-2), the Autism Diagnostic Interview-Revised (ADI-R), and clinician endorsement of DSM-5 criteria for ASD.
- FSIQ: 60-150 obtained via Differential Ability Scales (DAS-II).
- Stable medication for 8 weeks.
- Children without sensory or motor impairments, epilepsy, and genetic or neurological conditions.
- Children without ASD were not included in these analyses due to exclusion of children with elevated CASI-5 scores.

Participants	n	Age (SD)	FSIQ (SD)
ASD Males	213	8.75 (1.66)	95.29 (18.65)
ASD Females	65	8.43 (1.67)	101.25 (15.62)

Table 1. Participant demographics

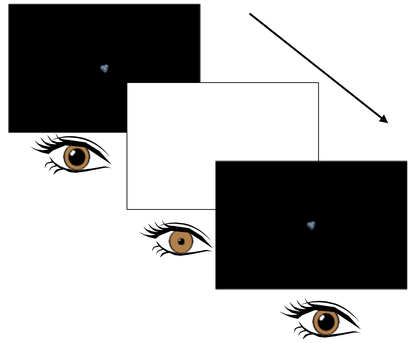
Clinical Measures:
- *Social Responsiveness Scale (SRS-2)*
  - Parent-reported rating scale that characterizes DSM-5 ASD symptoms.
- *Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2)*
  - Clinician-administered, semi-structured, play-based task to assess ASD symptomology.
- *Child and Adolescent Symptom Inventory, 5th Edition (CASI-5)*
  - Parent-reported behavior rating scale for DSM-5 emotional and behavioral disorders in children.
  - Major Depressive Episode (MDE) T-score was used to characterize depressive symptoms in children.

Methods, cont.

Eye-tracking Acquisition
- Binocular eye-tracking data were collected at 500 Hz using a SR Eyelink 1000 Plus.

Eye-tracking Experiment
- Participants were presented with 16 trials of a 6 second stimulus with the onset of the flash occurring randomly between 1600 and 2400 milliseconds. 6 experimental orderings were used.

A)



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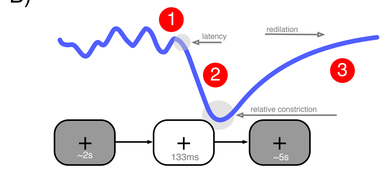


Figure 1: A) Stimuli included a screen with (1) a central fixation point on a black background that (2) flashed white for 75 milliseconds, and (3) then returned to black screen. B) The pupillary light response showing (1) latency to constrict, (2) relative constriction, and (3) re-dilation.

Statistical Analyses:
- Relationships between SRS RRB T-Scores, ADOS RRB severity, depressive symptoms, and PLR latency and RPC were analyzed using correlations and independent-samples t-tests.

Results

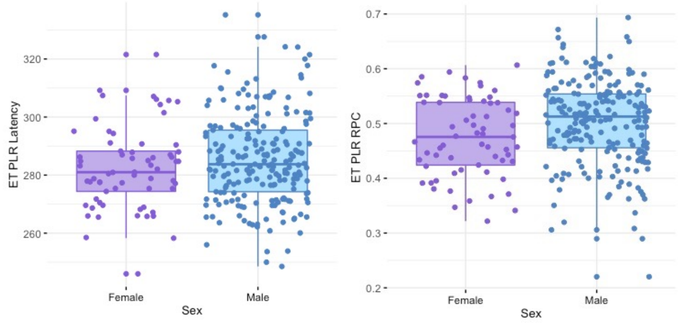
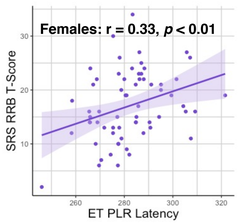


Figure 2. Distribution of ET PLR Latency and Relative Pupil Constriction across sex.

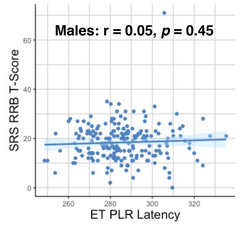
- There was a significant difference in PLR latency and RPC across sex ($p < 0.01$) with males demonstrating a larger latency and RPC (Figure 2).
- In females, there was a significant correlation of PLR latency and RPC with SRS RRB scores (r = 0.33, $p < 0.01$; r = -0.28, $p = 0.02$, respectively), such that increased latency and decreased RPC associated with greater RRB behaviors (Figure 3a, 3b)
- In males, there was a significant correlation of PLR RPC with MDE T-Score, such that increased constriction was associated with greater depressive symptoms (r = 0.17, $p = 0.01$) (Figure 3c).
- In males, PLR latency was also significantly correlated with ADOS RRB Severity (r = -0.16, $p = 0.01$) with lower latency corresponding to higher RRB symptoms (Figure 3d).
- There was a significant difference in the correlations for PLR Latency and SRS RRBs (Z = 2.03, p = 0.04) and PLR RPC and SRS RRBs across sex (Z = -2.41, p = 0.01) (Figure 3a-3c).

Results, cont.

A)



Z = 2.03 , $p = 0.04$ (two-tailed)



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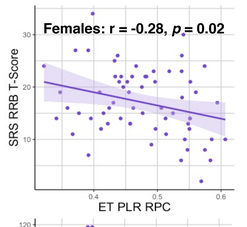
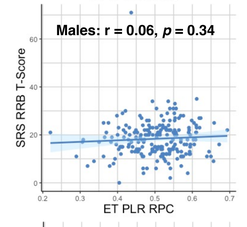
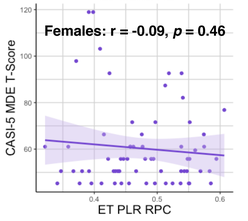


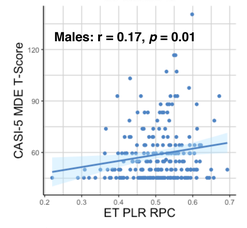
Z = -2.41 , $p = 0.01$ (two-tailed)



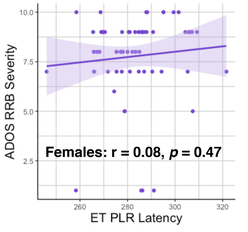
C)



Z = -1.74 , $p = 0.08$ (two-tailed)



D)



Z = 1.67 , $p = 0.09$ (two-tailed)

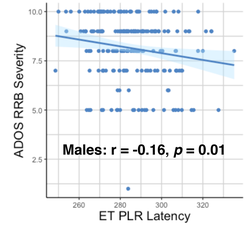


Figure 3: A) Relationship between ET PLR Latency and SRS RRB across sex, B) Relationship between ET PLR RPC and SRS RRB across sex, C) Relationship between ET PLR RPC and CASI MDE T-Score across sex, and D) ET PLR Latency and ADOS RRB Severity across sex.

Discussion

- These findings provide initial evidence of sex-based relationships among depressive and RRB symptoms and PLR response in children with ASD.
- Based on previous literature, greater PLR latency and smaller RPC with RRB symptoms may signal greater ANS dysregulation in females as compared to males.
- These results suggest that mechanistic differences in ANS function may influence differential expression of RRBs and depression in males and females.
- Understanding these relationships may help inform the impact of psychiatric co-occurring conditions on the experience of individuals with ASD.

References

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2. Fan, X., Miles, J. H., Takahashi, N., & Yao, G. (2009). Abnormal transient pupillary light reflex in individuals with autism spectrum disorders. Journal of Autism and Developmental Disorders, 39(11), 1499–1508.
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