Sex Differences in Anxiety Symptoms and Eye-Blink Rates in Children with Autism: Results from the Autism Biomarkers Consortium for Clinical Trials (ABC-CT)

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Background

- Children with autism spectrum disorder (ASD) experience higher rates of anxiety disorders than typically developing peers with a prevalence rate of roughly 40%.[1, 2]
- Spontaneous eye-blinking is an autonomic process, and rates are affected by emotional states, such as stress or anxiety.
- Spontaneous eye-blink rates (EBRs) predict abnormal neuromodulation activity, and plays a role in anxiety modulation.[3, 4]
- EBRs increase significantly during stressful situations or while watching stressful videos.[5, 6]
- However, EBRs in relation to anxiety symptoms in autistic children has yet to be explored.
- EBRs are a key autonomic marker of anxiety in the general population, making this an important function to explore and understand if EBRs function the same way in autistic youth with anxiety symptoms (AS).

Objectives

This study aimed to examine the relationship between EBRs and AS in autistic youth. Analyses were also conducted to explore sex differences in EBRs and AS.

Methods

PARTICIPANT CHARACTERISTICS

Table 1. Participant demographics; Mean (Standard Deviation)

Sex	N	Age in Years	FSIQ
Male	166	8.71 (1.65)	96.11 (19.06)
Female	45	8.26 (1.66)	101.82 (16.51)

BEHAVIORAL AND COGNITIVE MEASURES

- ASD diagnoses were confirmed with the Autism Diagnostic Observation Schedule, Autism Diagnostic Interview-Revised, and clinician endorsement of DSM-5 criteria for ASD.
- IQ was assessed with Differential Ability Scales-II.
- Parent-reported AS were assessed via the Child and Adolescent Symptom Inventory-5. T-scores from Category D, Generalized Anxiety, were used to analyze AS.

EYE-TRACKING AND EBR ACQUISITION AND ANALYSIS

- Eye-blinks were defined as periods of missing data between 50 and 250ms that were circumscribed by (1) valid on-screen data and (2) saccades as defined by the SR-research on-line event parser.
- Eye-tracking (ET) data was recorded at 500 Hz using the SR Eyelink 1000+.
- ET data was collected while participants viewed 5 paradigms: activity monitoring (AM), biological motion (BM), interactive social task (SI), static scenes (SS), and visual search (VS).
- EBRs were calculated as number of spontaneous eye-blinks per paradigm and across the entire ET experiment battery. EBRs were normalized with a log base 10 transformation.

Methods

STATISTICAL ANALYSIS

- T-tests were performed to compare AS and EBRs between groups.
- Linear regression models were performed to test the relationships between AS, EBRs, and sex for each ET paradigm and the entire ET experiment battery.

Results

- Sex differences were observed in AS severity and EBRs in autistic youth.

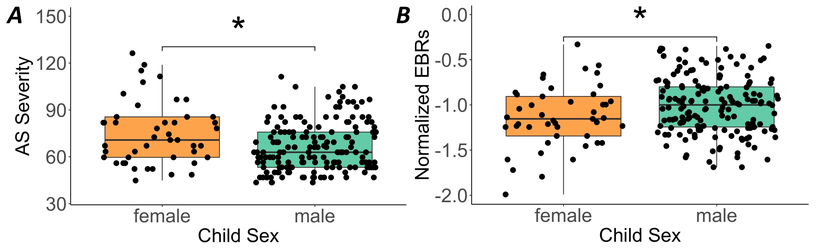

Figure 1. A) Comparison of AS severity T-scores by sex. Females had significantly higher AS than males (t(58)=2.6, *p*=.011). ***B)*** EBRs by sex. Females had significantly lower EBRs during the ET experiment battery (t(65)=2.1, *p*=.031).

- AS were not significantly related to EBRs across the individual paradigms and the entire ET experiment battery when only including AS and EBR in the model.
- Significant AS-by-sex interactions effect were observed when sex was added to the model for the entire ET experiment battery and the SI and AM paradigms. All effects remained non-significant for SS, BM, and VS.

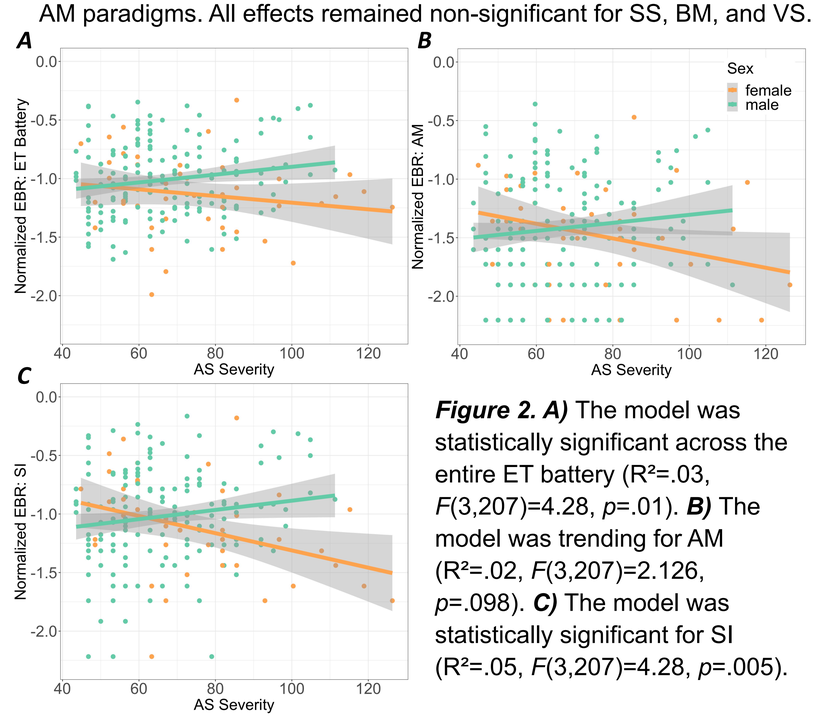

Figure 2. A) The model was statistically significant across the entire ET battery (R^2=.03, *F*(3,207)=4.28, *p*=.01). ***B)*** The model was trending for AM (R^2=.02, *F*(3,207)=2.126, *p*=.098). ***C)*** The model was statistically significant for SI (R^2=.05, *F*(3,207)=4.28, *p*=.005).

Results

Table 2. Regression model output on the effects of AS and sex on EBRs. Significant effects are indicated by green highlight and *.

	ET Battery	AM	SI
AS	ß=-.002, *SE*=0.002, *p*=.22	ß=-.006, *SE*=0.003, p=.06	ß=-.007, *SE*=0.002, *p*=.013*
Sex	ß=-.311, *SE*=0.211, *p*=.14	ß=-.006, *SE*=0.301, p=.06*	ß=-.07, *SE*=0.266, *p*=.008*
AS × Sex	ß=.006, *SE*=0.002, *p*=.029*	ß=.009, *SE*=0.004, p=.017*	ß=.01, *SE*=0.003, *p*=.001*
AS Male	ß=.003, *SE*=0.001, *p*=.031*	ß=.003, *SE*=0.002, *p*=.13	ß=.003, *SE*=0.001, *p*=.049*
AS Female	ß=-.002, *SE*=0.002, *p*=.268	ß=-.006, *SE*=0.003, *p*=.045*	ß=-.007, *SE*=0.002, *p*=.015*

Conclusions

- Partially consistent with our hypothesis and effects seen in the general population, results indicated higher AS were associated with increased EBRs. However, this relationship was only seen in autistic males.
- One potential explanation for this effect being unobserved in autistic female youth is that they may be not be anxious during ET, but have high trait levels of AS, resulting in reduced EBRs and increased AS in our analyses.
- Interestingly, these significant effects were only observed in 2 of the ET paradigms: AM and SI. These are of the only 2 paradigms that include videos of people interacting together or doing activities. This may have produced a more realistic situation or more stressful stimuli to observe for the participants because autistic people tend to experience difficulties with social situations.
- Results suggest that it is important to consider sex and co-occurring psychiatric conditions when studying EBRs in autistic populations and that EBRs can vary based on stimuli presentations.

References

1. Mingins, J. E., Tarver, J., Waite, J., Jones, C., & Surtees, A. D. (2021). Anxiety and intellectual functioning in autistic children: A systematic review and meta-analysis. Autism, 25(1), 18–32. https://doi.org/10.1177/1362361320953253
2. van Steensel, F. J., Bögels, S. M., & Perrin, S. (2011). Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. *Clinical child and family psychology review*, *14*(3), 302–317. https://doi.org/10.1007/s10567-011-0097-0
3. Jongkees, B. J., & Colzato, L. S. (2016). Spontaneous eye blink rate as predictor of dopamine-related cognitive function-A review. *Neuroscience and biobehavioral reviews*, *71*, 58–82. https://doi.org/10.1016/j.neubiorev.2016.08.020
4. de la Mora, M. P., Gallegos-Cari, A., Arizmendi-García, Y., Marcellino, D., & Fuxe, K. (2010). Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: Structural and functional analysis. *Progress in neurobiology*, *90*(2), 198–216. https://doi.org/10.1016/j.pneurobio.2009.10.010
5. Giannakakis, G., Pediaditis, M., Manousos, D., Kazantzaki, E., Chiarugi, F., Simos, P.G., Marias, K., Tsiknakis, M. (2017) Stress and anxiety detection using facial cues from videos. *Biomedical Signal Processing and Control*, 31, 89-101. https://doi.org/10.1016/j.bspc.2016.06.020.
6. Korda, A. I., Giannakakis, G., Ventouras, E., Asvestas, P. A., Smyrnis, N., Marias, K., & Matsopoulos, G. K. (2021). Recognition of Blinks Activity Patterns during Stress Conditions Using CNN and Markovian Analysis. *Signals*, *2*(1), 55–71. MDPI AG. Retrieved from http://dx.doi.org/10.3390/signals2010006

Funding Sources

Funding for the Autism Biomarkers Consortium for Clinical Trials was provided by NIMH U19 MH108206 (McPartland).

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