Background

- Autism Spectrum Disorder (ASD) is a collection of neurodevelopmental disorders characterized by social-communicative and behavioral impairments that affects approximately 1 in 59 children in the US (CDC, 2018).
- Children with ASD, on average, exhibit increased rates of externalizing behaviors compared to their typically developing peers (Beumerger, Soloman, & Rogan, 2010). Studies have shown that children with relatively low familial risk for ASD are more likely to develop ASD if they have a history of prenatal complications (Dodd et al., 2011) and that history of prenatal complication is related to the severity of externalizing behaviors (DeVico, Gable & Tudor, 2012).
- In typical development, prenatal complications are associated with a number of child psychiatric disorders and externalizing behaviors (Allen, Lewinsohn, & Seeley, 1996; Wadhil Bedard et al., 2004; Milberger, Biederman, Faraone, & Fudge, 2011) and males have increased levels of externalizing behaviors compared to females (Hicks, 2008; Bart, Koop, & Her, 2017).
- The aims of the study will:
  1. Compare externalizing behaviors in children with ASD who experienced prenatal complications to those children with ASD who did not experience prenatal complications.
  2. Compare sex differences in externalizing behavior scores.
  3. Compare externalizing behavior and sex differences in children with ASD who experienced prenatal complications to those children with ASD who did not experience prenatal complications.
- We hypothesize that:
  1. ASD children with prenatal complications compared to those without complications will demonstrate more externalizing behavior problems.
  2. Males with ASD will exhibit more externalizing behavior problems than females in the subscale mean scores.
  3. ASD makes with prenatal complications will exhibit more externalizing behavior problems.

Methods

Participants:
- Children between the ages of 8 and 17 years old participated in the Gender Exploration of Neuromotricity and Development to Advance Autism Research (GENEADAR) study. To be included in these analyses, children must (1) have a confirmed diagnoses of ASD, (2) have an IQ over 70. Mother provided information regarding whether or not she experienced pregnancy/prenatal complications with the participant child.

Table 1: Participants for Aim 1

<table>
<thead>
<tr>
<th></th>
<th>ASD with Prenatal Complications</th>
<th>ASD without Prenatal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61 (36 males, 25 females)</td>
<td>106 (57 males, 49 females)</td>
</tr>
<tr>
<td>Age (Mo.)</td>
<td>M = 149.30, SD = 5.435</td>
<td>M = 150.42, SD = 3.132</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>M = 104.56, SD = 2.637</td>
<td>M = 98.40, SD = 2.012</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>M = 104.03, SD = 2.503</td>
<td>M = 98.46, SD = 1.647</td>
</tr>
</tbody>
</table>

Table 2: Participants for Aim 2

<table>
<thead>
<tr>
<th></th>
<th>Male ASD Children</th>
<th>Female ASD Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>74</td>
<td>93</td>
</tr>
<tr>
<td>Age (Mo.)</td>
<td>M = 149.41, SD = 3.648</td>
<td>M = 150.76, SD = 3.911</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>M = 99.46, SD = 2.183</td>
<td>M = 102.17, SD = 2.934</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>M = 100.54, SD = 1.846</td>
<td>M = 100.45, SD = 2.158</td>
</tr>
</tbody>
</table>

Measures:
- Pregnancy/Prenatal Complications:
  - ACE Medical History Form: Parent interview administered by a clinician. Includes yes/no questions regarding whether or not any prenatal complications occurred. Pregnanancy/prenatal complications refers to a broad category, which includes health concerns for the mother or child, difficult birth, or concerning pregnancy diagnoses such as gestational diabetes or pre eclampsia.

- Externalizing Behaviors:
  - Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 1999): Parent completed questionnaire assessing the child's executive function behaviors at home and at school in children and adolescents ages 5-18. Higher scores indicate more executive functioning problems. Provides subscale scores such as:
    - Inhibit: Ability to control impulses (inhibitory control) and to stop engaging in a behavior.
    - Emotional Control: Ability to regulate emotional responses appropriately.
    - Monitoring: Ability to check work to and assess one’s own performance; ability to keep track of the effect of one’s own behavior on other people.
    - Plan/Organize: Ability to anticipate future events; to set goals; to develop steps; to grasp main ideas; to organize and understand the main points in written or verbal presentations.
    - Global Executive Composite (GEC): Takes into account all of the clinical scales and represents the child’s overall executive function.

Aim 1: Comparing Externalizing Behaviors between ASD with Prenatal Complications and ASD without Prenatal Complications

- A series of ANOVAs were implemented with Inhibit, Emotional Control, Monitoring, Plan/Organize, and GEC subscales of the BRIEF as dependent variables. We found that there were no significant differences in any subscale between ASD children with prenatal complications and ASD children without prenatal complications.

Aim 2: Measuring Externalizing Behaviors between Male ASD children and Female ASD children

- A series of ANOVAs were implemented with Inhibit, Emotional Control, Monitoring, Plan/Organize, and GEC subscales of the BRIEF as dependent variables. We found that there were no significant differences in any subscale between Male ASD children and Female ASD children.

Aim 3: Comparing Externalizing Behaviors by Sex, Comparison by History of Prenatal Complications

- We found that female ASD children with prenatal complications scored significantly higher (worse) on BRIEF subscale measures of Inhibit (p=0.052), Emotional Control (p=0.045), and Plan/Organize (p=0.009) and scored marginally higher (worse) on BRIEF subscale measures of Monitoring (p=0.057) & GEC (p=0.057) compared to male ASD children with prenatal complications.
- Furthermore, female ASD children with prenatal complications scored significantly higher (worse) on BRIEF subscale measures of Inhibit (p=0.054), Emotional Control (p=0.039) and GEC (p=0.034) compared to female ASD children without prenatal complications.
- Lastly, we found that female ASD children without prenatal complications scored significantly higher (worse) on BRIEF subscale measures of Monitoring (p=0.044) compared to male ASD children without prenatal complications.

Discussion

Summary:
- Overall, there were no significant differences on externalizing behaviors, in any subscales, when comparing children with ASD with or without prenatal complications or when comparing children with ASD by sex. This does not support my first and second hypotheses.
- However, when looking into both prenatal complication and sex together, female ASD children with prenatal complications demonstrate more externalizing behaviors compared to all three other groups. This finding did not support my third hypothesis.

Caveats:
- It is important to note that this study differs from other studies because it included only children with functional language and average to above average IQ. Furthermore, it also included a larger percentage of females with ASD.
- Prenatal complications may not have been as severe as in previous reports because we excluded any pregnancy/prenatal complications being relatively minor is worth noting.

Discussion

In conclusion, pregnancy/prenatal complications may impact males and females with autism differently. Furthermore, that we found differences in this population with strict limitations of our pregnancy complications being relatively minor is worth noting. However, these results do align with previous research showing a relationship between: fetal sex pregnancy/prenatal complications and externalizing behaviors. Follow up studies should include both higher rates of females with ASD and minor prenatal complications.

- Other reports show that rates of hypertensive disorders, especially preeclampsia and pregnancy-induced hypertension (PIH) may be higher in pregnant women carrying female fetuses compared to those carrying male fetuses due to higher levels of spermine metabolites (Shiokazi et al., 2011; Gong et al., 2018).

- Spermine synthesis expresses a spermatozoa metabolic called N1,N2-diacylthalamurine which was found to escape X-chromosome inactivation. As a result, it causes higher expression in female placentas and serum.
- Furthermore, there have been studies that linked fetal exposure to preglamycin with worsening externalizing behaviors and trigger aberrant neurodevelopment in fetuses (Robinson et al., 2009; Walker et al., 2015; Dachse et al., 2018).

Conclusions & Limitations:
- These findings emphasize the role of sex and prenatal complications in externalizing behaviors.