Phenotypic differences between males and females with autism spectrum disorders (ASD)

Somer L. Bishop, PhD
Department of Psychiatry and Weill Institute for Neurosciences
University of California, San Francisco
10/26/2016
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

(CONFUSED)
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

• Moving forward
  – Donna, Kevin, and Alison
Outline

• State of current knowledge
  – Discrepant findings
  – Methodological limitations

• Moving forward
  – Alison, Donna, and Kevin
  (HOPEFUL FOR THE FUTURE!)
Mix of consistencies and inconsistencies

• More males with ASD than females
  – Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)

• Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end
Nonverbal IQ: Simons Simplex Collection
Mix of consistencies and inconsistencies

• More males with ASD than females
  – Many changes in epidemiological trends, but preponderance of males remains (though ratio varies across samples)

• Relative to overall sex ratio in ASD, females are over-represented at the lower end of the IQ continuum and under-represented at the higher end

• Longstanding interest in examining sex differences
  – Discrepant findings related to phenotype
Social-communication

• Similar levels of ASD symptoms (Lord et al., 1982)
• Toddler/preschool boys had higher language, motor and social-competence (Carter et al., 2007)
• Preschool girls had fewer social-communication impairments (Zwaigenbaum et al., 2012)
• Adult females had fewer social-communication difficulties (Lai et al., 2011)
• Girls had fewer teacher-reported behavior problems (Mandy et al., 2012)
Restricted and repetitive behaviors

• Females exhibited lower repetitive behavior scores (e.g., Hartley et al., 2009; Mandy et al., 2011; Frazier et al., 2014)
  – Seen across multiple measures (3Di, ADI-R, RBS-R, ADOS)
• No sex differences in community-based sample of 288 toddlers with ASD (54 girls) (Reinhardt et al, 2014)
Questions persist

• Clinicians and researchers continue to wonder (and worry) about sex differences in behavioral manifestations of ASD
Clinician perceptions

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female: 86% (n=91)</th>
<th>Male: 14% (n=15)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement in dx</td>
<td>57% make dx (n=58)</td>
<td>31% perform assessments (n=32)</td>
<td>12% participate in evaluation (n=12)</td>
</tr>
<tr>
<td>Years experience</td>
<td>58% have 10+ years (n=56)</td>
<td>26% have spent 6-9 years (n=25)</td>
<td>13% have 1-5 years experience (n=12)</td>
</tr>
<tr>
<td>Primary age range seen</td>
<td>7% see mostly adults (n=7)</td>
<td>9% see primarily adolescents (n=8)</td>
<td>37% work with school age children (n=35)</td>
</tr>
<tr>
<td>Number seen per month</td>
<td>Mean = 15.8 people, median = 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of females seen per month</td>
<td>Mean = 3.4 females, median = 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Observed differences in core and associated symptoms

Jamison, Huerta, Bishop, & Halladay (under review).
Observed differences in social-communication

Jamison, Huerta, Bishop, & Halladay (under review).
Observed differences in RRBs

Jamison, Huerta, Bishop, & Halladay (under review).
Clinical observations vs. empirical data

• Why the mismatch?
  – Measurement issues
  – Sampling issues
  – Methodological issues
Measurement issues

• Existing measures may lack sensitivity for detecting some females with ASD
  – Diagnostic constructs (which in turn are reflected on measures) could be sex-biased

• Scores on ASD measures are affected by individual factors like IQ and emotional/behavioral problems (EBP)
ADI-R scores by diagnostic group and level of EBP

SRS scores by diagnostic group and level of EBP

Sampling Issues

• Measurement issues can affect ascertainment
  – Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)
Referral bias

Mean T scores in preschoolers with ASD (N=102) and non-ASD diagnoses (N=57)

Sampling Issues

• Measurement issues can affect ascertainment
  – Over-reliance on standardized screening or diagnostic measures could skew samples (e.g., toward girls with lower IQ and/or more behavior problems)

• Small clinical samples
  – Ns for females are particularly small
  – May not be powered to properly account for other important individual differences
### School-aged/adolescent; verbally fluent

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Participants</strong></td>
<td>396</td>
<td>85</td>
</tr>
<tr>
<td><strong>Age in years, M (SD)</strong></td>
<td>8.9 (2.9)</td>
<td>8.7 (2.8)</td>
</tr>
<tr>
<td><strong>VIQ, M (SD)</strong></td>
<td>99.6 (18.9)</td>
<td>104.6 (16.7)</td>
</tr>
<tr>
<td><strong>NVIQ, M (SD)</strong></td>
<td>104.7 (15.5)</td>
<td>104.3 (14.8)</td>
</tr>
</tbody>
</table>

ADOS-2 Module 3 ASD classification

0% 20% 40% 60% 80% 100%

Males
Females

Percent Meeting ASD cut-offs

Calibrated severity scores (CSS)

• Controlling for VIQ and age, sex significantly predicted:
  – Overall CSS ($B = -0.57$, CI 95% $-1.08$ to $-0.06$, $p = .03$)
  – RRB Domain Calibrated Scores ($B = -0.89$, CI 95% $-1.4$ to $-0.34$, $p = .002$)

• In this sample, even females with lower scores (including those who scored below instrument cut-offs) still received best-estimate clinical diagnoses of ASD

Methodological issues

• Detecting meaningful differences relies on identification of appropriate comparison groups
  – Who is a relevant control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)

• Clear need for longitudinal data
Employment/PSE at the First Time Point after High School Exit

Methodological issues

• Detecting meaningful differences relies on identification of appropriate comparison groups
  – Who is a *relevant* control? (e.g., IQ/age matched males with ASD vs. IQ/age matched non-ASD female?)

• Clear need for longitudinal data

• Need to move existing behavioral measures

• Incorporate different measurement strategies
Conclusions

• There do appear to be at least subtle sex differences in phenotype within certain groups
  – Ascertainment and measurement issues present major challenges
• Sex is **one** stratification variable worth considering, but it needs to be considered in the context of other behavioral and biological variables that we know are important
Thank you

• UMACC/CADB families, clinicians and researchers
  • Alycia Halladay
  • Alexandra Havdahl
  • Marisela Huerta
  • Rene Jamison

• Catherine Lord
  • Shanping Qiu
  • Michael Sweeney
  • Julie Taylor
EXTRA SLIDES
### Direction of Clinician Responses: Early Childhood

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>33% (n=22)</td>
<td>62% (n=41)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>33% (n=22)</td>
<td>60% (n=39)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>23% (n=15)</td>
<td>71% (n=46)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>32% (n=21)</td>
<td>65% (n=43)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>24% (n=16)</td>
<td>71% (n=47)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Restricted/Fixated Interests</td>
<td>33% (n=22)</td>
<td>65% (n=43)</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Hyperreactivity to sensory</td>
<td>9% (n=6)</td>
<td>86% (n=55)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Hyporeactivity to sensory</td>
<td>17% (n=11)</td>
<td>67% (n=43)</td>
<td>16% (n=10)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
Direction of Clinician Responses: School Age

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>48% (n=30)</td>
<td>48% (n=30)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>44% (n=27)</td>
<td>54% (n=33)</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>25% (n=15)</td>
<td>70% (n=43)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>55% (n=34)</td>
<td>40% (n=25)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>23% (n=14)</td>
<td>73% (n=45)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>38% (n=23)</td>
<td>59% (n=36)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=5)</td>
<td>85% (n=52)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Hypo-reactivity to Sensory</td>
<td>19% (n=11)</td>
<td>76% (n=43)</td>
<td>7% (n=4)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
### Direction of Clinician Responses: Adolescence

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social reciprocity</td>
<td>37% (n=23)</td>
<td>55% (n=34)</td>
<td>8% (n=3)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>41% (n=25)</td>
<td>56% (n=34)</td>
<td>3% (n=2)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>16% (n=10)</td>
<td>69% (n=42)</td>
<td>15% (n=9)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>47% (n=29)</td>
<td>48% (n=30)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>21% (n=13)</td>
<td>71% (n=44)</td>
<td>8% (n=5)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>31% (n=19)</td>
<td>63% (n=39)</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=5)</td>
<td>87% (n=52)</td>
<td>5% (n=3)</td>
</tr>
<tr>
<td>Hypo-reactivity to Sensory</td>
<td>23% (n=14)</td>
<td>74% (n=45)</td>
<td>3% (n=2)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
### Direction of Clinician Responses: Adult

<table>
<thead>
<tr>
<th>Criteria / Severity</th>
<th>Less Severe (M&lt;F)</th>
<th>Similar (M=F)</th>
<th>More Severe (F&gt;M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocity</td>
<td>31% (n=17)</td>
<td>59% (n=32)</td>
<td>9% (n=5)</td>
</tr>
<tr>
<td>Nonverbal behaviors</td>
<td>41% (n=22)</td>
<td>52% (n=28)</td>
<td>7% (n=4)</td>
</tr>
<tr>
<td>Developing, maintaining relationships</td>
<td>17% (n=9)</td>
<td>74% (n=39)</td>
<td>9% (n=5)</td>
</tr>
<tr>
<td>Stereotyped/Repetitive Behaviors</td>
<td>36% (n=19)</td>
<td>64% (n=34)</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td>Insistence on Sameness</td>
<td>19% (n=10)</td>
<td>78% (n=42)</td>
<td>4% (n=2)</td>
</tr>
<tr>
<td>Restricted / Fixated Interests</td>
<td>22% (n=12)</td>
<td>76% (n=41)</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Hyper-reactivity to Sensory</td>
<td>8% (n=4)</td>
<td>87% (n=45)</td>
<td>6% (n=3)</td>
</tr>
<tr>
<td>Hypo-reactivity to Sensory</td>
<td>13% (n=7)</td>
<td>80% (n=43)</td>
<td>7% (n=4)</td>
</tr>
</tbody>
</table>

Jamison, Huerta, Bishop, & Halladay (under review).
ADOS items showing significant score discrepancies by sex

ADOS scores by diagnostic group and level of EBP