PHENOTYPE EXPRESSION DIFFERENCES IN AUTISTIC MALES AND FEMALES

Implications for Diagnosis and Treatment

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In their own words:

What do you consider some of the most commonly misidentified or overlooked traits of autistic girls?

…One of the biggest things that has been missed…has been… "the chameleon effect." I was raised…to blend in….. It's not without a tremendous amount of effort, it was hammered into me as a child, and it's incredibly uncomfortable.
-Christine Langager, writer, advocate, parent

That we exist at all!
-Patricia George, writer and artist

Many autistic girls… are very social, even overpoweringly so. This can actually be an extreme attempt to replicate what they perceive as "normal " relationships.
-Olley Edwards, writer and filmmaker

S. De Roches Rosa (2016, April 22). How can we all do better by our autistic girls? [Web log post]. Retrieved from http://www.thinkingautismguide.com/2016/04/how-can-we-all-do-better-by-our.html

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Why is it so hard to diagnose ASD in girls?

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Case Study: Mary

- Early Development
  - Achieved basic milestones on time
  - Early social isolation → later great interactions with sister and overly high social motivation/poor boundaries
  - Early unusual play → later strong pretend play skills
  - Behavioral rigidity
  - Resistance to touch
  - Obsession with animals
  - Difficulty with preschool academics
- Kindergarten: Identified with language delay
- 3rd grade: Auditory processing disorder

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Case Study: Mary

- 4th grade: Sudden onset of intense chronic pain
  - Wheelchair-bound
  - Intense sensory sensitivities
  - Began medical and psychological treatment for pain

- 5th grade: Concussion and slowed recovery
  - Referred to neurology and developmental pediatrics → referral to Center for Autism Spectrum Disorders
  - Concerns for ADHD, Learning Disability
  - Gradual recovery from pain with introduction of structure
  - **By the time of referral to CASD had seen 50 medical professionals**

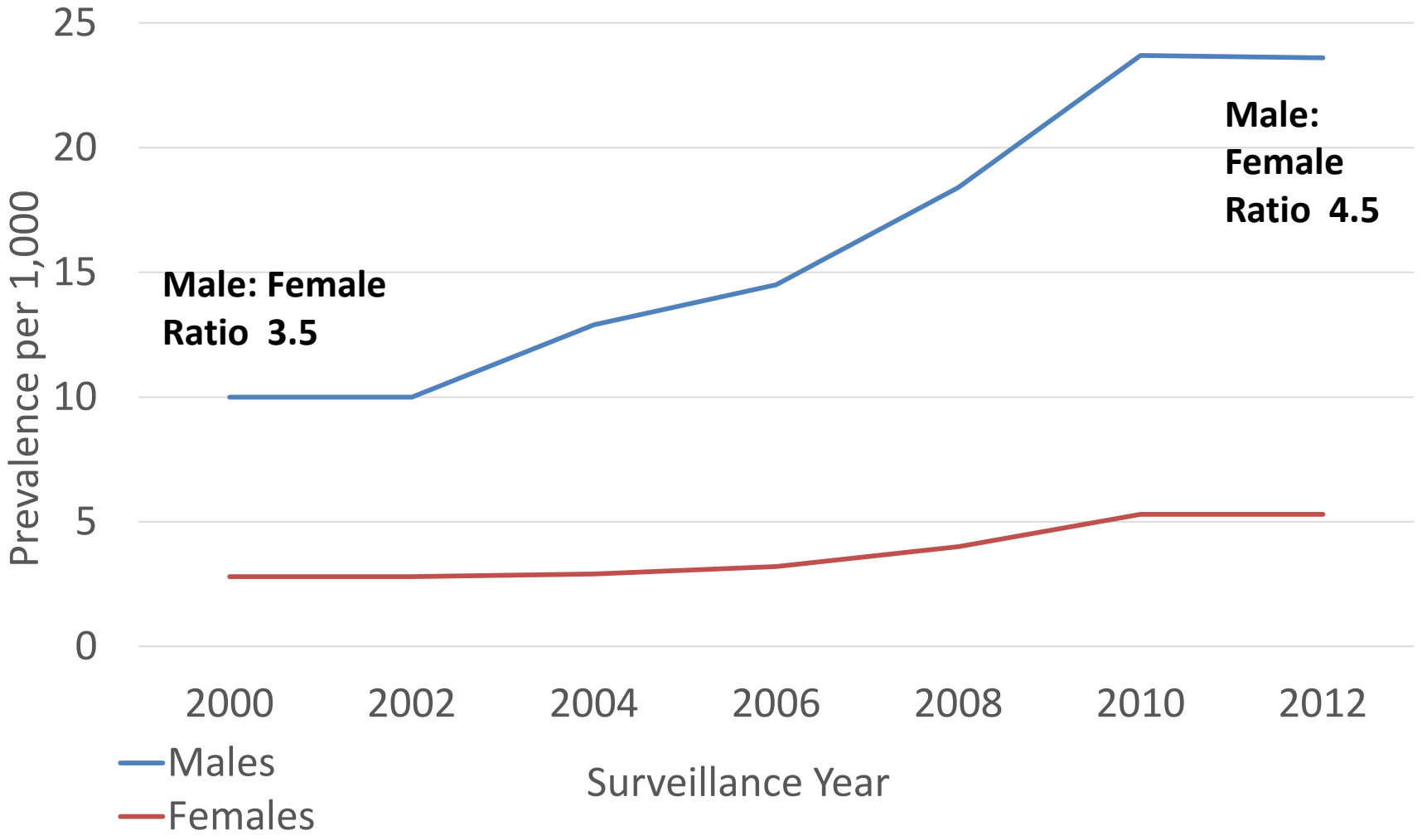
Case Study: Mary

- ASD Profile
  - Largely appropriate language and eye contact, but unusual intonation and prosody
  - Recognizes basic emotions, but struggles with subtle emotions and perspective taking
  - Socially responsive and motivated, but also socially naïve and often misses social cues
  - Lack of understanding of reality v. fantasy
  - Extreme rigidity around schedules, routines, eating, and order
  - Restricted interest in animals
  - No repetitive behaviors, but limited flexibility and creativity in play

Historical Research

- Research studies prior to 2007 rarely had more than 25 female participants enrolled and/or spanned a large age range
- Minimal longitudinal studies have been published focused on females with ASD
- Since 2007, there has been a greater effort in understanding the phenotype in a larger range of individuals, including females and individuals with gender dysphoria

Sex Ratios by Surveillance year in CDC ADDM Network



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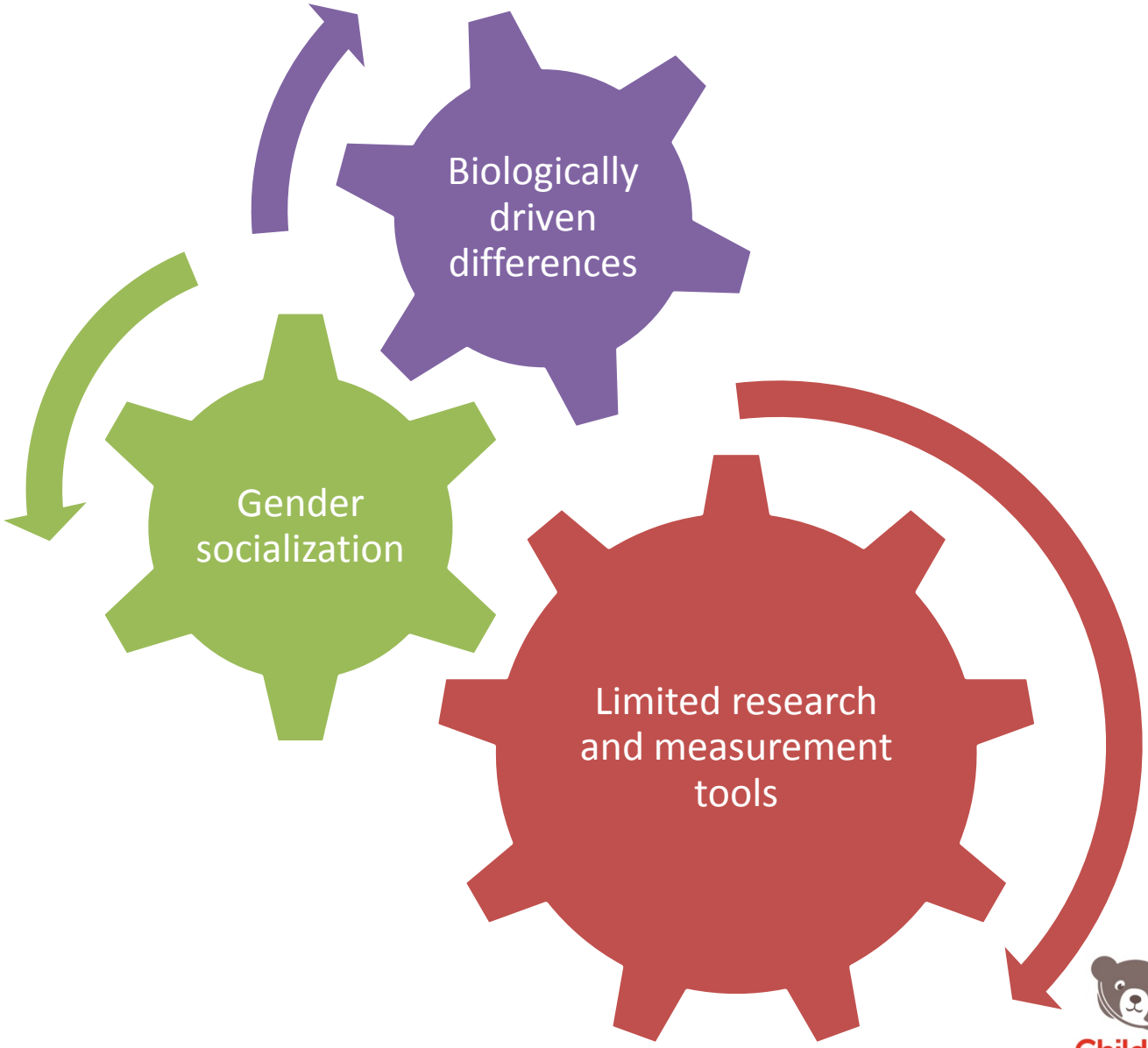
What contributes to sex differences in ASD rates?



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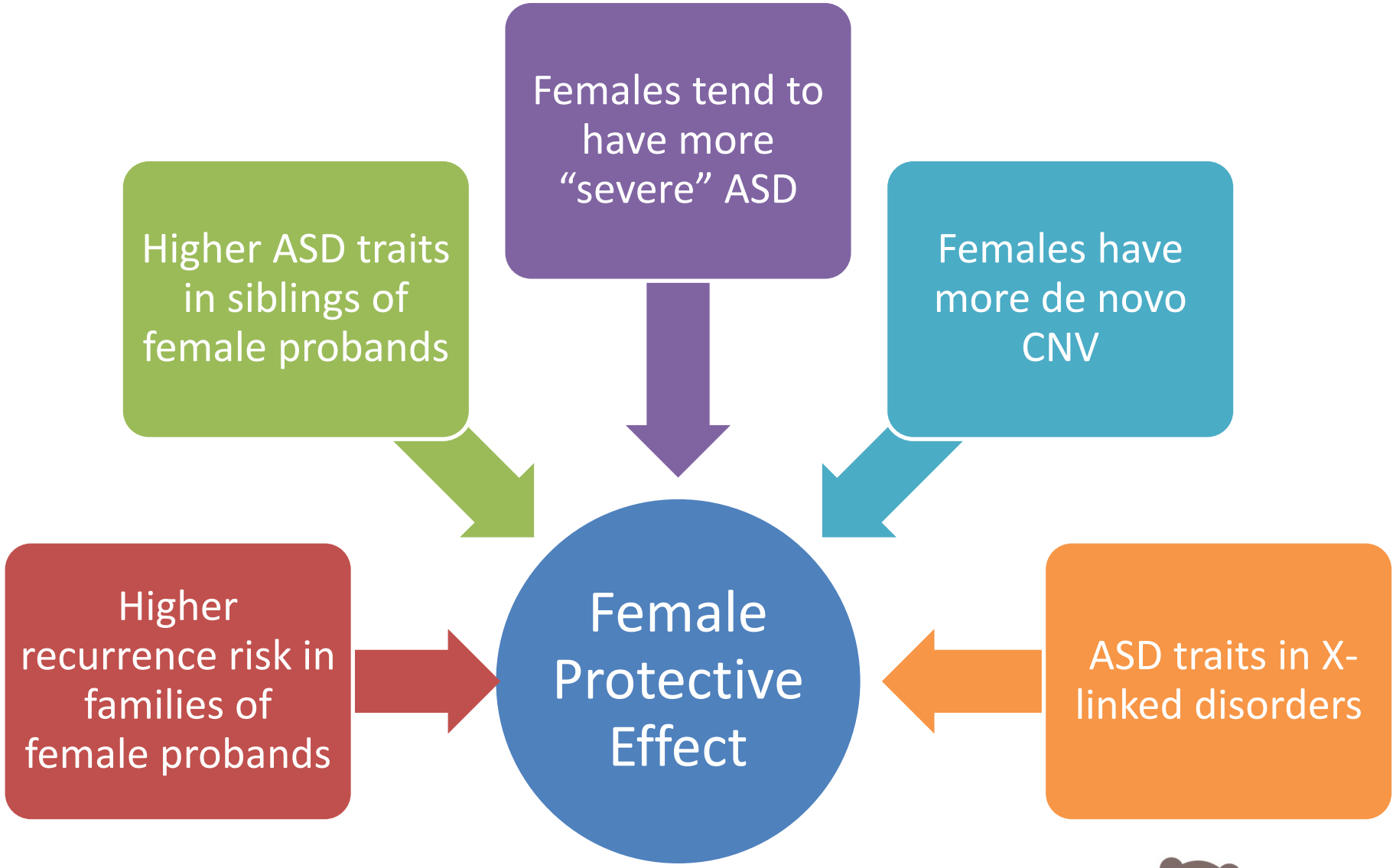
Biological Differences: Sex Differences in ASD Genetics



Bishop et al. (2011); Edens et al. (2011); Gillman et al. (2011); Robinson et al. (2013)

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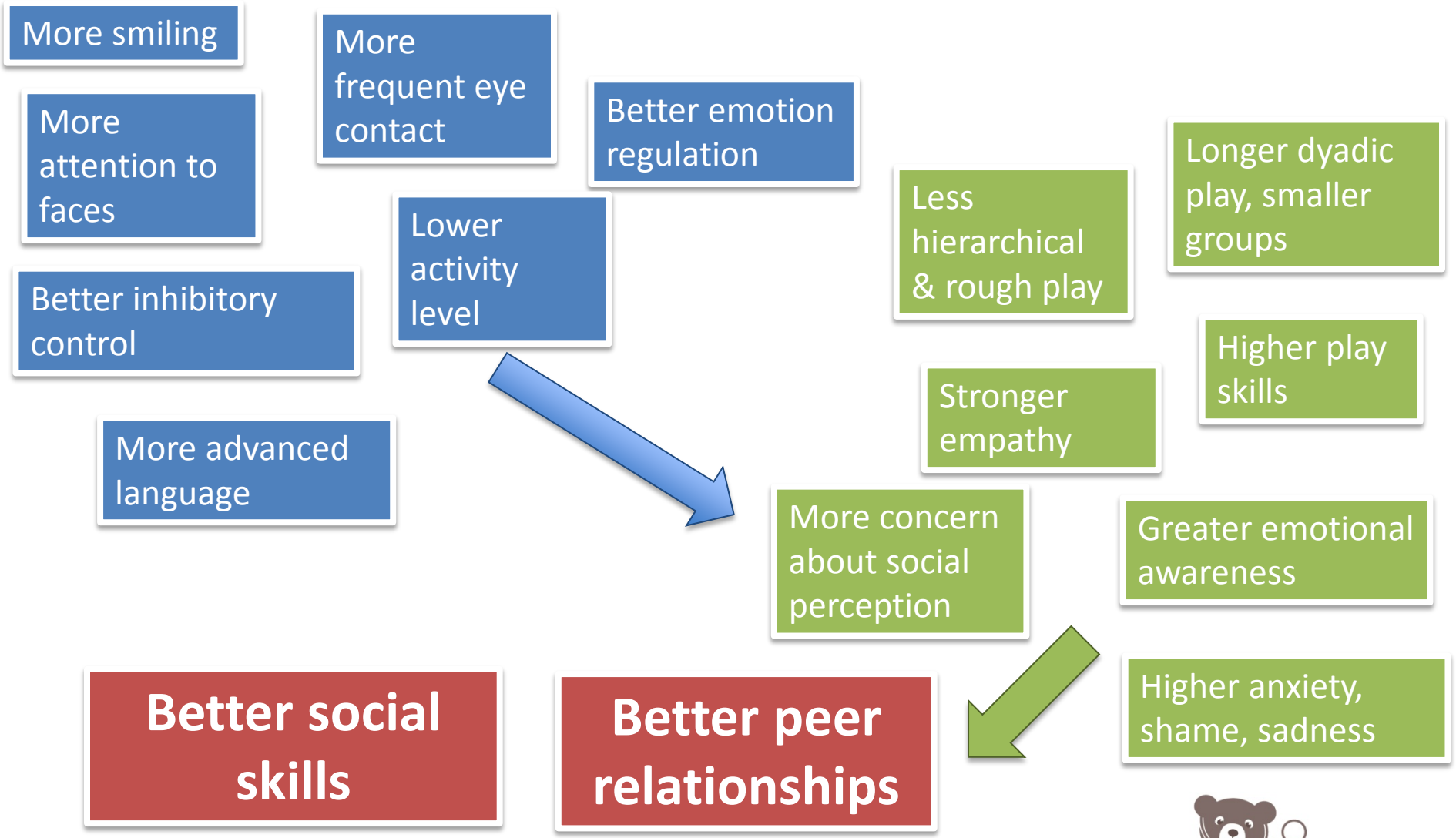
Gender Socialization: Early Sex Differences in Typical Development

Compared to boys, young girls show…



Baron-Cohen (2002); Else-Quest et al. (2006); Rose & Rudolph (2006); Zahn-Waxler et al. (2008)

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Measurement Tools: Sex Norms/Bias

	Sex-Normed	Evaluation of Sex Bias	Sex Ratio in Normative Sample
ADOS/ADOS-2:	✗	✗	Favors males, particularly clinical sample
ADI-R	✗	✗	Favors males
SCQ	✗	✗	Favors males
SRS/SRS-2	✓	✓	Roughly equivalent
Autism Quotient	✗	✓	Favors males, particularly clinical samples
Vineland-II	✗	✓	Roughly equivalent
BRIEF: Parent Form	✓	✓	Roughly equivalent

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The Important Questions

1. Does autism present differently in females?

2. Do females mask the symptoms better than males?

3. Are professionals less likely to diagnose females even when symptoms and behaviour are evident?

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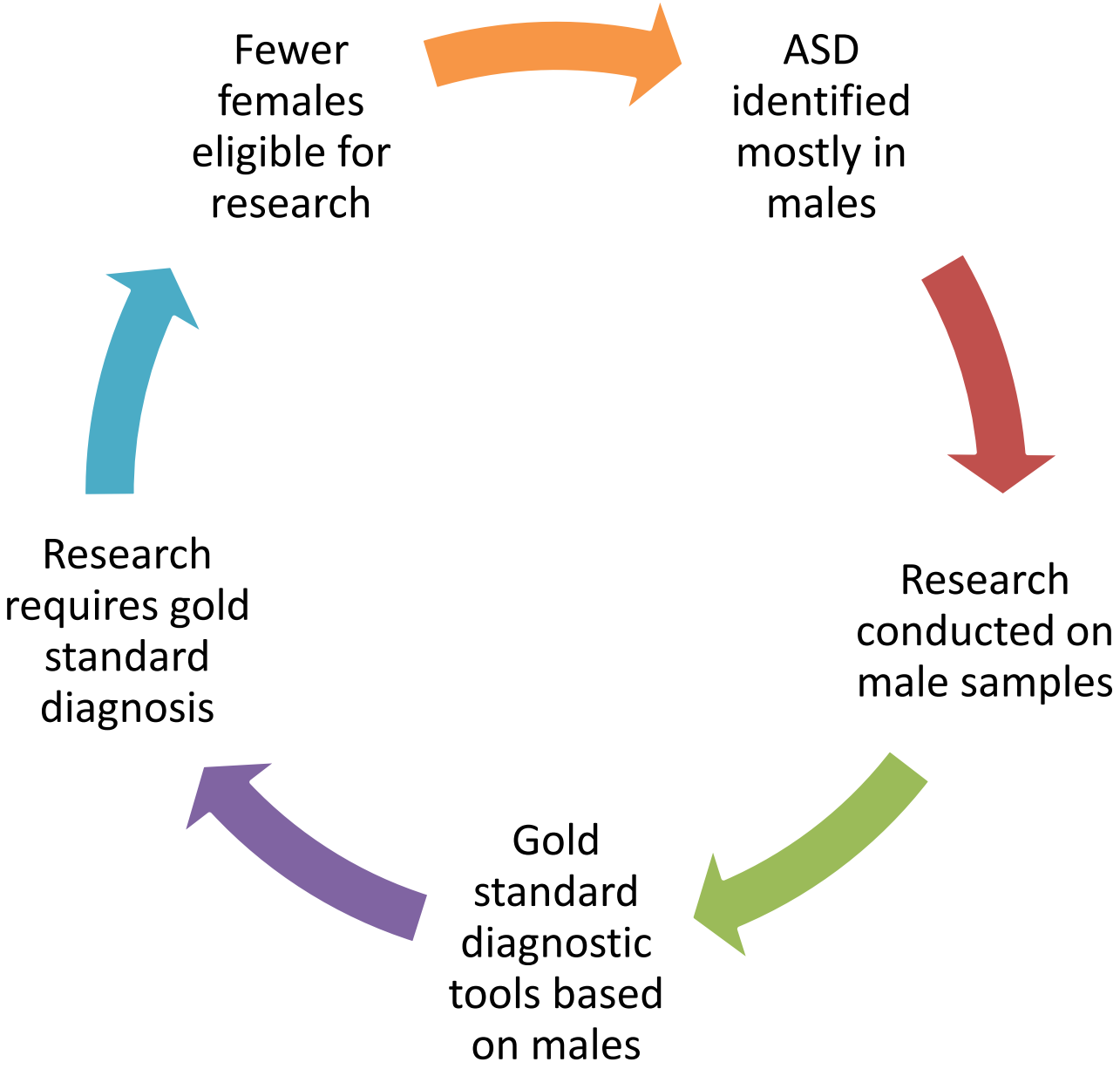

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So What Do We Know About Females with ASD?

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Diagnostic Experiences

- No differences in parental first concerns overall[1], but among non-ID sample, girls more likely to have first concerns about externalizing behavior[2]
- Later age at diagnosis and greater difficulty obtaining one[3-6]
- Less likely to meet diagnostic criteria and receive clinical diagnoses, particularly among those without ID[7-9]
- Females without ID may receive a series of inaccurate diagnoses over many years prior to an ASD diagnosis[10-12]

- In current diagnostic practice, females need to present with more concurrent behavioral, developmental or mental health issues for an ASD diagnosis to be made, compared to their male counterparts[13,14]

[1]Little et al., 2016; [2]Hiller et al., 2015; [3]Begeer et al.2012; [4]Lenhardt et al., 2015; [5]Shattuck et al., 2009; [6]Siklos & Kerns, 2007; [7]Dworzynski et al., 2012; [8]Giarelli et al., 2010; [9]Wilson et al., 2016; [10]Baldwin & Costley, 2016; [11]Bargiela et al., 2016; [12]Lenhardt et al., 2015; [13]Duvekot et al., 2017; [14]Dworzynski et al., 2012

Traditional Conceptualizations of Sex Differences in ASD

Females more impaired overall

No broad differences in social and communication deficits

Is ASD "camouflaged" in females without comorbid ID?

Males show more RRBIs

Kirkovski et al. (2013); Van-Winjgaarden-Cremers et al. (2014)

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Sex Differences: Early Childhood

- No studies yet with exclusively young children without ID cognitive delays
- No significant differences found in early social skills, and language skills are often equivalent (van Wijngaarden-Cremers et al., 2014; Lord et al., 2015; Oien et al., 2017; Hartley and Sikora, 2009; Andersson, Gillberg, & Miniscalo, 2013; Harrop et al., 2014)
  - Some have hypothesized intact imitation and early play, but not consistently supported by research (Kirkovski et al., 2013; Knickmeyer, Wheelwright, & Baron-Cohen, 2008; Lord et al., 1982)
- Some evidence of greater early language problems in girls (Hartley and Sikora, 2009; Carter et al., 2007); though others find better core language in girls, particularly at later ages (Halladay et al., 2015; Hiller et al., 2016; Messinger et al., 2015)
- Indications of fewer RRBI symptoms in girls (Hartley and Sikora, 2009; van Wijngaarden-Cremers et al., 2014; Hattier et al., 2011; Kirkovski et al., 2013)
- Some indications of differences in parent concerns
  - More externalizing behavior concerns and fewer concerns about social isolation for girls; lower RRBIs/different quality (Hiller et al., 2016)
  - Less specific concerns for girls with ASD, including fewer social concerns (Little et al., 2016)

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Middle Childhood: Social Profile

- Similar profiles among those with ID; among those without ID:
  - Females with higher verbal skills have similar or fewer social deficits on standardized measures (Head et al., 2014; Hiller et al., 2014; Howe et al., 2015; Mandy et al., 2012;Skuse et al., 2008; Wilson et al., 2016)
    - Better integrated nonverbal communication
    - Stronger conversation skills
  - Higher rates of intact pretend play skills (Kirkovski et al., 2013; Knickmeyer et al., 2008)
  - More likely to have (some) friendships (Head et al, 2014; Hiller et al., 2014; Mandy et al., 2012)
  - Tend to be neglected, rather than rejected, by peers (Dean et al., 2014)
  - Some indications of greater social dysfunction (Billstedet et al., 2007; Carter et al., 2007; Holtmann et al., 2007; Lord et al., 1982)

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The art of camouflage: Gender differences in the social behaviors of girls and boys with autism spectrum disorder

Dean, Harwood, & Kasari (2017)

- Observed 96 TD & ASD elementary schoolers during recess (10-15 minutes)

TD Boys

- Majority of recess in Games (more than any other group)
- Large amount of time in Joint Engage (team ball games)
- Rarely exhibited Solitary behavior

ASD Boys

- Solitary most salient state (wandering, talking)
- Less time in Games than TD boys
- Similar Joint Engagement to TD boys

TD Girls

- Majority of recess in Joint Engage (talking, flitting through many activities while maintaining joint engagement & groups while maintaining game)
- Only 4th/5th graders engaged in team games
- Rarely exhibited solitary behavior

ASD Girls

- Most of recess in Joint Engage (as much as TD girls)
- Significant amount in Solitary
- Compensatory behaviors to gain access to peer groups (weaving between joint engagement & solitary; swinging jump rope but not given chance to jump)

The art of camouflage (Dean, Harwood, & Kasari (2017)

"The female social landscape supports the camouflage hypothesis; the fluidity of female social groups created an ideal backdrop to conceal the girls with ASD who were often hovering close by. Regardless of engagement state status, girls with ASD tended to stay in close proximity to social groups and were therefore better situated than boys with ASD to capitalize on social opportunities. Scanning the playground environment would be insufficient to identify the social struggles of girls with ASD. From a distance, girls with ASD *looked like* TD girls. While the girls' social challenges are concealed from playground attendants, they do not appear to be hidden from peers."

- To untrained observers (recess aides, teachers), male social groups were as conducive to exposing the social challenges of boys, as female groups were to camouflaging girls' social challenges.
- If practitioners look for social isolation on the playground when identifying children with social challenges, girls with autism spectrum disorder will continue to be left unidentified.
- Mixed sex intervention groups may disadvantage females if content is male specific

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Sex Differences in Parent-Reported and Clinician-Rated Autism Symptoms in School-Age Youth with ASD without Intellectual Disability

Ratto, Wallace, Pugliese, Martucci, Register-Brown, White, Popal, Rothwell, Martin& Kenworthy (2016, May)

- 1:1 matched sample of 228 (n=114 females)
  - All met Lainhart criteria for ASD diagnosis (DSM criteria + ADOS or ADI-R)
  - Full-scale IQ>70
- Male and female participants were matched on
  - Age (within 1 year)
  - Full scale IQ (within 5 points)

	Mean (SD)
Age	10.11 (2.16)
Full-Scale IQ	101.09 (18.87)
Verbal IQ	101.77 (19.36)
Performance IQ	103.88 (17.72)
Race/Ethnicity	73% White
Maternal Education	90% At least some college

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ADOS Results

- 89% of females, 94% of males met ADOS-2 criteria

	Males	Females	F
ADOS-2: Social Affect	10.07 (4.57) N=114	9.76 (4.27) N=114	.813 (ns)
ADOS-2: RRB	3.33 (2.13) N=114	2.83 (1.88) N=114	3.54 (ns)

- Chi-square analyses of ADOS item-level data
  - Females more impaired on Facial Expressions (Pearson $\chi^2 = 9.05$, $p<.01$; $\phi = .199$, small effect)
  - Females less impaired on Excessive Interests (Pearson $\chi^2 = 5.80$, $p<.055$; $\phi = .159$, small effect)

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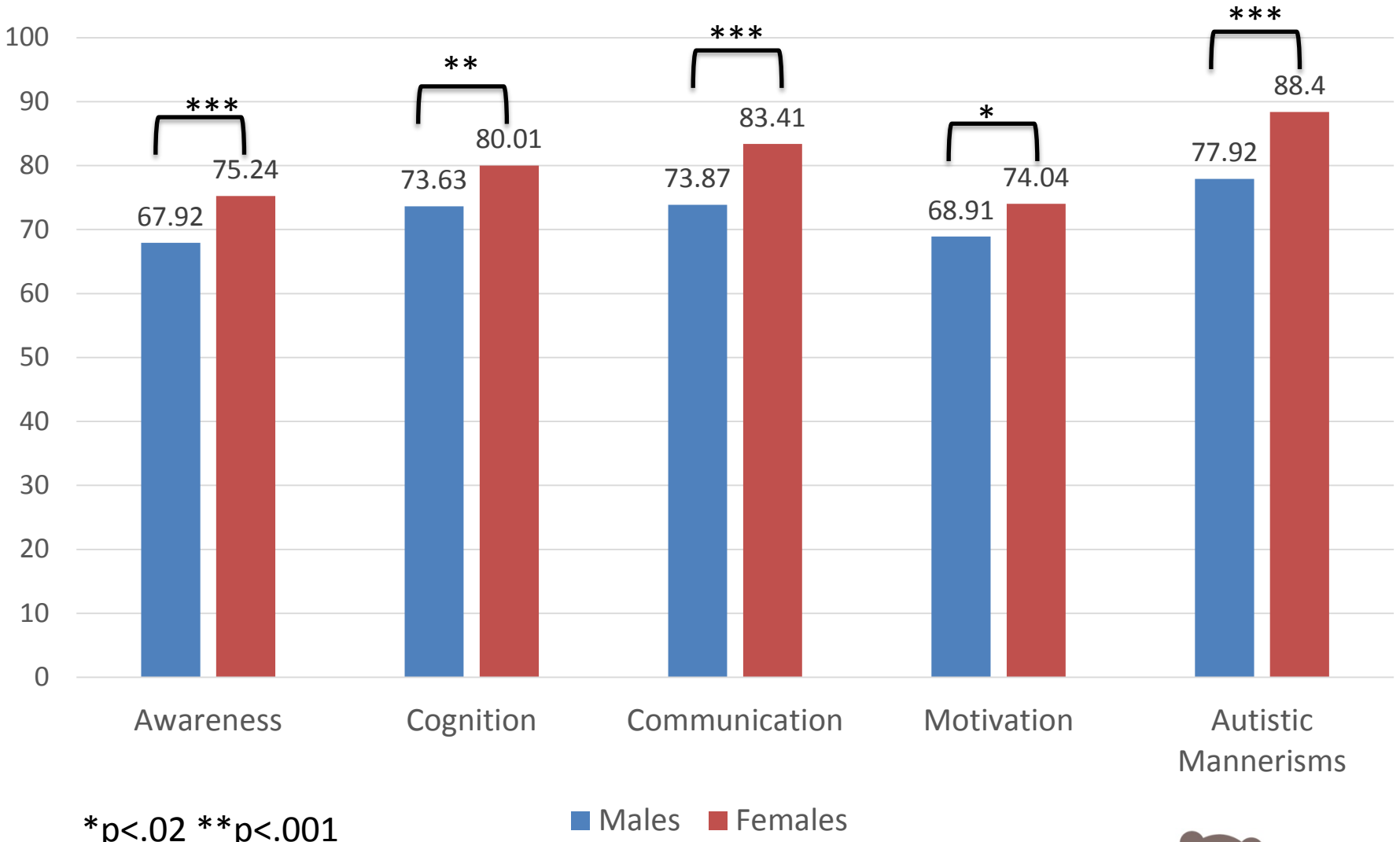
Social Responsiveness Scale



*p<.02 **p<.001
***p<.0001

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Adolescence & Adulthood

- Imitation of social interactions adequate to maintain friendships during childhood, but not sufficient during adolescence [1,2]
- Adolescent female relationships require more complex skills such as reciprocal sharing, emotional support, and social problem-solving[3]
- Adolescent girls with ASD need extended time to process and then respond to information [3], which impairs conversational ability
- Boys tend to display overt aggression, and girls display more socially complex and subtle relational aggression [3,4]
- Social landscape may contribute to higher rates of social isolation[5,6] and mental health problems[7-12] identified in adolescent girls with ASD, compared both to adolescent boys with ASD and to NTD adolescent girls.

[1]Bauminger et al. 2008; [2]Carrington et al. 2003; [3] Nichols et al. 2009;[4]Card et al. 2008; [5]Solomon et al. 2012; [6]Sullivan and Caterino 2008; [7]Chan and John 2012; [8]Cottenceau et al. 2012; [9]Rivet and Matson 2011; [10]Seltzer et al. 2004; [11]Solomon et al. 2012; [12]William et al. 2012

Being a Girl in a Boys' World: Investigating the Experiences of Girls with ASD During Adolescence (Cridland, Jones, Caputi, Magee, 2014)

- Late diagnosis means playing intervention "catch-up"
- Interventions not always salient to females
- Difficult time navigating female adolescent relationships
- Logical/factual attitude towards puberty
- Difficulty building hygiene routines
- Sexual vulnerability/ exploitation

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Sex Differences in Autism Symptomatology in Adolescents and Adults with ASD without ID: A Multi-site Study

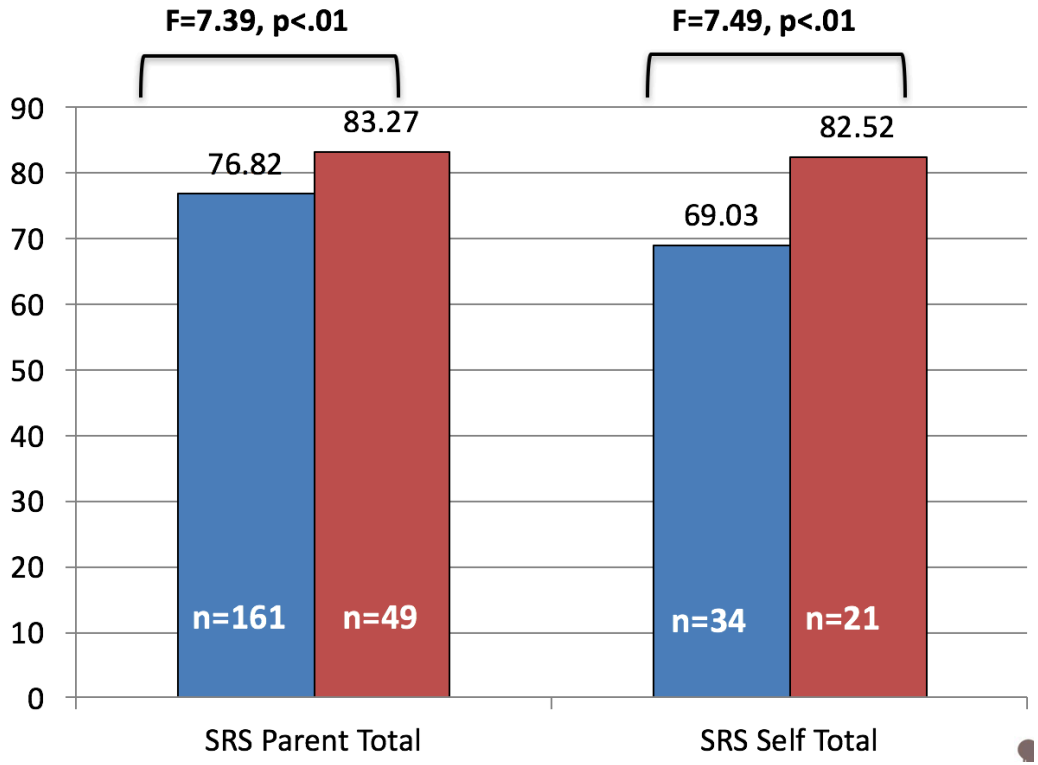
Pugliese et al., in prep

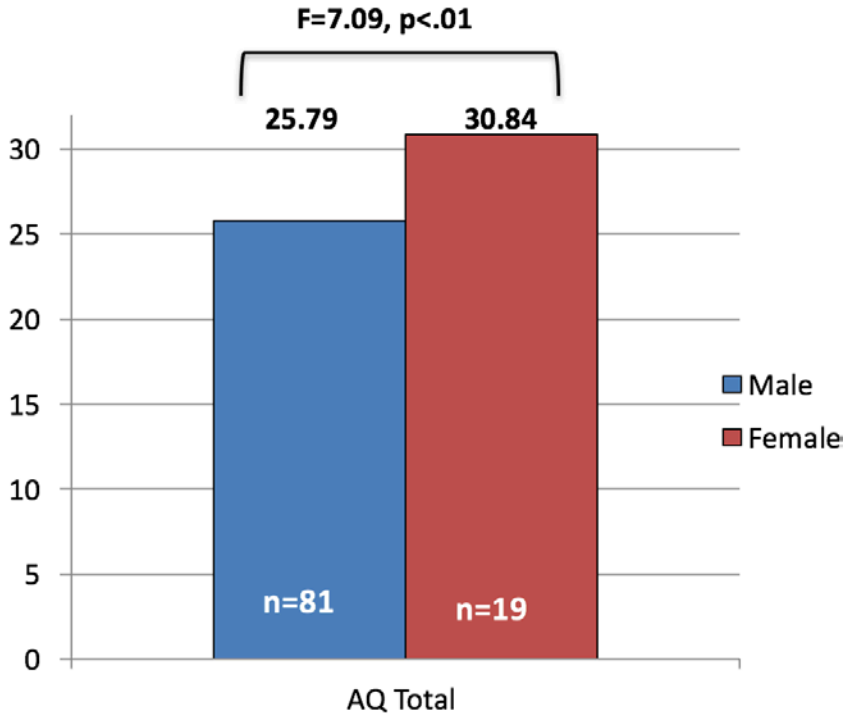
- 285 (71 females) participants with DSM-5 diagnoses of ASD
  - four ADOS research-reliable sites
  - 11-57 years (*M* = 19, *SD* = 7): 11-15 (n=91); 16-20 (n=136); 21-25 (n=35); Over 26 26-30 (n=23)
  - FSIQ >70 (*M* = 106, *SD* = ± 18) – no sex differences

- ADI: no significant sex differences

- ADOS
  - 85% of males and females met cut-off
  - No differences on SA or RRB domains or CSS
  - Males rated by clinicians as more impaired on
    - Immediate Echolalia
    - Stereotyped/Idiosyncratic Use of Words of Phrases
    - Offers Information
    - Conversation
    - Descriptive, Conventional, Instrumental or Informational Gestures
    - Communication of Own Affect
    - Empathy
    - Quality of Social Overtures

Parent & Self Report Measures





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The importance of critical life moments: An explorative study of successful women with autism spectrum disorder (Webster & Garvis, 2017)

- 10 women aged 28-55 years with postsecondary degrees, all diagnosed after 18 years

- Agents of Change: being able to shape ones future
- Belief of Others in their Capability: coaching

> He (boss) would train me about how to behave in meetings because that bothered him the most and it was something I could take away. We went to lots of meeting together and I would write down the different perspectives and I wouldn't say anything until I got a non-verbal signal. So I knew all the details of the topic and he knew the big picture and we became a brilliant team.

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The importance of critical life moments: An explorative study of successful women with autism spectrum disorder (Webster & Garvis, 2017)

- Changed identity after diagnosis

I was relieved because I said 'this is it'. This has been floating around, not knowing quite what it is. I can't put a name to it. I was quite overwhelmed, emotionally, I cried. It was cathartic because it explained so many of the reasons why I struggled so much as a child and as an adolescent in early adulthood.

The Asperger's is part of me … It's part of my character. It's part of who I am. I would not choose a cure … You cannot take half my character away from me because it is who I am. Asperger's is not really a disability. It's just a different way of viewing the world.

So often you see things about autism like 'autism is wonderful because I am fine' or 'because Mozart' or 'because Temple Grandin' and they're people who are either famous or they're awesome but they're not representative of the general population of people with ASD. So to see people that are just ordinary. I'm a person with autism and I work part time at Maccas, or I take care of my kids. Rather than these expectations that you have to be some kind of genius.

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What does "Camouflage" really mean?

(Bargiela, Steward, Mandy, 2016)

"I honed something of a persona which was kind of bubbly and vivacious, and maybe a bit dim, because I had nothing to say other than adult novels. So I cultivated an image, I suppose, that I brought out to social situations as my partner's girlfriend, that was not 'me'." (P09)

"I'll mask if I act weird which is typical of ASC, I'll make a joke about it." (P02)

"I honestly didn't know I was doing it [social mimicry] until I was diagnosed, but when I read about it, it made perfect sense. I copy speech patterns and certain body language." (P05)

"It's very draining trying to figure out everything all the time, everything is more like on a manual, you've got to use one of those computers where you have to type every command in." (P01)

Others reported having felt confused about their identity as a result of pretending to be someone else, indeed some had "acted neurotypical" (P07) so convincingly that at times they had doubted whether they had ASC.

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Summary: The Female Profile of ASD without ID

Social Communication	Intact pretend play skills	Strong verbal ability	Ability to mimic appropriate social behavior
	Seen as "shy" or anxious	May have some friendships	Good social initiation, but difficulty maintenance
RRBIs	Less unusual restricted interests	Perfectionism	Poor flexibility in play
Comorbidities	Anxiety/Depression	Eating Disorders	Trauma/Sexual victimization

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Co-Occurrence of Autism and Gender Dysphoria

- Up to 25% of youth gender referrals have significant autism symptoms Shumer et al., 2015; Skagerberg et al., 2015
- 5+% of autistic youth have the "wish to be the other gender" Strang et al., 2014; Janssen et al., 2016
- No identified etiology for the co-occurrence. Several theories:
    - Prenatal hormones? (> testosterone and estrogen predict ASD and gender differences?)
    - Overly rigid thinking? (all or nothing response to gender)
    - Heterogeneous? (different pathways)

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ASD+GD Care Consensus

Initial Clinical Guidelines For Co-Occurring Autism Spectrum Disorder and Gender Dysphoria or Incongruence in Adolescents

Strang et al., 2016

Screen for ASD in GD and GD in ASD

ASD should not preclude access to medical gender care, but assessments may unfold over time

Many autistic GD youth express gender in atypical ways – may be focused on medical transition over social

Executive function ASD weaknesses may impact transition – may need parental support

Julia Bascom: Advice for Parents

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Clinical Takeaways

- Nuanced discussion of social reciprocity (initiation vs. response)
  - Directs parent/ other children's play?
- Flexible, cooperative play even if interests seem qualitatively "typical"
- Ask about the effort required to engage in social interactions
- Ask whether intact social skills were always that way
  - Peer mentoring, intact imitation
- Social cognition vs. Social Skills
- Think about the standardization of your measures
- Include questions about gender dysphoria in ASD evaluations

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Future Directions and Considerations for Research

- Consider broadening research criteria to allow for inclusion of females who may meet clinical, though not research, criteria
- Investigate and define the female behavioral phenotype of ASD through both qualitative and quantitative methods
  - Assess sex differences in neurological underpinnings
  - Investigate sex differences in genetics/etiology
  - Determine moderators/confounding variables (e.g., age, IQ)
- Evaluate the intersection of gender identity with ASD traits
- Evaluate the validity of current diagnostic tools for females with ASD

Kirkovski et al. (2013); Lai et al. (2015)

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