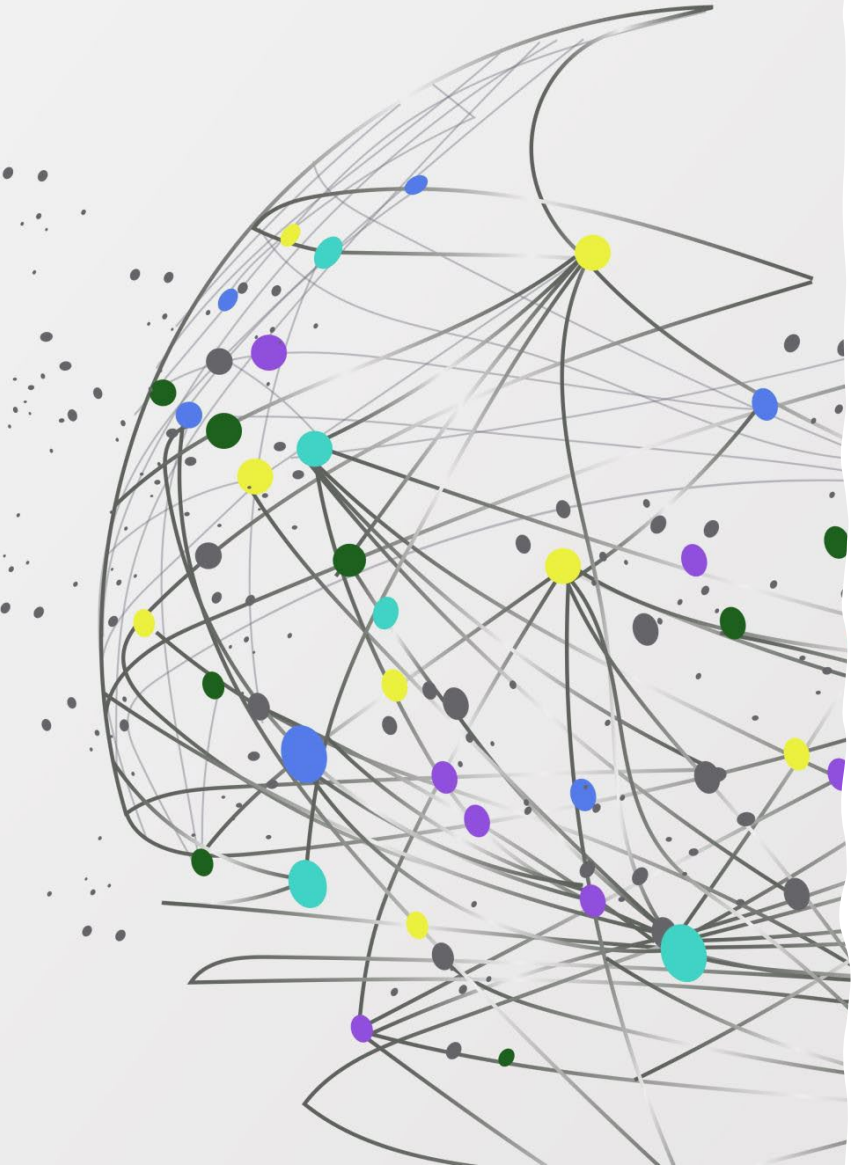


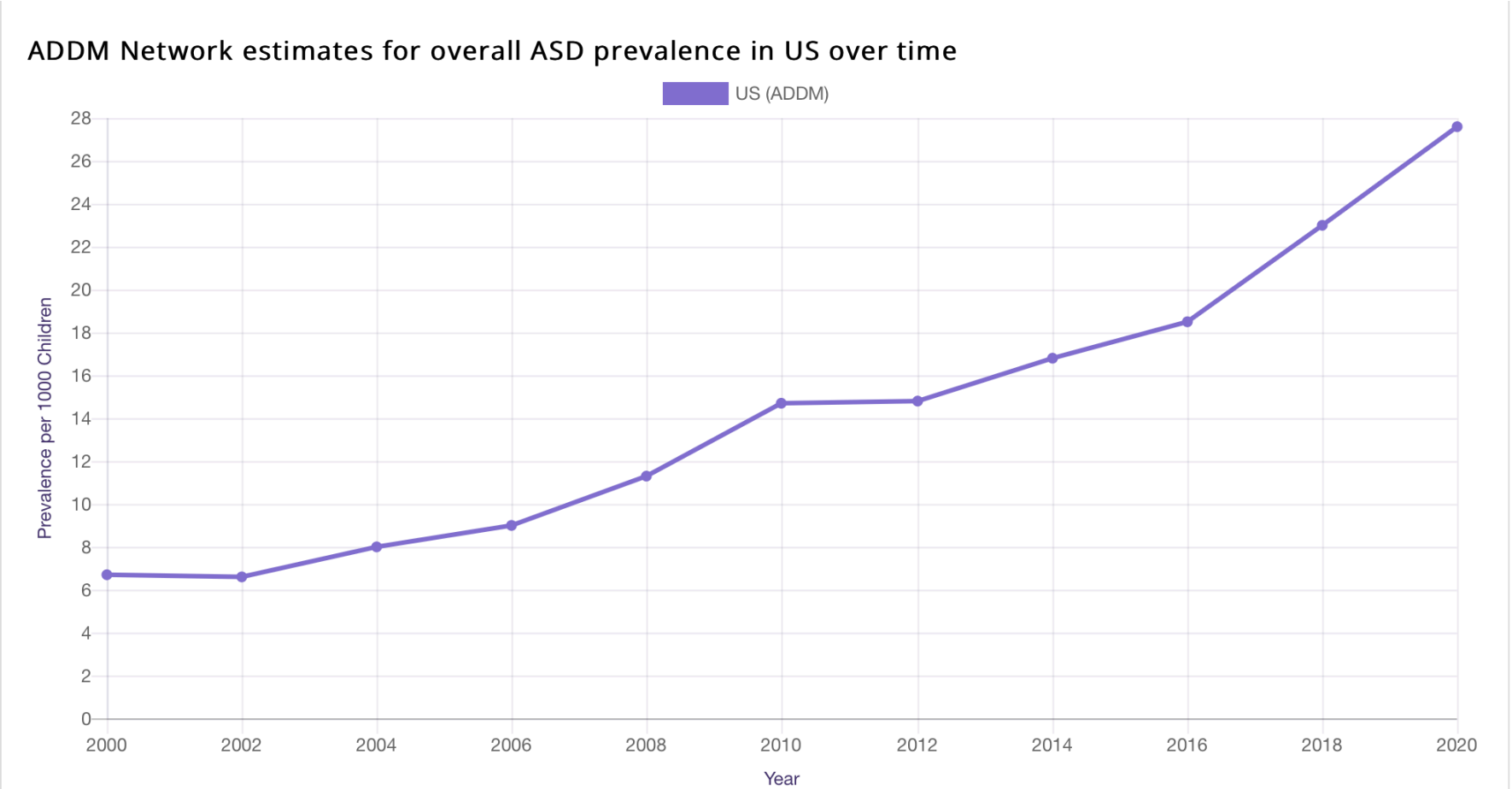
Girls and Autism

Sydney Rice, MD, MS

Developmental Behavioral Pediatrics

- *I have no conflicts of interest to disclose*

Autism Prevalence: 1 in 36

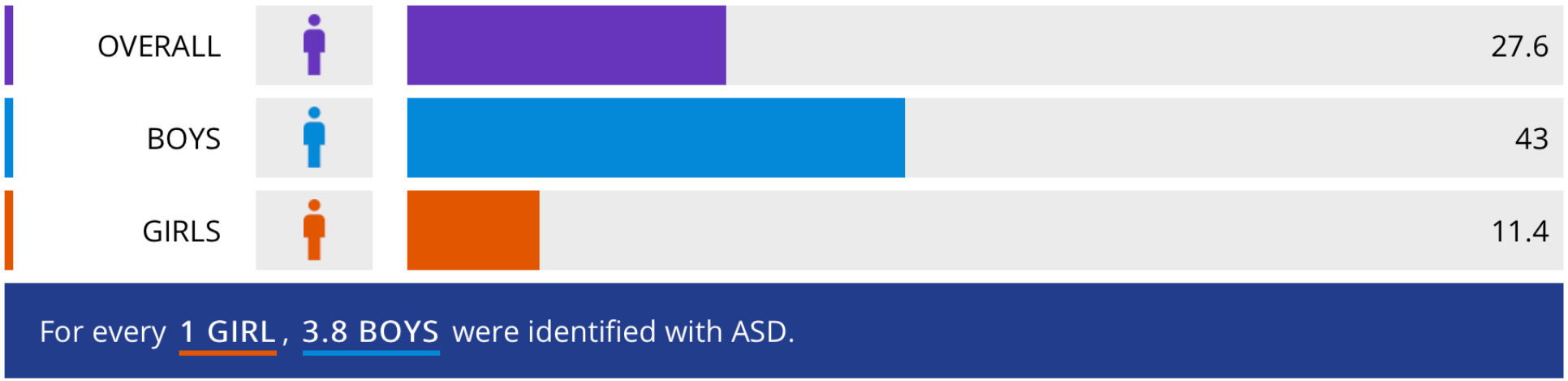


*ADDM data do not represent the entire state, only a selection of sites within the state.
**ADDM estimate = the total for all sites combined.
NSCH data are not comparable over time as data collection methods changed and the data are not provided here. See technical notes for further details.

https://www.cdc.gov/ncbddd/autism/data/index.html

Prevalence Estimates by Sex

Show ADDM prevalence estimates* for: U.S. or Total† Show prevalence for: 2020 Apply



Note: *Data for transgender and gender non-binary children are not reported at this time.*

**ADDM data do not represent the entire state, only a selection of sites within the state.*

†ADDM estimate = the total for all sites combined.

https://www.cdc.gov/ncbddd/autism/data/index.html

Why are there fewer females with autism?

- Differences in presentation
  - Same criteria for a diagnosis
  - Interests are different (TV versus gaming)

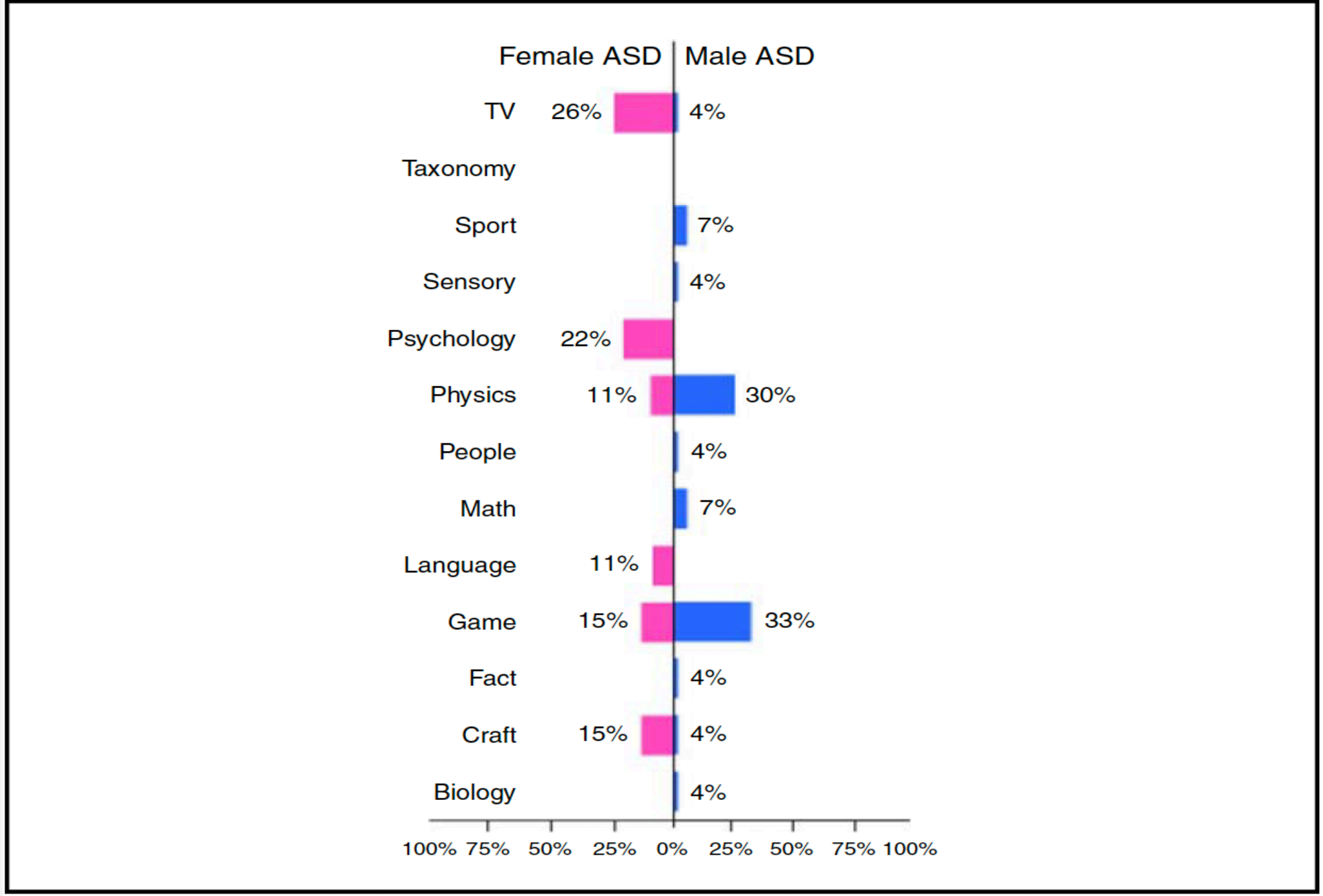
- Biology (Female Protective Effect)
  - Hormones
  - Neurocognitive networks

Fewer Females: Historical Perspective

- Females with autism have more severe symptoms
- More likely to have intellectual disability
- Higher overall autism scores
- Higher risk for siblings
- Diagnosed later

Where are the females?

- Differences in presentation
- Other diagnostic categories
- Masking



Nowell S, Jones D, Harrop C. Circumscribed interests in autism: are there sex differences? *Adv Autism*. 2019;5.

Recognition: Social Cognition

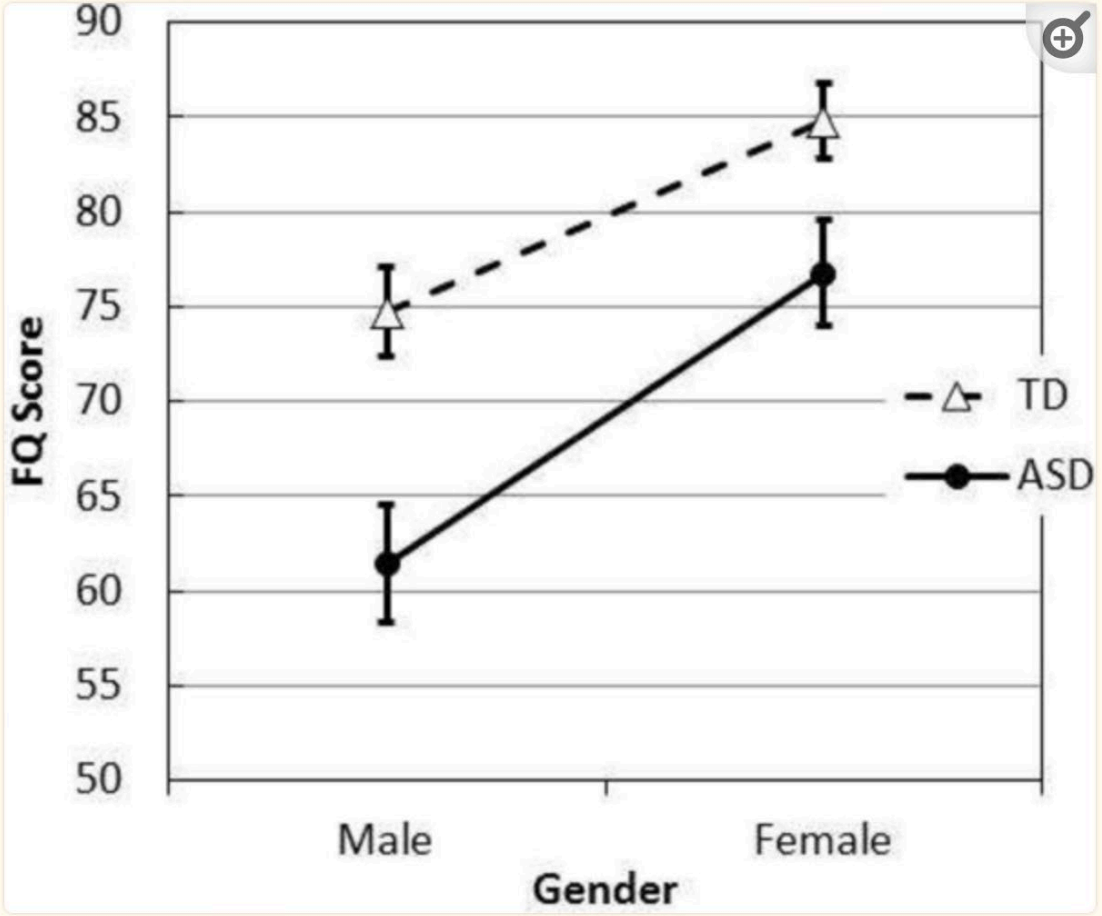


Figure 1

Total friendship questionnaire (FQ) scores by gender and diagnosis. Error bars represent standard errors of the mean. ASD, autism spectrum disorder; TD, typically developing.

Head AM, McGillivray JA, Stokes MA. Gender differences in emotionality and sociability in children with autism spectrum disorders. Mol Autism. 2014 Feb 28;5(1):19.

Other Diagnoses

- Anxiety
- Depression
- Obsessive Compulsive Disorder
- Oppositional Defiant Disorder
- **Anorexia nervosa**

Eating Disorder

- Anorexia disorder and autism-25-30%?

- Alexithymia
  1. difficulty identifying feelings
  2. difficulty describing feelings to other people
  3. a stimulus-bound, externally oriented thinking style
  4. constricted imaginal processes

Courty A, et al, Levels of autistic traits in anorexia nervosa: a comparative psychometric study. BMC Psychiatry. 2013 Sep 10;13:222.

Masking Autism

- Level 1 autism
- Aware of the presence of social stigma or societal expectations
- Have had experiences with bullying or social rejection
- Have a specific goal in mind, such as obtaining a job or a romantic relationship

Under-Recognition: Masking/Camouflage

- Missing girls are likely verbal with fewer repetitive behaviors
- “Masking”
- Criteria are the same for boys and girls
- Girls have fewer aggressive behaviors (think ADHD)

Masking

- Camouflage sensory difficulties
  - Reduce self-regulating behaviors such as rocking
- Cover up expressive and receptive language challenges
  - Mirror others' facial expressions or social behaviors
  - Rehearse scripted responses

Biology:
True Difference in Rate

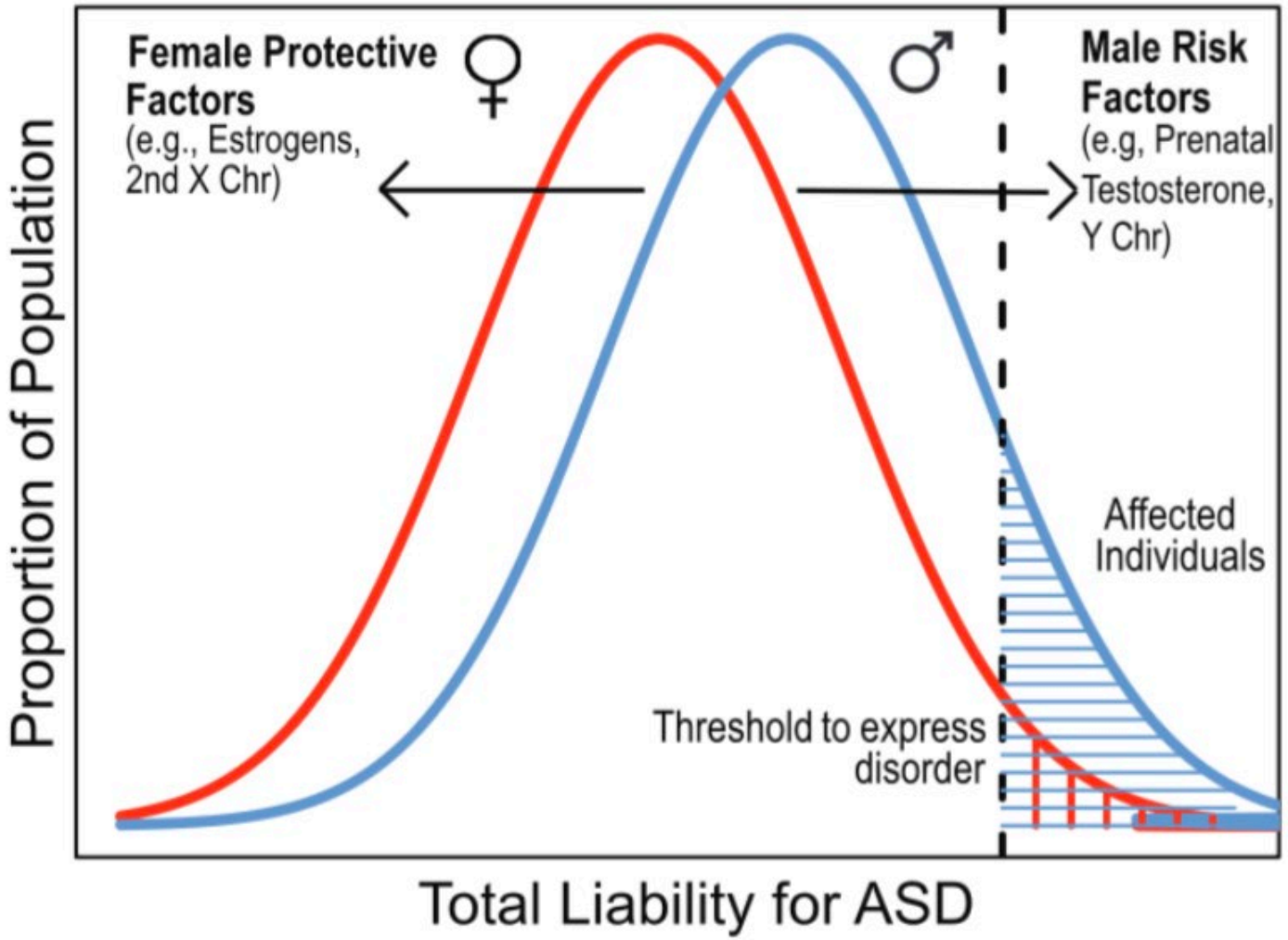
- Female Protective Effect
  - Environmental, Genetic or Epigenetic
- Extreme Male Brain
  - Testosterone
  - Polycystic Ovarian Syndrome
- Neurocognitive Network Differences

Biology: The Female Protective Effect

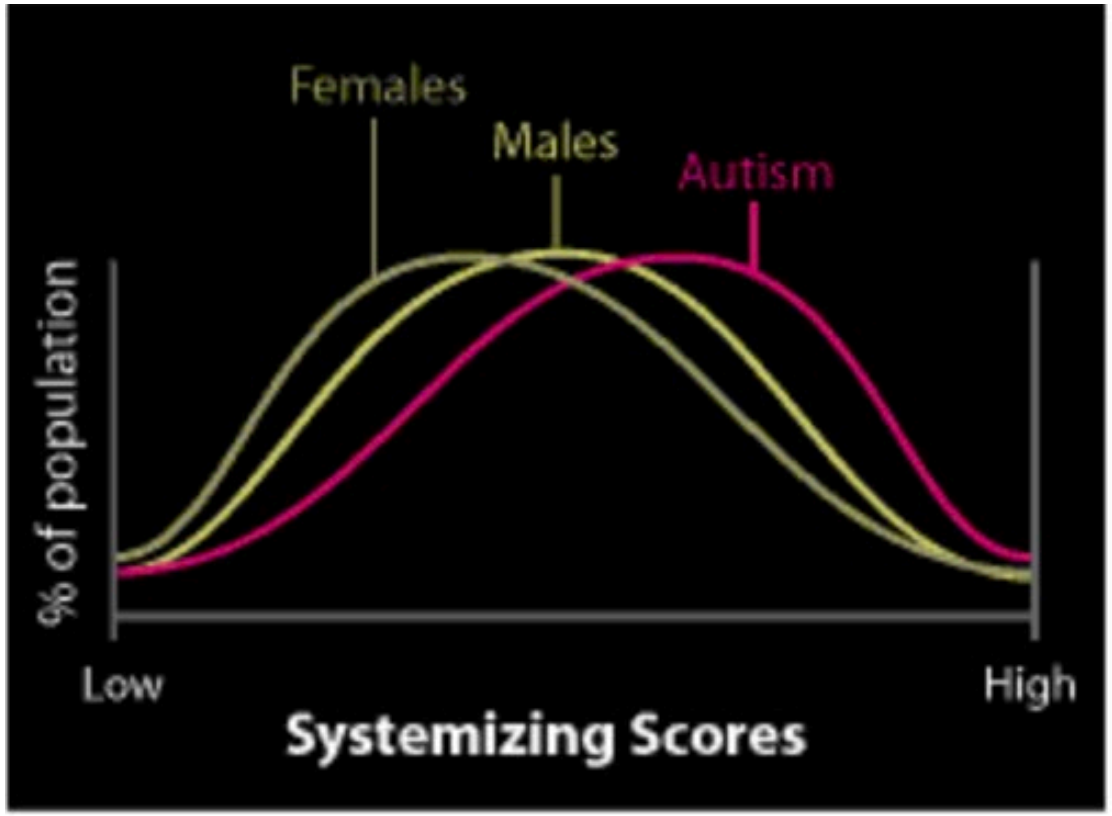
- Hormones
- Brain structure and connectivity
- Genetics

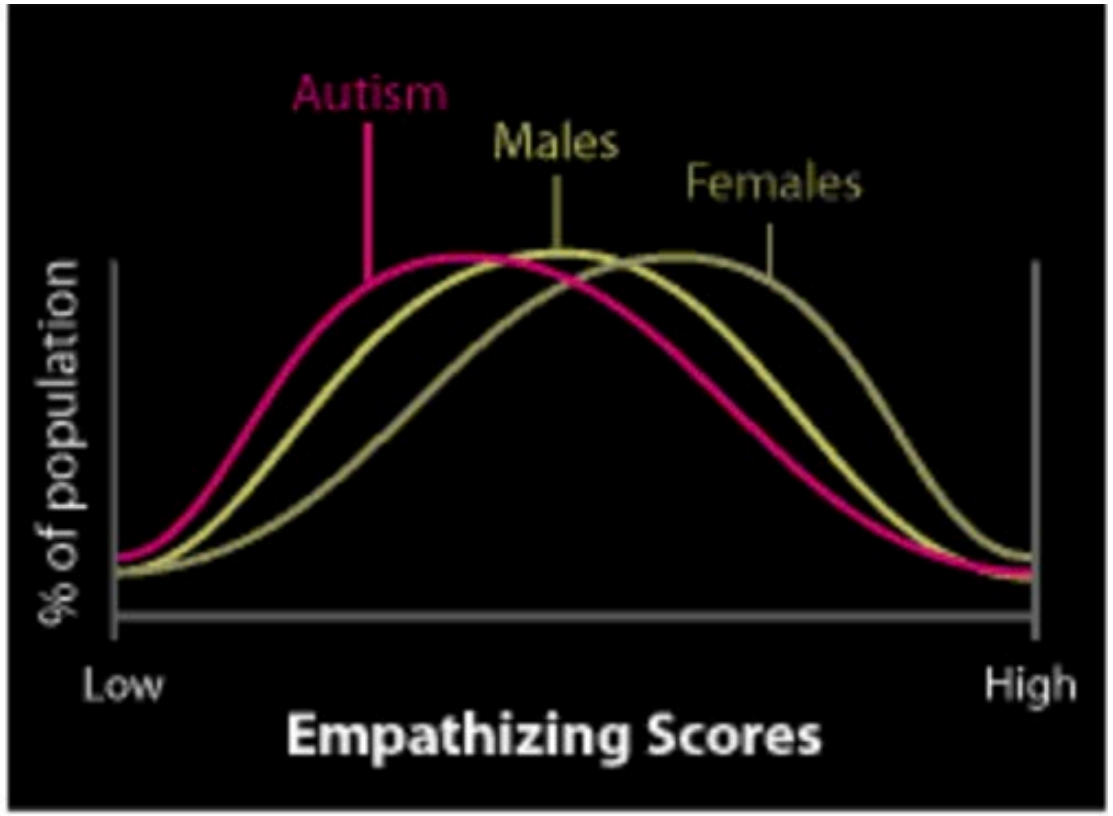
Female Protective Effect

- Joseph D. Dougherty et al, Can the “female protective effect” liability threshold model explain sex differences in autism spectrum disorder?,Neuron, Volume 110, Issue 20,2022,Pages 3243-3262,



Hormones: Extreme Male Brain



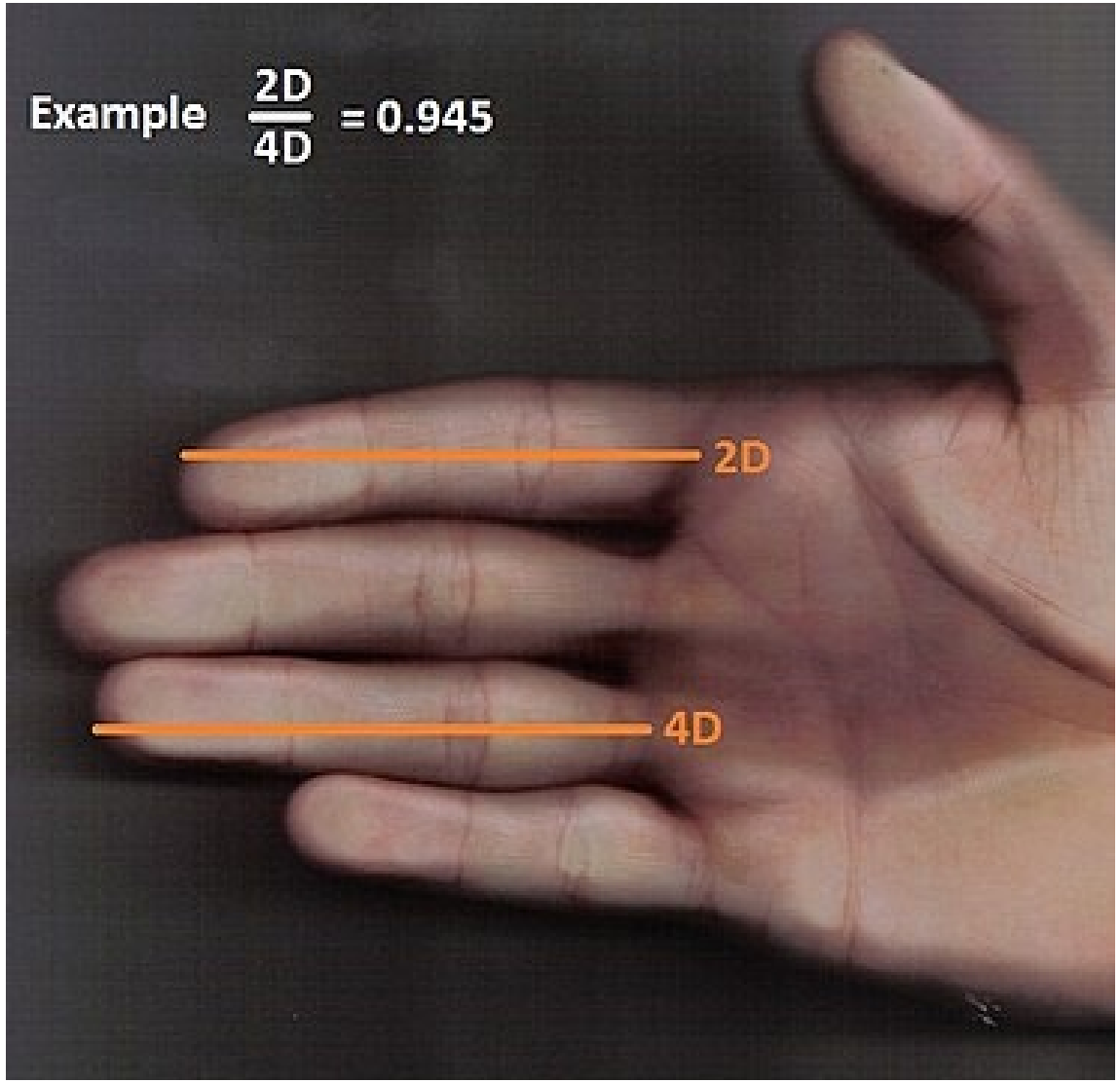


"The extreme male brain theory of autism," by Simon Baron-Cohen, Trends in Cognitive Science, June 2002.

Hormones: “Extreme Male Brain”

- 2D:4D ratios
- Boys have shorter index finger
- Recognized in the 1880’s

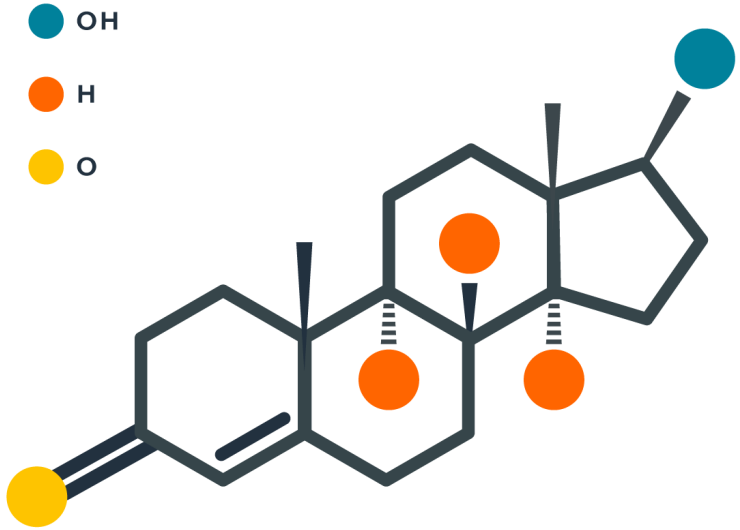
- Higher testosterone, lower estradiol levels by amniocenteses



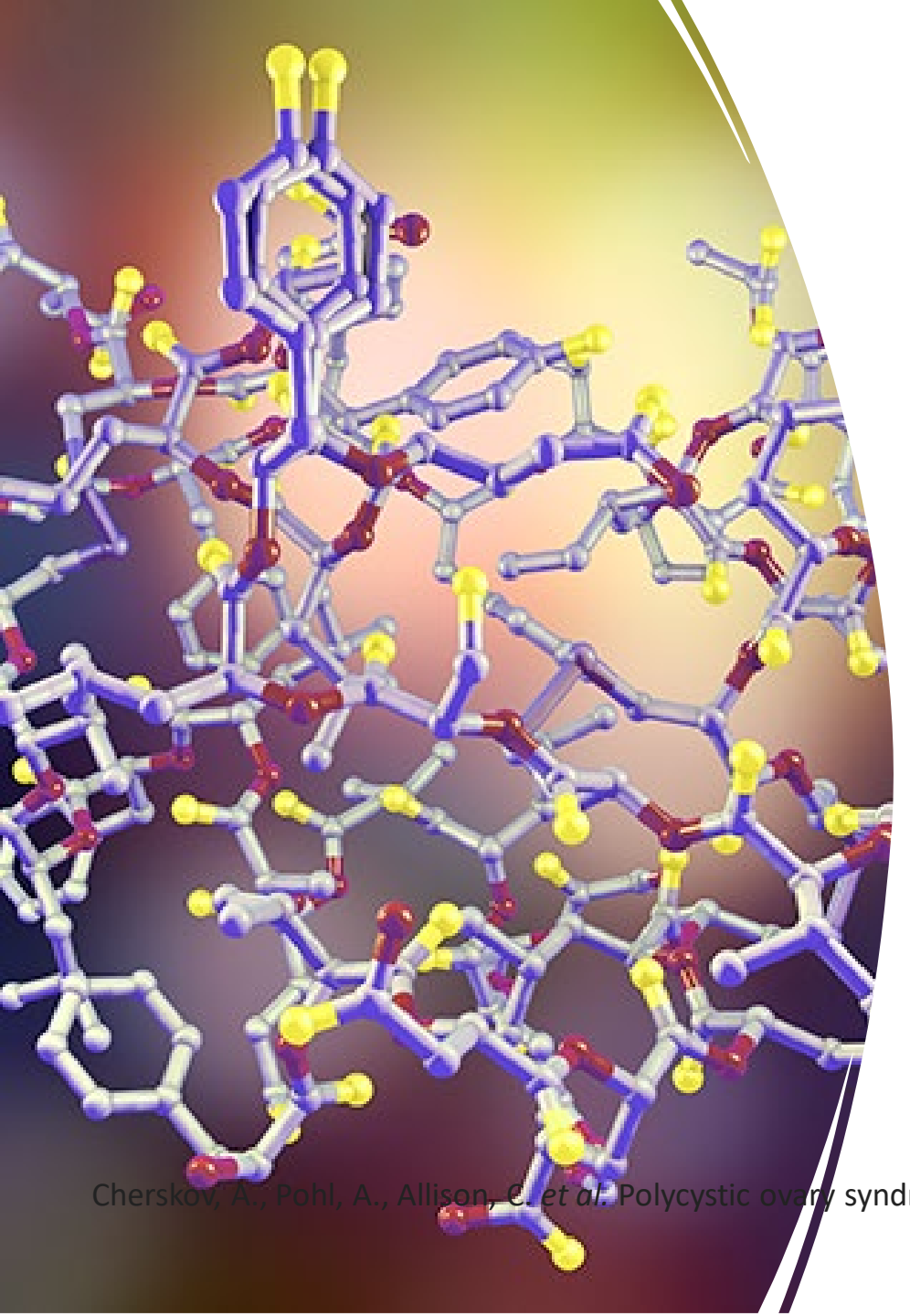
Lutchmaya S, Baron-Cohen S, Raggatt P, Knickmeyer R, Manning JT (April 2004). "2nd to 4th digit ratios, fetal testosterone and estradiol". *Early Human Development*. **77** (1–2): 23–28.

Hormones: Polycystic Ovarian Syndrome

- 23% of women
- Increased androgens due to high luteinizing hormone
- Increased insulin levels



TESTOSTERONE



Hormones: PCOS and Autism

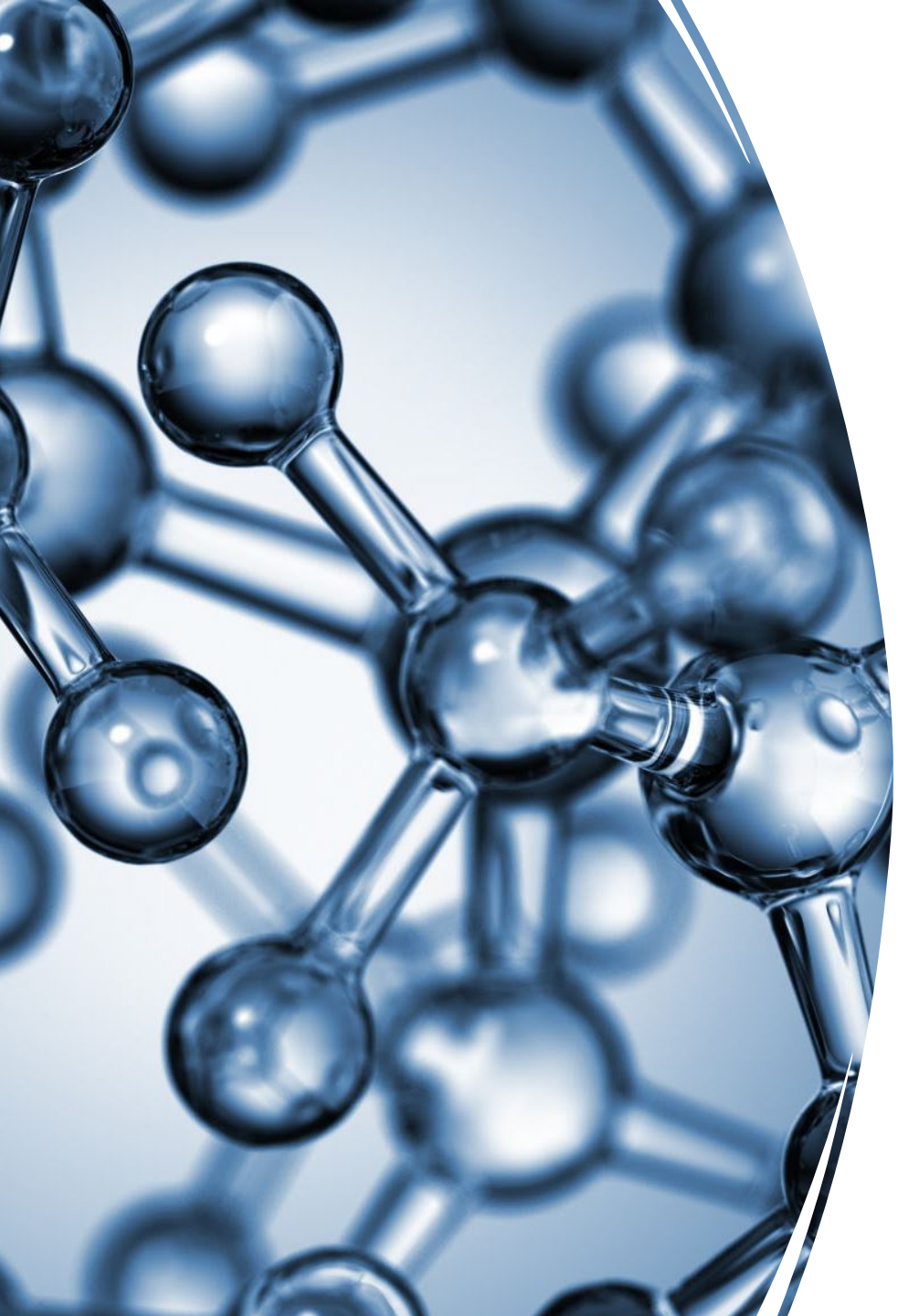
- Case controlled study in England
- Women with autism were 2x as likely as controls to have PCOS
- Women with PCOS were 2x as likely to have autism
- Children of women with PCOS were 2x as likely to have autism.

Cherskov, A., Pohl, A., Allison, C. *et al.* Polycystic ovary syndrome and autism: A test of the prenatal sex steroid theory. *Transl Psychiatry* **8**, 136 (2018)

Neurocognitive Networks

- Salience Network
  differentiate internal/external stimuli, reward processing
  - No difference M/F with ASD
- Default Mode Network
  introspection, autopilot, creativity
  - Females with ASD more connected than males with ASD
- Central Executive Network
  executive functioning
  - Females with ASD more connected than males with ASD

Lawrence, K., Sex Differences in Functional Connectivity of the Salience, Default Mode and Central Executive Networks in Youth with ASD Cerebral Cortex, 2020



Neurocognitive Networks

- ”Plasticity” reactions to genetic or environmental triggers
  - Reactions are more common in perception and language-based areas
  - Hyperlexia, perfect pitch, synesthesia
- >400 genes differentially expressed (M>F) **prenatally**
- Less effect in adults
- Females are protected

Neurocognitive Networks: Genetics

- A 2014 study by geneticist Sebastien Jacquemont of the University of Lausanne in Switzerland and his colleagues found that there was a 300 percent increase in harmful copy-number variants in females with autism, compared with males.

- Mottron L, Duret P, Mueller S, Moore RD, Forgeot d'Arc B, Jacquemont S, Xiong L. Sex differences in brain plasticity: a new hypothesis for sex ratio bias in autism. Mol Autism. 2015 Jun 5;6:33. doi: 10.1186/s13229-015-0024-1. PMID: 26052415; PMCID: PMC4456778.

- Under-recognition of females with Level 1 Autism
- Females are relatively protected biologically and genetically
- Extreme Male Brain
- Neurocognitive Networks

Thoughts?

EXTRA….

Genetics Autism

- 9000 dizygotic twins
- Siblings of female patients have more autistic traits=higher genetic burden

- Shank1 microdeletions in males are associated with autism
- Same Shank1 microdeletions in females are associated with anxiety

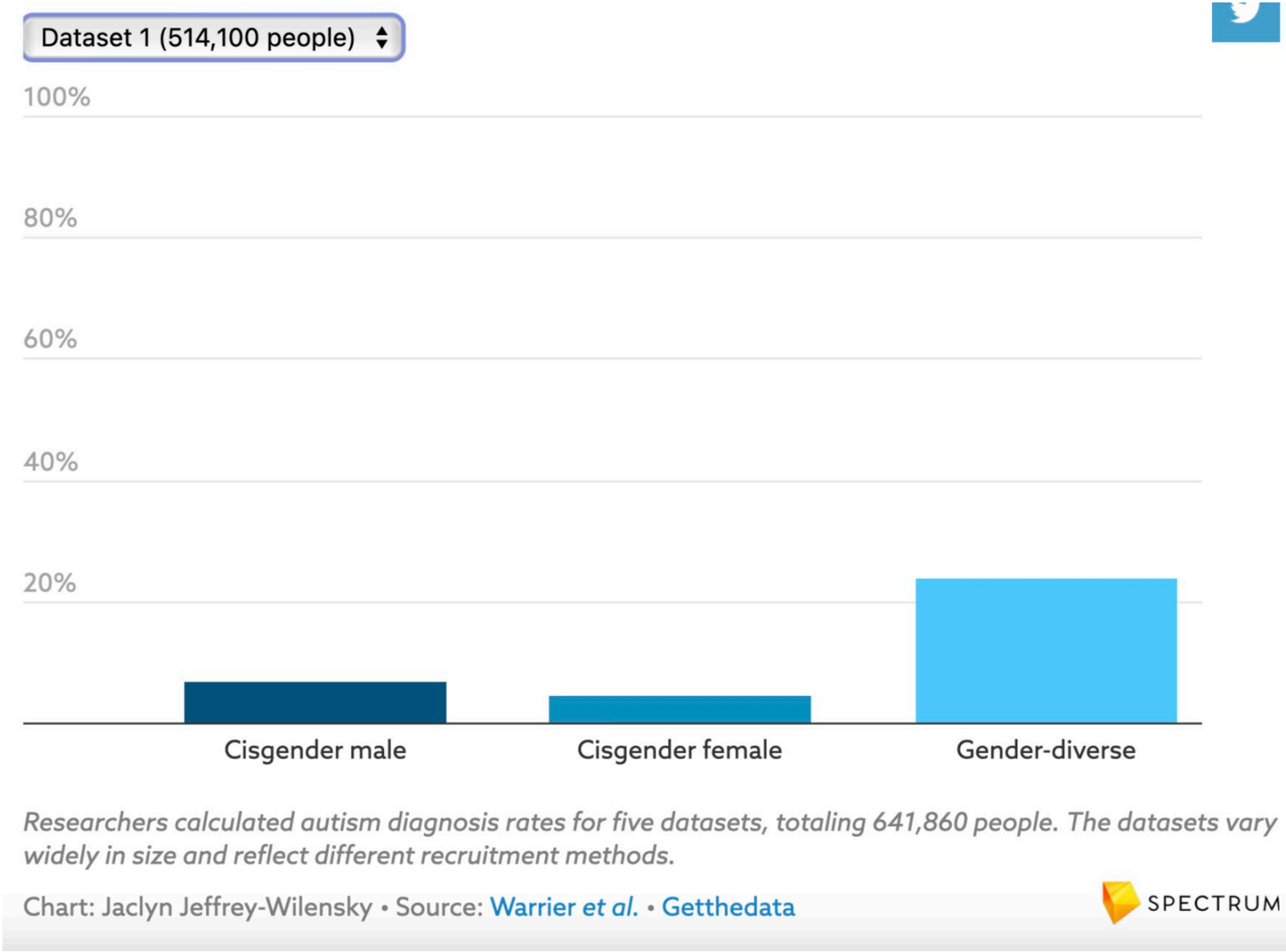
Extreme Male Brain vs. “Gender Defiant”

- Women with ASD
  - more masculine facial features
  - larger head circumference
  - higher testosterone levels

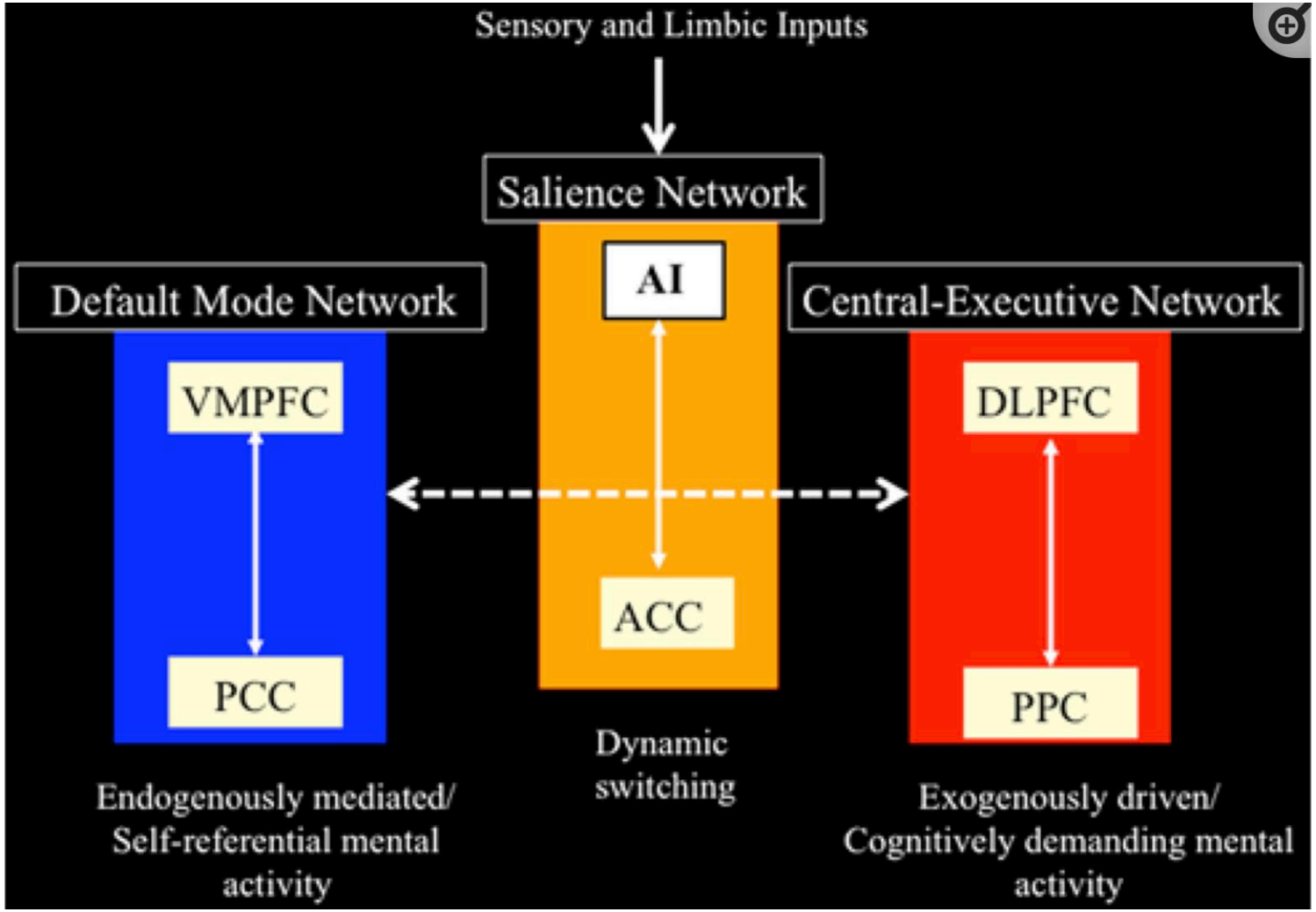
- Men in the ASD group
  - less masculine body characteristics and voice quality
  - higher (i.e. less masculine) 2D:4D ratios,
  - similar testosterone levels to controls.

Bejerot, S., Eriksson, J., Bonde, S., Carlström, K., Humble, M., & Eriksson, E. (2012). The extreme male brain revisited: Gender coherence in adults with autism spectrum disorder. *The British Journal of Psychiatry, 201*(2), 116-123. doi:10.1192/bjp.bp.111.097899

Gender Diversity



Warrier, V., Greenberg, D.M., Weir, E. *et al.* Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. *Nat Commun* **11**, 3959 (2020). https://doi.org/10.1038/s41467-020-17794-1



Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010 Jun;214(5-6):655-67. doi: 10.1007/s00429-010-0262-0.