- Listening to our Daughters: Girls & Women with Autism will Inform Novel Treatments

Kevin Pelphrey
Carbonell Family Professor and Director
Autism and Neurodevelopmental Disorders Institute

October 26, 2016

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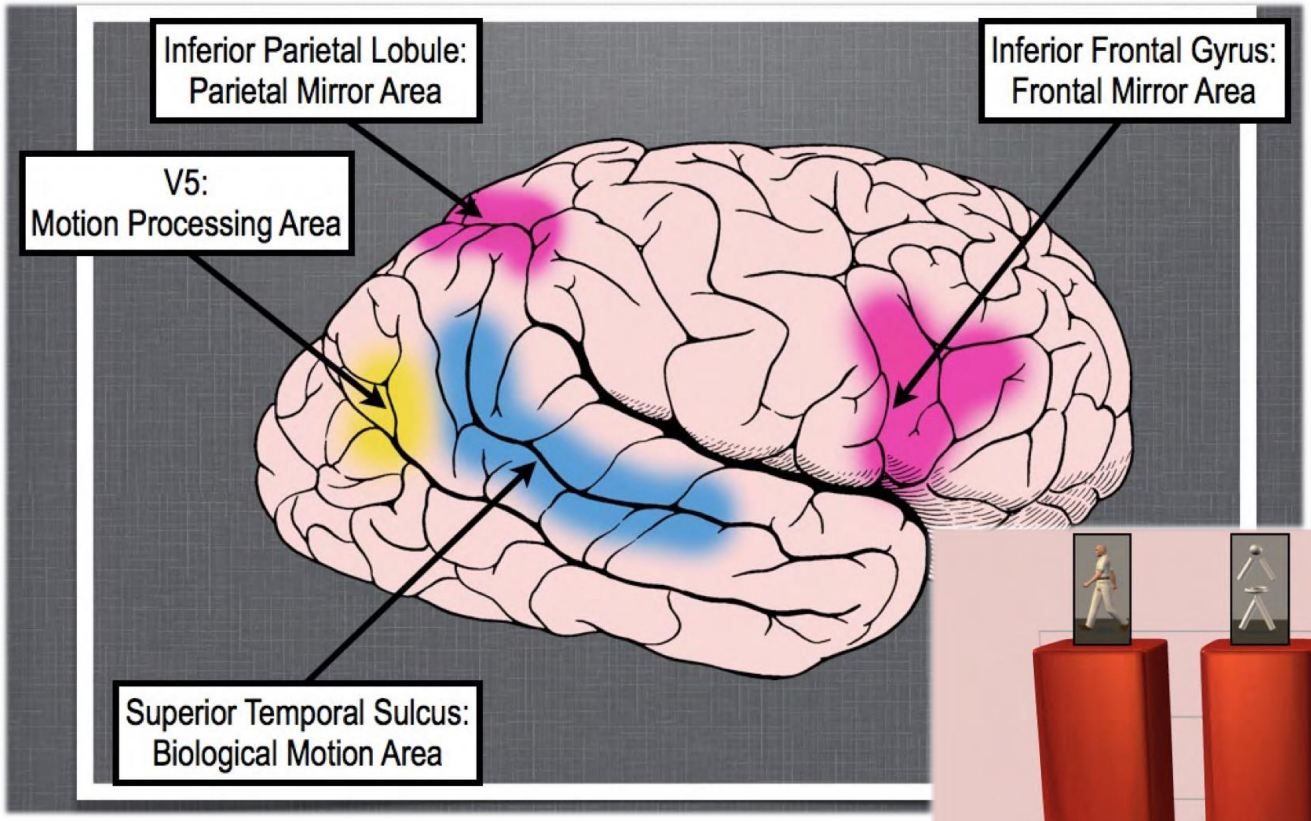
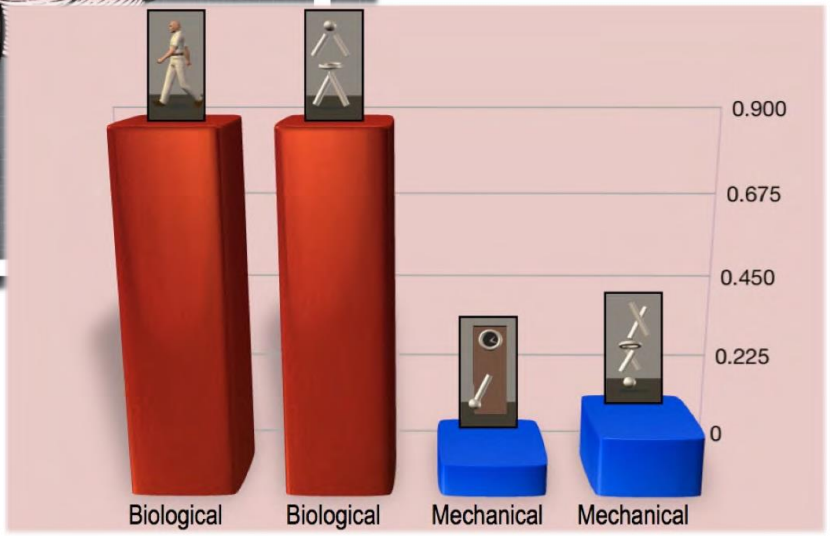
WASHINGTON, DC

Children's National™

Brain Systems for Social Cognition

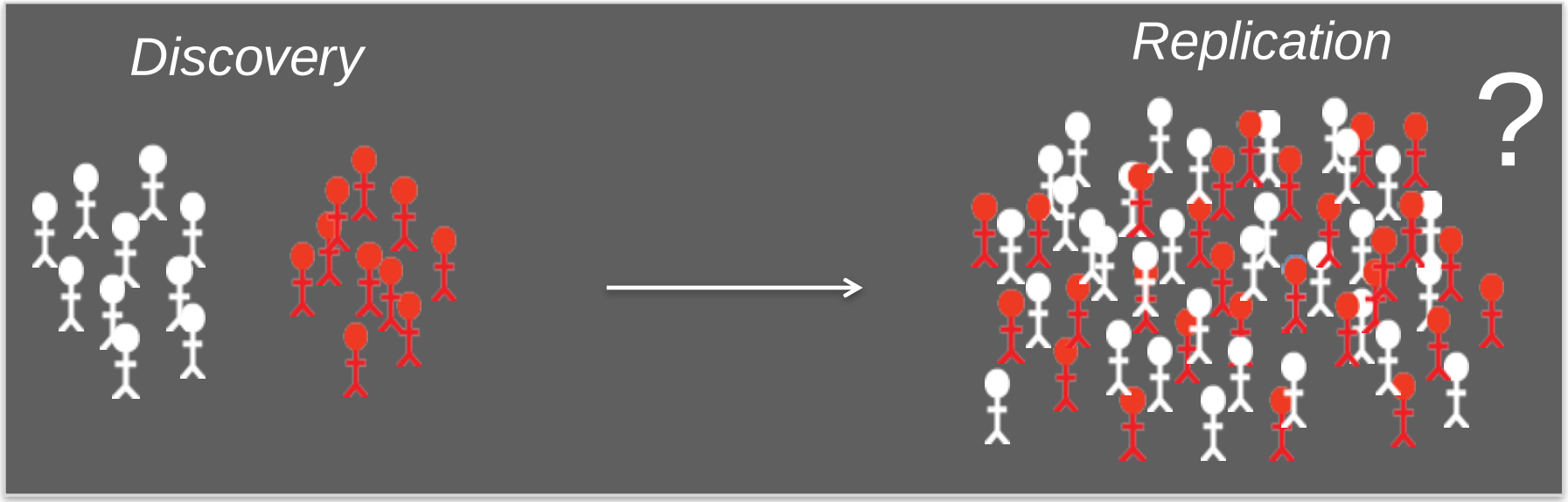




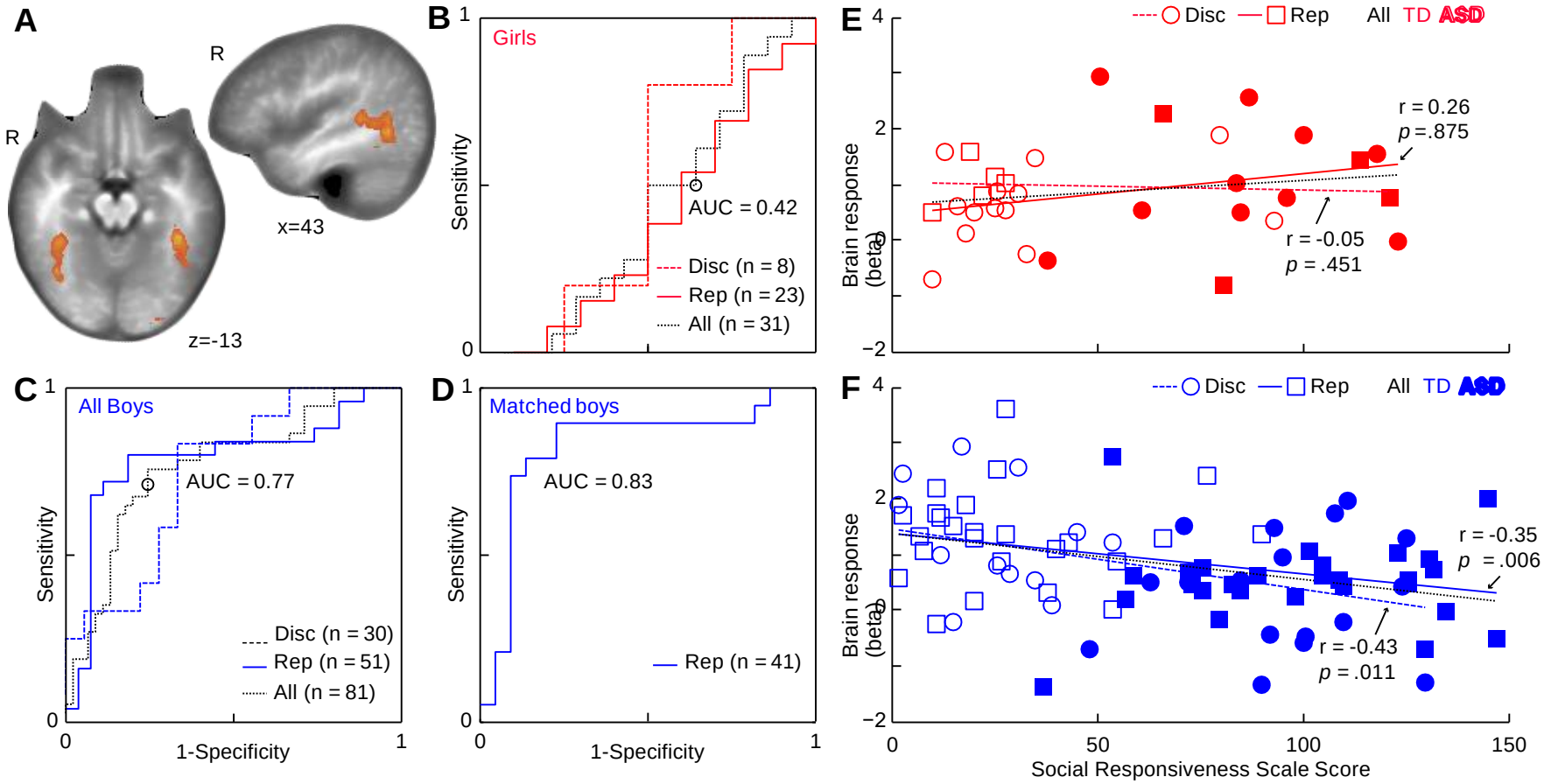
Pelphrey et al. (2003) *Journal of Neuroscience*

Can we see autism's signature in the individual brain?

Classification Analysis

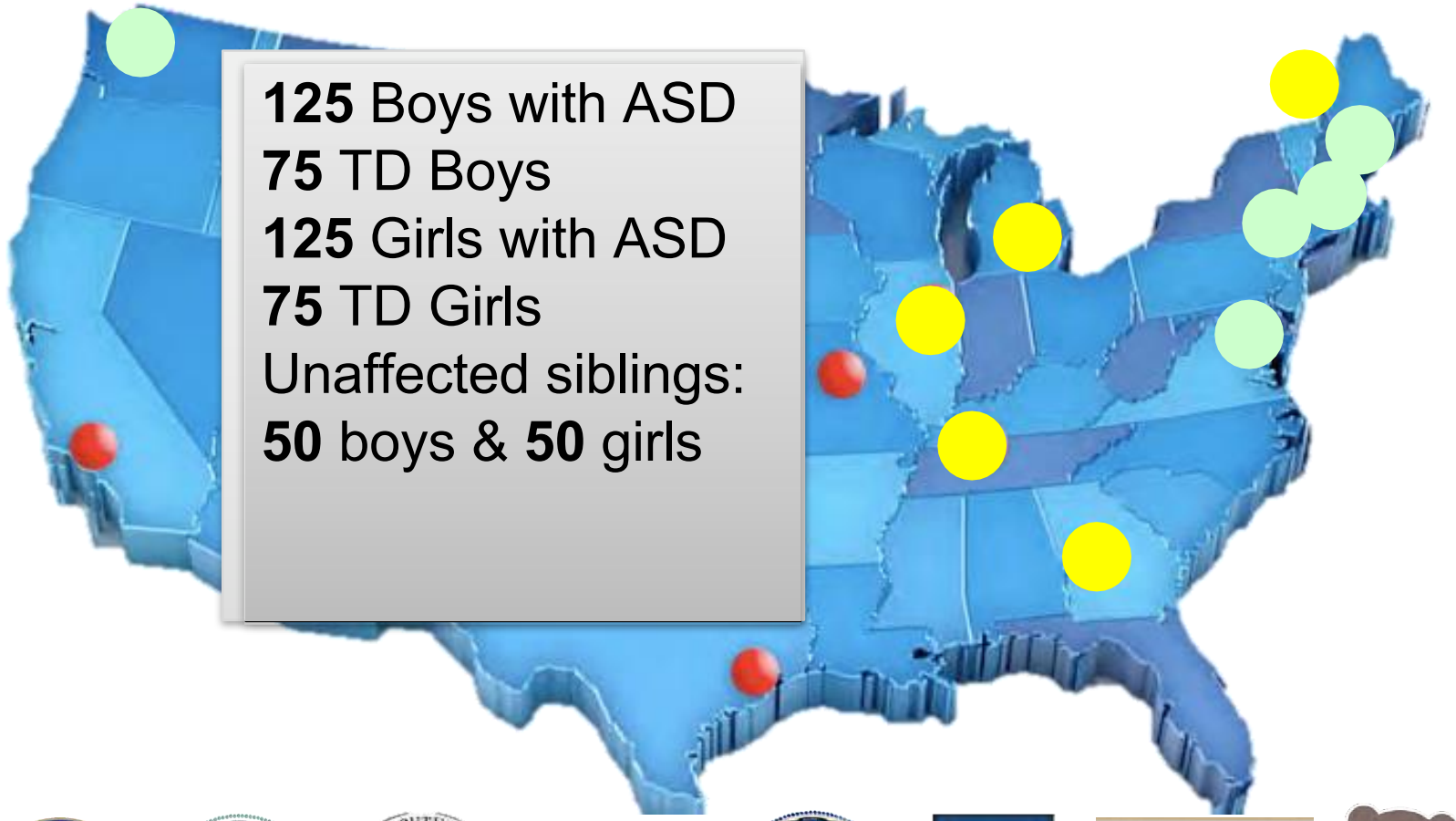


A weak response to biological motion is a marker of autism in boys (but not girls!)



Björnsdotter et al., *JAMA: Psychiatry*, 2016

Autism Center of Excellence: Girls Network



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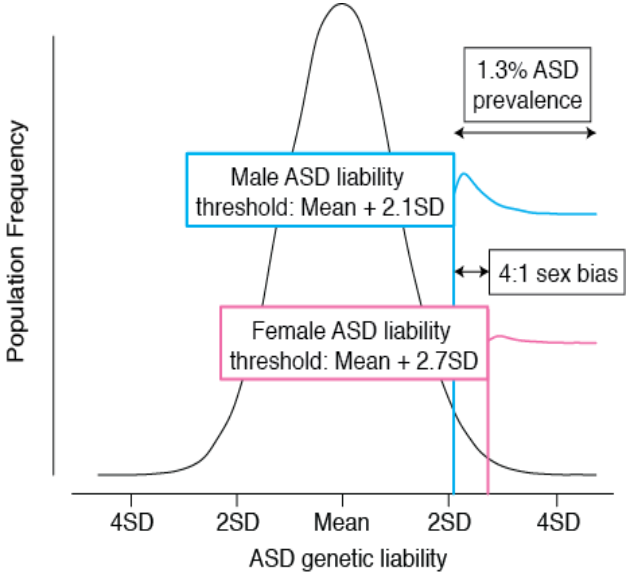
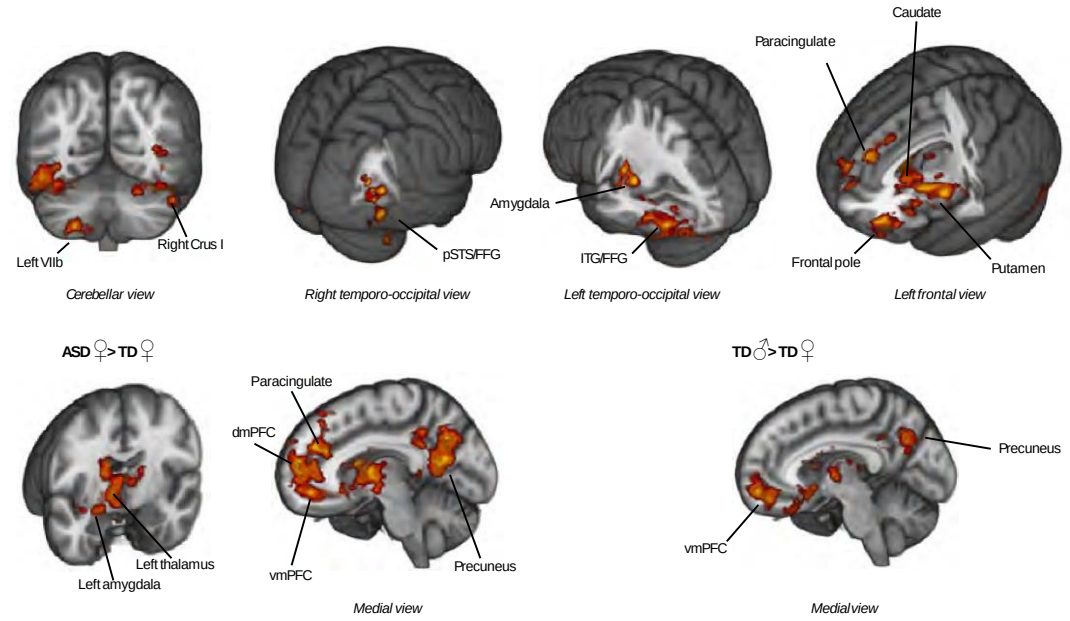
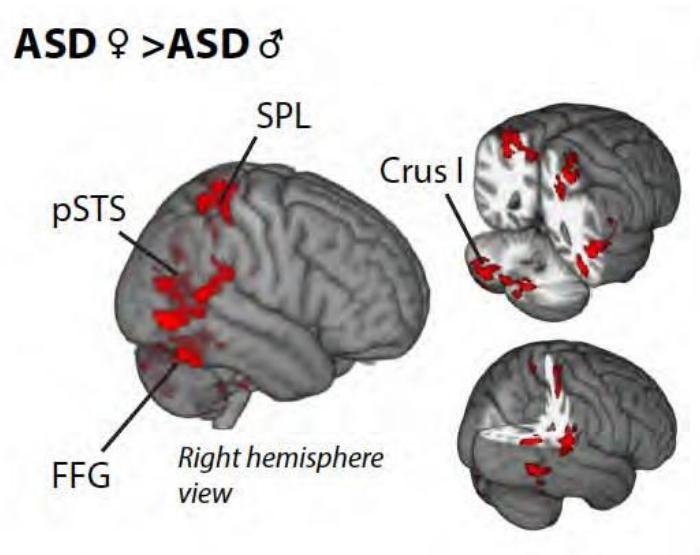
Milestones	April 1 2016
Target: Total Recruitment	374
Actual: Total Recruitment	454
Actual/Target Ratio: Total Recruitment	**121%**
Target: Racial Minority Recruitment	65
Actual: Racial Minority Recruitment	110
Actual/Target Ratio: Racial Minority Recruitment	**169%**
Target: Hispanic Ethnicity Recruitment	33
Actual: Hispanic Ethnicity Recruitment	60
Actual/Target Ratio: Hispanic Ethnicity Recruitment	**182%**

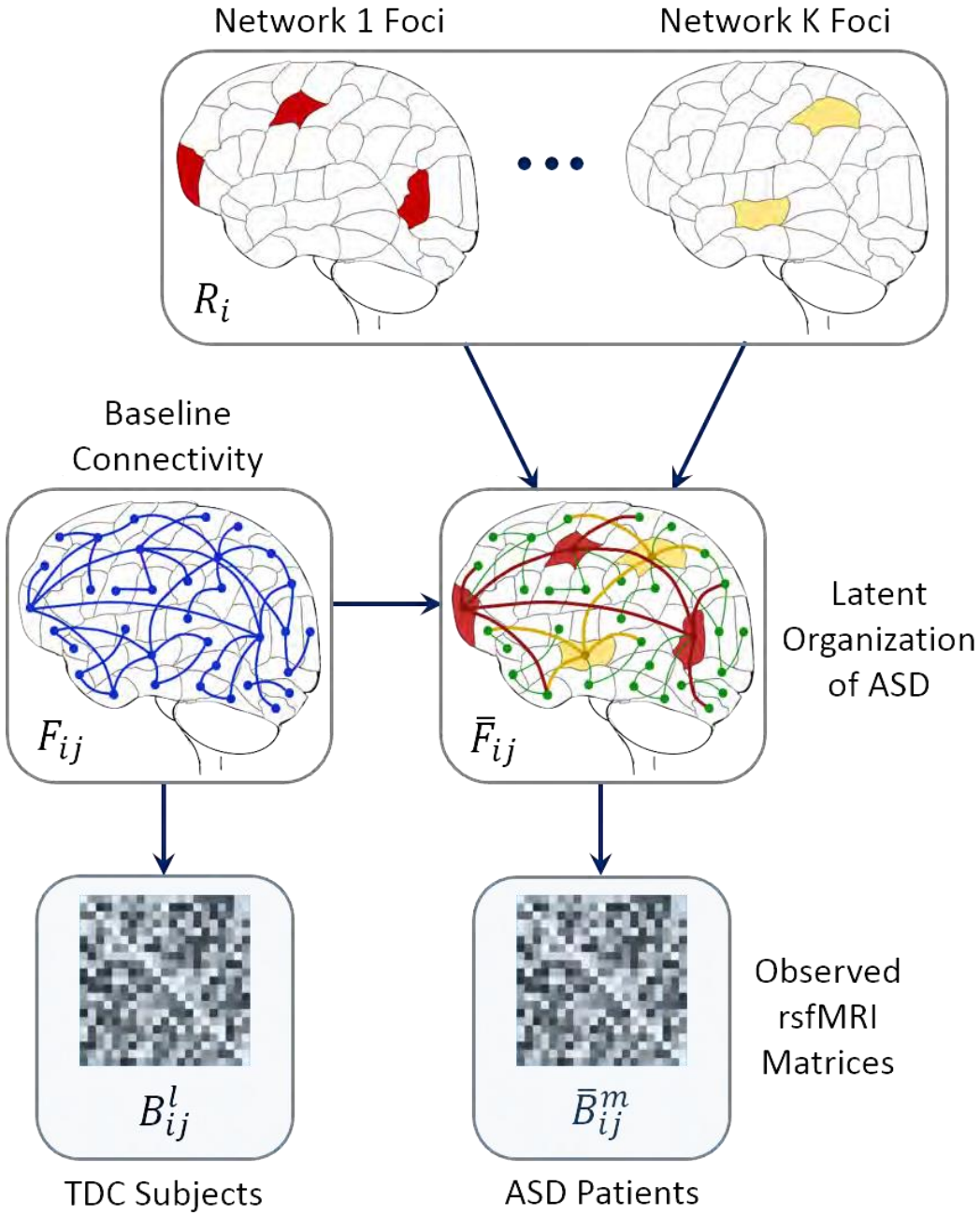
Sex differences in brain response to coherent versus scrambled biological motion ASD ♀ > ASD ♂



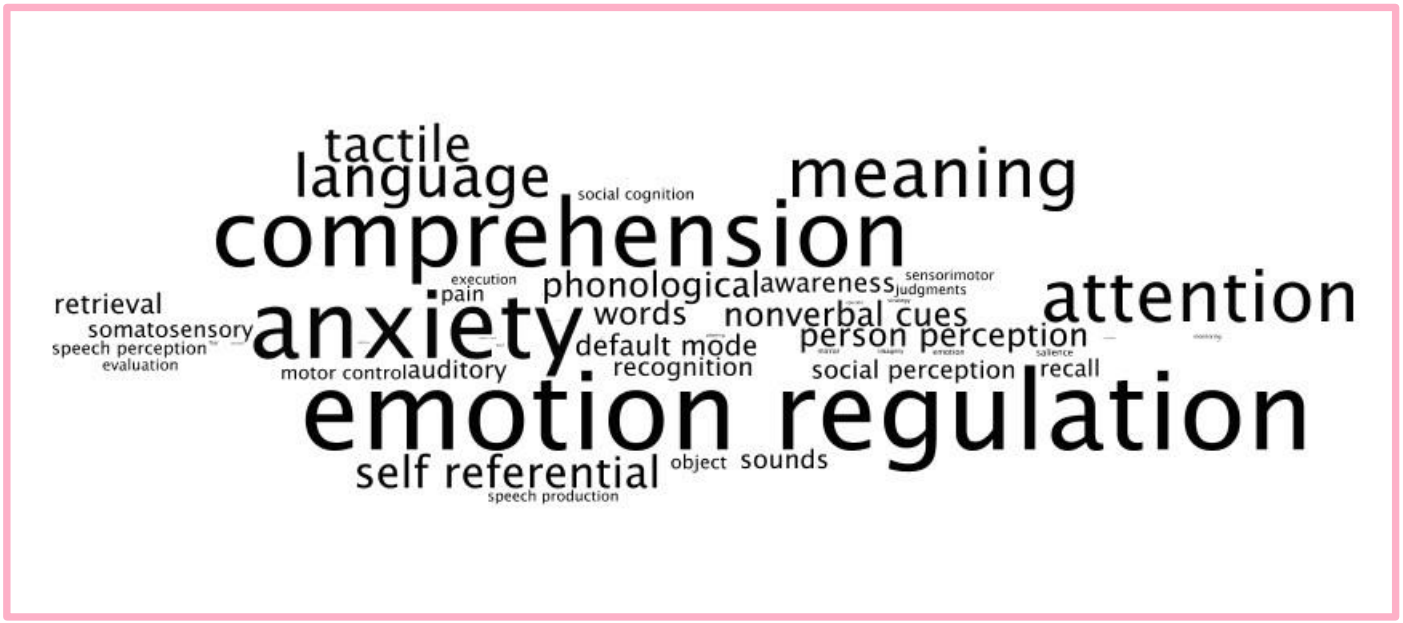


♀:female; ♂:male; **dmPFC:** dorsomedial prefrontal cortex; **FFG:** fusiform gyrus; **ITG:** inferior temporal gyrus; **pSTS:** posterior superior temporal sulcus **vmPFC:** ventromedial prefrontal cortex

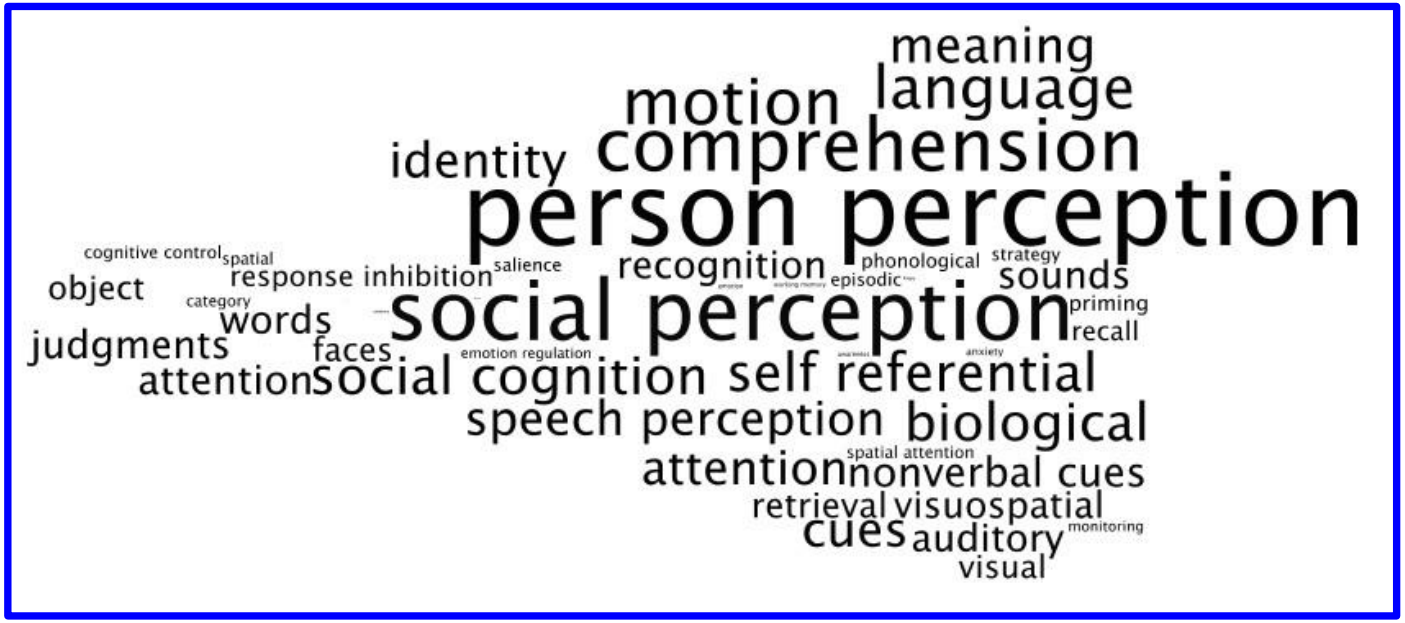



Network 1 Foci
Network K Foci
R_i
Baseline Connectivity
F_{ij}
$\bar{F}_{ij}$
Latent Organization of ASD
B_{ij}^{l}
$\bar{B}_{ij}^{m}$
Observed rsfMRI Matrices
TDC Subjects
ASD Patients

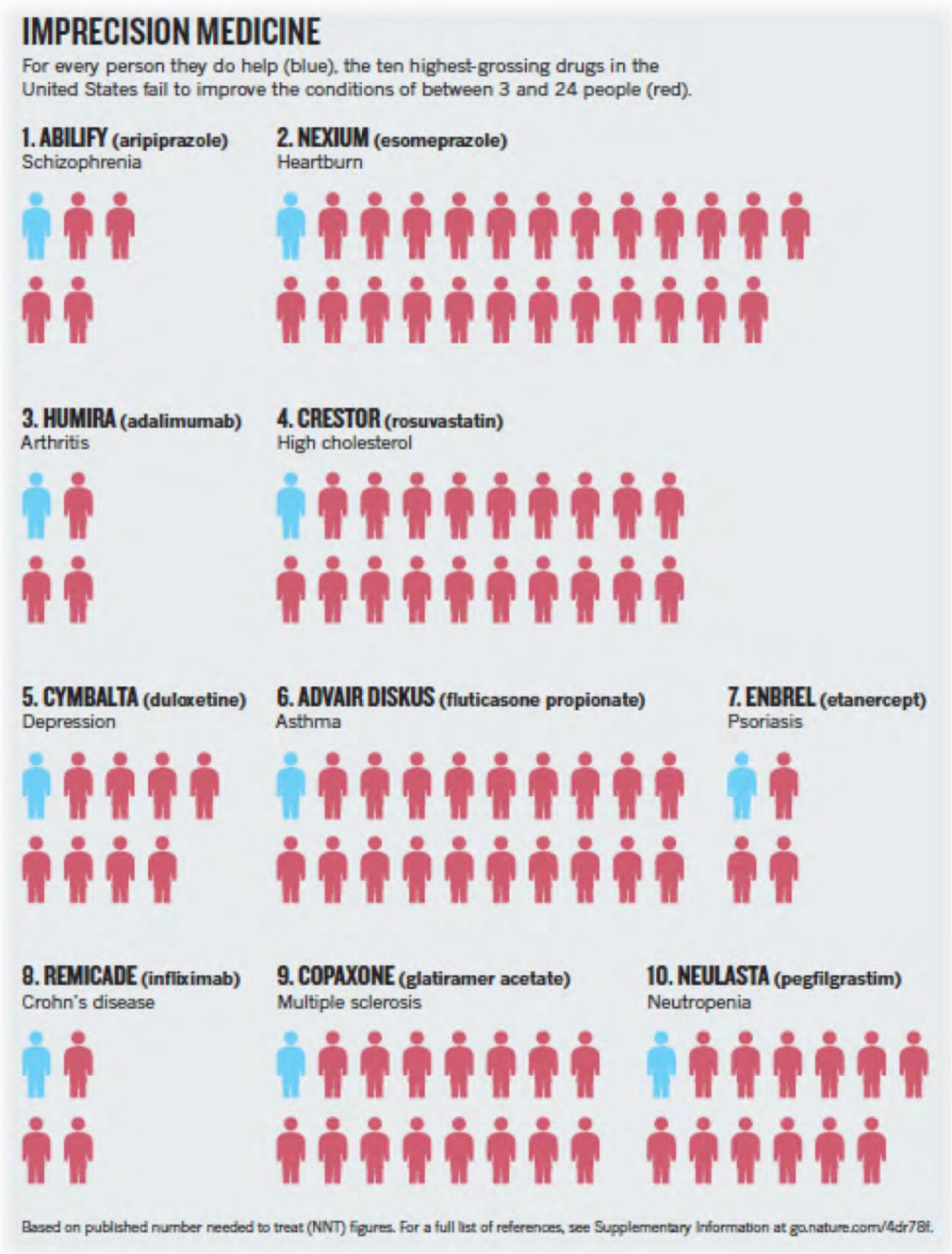
Girls


tactile
language
meaning
social cognition
comprehension
execution
pain
phonological
awareness
sensorimotor
judgments
attention
retrieval
somatosensory
speech perception
evaluation
anxiety
words
nonverbal cues
person perception
default mode
recognition
social perception
recall
motor control
auditory
emotion regulation
self referential
object
sounds
speech production

Boys


meaning
motion
language
identity
comprehension
person perception
cognitive control
spatial
response inhibition
salience
recognition
phonological
strategy
episodic
sounds
object
category
words
social perception
priming
recall
judgments
faces
emotion regulation
attention
social cognition
self referential
speech perception
biological
spatial attention
attention
nonverbal cues
retrieval
visuospatial
cues
auditory
monitoring
visual

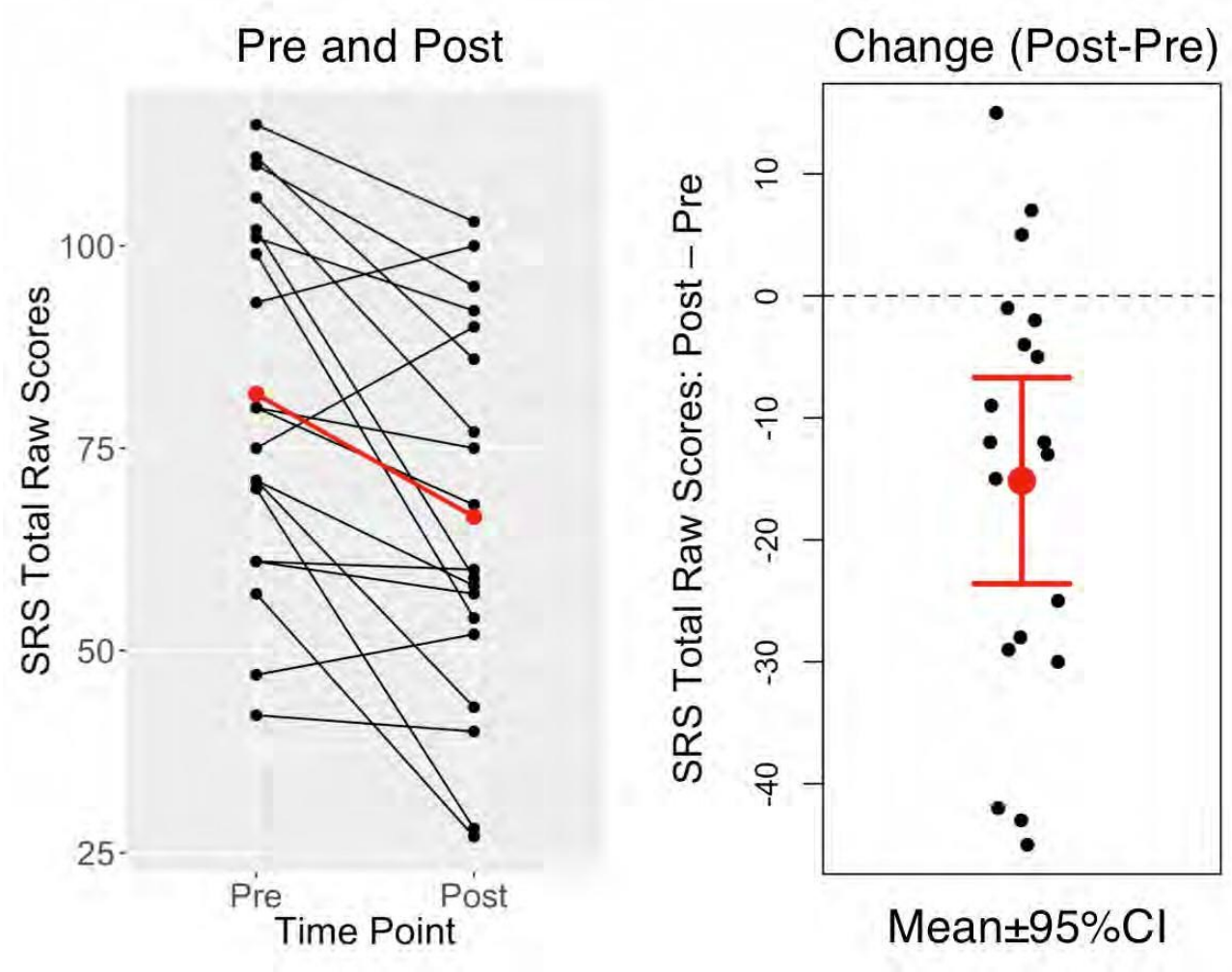
How do we translate basic science into practicable treatments aimed at *target engagement*?



Schork (2015) *Nature*

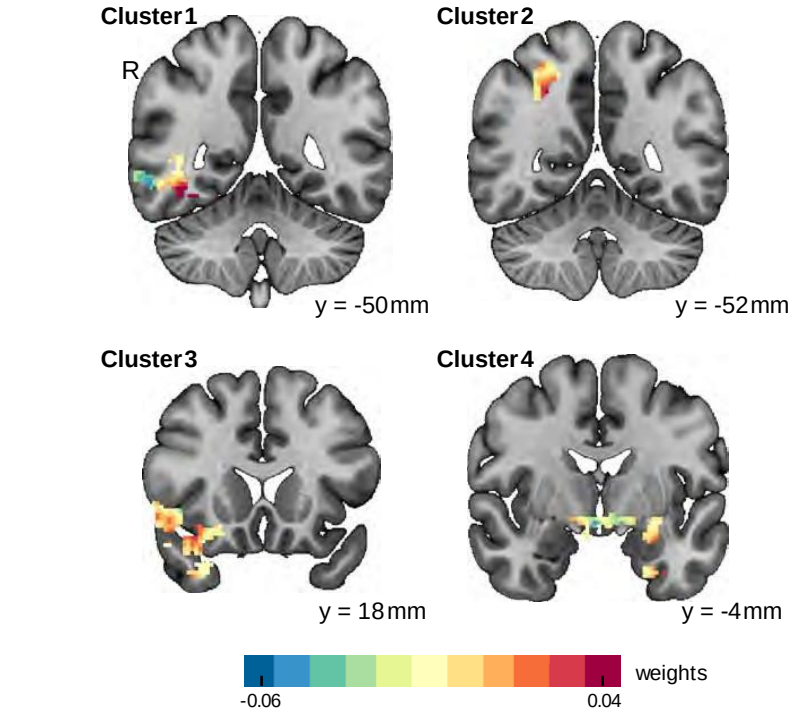
Pivotal Response Training (PRT)

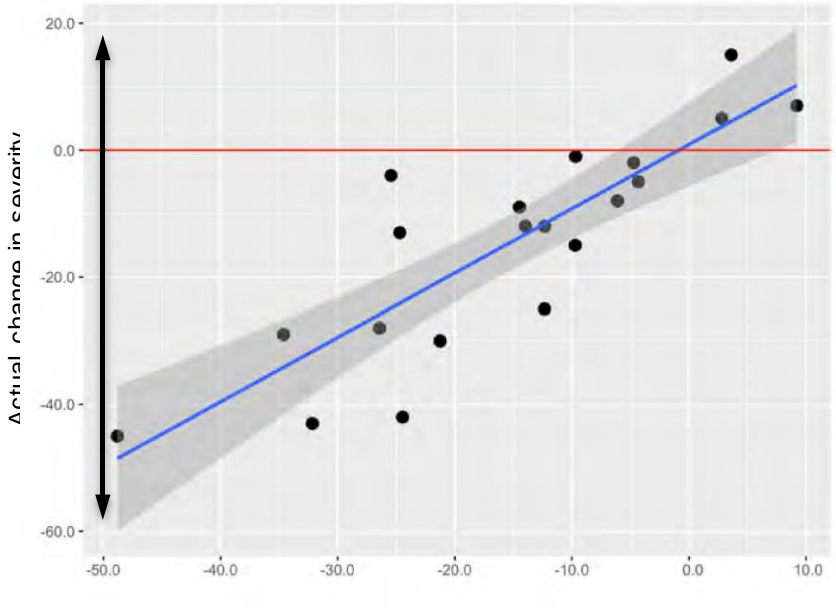
Change in Behavior: Social Responsiveness Scale (SRS)



Yang et al. (in press) *Nature: Translational Psychiatry*

Neuro-prediction of treatment response





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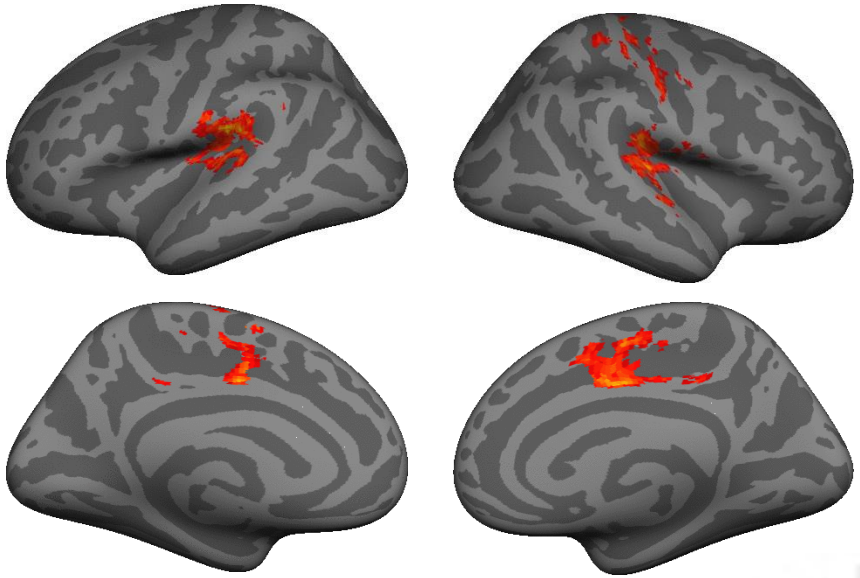
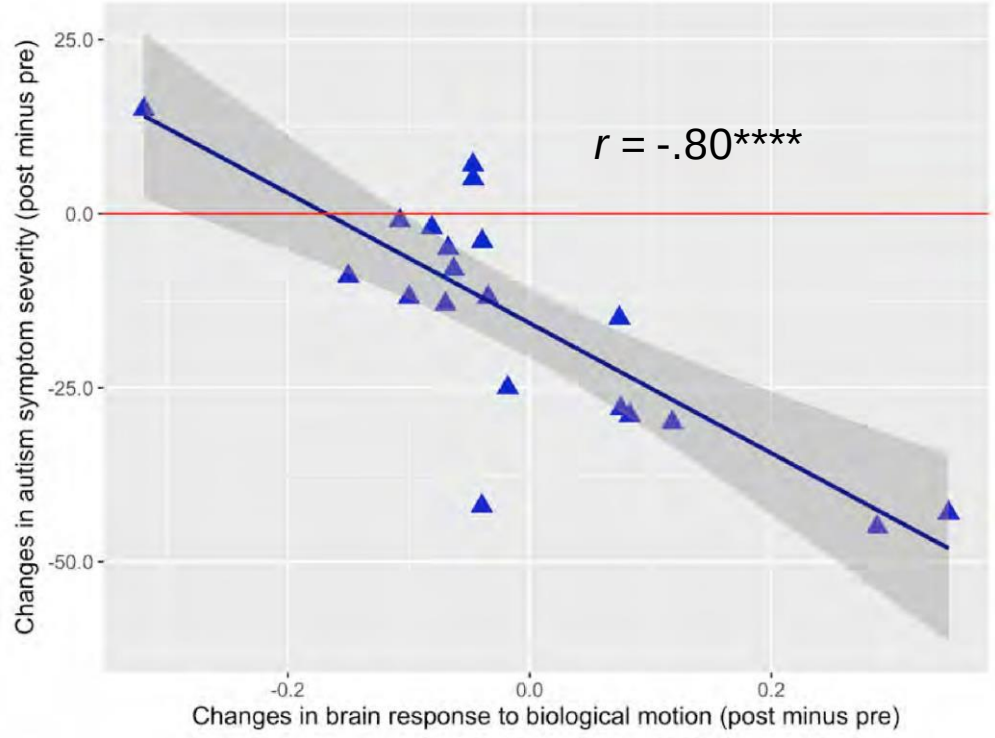


Change in brain, driving change in behavior



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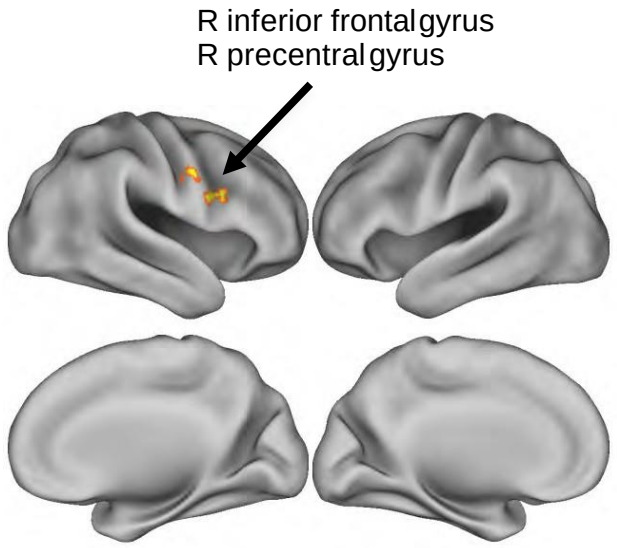
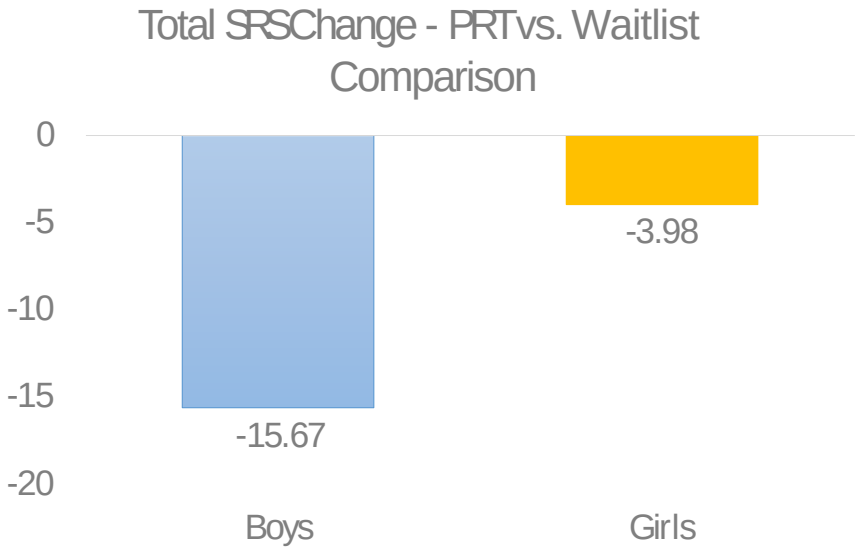
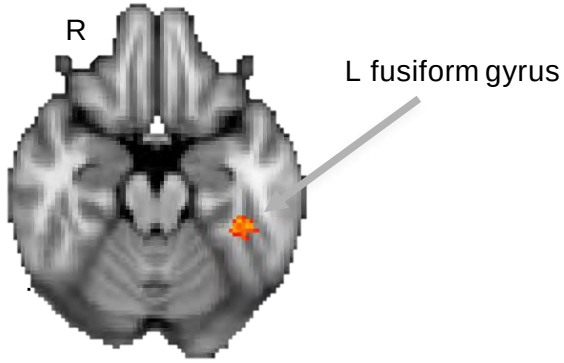


M ASD > F ASD





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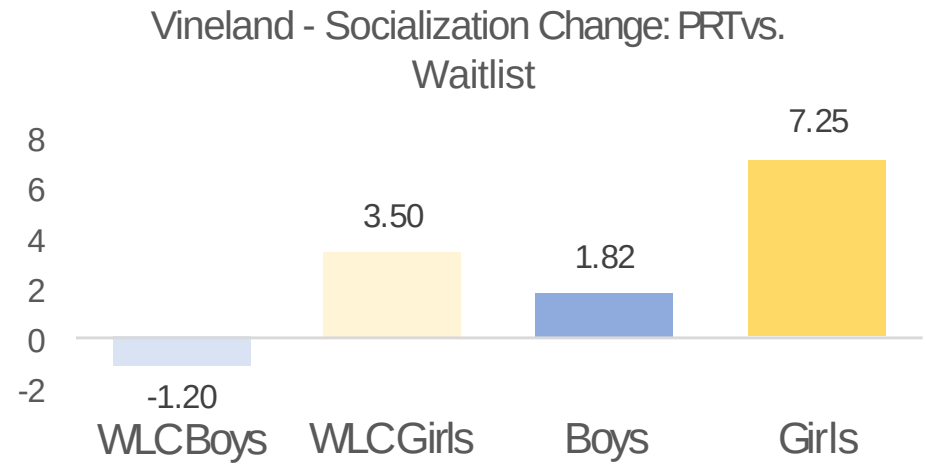
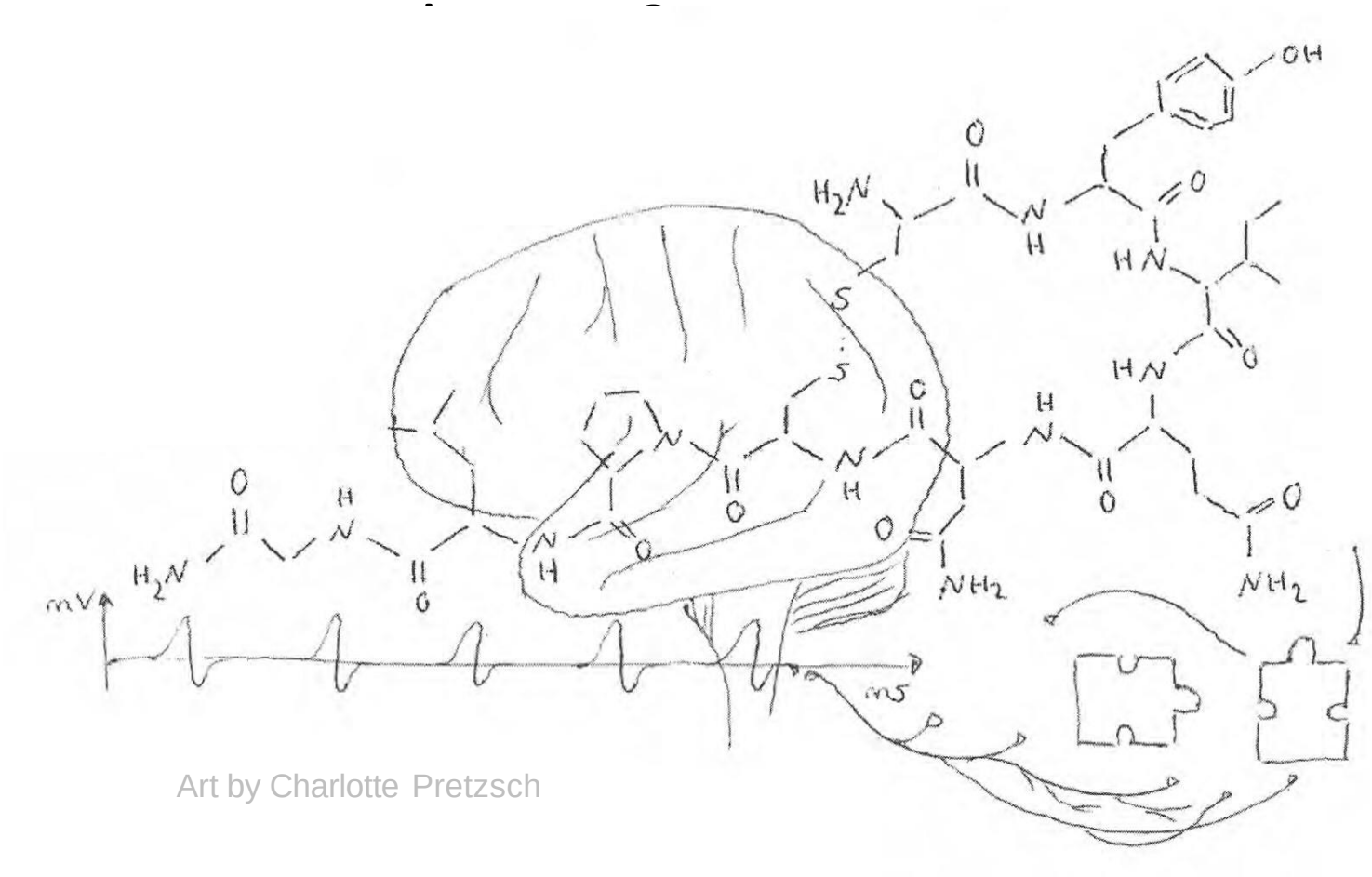
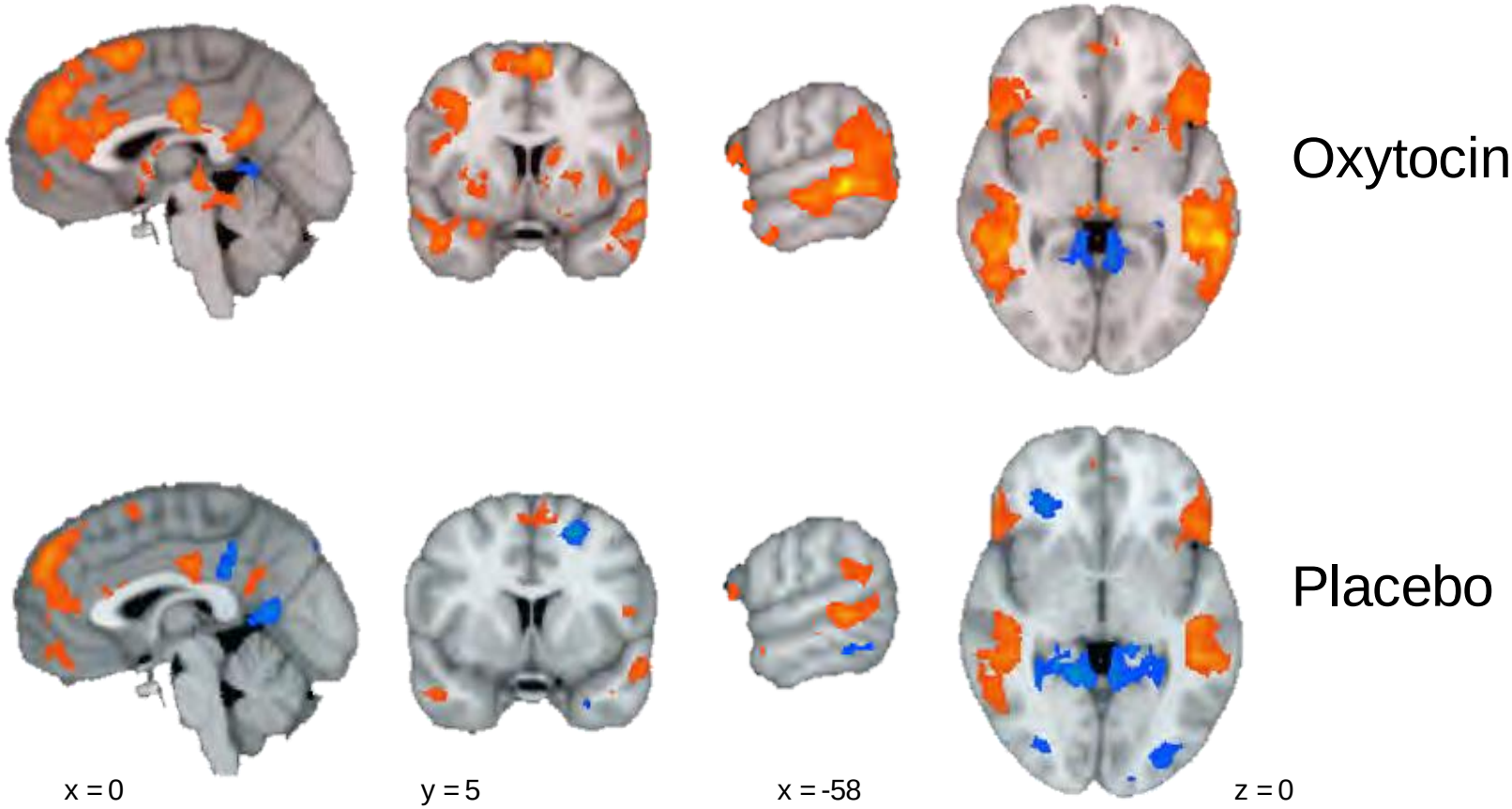


Can we boost brain responses before treatment, to make treatment work



Art by Charlotte Pretzsch

Intranasal Oxytocin – SocialJudgments

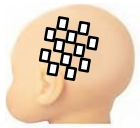


Gordon et al. (2013) *Proceedings of the National Academy of Sciences*

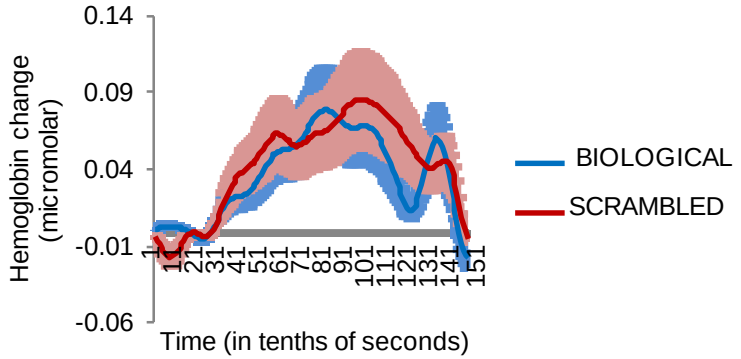
Linking neural signatures, genes, and behavior in to shape developmental trajectories

Results: fNIRS (LR and HR 3-Month-Old Infants)

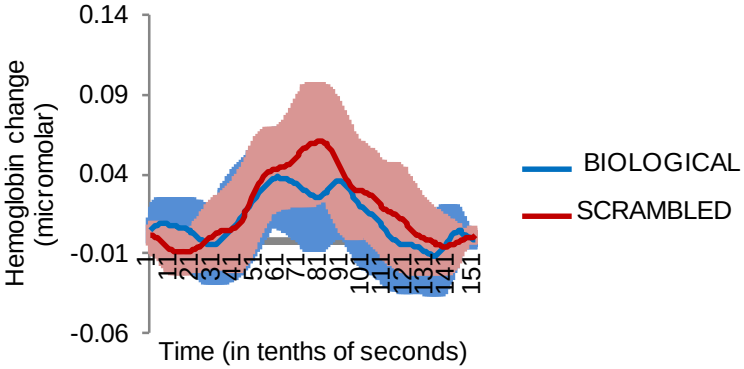
LEFT



Low Risk

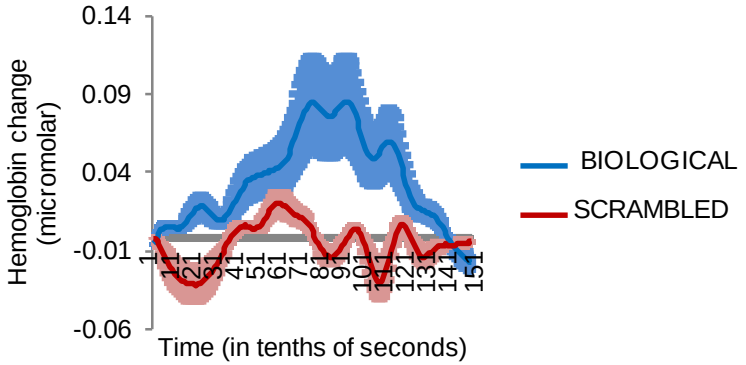


High Risk

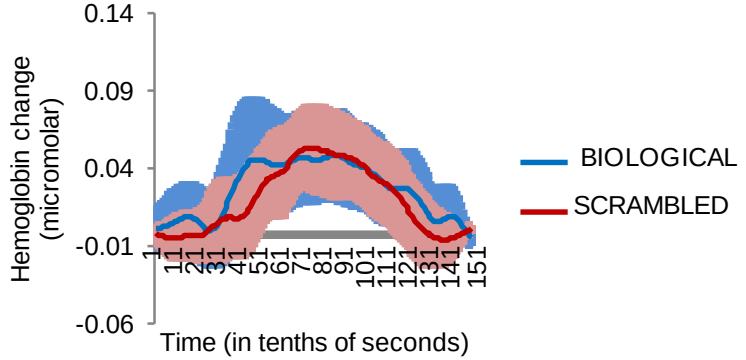


RIGHT

Low Risk



High Risk



Acknowledgments

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NICHD
NINDS
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Autism Speaks
Hilibrand Foundation
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Autism Science Foundation

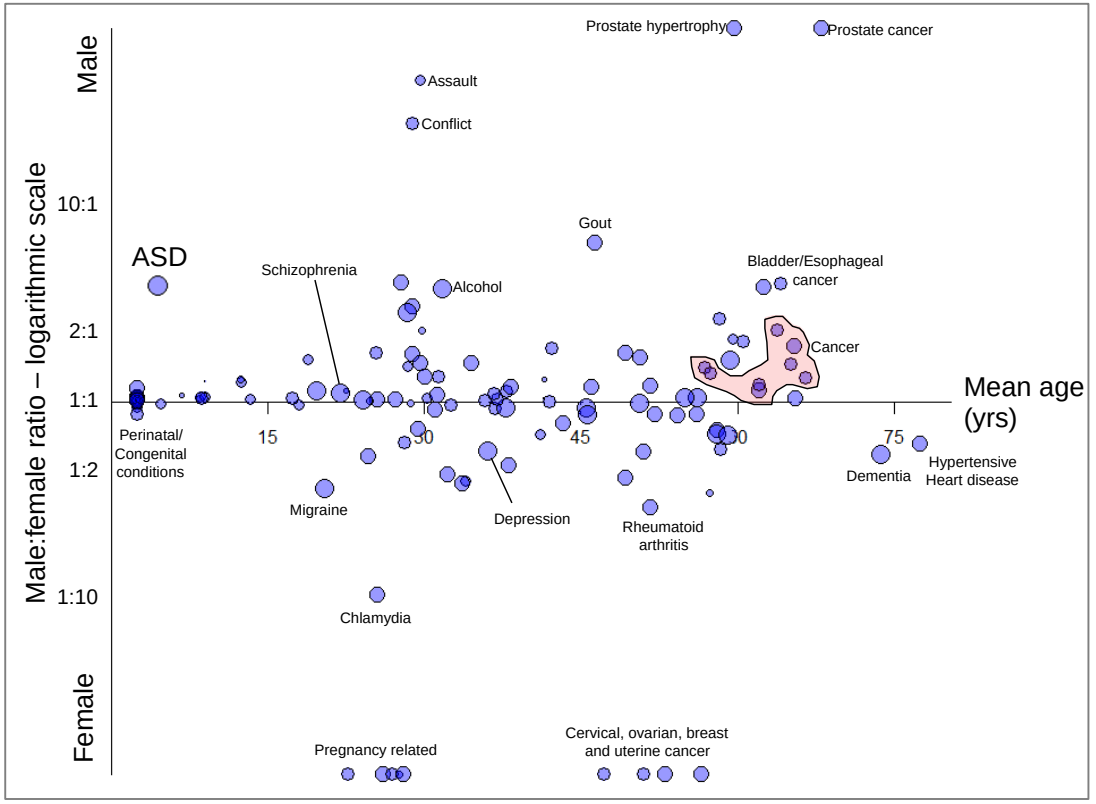
I thank the participants and their families for participating in our research.
I thank my colleagues who make this work so much fun.
kevinpelphrey@gwu.edu

The role of genetics and sex-differential biology in risk for autism

Donna Werling, PhD
Sanders & State Labs, UCSF
October 26, 2016

Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)



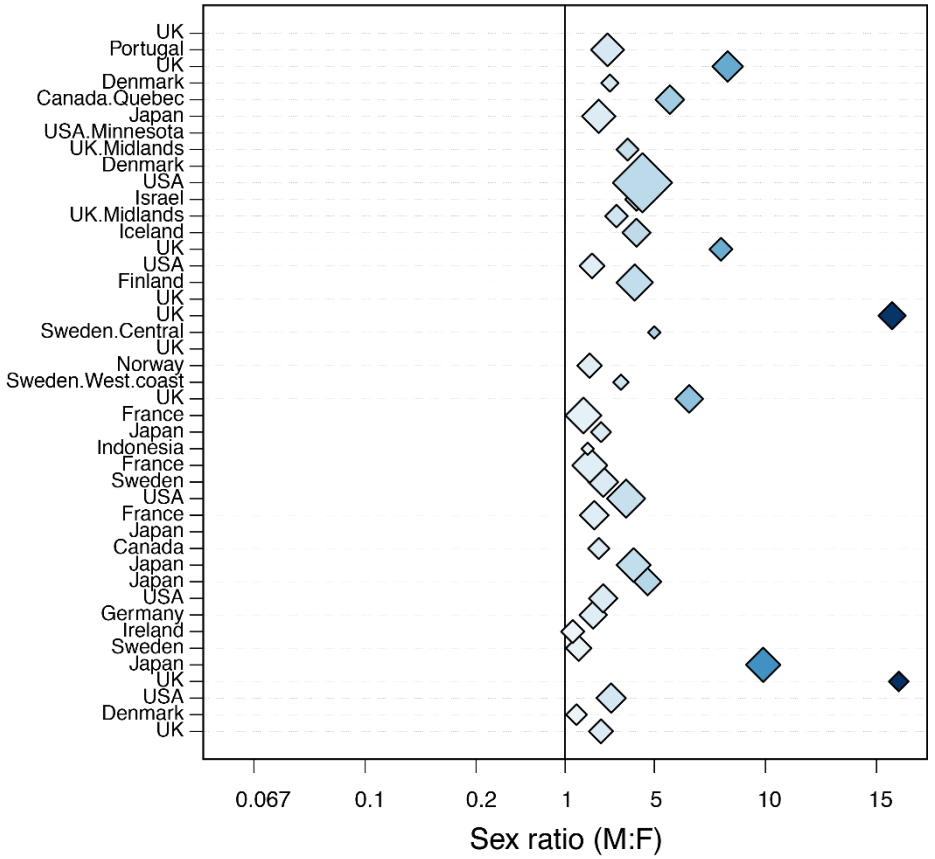
World Health Organization, The global burden of disease: 2004 update (2004).

Autism prevalence is sex-biased

- ~4:1 males:females have a diagnosis of autism spectrum disorder (ASD)[1]

- 8 males and 3 females in the 11 cases originally reported by Leo Kanner, 1943[2]

- Male bias consistent over time and across countries[1]



[1]Fombonne, 2009, *Pediatr Res.* [2]Kanner, 1943, *Nervous Child.*

Why study sex bias in ASD from a biological perspective?

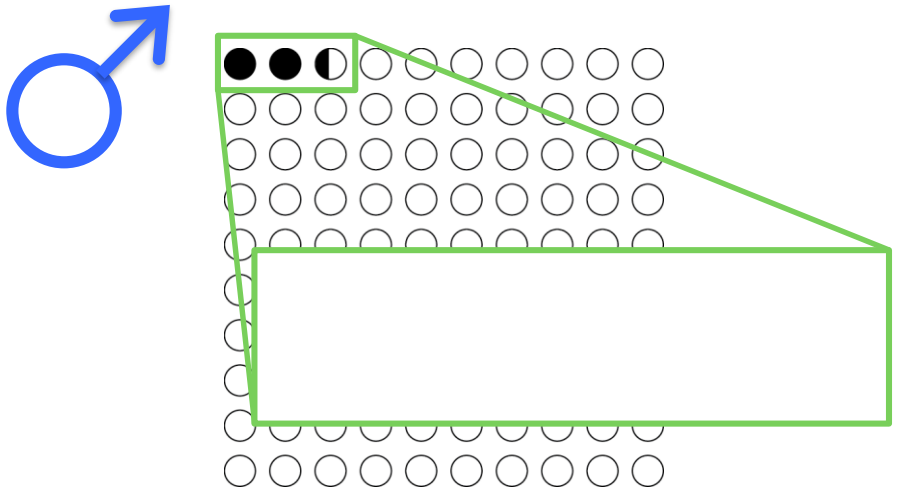
Sex appears to be a potent modulator of ASD risk

Males: 1 in 42 diagnosed

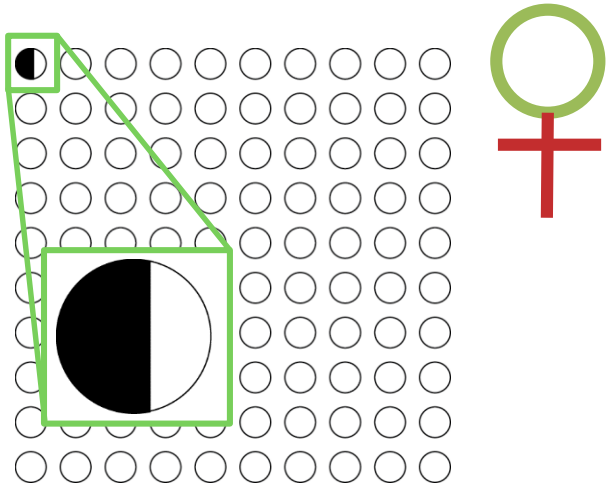
Females: 1 in 189 diagnosed

Why study sex bias in ASD from a biological perspective?

Sex appears to be a potent modulator of ASD risk



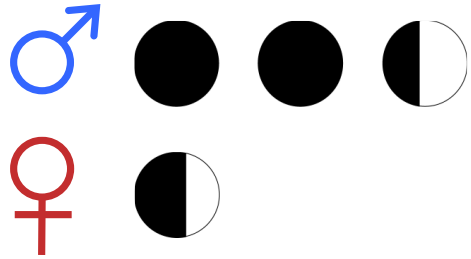
Males: 1 in 42 diagnosed

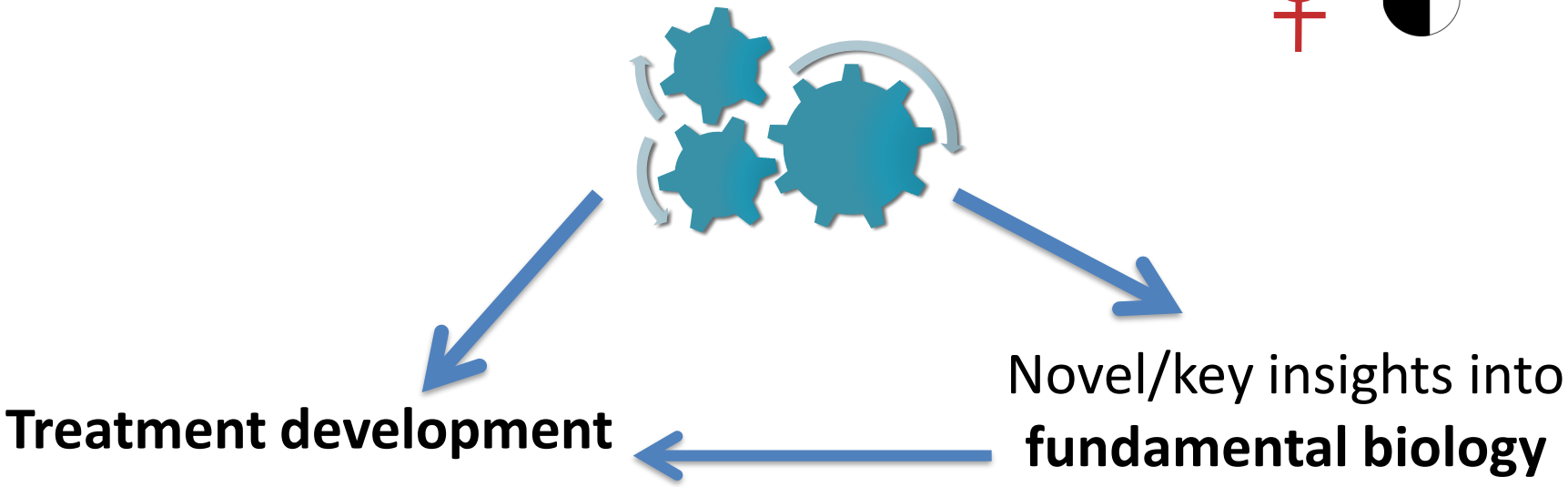


Females: 1 in 189 diagnosed

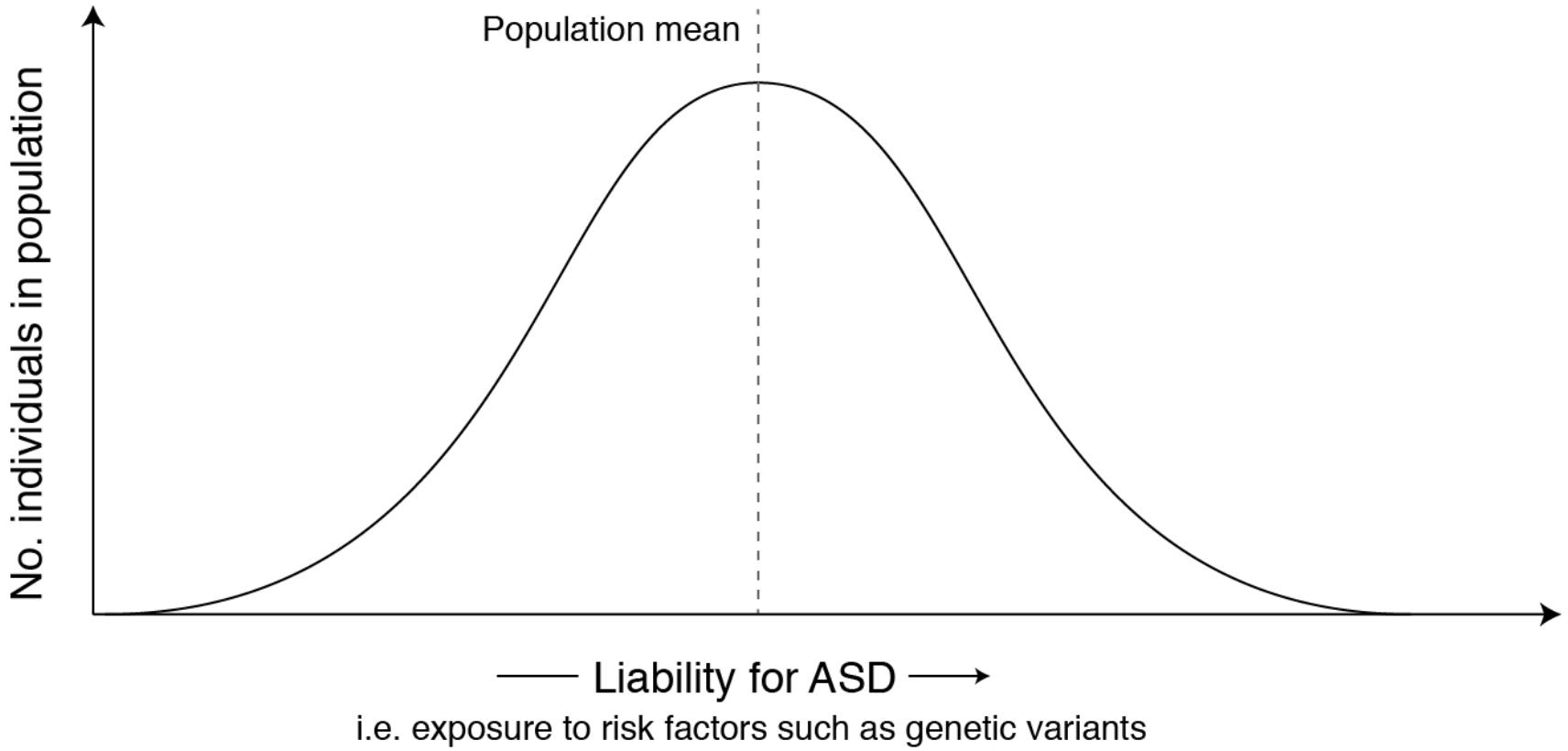
Why study sex bias in ASD from a biological perspective?

Sex appears to be a potent modulator of ASD risk





Female Protective Effect (FPE) Model for ASD = Liability model



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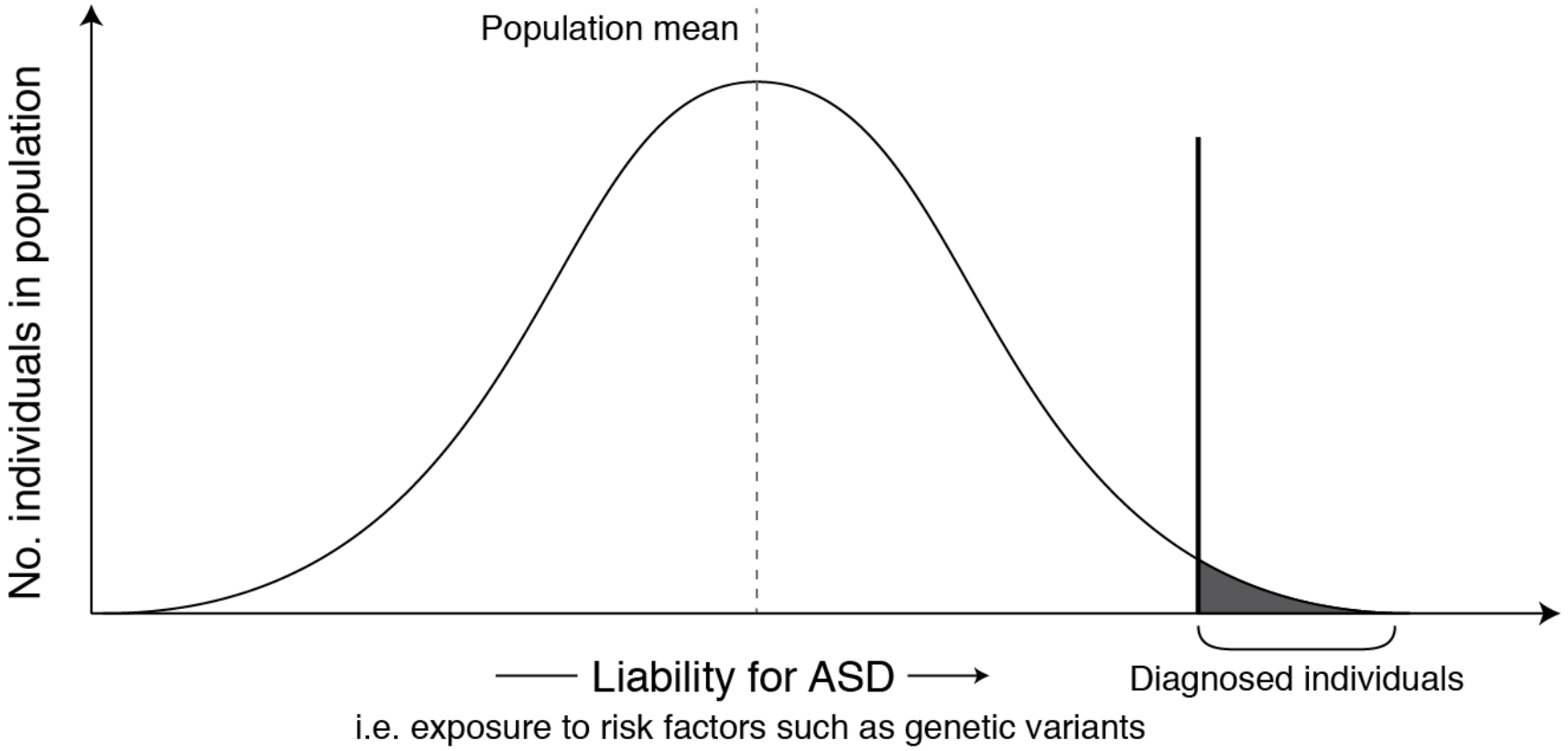
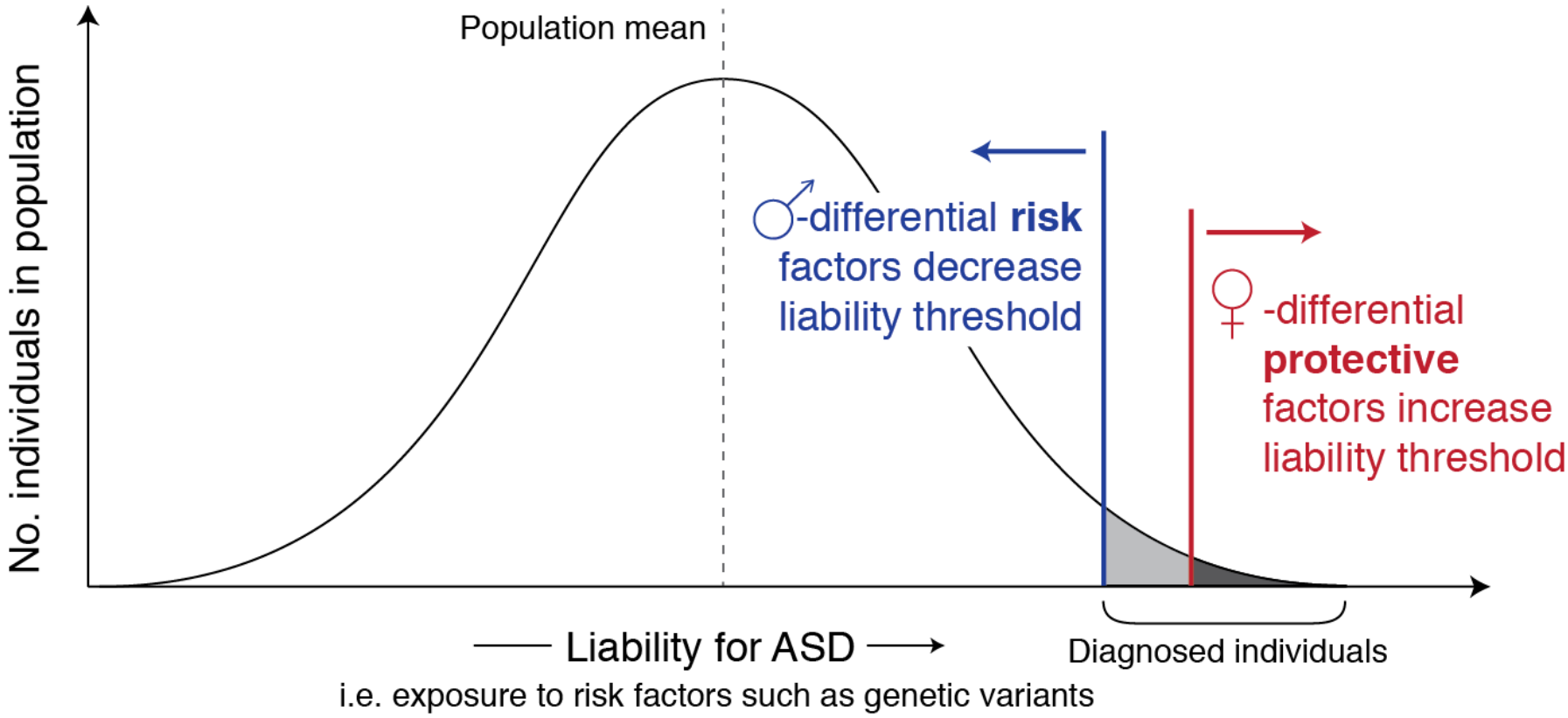
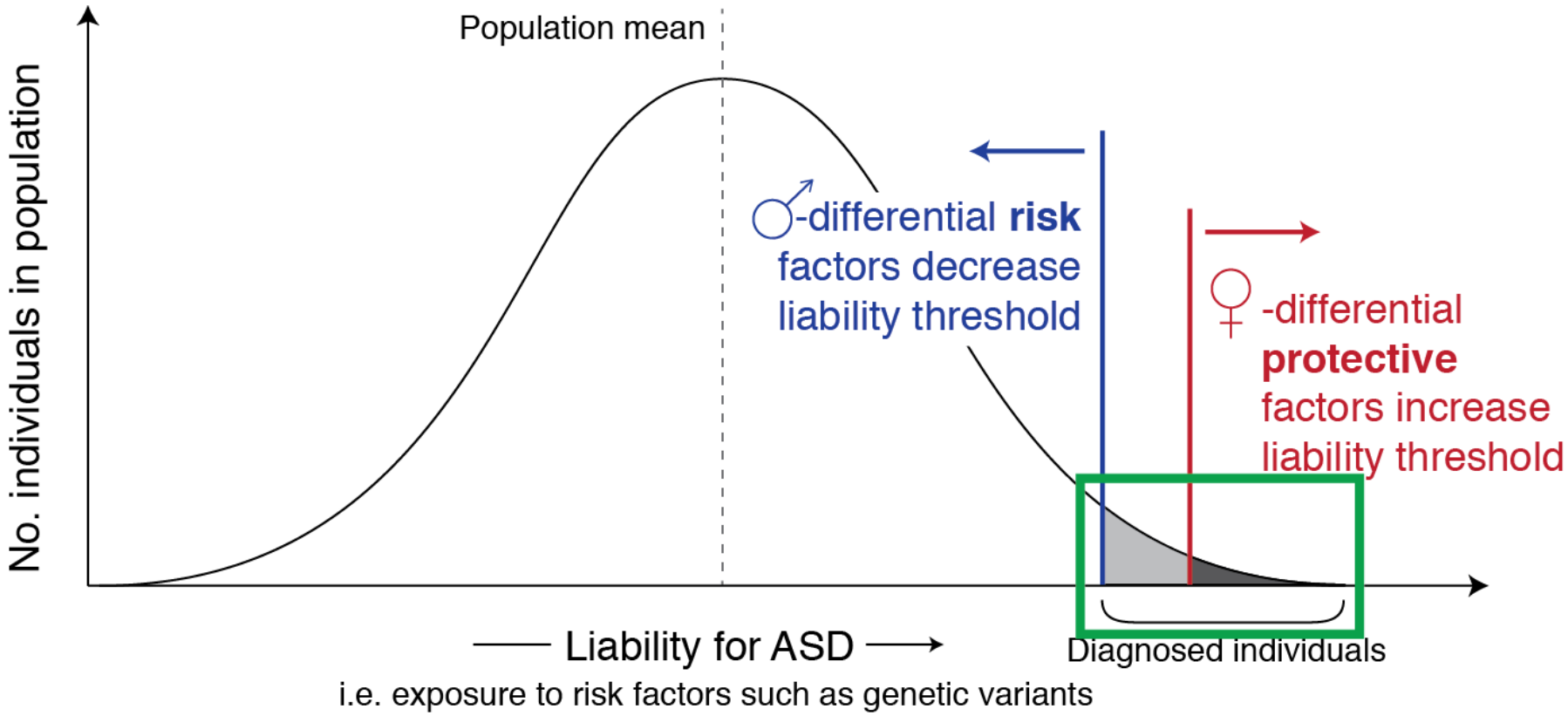


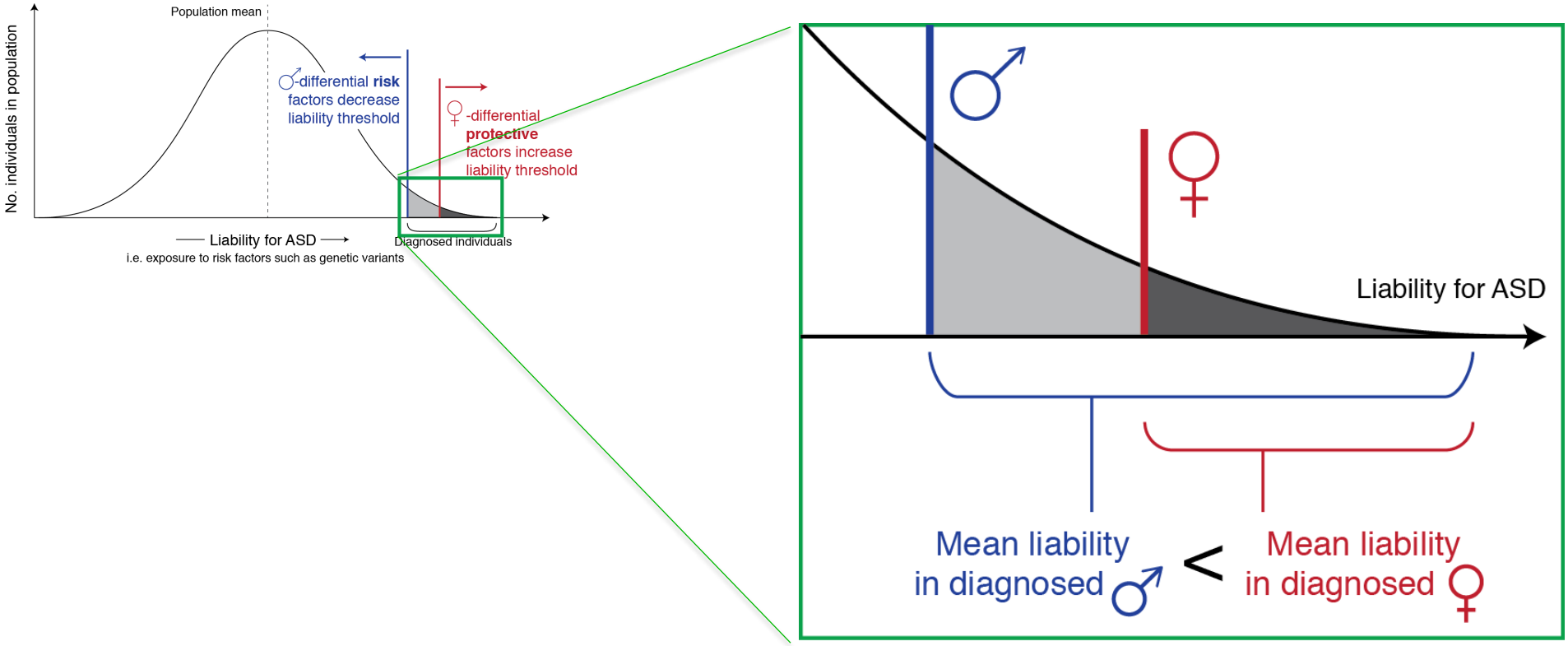
Female Protective Effect (FPE) Model for ASD = *Multiple threshold* liability model



Female Protective Effect (FPE) Model for ASD = *Multiple threshold* liability model



FPE model predicts that diagnosed females carry greater risk than males



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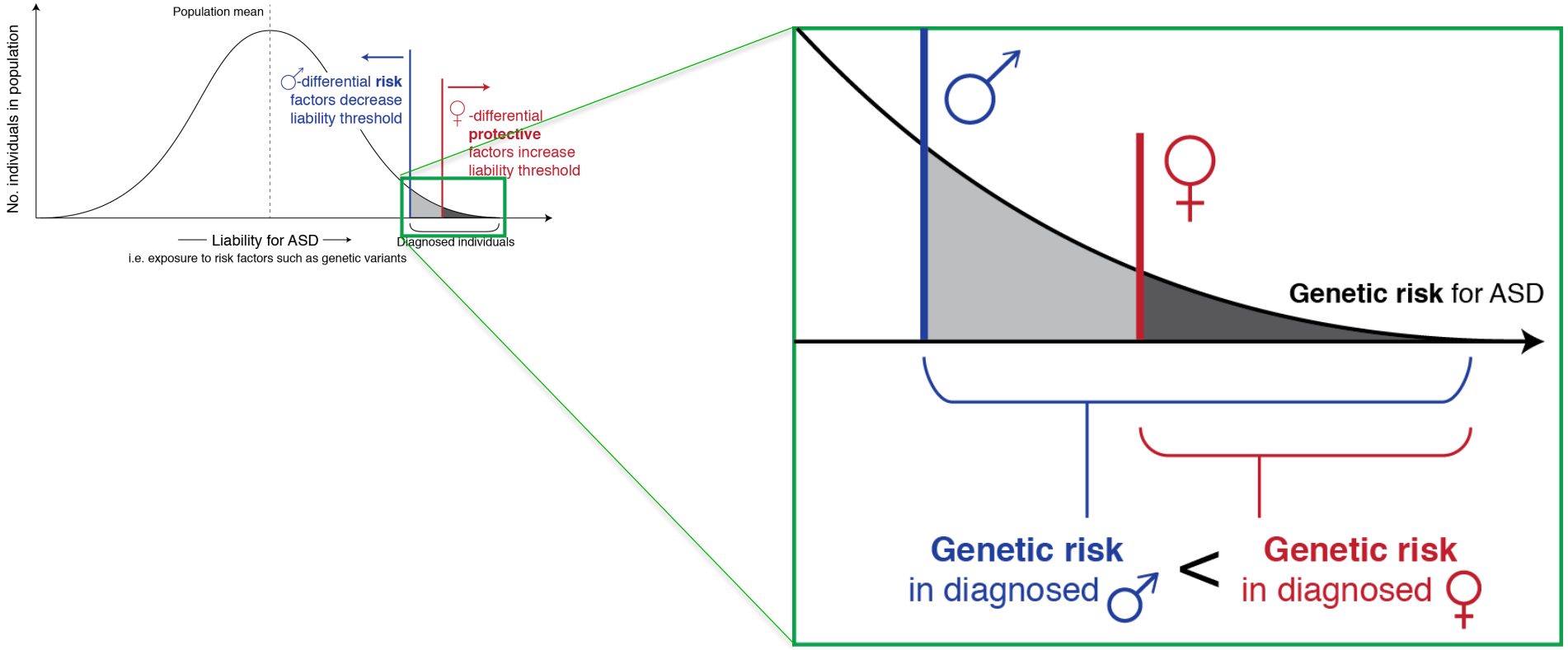

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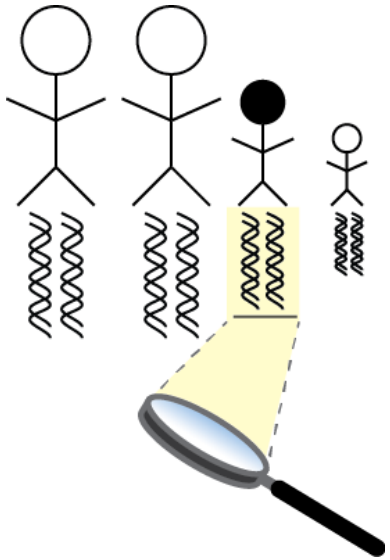

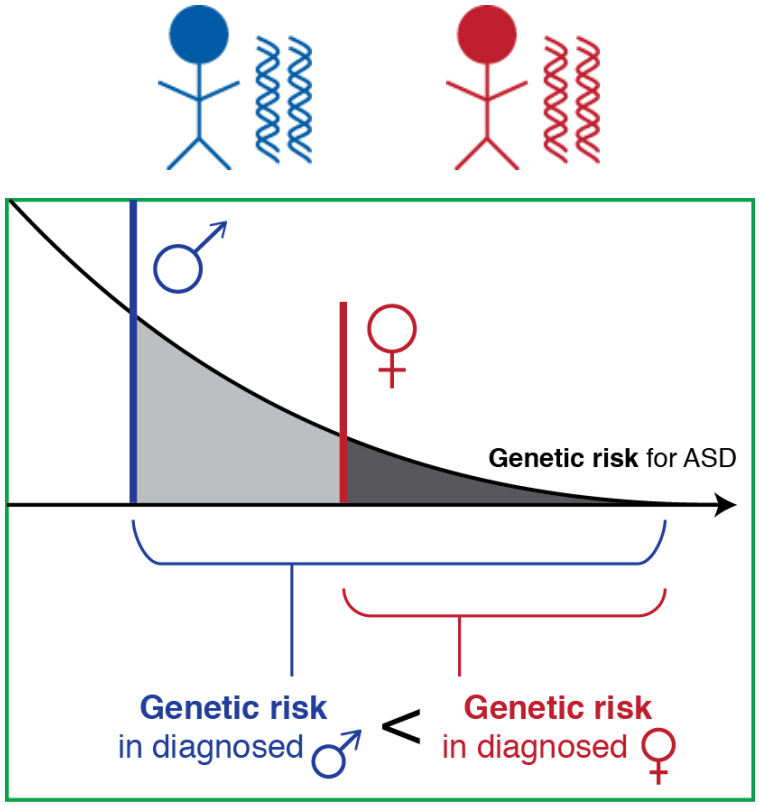

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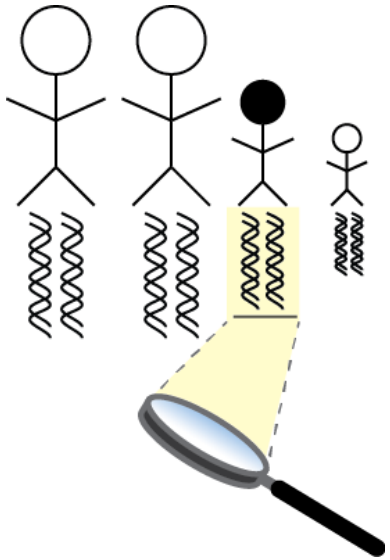

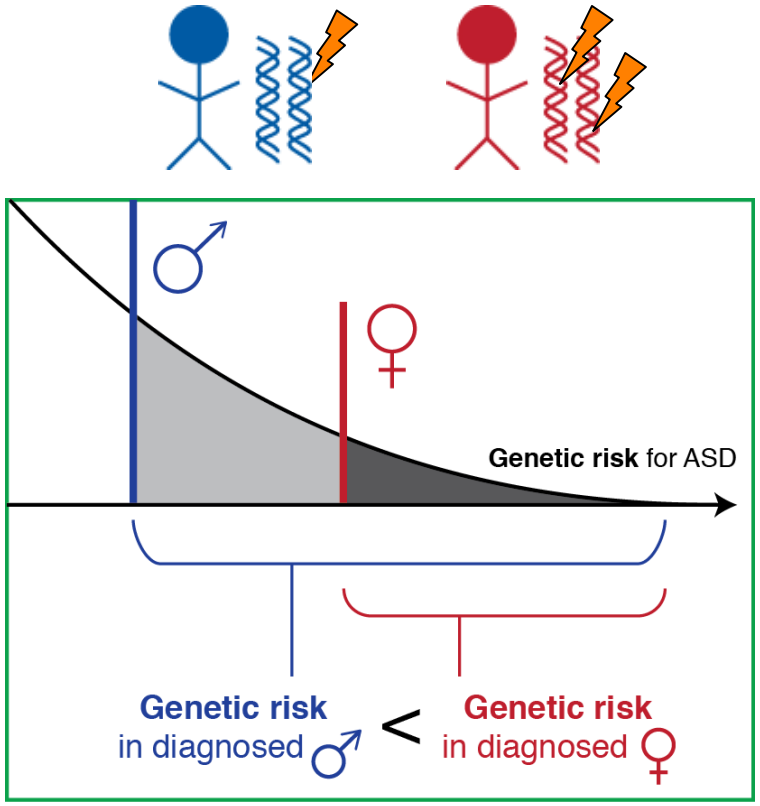

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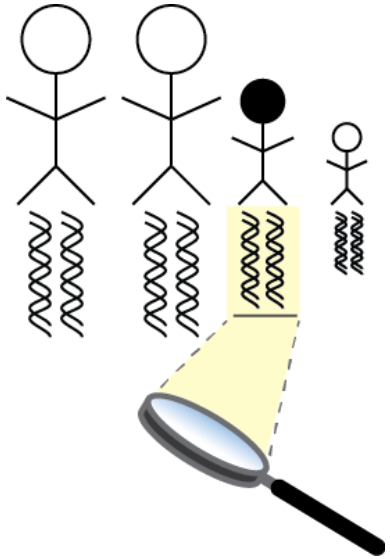
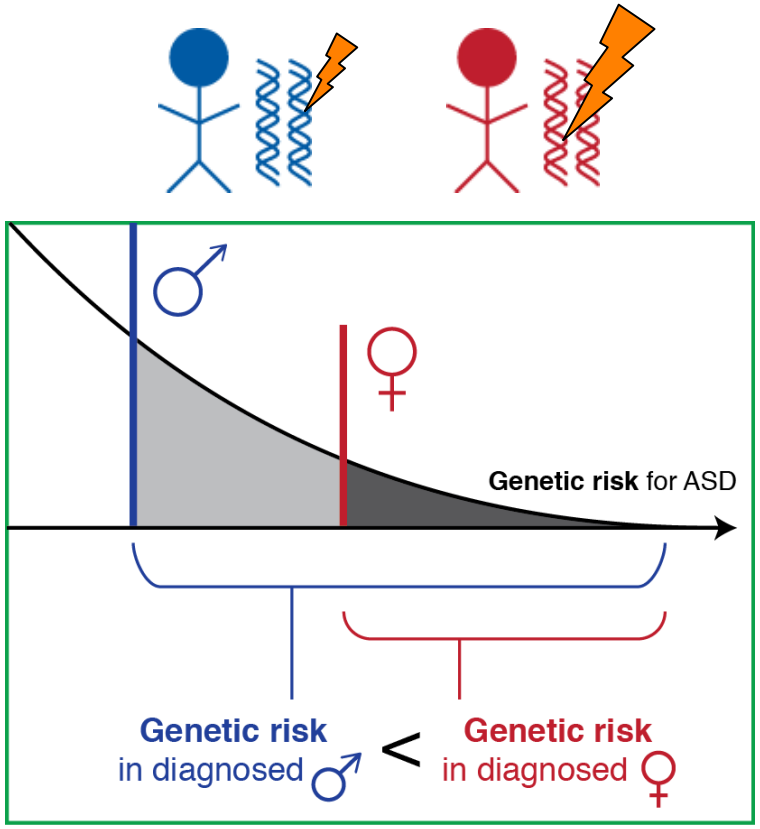
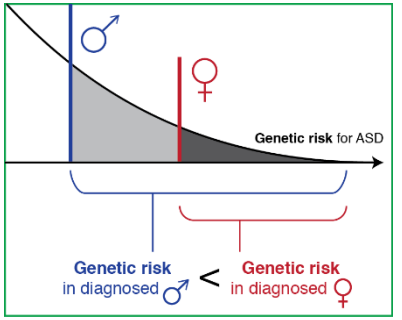
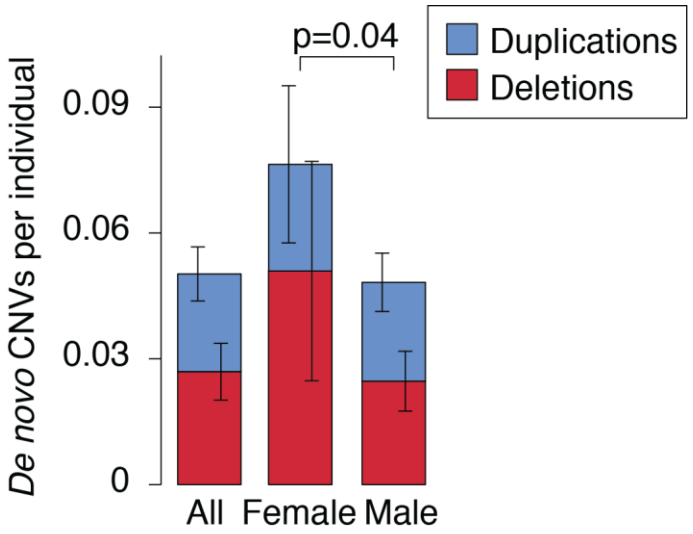




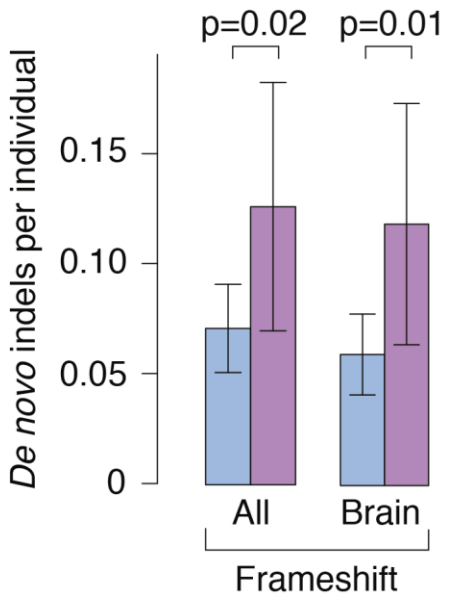
Higher incidence of disruptive, *de novo* variants in ASD females



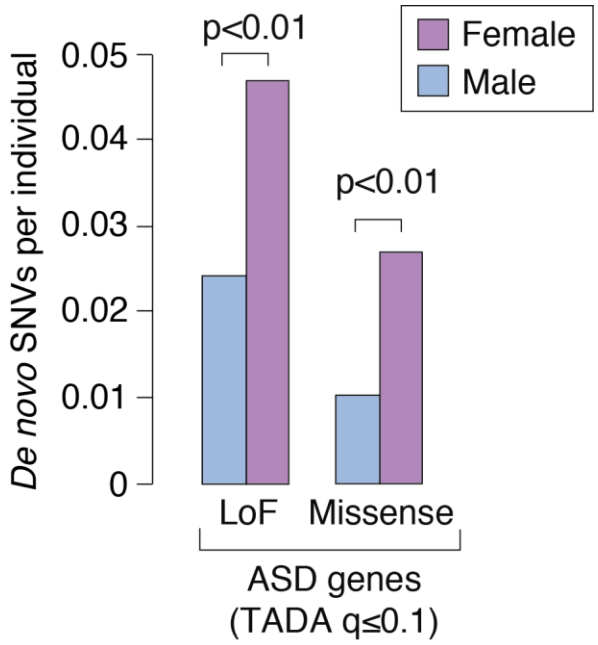
Copy number variants (CNVs)[1]



Insertion/Deletions (Indels)[2]

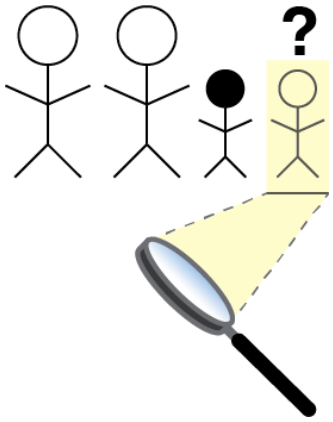


Single nucleotide variants (SNVs)[3]

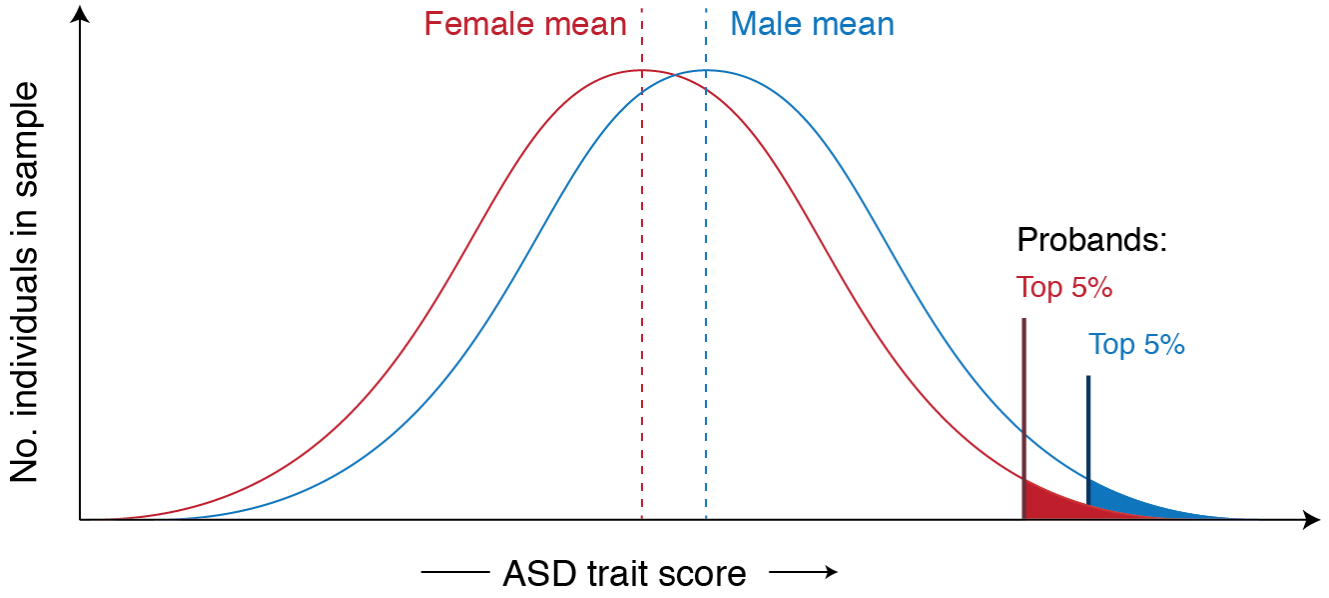


[1]Sanders et al, 2015, *Neuron.* [2]Dong et al, 2014, *Cell Rep.* [3]De Rubeis et al, 2014, *Nature.*

Siblings of female cases have higher ASD traits than siblings of male cases



Autistic traits in siblings?



Robinson et al, *PNAS*, 2013

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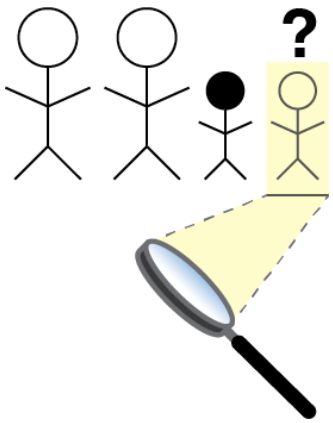
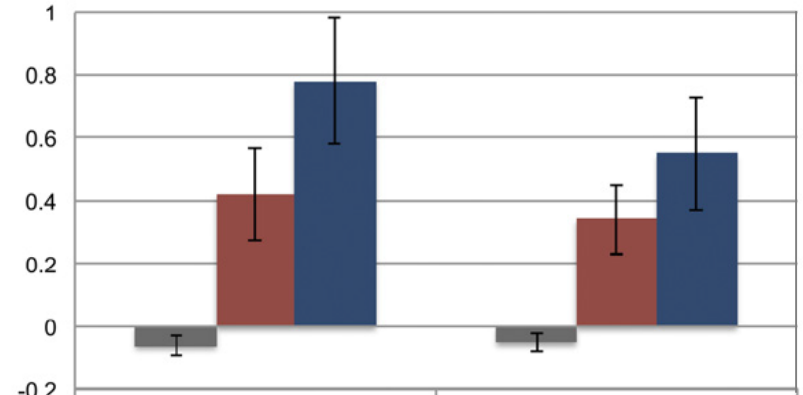


Autistic traits in siblings?

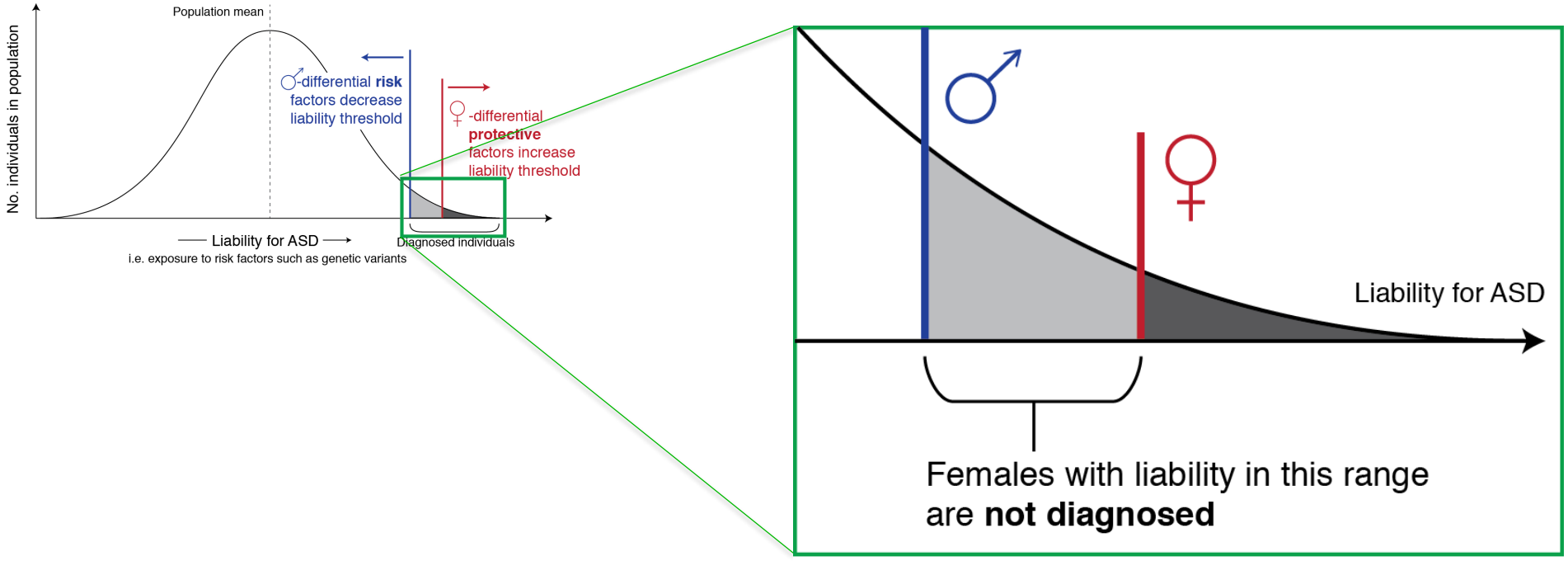
Increase in risk to siblings of female probands



	TEDS	CATSS
Siblings of All Non-Probands N(TEDS) = 3,444 N(CATSS) = 5,340	-0.06 (p<0.0001 *§)	-0.05 (p<0.0001 *§)
Siblings of Male Probands N(TEDS) = 262 N(CATSS) = 470	0.42 (p=0.002 §)	0.34 (p=0.02 §)
Siblings of Female Probands N(TEDS) = 136 N(CATSS) = 230	0.78	0.55

Robinson et al, *PNAS*, 2013

FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males



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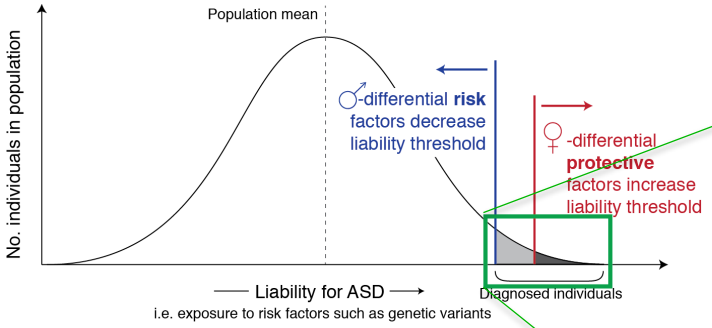
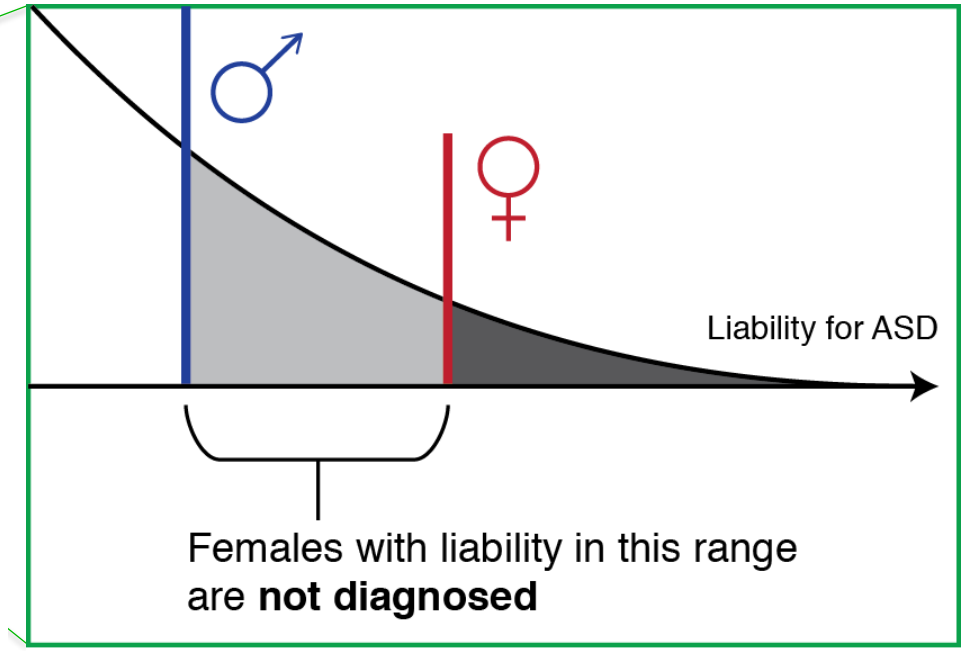




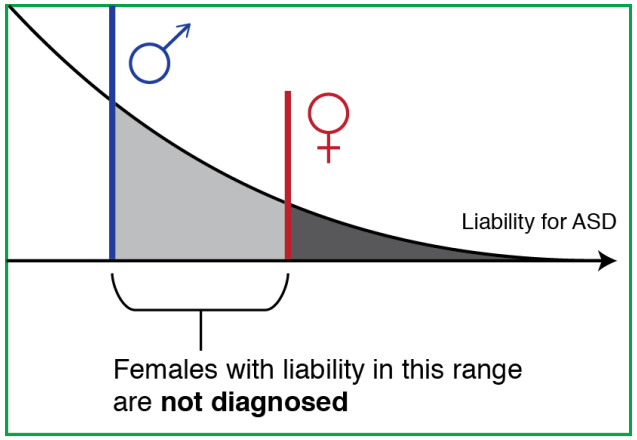
1. Quantitative:

   Females are protected and have neurotypical phenotype.

2. Qualitative:

   Females present symptoms differently than males, and are not diagnosed.

FPE model predicts that females respond differently to liability that is sufficient for diagnosis in males



Hypothesis:

Sex-differential biology contributes to male and female differences in ASD risk and/or symptom presentation

1. Quantitative:

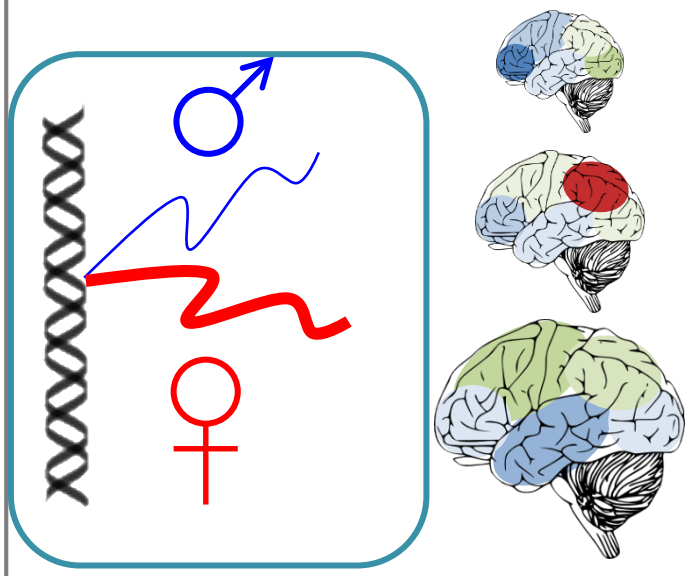
   Females are protected and have neurotypical phenotype.

2. Qualitative:

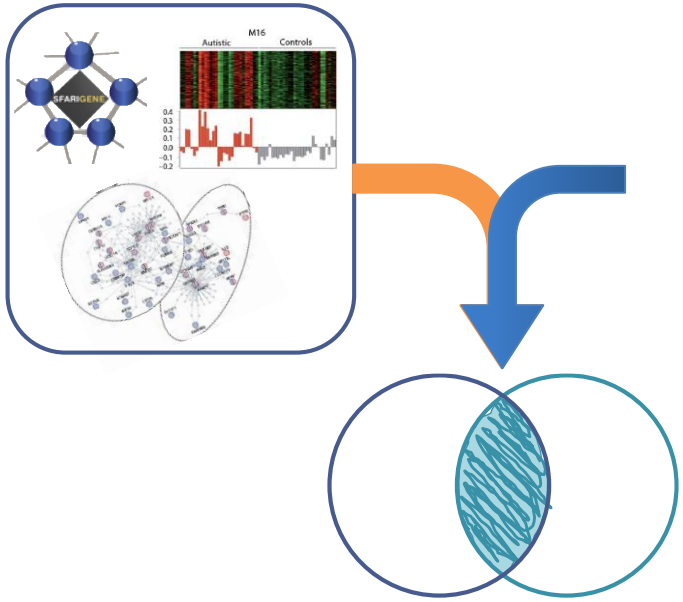
   Females present symptoms differently than males, and are not diagnosed.

We can use gene expression analysis to identify sex differences that contribute to the FPE

1. Identify genes with sex-differential expression levels in the human brain



2. Characterize the relationship between sex-DEX genes and ASD biology



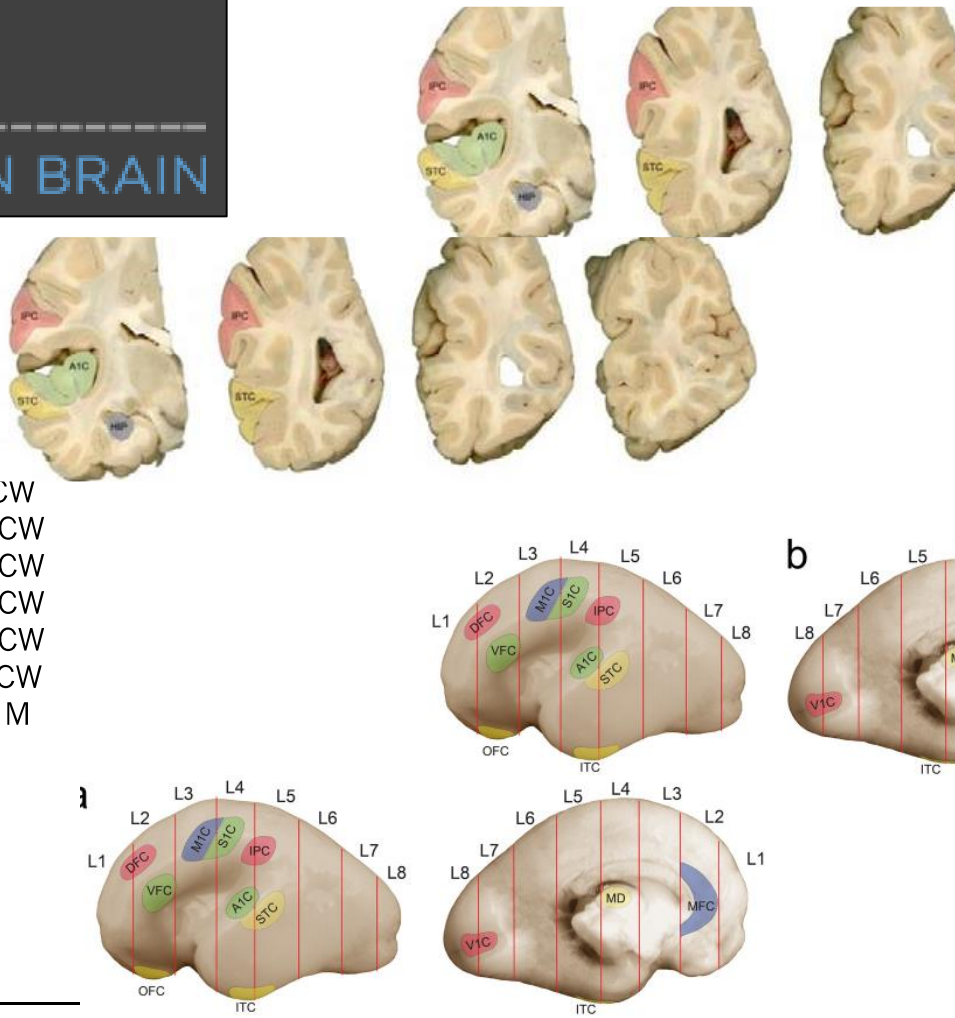
BRAINSPAN

ATLAS OF THE DEVELOPING HUMAN BRAIN

Table 1 | Periods of human development and adulthood as d in this study

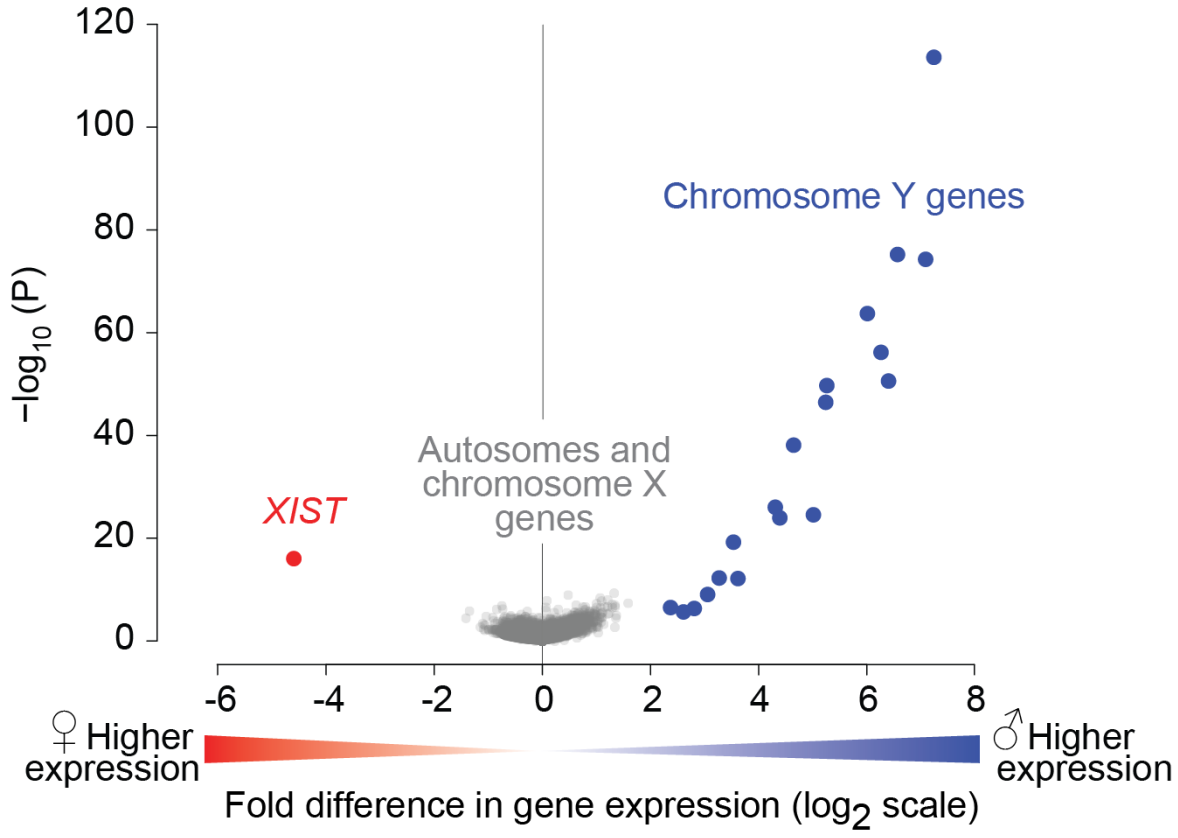
Period	Description	Age
1	Embryonic	4 PCW ≤ Age < 8 P(
2	Early fetal	8 PCW ≤ Age < 10 PCW
3	Early fetal	10 PCW ≤ Age < 13 PCW
4	Early mid-fetal	13 PCW ≤ Age < 16 PCW
5	Early mid-fetal	16 PCW ≤ Age < 19 PCW
6	Late mid-fetal	19 PCW ≤ Age < 24 PCW
7	Late fetal	24 PCW ≤ Age <38 PCW
8	Neonatal and early infancy	0 M (birth) ≤ Age <6 M
9	Late infancy	6 M ≤ Age < 12 M
10	Early childhood	1 Y ≤ Age <6 Y
11	Middle and late childhood	6 Y ≤ Age < 12 Y
12	Adolescence	12 Y ≤ Age < 20 Y
13	Young adulthood	20 Y ≤ Age < 40 Y
14	Middle adulthood	40 Y ≤ Age < 60 Y
15	Late adulthood	60 Y ≤ Age

M, postnatal months; PCW, post-conceptional weeks; Y, postnatal years.



Kang, *et al.*, *Nature*, 2011

There is no evidence of an autosomal gene with XY levels of sexual dimorphism in the brain



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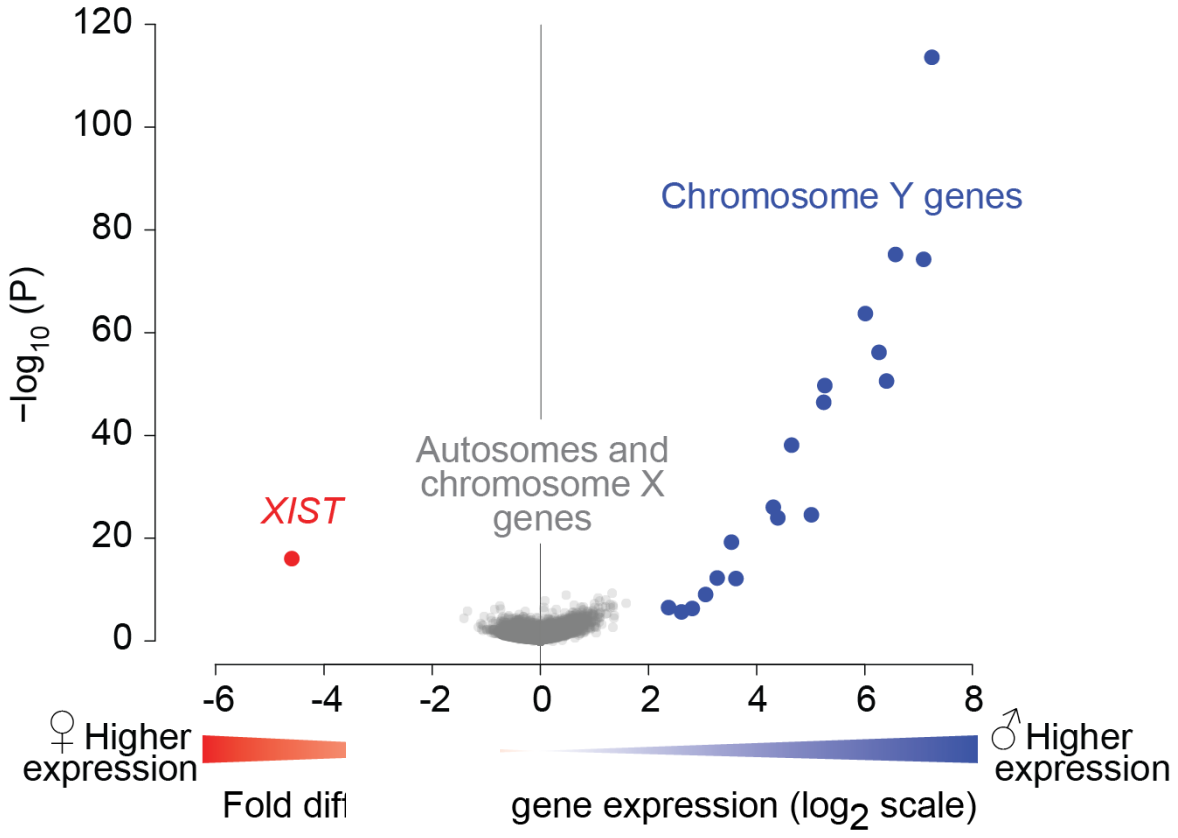
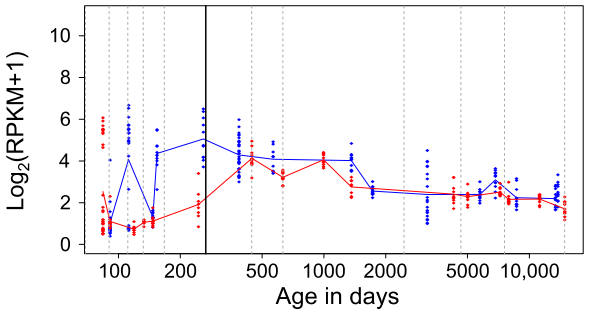
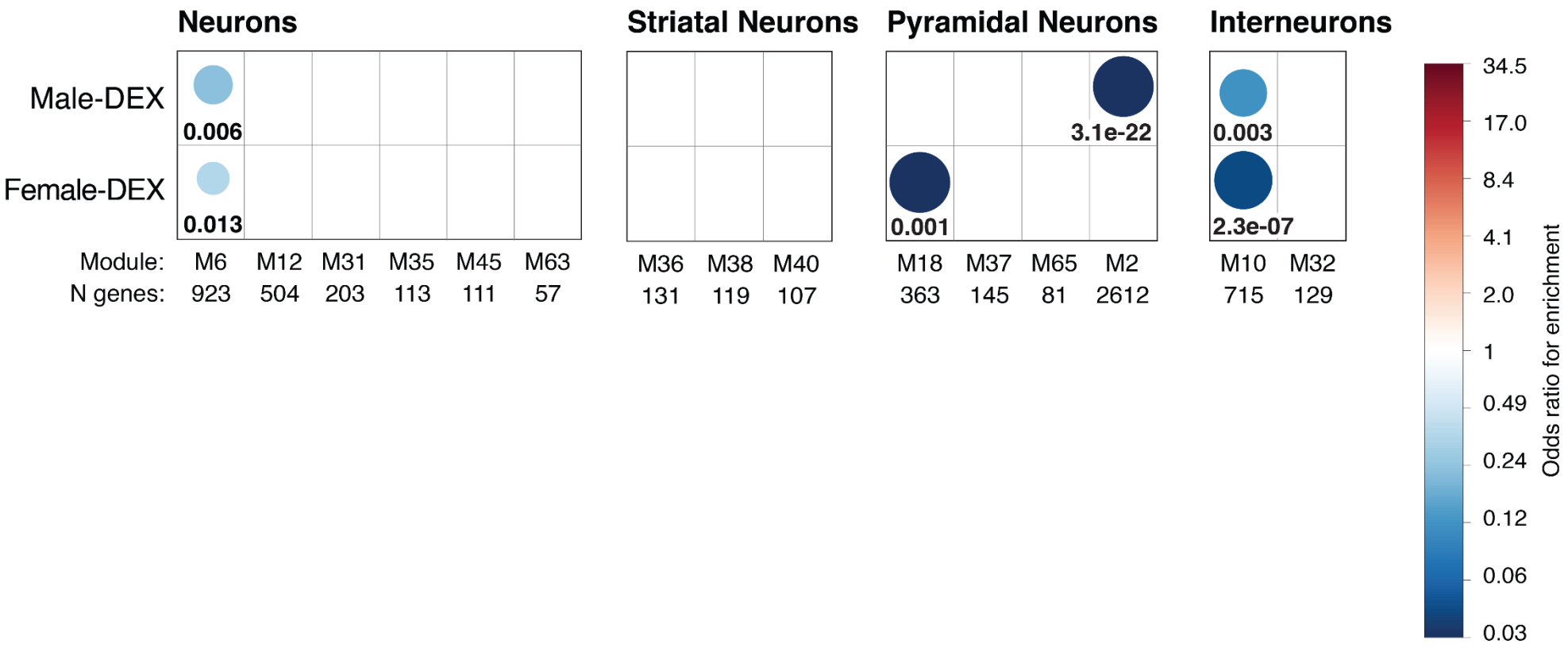


Sex-DEX genes identified by permutation approach (Q≤0.05; top-ranking sex-DEX in ≥2 consecutive developmental periods from same brain region):

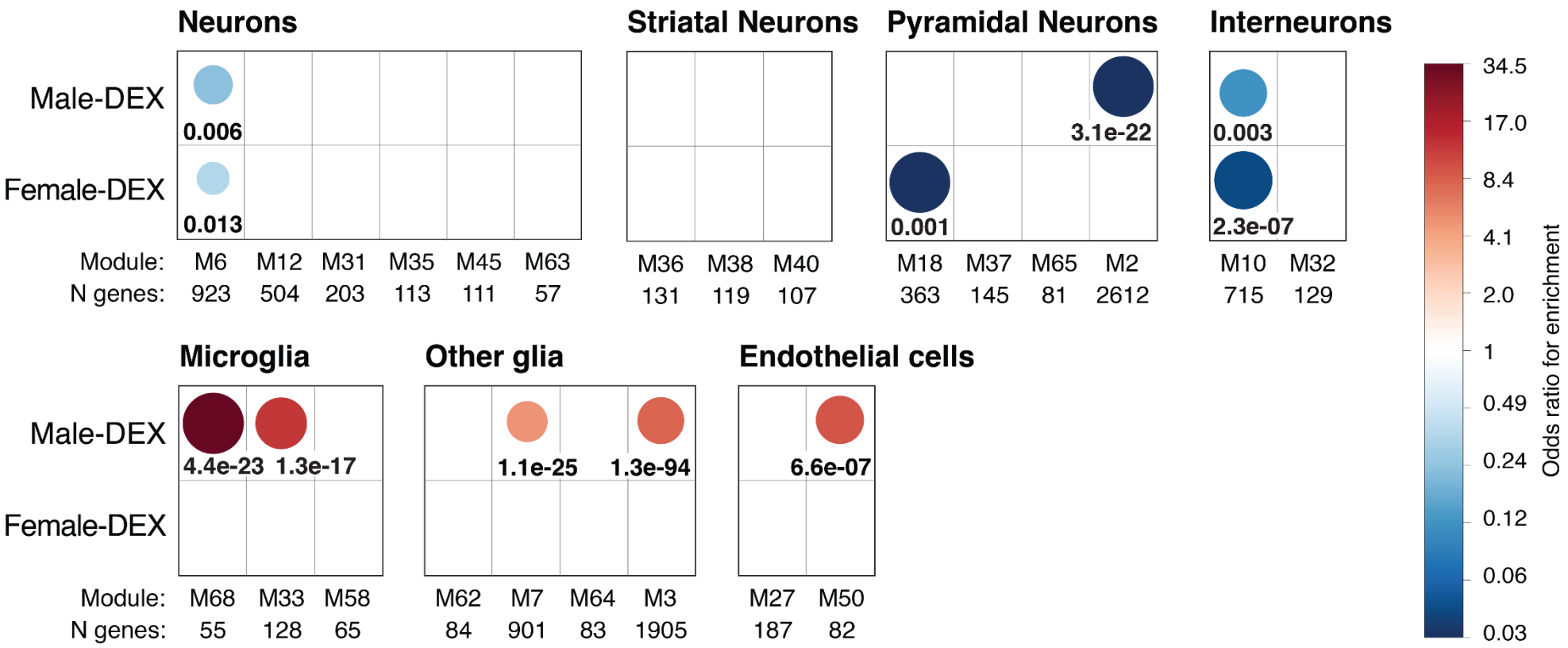
- Higher expression in males:
  - 505 protein-coding genes, 129 noncoding transcripts
- Higher expression in females:
  - 442 protein-coding genes, 466 noncoding transcripts



Sex-DEX genes are not enriched for neuronal markers



Male-DEX genes show enrichment for microglial and endothelial cell markers



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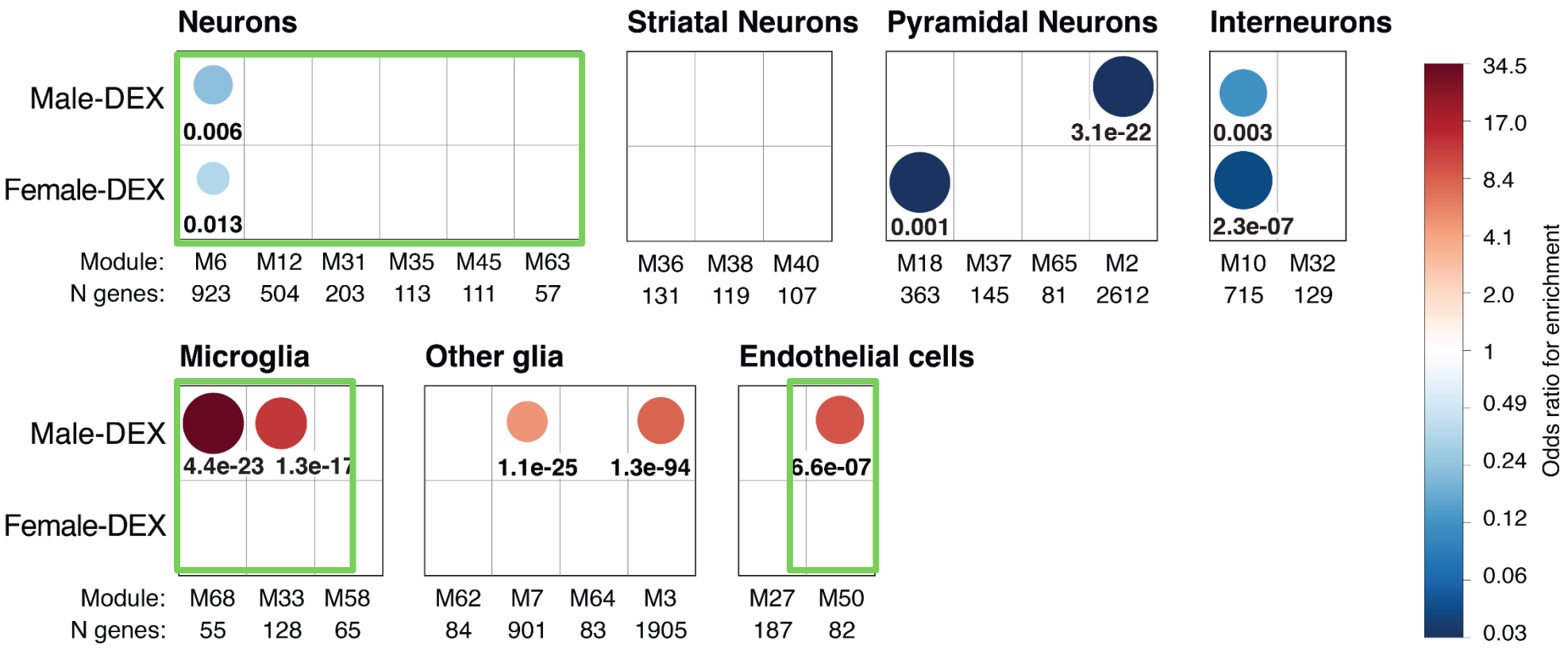

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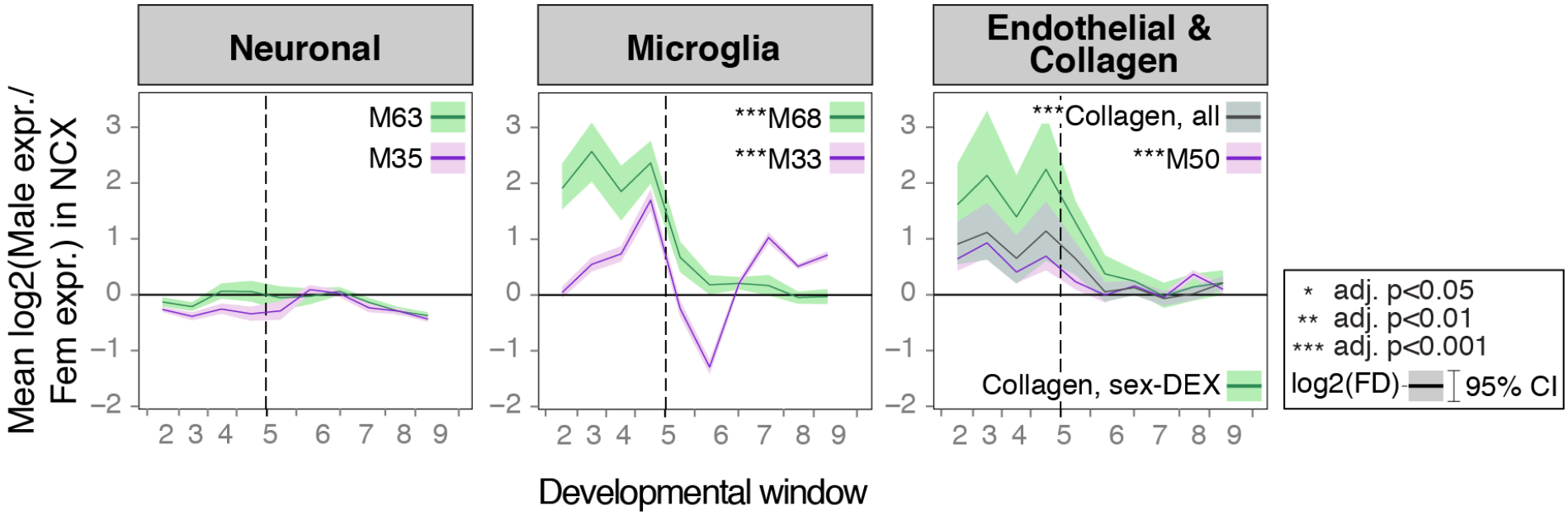
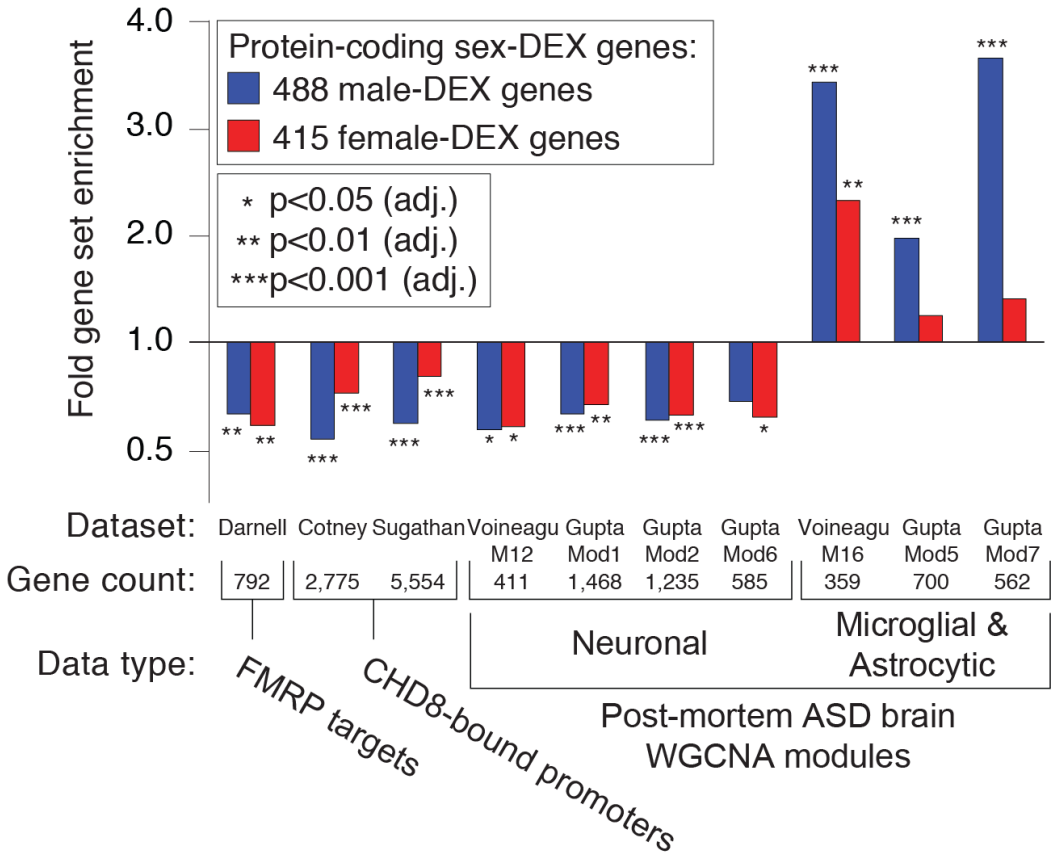


We observe a relationship between sex-DEX genes and ASD biology



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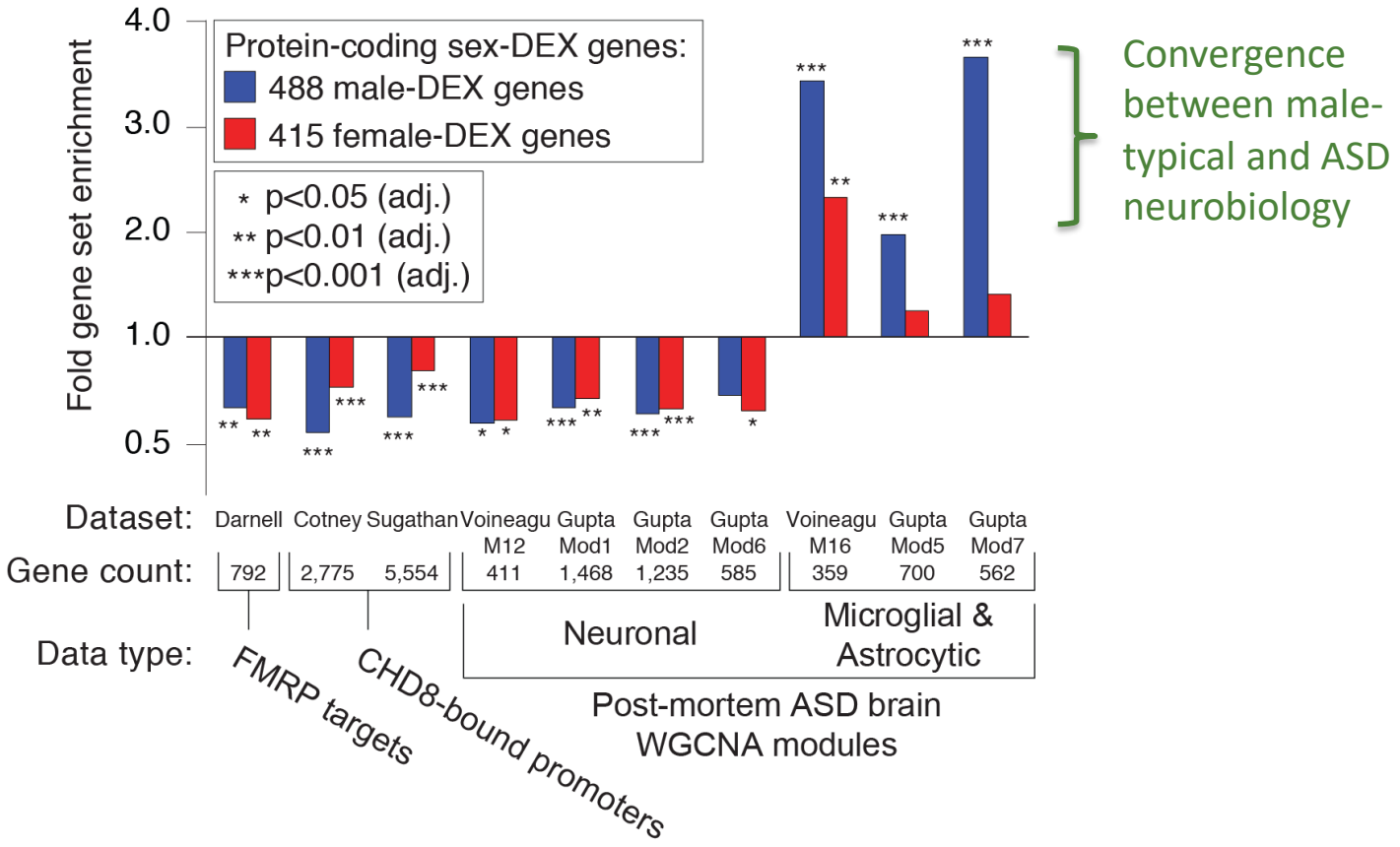
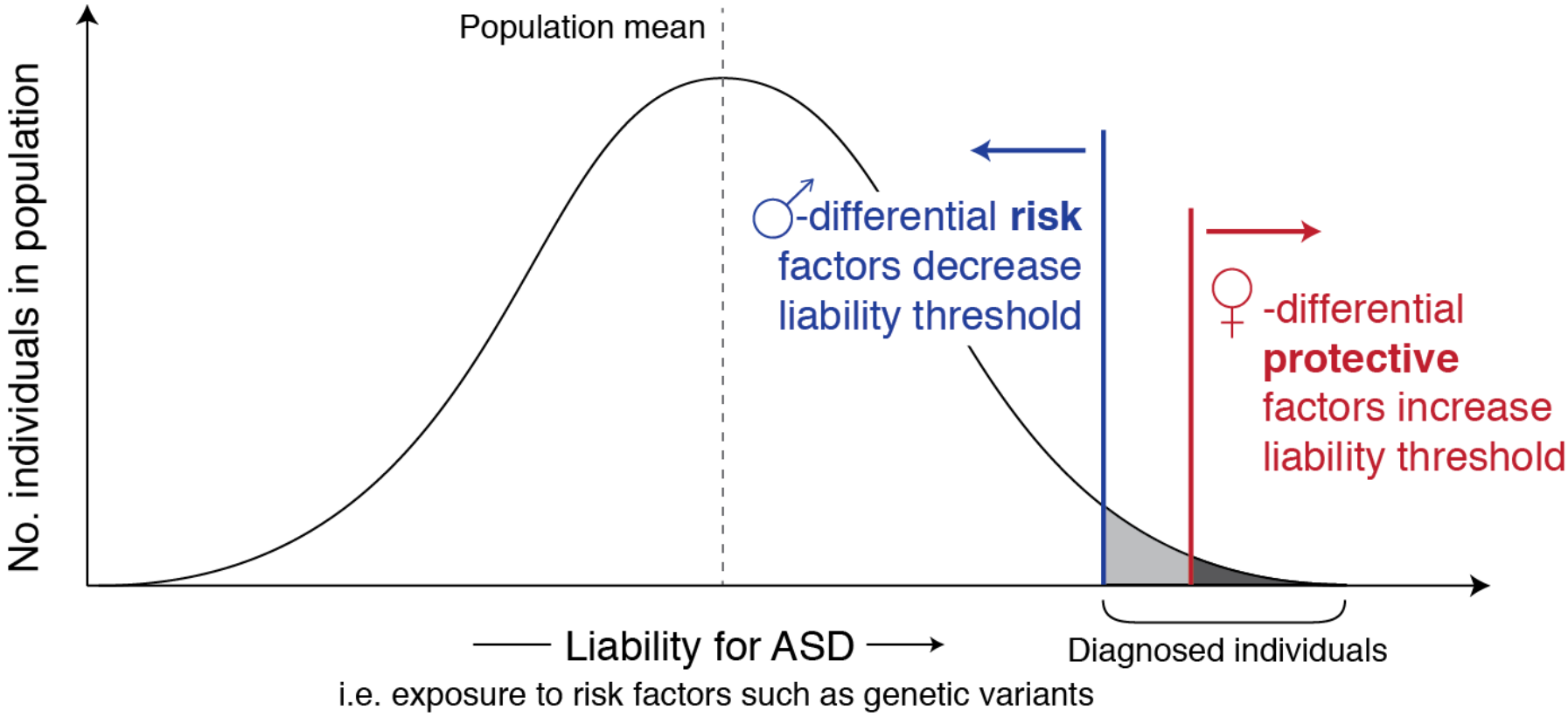


Enrichment evidence suggests a male sensitization model of ASD risk



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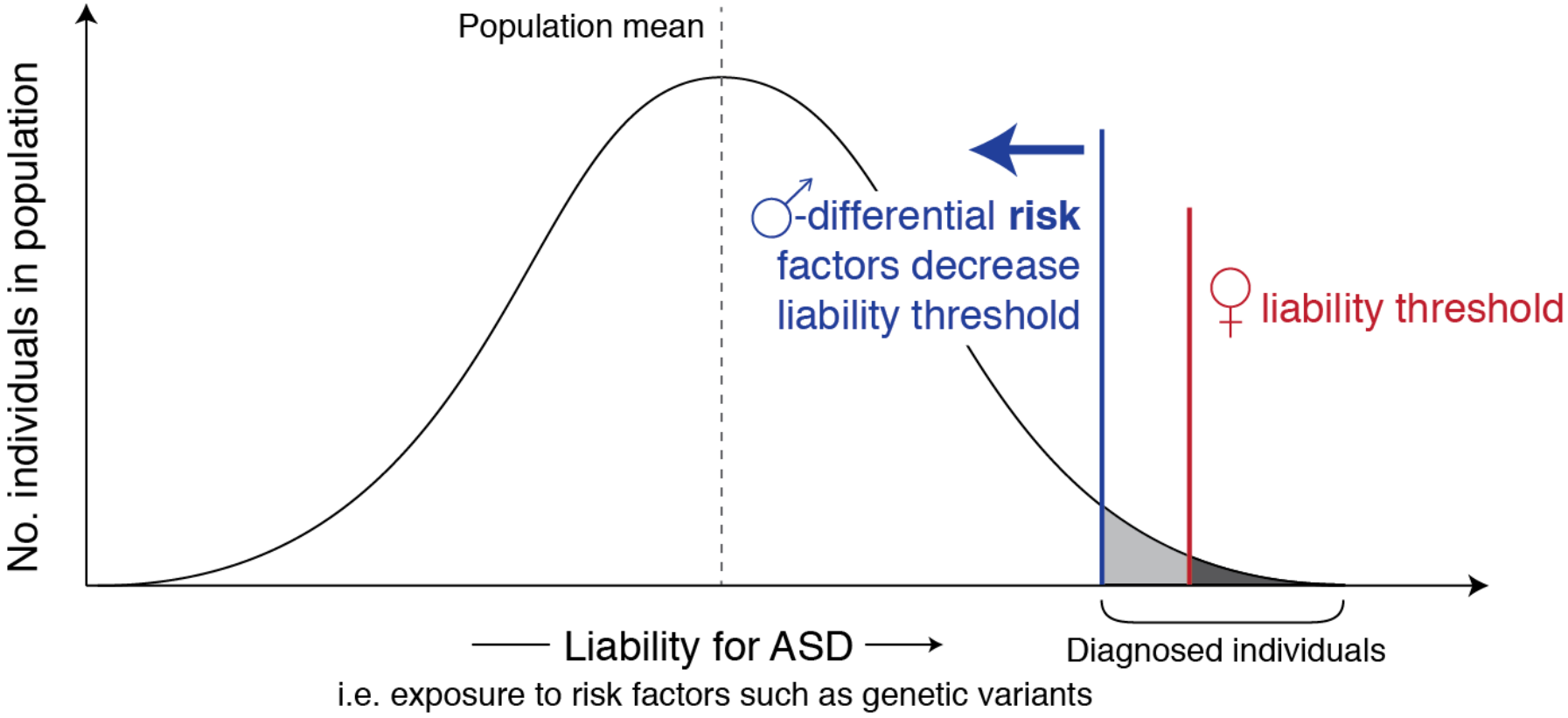

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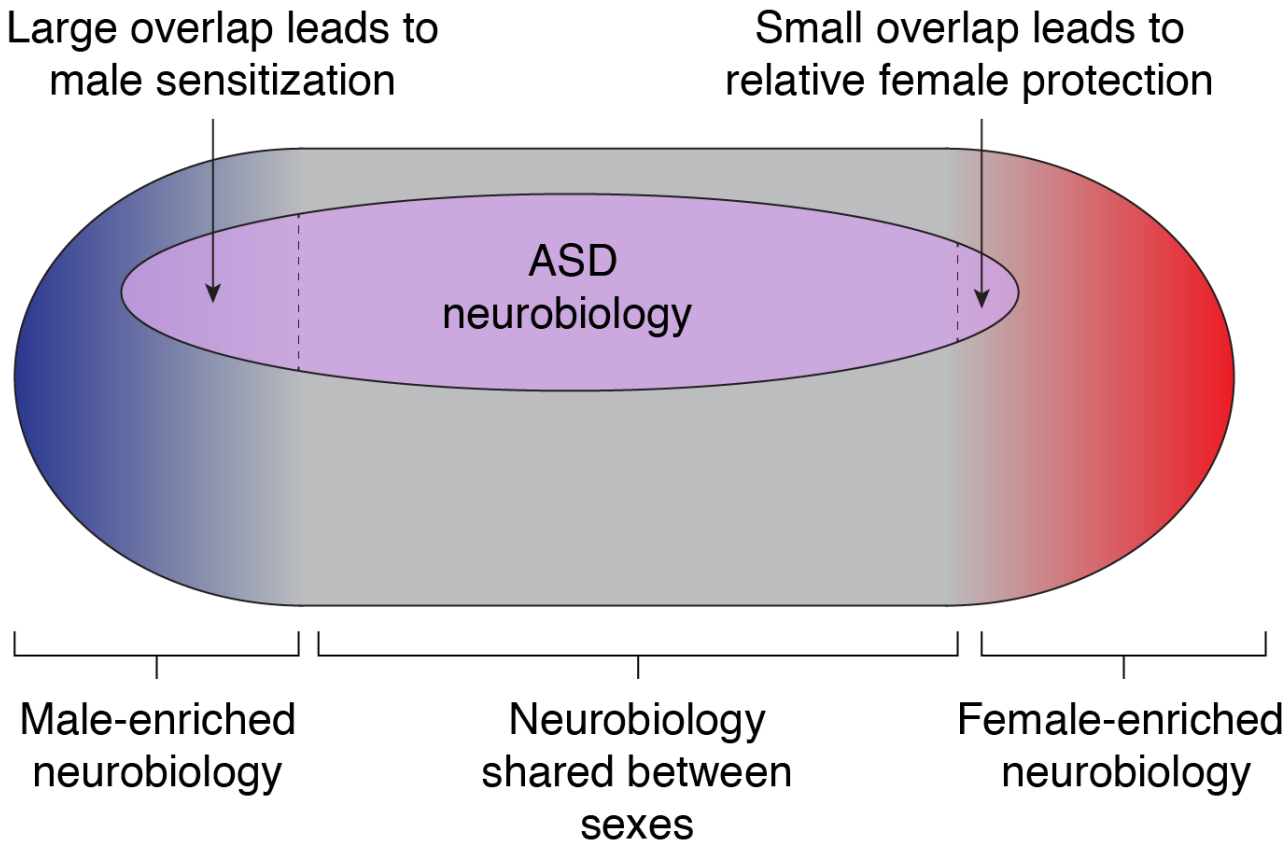

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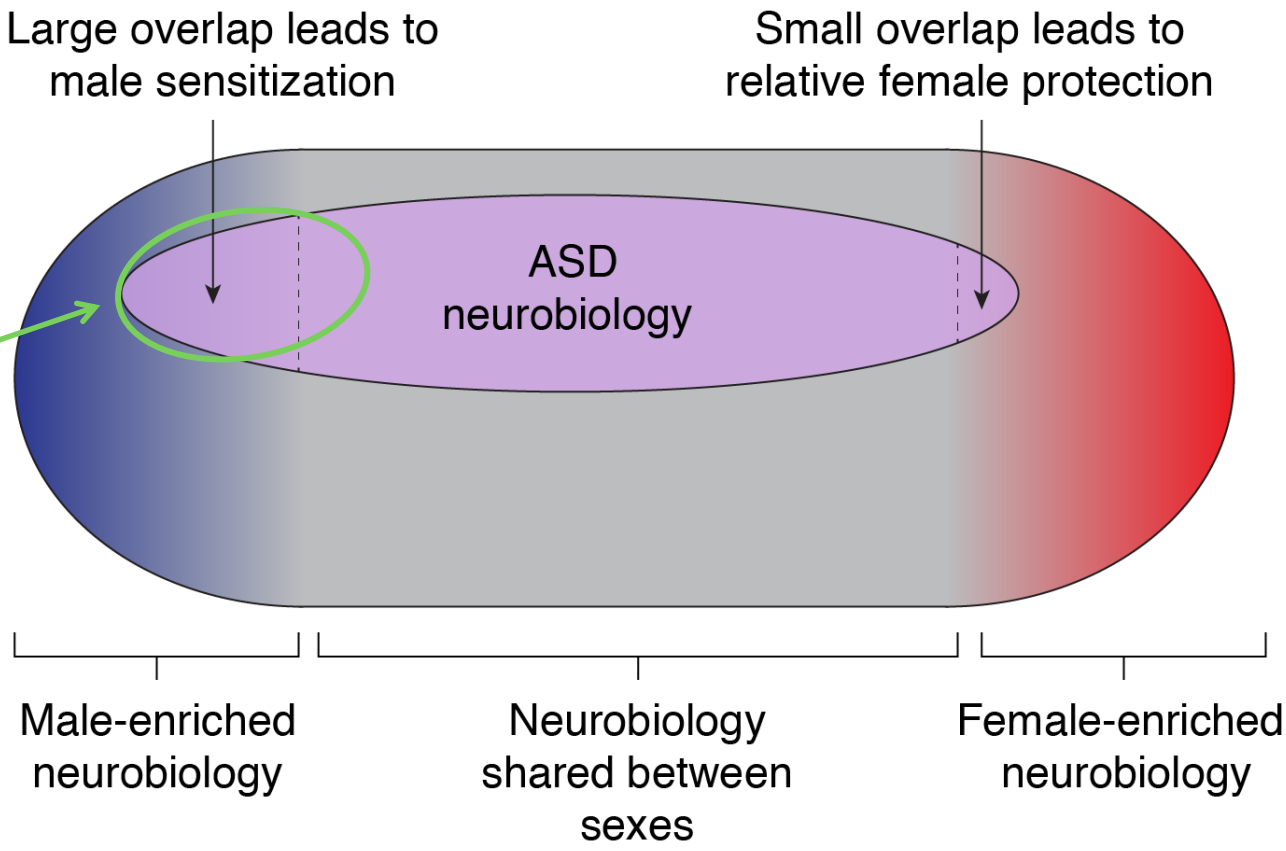


To understand ASD sex bias, we must characterize the intersection of typical male neurobiology and ASD neurobiology

Summary

- Intersection of ASD neurobiology and sex-differential neurobiology provides an approach to understand sex bias

- Male-biased expression:
  - Microglial genes
  - Collagen genes and endothelial cell markers
  - Glial genes dysregulated in ASD brain, suggesting a male-sensitization effect

- Validation in independent samples is needed
  - Results are preliminary and based on analysis of a single data set

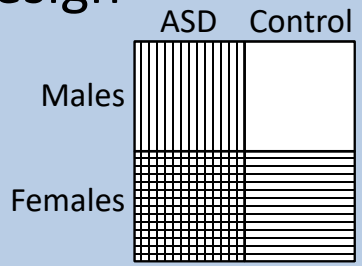
Looking forward

- Well powered, foundational data sets comparing males and females will be required for:
  - Rigorous validation of sex-differential patterns
  - Thorough investigation of relationships between sex-differential and ASD biology

Data types

- RNA sequencing for gene expression
- ChIP-seq for identifying gene targets of the estrogen and androgen receptors

2x2 design



Developmental stages

- Fetal
- Perinatal
- Early postnatal/childhood
- Puberty
- Adulthood

Cell types

- Neurons
- Microglia
- Astrocytes

Brain regions

- Neocortex
- Thalamus
- Striatum
- Cerebellum

Organisms

- Human
- Primate
- Mouse