

# Understanding Sex Differences in Autism Part 2: Neurobiology of Autism in Boys and Girls

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October 18, 2014

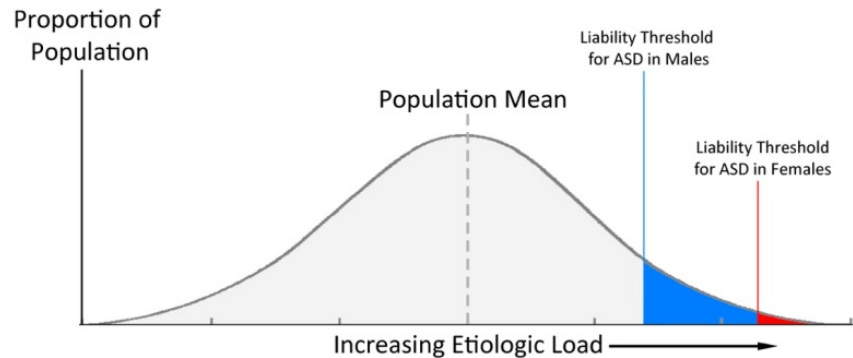
# Sex difference in prevalence rate of autism: 4 to 1 ratio

CDC sex ratios



<http://www.centerforsystemschange.org>

## 'Female Protective Effect'



(Adapted from Werling and Geschwind 2013)

Understanding the biological differences between boys and girls with autism could lead to more effective and individualized treatments and interventions

## Outline:

- 1) Why sex matters
- 2) Sex differences in typical brain development
- 3) Sex differences in ASD



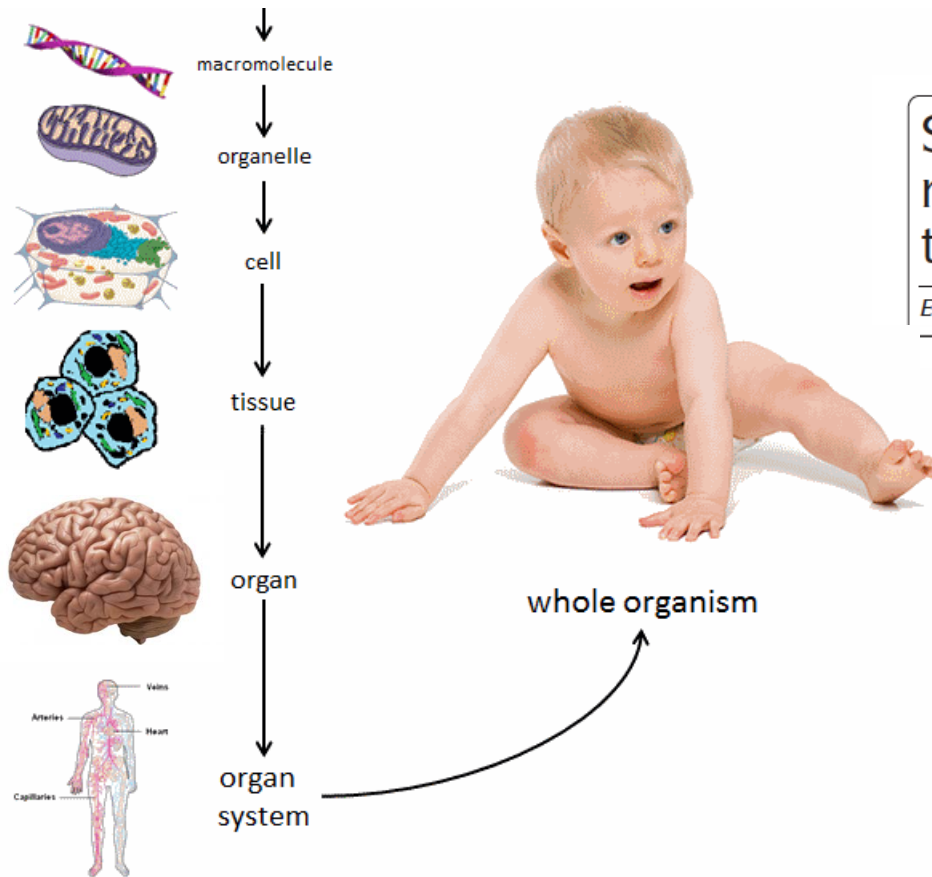
# Sex vs Gender

**Sex** – biological and physiological characteristics that define males and females

**Gender** – socially constructed roles, behaviors, activities, and attributes that define masculine and feminine traits



# Sex differences at all levels of neurobiological organization



## Sex differences in molecular neuroscience: from fruit flies to humans

Elena Jazin\* and Larry Cahill\*

NATURE REVIEWS | NEUROSCIENCE

VOLUME 11 | JANUARY 2010

- Gene expression in brain
- Regulation of programmed cell death
- Distribution of glial cells in brain
- Volumetric differences in brain structure
- Connectivity differences
- Functional brain activation differences

# Sex differences in pharmacology: The story of Ambien

- Zolpidem clearance is lower in women than men (Greenblatt et al 2000)
- Driving simulation studies show morning impairment 8 hours after dosing – 50 ng/ml threshold
- Morning blood levels: 15% of women vs. 3% men had > 50ng/ml zolpidem blood levels
- In Jan 2013, the FDA changed guidelines making Ambien the first prescription drug with different dosing recommendations for males and females



Implications for pharmacologic treatments being developed and utilized for neurodevelopmental disorders



ILLUSTRATION BY KATIE SCOTT

# NIH to balance sex in cell and animal studies

**Janine A. Clayton** and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

Nature, May 2014

# Sex differences in diagnostic symptoms: Heart attack

## Hallmark symptom – Chest pain

- Only 29% of women report chest discomfort
- 43% did not report any acute chest pain

Top 12 symptoms women reported experiencing the month before and during heart attacks.	
<i>Before attack</i>	<i>During attack</i>
Unusual fatigue (71%)	Shortness of breath (58%)
Sleep disturbance (48%)	Weakness (55%)
Shortness of breath (42%)	Unusual fatigue (43%)
Indigestion (39%)	Cold sweat (39%)
Anxiety (36%)	Dizziness (39%)
Heart racing (27%)	Nausea (36%)
Arms weak/heavy (25%)	Arm heaviness or weakness (35%)
Changes in thinking or memory (24%)	Ache in arms (32%)
Vision change (23%)	Heat/flushing (32%)
Loss of appetite (22%)	Indigestion (31%)
Hands/arms tingling (22%)	Pain centered high in chest (31%)
Difficulty breathing at night (19%)	Heart racing (23%)

From *Circulation*, 2003, Vol. 108, p. 2621

**SundayReview** | OPINION

## The Woman's Heart Attack

By MARTHA WEINMAN LEAR SEPT. 26, 2014



The New York Times, 9/26/2014



# Sex differences in diagnostic symptoms: Autism?

## How Different Are Girls and Boys Above and Below the Diagnostic Threshold for Autism Spectrum Disorders?

Katharina Dworzynski, Ph.D., Angelica Ronald, Ph.D., Patrick Bolton, Ph.D.,  
Francesca Happé, Ph.D.

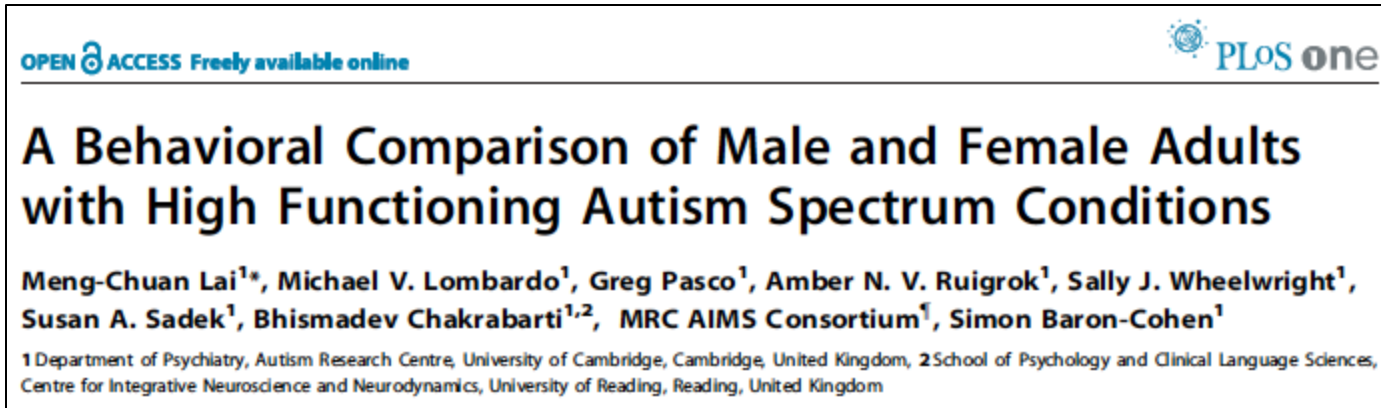
2012 JAACAP

- 15000 twin pairs, 10-12 years
- Compared two groups of girls who scored above the clinical threshold on a rating of autistic traits: one group had a clinical diagnosis, the other did not
- Girls with a clinical diagnosis of ASD had higher levels of ID or other behavioral problems

Do girls with autism 'fly under the radar'?

Girls less likely to receive a diagnosis of ASD (despite having high autism traits) unless there are additional problems to push them over the diagnostic threshold

# Sex differences in diagnostic symptoms: Autism?



- Adult males vs females with autism
- ADOS females exhibit less severe social communication deficits than males
- BUT – on a self report of autistic traits, females scored higher than males

Do females with autism learn to mask their difficulties?

Better adaptation/compensation in girls  
'camouflaging' or masking social deficits

## Summary – Why sex matters:

Different underlying biology may require sex-specific

- diagnostic criteria
- pharmacologic treatments
- interventions

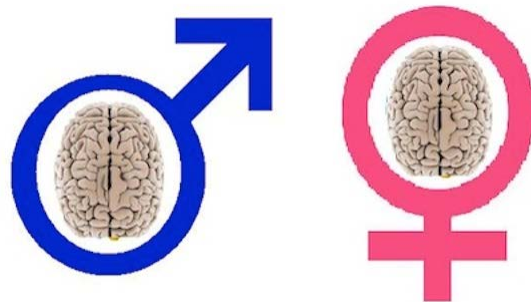


## Outline:

1) Why sex matters

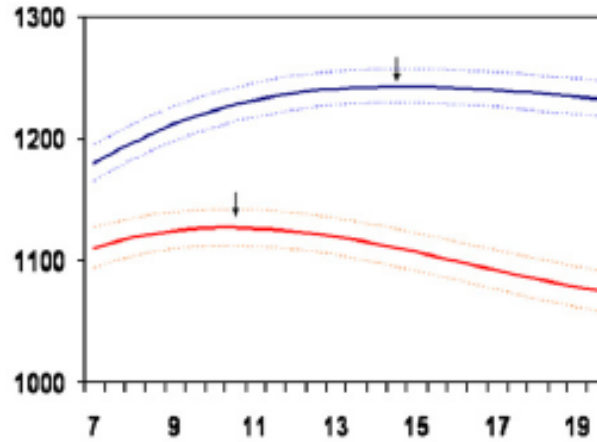
2) Sex differences in typical brain development

3) Sex differences in ASD

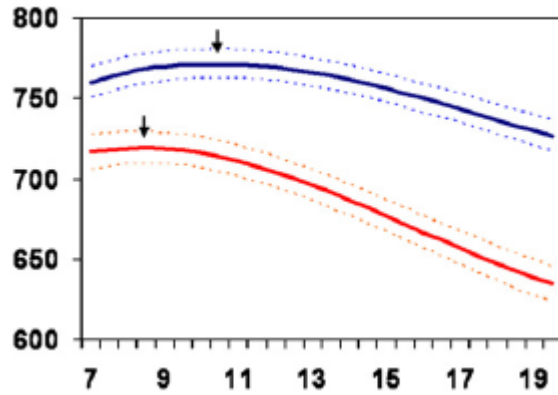


# Male and female brains grow at different rates

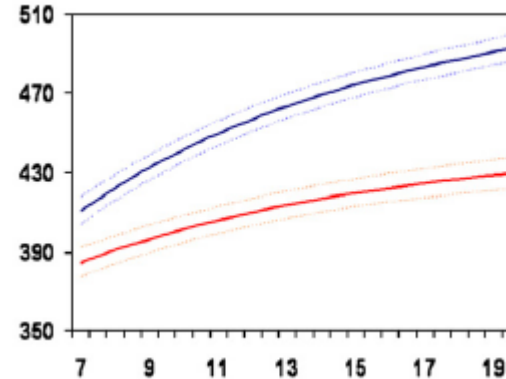
## Total cerebral volume



## Gray matter volume



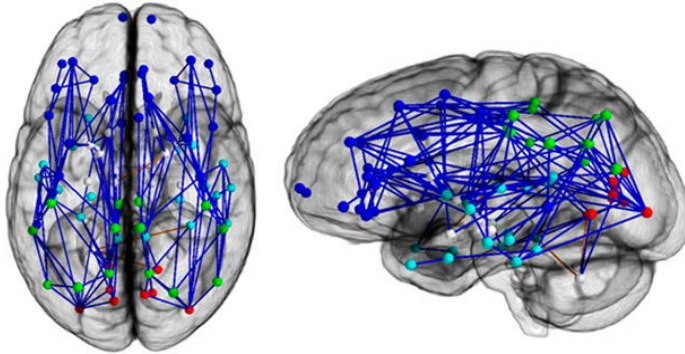
## White matter volume



# Males and Females have different structural connectivity patterns

A

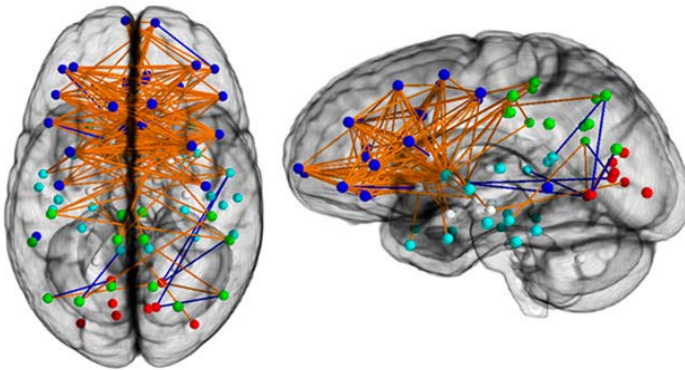
Males



Males have greater **within-hemisphere** connectivity

- perception and coordinated action

Females



Females have greater **inter-hemispheric** connectivity

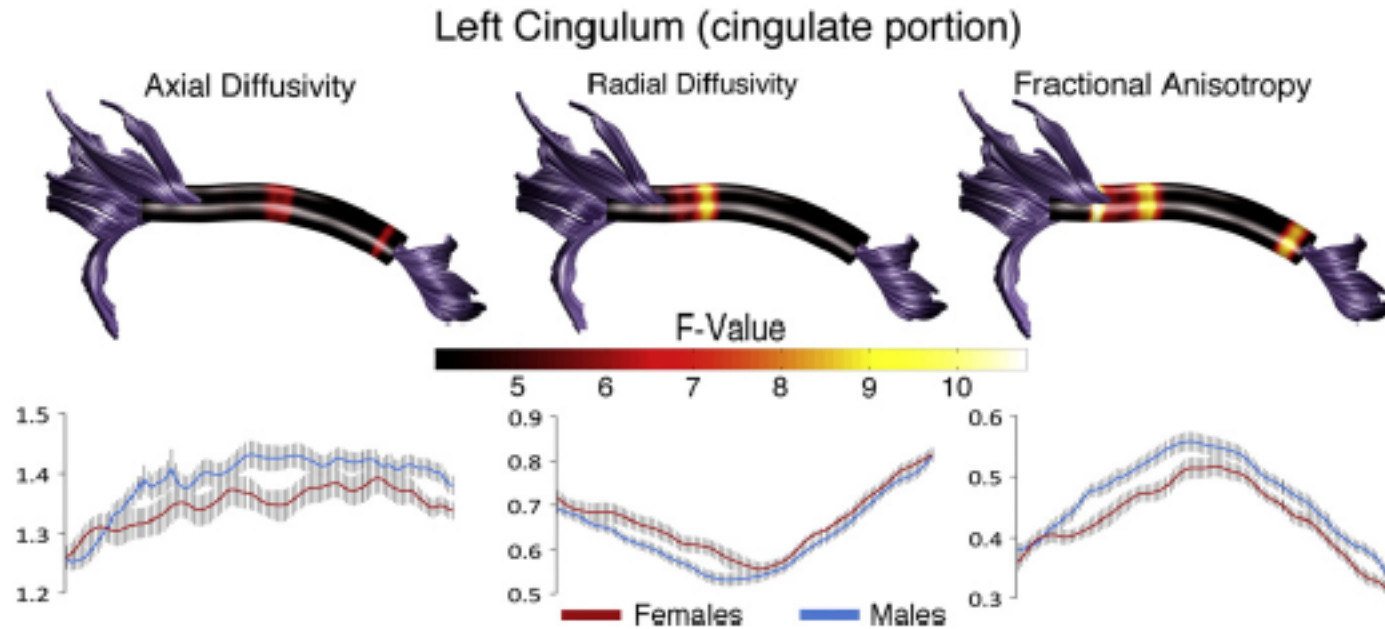
- Communication between analytical and intuitive processing modes

Ingalhalikar et al, PNAS 2014

Behavioral study (Gur et al 2012)

- males better on spatial processing, motor, and sensorimotor speed tasks
- females better on on attention, word and face memory, social cognition tasks

# Sex differences in specific white matter tracts



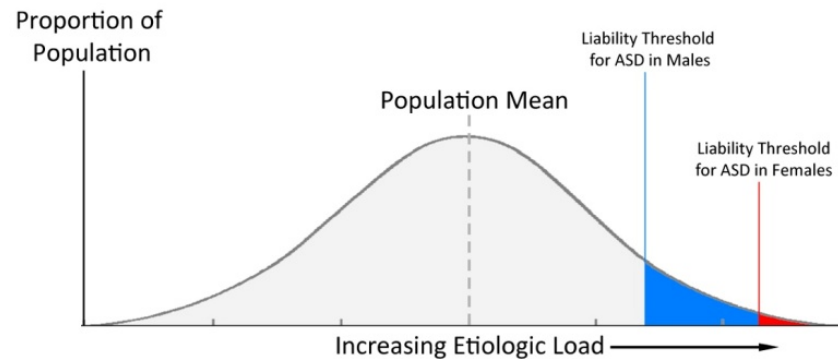
Johnson et al, 2013

# Outline:

1) Why sex matters

2) Sex differences in typical brain development

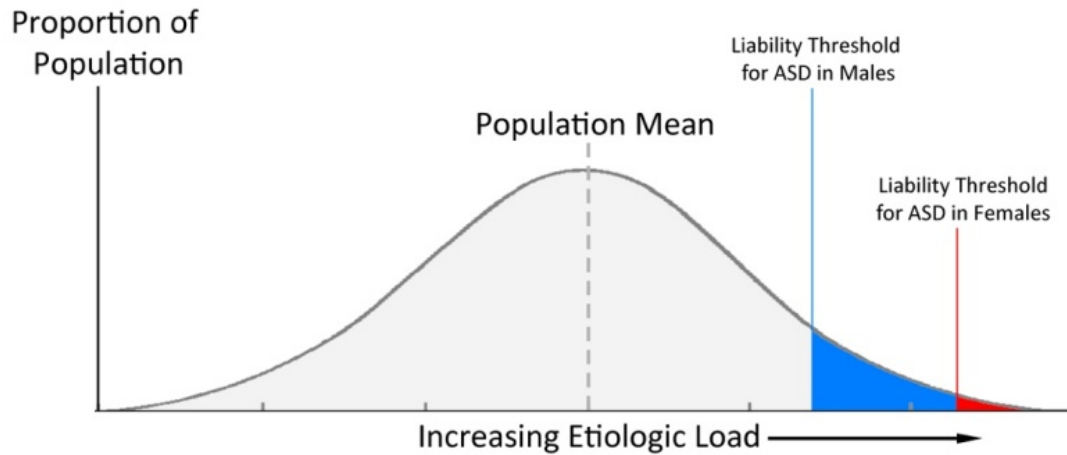
3) Sex differences in ASD



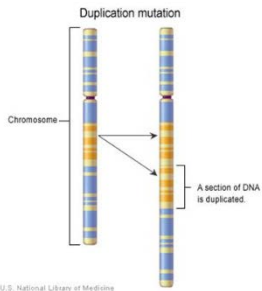
(Adapted from Werling and Geschwind 2013)



# 'Female Protective Effect'



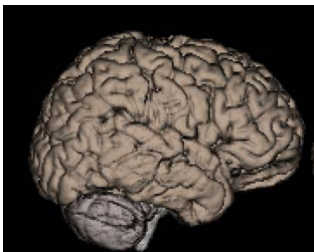
(Adapted from Werling and Geschwind 2013)



U.S. National Library of Medicine



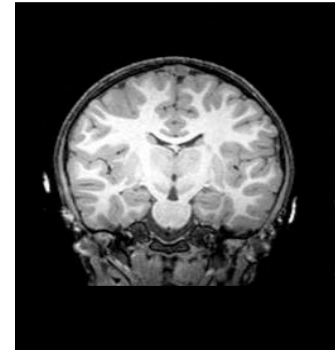
**Females with ASD have more frequent and more extensive CNVs than males**  
(Levy et al. 2011, Gilman et al 2011, Jacquemont et al 2014)



**Increasing Neuropathologic Load?**

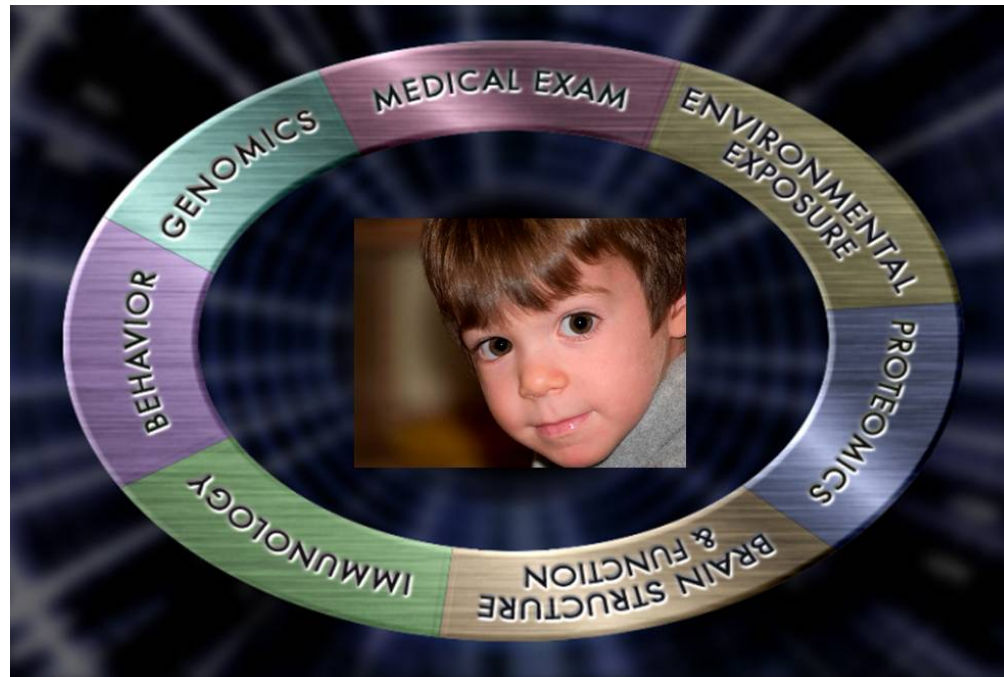
(Bloss and Courchesne 2007, Schumann et al 2009, 2011, Lai and Lombardo et al 2013)

# Females with ASD are under-represented in MRI research studies



- Females with ASD account for only 10% of ASD research participants in MRI studies
- Average sample size of females with ASD is 5!

# The Autism Phenome Project



# Autism Phenome Project



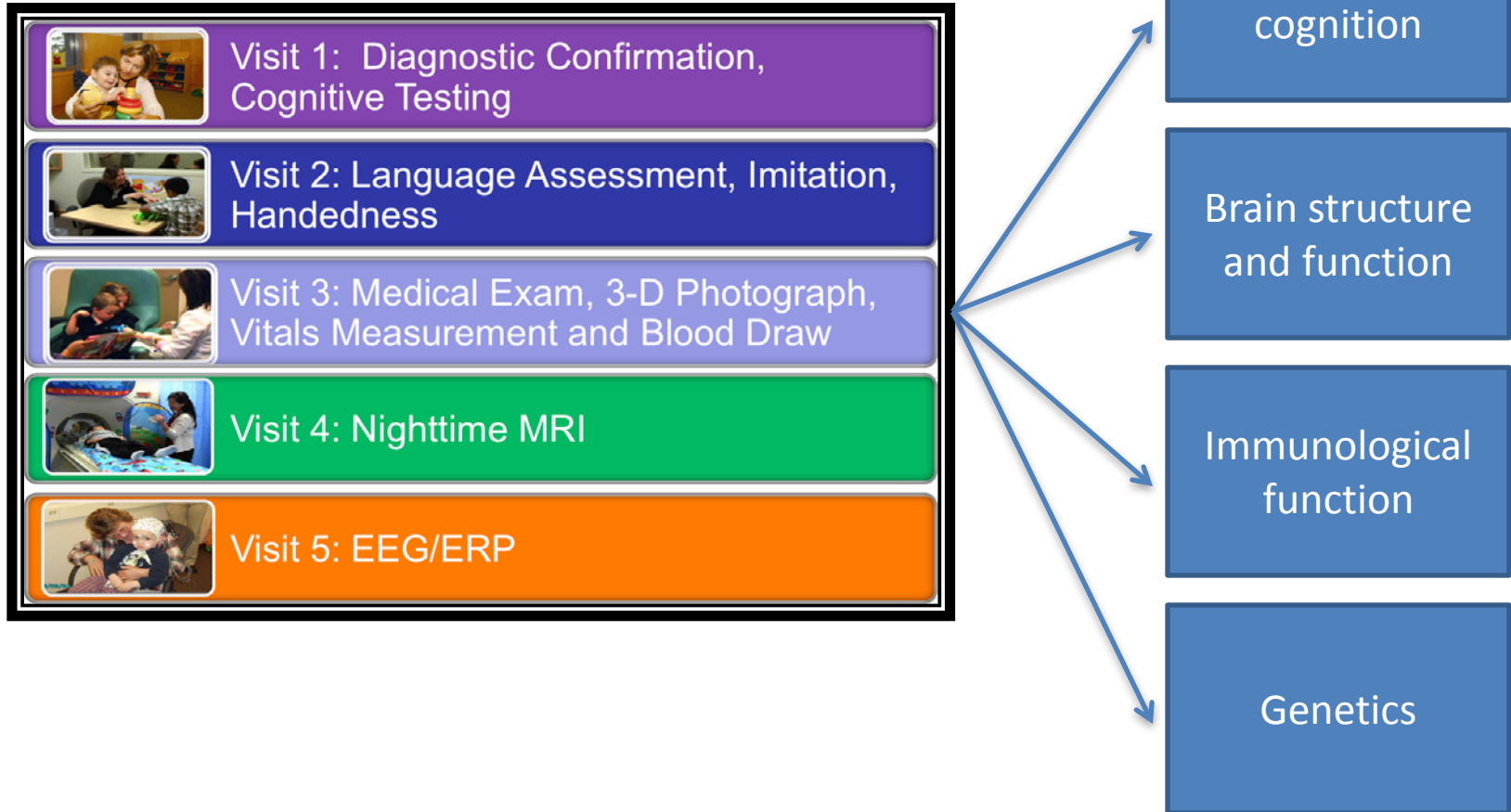
**UCDAVIS**  
MIND INSTITUTE

- Large scale – 300 families
- Children are recruited between 2 and 3.5 years of age
- Study includes all children with ASD with very few exclusions
- Both boys and girls are included
- Age-matched typically developing children serve as controls
- Longitudinal design

AIM: identify different subgroups (phenotypes) of Autism

Do girls have a distinct neural phenotype from boys with ASD?

# APP Summary

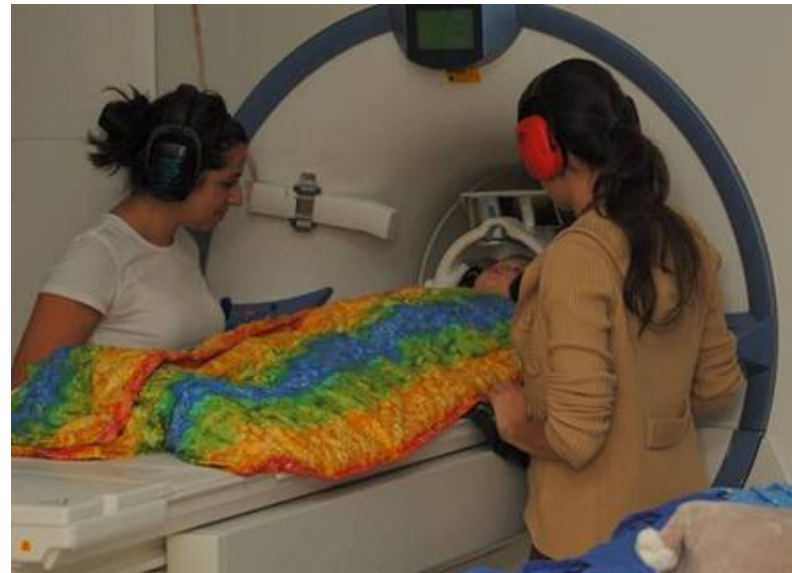


# Child-friendly scanning environment

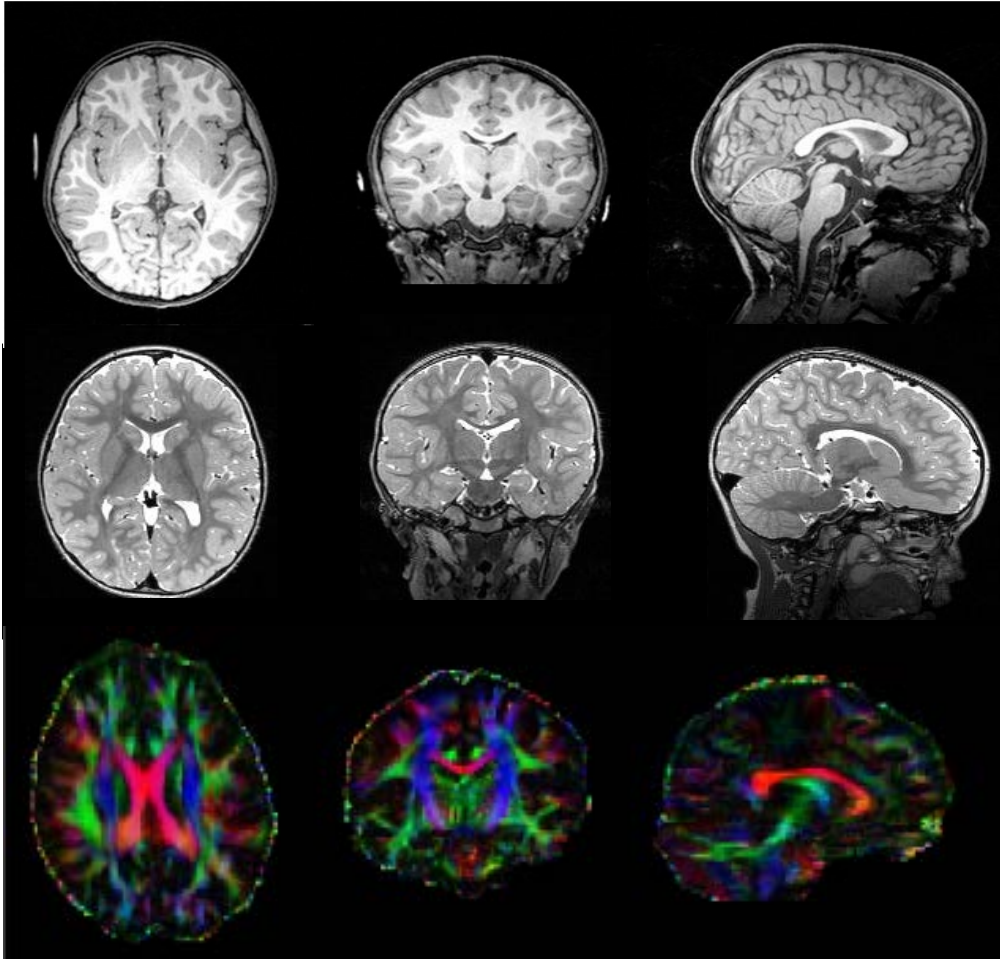
Before



After



# MRI Protocol



## Brain structure

- Volumetric
- Cortical folding patterns
- Cortical thickness and surface area

## Connectivity

- diffusion-weighted imaging
- resting state functional connectivity

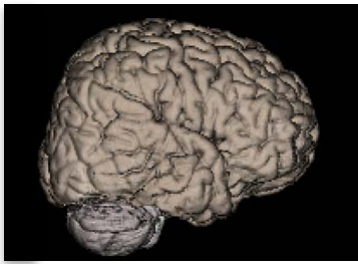
# APP sample to date

	n	Age (months)	DQ	ADOS severity
ASD male	155	37.6 (5.9)	63.5 (21.4)	7.9 (1.7)
ASD female	34	40.0 (7.4)	67.2 (23.1)	7.5 (1.9)
TD males	59	35.6 (4.9)	105.4 (12.1)	--
TD females	31	36.0 (5.4)	109.0 (10.5)	--

Females are still under-represented but, the sample size is larger than most studies





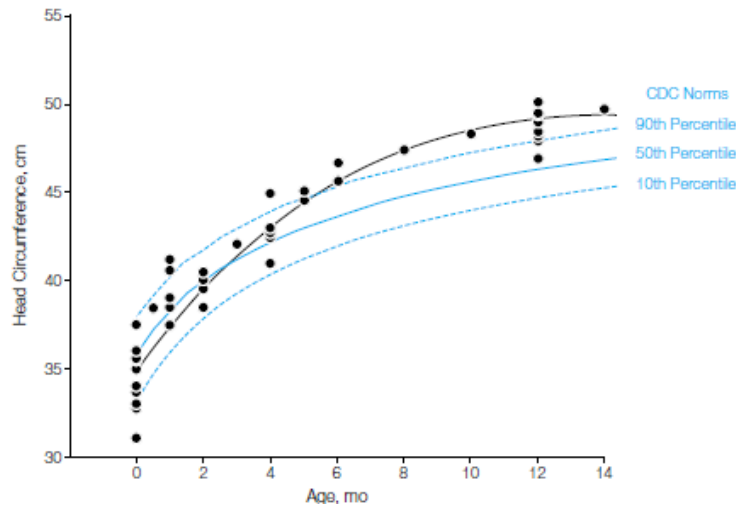


# Neuropathology of Autism: What is known?

## Abnormal trajectory of brain growth

### Head circumference studies

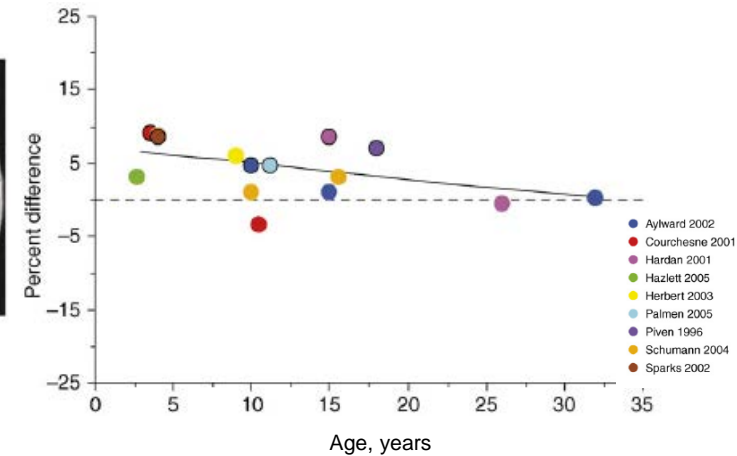
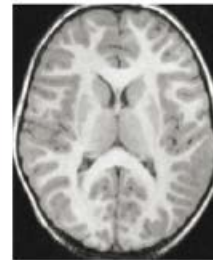
**Figure 4.** Growth of Head Circumference Measurements in Male Infants With Autistic Disorder by Age



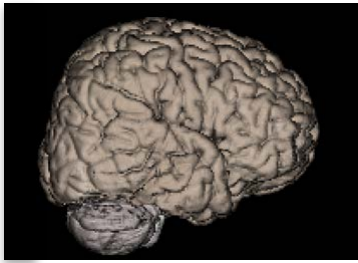
Courchesne 2003 JAMA

### MRI studies

(a) Total brain

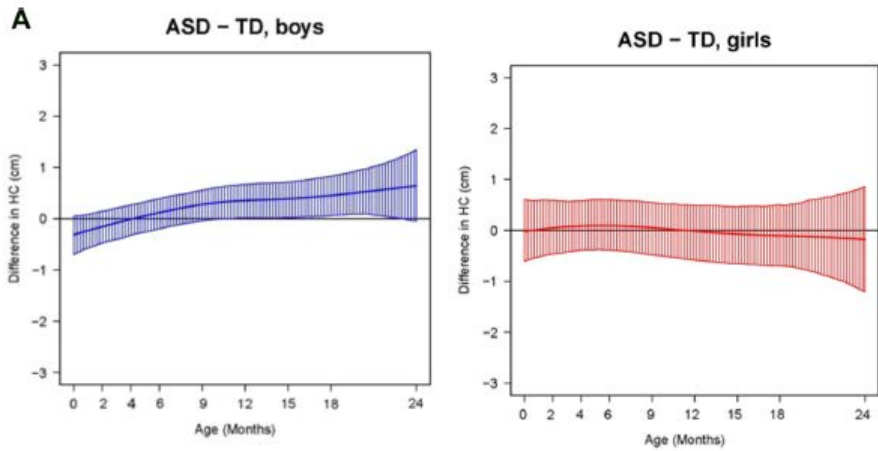


Amaral et al. 2008, TINS

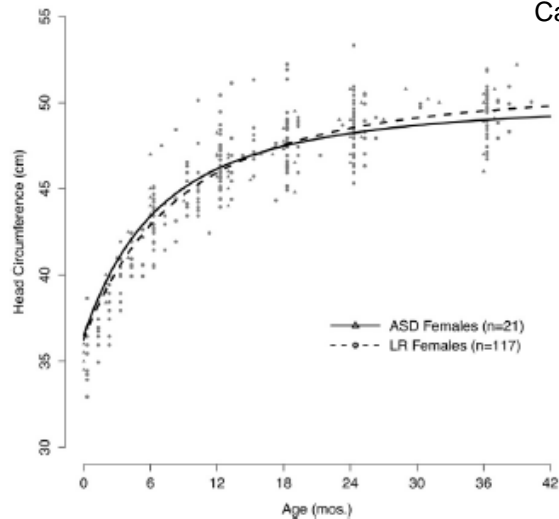


# Abnormal brain enlargement in early childhood: Do we see it in young girls with autism?

## Head circumference studies

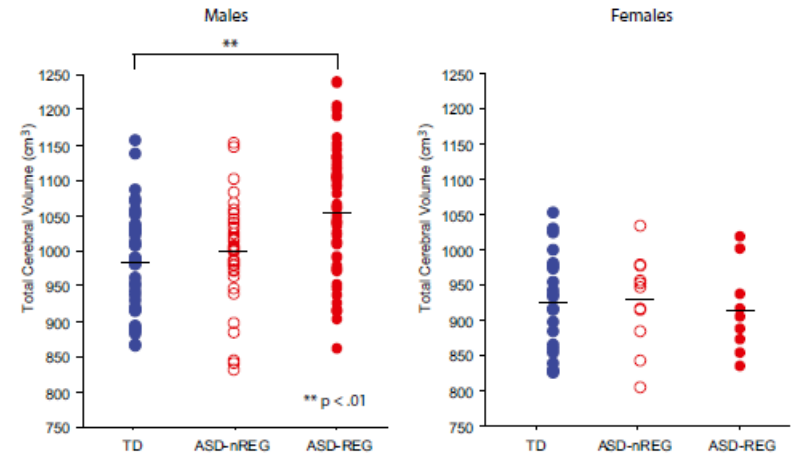


Campbell et al 2014



Zwaigenbaum et al 2014

## MRI studies



Nordahl et al 2011



# New study targets females with ASD to increase sample size

	APP	GAIN	Total
ASD male	155	--	155
ASD female	34	90	124
TD males	59	--	59
TD females	31	30	62





## The GAIN Study



### Eligibility

- Girls between the ages of 2 to 3-1/2 at the time of the first visit
- Have a diagnosis of autism spectrum disorder or typical development

### What can families expect?

- Comprehensive behavioral assessment
- Brain imaging
- Medical history
- Blood draw

For more information about the GAIN Study, please contact:

Michelle Huynh, Research Study Coordinator:  
(916) 703-0410 or

[michelle.huynh@ucdmc.ucdavis.edu](mailto:michelle.huynh@ucdmc.ucdavis.edu)

# Conclusions

Sex matters!

Brains differ in typical brain development and likely in autism as well

In order to develop the most appropriate treatments and interventions for ALL individuals with autism, we must strive to understand how the underlying biology may be different

## Future Directions

- Need for large sex-balanced cohorts
- Exploring other biological sex differences in autism: genetics, immunology
- Are there multiple neural phenotypes in females with ASD?



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The MIND Institute

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