Updates from the NIMH Study on X and Y Chromosome Variations

AXYS Meeting, Atlanta, 2025

National Institute of Mental Health

Intramural Research Program
Our Research Changes Lives

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Outline

- Quick overview of how the current NIMH study on X/Y variations came about
- Who is on the study team and what are our main goals ?
- What is our study design and what is it like to be a study participant?
- Some recent findings from the study
- Who to contact for more information

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Historical context for the current phase of our study

<u>First phase initiated 1990 by Dr. Jay Giedd</u>

Ran 1990 – 2010. Mainly focused on:

Cognitive development

Brain anatomy

150 participants age 5-25 years.

(XXX, XXXX, XXY, XYY, XXYY, XXXY, XXXXY)

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<u>Current phase of study was begun by our group @NIMH in 2015:</u>

- Over 3-times the size (funded to study over ~500 participants per time-point)
- More detailed cognitive and behavioral assessments for richer clinical feedback and science
- More information about first degree relatives
- More detailed measures of the brain and the genome

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Current + recent members of the NIMH clinical study team

+ our "behind the scenes" science team and a large network of collaborators in North America and Europe

Our goal: use data to advance clinical care

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“ We had to tell the doctor what [insert X/Y variation here] was “

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- Increase awareness of X/Y variations amongst clinicians and scientists
- Improve our understanding of development in X/Y variations and share this widely amongst care providers

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“ What can we do to help support his/her development ? “
“ Should we consider treatment A or treatment B ?“

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- Increase awareness of X/Y variations amongst clinicians and scientists
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- More fully describe the wide range of outcomes in X/Y variations
- Identify factors that might predict outcome

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“ Why is (s)he having these developmental difficulties ? “
“ Is there a test we can take to identify/predict issues early on ? ”

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- Increase awareness of X/Y variations amongst clinicians and scientists
- Improve our understanding of development in X/Y variations and share this widely amongst care providers
- More fully describe the wide range of outcomes in X/Y variations
- Identify factors that might predict outcome
- Define the brain and genetic changes that might be driving altered development in some people with X/Y variations

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- Some recent findings from the study
- Who to contact if you're interested in enrolling or getting more information

Our study design is shaped by 4 guiding ideas …

1. We will do a better job of understanding any individual X/Y variation group if we study all X/Y variation groups

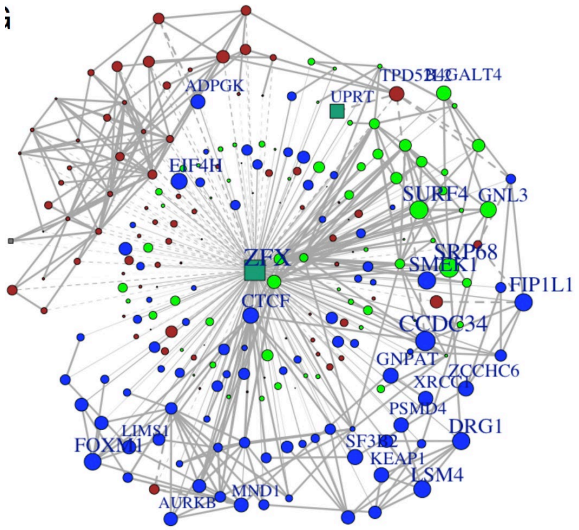
2. We have to understand *individuals* as well as groups : variability is the rule, not the exception

3. We need to get better at measuring development

4. We need to “link” up studies of genes, brain and behavior

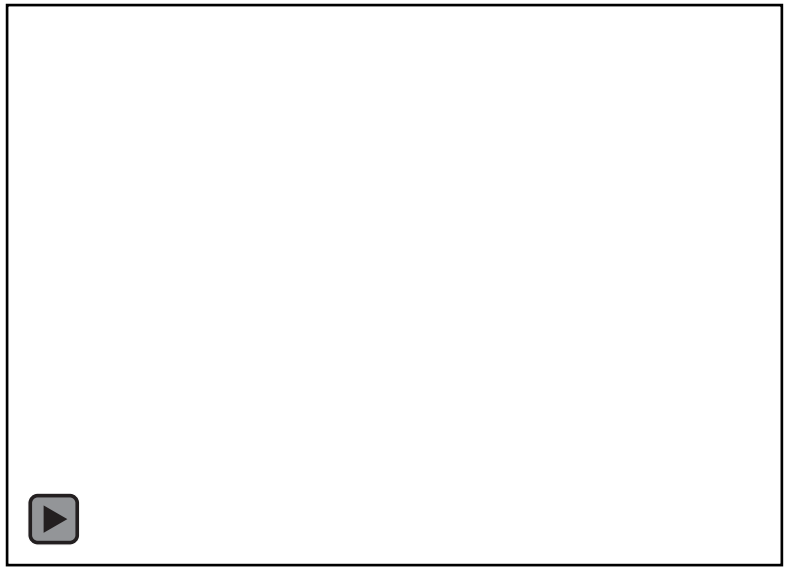
Study design: the data needed to address research goals

genes



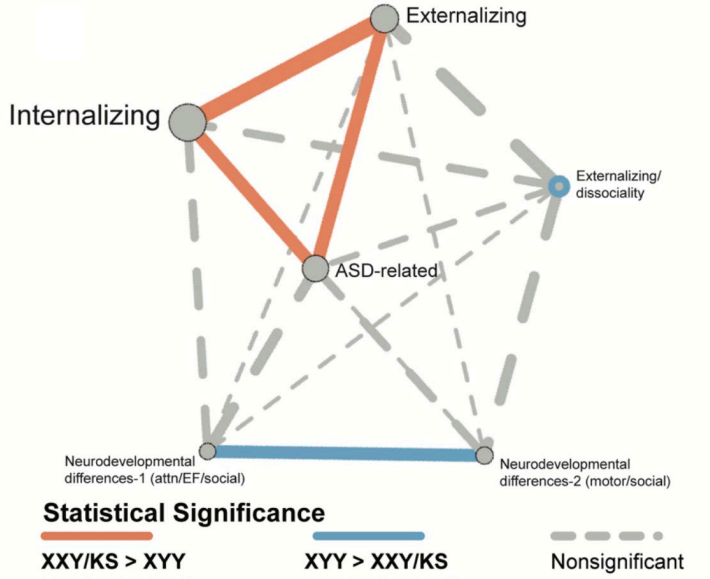
A network of connected genes that change their expression with changes in X-chromosome count

brain



A set of brain regions that change size with changes in the count of the X-chromosome, the Y-chromosome or either

behavior



Symptom network differences between XXY and XYY syndrome

Liu et al, *PNAS*, 2023 / Levitis et al, Biol Psych, 2024 / Larsen et al, Psychol Med, 2024

What a typical on-site study visit looks like (XXY in this example)

	Monday		Tuesday	
8am	**Welcome, Admissions, Consenting, Questionnaires** with Jonathan Blumenthal, MA, and Cassidy McDermott (in Outpatient Admissions)		Arrival (greeted by Cassidy)	**Endocrinology Consult** with Miranda Broadney, MD, from National Institute of Child Health & Human Development
9am	**Vitals** (HR, BP, Ht, Wt) with Gerald in Outpatient Clinic		**Histories and Physicals** with Erin Torres, Nurse Practitioner	
9:30am	**Neuropsychological and Autism Spectrum Evaluations** with Drs. Lauren Kenworthy, Srishti Rau, or Marissa Miller from Children's National Health System	**Practice MRI Scan** with Jonathan		
10am		**Neuropsychological Testing (son)** with Ajay Nadig	**MRI Scans** (son) with Francois Lalonde, Ph.D.	
11am		**Cognitive Testing (mother)** with Jonathan		
12pm	Lunch (Cafeteria or Starbucks Café)		Lunch (Cafeteria or Starbucks Café)	
1pm	**DEXA** (son) in Radiology	**Hand X-Ray** (son) Radiology	**Cognitive Testing (son)** with Liv Clasen, Ph.D.	**Diagnostic and Clinical Interview (parents)** with Erin Torres, Nurse Practitioner
2pm	**Parent Interview** with Liv Clasen, Ph.D.	**Diagnostic and Clinical Interview (son)** with Erin Torres, Nurse Practitioner		
3pm				

What comes out of the visit ?

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A multidisciplinary clinical team reviews and discusses material for each participant to generate a detailed reports to families

The data are stored on secure NIH servers and used for research on behavioral/learning issues as well as brain/genome changes

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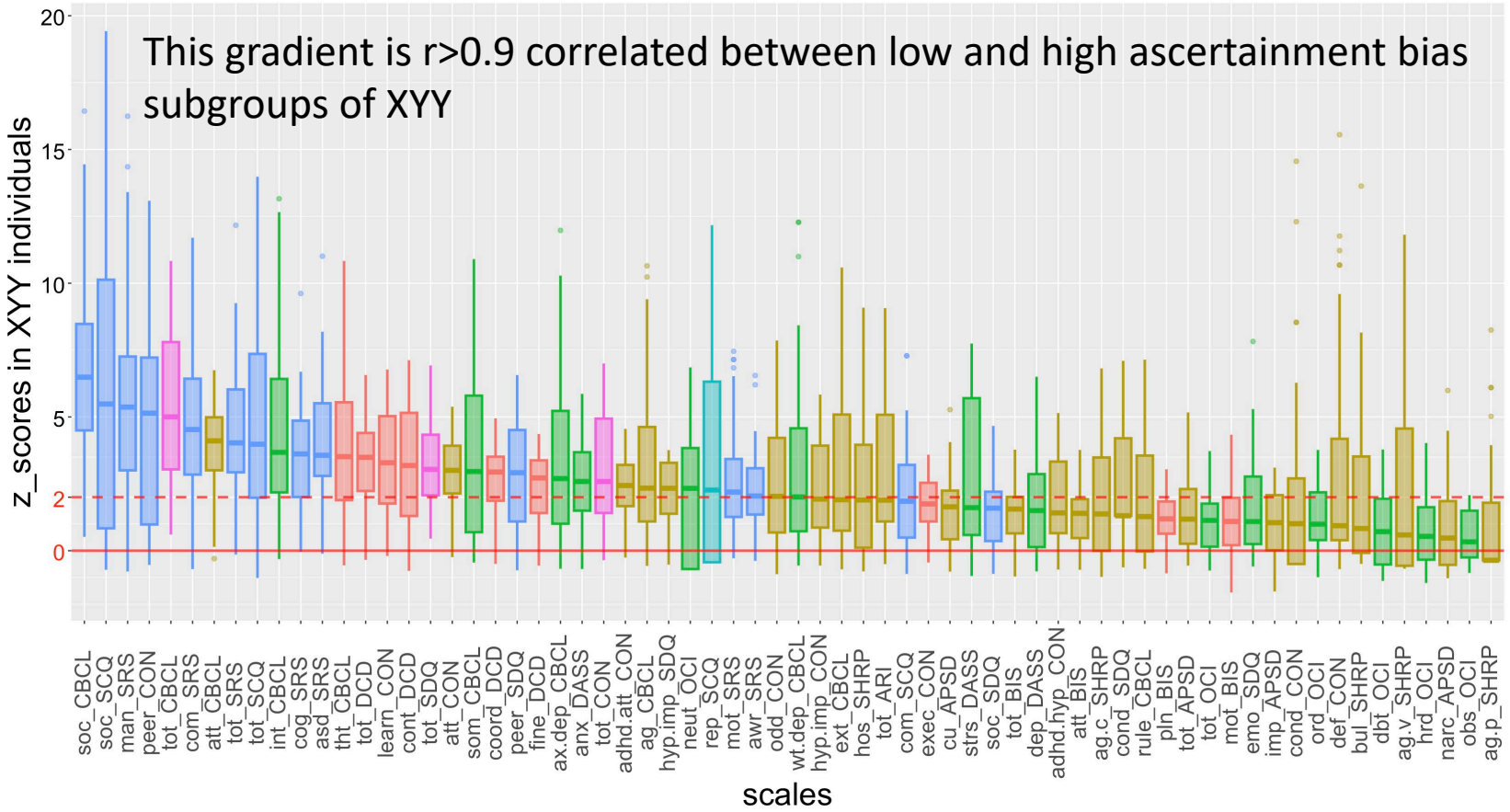
- **Some recent findings from the study – examples from XYY and XXY research, but relevant for all X/Y variations**
- Who to contact for more information

What aspects of mental health are most impacted in each of the X/Y variation subtypes (e.g. here in 64 participants with XYY syndrome), and how variable are these impacts across individuals ?



Domains

Social Impairment / Total Psychopathology / Externalizing / Internalizing / Cognitive / Repetitive

Scales

ARI – Affective Reactivity Index / APSD – Antisocial Process Screening Device / BIS – Barrett Impulsiveness Scale / CBCL – Child Behavior Checklist / SHRP – Children's Scale of Hostility and Aggression / CON – Conners Rating Scale for ADHD / DASS – Depression, Anxiety and Stress Scale / DCD – Developmental Coordination Disorder Questionnaire / OCI – Obsessive Compulsive Inventory / SCQ – Social Communication Questionnaire / SRS – Social Responsiveness Scale / SDQ – Strength and Difficulties Questionnaire

Raznahan et al, *JNDD*, 2023

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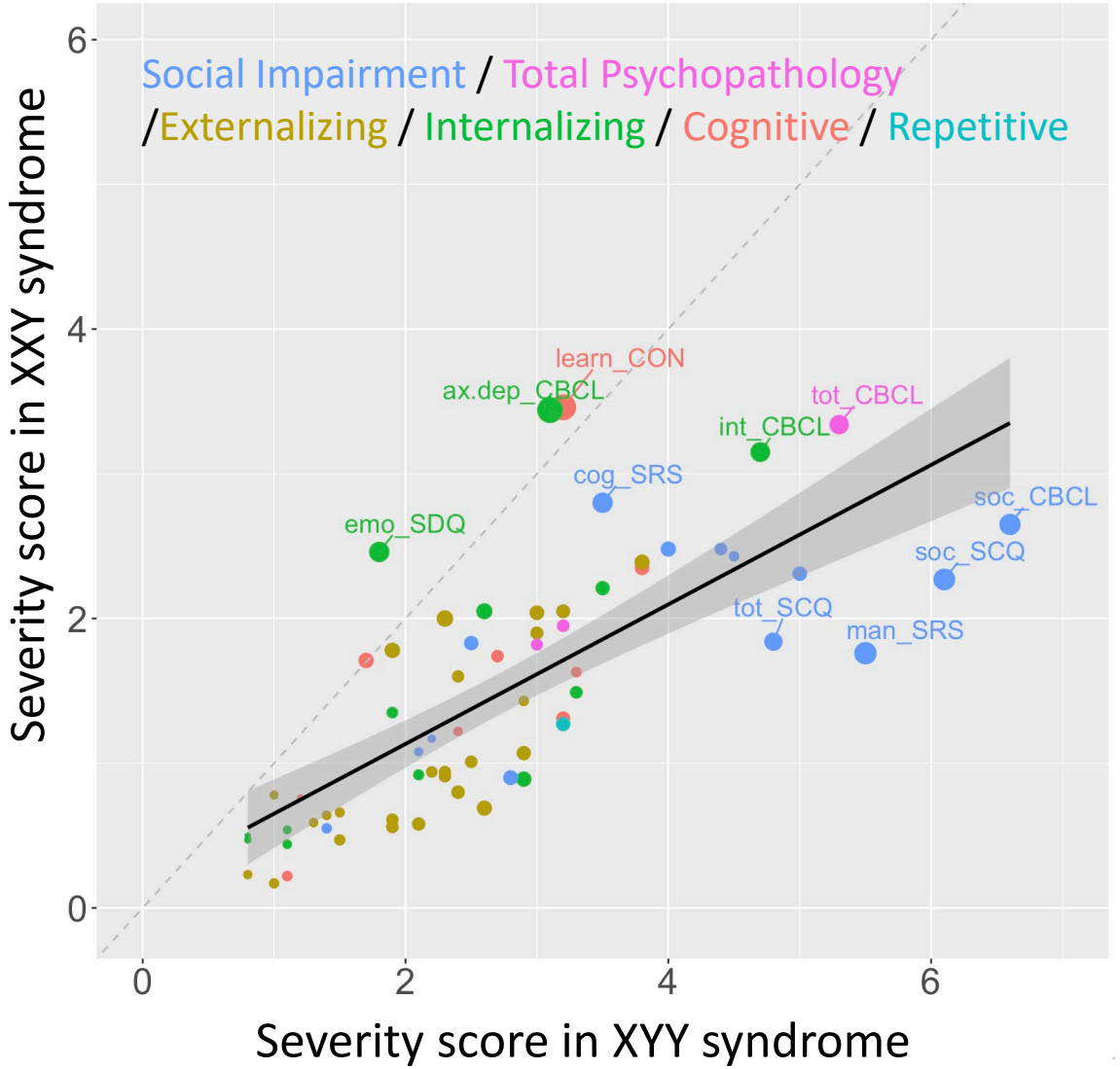

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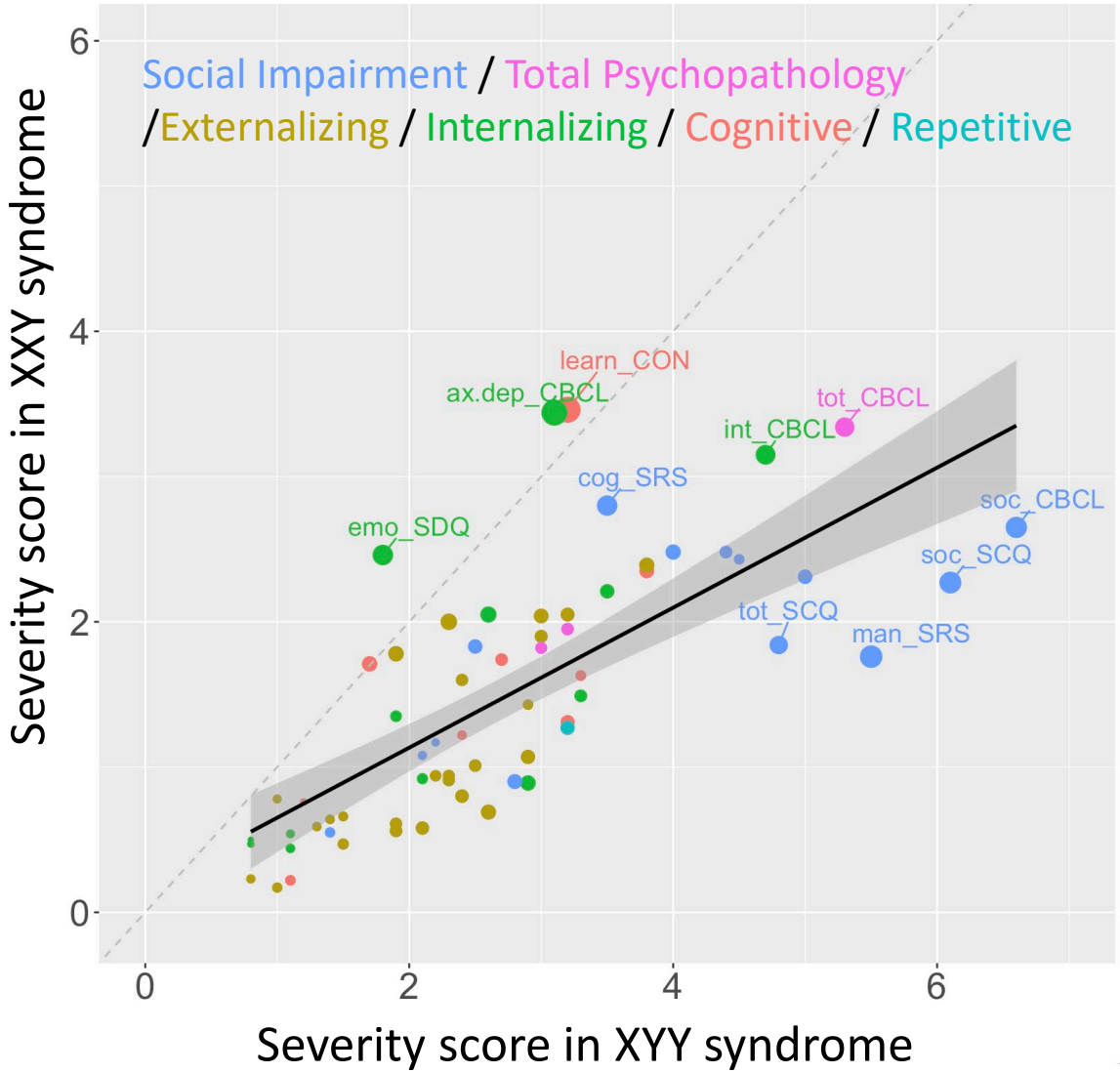

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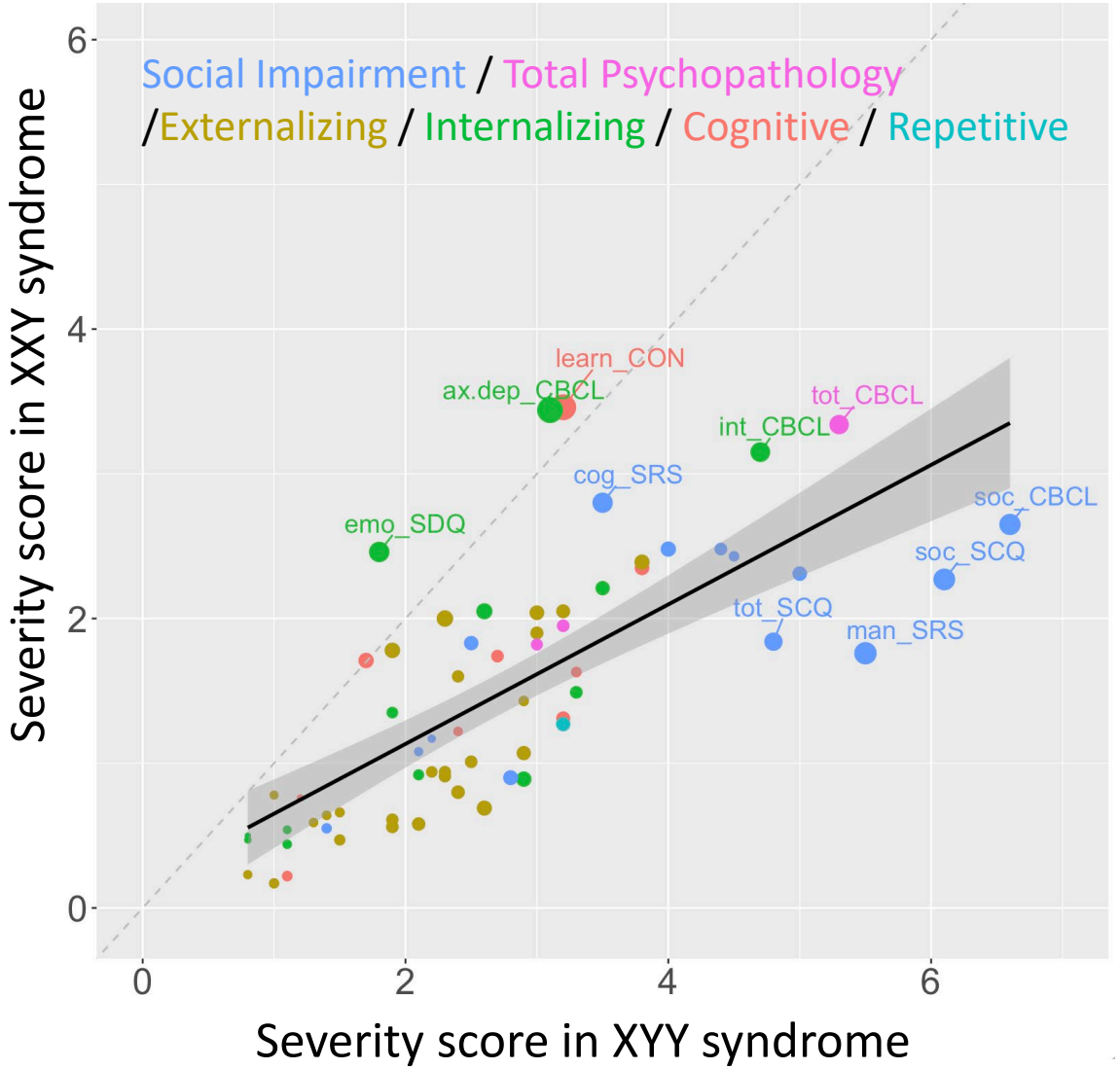

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2. *On average …*

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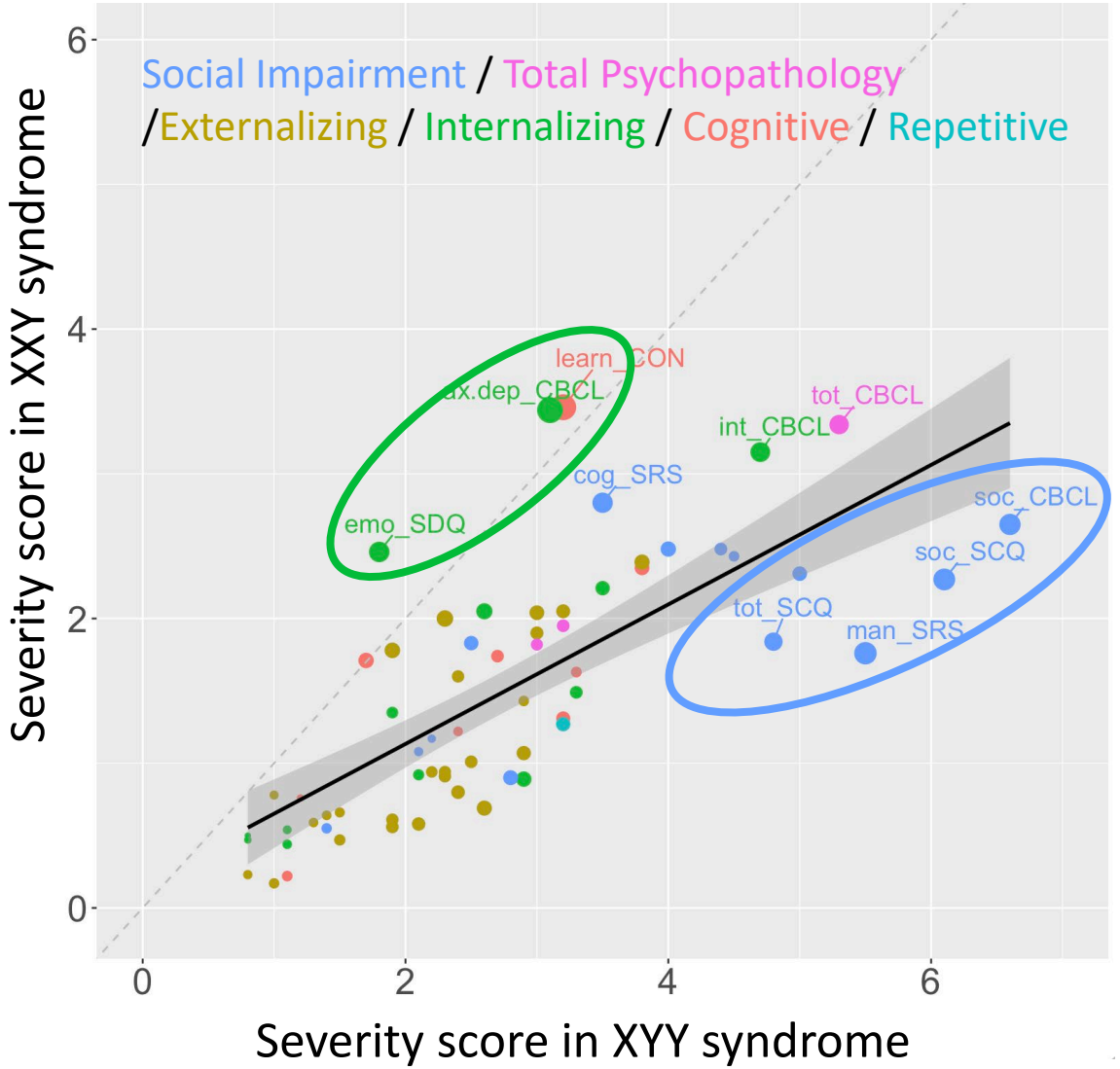

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2. *On average …*

   - social and learning skills tend to be the most impacted in both XYY and XXY syndromes
   - impacts tend to be more severe in XYY than XXY syndrome – especially for social functioning
   - but XYY and XXY syndrome are associated with similar levels of mood/anxiety difficulties

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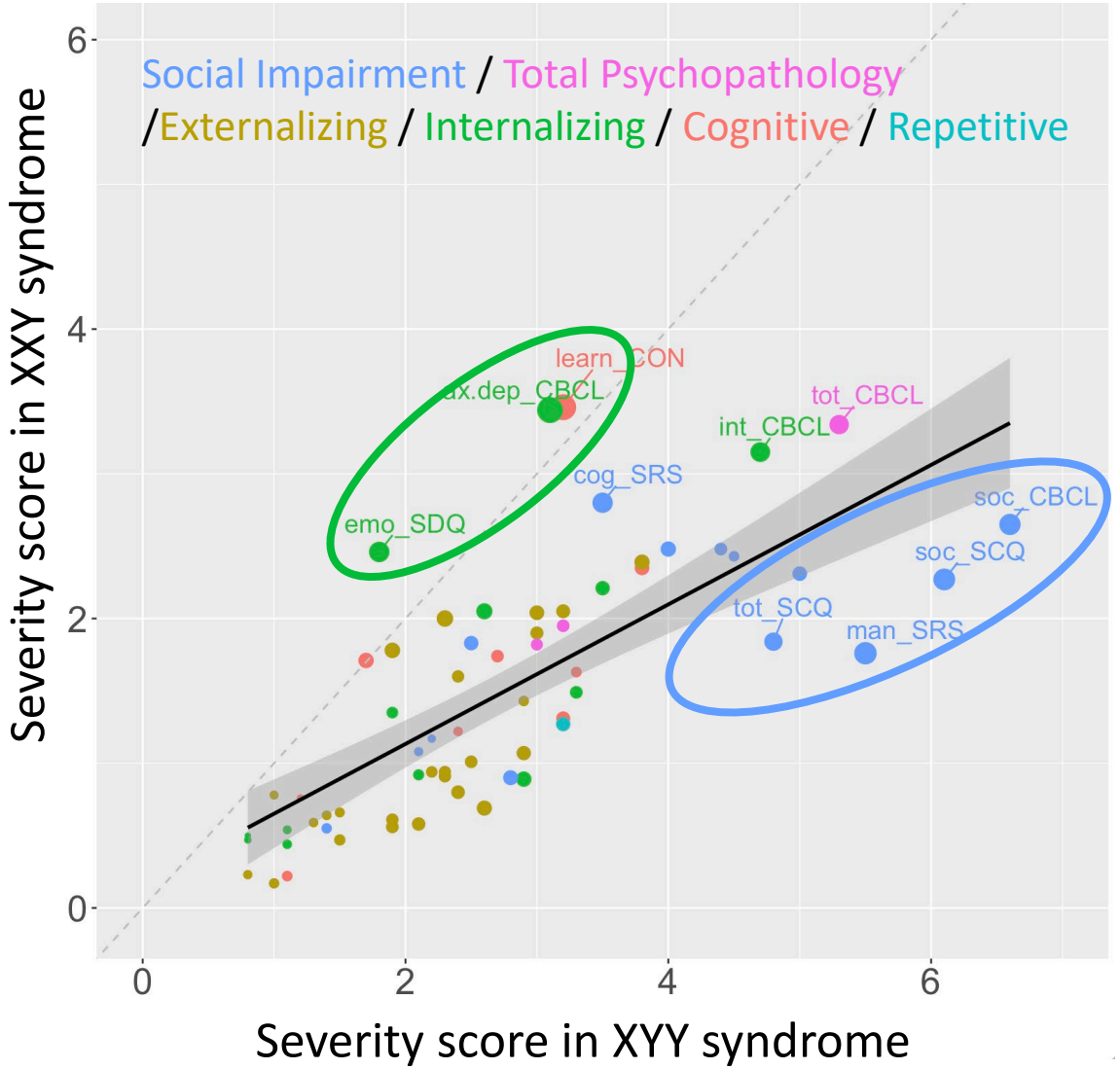

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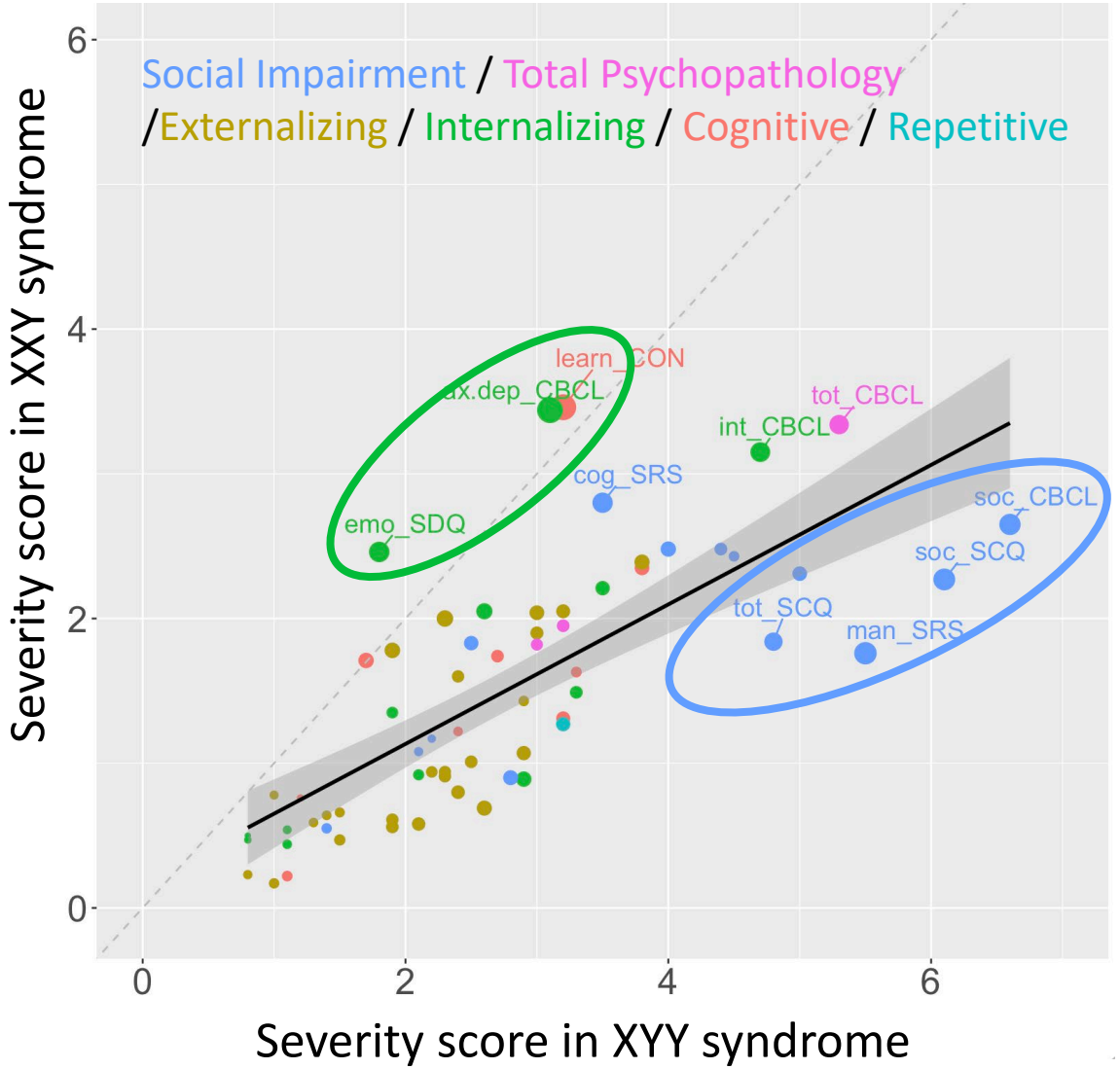

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3. We are now running similar analyses for Trisomy X syndrome

4. **There is high variation in outcome within each X/Y variation group, every child is unique, and there is lots of room for change**

Can we do any better at predicting how impacted a specific child with an X/Y variation will be?

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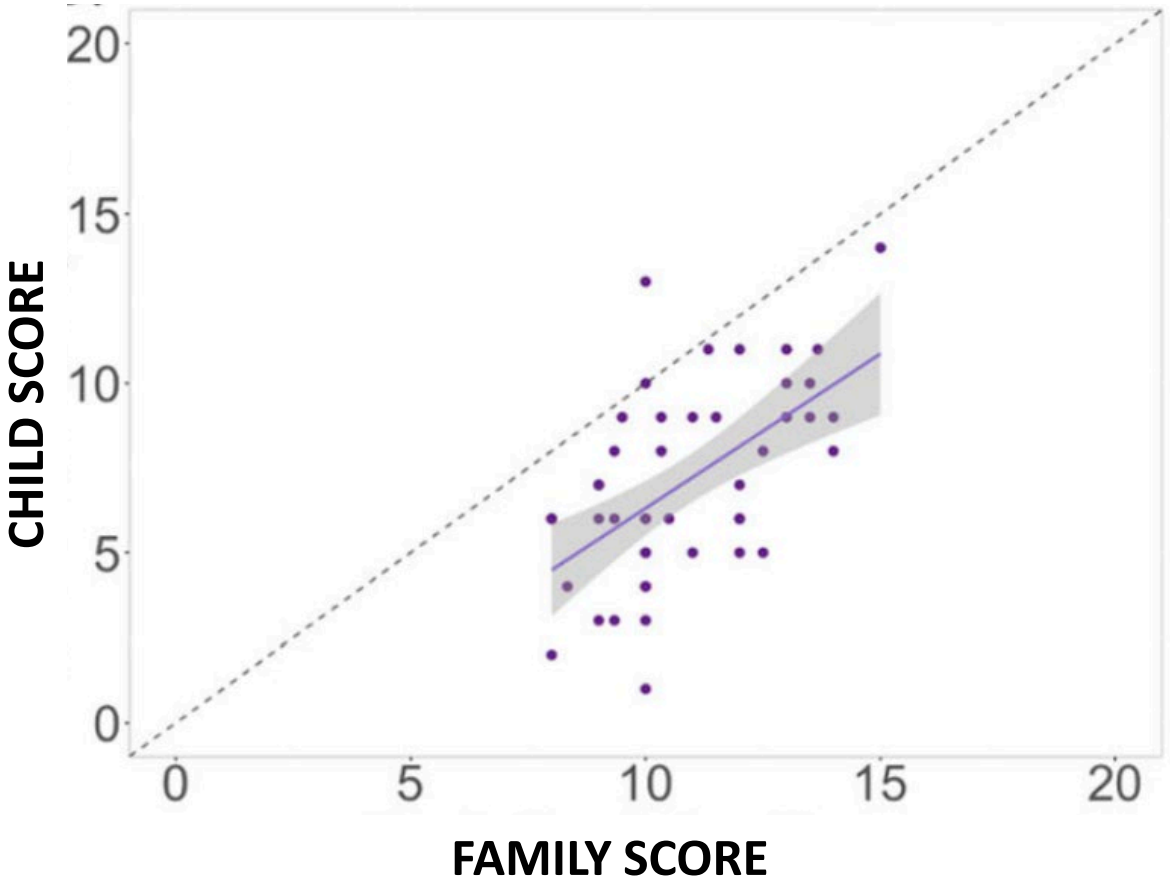
Predicting language outcomes in XYY syndrome



Wilson et al, *JNDD*, 2021

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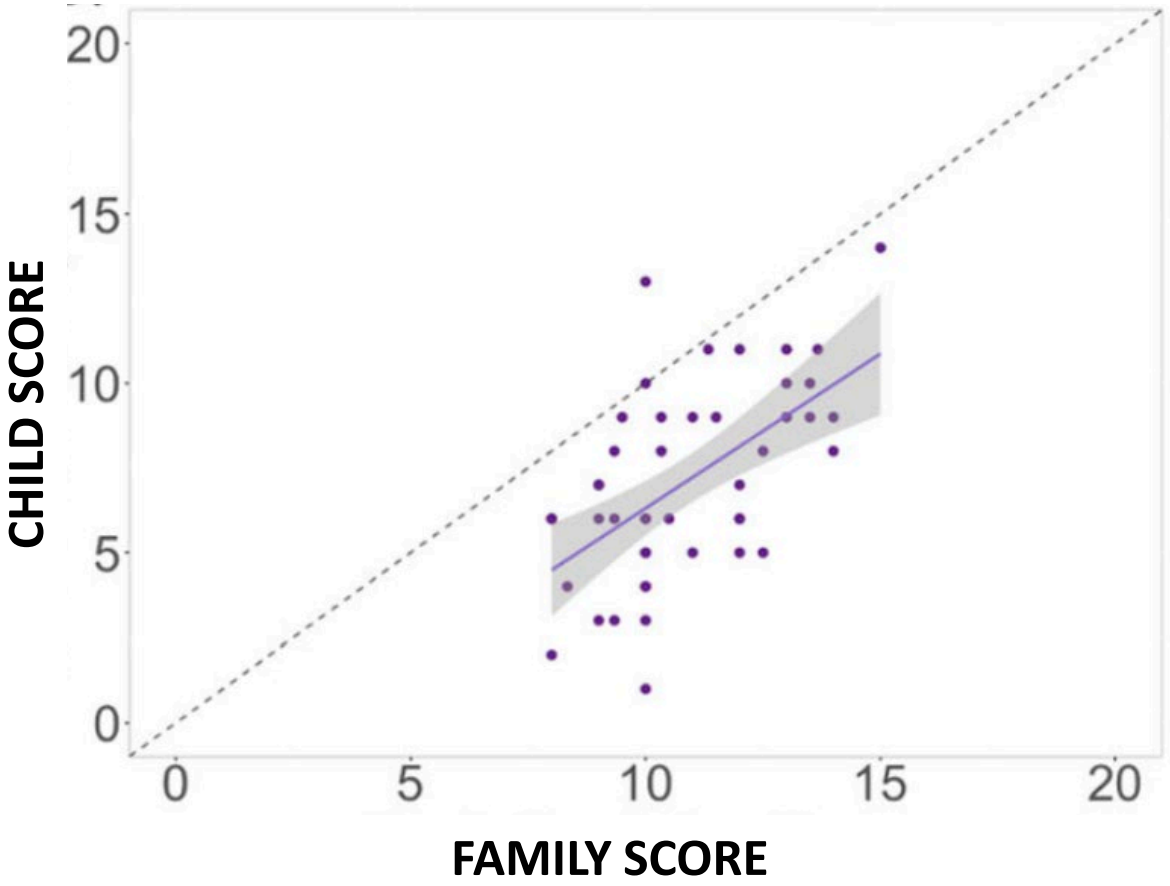
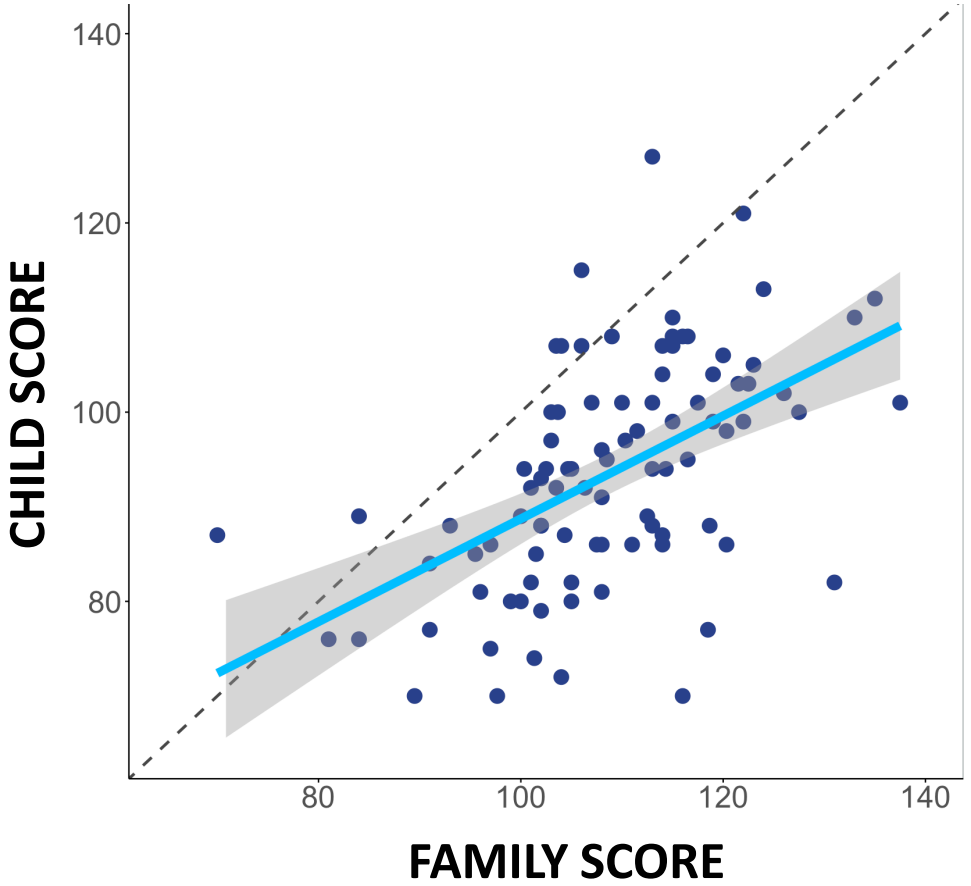


Wilson et al, *JNDD*, 2021

Predicting general cognitive ability in XXY syndrome



Reimer et al, *in preparation*

Can we do any better at predicting how impacted a specific child with an X/Y variation will be?

- So far, it seems that the main outcome that can be predicted from family data in both XYY and XXY syndrome is general cognitive ability
- General cognitive ability is important, but it's only one aspect of development
- Having family data significantly improves prediction, but there is still error
- More work is needed before this methods can be used "in real life"
- Predictions about development are never set in stone - there is lots of room for change
- Knowing who is at risk for more severe outcomes may help target follow-up/care

Which brain systems are most sensitive to X / Y variations ?

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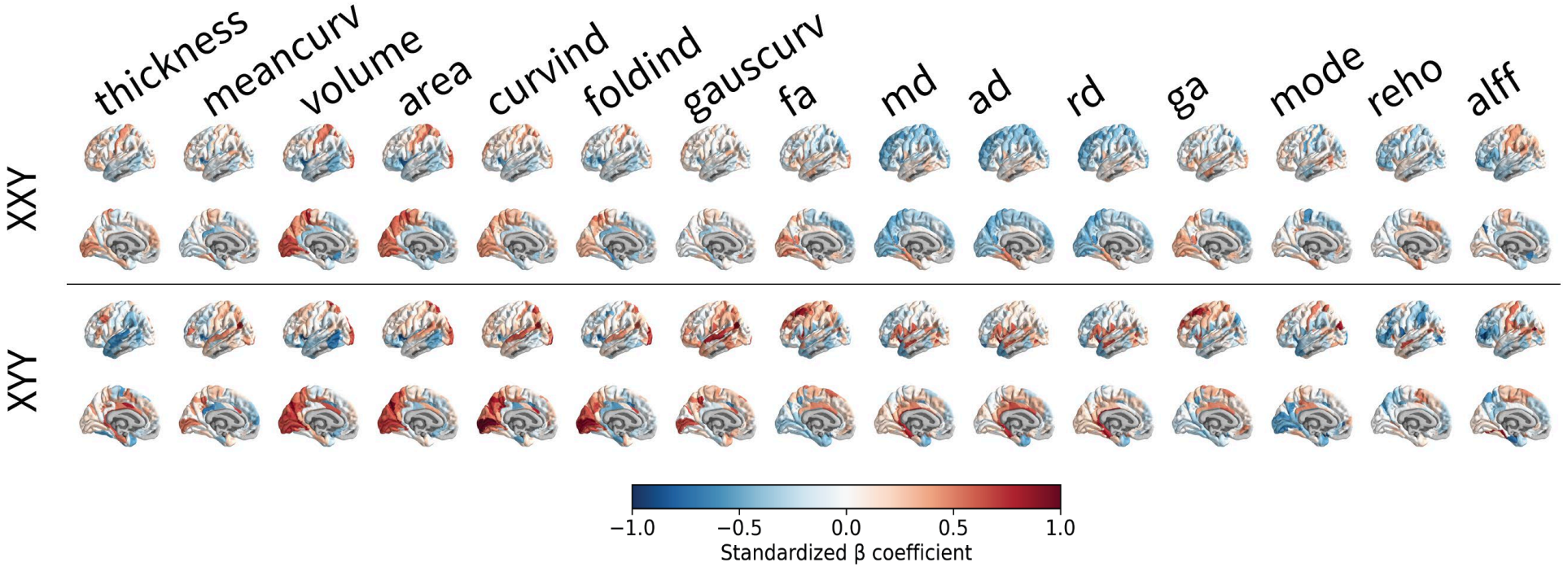

Levitis et al, *Biol Psych, 2024*

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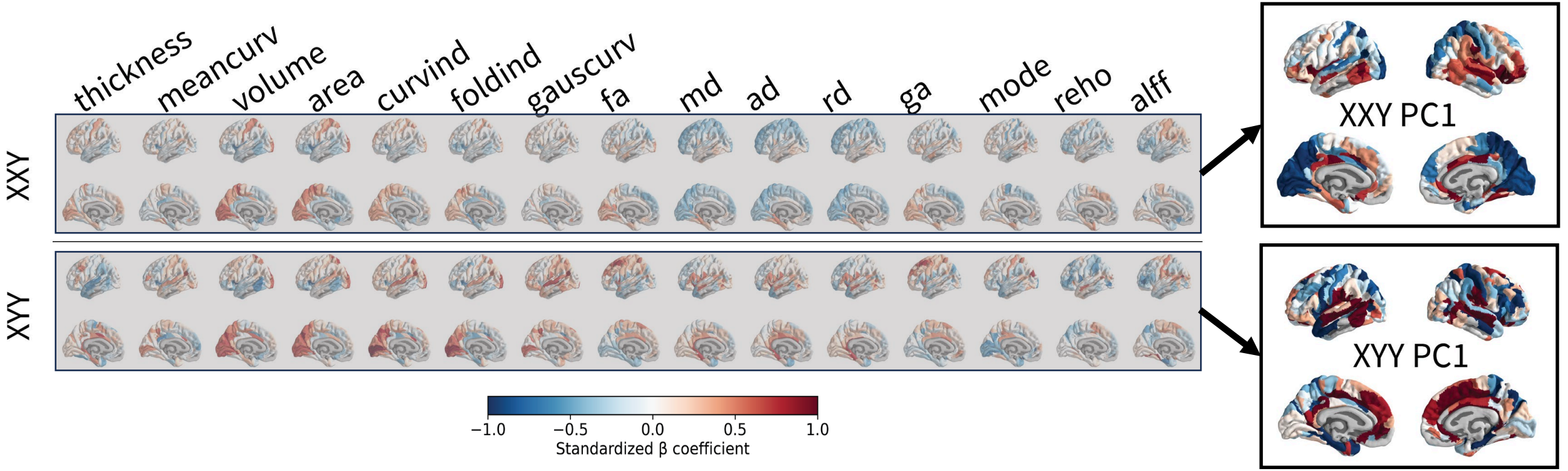

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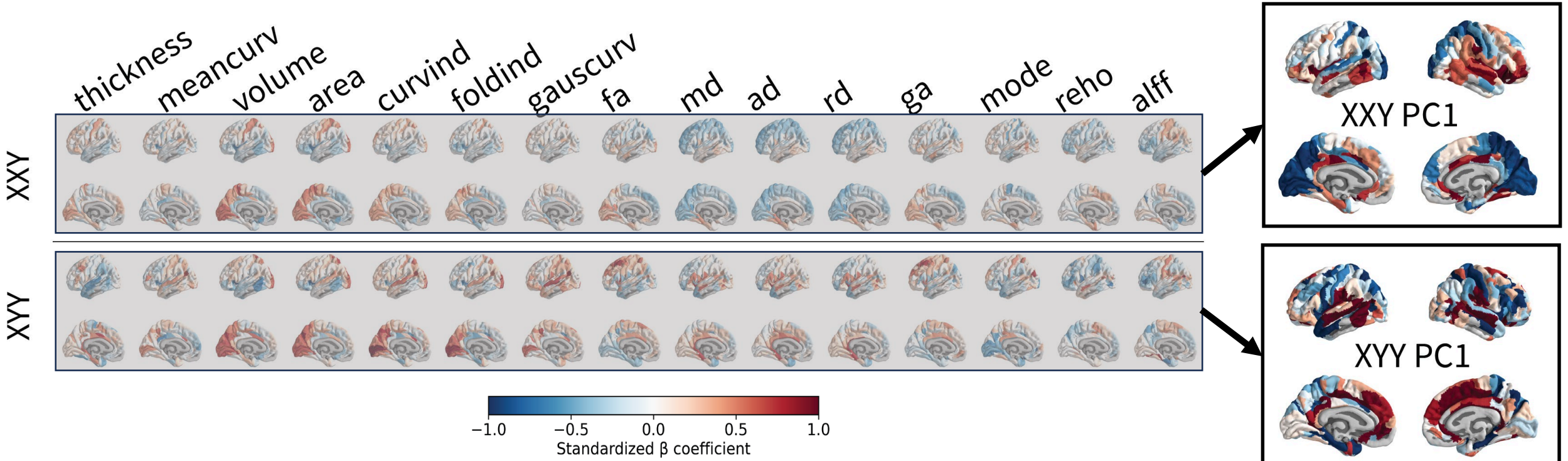

Knowing where these **red** and **blue** brain regions are provides clues into the developmental processes that might make a brain region vulnerable (Timing of development? Genes expressed ? Cell types? Connectivity? …) and how brain changes might influence mental health and cognition

Levitis et al, *Biol Psych, 2024*

Which genes are most sensitive to X / Y variations ?

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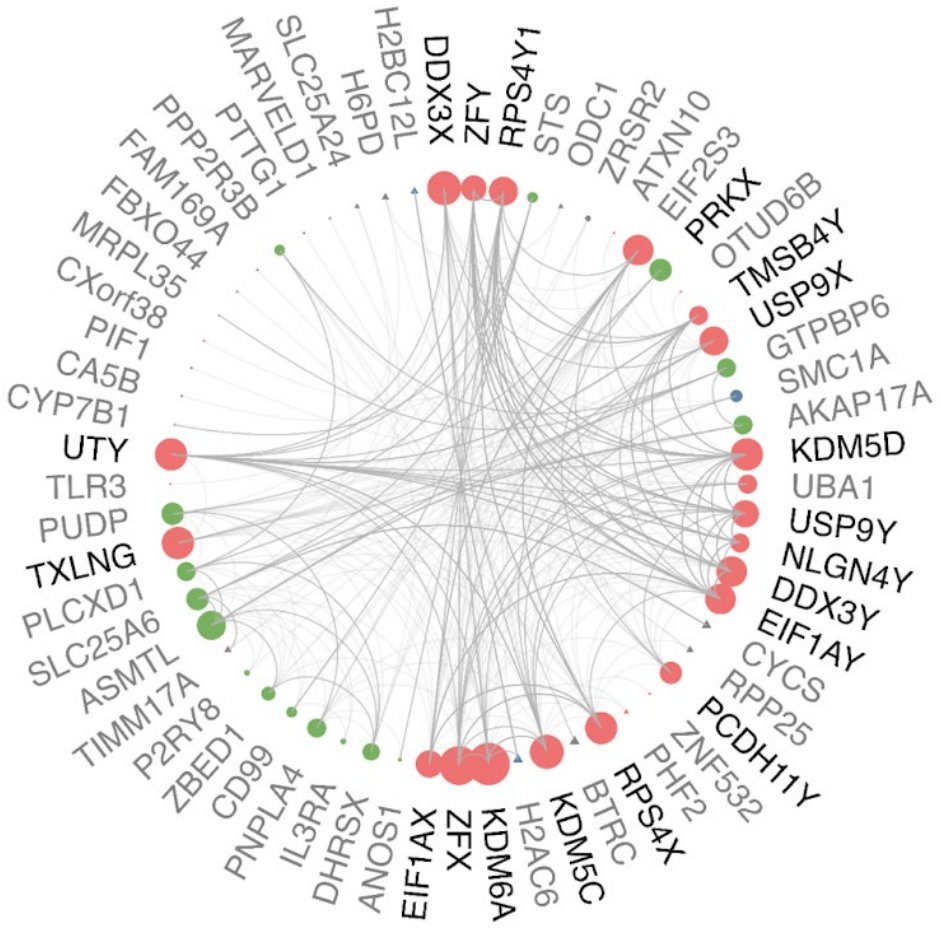
Combining results from previously published studies collectively including >400 individuals



Legue et al, *under review*

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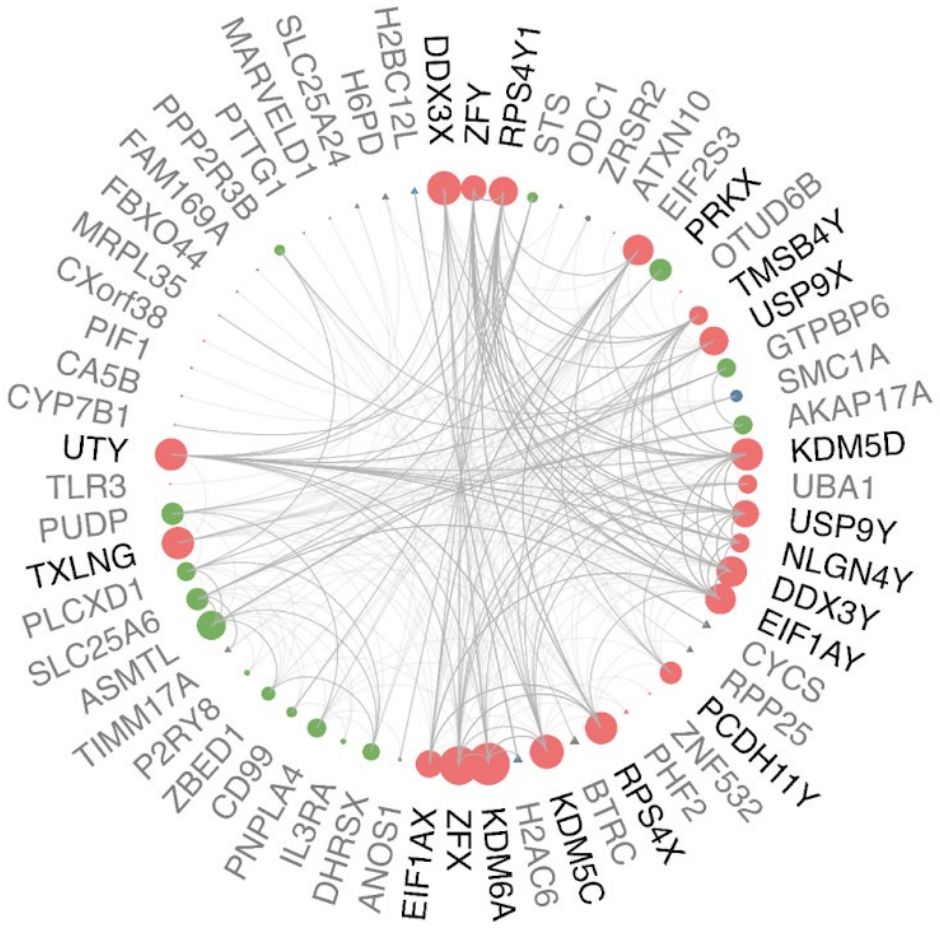
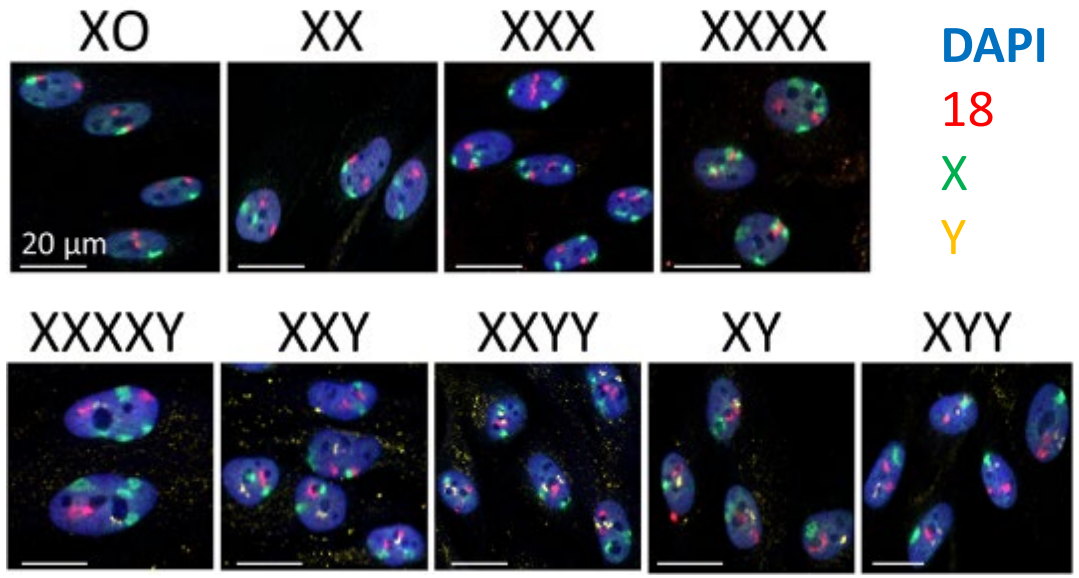
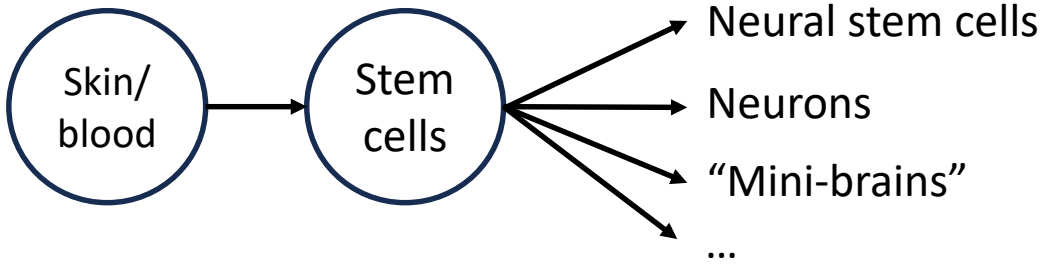


Directly measuring gene expression and regulation in ~100 cell lines from ~50 individuals with varying X/Y counts





Legue et al, *under review*

Liu et al, PNAS, 2023 ; Legue et al, *in preparation*

Summary of research projects underway and planned

- We are now collating all data from our most recent Trisomy X recruitment to detail the mental health, cognitive and brain scan findings in this group
- We will continue to combine clinical, neuroimaging and genomic data across X/Y variation groups – soon adding Trisomy X information to XYY and XXY groups
- We are focusing on genetic and endocrine sources of variable outcomes
- We are excited to be joining forces with multiple other research groups in the X/Y variations field (e.g, GALAXY, NASCARR + European collaborators)

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Dr. Erin Torres
Psychiatric Nurse Practitioner
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Rachel Gore
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Acknowledgments & Thanks

NIH IRP / NIMH

Section on Developmental Neurogenomics (SDN):

Current team: Shara Reimer, Siena Mollerstuen, Bella Larsen, Linh Pham, Liza Levitis, Will Snyder, Hyo Lee, Marcela Legüe, Rebecca Shafee, Erin Torres, Siyuan Liu, Liv Clasen, Francois Lalonde, Zhixiang Liao, Srishti Rau, Jyssica Seebeck, Lauren Kenworthy

Alums: Anastasia Wass, Allysa Warling, Melanie Staszewski, Melissa, Royal, Noemi Banda, Ethan Whitman, Kathleen Wilson, Bridget Mahony, Claire Hanson, Luke Schaffer, Maya Mastronardo, Tiffany Ajumobi, Elisa Guma, Jakob Seidlitz, Alex DeCasien,

Human Genetics Branch: Marlene Lawston, Rachel Smith, Nirmala Akula, Sevilla Detera-Wadleigh, Francis McMahon

Childrens Medical Center, DC
Srishti Rau

UCLA, CA
Daniel Geschwind

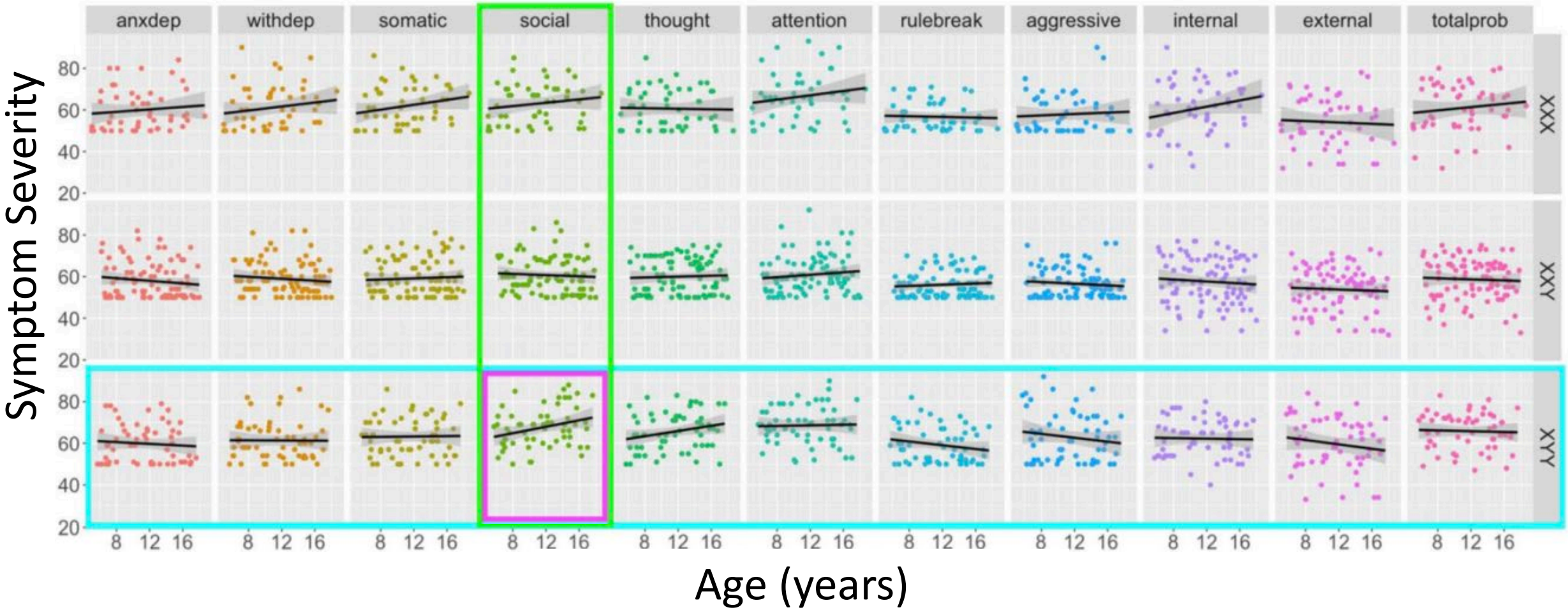
Harvard
David Glahn

Penn / Drexel, PA
Ted Satterthwaite, Taki Shinohara, Dani Bassett, Nancy Lee

UCL, London, UK
Konrad Wagstyl, Danny Alexander

Families in the study

Is there any evidence that the average severity of mental health difficulties could vary over time in each X/Y variation group ?



Roybal et al, *ECAP,* 2025