Cognitive and behavioral development of young children with 47,XXY, 47,XXX and 47,XYY aged 1 to 6 years: first results of the TRIXY study

Sophie van Rijn, PhD| AXYS 2019 Atlanta, USA

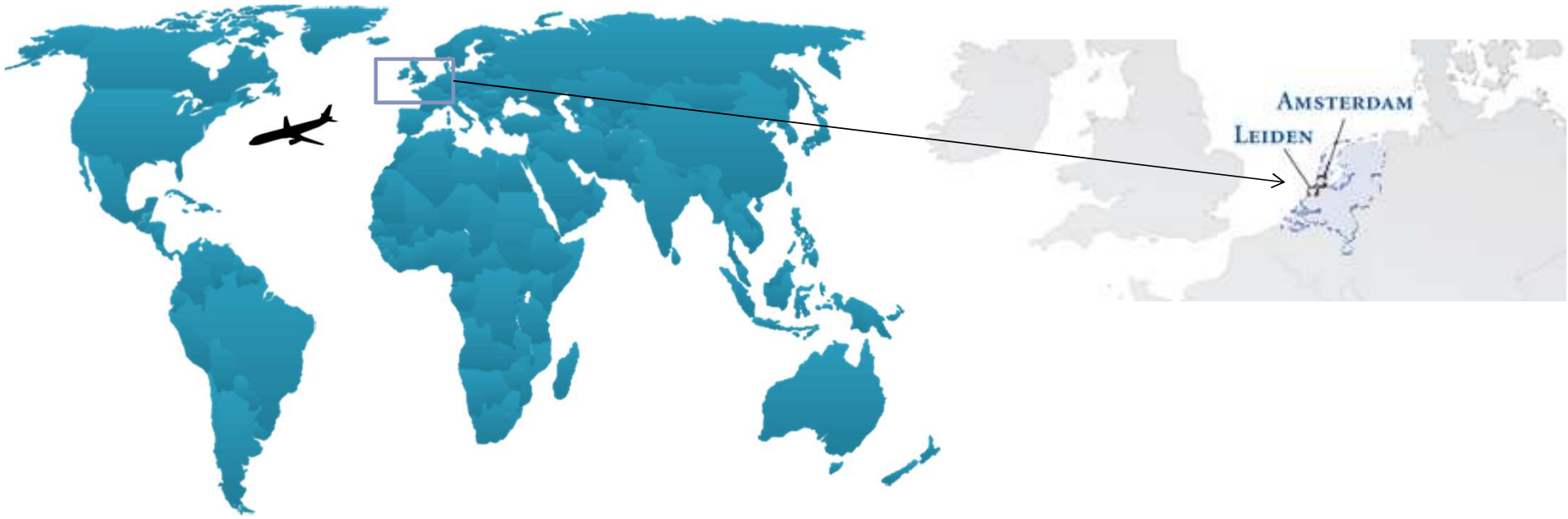
Universiteit Leiden
The Netherlands

Participating in the TriXY study at University of Colorado

LISA CORDEIRO, MS, CSP

University of Colorado
Boulder | Colorado Springs | Denver | Anschutz Medical Campus

Leiden University – The Netherlands

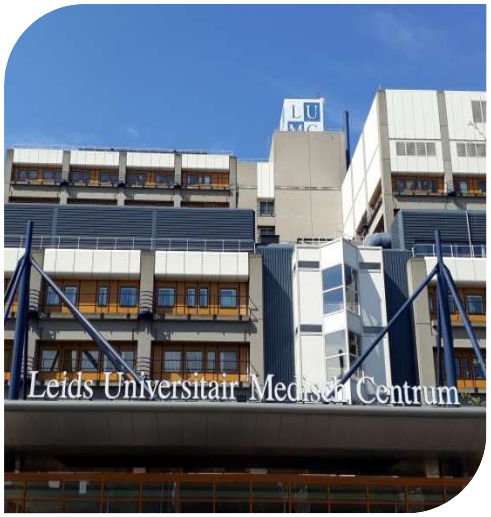


TRIXY Center of Expertise

Trisomy of the X and Y Chromosomes

Clinical Neurodevelopmental Sciences

Treatment and Expertise Center



Academic Medical Center

TRIXY team

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TRIXY Expertisecentrum

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Over ons
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TRIXY is een nationaal expertisecentrum, waar clinici en wetenschappers samen werken in de zorg voor kinderen met X en Y chromosoom trisomieën (47,XXY, 47,XXX en 47,XYY). TRIXY is een samenwerking tussen de Universiteit Leiden en het Leids Universitair Medisch Centrum.

Sociale Wetenschappen
Pedagogische Wetenschappen
TRIXY Expertisecentrum

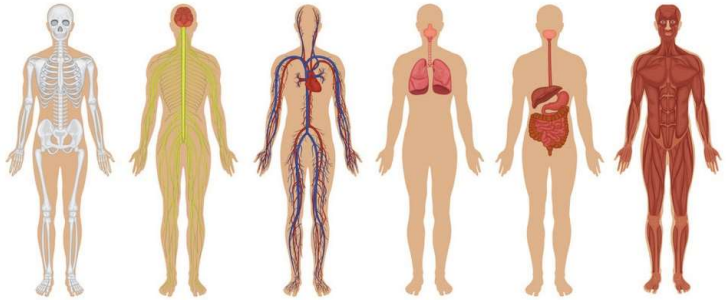
Meer over het TRIXY Expertisecentrum

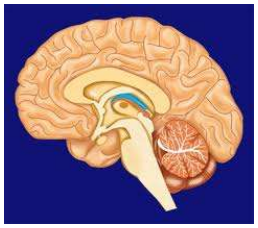
Bestel het TRIXY Handboek ››

Interesse deelname TRIXY Studie? ››

Meld u aan voor het TRIXY Spreekuur ››

Extra X/Y

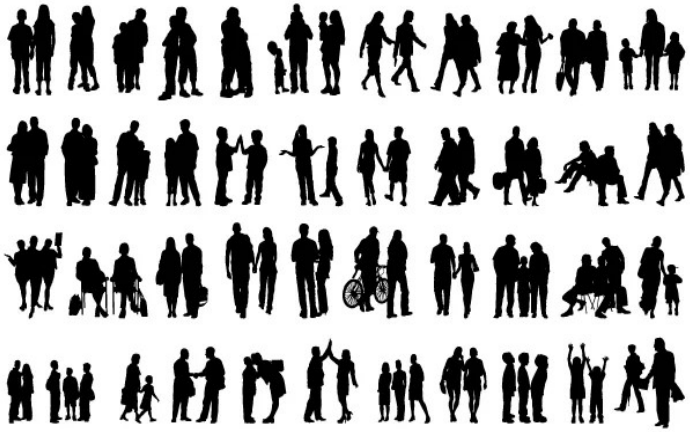




75 % of research focused on physical/medical issues (Pieters et al, 2011)

Studying neurobehavioral development in SCT

- How we adapt to & interact with our environment
- Meeting demands/expectations of society
- Functioning in daily life



➢ Social understanding and responding

➢ Dealing with emotions

education friendship hobby

family love career job

REVIEW

Current Opinion in Psychiatry, March 2019

A review of neurocognitive functioning and risk for psychopathology in sex chromosome trisomy (47,XXY, 47,XXX, 47, XYY)

Sophie van Rijn[a,b]

	general population	XXX	XXY	XYY
ASD	0.6 %	15 %	18 %	30 %
ADHD	7 %	30 %	35 %	36 %
Anxiety	7 %	20 %	27 %	26 %
Depression	13 %	18/54 %	20 %	13 %

➢Language, executive functioning, social cognition, emotion regulation

Risk for social difficulties 8-18 yrs

CBCL (Van Rijn et al, JADD, 2014)	Average (T<65)	Borderline (65<T<70)	Clinical (T>70)
Social problems	58.5 %	24.5 %	17.0 %
Attention problems	71.7 %	9.4 %	18.9 %
Thought problems	62.3 %	22.6 %	15.1 %
Anxious-depressed	71.7 %	15.1 %	13.2 %
Withdrawal	62.3 %	22.6 %	15.1 %
Somatic complaints	73.6 %	9.4 %	17.0 %
Aggressive behavior	84.9 %	11.3 %	3.8 %
Rule breaking behavior	88.7 %	9.4 %	1.9 %

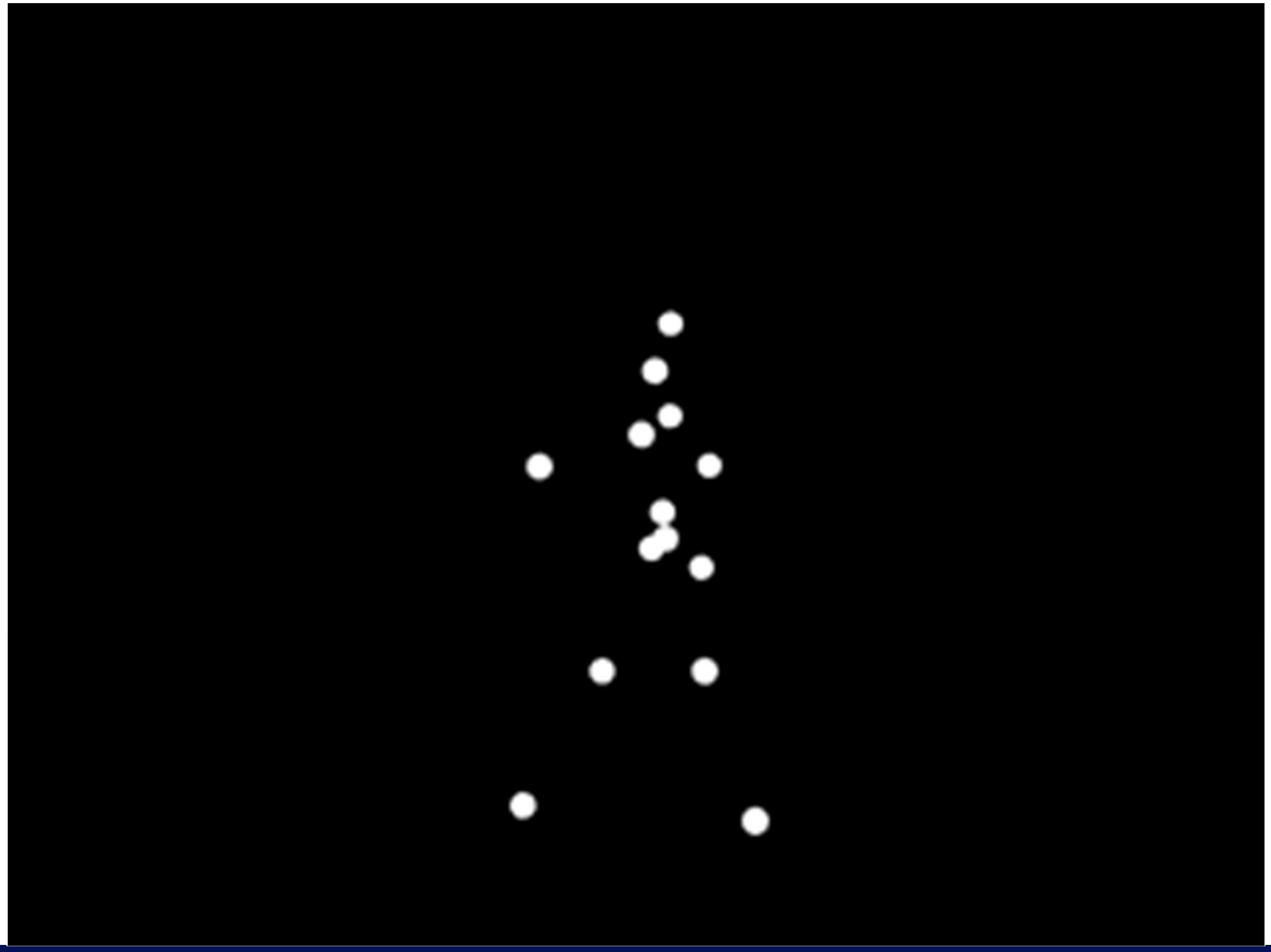
Children with an extra X

n=60

XXX and XXY

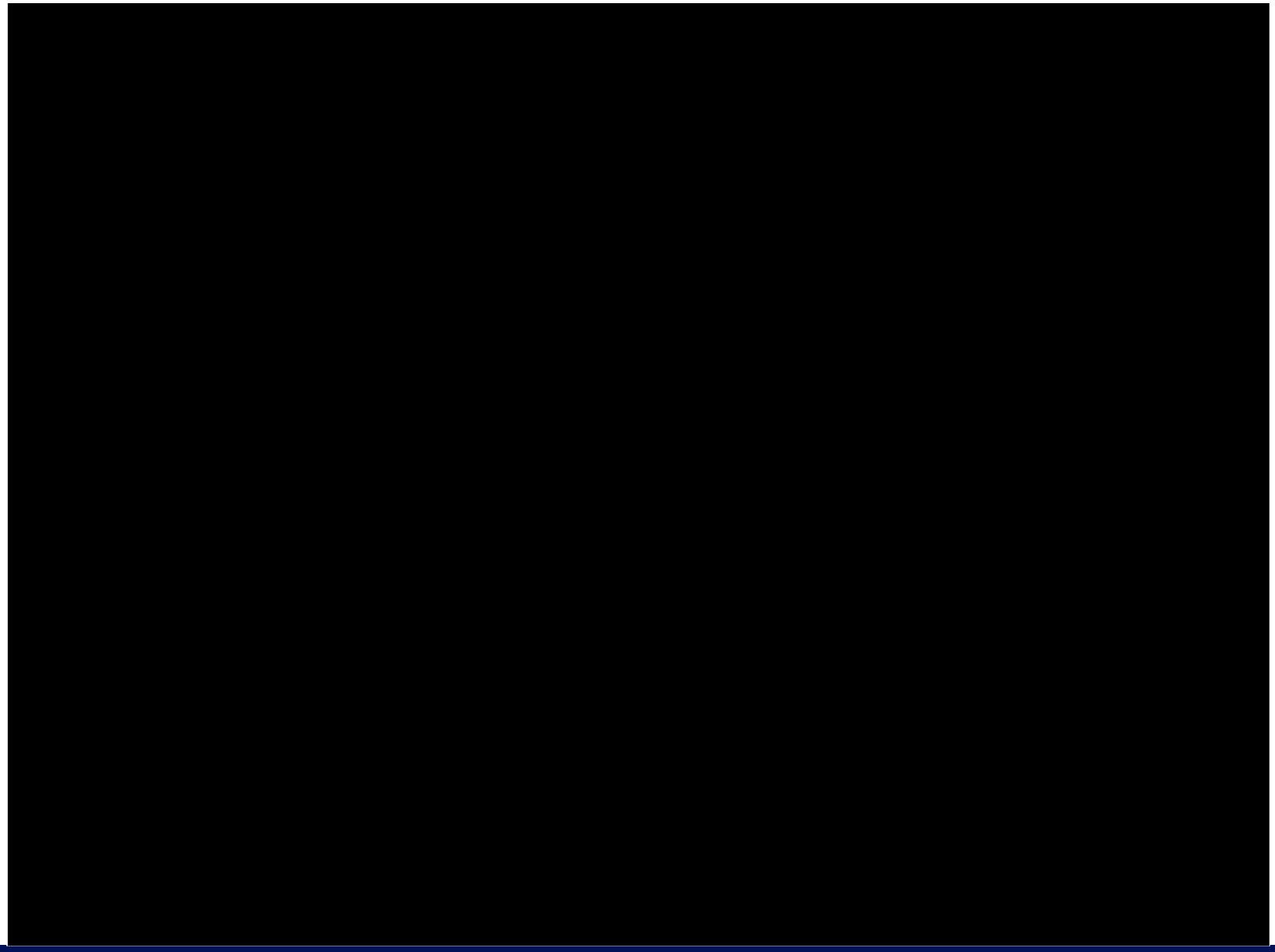
Social behavior anchored in brain development

1. includes automatic, unconscious brain processes



Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
2. very early in development



Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
2. very early in development
3. brain development continues into late 20's

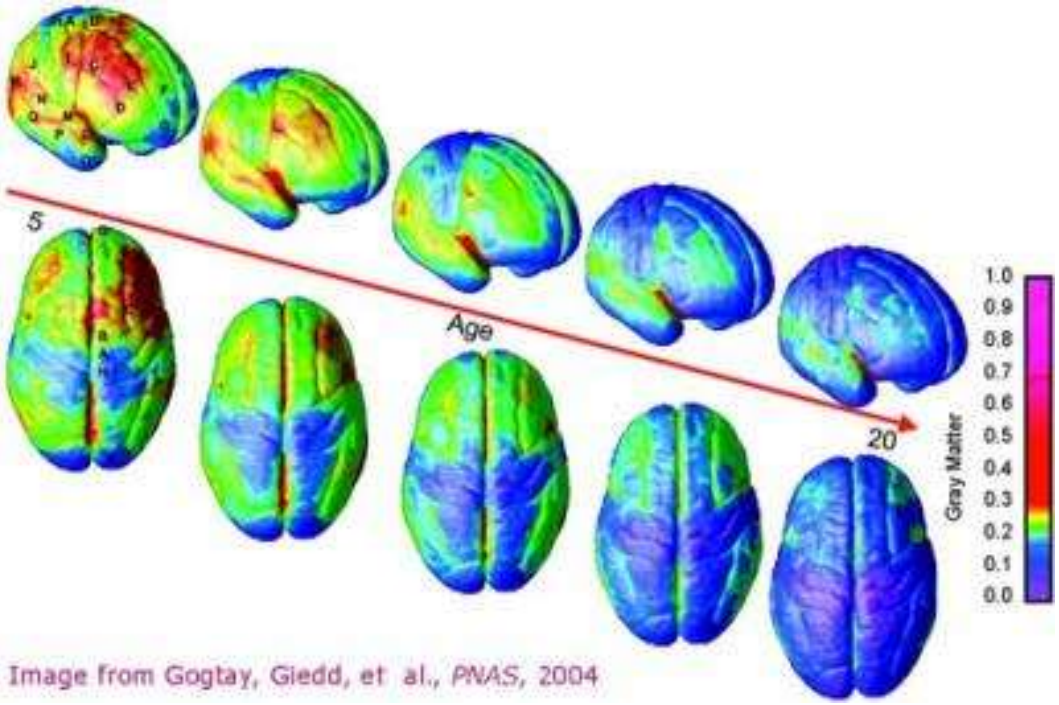
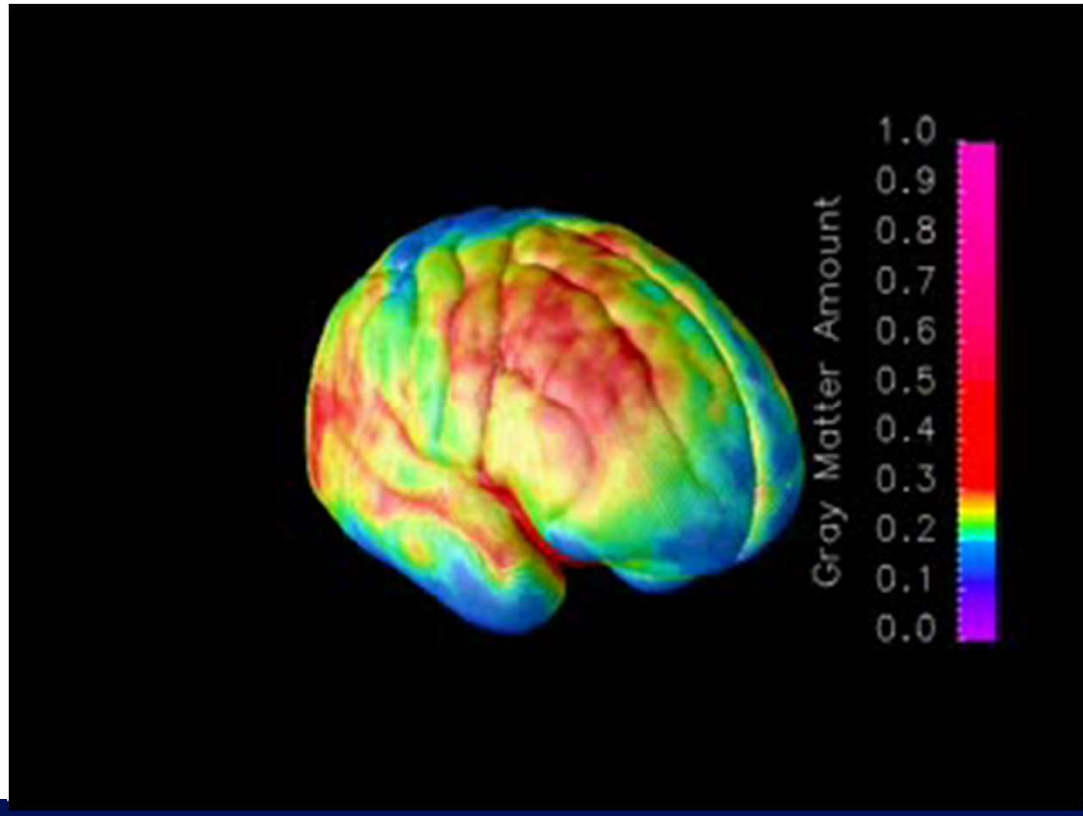


Image from Gogtay, Giedd, et al., *PNAS*, 2004



Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
2. very early in development
3. brain development continues into late 20's
4. it's not all about the (X/Y) genes

Genetics of cognitive ability in 11,000 twin pairs (Haworth, 2009):

50% genetic influences
28% shared environment influences
22% unique environment influences

Extra X or Y chromosome

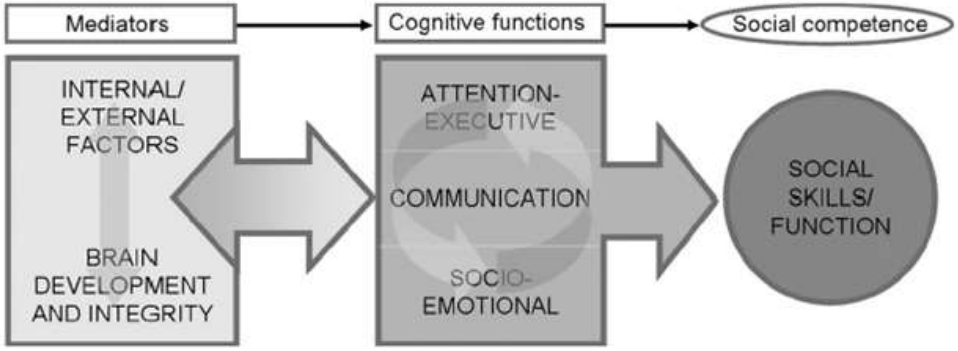
- Environmental influences
- Especially in childhood

Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
2. very early in development
3. brain development continues into late 20's
4. it's not all about the (X/Y) genes

What does this mean?

- Look beyond behaviors: How does the brain process information?



The socio-cognitive integration of abilities model (SOCIAL).

- Look beyond the X and Y chromosomes: environmental influences
- Vulnerabilities at different ages: functions become 'on line'
- Opportunities to positively influence social development
- Earlier support/intervention = better effects

What do we know about early cognitive development in SCT?

- Review article, Clinical Genetics (in press)
- Identifies need for studies focusing on executive functioning, emotion regulation and social cognition


REVIEW

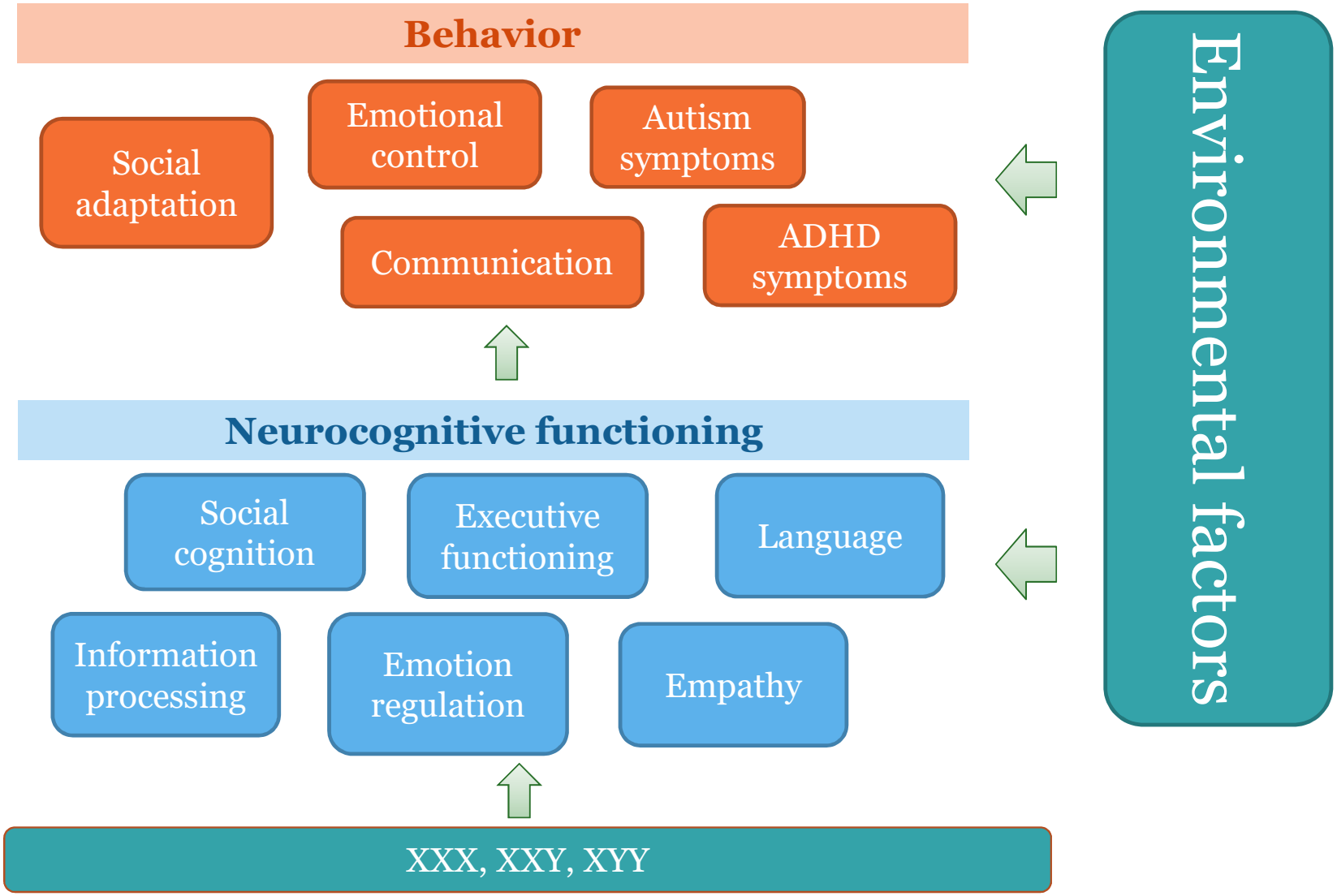
CLINICAL GENETICS WILEY

A review of neurocognitive functioning of children with sex chromosome trisomies: Identifying targets for early intervention

Evelien Urbanus[1,2] | Sophie van Rijn[1,2] | Hanna Swaab[1,2]

The TRIXY study

- 800.000 euro funding in 2016
- XXX, XYY, XXY
- aged 1 to 6 years
- Longitudinal study
- Based at Leiden University
- Collaboration with all academic medical centers in NL and BE
- TRIXY Partner site: XtraordinarY kids clinic, Denver CO


Behavior
Social adaptation
Emotional control
Autism symptoms
Communication
ADHD symptoms
Neurocognitive functioning
Social cognition
Executive functioning
Language
Information processing
Emotion regulation
Empathy
XXX, XXY, XYY
Environmental factors

Behavior

- Questionnaires
- Systematic observations

Cognitive tests

Social perception: Eyetracking

Emotion regulation: Arousal markers in heart rate

Environmental factors

- Life events
- Stress
- Socio-economic status
- Parenting styles
- Family functioning

TRIXY study – update June 2019

SCT group:	71 children
Control group:	74 children
SCT variations:	23 children with XXX
	36 children with XXY
	12 children with XYY
Age groups:	20 children with SCT aged **1-2** years
	51 children with SCT aged **3-6** years

Recruitment:

- 55 % active follow-up/monitoring after prenatal diagnosis
- 24 % interested in research (study flyer / support groups)
- 21 % in clinical care because of physical/medical issues
- 5 % in clinical care because of neurobehavioral issues

Diagnosis

Time of diagnosis: 63 % prenatal diagnosis

37 % postnatal diagnosis

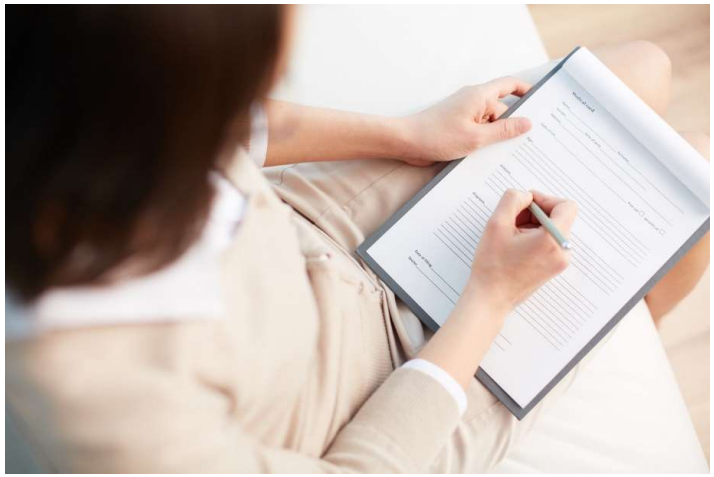
Postnatal diagnosis:

Who first became concerned or suspected SCT?

52 % parents

18 % physicians

30 % other



Received interventions/support

Has your child ever received psychological and/or developmental evaluations?

65 % yes

35 % no

Received interventions/support in SCT group:

49 % speech-language therapist

38 % early intervention

32 % physical therapy

30 % developmental pediatrician

23 % occupational therapy

13 % special education

XXY group: 55 % ever received testosterone supplements (almost all < 1 year)

Top 10 behavior observations of parents

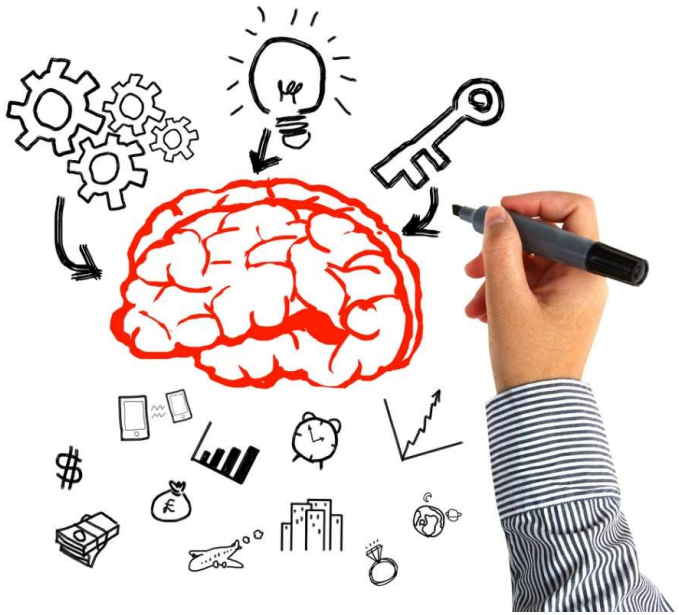
Does your child currently have, or had in the past, any of the following behaviors on a regular basis?

54 %	Tamper tantrums
33 %	Shy
31 %	Short attention span/distractable
27 %	Bothered by things touching him / her
23 %	Immature
21 %	Resistance to change in routines
17 %	Anxiety
15 %	Poor eye contact
14 %	Impulsive
13 %	Moodiness

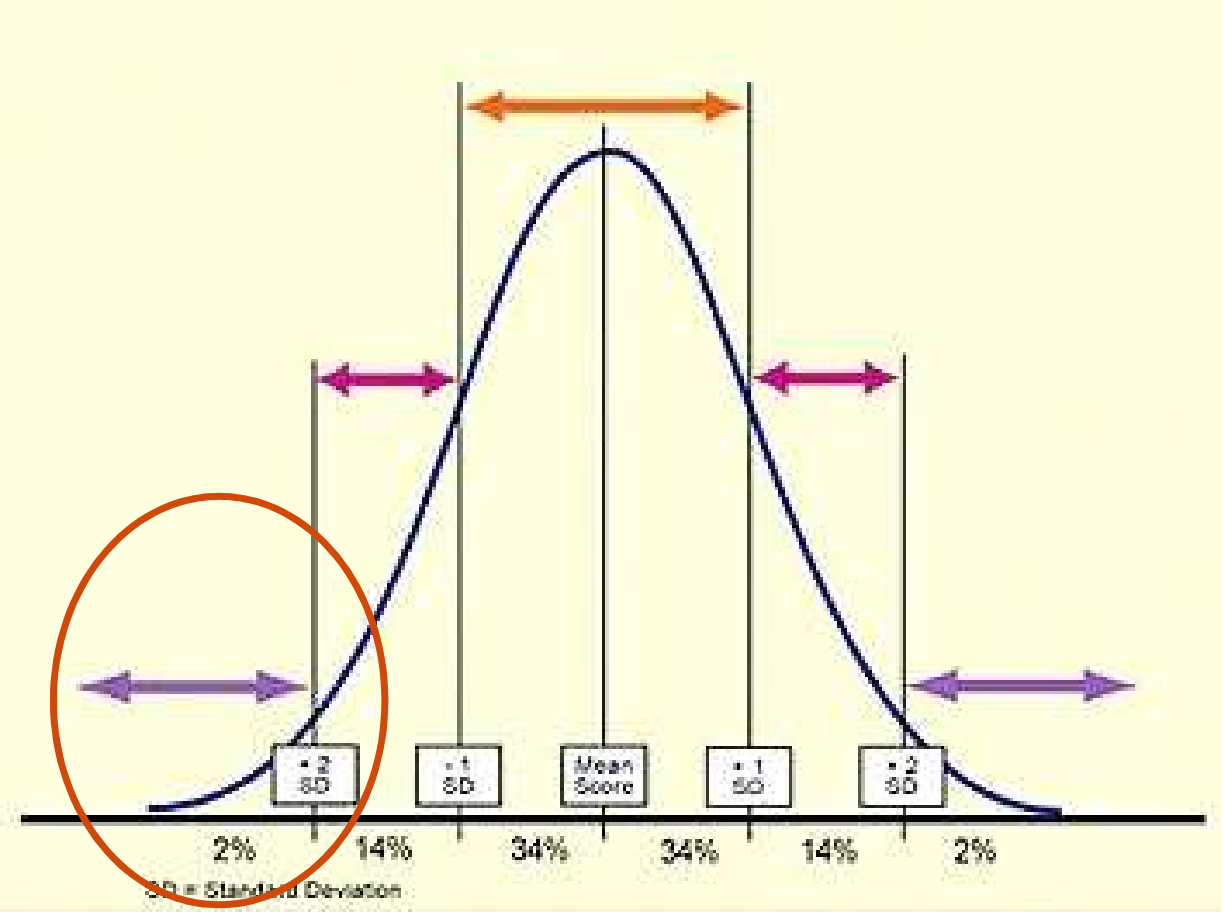
Important themes: Emotional control, social development, executive functioning

What is executive functioning?

- flexibly shift the mind in response to changing demands
- inhibit irrelevant or inappropriate thoughts and actions
- organize thoughts, behaviors, and emotions in a goal-directed way when faced with complex and dynamic environments



Cognitive and behavioral risks



Risk for behavioral difficulties 1-6 yrs

CBCL	Average (T<65)	Borderline (65<T<70)	Clinical (T>70)	Different from control group?
Emotionally reactive*	77 %	18 %	5 %	yes (p = 0.037)
Withdrawn*	83 %	6 %	11 %	yes (p < 0.001)
Somatic complaints	84 %	13 %	3 %	yes (p = .008)
Anxious-depressed*	88 %	6 %	5 %	yes (p < 0.001)
Attention problems				no
Sleep problems				no
Aggressive behavior*				no

No significant differences between XXX, XXY and XYY

* Also significantly different in the 'active follow up' SCT group vs control group

DSM scales 1-6 yrs

CBCL	Average (T<65)	Borderline (65<T<70)	Clinical (T>70)	Different from control group?
Pervasive developmental problems*	71 %	11 %	18 %	yes ($p < 0.001$)
Affective problems*	87 %	5 %	8 %	yes ($p < 0.001$)
Anxiety problems*	87 %	2 %	11 %	yes ($p = 0.014$)
Oppostional defiant problems				no
Attention problems				no

No significant differences between XXX, XXY and XYY

* Also significantly different in the 'active follow up' SCT group vs control group

Social behavior

Social Responsiveness Scale	Average (T<65)	Mild range (65<T<70)	Clinical range (T>70)	Different from control group?
Social awareness	74 %	16 %	10 %	yes ($p < 0.001$)
Social cognition	66 %	10 %	24 %	yes ($p = 0.026$)
Social communication	72 %	12 %	16 %	yes ($p = 0.001$)
Social motivation	74 %	10 %	16 %	yes ($p < 0.001$)
Restricted interests and repetitive behaviors	84 %	10 %	6 %	yes ($p < 0.001$)

Behavior: Taken together

- No differences between XXX, XXY, XYY
- So far: no evidence for ADHD symptoms at this age
- Across the 1-6 age range: Social and emotional development should be evaluated/monitored
- 1-2 & 3-6 year olds with SCT more 'emotionally reactive' in comparison to control group
- Targets for support based on neurocognitive profile

Neurocognitive tests

Global intelligence

1-2 year olds:

Bayley	Cognitive	Language*	Motor
Control	97	107	96
SCT	100	92	92

3-6 year olds:

WIPPSI	FSIQ*	VIQ*	PIQ*
Control	107	109	105
SCT	96	96	95

No significant differences between XXX, XXY and XYY

Language (NEPSY, PPVT) 3-6 yrs

- Phonological processing in SCT:
  no significant differences from control group

- Receptive language in SCT:
  no significant differences from control group

- Expressive language:
  lower scores in SCT (p=0.04)

No significant differences between XXX, XXY and XYY

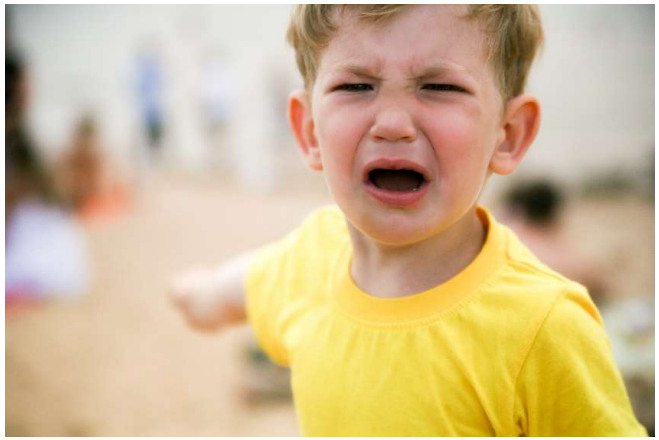
Social cognition (NEPSY) 3-6 yrs

Affect recognition in SCT: no significant differences from control group

Perspective taking (Theory of mind, understanding believes, intentions of others)

Lower scores in SCT ($p = 0.001$)

- 32 % moderate problems
- 3 % severe problems



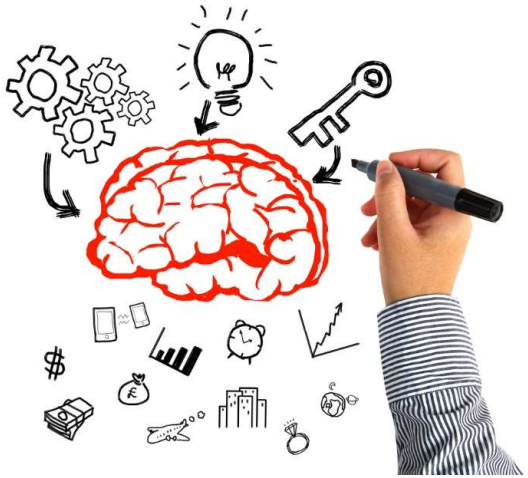
No significant differences between XXX, XXY and XYY

Executive functioning (BRIEF) 3-6 yrs

	Borderline range	Clinical range	Different from control group?
Emotional control	26 %	17 %	yes ($p < 0.001$)
Shifting	29 %	9 %	yes ($p = 0.01$)
Planning/organizing	26 %	9 %	Borderline
Working memory			no
Inhibition			no

No significant differences between XXX, XXY and XYY

Cognitive mechanisms



Children with tamper tantrums:

Language: n.s.

Social cognition: n.s.

Executive functioning: more problems in flexibility and inhibition

Children showing 'emotionally reactive' behaviors:

Language: lower verbal IQ, but not expressive/receptive language

Social cognition: n.s.

Executive functioning: more problems in flexibility, inhibition and working memory

Neurocognition: Taken together

- No differences between XXX, XXY, XYY
- Language development vulnerable from an early age
- At age 3-6 yrs: executive functioning and social cognition also important targets in addition to language
- Neurocognitive risks in 1-2 yr olds…?
- Problems in executive functioning (flexibility/inhibition) may contribute to emotional ‘outbursts’
- Self-regulation/emotion regulation is important to support from an early age

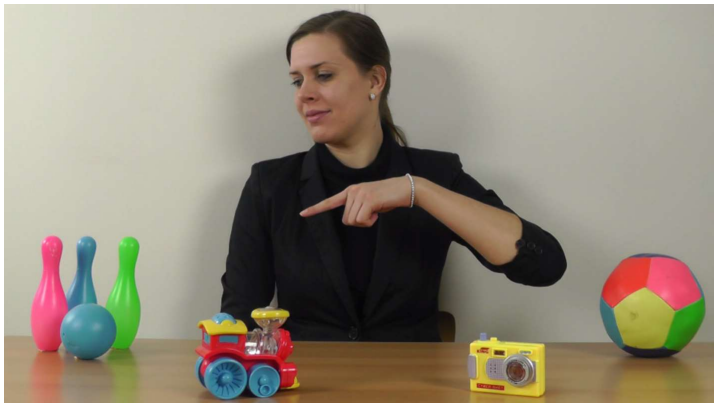
What's next?

Mechanisms of emotion regulation:

- (precursors of) executive functioning
- Arousal regulation, based on heart rate
    - unexpected events
    - when frustrated
    - in response to (emotions of) others

Mechanisms of social behavior:

- Recognizing and understanding emotional expressions of others
- Empathy (emotional sharing)
- Following social gaze (including joint attention)
- Attention to social cues: social orienting
- Perspective taking (theory of mind)



Proactive, preventive, early intervention!

- Preventive intervention study in The Netherlands
- Early stimulation of socio-emotional development
- Age 3 to 8 yrs
- Home-based DVD training program, daily for 4 weeks
- Pre-post measurements eyetracking + social cognition tests

We thank all participating families!

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Participating in

at University of Colorado

LISA CORDEIRO, MS, CSP

University of Colorado
Boulder | Colorado Springs | Denver | Anschutz Medical Campus

eXtraordinarY Kids Clinic

trixy@ucdenver.edu

Study Visits…

University of Colorado, Medical Campus in Aurora, CO in a family-friendly environment

can be coordinated with clinical evaluations at the eXtraordinarY Kids Clinic

in-person feedback of results, followed by research summary report

scheduled for 1.5 – 2 days

funding for lodging and airfare

What is our schedule like?

DAY 1: (~9:00am – 3:00pm)

- Play-based assessments
- *Break*
- Developmental Testing
- *Lunch*
- Play-based assessments
- *Break*
- Practice physiology
- Interviews with parent (child can nap or play)

DAY 2: (~9:00am – 3:00pm)

- Developmental Testing
- *Break*
- Play-based assessment
- *Break*
- Eye-tracking & Physiology w/videos
- *Lunch*
- Finish any remaining assessments
- Feedback with Dr. Nicole Tartaglia

Sample schedule – we strive to accommodate the child's sleep & feeding needs, family travel and other evaluations, as appropriate.

What should I expect?

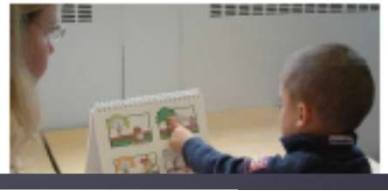
What to Expect as part of the TRIXY study

There are 4 broad categories of tasks included in this study:

1. Cognitive & play-based tasks
2. Physiology during unexpected events
3. Eye-tracking (looking behavior) & Physiology while watching video clips
4. Questionnaires/interview for parents to complete

Cognitive & Play-based tasks

One of the researchers will sit down with your child to do a range of different cognitive tests in areas of language, social cognition and executive functioning, depending on your child's age. We use testing materials that have been developed for young children and that are often used by neuropsychologists or clinical psychologists. The tests have been designed to look like fun games, and typically involve materials that are also part of your child's daily life such as toys, books, or blocks. Researchers typically start with introducing what they will ask your child to do, accommodating to your child's age and level of language and abilities. Before starting the test, your child can practice first, to make sure (s)he feel comfortable with the materials. The researchers will record your child's scores. During some tests a video camera will record your child's responses, so that we can evaluate this in more detail afterwards.



How can I prepare my child for the visit?

What Families Tell Us…

"I wanted to say Thank You again for all of your help. It meant a lot to come out here and to have someone like you take care of us. What you have done is truly appreciated!"

mother of 4 year old girl with Trisomy X

"Hi Lisa- Just wanted to thank you & the rest of the team for an incredible visit to Denver last week. [Our son] had such a blast and it was wonderful to know that we had a team of great people who are just as invested in their well-being."

mother of 5 year old boy with XXY

"Lisa- Thanks to you and your team for a great visit. We feel very thankful to have your help."

mother of 6 year old boy with XXY

"[Our son] was so sad to leave you all. I don't think I have ever seen him show such emotion like that before. Thank you all SO much for making him feel comfortable and I hope this is see you later and not goodbye! We can't wait until next year!"

mother of 3 year old boy with XXY

"Hi Lisa- A VERY overdue THANK YOU for your time and for including my son in the TriXY study. He had an absolute ball with you and your team, rather than feeling like a patient. My family is so thankful for your team and all the effort you are putting into learning more about XYY and children with chromosomal abnormalities. I can't even begin to tell you how refreshing it was to walk away from our weekend at the eXtraordinarY kids clinic feeling heard and understood, and full of insightful information. I can only hope that in the future, more parents can leave a doctor's office having spoken to a medical professional who understands XYY and knows something about it, thanks to the efforts you all are putting in. We are looking forward to our visit back next year...Hope you are doing well and looking forward to our next visit in Colorado, laughing with you again."

mother of 19 month old boy with XXY

Thank you to all of the wonderful families who have participated!

Enrollment ends Summer 2019!

- Ages 12 – 23 months with XYY or Trisomy X
- Ages 3 years – 6 years with XYY or Trisomy X

University of Colorado
Boulder | Colorado Springs | Denver | Anschutz Medical Campus

eXtraordinarY Kids Clinic

TRIXY

trixy@ucdenver.edu