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
Participating in the TriXY study at University of Colorado

LISA CORDEIRO, MS, CSP
Leiden University – The Netherlands

Discover the world at Leiden University
TRIXY Center of Expertise
Trisomy of the $X$ and $Y$ Chromosomes

Clinical Neurodevelopmental Sciences

Treatment and Expertise Center

Academic Medical Center

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TRIXY Expertisecentrum

TRIXY is een nationaal expertisecentrum, waar cliënt 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.

Meer over het TRIXY Expertisecentrum

Bestel het TRIXY Handboek ➞
Interesse deelname TRIXY Studie? ➞
Meld u aan voor het TRIXY Spreekuur ➞
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**

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

_Sophie van Rijn*<sup>a,b</sup>

<table>
<thead>
<tr>
<th></th>
<th>general population</th>
<th>XXX</th>
<th>XXY</th>
<th>XYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>0.6 %</td>
<td>15 %</td>
<td>18 %</td>
<td>30 %</td>
</tr>
<tr>
<td>ADHD</td>
<td>7 %</td>
<td>30 %</td>
<td>35 %</td>
<td>36 %</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7 %</td>
<td>20 %</td>
<td>27 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Depression</td>
<td>13 %</td>
<td>18/54 %</td>
<td>20 %</td>
<td>13 %</td>
</tr>
</tbody>
</table>

➢ Language, executive functioning, social cognition, emotion regulation
## Risk for social difficulties 8-18 yrs

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

Children with an extra X
n=60
XXX and XXY

Discover the world at Leiden University
Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
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Social behavior anchored in brain development

1. includes automatic, unconscious brain processes
2. very early in development
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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
Discover the world at Leiden University
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?

• 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

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

Evelien Urbanus\textsuperscript{1,2} | Sophie van Rijn\textsuperscript{1,2} | Hanna Swaab\textsuperscript{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
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XXX, XXY, XYY

Environmental factors

Neurocognitive functioning
- Social cognition
- Executive functioning
- Language
- Information processing
- Emotion regulation
- Empathy

Behavior
- Social adaptation
- Emotional control
- Autism symptoms
- Communication
- ADHD symptoms

XXX, XXY, XYY
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

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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

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

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

<table>
<thead>
<tr>
<th>CBCL</th>
<th>Average (T&lt;65)</th>
<th>Borderline (65&lt;T&lt;70)</th>
<th>Clinical (T&gt;70)</th>
<th>Different from control group?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pervasive developmental problems*</td>
<td>71 %</td>
<td>11 %</td>
<td>18 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Affective problems*</td>
<td>87 %</td>
<td>5 %</td>
<td>8 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Anxiety problems*</td>
<td>87 %</td>
<td>2 %</td>
<td>11 %</td>
<td>yes (p = 0.014)</td>
</tr>
<tr>
<td>Oppostional defiant problems</td>
<td></td>
<td></td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>Attention problems</td>
<td></td>
<td></td>
<td></td>
<td>no</td>
</tr>
</tbody>
</table>

No significant differences between XXX, XXY and XYY

* Also significantly different in the ‘active follow up’ SCT group vs control group
## Social behavior

<table>
<thead>
<tr>
<th>Social Responsiveness Scale</th>
<th>Average (T&lt;65)</th>
<th>Mild range (65&lt;T&lt;70)</th>
<th>Clinical range (T&gt;70)</th>
<th>Different from control group?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social awareness</td>
<td>74 %</td>
<td>16 %</td>
<td>10 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Social cognition</td>
<td>66 %</td>
<td>10 %</td>
<td>24 %</td>
<td>yes (p = 0.026)</td>
</tr>
<tr>
<td>Social communication</td>
<td>72 %</td>
<td>12 %</td>
<td>16 %</td>
<td>yes (p = 0.001)</td>
</tr>
<tr>
<td>Social motivation</td>
<td>74 %</td>
<td>10 %</td>
<td>16 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Restricted interests and repetitive behaviors</td>
<td>84 %</td>
<td>10 %</td>
<td>6 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Language*</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bayley</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>97</td>
<td>107</td>
<td>96</td>
</tr>
<tr>
<td>SCT</td>
<td>100</td>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>

#### 3-6 year olds:

<table>
<thead>
<tr>
<th></th>
<th>FSIQ*</th>
<th>VIQ*</th>
<th>PIQ*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WIPPSI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>107</td>
<td>109</td>
<td>105</td>
</tr>
<tr>
<td>SCT</td>
<td>96</td>
<td>96</td>
<td>95</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Borderline range</th>
<th>Clinical range</th>
<th>Different from control group?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional control</td>
<td>26 %</td>
<td>17 %</td>
<td>yes (p &lt; 0.001)</td>
</tr>
<tr>
<td>Shifting</td>
<td>29 %</td>
<td>9 %</td>
<td>yes (p = 0.01)</td>
</tr>
<tr>
<td>Planning/organizing</td>
<td>26 %</td>
<td>9 %</td>
<td>Borderline</td>
</tr>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>Inhibition</td>
<td></td>
<td></td>
<td>no</td>
</tr>
</tbody>
</table>

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)
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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!

srijn@fsw.leidenuniv.nl
www.trixyexpertisecentrum.nl
Participating in

TRIXY

at University of Colorado

LISA CORDEIRO, MS, CSP
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 scheduled for 1.5 – 2 days.

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

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?

**Play Time**
Now me and Nana will sit on the floor and play. I can play with any toys I want! We will play for about 15 minutes.

**Play Time with Mom or Dad**
1. First I will sit on the floor and play with mom or dad.
2. Now me and mom or dad will do a puzzle!
What Families Tell Us...

"Hi Lisa- Just wanted to thank you & the rest of the team for an incredible visit to Denver last week. [Our son] hadn't been to a place like this before. He had so much fun at the TriXY study. What you have done is truly appreciated.

Hope this is see you later...not invested in being into learning more about XYY and children with chromosomal abnormalities...can't even begin to tell you how refreshing it was to walk away from our weekend at the xY 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 5 year old boy with XXY

"Lisa- Thanks to you and your team for a great visit. We feel very thankful to have your care including my son in the TriXY study. 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.

My son had an absolute ball with you and your team and felt like a patient rather than a subject in your study. We can't wait to see you later...not invested in being into learning more about XYY until next year!"

mother of 3 year old boy with XXY

"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 to think of if you believe your child has something like XYY. What you have done is truly appreciated!

mother of 4 year old girl with Trisomy X

"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 don't think I've ever seen him show such emotion like that before! Thank you so much for making him feel comfortable and understood!"

mother of 19 month old boy with XYY

"Our song was to say thank you all... We can't wait to see you again...not invested in being into learning more about XYY until next year!"

mother of 3 year old boy with XXY

"Hi Lisa- Thanks to you and the rest of the team for an incredible visit to Denver last week. [Our son] hadn't been to a place like this before. He had so much fun at the TriXY study. What you have done is truly appreciated.

Hope this is see you later...not invested in being into learning more about XYY and children with chromosomal abnormalities...can't even begin to tell you how refreshing it was to walk away from our weekend at the xY 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 XYY
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