Developmental risks in children with an extra X chromosome

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In 2009, the government has awarded a grant to Sophie van Rijn to study the developmental risks in children with an extra X chromosome. Our overall aim was to share more complete and thorough knowledge about the impact of an extra X on development with parents and professionals in the health care services. In this way, we hope that children and children with an extra X chromosome can benefit from our scientific research. The study, of which the results are presented in this newsletter, has been completed in 2012. Apart from this specific study, we conduct more research on Klinefelter syndrome and Triple X syndrome. Recently, we have started new research projects to answer new questions that have raised as a result of the study we present here.

The studied group:
A total of 60 children and children with an extra X chromosome have taken part in the study. They were between 8 and 18 years of age at time of the study. The group included 25 girls with an extra X and 35 boys with an extra X chromosome. Thirty-two of the 60 children were brought in contact with us with help of departments of clinical genetics. These children were diagnosed with Klinefelter syndrome or Triple X syndrome before birth by prenatal diagnostics. The other 28 children with an extra x chromosome were brought in contact with us in other ways; with help of the Dutch Klinefelter Association (Nederlandse Klinefelter Vereniging) and the Triple X Contact Group (Triple X Contactgroep). These organizations were very helpful by distributing calls for participation to their members and visitors. This group also included children who were diagnosed after birth, for example because there were developmental problems. In addition to the children with an extra X chromosome, 110 boys and girls without an extra X chromosome participated (the control group). In this newsletter, the results of the study will be presented separately for girls with Triple X syndrome and boys with Klinefelter syndrome. These results will be compared to the results in the control group. By comparing to a control group, we can identify strengths and weaknesses in the group of children with an extra X chromosome compared to their peers.

We would like to thank all the children and their parents for their costly time, efforts, and enthusiasm. We would not have been able to complete this research without them. We hope the outcomes of the study are useful and interesting for them. Thank you!

What did we do with all the collected information?

We would like to underline that the results in this newsletter represent the outcomes on group level, i.e. general characteristics of the groups as a whole are reported. Please note that there are large individual differences within the groups.

First, we compared mean scores in the group of children with an extra X chromosome with the control group (peers), separately for boys and girls. We used statistical programs to assess if any differences were indicative of substantial risk. Based on mean scores being *significantly* deviant in the extra X group, we identified developmental risks.

In case of developmental risk, it is important to indicate what percentages of the children with an extra X chromosome have a mildly deviant score, a somewhat deviant score or a severely deviant score. To illustrate this, we have added figures for each developmental area, in which you can find the percentage of the children with an extra X chromosome having a severely deviant score. Because deviant scores can also occur in children without an extra X chromosome (the control group), we have indicated the percentage of children in the control group having a ~~deviant~~ score by a dotted line.

Finally, we would like to highlight that the results of this study are comparable for all the groups of children with an extra X who were included from different sites: clinical genetics departments, support groups or other. Thus, when it comes to developmental risks, the results are comparable for all the children with an extra X, regardless of the inclusion method.

We investigated developmental risks in various areas. When focussing on daily life functioning, we assessed behavioural adaptation of children in different situations, social skills, emotional wellbeing, drive and persistence, stress handling, and the ability to plan and organize their daily affairs. We also studied how children think, in which we made a distinction between different areas, among which language, visuo-spatial ability, attention, concentration, control over impulses, mental flexibility, memory, recognition of facial expressions, and taking perspective of others. We will present the outcomes per area.

General

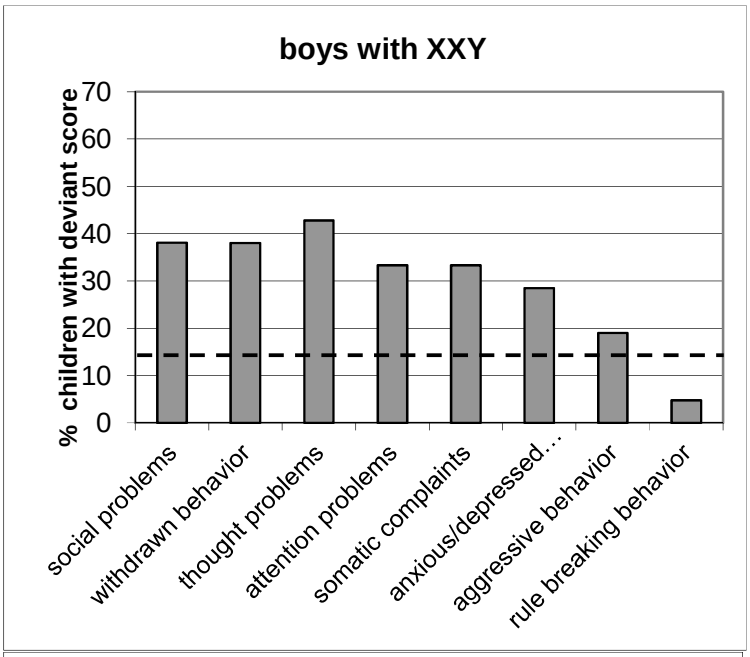
Many parents in this study described their sons and daughters with an extra X chromosome as loving, caring and helpful. Many parents indicated that their child with an extra X chromosome was particularly comfortable in a familiar surroundings, and enjoyed playing board games with family members, cooking together, watching television or doing other activities together with their family members. Reported hobbies for girls with an extra X were often doing something creative, like drawing or stencilling. Many girls enjoyed attending school according to their parents, but often found it difficult to ask for help in the classroom. Many parents also described their daughters as being precise and perfectionist in the things they do, which sometimes causes frustration if things do not work out the way they plan or wish. For boys with an extra X, parents reported they enjoyed working on their computers or playing games. Many parents described their sons a gentle and shy with unfamiliar persons. Many parents reported that their son or daughter found it difficult to express their emotions, leading to outburst of boiled-up emotions in some instances.

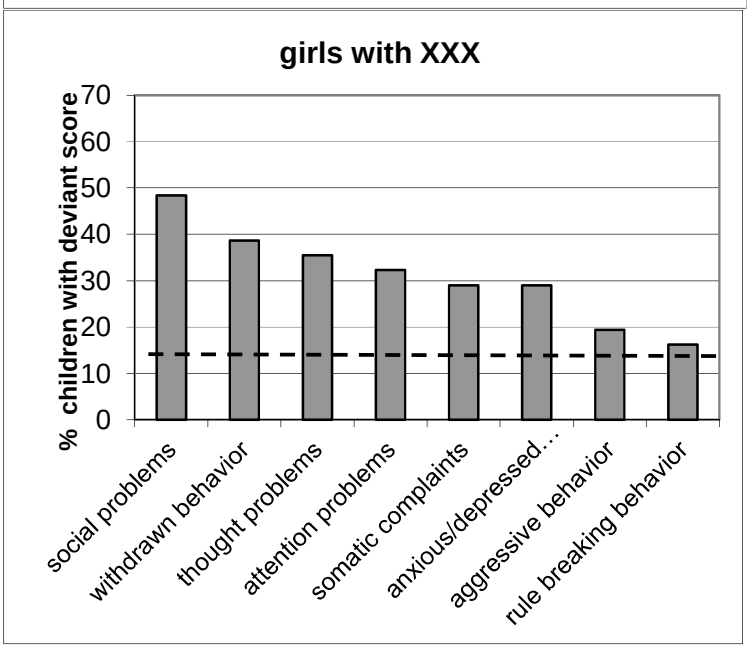
Behavioral problems in daily life

We assessed if behavioral problems were more present in girls or boys with an extra X compared to their peers. In the figures below is described in how many children with an extra X deviant scores were found for different kinds of behavioural problems.

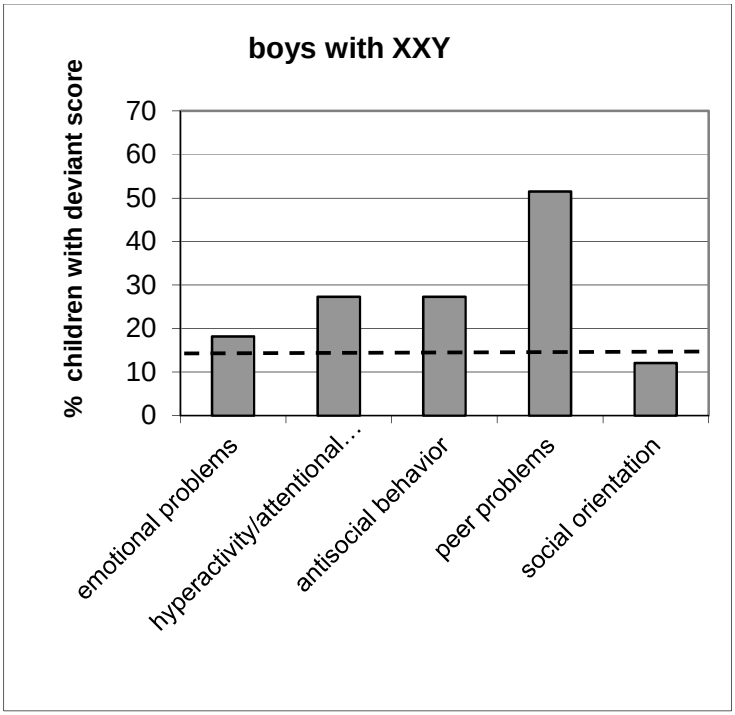
Which specific areas show developmental risks? Our analyses showed that children with an extra X have an increased risk for different kinds of behavioural problems, such as described in the figures below. For some behavioural problems, however, the risk was higher than for others.

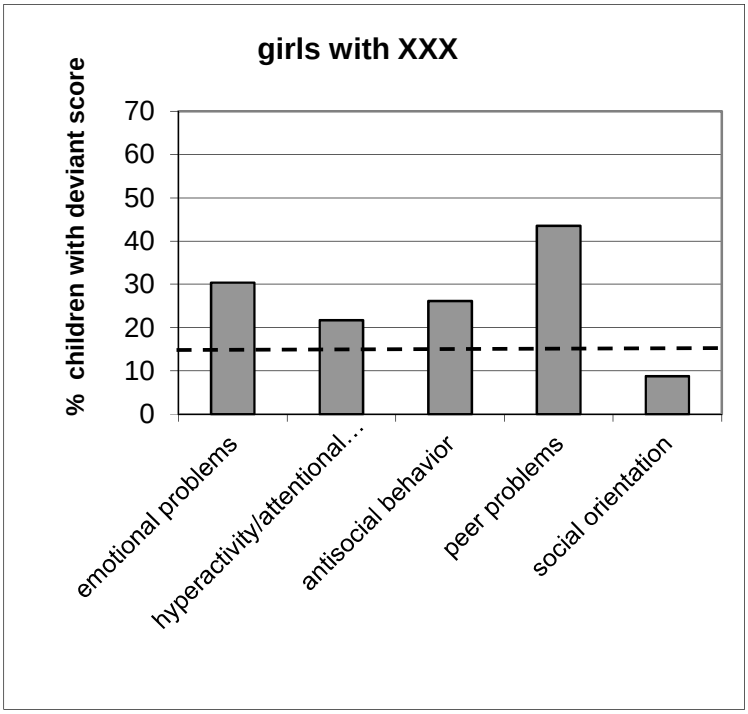
Are the developmental risks for behavioral problems different between boys and girls with an extra X? No, our analyses showed that the developmental risks per area were comparable between girls and boys with an extra X.





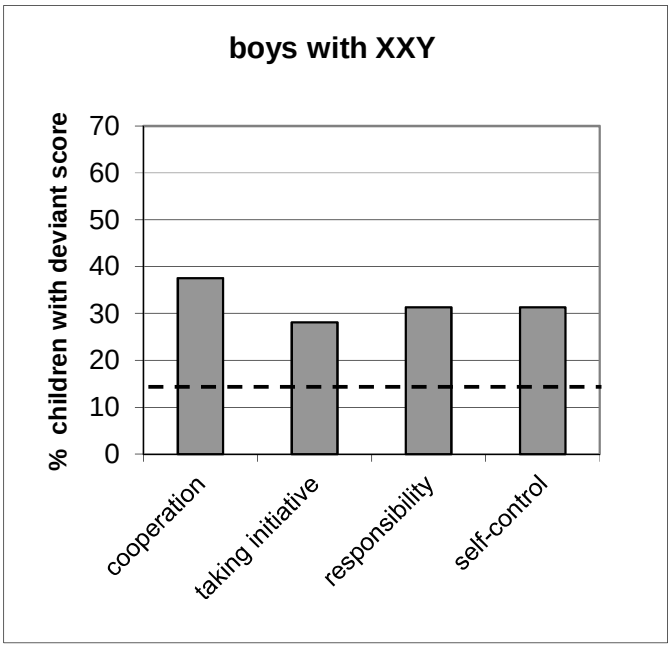
Developmental risks in the areas presented in the figures below were seen as well. Again, the developmental risks were comparable between boys and girls with an extra X. Notable is that social orientation was a relatively strong in the children as compared to other domains. Whereas their social orientation was relatively strong, children with an extra X had more difficulty in initiating and maintaining social interactions with peers.

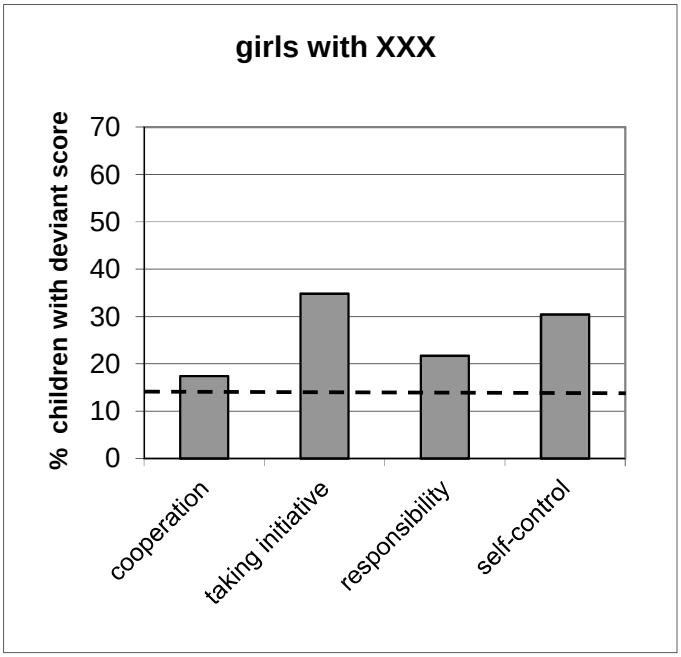




Social skills

When it comes to social skills, we observed that girls with an extra X had more difficulties taking initiative, taking responsibilities and having self control in social situations. In the group of girls with an extra X, working together in social situations was similar to peers. Boys with an extra X had more difficulties with working together, taking initiative, taking responsibilities and having self control in social situations. Our analyses indicated that the overall risks in the area of social abilities were comparable between boys and girls with an extra X, except for the area of working together. In this area, girls with an extra X scored comparable to the score of peers.

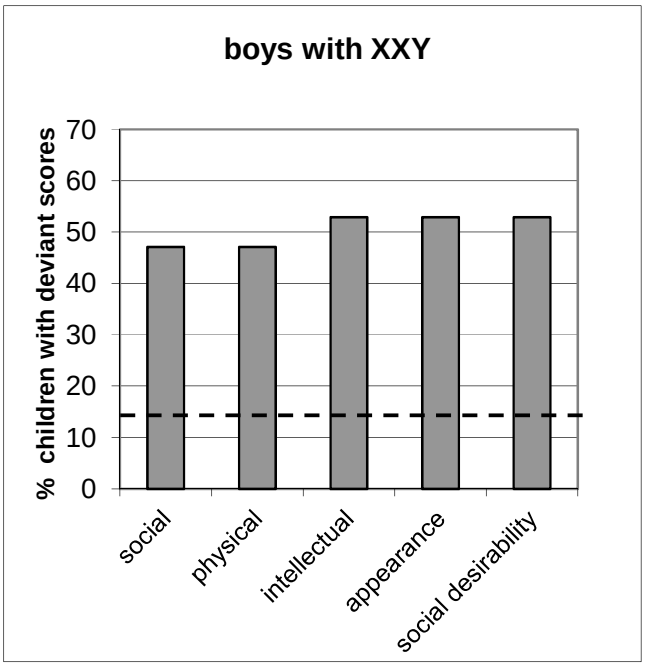


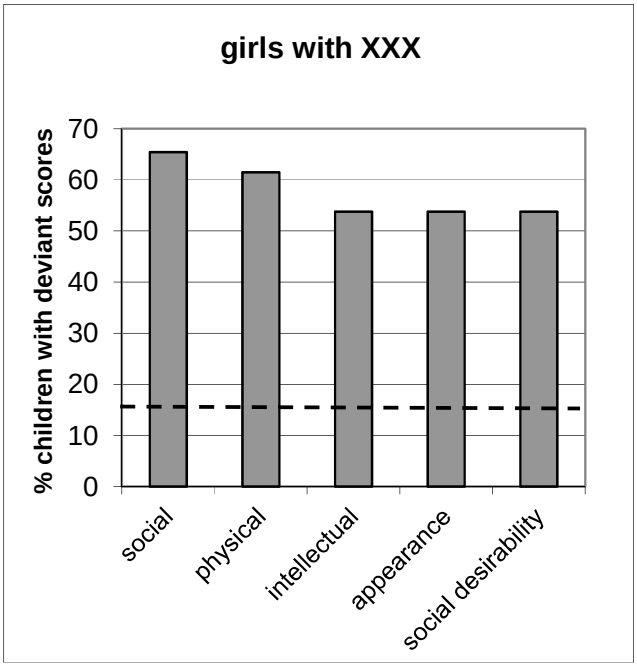


When it comes to how children experience social situations, we observed that boys and girls with an extra X feel more anxious and tense compared to peers in situations where:

- Social contacts plays a role
- Physical abilities come into play
- Intellectual capacities come into play
- Appearance comes into play
- Social desirability comes into account

The developmental risks in this area turned out to be equal for boys and girls with an extra X. The percentage of children with significant problems in this area can be found in the figures below.



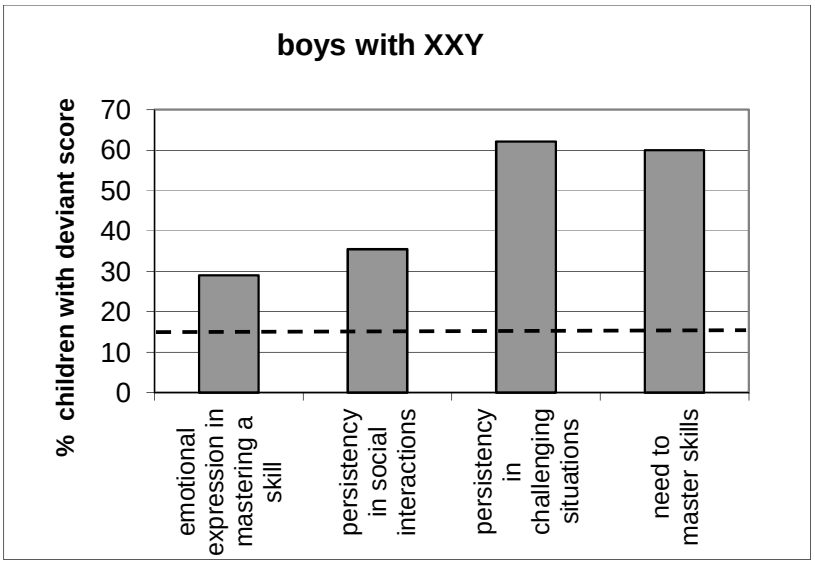


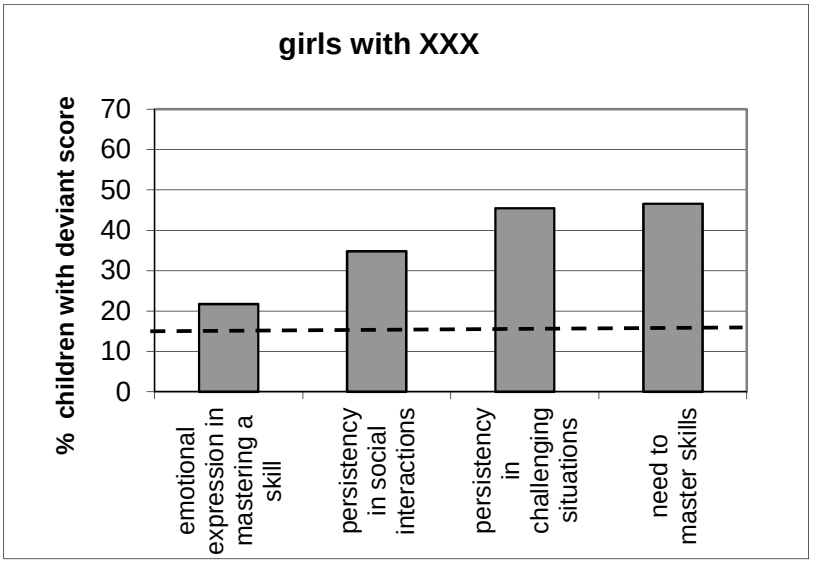
Dealing with challenges

Children can respond differently when it comes to dealing with challenges in their environment.
In this study we found that boys and girls with an extra X, compared to peers, have a reduced tendency to:

- show they find something difficult by expressing emotions to others
- actively engage with and respond to social input and social challenges
- act persistent and follow through when something is challenging and difficult
- have the ability to master something that is challenging and difficult

Our analyses indicated that the risks in this area are comparable for boys and girls with an extra X.





Dealing with negative emotions

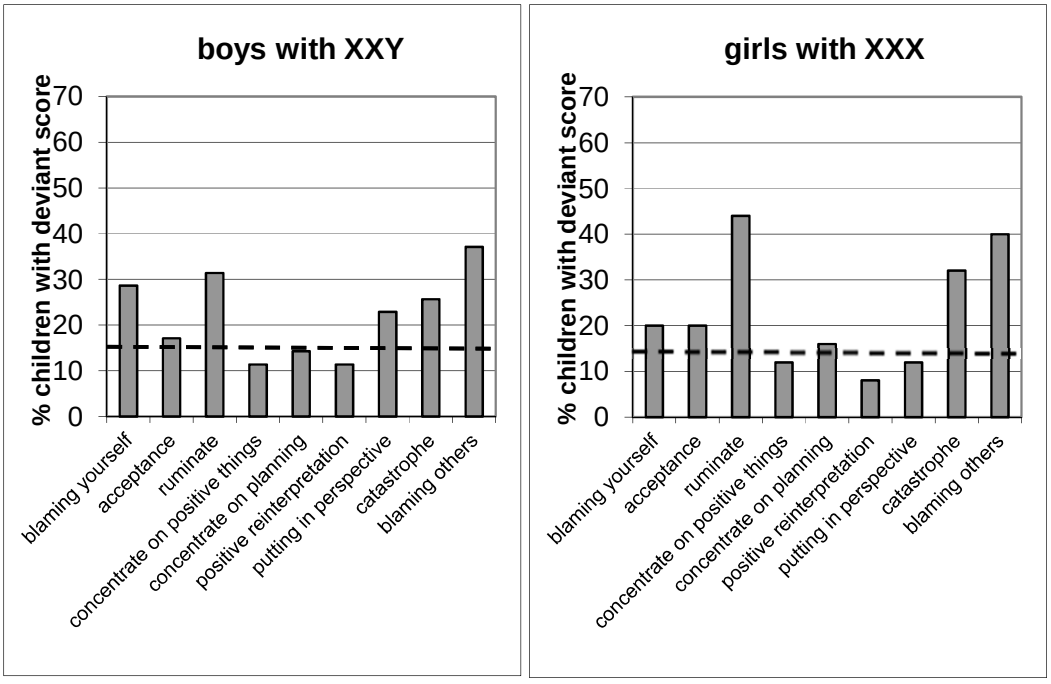
Influencing and handling feelings and emotions through thinking patters is often needed in daily life. Thinking strategies help people to regulate their emotions or feelings and prevent that they become overwhelmed by the intensity of these emotions, during or after experiencing, for example, unhappy or difficult events. Thinking strategies are often 'helpful thoughts'. However, there are thinking strategies that are less helpful, resulting in negative impact of emotions. We studied to what extent children are inclined to use the following (more or less helpful) thinking strategies in situations that evoke negative emotions:

1. *Blaming yourself*: referencing to thoughts about keeping yourself responsible for what has happened to you
2. *Acceptance*: referencing to thoughts about resigning yourself to what has happened
3. *Ruminate*: referencing to thinking repeatedly of feelings and thoughts which are associated with the negative event
4. *Concentrate on other, positive, things*: referencing to thinking of other, pleasant things instead of the actual event
5. *Concentrate on planning*: referencing to thinking which steps have to be taken to deal with the event
6. *Positive reinterpretation*: referencing to assigning a positive labeling of the event in the sense of personal growth
7. *Putting in perspective*: referencing to saying to yourself that there are worse things in the world
8. *To catastrophe*: referencing to returning thoughts about how terrible the event was
9. *Blaming others*: referencing to thoughts about holding others responsible for what happened to you

Children with an extra X scored differently compared to the control group in the following way:

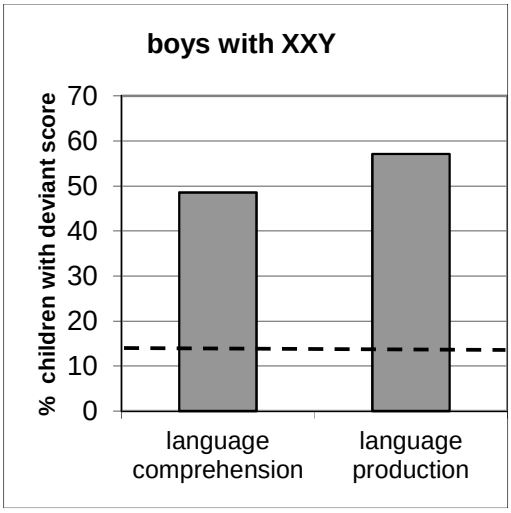
- Girls and boys with an extra X were more inclined to 'ruminate' than their peers, i.e. they tended to keep on thinking about the emotional event, remained emotional and were less able to move forward and overcome these negative emotions.
- They also showed a stronger tendency to explain negative emotional events in terms of how others were responsible for this rather than themselves.

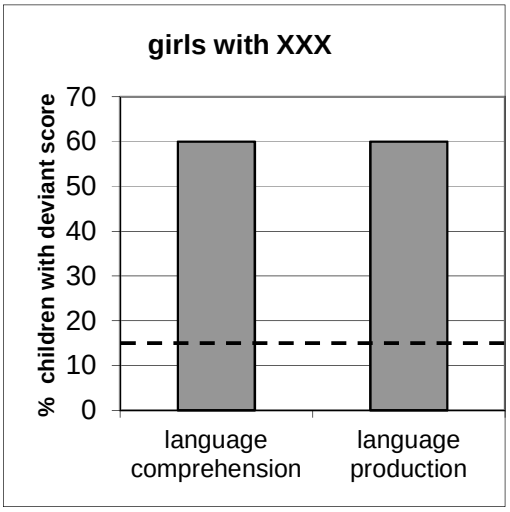
The other strategies were used as much as peers did.



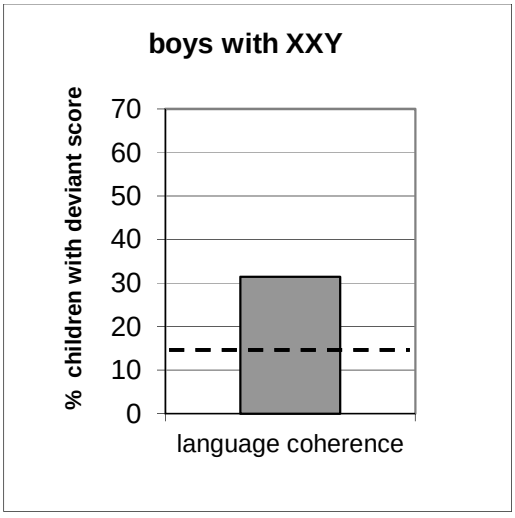
LANGUAGE

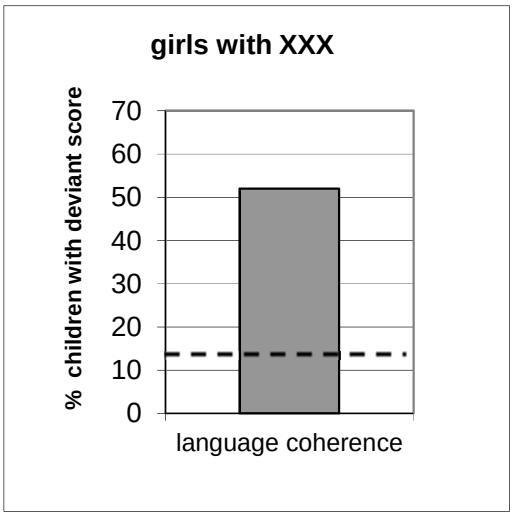
Compared to peers, boys and girls with an extra X had more difficulties with understanding language and producing language. This means that children with an extra X have relatively more difficulties in communication, understanding what others say and formulating their own thoughts. The percentage of children with developmental risks in these language abilities can be found in the figures below. Our analyses indicated a relatively, slightly lower risk for boys with an extra X in understanding language than for girls with an extra X.



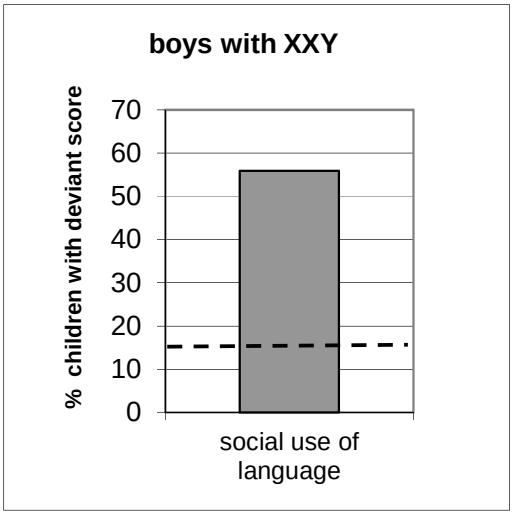


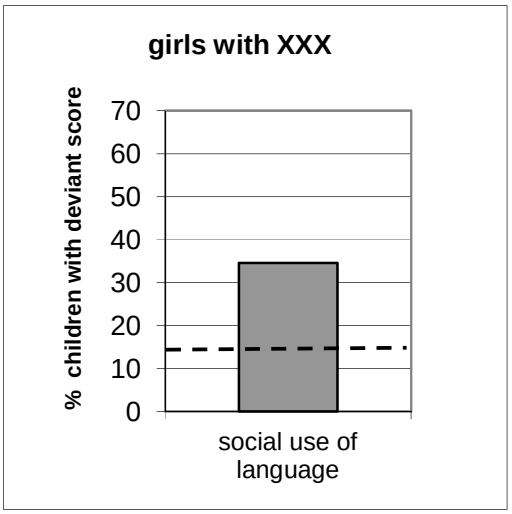
We studied the level of coherence in spoken language as well, in which children with an extra X showed more difficulties on average than peers. Coherence in speech is needed to effectively organise thoughts and communicate with others. Our analyses indicated comparable risks for girls and boys with an extra X. The percentage of children with developmental risks in this area can be found in the figures below:





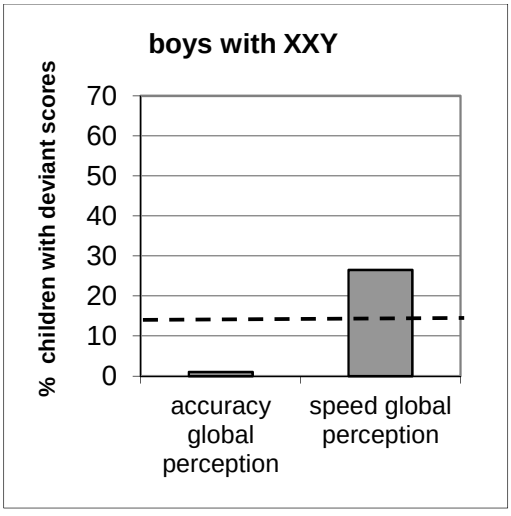
Finally, we studied the social use of language, like noting when it is your turn to speak, introducing appropriate topics for discussion or introducing yourself to others. Our study indicated that boys and girls with an extra X had more difficulties with this compared with peers. The risk of problems in using language in social situations (pragmatic language) appeared equal for boys and girls with an extra X. The percentage of children with developmental risks in this area can be found in the figures below.

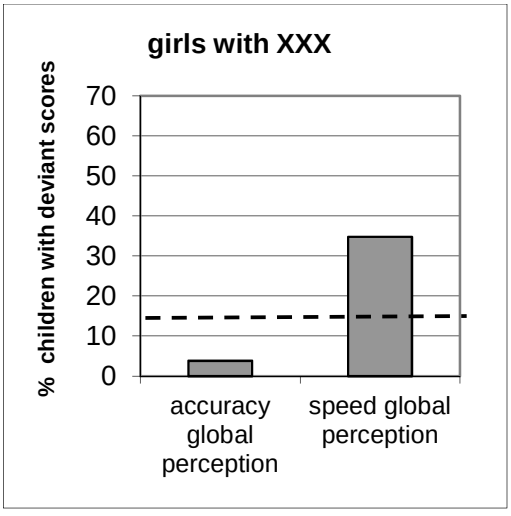




VISUAL PERCEPTION

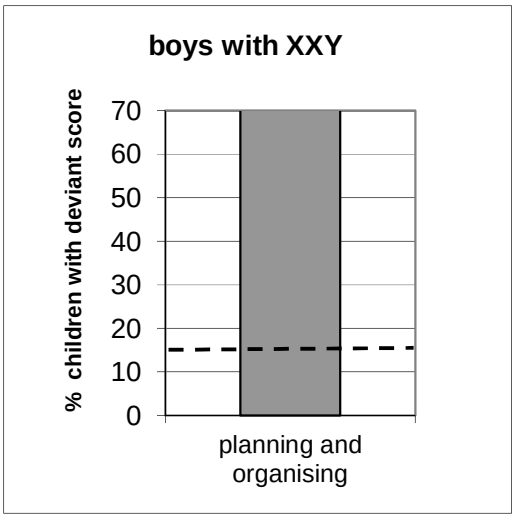
In the study we also focused on visual perception, more specifically the ability of children to rapidly oversee the 'big picture' in visual scenes, which is important to understand social situations quickly. Our analyses indicated that boys and girls with an extra X chromosome have no difficulties observing the global picture compared to their peers. In other words, accuracy was comparable to peers. When we focused at speed, we did see that girls and boys with an extra X needed more time to oversee the global picture compared to peers. The risk of problems in global perception when it comes to accuracy and speed can be seen in the figures below.

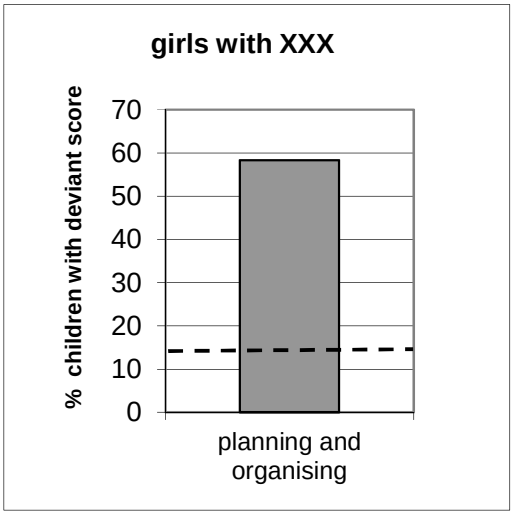




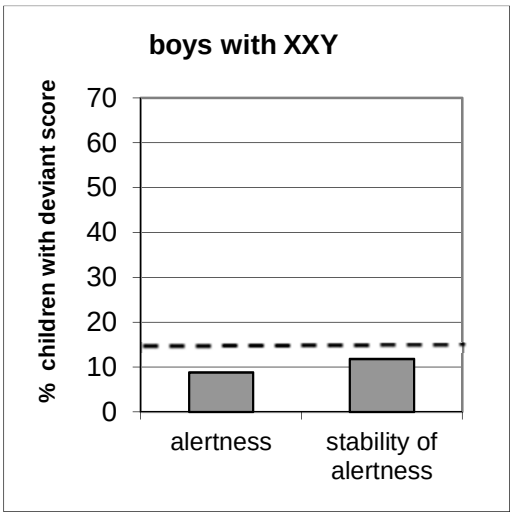
COGNITIVE CONTROL

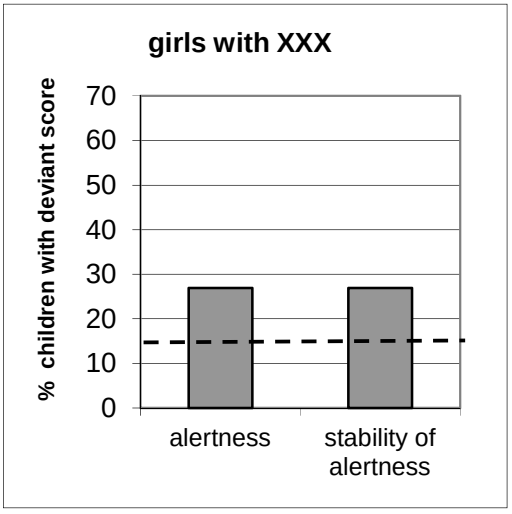
Planning and organizing
Adequate organized behavior requires that a child is goal oriented, is able to ignore distracting factors, plan the order of operations, execute the tasks that are necessary step by step, check if the goal is successfully achieved and, if necessary, correct plans and goals. Our study shows that this is, on average, more difficult for both boys and girls with an extra X compared to peers. Our analyses indicated comparable risks for boys and girls with an extra X.



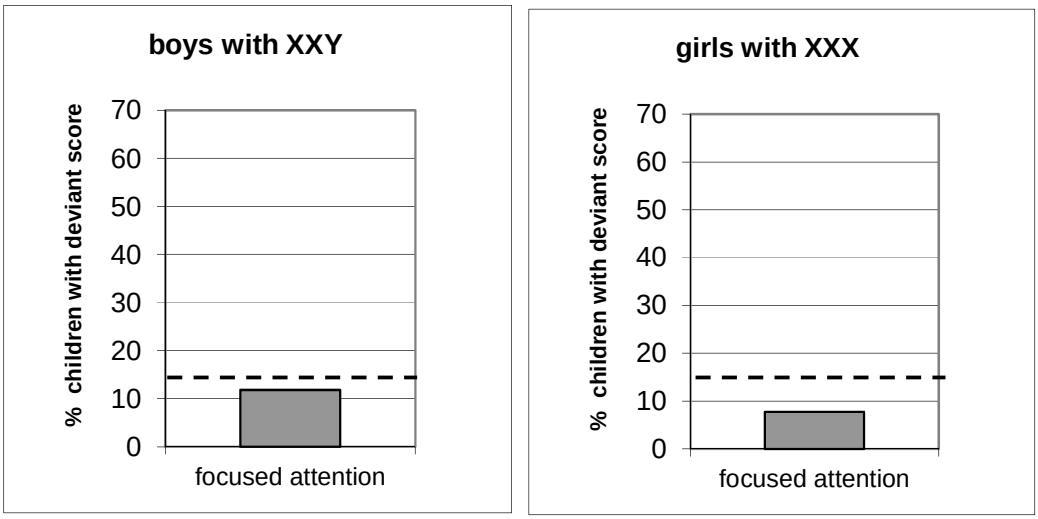


Alertness
Alertness reflects the ability to concentrate and rapidly respond to changing cues in the environment. Our study showed that girls with an extra X were less alert than their peers. Alertness in boys with an extra X appeared to be comparable to peers. In the figure below, you can find the percentage of children with severely deviant scores in this area.

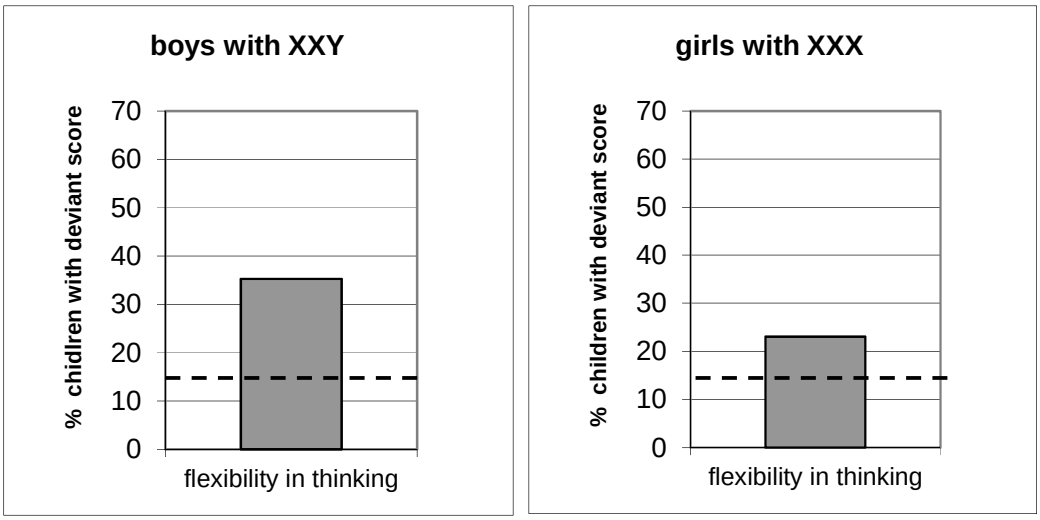




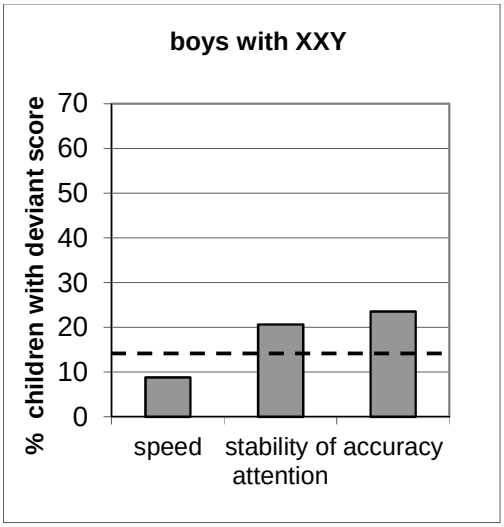
Focused attention
With regard to the ability to focus attention on one single aspect and ignore distracting factors, there were no developmental risks in the groups with an extra X chromosome. Performance was similar to peers.

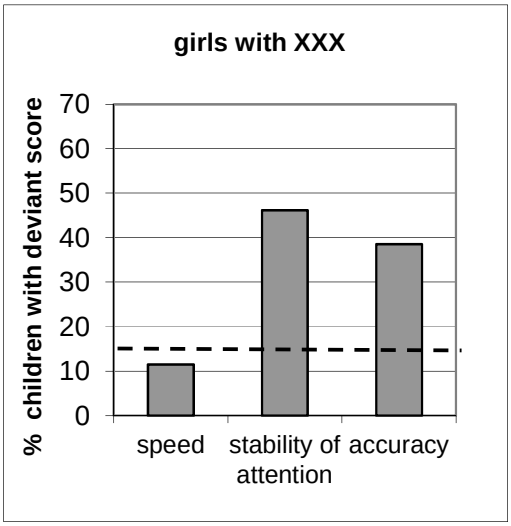


Flexibility in thinking
Flexibility in thinking refers to the ability to deal with changing sources of information and the ability to switch between various behaviors. This ability is important when for example plans change and unexpected events happen. On average, for both girls and boys with an extra X, this seemed to be more difficult compared to peers. The risk of problems in this area appeared to be comparable for boys and girls with an extra X.

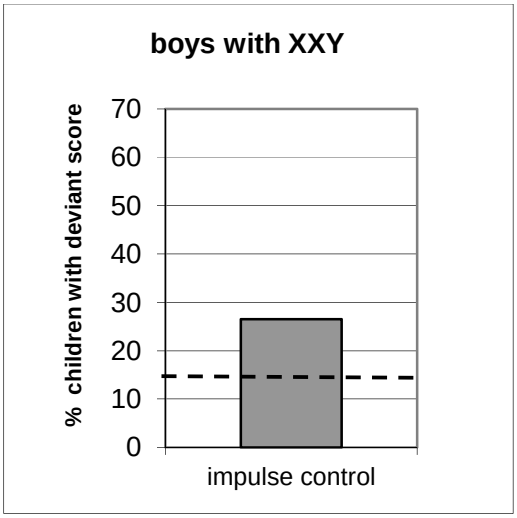


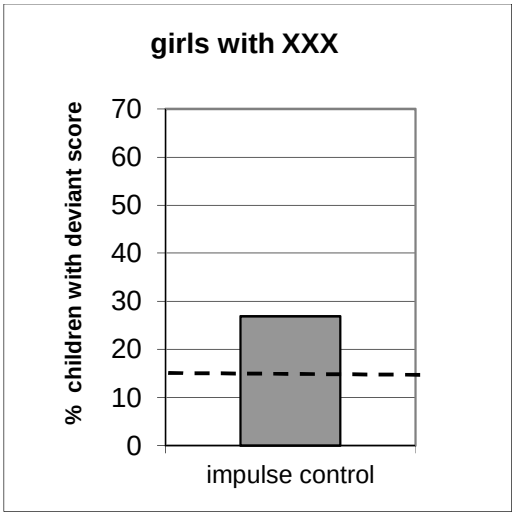
Sustained attention
When it comes to the ability to stay concentrated for a longer period of time, our study indicated that this was on average more difficult for boys and girls with an extra X. Developmental risks in this area appeared to be somewhat smaller for boys than for girls with an extra X. The percentage of children with problems in this area can be found in the figures below.





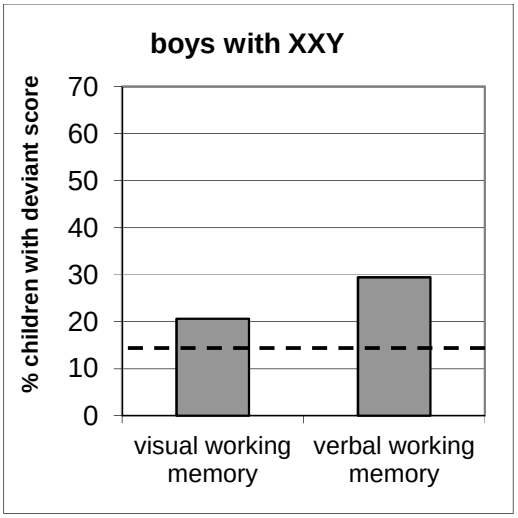
Impulse control
On average, boys and girls with an extra X had more difficulties with controlling impulses. The risk of problems in this area was equal for boys and girls with an extra X.

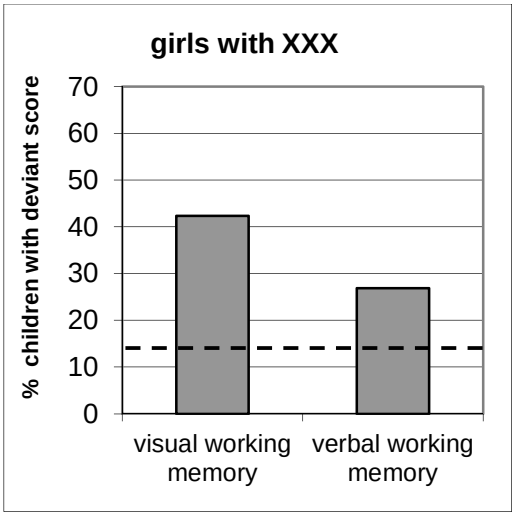




Working memory

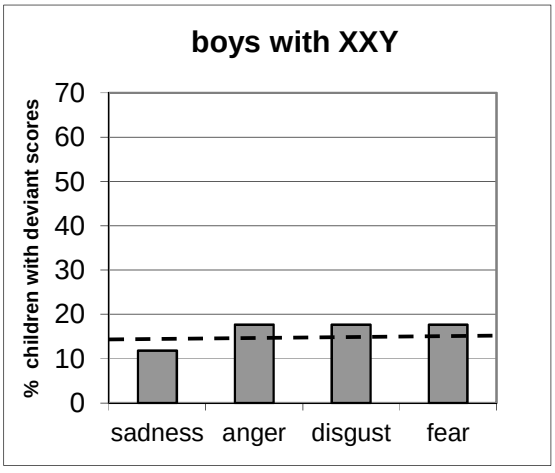
Working memory refers to the ability to hold on to information for some time, in order to be able to process it further (for example when you cannot write down a phone number and need to keep it in mind). We studied verbal working memory and visual working memory. Our analyses indicated that on average girls and boys with an extra X have more difficulties with both verbal and visual working memory compared to peers. The risks of problems in working memory were comparable between girls and boys with an extra X.

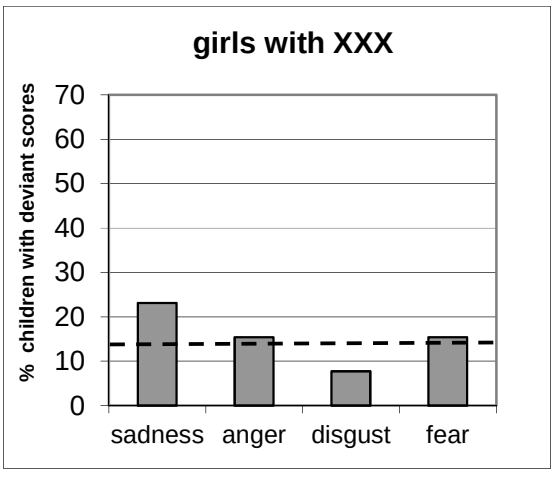




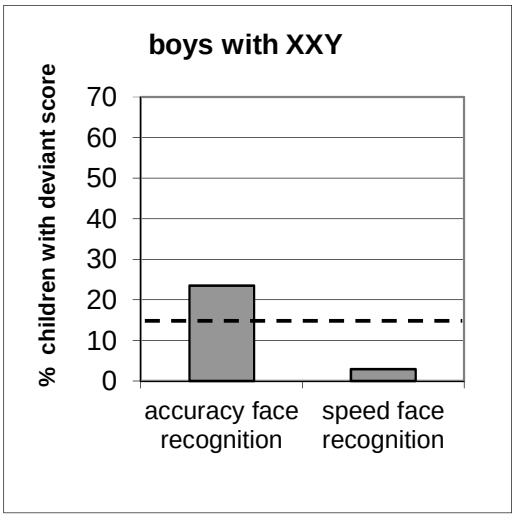
SOCIAL INSIGHT

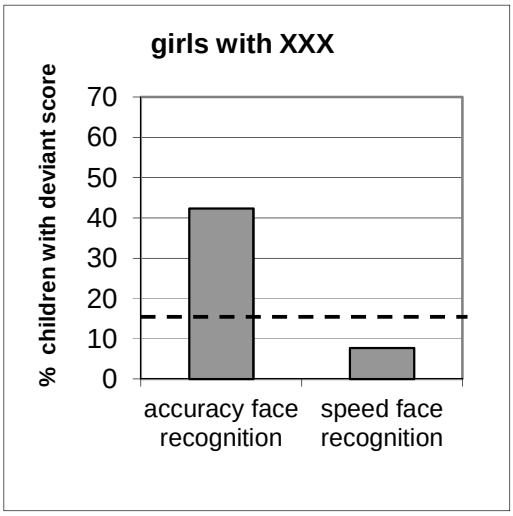
In the study, we also focused on how well children can recognize facial expressions of others. Our analyses indicated that boys and girls with an extra X have more difficulties on average with recognizing the emotions sadness, anger and disgust on the faces of others, compared to peers. Overall, the risk of problems in understanding facial expressions was equal for boys and girls with an extra X. The percentage of children with serious problems in this area can be found in the figures below.



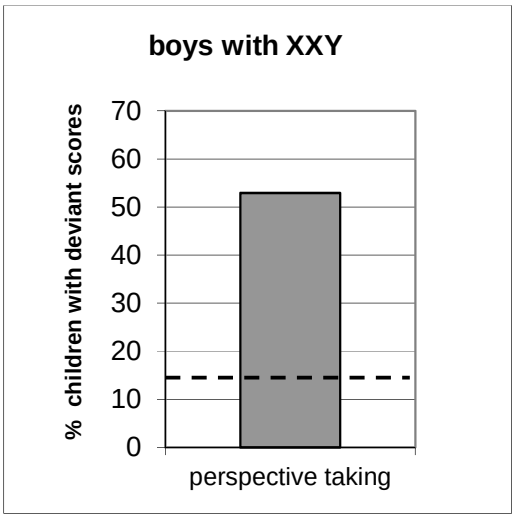


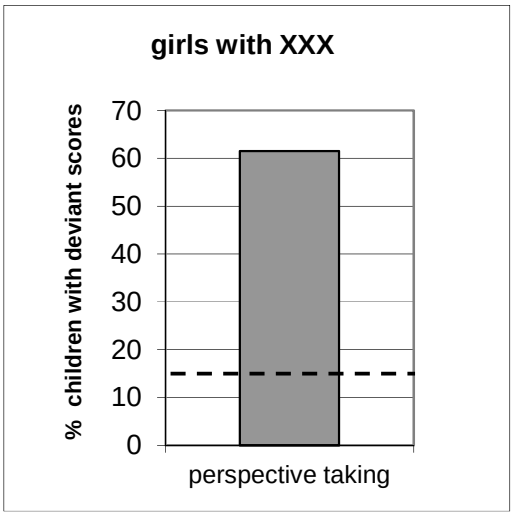
We studied the ability to remember faces of others as well. On average, the children with an extra X found it somewhat more difficult to indicate if they had already seen a face before. Their speed of responding was similar to peers, but the groups were less accurate in remembering faces. Developmental risks in this area appeared to be equal for boys and girls with an extra X.





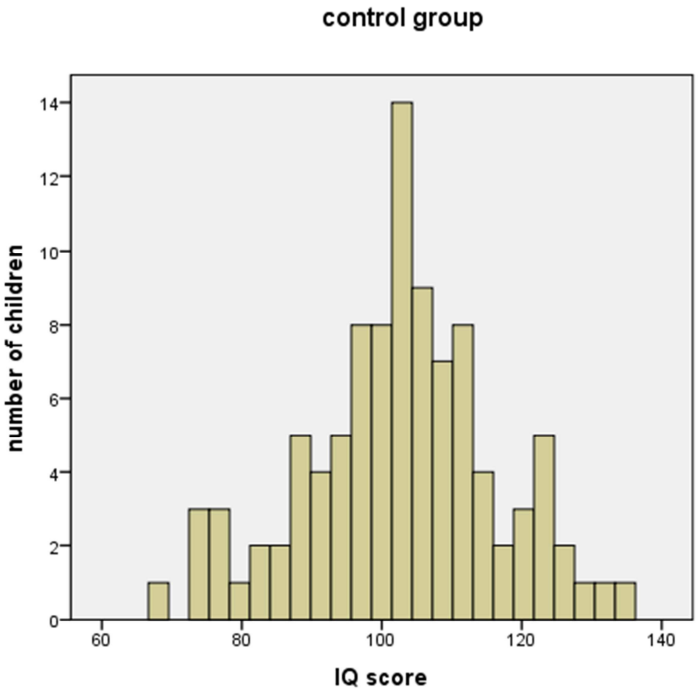
We also studied the ability to take perspectives of others. This involves understanding that other people may have other wishes, emotions and thoughts than you have (also termed 'theory of mind'). This skill is needed to understand the needs and the position of others and to respond socially appropriate. Our analyses indicated that boys and girls with an extra X had more difficulties in perspective taking compared to peers. The risk of problems in perspective taking was equal for boys and girls with an extra X. The percentage of children with a developmental risk in this area can be found in the figures below.

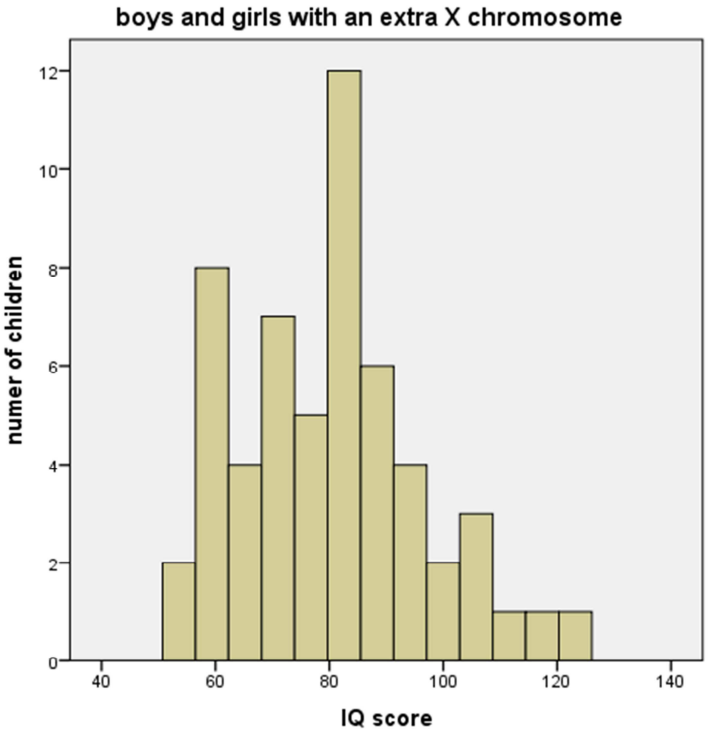




Intelligence

Intelligence Quotient (IQ) reflects, overall, the ability to learn. On average, the global intelligence score was lower for the boys and girls with an extra X chromosome compared to peers. This means that children with an extra X have more risks in the area of learning. The distribution of the IQ scores can be found in the graphs below.





Finally

The out-patient clinic (Ambulatorium) at Leiden University specializes in diagnosis and treatment of children with an extra X chromosome. More information can be found below:

Team Klinefelter and Triple-X Leiden
The Team Klinefelter and Triple-X Leiden consists of clinicians of the Ambulatorium (i.e. clinical neuropsychologists, clinical psychologists, developmental therapists, mental health practitioners) under management of prof. dr. Hanna Swaab, and paediatricians-endocrinologists of the Leiden University Medical Center under management of prof. dr. Henriëtte Delemarre. Necessary support and care is provided by this multidisciplinary team, allowing optimal fine-tuning of both physical and psychological health care.

What support is offered?
Clinicians at the Ambulatorium inform and support parents and children with regard to developmental risks associated with growing up with an extra X chromosome. We offer (neuro)psychological assessment in order to determine the progress of development in various important areas, such as language, learning, social insight, etc. We aim to support children in their development of skills, and support parents by increasing their understanding of the impact of the syndrome on psychological development of their child as well as helping in supporting their child. The paediatricians-endocrinologists monitor the physical development. Because of the extra X chromosome, the hormone system in the body can be disrupted in boys with an extra X chromosome. For this reason, hormone treatment is often started in order to positively influence growth and development.

For whom?
The Ambulatorium offers multidisciplinary assessment, support, and treatment to parents and children in the age range of 0-21 years. Adults with an extra X chromosome can address the Ambulatorium with questions as well.

Contact?
Adults can sign-up via the digital form on the website, www.zorgteamklinefelter.leidenuniv.nl, or by telephone, (+31) (0)71- 5274063.

Health insurance
The care that is offered at the Ambulatorium is, in principal, covered by health insurance and thereby dependent on the individual situation. A referral letter of the general practitioner or medical specialist is necessary.

Questions?
For more information about assessment, support, or treatment, we gladly refer to the Ambulatorium, 071-5274063. For more information about research you can turn to Sophie van Rijn, srijn@fsw.leidenuniv.nl

Kind regards,

also on behalf of prof. Hanna Swaab, the clinical team and research team,

Sophie van Rijn, PhD
Leiden University
Clinical Child and Adolescent Studies