

**Executive dysfunction and the relation with behavioral problems in  
children with 47,XXY and 47,XXX**

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**Abstract**

Neuroimaging studies have shown that having an extra X chromosome is associated with abnormal structure and function of brain areas in the frontal lobe, which is crucially involved in executive functioning. However, there is little of knowledge of the type and severity of executive dysfunction, and the impact on emotional and behavioral problems. The present study aims to provide in this.

In total, 40 children (23 boys with 47,XXY and 17 girls with 47,XXX) with an extra X chromosome and 100 non-clinical controls (47 boys and 53 girls) participated in the study. The participants were 9 to 18 years old. Processing speed and executive functioning were assessed using the Amsterdam Neuropsychological Testbattery (ANT) and the Dysexecutive Questionnaire (DEX). Problems in emotional and behavioral functioning were assessed with the Childhood Behavior Checklist (CBCL).

Children with an extra X chromosome showed deficits in inhibition, mental flexibility, sustained attention and visual working memory. Parental report showed high levels of everyday manifestations of executive dysfunction. More severe inhibition difficulties were associated with higher levels of thought problems, aggression, and rule breaking behavior. Boys and girls with an extra X chromosome could not be differentiated based on severity of executive dysfunction, however girls had lower information processing speed than boys.

These findings suggest that executive dysfunction may be part of the phenotype of children with an extra X chromosome, impacting the ability to function adequately in everyday life. Furthermore, children with impairments in inhibition may have more problems in regulating their thinking, emotions and behavior.

**KEYWORDS**

Sex chromosome disorders; executive functions; Klinefelter syndrome; Trisomy X; cognition; behavioral problems

**Introduction**

There is a growing interest in the study of the neurodevelopmental risks in individuals with sex chromosome trisomies (SCT). Approximately 1 to 2 in 1000 children are born with an extra X chromosome, known as 'Klinefelter syndrome' in boys (47,XXY chromosomal pattern) and 'Trisomy X' in girls (47,XXX chromosomal pattern). This increasing interest is fueled by accumulating evidence over the past decades that such genetic conditions not only impact physical development, but also psychological development, which is not surprising considering the exceptional high density of genes on the X chromosome that are essential for neural, and thus cognitive and behavioral development (Zechner *et al.*, 2001).

Evidence from neuroimaging shows that brain architecture and -functioning may be deviant in individuals with SCT (Lenroot *et al.*, 2009, Steinman *et al.*, 2009), which is also expressed in information processing deficits, that are found in the face of intellectual functioning within the normal range (although at the lower end, particularly for verbal IQ). These information processing deficits are typically found in the domains of speech, reading and language, motor development and educational achievement (Boada *et al.*, 2009, Leggett *et al.*, 2010). Several neuroimaging studies have shown abnormal structure (Bryant *et al.*, 2011, Delisi *et al.*, 2005, Giedd *et al.*, 2007, Rezaie *et al.*, 2009, Skakkebaek *et al.*, 2014) and function (Brandenburg-Goddard *et al.*, 2014, Van Rijn *et al.*, 2008a) of brain areas in the frontal lobe in individuals with SCT. As the frontal lobe is crucially involved in executive functioning (Stuss, 2011), these findings underline the importance of investigating executive functioning in individuals with SCT.

Executive functions (EF) are essential for flexible adaptive functioning in complex situations that have a high load of information, for inhibition of irrelevant thoughts and actions, for responding to changing environmental demands, and for organization of thoughts and actions in a goal-directed way. Several components of this regulatory system can be distinguished, such as strategic planning, organized search, inhibition, focused and sustained attention, monitoring, holding a mental representation "on-line" in working memory and flexibility of thought and action (Anderson, 2001).

So far, studies that have investigated EF in individuals with an extra X chromosome (Bender *et al.*, 2001, Bender *et al.*, 1993, Boone *et al.*, 2001, Fales *et al.*, 2003, Kompus *et al.*, 2011, Lee *et al.*, 2011, Ross *et al.*, 2009, Stewart *et al.*, 1982, Van Rijn *et al.*, 2009, Van Rijn *et al.*, 2012), indicate that EF dysfunctions may be characteristic for individuals with SCT, although evidence is still somewhat mixed and the role of EF deficits in risk for emotional

and behavioral problems is largely understudied. Also, there have been very limited systematic studies on EF in girls or women with XXX.

Establishing a profile of executive dysfunction in children with SCT may help in the early identification of children at risk for psychopathology, and offer the opportunity to provide support and possibly influence these cognitive functions to improve outcome over the course of development. Thus, there is a need for studies in children with SCT, focusing on a broad range of EF functions, assessing the impact on risk for emotional and behavioral problems and including both boys and girls with an extra X chromosome. The present study aims to provide in this.

## **Material and methods**

### *Participants*

In total, 40 children (23 boys and 17 girls) with an extra X chromosome and 100 non-clinical controls (47 boys and 53 girls) participated in the study. The participants were 9 to 18 years old. The group of children with an extra X chromosome consisted of two subgroups. The first group included children from those families that were actively followed up after prenatal diagnosis with the help of clinical genetics departments. These departments of academic medical centers in the Netherlands and Belgium screened their databases for families who had received a prenatal diagnosis of Klinefelter syndrome or Trisomy X. Individuals in this group were considered 'prenatal follow-up' cases and constituted 52.5 % of the extra X group. The second group included children from those families that were actively seeking information about the condition of their child (recruited through support groups and calls for participants) and those who were seeking help for developmental problems (recruited through pediatricians, psychologists, psychiatrists, clinical genetics departments). These were considered 'referred' cases and constituted 47.5 % of the total extra X group. The prenatal follow up group and referred group were similar in terms of sex distribution, age and IQ. Diagnosis of Klinefelter syndrome and Trisomy X was confirmed by standard karyotyping, all had non-mosaic karyotypes. In the group of boys with 47,XXY, six used testosterone supplements.

Controls from the general population were recruited from schools distributed across the western part of The Netherlands. Children in the control group were screened for emotional and behavioral problems: none scored in the clinical range ( $\geq 70$ ) on the Childhood Behavior

Checklist (CBCL) (Achenbach & Rescorla, 2001). Inclusion criteria for all participants were Dutch as the primary language and an age between 9 and 18 years. Exclusion criteria were a recent history of substance abuse, intellectual disability (<60 IQ points) as assessed with the WISC-III (Wechsler, 1991) and neurological conditions. After providing a complete description of the study to the subjects and to their parents, we obtained written informed consent according to the Declaration of Helsinki. The study was approved by the Ethical Committee of Leiden University Medical Center, the Netherlands.

MANOVA with the fixed factors group (control, XXY) and sex (boy, girl) and the dependent variables age and IQ, showed no significant main effect of group for age. However, there was a main effect of group for IQ,  $F(2,187)=23.0$ ,  $p<0.001$ . There were no significant group by sex interactions. Table 1 provides an overview of these variables.

## Instruments

### *Intellectual functioning*

Intellectual functioning was assessed using the subtests Blockdesign and Vocabulary of the of the Dutch adaptations of the Wechsler Intelligence Scales for Children (Wechsler, 1991), i.e. V-BD short form. The V-BD short form is often used to estimate full scale IQ (FSIQ) according to the algorithm  $(2.9 * (\text{sum of normed scores}) + 42)$  (Campbell, 1998). The V-BD short form correlates highly with full scale IQ ( $r=.88$ ) (Herreragraf *et al.*, 1996) and the V-BD short form has been found valid for the estimation of intelligence, with a good reliability ( $r=.91$ ) and validity (.82) (Campbell, 1998).

### *ANT testbattery*

The Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville, 1999) has proven to be helpful in defining neurocognitive deficit profiles in different clinical and nonclinical populations (Rommelse *et al.*, 2008, Serra *et al.*, 2003) and several studies have demonstrated satisfactory psychometric properties of ANT paradigms (for a review, see De Sonneville, 2005). Stimuli were presented on the computer screen and participants respond by pressing the mouse buttons with the index fingers or by using the mouse as a tracking

device. To verify that subjects understand the instructions and are able to meet task demands, each subtest is preceded by illustration trials and practice trials. The ANT automatically generates normscores based on nonlinear regression functions capturing the normdata in the age range of 4 to 66 years with total sample sizes varying between 2500 and 6000 subjects, depending on type of task, with higher (positive) Z scores representing more impaired performance.

*ANT: information processing speed*

Information processing speed was measured using a motor responding task. On the screen a (fixation) cross is continuously projected. This cross changes into a block unexpectedly. As soon as a block is present the button must be pressed. The cognitive level of this task is therefore limited to detection of the mere presence of the stimulus. This task consists of two parts: for the left and the right index finger ( $n = 32$  trials, both parts). Outcome parameters are mean reaction time and within-subject standard deviation of the 32 reaction times (fluctuation), per part.

*ANT: Sustained attentional control*

Sustained attentional control was measured by a sustained attention task. 600 stimuli are presented in 50 series of 12 consecutive patterns that contain 3, 4 or 5 dots in a pseudo random sequence. The subject is asked to press the “yes” button only when a 4-dot pattern (target signal) appears. The “no” button must be pressed when the 3- and 5-dot patterns (nontargets) appear. Whenever the subject commits an error, auditory feedback (beep signal) is given. The outcome parameters are number of misses, mean completion time per series and the within-subject standard deviation of the 50 series completion times (fluctuation in tempo). The latter parameter is taken as the primary marker of sustained attention skills.

*ANT: Inhibition and mental flexibility*

Inhibition and mental flexibility were measured using the Shifting Set Task. The Shifting Set Task assesses inhibition of prepotent responses as well as mental flexibility. This paradigm has successfully been used to demonstrate deficits in these executive functions in subjects with diseases that are known to be associated with impaired frontal functioning,

such as phenylketonuria (Huijbregts *et al.*, 2002) and multiple sclerosis (De Sonneville *et al.*, 2002). A coloured square moves randomly to the right and to the left on a horizontal bar that is permanently present on the computer screen. Depending on the colour of the square after the jump, the subjects should copy the movement, i.e. press right (left) when the square jumped to the right (left), or is required to 'mirror' the movement, i.e. press left (right) at a right (left) movement. The task consists of three parts. In part 1 (40 trials, green squares) the subject is required to copy the movements (fixed compatible condition). This part is used to obtain a response tendency. In part 2 (40 trials, red squares) only trials that call for 'mirror' responses are presented (fixed incompatible condition), requiring the inhibition of prepotent responses. In part 3 (80 trials, red and green squares) the square may change colour upon each jump in a random fashion which forces the subject to switch between response sets, which requires mental flexibility. Performance in part 3 is registered separately for green squares (part 3A: variable compatible condition) and red squares (part 3B: variable incompatible responses). The following dependent measures were used: accuracy (i.e. percentage errors) in the 'incompatible fixed (part 2) condition, as a measure of inhibition and accuracy (i.e. percentage errors) in the 'variable compatible condition (part 3A), as a measure of mental flexibility.

*ANT: Focused attention*

In this task a fruit basket is continuously present on screen. Each trial consists of the simultaneous presentation of four pieces of fruit in the basket. Two pieces are aligned in a horizontal fashion (left and right) and two pieces of fruit are aligned in a vertical fashion (top and bottom). The participant is instructed to attend the vertical axis and to ignore the pieces of fruit on the horizontal axis. The participant is required to press the 'yes' key whenever there are cherries on the horizontal axis (relevant target signal). If cherries are on the vertical axis (irrelevant target signal) or there are no cherries (non-target signal) the participant is required to press the 'no' key. These three signal types are presented in a random order (28 target signals, 14 irrelevant target signals, and 14 non-target signals). The reaction time difference between target signals and irrelevant target signals are a parameter for focused attention, with higher scores (lower reaction times for responding to cherries on the target axis versus the non-target axis) reflecting increased focused attention.

### *ANT: Visual working memory*

In this spatial-temporal working memory task participants are presented with a matrix on screen, with nine circles that are highlighted in a specific location and in a specific order. After each stimulus presentation, participants are required to indicate the locations probed on the screen by mouse clicks on those locations, in the reverse order as they appeared on the screen. The number of correctly identified targets (correct location, reverse order) is a measure of visual working memory.

### *Verbal working memory*

To assess verbal working memory, the subtest 'number repetition backwards' of the Clinical Evaluation of Language Fundamentals (CELF) was used (Semel *et al.*, 2003). In this subtest children are asked to repeat orally presented strings of numbers (which increase in size) in reverse order.

### *Daily life executive dysfunction*

The Dysexecutive (DEX) Questionnaire (Burgess *et al.*, 1996) is designed to quantify observable everyday manifestations of executive dysfunction. It contains 20 items, which covers a wide range of EF problems including difficulties with attention, memory, information processing, behavioural control, emotion regulation and awareness. Items are rated on a five-point Likert scale with each point representing a greater level of problem severity (ranging from "never" to "very often"). In this study the parental report version was used.

### *Emotional/behavioural problems*

The norm-referenced Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001) describes a child's emotional and behavioural functioning during the previous six months. We used the parental report version for children aged 6 to 18 years. The items measure a range of emotional and behavioral problems on a three point Likert scale (0 = "Not True," 1 = "Somewhat or Sometimes True," or 2 = "Very True or Often True"). It has two empirically derived broadband scales (Externalizing and Internalizing) and eight syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Rule Breaking Behavior, Aggressive Behavior, Social Problems, Thought Problems, and Attention Problems). A Raw scores for each scale are converted to norm-referenced T-scores (M = 50, SD = 10).



### *Procedures*

All children were tested individually in the research center, in a quiet room. Testing assistants trained in the field of neuropsychology administered the tests, which was done in a fixed order. All tests were preceded by practice trials and test instructions were repeated if necessary. Practice trials were run until children scored above chance level (based on inspection of the practice feedback reports the ANT), indicating that children were able to perform the test. Some of the children did not complete all ANT tests, reasons for which varied from premature ending of the test session due to overall fatigue of the children in the clinical group, more limited testing time due to increased travel-time for families in the clinical group, or technical problems.

### *Statistical analyses*

Group differences were tested with MANOVA. If cognitive performance correlated with IQ, MANCOVA was used with IQ as a covariate. The fixed factors were 'group'(control, extra X) and sex (boy, girls), and accuracy or speed in cognitive tests were the dependent variables. For correlational analysis with emotional/behavioural problems, Spearman's rho was used. Level of significance was set at  $p=0.05$ .

## **Results**

### *ANT: Information processing speed*

Multivariate MANOVA with the fixed factors group (control, extra X) and sex (boy, girl), and the dependent variables speed of information processing and stability of speed of information processing, showed no significant main multivariate effect of group ( $p=0.60$ ) and no significant multivariate group by sex interactions ( $p=0.37$ ). As none of the independent variables correlated with IQ ( $p=0.20$  for speed and  $p=0.09$  for stability of speed), it was not necessary to add IQ as a covariate. See table 2 for mean scores and table 3 for percentages of children with deviant scores.

### *ANT: Sustained attentional control*

In order to assess attentional control over time (i.e. time on task effects), a repeated measures analysis was used with group (control, Extra X) and sex (boy, girls) as the between subjects factors and percentage errors over the five blocks of trials as the within subjects factor (the factor 'attention'). Only children that completed all blocks were included in the analyses, resulting in exclusion of one child in the control group and one child in the Extra X group. As none of the parameters in this test correlated with IQ ( $p > 0.13$ ), it was not necessary to add IQ as a covariate.

There was a significant main multivariate effect of group  $F(4,131)=2.69$ ,  $p=0.03$ . There was no significant main multivariate group by sex interaction ( $p=0.71$ ). On univariate level, within subject contrasts (linear) showed a significant group by attention interaction  $F(1,134)=8.19$ ,  $p=0.005$ , indicating that group differences in accuracy increased over the five blocks. Cohen's  $d$  for group differences in the final block was 0.34. There was no significant group by attention by sex interaction ( $p=0.16$ ). Mean scores are presented in table 2 and percentages of children with deviant scores is given in table 3.

#### *Inhibition*

Data from five controls and one child in the Extra X group were missing. As number of errors in the inhibition task did not significantly correlate with IQ, ( $p=0.10$ ), it was not necessary to add IQ as a covariate in analysis. MANOVA with the fixed factors group (control, Extra X) and sex (boy, girl), and the number of errors as the dependent variable, showed a significant main effect of group,  $F(1,130)=5.37$ ,  $p=0.02$ . Cohen's  $d$  for the group difference was 0.38. There was no significant group by sex interaction ( $p=0.29$ ). See table 2 for mean scores and table 3 for percentages of children with deviant scores.

#### *Mental flexibility*

Data from one child in the control group and one child in the Extra X group were missing. As number of errors in the inhibition task did not significantly correlate with IQ, ( $p=0.06$ ), it was not necessary to add IQ as a covariate in analysis. MANOVA with the fixed factors group (control, Extra X) and sex (boy, girl), and the number of errors as the dependent variable, showed a significant main effect of group,  $F(1,134)=6.95$ ,  $p=0.009$ . Cohen's  $d$  for the group difference was 0.45. There was no significant group by sex

interaction ( $p=0.65$ ). See table 2 for mean scores and table 3 for percentages of children with deviant scores.

#### *Focused attention*

Data from 10 children were missing in the Extra X group; these children were not able to complete the full testbattery within the test session. As the primary test parameter, i.e. gain in reaction time resulting from focusing on the target, did not significantly correlate with IQ ( $p=0.26$ ) it was not necessary to add IQ as a covariate. MANOVA with the fixed factors group (control, Extra X) and sex (boy, girl), and gain in reaction time resulting from focusing on the target as independent variable, showed no significant main effect of group ( $p=0.68$ ) and no significant main group by sex interaction ( $p=0.66$ ). See table 2 for mean scores and table 3 for percentages of children with deviant scores.

#### *Visual working memory*

Data from 3 children in the Extra X group were missing. As the primary parameter, i.e. number correct, was significantly correlated with IQ ( $r=0.46$ ,  $p=0.004$ ), IQ was added as a covariate in the analysis. MANCOVA (covaried for IQ) with the fixed factors group (control, Extra X) and sex (boy, girl), and the number correct as the dependent variable, showed a significant main effect of IQ,  $F(1,132)=7.08$ ,  $p=0.009$ , a significant main effect of group  $F(1,132)=4.21$ ,  $p=0.04$ , and no significant group by sex interaction ( $p=0.56$ ). Cohen's  $d$  for group differences was 0.70. See table 2 for mean scores and table 3 for percentages of children with deviant scores.

#### *Verbal working memory*

Data from 3 children in the Extra X group and 1 child in the control group were missing. As the primary parameter, i.e. number of correct series, was significantly correlated with IQ ( $r=0.45$ ,  $p=0.004$ ), IQ was added as a covariate in the analysis. MANCOVA (covaried for IQ) with the fixed factors group (control, Extra X) and sex (boy, girl), and the number of correct series as the dependent variable, showed a significant main effect of IQ,  $F(1,131)=10.6$ ,  $p=0.001$ , no significant main effect of group ( $p=0.22$ ), and no significant group by sex interaction ( $p=0.44$ ). See table 2 for mean scores and table 3 for percentages of children with deviant scores.

### *Daily life executive functioning difficulties (DEX)*

Data from six controls and 2 children in the Extra X group were missing. As the DEX score was significantly correlated with IQ ( $r = -0.43$ ,  $p = 0.007$ ), IQ was added as a covariate in the analysis. MANCOVA (covaried for IQ) with the fixed factors group (control, Extra X) and sex (boy, girl), and the total DEX score as the dependent variable, showed a significant main effect of IQ,  $F(1,127) = 19.89$ ,  $p < 0.001$ , a significant main effect of group  $F(1,127) = 7.08$ ,  $p < 0.001$ , and no significant group by sex interaction ( $p = 0.42$ ). Cohen's  $d$  for group differences was 1.35. See table 2 for mean scores and table 3 for percentages of children with deviant scores.

### *Differences between boys and girls with an extra X chromosome*

Although the multivariate analyses including the control and extra X groups did not point to significant group by sex interactions, we also directly compared scores between boys and girls with SCT. ANOVA showed that boys and girls with SCT could not be differentiated on EF measures in this study. However, processing speed was slower in girls than in boys,  $T(1,39) = 7.2$ ,  $p = 0.01$ . See table 4 for means and standard deviations.

### *Recruitment bias and country of origin bias*

Within-group analyses (ANOVA) comparing scores in the extra X group according to recruitment strategy, revealed no significant differences between 'prenatal follow-up cases' and 'referred cases', see table 5. Similarly, within-group analyses (ANOVA) comparing scores in the extra X group according to country of origin (The Netherlands and Belgium), revealed no significant multivariate effect of country of origin ( $p = 0.27$ ).

### *Emotional/behavioural problems*

Multivariate MANOVA with the fixed factors group (control, extra X) and sex (boy, girl), and T scores for the eight syndrome scales of the CBCL as dependent variables, showed a significant main multivariate effect of group ( $F(8,118) = 9.1$ ,  $p < 0.001$ ) and no significant multivariate group by sex interactions ( $p = 0.85$ ). On univariate level, the group effects were significant for all syndrome scales, at  $p < 0.001$ . To illustrate individual differences in elevated levels of emotional/behavioral problems in the extra X group, the percentages of children in

the extra X group with scores in the borderline and clinical range ( $T > 65$ ) were as follows: Anxious/depressed: 27 %, Withdrawn/depressed: 37.8 %, Somatic complaints: 27.0 %, Social problems: 43.2 %, Thought problems: 37.8 %, Attention problems: 27.0 %, Rule breaking behavior: 10.8 %, Aggression: 16.2 %.

#### *Correlations between executive functioning and emotional/behavioral problems*

Correlational analysis was done within the Extra X group, with CBCL data from five children missing. Cognitive measures that showed significant group differences (i.e. Inhibition, Mental flexibility, Sustained attention and Visual working memory) were entered in Spearman correlational analysis, together with the Externalizing scores and Internalizing scores of the CBCL (resulting in a total of ten correlations that were tested). This yielded a significant correlation between inhibition skills and the CBCL Externalizing score,  $r=0.39$ ,  $p=0.02$ . To pursue this further, we examined correlations between inhibition skills and the eight individual subscales of Externalizing (resulting in a total of eight correlations that were tested). This showed significant correlations between inhibition skills and level of Aggression ( $r=0.37$ ,  $p=0.02$ ), Rulebreaking Behavior ( $r=0.36$ ,  $p=0.03$ ) en Thought Problems ( $r=0.39$ ,  $p=0.02$ ). To assess if these correlations were mediated by IQ, we reran all analyses using partial correlations, covarying for IQ. This did not change the pattern of results, as the correlations remained significant.

#### **Discussion**

The aim of the present study was to determine if sex chromosome trisomies (SCT) are associated with executive dysfunction, and to assess the impact on emotional and behavioural functioning. Overall, our findings do indicate executive dysfunction in several domains, in both boys and girls with an extra X chromosome. Using cognitive performance tests, the group of children with an extra X chromosome showed more difficulties (as compared to non-clinical controls) in areas of inhibition, mental flexibility, sustained attention and working memory. In line with this, parental report showed high levels of observable, everyday manifestations of executive dysfunction. The impact of executive dysfunction on emotional and behavioural functioning in children with SCT was illustrated by the finding that children with more inhibition difficulties had higher levels of thought

problems, aggression, and rule breaking behavior, i.e. these children had more problems in regulating their thinking and behavior.

The observation that, on average, children with SCT have difficulties with inhibition, mental flexibility, sustained attention and visual working memory, fits with some of the previous studies on cognitive functioning in SCT showing deficits in working memory (Fales *et al.*, 2003, Stewart *et al.*, 1982), inhibition (Kompus *et al.*, 2011, Stewart *et al.*, 1982, Van Rijn *et al.*, 2009), mental flexibility (Bender *et al.*, 2001, Bender *et al.*, 1993, Van Rijn *et al.*, 2009, Van Rijn *et al.*, 2012), attention (Ross *et al.*, 2009), or composite EF deficits (Boone *et al.*, 2001, Lee *et al.*, 2011). However, intact inhibition and mental flexibility has also been reported (Ross *et al.*, 2008). In the current study, between 23% and 37% of the children had severe problems in executive functioning (EF), depending on EF domain. Although many of the children showed difficulties in these areas of EF, we did not find significant impairments in other areas, such as (instability of) information processing speed, focused attention problems and difficulty in verbal working memory. However, for certain tests, such as the focused attention test, data of some children with SCT were lacking, reasons for which varied from premature ending of the test session due to overall fatigue of the children, more limited testing time due to increased travel-time for families in the clinical group, or technical problems. This may have resulted in less statistical power to detect group differences. The lack of group differences in verbal working memory was unexpected, considering that typically verbal working memory impairments are found, although in most studies working memory is solely assessed within the verbal domain. Our findings show that at least visual working memory is impaired, suggesting that working memory deficits (also) exist outside the verbal domain. Overall, our finding that some areas of EF are intact, merely underlines the specificity of the EF deficits, and argues against a profile of 'overall' lower functioning.

This study was unique in evaluating a broad range of EF functions, and showed that boys and girls with SCT could not be differentiated in terms of severity of deficits in EF. However, processing speed was lower in girls with XXX than boys with XXY. The evidence for similarities and differences in phenotype of boys and girls with an extra X chromosome is mixed. A review of cognitive studies (Leggett *et al.*, 2010) suggests that overall intellectual functioning is typically lower in girls than boys with SCT, which is in line with our finding of lower processing speed in girls than boys. At the same time, a more selective impairment in verbal IQ is usually found in boys. With regard to behavioural/emotional problems, Tartaglia

et al. (2012) found higher rates of ADHD in girls (52 %) as compared to boys (36 %) with SCT. In the prenatal group of Bishop et al. (2011) the profile of communication impairment was similar for boys and girls with SCT, but there was a trend for greater overall severity of impairment in boys than girls. Other studies show that boys and girls with an extra X chromosome do not differ in degree of social behavioural problems and level of autism traits (Van Rijn *et al.*, 2014), and in line with that no differences between boys and girls with SCT were found in degree of social cognition impairments (Van Rijn, in press). Our findings of lack of differences between boys and girls in the domain of EF require replication in studies with larger sample sizes, as we cannot exclude the possibility that this study may have been underpowered to detect such differences.

If replicated, it may indicate that EF deficits may be related to a characteristic that the boys and girls with SCT have in common, i.e. the extra X chromosome, rather than characteristics that differ between boys and girls, such as hormonal profiles. It is important to note here that in this study 6 out of 23 boys with an extra X chromosome were using testosterone supplements. Although this subgroup is too small for groupwise comparisons, excluding these boys from analyses did not change the pattern of significant findings. Although this is merely illustrating that our findings were not driven by this specific subgroup, we need larger studies that are specifically focused on the effects of testosterone supplements on cognitive functioning. We hope that our findings also stimulate genetic studies to explore a possible genetic contribution to executive dysfunction in SCT.

Although in many studies the boys and girls with an extra X chromosome are considered as separate groups or conditions, our findings support the notion that it may be helpful to assess the phenotype of children with an extra X with sex as a between subjects factor. This allows for a direct comparison of profiles of functioning between boys and girls, and may contribute to understanding similarities and differences between boys and girls in the context of typical sex differences in the general population. In such analyses, ascertainment strategy should also be included as a factor of interest. Although our analyses did not show differences in EF functioning between 'referred cases' and 'prenatally followed up cases', we cannot exclude that this study was underpowered to detect such differences. In terms of opportunities for early support and treatment in those who are prenatally diagnosed, it would be interesting to evaluate in future studies the impact of early support and treatment on developmental outcome, also focusing on EF.

This study was also unique in assessing the implications of EF deficits for emotional and behavioural functioning. Executive functions are typically relied upon to adapt and respond appropriately to the environment, as well as prioritize and maintain focus on goals. Therefore, impairments in EF can severely impact on a child's ability to function independently and productively in everyday life. Indeed, parents reported more daily life executive functioning problems, with a large effect size (i.e. 1.3 standard deviations increased), which shows that EF dysfunctions on cognitive performance tests do translate to 'real world' daily life difficulties in the regulation of thought, emotion and behavior. Considering the importance of understanding the impact of EF dysfunction on regulation of emotion and behavior, we also explored the relation between EF deficits and emotional and behavioral problems as measured with the Childhood Behavior Checklist (CBCL), which indicated increased T scores across all syndrome scales in the SCT group. This showed that within the SCT group, inhibition impairments were associated with increased levels of aggression/rule breaking behavior and thought problems. Thought problems were evident in a subgroup of 37.8 % who scored in the borderline and clinical range, whereas aggression was found in 16.2 % and rule breaking behavior in 10.8 % of the children with SCT. This indicates that although only a proportion of the children may be at serious risk for developing psychopathology, the correlation between EF deficits and behavior problems suggests that the children that do have EF deficits may be most vulnerable in this respect and may benefit from close monitoring. Obviously, in terms of risk for cognitive dysfunction in SCT, impaired cognitive functioning in other areas than EF has been well-documented, particularly in areas in speech and language, motor development and educational abilities (for reviews see Boada *et al.*, 2009, Leggett *et al.*, 2010). Thus, EF dysfunction should be considered in the context of a broader cognitive profile of various cognitive deficits to various degrees, which in interaction may contribute to such emotional/behavioral problems. In the current study the level of emotional/behavioral problems was assessed based on parental report, which is a limitation of the study. Not only because parental report may come with an observer bias, but also because it would be interesting to compare this to self-reports of children and adolescents.

Meta analysis has supported the notion that inhibition impairments constitute a key characteristic of aggressive behavior in children with disruptive behavior disorder (Oosterlaan *et al.*, 1998). Weak inhibitory control can lead to impulsive behaviors and acting



without taking into account the associated risks and consequences of the action. Thus, rather than 'instrumental/premeditated aggression', the children with SCT who have severe inhibition deficits may show 'reactive/impulsive aggression'. This is reflected in an (unplanned) reaction that is disproportionate to the situation, arising from difficulties in controlling emotions, thoughts and actions. Children with reactive/impulsive aggressive behavior have a tendency to 'lose their temper easily' and may (unwillingly) violate social norms due to loss of self-control, yet often show feelings of frustration, regret, guilt and fear afterwards.

Our finding that children with specifically more inhibition problems showed more severe thought problems, would be expected based on a meta-analysis identifying deficient inhibition as a significant predictor of level of thought disorder in individuals with schizophrenia (Kerns & Berenbaum, 2002). Our findings in children match up with our earlier finding that adult men with an extra X chromosome characterized by more inhibition impairments, have higher levels of thought disorder symptoms (Van Rijn *et al.*, 2009), although not necessarily as part of a psychiatric condition. Loss of cognitive inhibition may result in loss of organization and planning of thought (failure to follow a train of thought), increased thought associations, and a reduced ability to suppress irrelevant thoughts and actions.

It would be interesting to investigate in future studies if children with SCT who have the most severe EF deficits, are also the children at highest risk for neurodevelopmental disorders associated with EF dysfunction, such as autism spectrum disorder, attention deficit hyperactivity disorder and psychotic disorders (for reviews see Kenworthy *et al.*, 2008, Lipszyc & Schachar, 2010). Although the behavioral phenotype shows substantial individual variability in the SCT group, with only a proportion of the children and adults who are at serious risk for meeting clinical criteria for psychiatric conditions, there is accumulating evidence for increased vulnerability in these domains of psychopathology. A recent Swedish epidemiological study including 850 men with an extra X as compared to 86000 controls, showed increased risk for being diagnosed with ADHD (odds ratio 5.6), autism (odds ratio 6.2) and psychotic disorders (odds ratio 3.6 for schizophrenia and 3.8 for bipolar disorder) (Cederlof *et al.*, 2014). When focusing on symptoms and traits rather than psychiatric conditions, there are reports of increased levels of ADHD symptoms, autism symptoms and psychotic symptoms in a proportion of boys and men with an extra X

chromosome (Bishop *et al.*, 2011, Bruining *et al.*, 2009, Tartaglia *et al.*, 2010, Tartaglia *et al.*, 2012, Van Rijn *et al.*, 2006, Van Rijn *et al.*, 2014, Van Rijn *et al.*, 2008b). Although for females with an extra X less information is available, increased risk for ADHD symptoms has been observed by Tartaglia *et al.* (2012), and a recent study from our lab showed an increased risk for autism symptoms in girls with an extra X similar to boys with an extra X (Van Rijn *et al.*, 2014).

We propose that executive dysfunction is symptom-specific, rather than disorder-specific. Our findings suggest that executive dysfunction is also part of the phenotype of individuals with an extra X chromosome, although there are individual differences in severity, which are also seen in behaviorally defined disorders such as autism (Pellicano, 2012). Our findings call for larger and longitudinal studies in which we can study to what degree executive dysfunction is predictive of risk for psychopathology prospectively. As an extra X chromosome can be identified as early as prenatally, there are opportunities to study the development of such cognitive functions already early in development.

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## TABLES

**Table 1** Demographic characteristics of the Control group and Extra X group

	Controls (n=100)		Extra X (n=40)		Group differences
	Boys (n=47)	Girls (n=53)	Boys (n=23)	Girls (n=17)	
<b>age</b>	12.27 (2.89)	12.52 (3.15)	13.52 (3.12)	12.20 (2.56)	Group: p=0.42 Group by sex: p=0.17
<b>IQ</b>	101.59 (13.08)	102.34 (12.46)	87.03 (10.69)	86.52 (14.38)	Group: F(1,136)=40.44, p<0.001 Group by sex: p=0.79

**Table 2.** Means and standard deviations for specific domains of cognition in the Extra X group as compared to the control group. \* significant at  $p < 0.05$

	<b>Controls</b> <i>n=100</i> (mean $\pm$ SD)	<b>Extra X</b> <i>n=40</i> (mean $\pm$ SD)	<i>Univariate</i> <i>group</i> <i>differences</i>	<i>Univariate</i> <i>group by sex</i> <i>interactions</i>
Information processing speed (ms)	332.69 $\pm$ 72.38	332.38 $\pm$ 66.06	$p=0.75$	$p=0.17$
Stability of information processing speed (ms)	124.54 $\pm$ 76.58	137.20 $\pm$ 122.47	$p=0.34$	$p=0.52$
Inhibition (number of errors)	3.50 $\pm$ 4.73	5.56 $\pm$ 6.01	$p=0.02^*$	$p=0.29$
Mental flexibility (number of errors)	5.77 $\pm$ 7.28	9.25 $\pm$ 8.17	$p=0.009^*$	$p=0.65$
Focused attention (RT gain)	163.89 $\pm$ 141.82	149.16 $\pm$ 109.43	$p=0.68$	$p=0.66$
Sustained attention (% errors)	7.28 $\pm$ 4.47	9.40 $\pm$ 7.91	$p=0.03^*$	$p=0.71$
Visual working memory (number correct)	58.75 $\pm$ 18.26	46.24 $\pm$ 18.31	$p=0.04^*$	$p=0.56$
Verbal working memory (number correct series)	5.3 $\pm$ 1.6	5.1 $\pm$ 2.2	$p=0.22$	$p=0.44$
Daily life executive dysfunction (total DEX score)	15.83 $\pm$ 10.37	31.61 $\pm$ 12.61	$p < 0.001^*$	$p=0.42$

**Table 3.** Frequencies of normscores in the Extra X group.

	% children with extra X chromosome		
	<i>Intact</i> ( $Z < 1.5$ )	<i>Borderline</i> ( $1.5 > Z < 2$ )	<i>Impaired</i> ( $Z > 2$ )
information processing speed	86.8 %	2.6 %	10.5 %
stability of information processing speed	84.2 %	2.6 %	13.2 %
attentional control: tempo	78.4 %	5.4 %	16.2 %
attention regulation (stability of tempo)	78.4 %	5.4 %	16.2 %
attentional control: number of misses	70.3 %	5.4 %	24.3 %
Inhibition (errors part 2 minus part 1)	71.0 %	5.3 %	23.7 %

mental flexibility (errors part 3 minus part 1)	54.1 %	8.1 %	37.8 %
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**Table 4 .** Means and standard deviations for specific domains of cognition in boys (XXY) versus girls (XXX) with an extra X chromosome.

	<i>XXY</i> <i>n=23</i> <i>(mean ± SD)</i>	<i>XXX</i> <i>n=17</i> <i>(mean ± SD)</i>	<i>Group</i> <i>differences</i>
Information processing speed (ms)	309.87 ± 55.78	362.82 ± 68.15	p=0.01*
Stability of information processing speed (ms)	119.43 ± 112.41	161.24 ± 134.6	p=0.30
Inhibition (number of errors)	4.56 ± 5.28	6.17 ± 7.46	p=0.26
Mental flexibility (number of errors)	8.39 ± 7.47	10.50 ± 9.20	p=0.93
Focused attention (RT gain)	139.58 ± 132.27	161.69 ± 72.87	p=0.77
Sustained attention (% errors)	7.76 ± 6.63	11.51 ± 9.09	p=0.14
Visual working memory (number correct)	48.71 ± 16.88	43.00 ± 20.11	p=0.75
Verbal working memory (number correct series)	5.45 ± 2.55	4.76 ± 1.7	p=0.35

Daily life executive dysfunction (total DEX score)	33.73 ± 10.23	28.69 ± 15.17	p=0.23
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**Table 5.** Means and standard deviations for specific domains of cognition within the Extra X group specified according to recruitment strategy

	<i>Prenatal follow-up</i> <i>n=21</i> <i>(mean ± SD)</i>	<i>Referred</i> <i>n=19</i> <i>(mean ± SD)</i>	<i>Group differences</i>
Information processing speed (ms)	350.52 ± 74.53	312.32 ± 49.73	p=0.08
Stability of information processing speed (ms)	169.24 ± 156.18	101.79 ± 53.62	p=0.08
Inhibition (number of errors)	4.19 ± 6.54	6.42 ± 5.88	p=0.27
Mental flexibility (number of errors)	8.80 ± 8.55	9.77 ± 7.92	p=0.72
Focused attention (RT gain)	137.58 ± 110.34	164.30 ± 110.75	p=0.52
Sustained attention (% errors)	7.30 ± 5.34	11.85 ± 9.73	p=0.08
Visual working memory (number correct)	49.26 ± 22.56	43.06 ± 12.24	p=0.31
Verbal working memory (number correct series)	4.95 ± 2.18	5.37 ± 2.36	p=0.57



Daily life executive dysfunction (total DEX score)	31.62 ± 13.53	31.59 ± 11.79	p=0.99
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