# Executive functions and autism traits in Sex Chromosome Trisomies compared to typically developing children

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## Abstract

Individuals with a SCT characterized with an additional X chromosome encounter difficulties in social functioning, which is most prominent in there higher susceptibility for developing autism. The current study aimed to systematically address underlying mechanisms related to these difficulties by examining differences in executive functions of children with a SCT karyotype and typically developing children. Furthermore, we examined to what extent executive function deficits were related to higher autism traits. 135 boys and girls ($M$ = 11.4, $SD$ = .2) participated in this study, 85 typically developing children and 50 children with a SCT. We used computerized tasks, a questionnaire, and a verbal task to asses a wide range of executive functions. A questionnaire was used to address autism traits. Children with a SCT showed increased difficulties in encoding verbal information, cognitive flexibility, sustained attention, and more difficulties in executive functions during daily life compared to the typically developing children. Higher autism traits were associated with more difficulties in executive functions during daily life, cognitive flexibility, and encoding verbal information. This provides evidence for impairments in executive functions among individuals with a SCT of which some of them are related to increased difficulties in social functioning. Limitations and implications for future research are discussed.

**Executive functions and autism traits in Sex Chromosome Trisomies compared to typically developing children**

Sex chromosome trisomies (SCT) occur as a consequence of deficiencies during the maternal or paternal meiosis process. Klinefelter syndrome (KS), characterized by the karyotype 47 XXY, is the most common sex chromosomal disorder among males. Its prevalence is estimated on one in 650 men (Bojesen, Juul, & Gravholt, 2003). Individuals with KS are infertile and encounter androgen deficiencies which can lead to the development of small testis or breast development (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009). Although KS is not rare, recognizing individuals with KS is difficult due to the fact that the physical impairments are not always clearly apparent, in particular during early development. The androgen deficiencies can become clearer during puberty when the secretion of testosterone appears to be insufficient. Further medical examinations can lead to an identification of Klinefelter syndrome. However, some individuals with KS even remain unidentified.

Women can also be born with an additional X chromosome, resulting in the karyotype 47 XXX. This syndrome is often referred to as Triple X syndrome and its prevalence is estimated on one in 1000 females (Jacobs, 1979). The majority of these females tend to have a tall stature, others can encounter epicanthal folds, hypotonia during infancy, and genitourinary malformations ranging from unilateral kidney and renal dysplasia to ovarian malformations (see for an overview Tartaglia, Howell, Sutherland, Wilson, & Wilson, 2010). However, there is a need for more medical and psychological research with regard to the Triple X population (Tartaglia et al, 2010).

Although the behavioral phenotype among individuals with KS and Triple X is variable, studies have repeatedly shown higher risks for developing psychopathology among both syndromes (e.g. Bojesen, Juul, Birkebaek, & Gravolt, 2006; Van Rijn, Swaab, Aleman, & Kahn, 2008; Van Rijn & Swaab, 2011; Linden, Bender, Harmon, Mrazek, & Robinson, 1988; Bender, Harmon, Linden, & Robinson, 1995). In particular a susceptibility for developing difficulties in social functioning, which is most clear in their higher vulnerability for developing autism spectrum disorders (Van Rijn et al., 2008; Tartaglia et al., 2010). Social functioning is essential for forming relationships with others, which in turns facilitates functioning in this complex society (Cacioppo, 2002). Difficulties in social functioning can have negative consequences, e.g. psychological distress, low self-esteem, and social isolation (Beauchamp & Anderson, 2010), which have been observed in individuals with KS and Triple X syndrome (Rattcliffe, 1982; Linden et al., 1988; DeLisi, 1994; Woodhouse, Holland,

McClean, & Reveley, 1992; Kusumi & Prange, 1973). The challenges that individuals with KS and Triple X encounter with regard to their susceptibility for difficulties in social interaction and their higher vulnerability for developing psychopathology including autism spectrum disorders stresses the importance to search for underlying mechanisms.

From a neuropsychological perspective we are able to examine which cognitive mechanisms are possibly associated to this vulnerability. Previous studies among individuals with KS and Triple X provides us the ability to speculate about different mechanisms. For instance, we know that one of the core deficits among individuals with KS and Triple X are language deficiencies (e.g. Rattcliffe, 1982; Geschwind & Dykens, 2004; for an overview see Boada et al., 2009; Legget, Jacobs, Nation, Scerif, & Bishop, 2010). Encountering difficulties in language obviously affect social interaction and communication. Additionally, difficulties in the recognition of facial expressions such as anger have also been found among males with KS (Van Rijn, Swaab, Aleman, & Kahn, 2006b). Being less efficient in recognizing facial affect can result in difficulties in social functioning. However, higher order cognitive functions, referred to as executive functions, may also be involved and of specific interest to examine. Executive functions are essential during daily life, they are associated with the regulation of behavior and emotion (Beauchamp & Anderson, 2010), which is suggested to be impaired among individuals with KS and Triple X (Visootsak & Graham, 2009; Boada et al., 2009; Tartaglia et al., 2010; Legget et al., 2010). An important component of executive skills is cognitive flexibility. It is ‘the ability to shift to a different thought or action according to a changing situation’ (Hill, 2004, p. 197). Other important components are attention skills, inhibition and the ability to shortly hold information online in order to plan a response; working memory (Baddeley, 2000). Earlier studies have suggested impairments in inhibition and verbal working memory among individuals with KS (Temple & Sanfilippo, 2003; Kopmus et al., 2011; Fales et al., 2003). However, due to methodological limitations across these studies, such as small samples, no standardized measurements, and no control groups (Boada et al., 2009), firm conclusions concerning this matter are unable to be drawn. Especially with regard to Triple X syndrome, since no studies to date have investigated the executive functions among females with Triple X (Tartaglia et al., 2010).

The social difficulties that individuals with KS can encounter are most prominent in their higher susceptibility for developing autism (Van Rijn, Swaab, Aleman, & Kahn, 2008). The literature on autism spectrum disorders could therefore provide us additional knowledge about possible underlying mechanisms related to difficulties in social functioning in children

and adults with an extra X chromosome. From this literature it is frequently suggested that individuals with autism tend to encounter difficulties on several executive skills, including working memory, attention skills (Hill, 2004; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006; Williams, Goldstein, Carpenter, & Minshew, 2005; Steele, Minshew, Luna, & Sweeney, 2007; Burack, 1994; Goldstein, Johnson, & Minshew, 2001) and cognitive flexibility (Geurts, Roeyers, Oosterlan, & Sergeant, 2004; Hill, 2004). However, earlier studies are repeatedly unclear whether there is a deficit in inhibition among individuals with autism, or that this skill is partly affected (e.g. Tsai, Pan, Wang, Tseng, & Hsieh, 2011; Christ, Kester, Bodner, & Miles, 2011; Russell, Mauthner, Sharpe & Tidswell, 1991; Hughes & Russell, 1993; Lemon, Gargaro, Enticott, & Rinehart, 2010; Mosconi et al., 2009). More specifically, it seems to be unclear whether individuals with an autism spectrum disorder have difficulties in inhibition to prepotent responses or that the broader skill is affected (for an overview see Hill, 2004).

In the current study executive skills are of specific interest due to their importance in daily life and their association with regulating behavior and emotions (Beauchamp & Anderson, 2010), which is important in social interactions. More specifically, this study aims to examine to what extend children with KS and Triple X syndrome between 9 and 18 years of age encounter executive function deficits compared to typically developing children and whether this is related to a higher susceptibility for social difficulties and autism traits. This study will contribute to retrieving more insight into possible underlying cognitive mechanisms possibly related to difficulties in social interaction among KS and Triple X syndrome. This knowledge can be used to enhance treatments, diagnosis, and prevention. Having knowledge about the cognitive profiles of both syndromes, creates the opportunity to rely on their strengths and stimulate their weaknesses during treatments. Moreover, it provides guidelines for diagnostics, and helps in identifying those functions that require monitoring during development.

## Methods

### Sample

In total 134 boys and girls participated in this study consisting out of 85 typically developing children, 27 boys with KS and 23 girls with Triple X. Further characteristics of the sample size are presented in Table 1. Participants with KS were recruited through the Dutch Klinefelter Association, whereas the participants with Triple X syndrome were recruited

through the Triple X association. Both groups were also recruited via clinical genetics departments for follow-up after prenatal diagnosis. Controls were recruited through local schools in the south-west part of the Netherlands. Five boys with KS used testosterone supplements. Diagnosis with karyotype 47 XXY and XXX was examined and confirmed using standard procedures. One-way ANOVA revealed differences in cognitive abilities between the SCT's and the controls based on the subtests block design and vocabulary of the Dutch version of the Wechsler's Intelligence Scale (Kort et al., 2005), $F(1, 126) = 68.28$, $p < .001$. Children with a SCT ($M = 79.83$, $SD = 16.68$) had a lower estimate full scale IQ compared to controls ($M = 103.24$, $SD = 14.30$). However, their cognitive abilities were still within the normal range. Exclusion criteria for all participants were neurological conditions and intellectual disability. Written informed consents were obtained after full clarification was given with regard to the study.

Table 1

*Sample size and mean ages in SCT and typically developing participants*

| Group | *N* | *M* | *SD* | Min | Max |
|---|---|---|---|---|---|
| 47 XXY | 27 | 13.6 | .6 | 8.1 | 19 |
| 47 XXX | 22 | 12.1 | .6 | 7.4 | 18.2 |
| Total SCT | 49 | 13 | .4 | 7.4 | 19 |
| Control | 85 | 10.6 | .1 | 9 | 14.2 |
| Total | 134 | 11.4 | .2 | 7.4 | 19 |

**Procedure**

Children were asked to visit Leiden University with their parents for either two mornings (9-13 years) or one day depending one day (older than 13 years) . Trained research assistants administered all the tests. The child completed several computer tasks and paper-pencil tasks interrupted by sufficient breaks in a quiet room without distractions. After completing the tasks children received a token. The parents completed the questionnaires and the Autism Diagnostic Interview (Lord, Rutte, & Le Couteur, 1994) with a certified neuropsychologist.

## Measurement instruments

### Autism traits

The degree of autism traits were measured using the Autism-spectrum Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). This questionnaire aims to measure the degree of autism traits among individuals who have intelligence within the normal range (Baron-Cohen et al., 2001). Different questionnaires are developed, one self-administered questionnaire for adults and adolescents, whereas a parental version has been developed for children. Test-retest reliability and discriminative validity is sufficient for individuals with Asperger syndrome within a clinical population using a cut off score of 26 (Woodbury-Smith, Robinson, Wheelwright, Baron-Cohen, 2005) and within the general population using a cut off score of 32 (Baron-Cohen et al., 2001). The AQ-questionnaire consists out of 50 questions equally divided in the following subscales: social skills, communication, imagination, attention to detail, and attention switching (Baron-Cohen et al., 2001). A higher the score on the AQ-questionnaire indicates a higher degree of autism traits (Baron-Cohen et al., 2011).

### Executive functions

#### *Amsterdam Neuropsychological Tasks (ANT)*

Speed and stability of information processing, visual working memory, inhibition, cognitive flexibility, sustained attention, and divided attention were all measured using the ANT (De Sonneville, 1999). The ANT test battery has been proven to be helpful in assessing neurocognitive deficit profiles in clinical and typically developing populations (Rommelse et al., 2008; Serra et al., 2003). Moreover, several studies found satisfactory psychometric properties of the test battery (for an overview see De Sonneville, 2005).

#### *Speed and stability of information processing*

Speed and stability of information processing was measured using the Baseline Speed (BS) of the ANT (De Sonneville, 1999). During this task a cross changed unexpectedly into a square. Children were instructed to press the mouse button when the cross changed into a square and not when they expected the cross to change. Furthermore, they had to maintain their focus on the cross since it could change unexpectedly into a square again. This was done

twice, first with the not preferred hand and secondly with the preferred hand of the child. Dependent measure of the task was reaction time.

***Visual Working memory***

Visual working memory was measured using the Spatial Temporal Span (STS) of the ANT (De Sonneville, 1999). The STS task consisted out of a forward and backward condition each consisting out of three sessions: an instruction session, a practice session, and a test session. Children were asked to watch the computer screen in which a three by three square grid appeared. They were instructed to press space on the keyboard after which a computer hand appointed several squares in a particular order. After the computer hand pointed to the last square, children had to point to the same squares in the same sequence and confirm their answer by pressing space. This was repeated until children were unable to complete five sequences in a row. Difficulty level was increased by increasing the number of squares in the sequence. During the backward trial, children were asked to appoint to the square in reversed order. Main outcome parameters are amount of correct completed series forward and correct completed series backward separately. The correct completed series forwards indicates imprinting abilities, whereas the amount of correct completed series backward indicate actual working memory since the children had to hold the particular sequence 'online' to manipulate that information in order to appoint the reversed sequence.

***Cognitive flexibility and inhibition***

Cognitive flexibility and inhibition were measured using the task Shifting Attentional Set (SSV) of the ANT (De Sonneville, 2005). During this task a colored square randomly moved to the right or the left on a horizontal bar which was presented on the screen. Depending on the color of the square children had to either copy the movement of the square or 'mirror' the movement of the square. The children had to copy the movement of the square by pressing in the same direction as the square went; if the square moved to the right (left) children had to press right (left). If the children had to 'mirror' the movement of the square they had to press right (left) when the square moved to the left (right). The SSV task consisted out of three parts each proceeded by an instruction and a practice session. The first part consisted out of 40 trials in which the children had to copy the movements of green squares. During the second condition the children had to 'mirror' the movements of red squares in again 40 trials, which required the inhibition of prepotent responses. During the third condition the copy and mirror parts were combined. The third condition consisted out of 80

trials in which the green and red squares appeared in random fashion on the horizontal bar which forced the children to shift between response set, which requires cognitive flexibility. Latter condition was measured separately for the green and red squares; a variable copy condition and a variable 'mirror' condition. Preceding all test conditions there was an instruction and practice session. Accuracy and reaction times were the dependent measures, with percentage errors and reaction time of the mirror trial indicating inhibition and percentage errors and reaction times of the mixed trial indicating cognitive flexibility.

***Sustained attention***

Sustained attention was measured using the Sustained attention dots task (SAD) of the ANT. This task consisted out of an instruction, practice, and test session. During this task a square appeared at the middle of the computer screen in which three, four, or five dots were equally presented over 600 trials in random order. Children were asked to press 'yes' when four dots appeared at the screen, when more or less than four dots appeared children were instructed to press 'no'. Auditory feedback was given to the children when they made an error. Sustained attention capability was measured in terms of accuracy and reaction time as well as stability of reaction times (attention fluctuation). Accuracy was measured using mean percentage errors, false alarms (pressing a button while no target stimulus was apparent), and missed responses (no response was given to a target stimulus) over all 600 trials. The 600 trials were divided over five separate blocks which create the opportunity to measure sustained attention capabilities during the task; measuring time on task effects. Dependent measures during the time on task effects were also percentage errors, in terms of percentage false alarms, missed responses, and rate of attention fluctuation over the five different time blocks.

***Focused attention***

Focused attention was measured using the Focused Attention Objects 2 (FAO2) of the ANT (De Sonneville, 1999). A fruit plate appeared at the computer screen in which four different types of fruit were presented on an invisible horizontal and vertical line. Children were instructed that the place of cherries on the fruit plate were most important. If the cherries were on the invisible horizontal line children had to press 'yes' on the mouse, when the cherries were on the vertical line or not presented on the fruit plate, they had to press 'no'. Preceding the task instruction was given and children were able to practice. Dependent measures were accuracy and reaction time. Accuracy was measured with regard to the

difference in amount of errors when the cherries were on the correct place and the amount of errors when the cherries were in the wrong place. Reaction time was measured using the difference between reaction time when the cherries were on the correct line and the reaction time when the cherries were on the incorrect line.

***Verbal working memory***

Verbal working memory was measured using the subtest digit span of the Clinical Evaluation of Language Fundamentals (CELF) – 4 NL (Kort, Compaan, Schittekatte, & Dekker, 2008). This task consisted out of two conditions; a forward and a backward condition. During the forwards condition the children were asked to repeat verbally a particular sequence of digits. During the backward condition, children were asked to manipulate the digit spans in working memory by verbally repeating the digit sequence in reversed order. In both conditions difficulty level was increased, by increasing the amount of digits to repeat. Each condition was aborted when the participant was unable to complete two trials of similar difficulty level. Children were able to obtain a maximum score of sixteen on the first condition and fourteen on the second condition. Amount of correct repeated sequences during the forward condition indicated imprinting abilities whereas the amount of correct completed backward sequences indicated working memory abilities.

***Executive functions in daily life***

The Dysexecutive (DEX) questionnaire aims to measure behavior that is associated with difficulties in executive functioning during day to day life (Wilson, Alderman, Burgess, Emslie, & Evans, 2003). The questionnaire consists out of 20 items in which participants, in the current study parents, are asked to rate on a Likert scale (from ‘never’ to ‘often’) to what extent an item applies to their child. The questionnaire covers a wide range of executive functions including, inhibition, attention, memory, information processing, awareness, and behavioral and emotional control (Simblett & Bateman, 2011). The questionnaire is found to be sensitive in measuring executive dysfunctions after brain injury (Bennet, Ong, & Ponsford, 2005; Chan, 2001) and is recently been used as a quantitative instrument for diagnostic purposes (Bennet et al., 2005). The total score on the DEX questionnaire was used as dependent measure during analyses; higher total score indicated more difficulties with activities that require executive functions during daily life.

**Statistics**

Primarily, ANOVA's were used to investigate whether there are differences in autism traits between typically developing children (control group) and participants with a SCT (SCT karyotype), using both as the independent variable and the different AQ scales as the dependent variables. Second, ANCOVA's were used to examine whether there were differences between typically developing children and the SCT karyotype on several executive functions, using controls and SCT karyotype as the independent variable and the different dependent measures of the executive functions as the dependent variables. For speed and stability of information processing this was reaction time, for visual and verbal working memory amount of correct recalled series forward and backward, for inhibition and cognitive flexibility percentage errors and reaction time. For sustained attention the dependent measures were percentage errors and attention fluctuation. Significant differences in ages were found between the three groups, $F$ (1, 128) = 44.2, $p < .001$ (means and standard deviations are presented in Table 1). Therefore, age was used as a covariate variable together with education of the father as indicator of SES. Reason to control for SES is that SES can influence cognitive abilities (Sarsour et al., 2011). Since the current study is focused on differences in executive functions independent of SES, controlling for SES is desirable. Furthermore, five Repeated Measures ANOVA's were analyzed in order to assess time on task effects during the sustained attention task. Controls and SCT karyotype were used as between-subject variables, the five different time blocks as within-subject variables with regard to percentage errors, percentage misses, and percentage false alarms, together with attention fluctuation in mean rate of fluctuation and mean tempo during the task. Again, age and SES were used as covariates. One participant was removed during this analysis since this participant fell with more than two standard deviations outside the sample distribution. Finally, Spearman's correlations were calculated between the AQ total score and the executive functions that were significantly impaired in the SCT children as compared to the control group. All analyses were done using statistical software SPSS version 19. Level of significance was set at $\alpha = 0.05$.

## Results

### Autism traits

A significant difference was found between typically developing children (controls) and the SCT karyotype on the total score of the AQ questionnaire, $F$ (1, 121) = 37.5, $p < .001$. The SCT group had a higher total score ($M$= 21.6, $SD$= 8) on the AQ questionnaire than the control group ($M$= 12.8, $SD$= 5.6). Furthermore, differences were also found between the controls and SCT karyotype on subscale level with regard to: social skills, dividing attention, communication, and imaginary skills (Table 2). Children with SCT karyotype had a higher score on all those subscales compared to the control group (Table 2). However, on the attention to detail scale no differences were found between the groups. The SCT group did not have a higher or lower score compared to the control group on this scale.

Table 2

Autism traits among SCT karyotype and controls

| | Controls | SCT | |
|---|---|---|---|
| Scale | *M (SD)* | *M (SD)* | *p* |
| Social skills | 1.6 (1.6) | 3.77 (2.73) | < .001* |
| Dividing attention | 2.93 (1.86) | 5.47 (1.91) | < .001* |
| Communication | 1.94 (1.72) | 4.20 (2.14) | < .001* |
| Attention to detail | 4.28 (2.00) | 4.23 (2.25) | .79 |
| Imaginary skills | 2.04 (1.54) | 3.73 (2.42) | .001* |
| Total score | 12.80 (6.03) | 21.40 (8.52) | < .001* |

*Note.* SCT's $N$ = 39, controls $N$ = 84, $df$ = 1, 121, * = $p < .01$

### Speed and stability of information processing

No significant differences were found in mean reaction time between the SCT karyotype and the control group, $F$ (1, 106) = .16, $p$ = .70. These findings indicate that the SCT karyotype ($M$= 329.04, $SD$= 64.84) did not had a slower or faster reaction time compared to the control group ($M$= 356.45, $SD$= 68.24) on the task, indicating no impairments in speed and stability of information processing in the SCT karyotype.

**Visual working memory**

For the correct recalled series forward, no significant difference was found between the SCT karyotype and the control group, $F(1, 103)= 1.37$, $p = .24$. Findings indicate that the performance of SCT karyotype ($M= 10.44$, $SD= 2.22$) on the visual working memory task is comparable to the control group performance ($M= 10.48$, $SD= 2.04$), indicating no difficulties in memory encoding in the SCT karyotype.

With regard to the backward condition, again no significant difference was found between the SCT karyotype and the control group, $F(1, 103) = .28$, $p = .60$. This indicates that the performance of the SCT karyotype ($M= 10.48$, $SD= 3.43$) on the visual working memory task is comparable to the control group performance ($M= 9.57$, $SD= 2.11$). In other words, no evidence for impairments in visual working memory.

**Verbal working memory**

A significant difference was found between the SCT karyotype and control group in the percentage correct recalled digit sequences forwards $F(1, 105) = .02$, $p < .05$, *partial* $\square = .05$. The SCT group ($M= 46.31$, $SD= 10.29$) obtained a lower percentage correct recalled digit sequences than the control group ($M= 49.33$, $SD= 8.84$). In other words, the SCT karyotype showed impairments in verbal memory encoding independent of age en SES.

For the backward condition no significant difference was found between the SCT karyotype ($M= 38.78$, $SD= 13.60$) and the control group ($M= 34.17$, $SD= 9.87$) in the percentage correct recalled digit sequences, $F(1, 105) = .52$, $p = .47$. These findings indicate no impairments in visual working memory among SCT karyotype.

**Inhibition**

No significant difference was found in amount of errors between the SCT karyotype ($M= 7.54$, $SD= 7.37$) and the control group ($M= 5.99$, $SD= 6.65$), $F(1, 106) = 1.83$, $p = .18$. Furthermore, no significant difference was found between the SCT karyotype ($M= 682.32$, $SD= 192.05$) and the control group ($M= 848.90$, $SD= 261.43$)in reaction time, $F(1, 106) = 3.21$, $p = .08$. These findings indicate no impairments in inhibition among the SCT karyotype.

**Cognitive flexibility**

A significant difference was found in accuracy during the cognitive flexibility task between the SCT karyotype and the control group, $F(1, 104) = 3.83$, $p = .05$, *partial* $\square^2 = .04$. The SCT karyotype ($M = 9.96$, $SD = 7.06$) made more errors during the task compared to the control group ($M = 7.06$, $SD = 6.55$). Additionally, a significant difference was found in reaction time between the SCT karyotype and the control group, $F(1, 104) = 4.67$, $p < .05$, *partial* $\square^2 = .04$. The control group ($M = 1156.57$, $SD = 276.16$) obtained a higher reaction time compared to SCT karyotype ($M = 937.11$, $SD = 357.85$). The SCT karyotype was less accurate and had a lower reaction time (i.e. a higher speed) during the cognitive flexibility task than the control group, indicating difficulties in cognitive flexibility in the SCT karyotype group.

**Focused attention**

No significant difference was found in accuracy between the SCT karyotype ($M = -.85$, $SD = .99$) and the control group ($M = -1.10$, $SD = 1.82$), $F(1, 103) = .15$, $p = .70$. Moreover, no significant difference was found in reaction time when comparing to the SCT karyotype ($M = 142.63$, $SD = 106.60$) and the control group ($M = 178.44$, $SD = 148.44$), $F(1, 103) = .52$, $p = .47$. In other words the SCT karyotype did not have a higher or lower reaction time, nor were they more or less accurate during the focused attention task compared to the control group, indicating no impairment in focused attention.

**Sustained attention**

Significant difference was found in accuracy between the SCT karyotype and the control group for the sustained attention task. The SCT karyotype made more errors compared to the controls including more false alarms and missed responses. Results, means, and standard deviations are presented in Table 4. No significant difference was found in reaction time after an error between both groups, $F(1, 103) = .18$, $p = .67$.

When analyzing time on task effects, the repeated measures ANOVA yielded significant interaction effects between the two groups on percentage errors and percentage missed responses over the five time periods. Mauchly's test indicated that that the assumptions of sphericity had been violated for both percentage missed responses, $\chi^2(9) = 15.42$, $p < .05$ and percentage errors, $\chi^2(9) = 25.29$, $p < .05$, therefore multivariate tests are reported using Pillai's Trace. Results indicate that the SCT karyotype made increasingly more

errors compared to the control group from the first to the fifth time period, $V = .11, F(4, 101), p < .05$. More specifically, the SCT karyotype had more missed responses than the control group $V = .10$, $F(4, 101)$, $p < .05$. Figure 1 and Figure 2 illustrate this effect. No significant interaction was found between both groups and percentage false alarms, $V = .06$, $F(4, 101) = 1.72$, $p = .15$. Again multivariate statistics were reported since Mauchly's test indicated that the assumptions of sphericity had been violated, $\chi^2(9) = 17.38$, $p < .05$.

With regard to mean rate of fluctuation during the task, findings indicated a main effect meaning in that all participants obtained a higher mean rate of attention fluctuation from the first to the fifth time period of the task (Figure 3), $V = .09$, $F(4, 101) = 2.46$, $p = .05$. Again Mauchly's test was significant, $\chi^2(9) = 20.52$, $p < .05$, therefore multivariate tests are reported using Pillai's Trace. No significant interaction was found between the two groups on mean rate of fluctuation during the task $V = .04$, $F(4, 101) = .95$, $p = .44$, indicating that the SCT and control group did not differ in the attention fluctuation during the task.

In sum, the SCT karyotype showed impairments in sustained attention in that they became less accurate during the task than the controls; they made increasingly more errors during the task. They showed an increase in their attention fluctuation but did not differ in that from controls.

Table 4

*Sustained attention among controls and SCT karyotype*

| | Controls | SCT | | |
|---|---|---|---|---|
| Accuracy indices | *M (SD)* | *M (SD)* | *p* | □² |
| Percentage errors | 6.93 (4.09) | 8.11 (7.07) | .02* | .05 |
| Percentage false alarms | 3.70 (2.82) | 4.41 (4.70) | .03* | .047 |
| Percentage missed | 13.38 (8.24) | 15.51 (12.72) | .03* | .044 |
| Attention fluctuation | 2.55 (1.03) | 2.46 (1.13) | .42 | .006 |

*Note.* Controls ($N = 82$), SCT ($N = 28$), $df = 1, 106$, * = $p < .05$

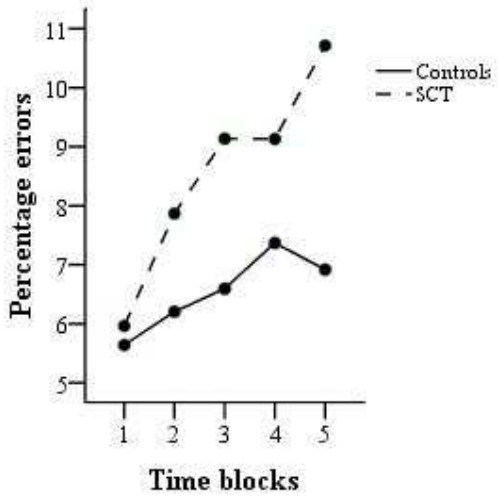


*Figure 1.* Percentage errors for controls and SCT

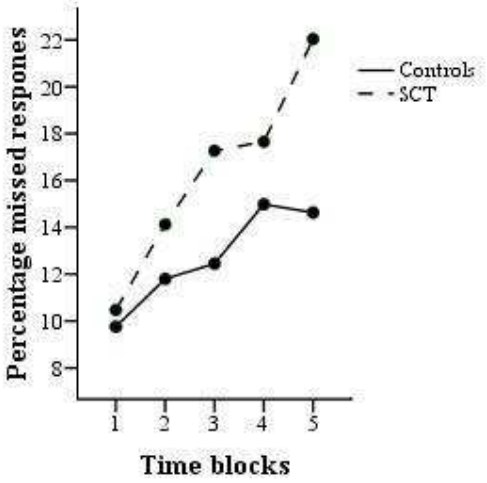


*Figure 2.* Percentage missing for controls and SCT

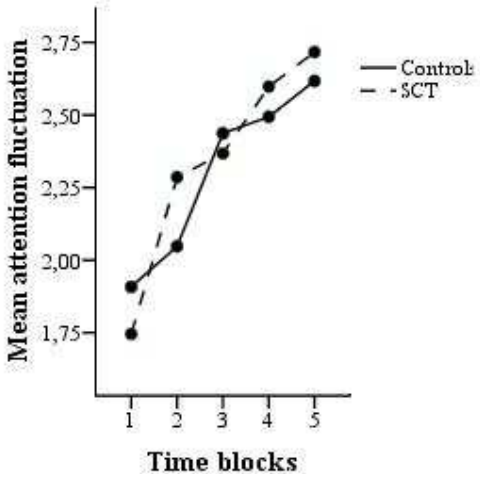


*Figure 3.* Mean rate fluctuation for controls and SCT

**Executive functions in daily life**

A significant effect was found of group on total score on the DEX questionnaire, $F(1,106) = 20.10$, $p < .001$, *partial* $\square^2 = .16$. The SCT karyotype ($M = 27.83$, $SD = 13.29$) obtained a higher score on the DEX questionnaire compared to the control group ($M = 16.43$, $SD = 10.81$) in this sample.

**Higher autism traits association with executive functions**

Spearman's correlation was computed between the executive functions that were found to be significant in the SCT karyotype and autism traits using the AQ total score. More specifically, Spearman's correlation was computed for the variables cognitive flexibility, digit

span forward, total score of the DEX questionnaire, and the overall accuracy indices of the sustained attention task mean percentage errors, percentage false alarms, and percentage missed responses with autism traits. Results showed a significant association between amount of errors during the cognitive flexibility task and total score on the AQ questionnaire, $r_s = .19$, $p < .01$. Higher autism traits were related to the percentage errors of the cognitive flexibility task. Digit span forward was negatively related to the AQ total score indicating that higher autism traits were related with lower performances on imprinting abilities, $r_s = -.20$, $p < .05$. Furthermore, a significant association was found between the total score of the DEX questionnaire and the total AQ score, $r_s = .63$, $p < .01$. Higher autism traits were related to more difficulties in executive functions in daily life. Percentage errors, $r_s = .04$, $p = .65$ false alarms, $r_s = .05$, $p = .59$ and missed responses, $r_s = .04$, $p = .66$ of the sustained attention task were not significantly related to the AQ total score. This indicates that autism traits were not related to accuracy in sustained attention.

## Discussion

The current study addressed to what extend children with a SCT characterized with an additional X chromosome have executive function deficits compared to typically developing children. A second aim of the study was to examine whether the executive function deficiencies among the children with a SCT karyotype were related to impaired social functioning, including autism traits. A wide range of executive functions were examined including speed and stability of information processing, working memory, cognitive flexibility, inhibition, focused attention, sustained attention, and functioning of executive skills in daily life.

The present study found that children with a SCT encounter more difficulties in daily activities that require executive functions measured with the DEX questionnaire than typically developing children. They also showed deficits in encoding verbal information. With regard to their cognitive flexibility, the children with a SCT showed a low reaction time (i.e. high speed) during the task but at a cost of accuracy; they made more errors than the typically developing children. These findings suggest that individuals with a SCT encounter difficulties in cognitive flexibility. Another interesting finding is that during the sustained attention task children with a SCT were less accurate than the control group. They had more missed responses and made more false alarms than the controls. Moreover, time on task effects additionally revealed that the children with a SCT made increasingly more missed responses

in turn making them increasingly less accurate during the sustained attention task than controls. Children with a SCT karyotype also showed an increase in their attention fluctuation during the task. However the typically developing children did as well, meaning that there were no differences in increased attention fluctuation between both groups. The findings suggests that children with a SCT can encounter difficulties in activities that require sustained attention skills, which becomes apparent in inaccurateness and an increase in attention fluctuations. However, studies among individuals with a SCT reported mixed results with regard to executive functioning including sustained attention and cognitive flexibility (e.g. Ross et al., 2008; Van Rijn & Swaab, 2011; Bender et al., 2001; Leggette et al., 2010; Temple & Sanfilippo, 2003; Boone et al., 2001), which could be the consequence of small samples and methodological limitations. The present study failed to provide evidence for deficiencies in speed and stability of information processing, inhibitory skills, and working memory. Other studies conducted on individuals with a SCT were also unable to find unambiguous evidence for deficiencies in these particular skills (for an overview see Boada et al., 2009).

The executive function deficits found in the current study may contribute to social difficulties. Indeed, our findings showed and replicated (Van Rijn et al., 2008; Bishop et al., 2011) that the children with a SCT had higher autism traits than the typically developing children. In addition, higher autism traits were related to increased difficulties in executive functions, cognitive flexibility and encoding verbal information. The relationship with social dysfunctioning is in line with findings in individuals with an autism spectrum disorder. Multiple studies have revealed difficulties in, for example, sustained attention and cognitive flexibility (e.g. Tsai, et al., 2011; Christ et al., 2011; Russell et al., 1991; Hughes & Russell, 1993; Lemon et al., 2010; Mosconi et al., 2009). The deficits in encoding verbal information are in line with the traditional view that individuals with an autism spectrum disorder have strength in nonverbal skills compared to their verbal skills (Siegel, Minshew, & Goldstein, 1996). The higher autism traits among individuals with a SCT and their difficulties in verbal information processing stresses the significance of verbal skills in communication, but also metalizing which is usually impaired among individuals with autism (Astington & Jenkins, 1999). Although the focus is generally on language skills among individuals with a SCT, the visuospatial skills should not be disregarded. A study by Van Rijn and Swaab (2011) have found that males with KS having a PIQ < VIQ showed more schizotypical traits whereas males having a VIQ < PIQ showed more autism traits. In addition the schizotypical traits were dependent on developmental stage in that higher schizotypical traits were found in adults

compared to the children with KS (Van Rijn & Swaab, 2011). The differences in contrasting cognitive profiles with regard to schizotypical traits and autism traits suggest for subgroups among individuals with KS. The current study suggests that individuals with a SCT with higher autism traits additionally have impairments in executive functions. Future studies should explore whether there are also differences in specific impaired executive functions between autism traits and schizotypical traits.

The higher vulnerability for developing autism and schizophrenia, but also higher rates of ADHD (Bruining et al., 2009), shows that the phenotype of a SCT is variable. This could be the consequence of differences in social cognition. Difficulties in social cognition have also been suggested in other studies (e.g. Van Rijn et al., 2006). Males with KS tend to encounter deficits in the perception of social cues, they show increased levels of emotional arousal when being exposed to emotional inducing events, but tend to be less proficient in verbalizing their emotions (Van Rijn et al., 2006). This could in turn be the consequence of underlying biological mechanisms in which the additional X chromosome plays a crucial role. There are suggestions for an association between the additional X chromosome and the development of psychopathology including autism and schizophrenia (Gauthier et al., 2006; Van Rijn et al., 2005). Furthermore, the parental origin of the genes on the X chromosome are hypothesized be related to the variability in phenotype among individuals with a SCT karyotype (Isles et al., 2006; Bruining et al., 2010).

The hypothesis with regard to the association between the additional X chromosome and psychopathology is derived from several factors. First of all, the difficulties of males with KS in verbalizing and identifying emotions on the one hand and being more emotionally aroused on the other hand, is in line with the clinical features apparent in patients with schizophrenia (Van Rijn et al., 2005). These deficits are suggested to be the consequence of structural abnormalities of the amygdala, which have also been found in males with KS (Van Rijn et al., 2005). These structural abnormalities are also found in another chromosomal disorder with a partial or complete absence of the X chromosome, referred to as Turner syndrome. Individuals with Turner syndrome tend to show impairments in processing fearful and angry facial expressions (left amygdala mediated) while they tend to show a relative strength in somatic responses to emotional faces (right amygdala mediated) (Skuse, Morris, & Dolan et al., 2005). Individuals with Turner syndrome have higher difficulties in social functioning and increased risks for developing autism (Skuse et al., 2005). Apparently, both KS and Turner syndrome show X chromosomal deficiencies together with structural

amygdala abnormalities and difficulties in social cognition which in turn is suggested to lead to an increased risk for psychopathology. This supports the hypothesis that X chromosomal abnormalities is related to the development of psychopathology.

The reason why this X chromosomal abnormality found in SCT could lead to the variability in phenotype could be related to what is known as genomic imprinting. Genomic imprinting refers to the different expression of genes dependent on the parental origin of the genes. There are assumptions for an association between the parental origins of the genes and social functioning (Davies et al., 2006; Badcock & Crespy, 2006). Studies among individuals with Tuner syndrome support this. For example, Skuse and colleagues (1997) have found that females with a single X chromosome of maternal origin showed higher autism traits when comparing them with females with a single X chromosome of paternal origin. Genomic imprinting has also been investigated among males with KS. Bruining et al. (2010) have found that imprinted X chromosomal genes may have differential effects on autistic as well as schizotypical traits. Furthermore, Stemkes et al. (2006) have found that the additional X chromosome among males with KS of parental origin lead to increased difficulties in motor and speech development. The scarce studies of genomic imprinting effects stress the importance to investigate to what extend this matter effects variability in phenotype among SCT.

Another underlying biological mechanism which should be taken into account while hypothesizing about possible underlying mechanisms related to differences in phenotype among SCT, is the role of testosterone. Androgen deficiencies are present in males with KS becoming apparent during puberty by lower levels of testosterone (Salbenblatt, Bender, & Puck, 1985). To date it remains unclear to what extend testosterone levels affect behavioral impairments (Craig, Harper, & Loat, 2004). There are speculations that the behavioral impairments in KS are the consequence of the additional X chromosome instead of hormone deficiencies. This speculation is supported by the fact that females with Triple X syndrome have typical androgen levels but do show impairments in language and cognitive deficits similar to KS (Bender et al., 1999).

Several limitations of this study should be taken into account while interpreting the findings. First, the SCT group consisted out of two subgroups: boys with KS and girls with Triple X syndrome. The reason for combining both groups into one was to increase power, this at a certain cost since we were unable to examine the executive functions and autism

traits of both groups separately. Second, in the current study we only addressed autism traits while we know from previous studies that individuals with KS also tend to have a higher susceptibility for developing schizotypical and ADHD traits. Third, age differences were apparent together with differences in intellectual functioning. However, during analyses we accounted for age together with SES aiming to control for confounding effects. Although the children with a SCT had lower overall intellectual functioning than the controls, their intellectual functioning still fell within the average range. Furthermore, children with IQ < 70 were removed from the analyses. Another factor which requires consideration is that the cognitive abilities of the children are still subject to the dynamics of development. Based on current findings it remains unclear to what extend the executive function deficits develop among individuals with a SCT. Moreover, it remains unclear whether androgen deficiencies in boys with KS influenced the results since only 7 participants used testosterone supplements. Fatigue should therefore be taken into account while interpreting the results.

To conclude, the present study is one of the first that systematically addressed multiple executive functions in individuals with a SCT. The current study provides evidence for difficulties in executive functions among children with a SCT, especially in cognitive flexibility and sustained attention. Importantly, some of them were related to higher autism traits. This shows that impaired executive functions partly explain difficulties in social functioning, supporting the suggestion of impairments in social cognition among individuals with a SCT karyotype. Future studies should however focus on differences in executive functions between individuals with an autism spectrum disorder without a SCT and individuals with a SCT displaying higher autism traits. Furthermore, it should be examined which executive skills are related to autism traits and whether individuals with a SCT and individuals without a SCT show differences in that matter. This creates the opportunity to see whether different underlying executive functions contribute to the same behavioral phenotype; autism traits. This can in turn provide evidence for disorder specific and deficit specific differences. In addition, it helps to clarify cognitive risk profiles of individuals with a SCT for developing psychopathology including autism spectrum disorders. This provides guidelines for diagnostics, and helps in identifying the functions that require monitoring during development. Results also call for longitudinal studies to examine the developmental trajectories of the cognitive risks and to what extent testosterone levels during puberty influence the developmental trajectory of executive functions.

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