Neurodevelopmental impact of sex chromosome trisomy in young children: the regulation of emotion, cognition, and behavior

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(Not) getting what you want: Frustration and emotion regulation in children with sex chromosome trisomies

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Abstract

The presence of an additional X or Y chromosome (sex chromosome trisomies, SCT) is associated with an increased risk for neurodevelopmental difficulties, including socio-emotional problems, across the life-span. Studying emotion regulation in early childhood in children with SCT could signal deviations in emotional development that serve as risk markers to guide clinical care. This study explored the presence and variety of emotion regulation strategies in XX SCT children and XX population-based controls, aged 1 to 7 years, during a blocked-goal event in which physiological (heart rate) and observational data (behavioral responses) were collected. Children with SCT showed more difficulties regulating their emotions as compared to typically developing children, had a more limited range of behavioral strategies to implement, and tended to rely longer on inefficient strategies with increasing age. The field of practice needs to be made aware of these early disturbances in emotion regulation in SCT, which potentially lay the fundamental groundwork for socio-emotional problems, given the significant impact of emotion regulation on childhood and adult mental health outcomes, including school readiness and psychopathology. These results help to design tailored interventions to reduce the impact of the additional sex chromosome on social and adaptive functioning.

(Not) Getting What You Want: Frustration and Emotion Regulation in Children with Sex Chromosome Trisomies

One in every 1000 children are born with an additional X or Y chromosome, resulting in a trisomy of the sex chromosomes (SCT, Berglund et al., 2019; Groth et al., 2013). Individuals with SCT are at risk for a wide range of neurodevelopmental difficulties, including behavioral, social, and cognitive problems, that can be present across the life span (for review see: van Rijn, 2019). There is growing support that emotion regulation difficulties are also a serious concern for the SCT population (Tartaglia et al., 2010; van Rijn, Stockmann, et al., 2014; Visootsak & Graham Jr, 2009). **Emotion regulation** refers to all processes that influence the occurrence, intensity, duration, and expression of emotions (Gross, 2013). The ability to regulate emotions is a crucial developmental milestone for children to achieve, in order to adaptively function in our complex social world (Denham et al., 2003). Emotions provide us with key information on how to perceive the world around us (information-oriented), how to accomplish our goals (goal-oriented), and how to respond adaptively to complex situations (action-oriented)(Thompson, 1994). It is thus not surprising that the ability to regulate emotions in early childhood is associated with adaptive outcomes in multiple domains, including school readiness (Blair & Razza, 2007), better social skills (Eisenberg et al., 2010) and fewer externalizing problems (Olson et al., 2005). Whilst individuals with SCT are at significant risk for developing psychopathology, both internalizing and externalizing (van Rijn, 2019), empirical studies on emotion regulation in young children with SCT are scarce. There is a need for more knowledge on emotion (dys)regulation and types of regulatory strategies children with SCT tend to employ in challenging situations. This information could be useful in designing more tailored interventions targeting emotion regulation strategies and to reduce the impact of the additional sex chromosome on social and adaptive functioning throughout the lifespan.

Emotion regulation manifests across multiple systems, including physiological changes, subjective experiences, and behavioral responses (Tracy, 2014). Studies showed that adolescents and adults with SCT can have difficulties in one or more of those systems. To start, emotional reactivity, i.e., the tendency to experience emotional arousal to an event (Rothbart et al., 1981), appears different in SCT compared to controls. Van Rijn and colleagues (2014) found that the affective arousal (in terms of skin conductance levels) in response to emotion evoking video clips was overall increased in adult men with 47,XXY, compared to controls. This is in line with self-reported data, where men with 47,XXY also described themselves as being more easily aroused by emotion-evoking situations than peers (Van Rijn et al., 2006). In addition to emotional reactivity difficulties, having an additional sex chromosome has also been associated with the use of atypical emotion regulation strategies in adult men (van Rijn & Swaab, 2020), including increased expression of emotions, avoiding, distraction seeking, and passive coping. Furthermore, emotional outbursts (Visootsak & Graham Jr, 2009), affective problems (van Rijn, Stockmann, et al., 2014), and depressive symptoms (Tartaglia et al., 2010) are commonly present in SCT in the age range from school-aged children to adulthood.

Studies thus far provided key information on emotional regulation and its difficulties in school-aged children, adolescents, and adults with SCT. However, knowledge of early development is scarcely available. Because of technological advances in prenatal testing, studies on very young children with SCT become more accessible (Tartaglia et al., 2020). Recently, it was found that deviations in emotional reactivity can be present from early toddlerhood on (Kuiper et al., in press): when faced with an unexpected event (e.g., a moving and sound-producing robot), children with SCT show a blunted affective arousal (in terms of heart rate) compared to non-clinical controls. Moreover, their physiological response was less predictive of a coherent behavioral response (in terms of facial emotional expressions). In addition, Urbanus and colleagues (2020) showed difficulties with overall social–emotional functioning, already present in 1-year-olds with SCT, and elevated scores persistent across the age span of 1 to 5 years old. Affective, pervasive developmental problems, anxiety, attention deficit, and oppositional defiant behaviors were already part of their social-emotional profile. Thus, there is a great need to further understand the developmental processes of emotion regulation and dysregulation in children with SCT. What remains unknown is what young children with SCT explicitly do in terms of regulating their emotions: how do they organize their behavior when emotions arise? Are these children able to adjust their behavior accordingly so that they can acquire and accomplish their goal, despite arising emotions? The current study aims to provide the answers to these questions.

In studying emotion regulation in young children with SCT, it is important to take into account the developmental process of emotion regulation. Early childhood is characterized by immense progress on multiple developmental domains, including that of emotional control. Whereas early forms of regulation are mainly supported by caregivers in the first year of life (Crockenberg & Leerkes, 2004) and appear more automatic (e.g., avoidance and self-soothing), around the age of 2 years old children develop the ability to control their attention to use it in service of emotion regulation and show more volitional forms of regulation (Posner & Rothbart, 2000). Amongst others, processes that support this are the increase of physical and behavioral opportunities (e.g., moving away from unpleasant situations) as well as developing frontal cortical networks associated with attentional control. As such, the development of emotion regulation in infancy and early childhood can also be seen as a stepping stone through which children attempt to regulate their emotions through behavioral strategies, with the prospect that such regulation will also set the stage for the development of other higher order self-regulation abilities, such as executive functions (Blair & Ursache, 2011). In SCT, a couple of studies have provided initial evidence that the developmental trajectory of children with SCT seems to be different compared to nonclinical controls (Urbanus, Swaab, et al., 2020; Kuiper, et al., 2022) with more pronounced behavioral problems in late early childhood compared to toddlerhood, thus highlighting the importance on studying children with SCT in infancy and preschool period.

The results of the current study are of significant importance. First, it provides information on early markers that could signal at-risk development in young children with SCT. Furthermore, it could help develop specific tools for early and preventive intervention aimed at emotion regulation, to reduce the impact of the additional sex chromosome on social and adaptive functioning throughout the lifespan. This study will examine the presence and variety of emotion regulation skills within a genetically vulnerable group (SCT) compared to a general population sample. A specific focus is on how children with SCT cope with arising emotions in the context of a frustrating situation compared to controls and whether developmental aspects such as age are also relevant. Of interest to the current study is not the sole use of a single strategy, but rather the variety of emotion regulation strategies that are essential to adequately influence the occurrence, intensity, duration, and expression of emotions (Gross, 2013).

Methods

Participants

The current study is part of a larger international study, the TRIXY Early Childhood Study, based at Leiden University in the Netherlands. The TRIXY Early Childhood Study investigates the social, emotional, and behavioral development of young children with a trisomy of the X/Y chromosomes (TRIXY). Children aged 1 to 7 years were recruited from two sites: the Centre of Expertise for Trisomy of the X and Y chromosomes (TRIXY) in the Netherlands and the eXtraordinarY Kids Clinic in Developmental Pediatrics at the Children's Hospital Colorado (CHCO) in the United States (USA). TRIXY recruited children from Dutch-speaking countries in Western Europe (*n* = 39) and the eXtraordinarY Kids Clinic recruited children from across the USA (*n* = 36). Recruitment of SCT children took place with the help of clinical genetics departments, pediatricians, and national advocacy or support groups for (parents of) individuals with SCT using recruitment flyers and postings on the internet and social media. Based on how SCT children enrolled into the study, three different inclusion trajectories could be identified (see Table 1). Children in the control group were recruited from day care centers, public institutions, and elementary schools from the western part of the Netherlands. To be included in the study, both parents and children needed to be Dutch- or English-speaking and children needed to be free of (history of) head injuries, severely impaired hearing or sight, and/or colour-blindness.

Table 1 Demographic Characteristics of the Sex Chromosome Trisomies (SCT) and Control Group

	SCT	Controls	Group differences
	n = 75	*n* = 81	
Age in years – *M* (SD)	3.82 (1.90)	3.82 (1.60)	$t(154) = .01$, $p = .992$
Gender	M = 49, F = 26	M = 35, F = 46	$X^2(1) = 7.669$, $p < .01$
Parental education level – median (range)	6 (4 – 7)	6 (2 – 7)	$p = .794$
Karyotype		N/A	
XXX	26		
XXY	39		
XYY	10		
Recruitment strategy - *n* (%)			
Information-seeking parents	38 (50.7%)		
Prospective follow-up	25 (33.3%)		
Clinically referred	12 (16.0%)		

In the current study, 75 children with SCT and 81 age matched population-based controls participated (Table 1). The SCT group consisted of 26 girls with 47,XXX, 39 boys with 47,XXY, and 10 boys with 47,XYY. More than half (56%, *n* = 42) had a prenatal diagnosis (i.e., because of [routine] prenatal screening, abnormal ultrasound findings, or advanced maternal age) next to 33 children (44%) who had a postnatal diagnosis (i.e., because of developmental delay, physical and/or growth problems, or medical concerns). Confirmation of trisomy in at least 80%

of the cells was provided by standard karyotyping. Parents were asked to present a copy of the karyotyping report of the child that was provided by their clinician at time of diagnosis. Children from the control group were not subjected to genetic screening. Given the prevalence of SCT (1 in 1000) in the general population, we decided that the burn of blood draw for testing for SCT in our control group outweighed its potential utility. We reviewed the possible risk of having a child with undiagnosed SCT in our control group minimal and acceptable. Parental education level was assessed according to the Hollingshead criteria and ranged from category 1 (no formal education) to 7 (graduate professional training) (Hollingshead, 1975). When the child was raised by two parents (96% of the children in the current sample), educational level was averaged over both parents. Parental education level was comparable over research groups, as well as age (also see Table 1).

Ethics and Procedure of the Assessment

Both the Ethical Committee of the Leiden University Medical Centre in the Netherlands and the Colorado Multiple Institutional Review Board (COMIRB) in the USA approved the TRIXY Early Childhood Study. Researchers from Leiden University supervised project and data-management, including training of experimenters and processing of data. Primary caregivers of all participating children signed a written informed consent prior to the research visit. Additionally, caregivers received a visual information brochure and a copy set of the electrodes for the physiological assessment to help children prepare. Research visits took place in a quiet stimuli-low room either at the university or the family's home, using written protocols detailing all procedures and verbal instructions to standardize assessments across countries. During assessment children had additional time to familiarize before and after the electrodes were applied by playing an age-appropriate game, while seated in a car seat to have a stable and framed position suited for physiological measurement.

Physiological Arousal

Two electrodes were attached at the top center of the chest (10 centimeters below the suprasternal notch) and the bottom left of the ribs (10 centimeters above the bottom of the rib cage). Heart rate was recorded continuously during baseline and locked box task with AcqKnowledge (version 5.0.2, BIOPAC Systems Inc.). An Electrocardiogram amplifier (ECG100C) and a BIOPAC data acquisition system (MP150 Windows) with a sampling rate of 1.000 Hz were used for recording. In AcqKnowledge a 0.5 Hz highpass filter and 50 Hz notch filter were applied to stabilize the ECG signal. Recorded physiological data was further processed by inspecting the detected R peaks in PhysioData Toolbox version 0.5.0 (Sjak-Shie, 2020). Motion artifacts were visually identified and excluded from the data. Heart rate data (beats per minute: BPM) were summarized in 30-second epochs in concordance with the behavioral data. To establish a baseline heart rate, children watched a 3 minute video of a fish tank, which has been shown to be an adequate measure of resting state (Piferi et al., 2000). Heart rate (in BPM) over the course of the video was analyzed in epochs of 30 seconds each and the epoch in which children had the lowest heart rate was identified as representing resting state. This was done on group level, for the control group and the SCT group separately.

Frustrating Task (Blocked-Goal Paradigm)

The locked box task from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith et al., 1999) was selected to elicit behavioral and emotional responses, including frustration, given that it incorporates a blocked-goal paradigm. The experimenter placed three age-appropriate attractive toys in front of the child but outside the child's reach. The child was encouraged to choose one preferred toy, which was then placed in a transparent locked box. The unwanted toys were removed from sight and children were instructed to try to acquire the selected toy in any way they can (although they were unable to succeed given that the box is locked). The experimenter left the child alone to deal with the box. Following 3 minutes of manipulation (i.e., frustration phase), the experimenter returned to the child and opened the box, after which the child was encouraged to play with the toy for 1 minute (i.e., recovery phase). This paradigm deliberately prevents children from playing with a preferred toy and thus provides the opportunity to examine how children naturally cope with their emotions and organize their behavior when goals are blocked (i.e., to acquire a toy). The procedure of the task followed the Lab-TAB manual (see Figure 1 for a timeline) with one exception. For the current study, we used two boxes depending on the child's age: a locked box with keys for children aged 3 and up (as described in the Lab-TAB manual) and a modified box for the youngest age group (1 to 2 years old) in which the lid was not locked with keys, but strongly secured with additional grip. This adjustment was necessary to prevent bias due to differences in motor skills, given that not all children before the age of 2 already have the developed fine motor skills essential to use and open a lock with keys, whereas most children have developed gross motor skills essential to remove a lid. Caregivers were instructed to sit in the back of the room out of direct sight, filling out questionnaires or reading magazines, and to remain as uninvolved as possible while displaying a neutral face. Only during recovery, caregivers were allowed to sooth and comfort their child, but the child stayed in the car seat for the remainder of play time to stabilize the physiological recovery assessment. The entire procedure was videotaped from two angles.

Figure 1 Timeline Locked Box Task

Note. Original locked box task described in Lab-TAB (Goldsmith et al., 1999).

Data from the locked box were analyzed in 30 second epochs. Of the total of 180 seconds (3 minutes), the first 30 seconds were discarded to allow for a build-up of frustration (i.e., children first need to try the most obvious ways to find out that the box is indeed locked). The majority of the children were able to complete the full 3 minutes (n = 72 of the SCT children and n = 81 of the control children), however some children could not and for example started fidgeting with the electrodes which could have compromised physiological recording. To prevent bias due to the duration of the task, it was decided to use the epochs that included data from all children, resulting in seconds 30 through 120.

Observational Coding of Emotion Coping Strategies

Videos of the locked box task were coded and categorized in 10-second epochs (with sound on) for emotional coping strategies, as described in Jahromi et al. (2012). In total 14 emotion coping strategies were coded in 10-second intervals as either present or absent (scored as 1 or 0). These 14 coping strategies were assessed independently which means that more than one strategy can occur in the same 10-second interval. Strategies were grouped into three categories and their average inter-rater reliability (expressed in Cohen's kappa) were (a) *constructive* strategies (consisting of strategy behaviors such as goal-directed behaviors, orienting to experimenter or parent, and social support seeking); k = .90, (b) *venting* strategies (vocal venting, self-soothing, and self-speech); k = .86, and (c) *avoidance* strategies (avoidance, distraction, and alternate strategies); k = .78. Inter-rater reliability (IRR) was assessed using a two-way mixed, absolute agreement intra-class correlation model (Hallgren, 2012). Six trained independent coders scored all recorded videos. IRR was monitored continuously in regular consensus meetings. Discrepancies were discussed within the team to obtain a final consensus score. Four strategies (disruptive behavior, physical venting, staring, and other-directed comfort-seeking) occurred too infrequent to be included in subsequent behavioral composites or analyses.

Statistical Analyses

As preliminary analyses, to examine whether certain SCT group characteristics were relevant to emotional processing, three MANOVA's were performed with recruitment site, karyotype, and recruitment strategy as (three) independent variables and the two main outcome parameters (including peak arousal response and three emotion regulation strategies) as dependent variables. In addition, to establish that the locked box task was successful in eliciting emotional arousal, a GLM repeated measures analysis was performed with the between subject factor Group (SCT, control) and the within-subjects factor Task (30 seconds baseline heart rate, 90 seconds frustration, and 60 seconds recovery). To further analyze the heart rate pattern over time and potential group differences, tests of within-subjects contrasts were done within the GLM RM analysis. After visual inspection, the highest peak in arousal for each individual was subtracted with baseline heart rate to reflect individual arousal response.

To answer the main research question, a Multivariate Analysis of Variance (MANOVA) with group (SCT, control) as fixed factor and coping strategies (Constructive, Venting, and Avoidance) as dependent variables was performed. Arousal response was included as a covariate to exclude any interference from individual arousability during the frustrating task. The moderating effect of age was assessed using PROCESS, a bootstrapping, nonparametric resampling procedure (Hayes, 2009). Bootstrapping analysis with 5000 resamples was done to test for a significant moderating effect using the SPSS macro developed by Hayes (2017). Outcome variables and moderator variable (i.e. child's age) were centered, peak arousal response was included in the analysis as a covariate to control for individual arousability. In this analysis, the moderation effect is significant if the 95% bias corrected confidence interval for the moderator effect does not include zero.

For correlation analyses with age, Pearson's product moment correlation coefficient was used. Level of significance was set at $p = .05$. For all significant effects, Cohen's d and η^2 addressed effect size (.2 = small effect; .5 = medium effect; .8 = strong effect, Cohen, 1977).

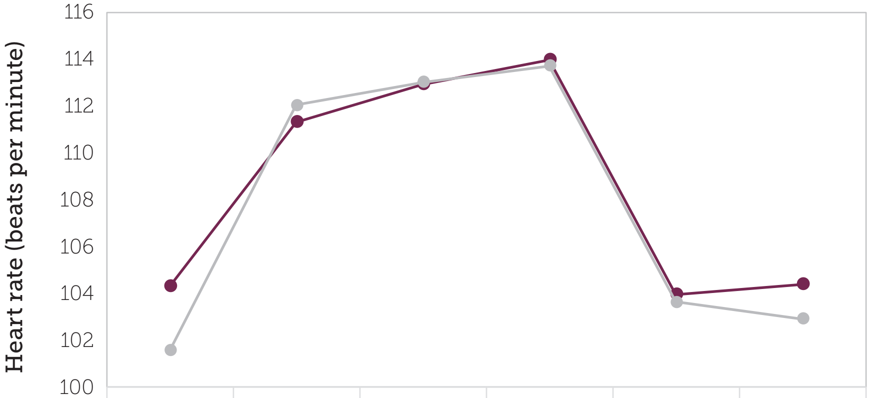
Results

Preliminary Analyses

Results from the preliminary analyses revealed no evidence of significant differences in the SCT group regarding recruitment site, karyotype, and recruitment strategy on psychophysiological and emotion regulation outcomes. Children with SCT from the Netherlands had similar results as the children from the United States on the main emotion outcome parameters (including arousal response and three emotion regulation strategies, Pillai's trace = .108, $F(4,70) = 2.120$, $p = .087$). In addition, which karyotype a child carried (XXX, XXY, and XYY) had no influence on the main outcome parameters (Pillai's trace = .058, $F(8,140) = .522$, $p = .838$). Finally, how children with SCT enrolled in the study (prospective follow-up, information seeking parents, and clinically referred cases) had no significant effect (Pillai's trace = .028, $F(8,140) = .245$, $p = .981$). These results provided the support to pool SCT children from various recruitment sites, karyotypes, and recruitment strategies together and include the total group of SCT children in further analyses.

Efficacy of the Arousal-Inducing Paradigm

Prior to examining emotion regulation strategies, analyses were performed to establish whether the locked box task was indeed successful in inducing emotional arousal. First, in terms of baseline heart rate, there was no significant difference between children with SCT (M 104.32, SD 17.27) and children from the control group (M 101.67, SD 14.10) ($t(154) = 1.050$, $p = .295$). With regards to the pattern of arousal response (corrected for baseline heart rate), a GLM repeated measures analysis was performed and revealed a significant main effect of Task ($F(5,149) = 57.105$, $p < .001$, $\eta p^2 = .657$), no main effect for Group ($F(1,101) = .059$, $p = .808$), and no interaction effect ($F(5,149) = 1.623$, $p = .157$). These results showed no significant difference in the pattern of arousal response across groups during the locked box task (also see Figure 2). Thus, the locked box task was successful in evoking an emotional response in both groups, laying the fundamental ground to examine emotion regulation strategies in the context of frustration. Noteworthy: tests of within subjects contrasts revealed similar increases and decreases for both groups during the full locked box task, with one exception. There was a significant interaction Task x Group effect from baseline to the frustration phase ($F(1,153) = 6.586$, $p < .02$, $\eta p^2 = .041$), indicating that the increase in initial arousal response was significantly stronger for control children than for SCT children. However, there were no other significant interaction effects during any of the other time-points of the frustrating task. Finally, all children (both SCT and controls) were able to return to resting state during recovery.



	Baseline	Frustration 30-60s	Frustration 60-90s	Frustration 90s-120s	Recovery 0-30s	Recovery 30-60s
SCT	104,32	111,33	112,94	113,97	103,96	104,41
Control	101,58	112,05	113,03	113,72	103,65	102,93

Figure 2 Heart Rate Pattern During Locked Box Task for SCT Group and Control Group

Note. The initial 30 seconds from the frustrating task were excluded from analysis to allow for the build-up of frustration. SCT: Sex Chromosome Trisomies.

Behavioral Regulation: Emotion Regulation Strategies

The main research objective was to examine the presence and variety in emotion regulation strategies in the context of frustration and compare group differences between SCT and controls. Examination of the descriptives revealed that during the locked box task, all children (both SCT and controls) most often showed Constructive Strategies followed by Venting Strategies and then Avoidance Strategies (Table 2). To compare group differences between SCT and controls, peak arousal response was included as a covariate in a MANCOVA to account for individual differences in arousability, with the three emotion coping strategies (Constructive, Venting, and Avoidance) as dependent variables and Group (SCT, control) as fixed factor. The results revealed a significant main effect for arousal response ($F(3,151) = 7.345$, $p < .001$), $np^2 = .127$) and Group during the locked box task ($F(3,151) = 3.253$, $p < .05$; Pillai's trace = .061, $\eta p^2 = .061$). When confronted with blocked-goals, children with SCT engaged significantly less in Constructive strategies as compared to children in the control group, even while correcting for individual arousability. For Venting or Avoidance strategies, there were no significant group differences (also see Table 2 and Figure 3).

Role of Age in Emotion Regulation Strategies

To examine whether group differences in emotion regulation strategies (given individual arousability) were present across all ages in children with SCT, bias-corrected bootstrapping analyses (PROCESS) were conducted. A significant interaction effect of child's age x group was found for Avoidance strategies (b = -.17, SE = .06, t = -2.70, p < 0.01, 95% confidence interval = -.29 and -.05). As shown in Figure 3, the use of avoidance strategies declines with age for both groups, but less rapidly for the SCT group. No significant interaction effect was found for Venting (b = -.07, SE = .11, t = -.61, p = .542, 95% confidence interval = -.29, .15) or Constructive strategies (b = .01, SE = .09, t = .09, p = .931, 95% confidence interval = -.16, 18), also see Figure 3 for a visual representation.

Table 2 Descriptives and MANCOVA Test Results for Emotion Regulation Strategies

	SCT	Control		
	M (SD)	*M (SD)*	*F*	*p*
Avoidance	0.65 (0.83)	0.65 (0.80)	.006	.936
Venting	1.13 (1.16)	1.49 (1.45)	1.614	.206
Constructive	2.32 (1.11)	2.62 (0.92)	4.443	**.037**

Note. SCT: Sex Chromosome Trisomies.

CHAPTER 5

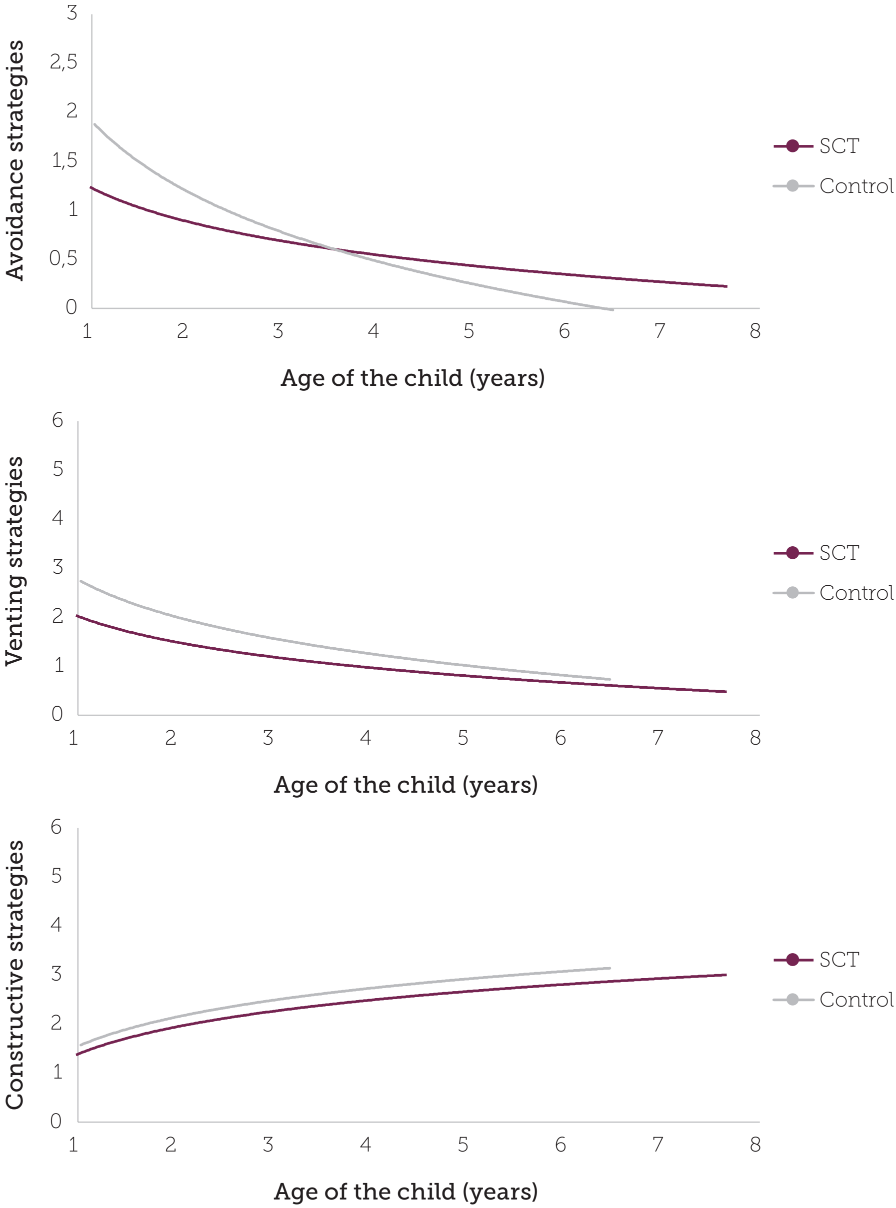


Figure 3 Scatterplots of Child's Age by Mean Emotion Regulation Strategies Across Research Groups

Discussion

The present study examined emotion regulation processes in young children with a sex chromosomal trisomy (SCT) compared to controls when faced with a frustrating task (blocked-goal paradigm). The results show that while children with SCT experienced a significant increase in arousal response, when blocked in achieving a desired toy, their behavioral response did not follow suit. While controlling for individual arousability, observational measures of behavioral regulation revealed significant differences between groups in those strategies that are most frequently implemented, namely constructive strategies. An interesting developmental effect was also found; whereas avoidance strategies tend to decline with age in typically developing children, this was significantly less so in children with SCT. Furthermore, these results were consistent over karyotypes (XXX, XXY, and XYY), recruitment sites (The Netherlands/the USA), and recruitment strategies, suggesting that emotion regulation is a relevant risk marker in the development of all children with SCT.

The current results indicate that children with SCT may have more difficulties regulating their emotions as compared to typically developing children, may have a more limited range of behavioral strategies to implement, and tend to rely longer on more inefficient strategies with increasing age. To start, one of the key results is that compared to their peers, children with SCT showed less emotion regulation strategies that can be considered constructive. Constructive strategies represent behavioral responses as goal-directed actions and support seeking behavior, in order to achieve a goal at hand. Emotion regulation, in definition, is the ability to organize behavior that could lead to an decrease (or an increase) of negative (or positive) emotions in order to meet the demands of the environment (Gross, 2013). Consequently, these current results indicate that while children with SCT become emotionally affected in the face of frustration, they appear less equipped to regulate their arousal compared to peers: their repertoire of (cognitive) behavioral responses is limited. Furthermore, another key result of the current study is that with older age, children with SCT tend to rely longer on other less volitional forms of regulation, such as avoidance. Avoiding (displeasant situations) is one of the earliest and automatic forms of emotion regulation, that gradually decreases in use starting at around the age of 18 to 24 months alongside the emergence of other types of regulation strategies (Harman et al., 1997). This shift from automatic to volitional forms of regulation is amongst others associated with the developing (pre)frontal cortical networks during this age period, that at the same time sets the stage for the development of other cognitive functions, including executive functions (Ursache et al., 2013). Taken together with the fact that the genes on X and Y chromosome are densely involved in brain development (Zechner et al., 2001), our results suggests that emotion regulation difficulties might be anchored into early brain maturation of children with SCT. However, it is also important to note here that not all children with SCT were equally impaired and that variety in the use of emotion regulation strategies was also observed. Increasing number of studies are showing that it is not solely the excessive use of maladaptive strategies or the limited use of adaptive strategies that leads to psychological distress and psychopathology, but rather a combination of the two (Braet et al., 2014; Cracco et al., 2015; Schäfer et al., 2017). This suggests that not "one" perfect emotion regulation strategy exist and that rather the variety in strategies, thus the ability to choose from strategies to adapt your behavior to the difficult situations, is truly important for good emotional health.

The current findings fits with behavioral observations of emotion regulation difficulties in daily life, found in children with SCT already from the age of 3 years old (Kuiper, Swaab, Tartaglia, van Buggenhout, et al., 2022; Lee et al., 2011). It is also in line with findings in adults with SCT, that showed atypical emotion regulation strategies in men with Klinefelter (Van Rijn et al., 2006; van Rijn & Swaab, 2020), including difficulties with verbalizing their emotions and higher indices of avoidance, distraction seeking, and passive coping strategies. In addition, the current study add to other findings on psychophysiological reactivity, that suggested that emotional arousal could relate differently to empathic behavior in men with 47,XXY compared to controls (van Rijn, Barendse, et al., 2014) as well as a differential arousal response in young children with SCT (Kuiper et al., 2022). All these findings taken together indicate just how vulnerable individuals with SCT are in their emotional development. Given that emotion regulation is essential for daily life functioning and an important developmental task in early childhood, our results show that individuals with SCT face significant challenges in dealing with day-to-day conflicts that require children to cope with their emotions adaptively, from an early age on.

Successful emotion regulation in preschool years is associated with social competency, school engagement, and academic performance, in early school years (Robson et al., 2020). On the other hand, emotion regulation is also considered an important process in the etiology and maintenance of different forms of psychopathology (Aldao et al., 2010). It is therefore not surprising that emotion regulation has been acknowledged as a transdiagnostic mechanism in mental health (Insel et al., 2010). Many neurodevelopmental disorders and psychopathology are characterized by difficulties in the emotion regulation system, including mood and affective disorders, autism spectrum disorders, and attention deficit/hyperactivity disorder (American Psychology Association, 2013). From existing literature, it is known that the SCT population is at significantly increased risk for these types of mental health problems (van Rijn, 2019). Studying a genetically vulnerable population such as SCT provides the opportunity to examine gene-brain-behavior pathways of important developmental domains (including emotion regulation) over time. A prenatal diagnosis of a genetic condition such as SCT helps to identify populations at risk, before any significant problems or psychopathology emerge. This information is crucial to understand how neurocognitive skills and processes develop over time and contribute to potential psychopathology. Furthermore, it could reveal risk markers in early development that can guide early (preventive) intervention, not limited to only those individuals with SCT.

In addition to understanding gene-brain-pathways from a theoretical point of view, these results are also highly relevant to individuals affected with SCT and the professionals working with them and their families. The early signs of emotion regulation dysfunction inform us that children with SCT have difficulties in regulating their emotions, may have a more limited range of behavioral strategies to implement, and tend to rely longer on more inefficient strategies with increasing age. In supporting their development, emotion regulation may serve as a relevant target for prevention and intervention. Emotion regulation training, especially in young children, should be focused on educating children, their parents/caregivers, and their teachers as well. Children learn emotion regulation skills through observation, adult(parent)-child interactions, and their development is also influenced by the emotional climate in the family (Morris et al., 2007). Training emotion regulation skills in the early years is especially relevant given that the growth in development of emotion regulation skills in early childhood is substantial (Kopp, 1989). Although speculative, our results suggest that it might be helpful to address and teach the use of emotion regulation skills in interventions from a cognitive top-down approach: how to shape your behavior through the use of adaptive emotion regulation strategies in order to control your emotions. Existing programs that incorporates elements of modeling and teaching emotion regulation skills as well as relaxation techniques, that could also be meaningful for the SCT population, are EUREKA in children (Braet & Berking, 2019) or Affect Regulation Training (ART) in adolescents and adults (Berking & Whitley, 2014). Recent developments in (preventive) interventions for individuals with SCT are promising, in terms of improving emotional skills through neurocognitive training. For example, Martin and colleagues (2020) showed that a social management training, that included emotion regulation techniques, led to improvements in emotional stability and self-regulation in adolescents and adults with 47,XXY. Even more promising is the study of Bouw and colleagues (Bouw, Swaab, & van Rijn, 2022) that showed that young children with SCT (before the age of 8 years) can improve their emotion recognition skills through the means of a parent-child at home training program. Concluding, early monitoring on emotion regulation is essential given it allows for the implementation of early (preventive) strategies, which has the potential to influence child development towards more optimal outcomes (Guralnick, 2011).

The study also had some limitations. The current design did not allow for the investigation of interactive dynamics between regulation strategies and subsequent changes in arousal. Also, although the current study showed that the role of age was different for different emotion regulation strategies, these results are based on a cross-sectional design. Longitudinal studies are needed to further study developmental impact of the extra X or Y chromosome over time, as well as its relation to neurodevelopmental disorders and mental health problems. With regards to direction for future research, emotion regulation (and emotions in general) is considered a complex and multifaceted construct, linking to many child factors, including executive and cognitive functioning and temperament, as well as family context characteristics, including attachment style, childrearing behavior (Morris et al., 2007). Including all relevant factors goes beyond the scope of this study and would require a vastly larger sample. However, future research should try to examine these factors related to emotion regulation, given that it could provide additional markers for early and preventive interventions.

In sum, children with SCT show early deviations in the use of emotion regulation strategies, compared to controls, which could impact their developmental outcomes. Emotion regulation is a valid candidate as a underlying mechanism in explaining the heterogeneity and variabilities in psychopathology and mental health problems, given the significant impact of emotions on adaptive day-to-day functioning. The current findings provide essential information for those involved in care for individuals with an additional X and Y chromosome and help develop specific tools for early and preventive intervention.

Appendix A

Figure A1 Professionally Edited Photo of the Locked Box Task.

Note. This photo was not part of the original submitted manuscript and was originally made for PR purposes of the TRIXY Early Childhood Study. Photo: ARNICK.nl, printed with permission.