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RESEARCH

(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 young 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 75 SCT children and 81 population-based controls, aged 1–7 years, during a frustration-inducing event in which physiological (heart rate) and observational data (behavioral responses) were collected. Children with SCT were equally physiologically aroused by the event as compared to controls. However, they showed more emotion regulation difficulties in terms of behavior compared to controls that were not explicable in terms of differences in general intellectual functioning. Specifically, they had a more limited range of behavioral alternatives and tended to rely longer on inefficient strategies with increasing age. The field of practice should be made aware of these early risk findings regarding emotion regulation in SCT, which may potentially lay the foundation for later socio-emotional problems, given the significant impact of emotion regulation on child and adult mental health outcomes. The current results may help to design tailored interventions to reduce the impact of the additional sex chromosome on adaptive functioning, psychopathology, and quality of life.

Key Words

- emotion regulation
- sex chromosome trisomies
- child development
- neuropsychology

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Introduction

One in every 1000 children is born with an additional X or Y chromosome resulting in a trisomy of the sex chromosomes (SCT) (1, 2). 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 a review see (3)). There is growing evidence that emotion regulation difficulties are also part of the daily challenges that may be experienced by the SCT population (4, 5, 6). Emotion regulation refers to all processes that influence the occurrence, intensity, duration, and expression of emotions (7). The ability to regulate emotions is a gradually developing but crucial ability for children to learn, in order to function adaptively in our complex social world (8). 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) (9). It is thus not surprising that the increasing ability to regulate emotions in childhood is

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associated with adaptive outcomes in multiple domains, including school readiness (10), better social skills (11), and fewer externalizing problems (12). Whilst individuals with SCT are at significant risk for developing psychopathology, both internalizing and externalizing problems (3), empirical studies on emotion regulation in young children with SCT are currently non-existing. There is a need for this knowledge given that it could be useful in designing tailored interventions targeting emotion regulation strategies to reduce the impact of the additional sex chromosome on social-emotional development and adaptive functioning.

Emotion regulation manifests in multiple biological, cognitive, and behavioral systems, including physiological changes and behavioral responses (13). Studies showed that adolescents and adults with SCT can have difficulties in one or more of those systems. To start, SCT has been associated with the use of atypical behavioral strategies in adult men (14), including increased expression of emotions, avoiding, distraction seeking, and passive regulation. Furthermore, emotion regulation problems like emotional outbursts (4), anxiety symptoms (5), and depressive symptoms (6) are commonly present in SCT in the age range from school-aged children to adulthood. In addition, differences in physiological arousal (expressed in skin conductance levels) are also found. Van Rijn and colleagues (15) found that the physiological arousal in response to emotion-evoking social situations (on video) was overall increased in adult men with 47,XXY. This is in line with the self-reported experience of emotion, given that men with 47,XXY typically describe themselves as being more easily aroused by emotion-evoking situations than peers (16).

Studies thus far provide key information on emotion regulation and its difficulties in school-aged children, adolescents, and adults with SCT. However, knowledge of early development in emotion regulation is not yet available. Because of technological advances in prenatal testing, studies on very young children with SCT have become more accessible (17). Recently, Urbanus and colleagues (18) showed difficulties with overall social-emotional functioning, already present in 1-year-olds with SCT, and elevated scores persisted across the age span of 1–5 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 young children with SCT. What remains unknown is the type of strategies available to young children with SCT to regulate their emotions: how do they organize their cognition and behavior when emotions arise? Are these children able to adjust their behavior in a way that they can acquire and accomplish their goals, despite arising emotions? The current study aims to search for answers to these questions.

In studying emotion regulation in young children with SCT, it is important to take into account that emotion regulation develops gradually with age. Early childhood is characterized by immense progress in multiple developmental domains, including that of emotional control. Whereas early forms of regulation are mainly environmental, in which caregivers largely support regulation in the first year of life (19), child-controlled regulation becomes more prominent in the second year of life (e.g. avoidance and self-soothing). Around the age of 2, children develop the ability to control their attention to use it in service of emotion regulation and show more volitional forms of regulation (20). Among others, processes that support this gradual development are increased physical and behavioral skills (e.g. moving away from unpleasant situations) as well as development of frontal cortical networks associated with attentional control. As such, the development of emotion regulation in infancy and early childhood can be seen as a crucial developmental phase in which children regulate their emotions mainly through behavioral strategies (21). In SCT, a few studies have provided initial evidence that the developmental trajectory of children with SCT can be different compared to nonclinical controls (18, 22) with more pronounced behavioral problems in 4- to 6-year-olds compared to earlier years, thus highlighting the importance the role of age when studying children with SCT.

The results of the current study are of significant importance. First, the search for early markers could signal at-risk development in young children with SCT. This in turn could support the development of specific tools for early and preventive interventions aiming at strengthening emotion regulation and potentially reducing the impact of SCT on social-emotional development and adaptive functioning. This study will examine the presence and variety of emotion regulation skills within the genetically vulnerable group of young SCT children compared to a general population sample. A specific focus is on how children with SCT cope with emotions in a frustrating situation. A frustration-inducing event was chosen, given that frustration is an excellent motivator for children to organize their behavior in more than one way to ensure they reach their goal. Of interest to the current study is not whether the SCT children can

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use a single strategy, but rather if they can cope with the unexpected by adaptive and flexible choice of different strategies. It is suggested that the availability of the variety of emotion regulation strategies is essential to adequately influence the occurrence and cope with the intensity, duration, and expression of emotions (7). In this study, physiological arousal (as an indicator of emotional stress response) and behavioral regulation will be evaluated.

Method

Participants

The current study is part of a larger international study, the TRIXY Early Childhood Study, initiated and conducted by the TRIXY Expertise Center 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 1–7 years were recruited from two sites: the Center 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. TRIXY recruited children from Dutch-speaking countries in Western Europe ($n=39$) and the eXtraordinarY Kids Clinic recruited children from across the United States ($n=36$). 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 color blindness.

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) and 33 children (44%) 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 the 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 burden of blood draw for testing for SCT in the control group outweighed its potential utility. We reviewed the possible risk of having a child with undiagnosed SCT in the control group as minimal and acceptable. Just under half of the children with

Table 1 Demographic characteristics of the sex chromosome trisomies (SCT) and control group.

	SCT $n=75$	Controls $n=81$	Group differences
Age in years – *M* (s.d.)	3.82 (1.90)	3.82 (1.60)	$t(154)=0.01$, $P=0.992$
Gender	M = 49, F = 26	M = 35, F = 46	$X^2(1)=7.669$, $P=0.006$
Global intellectual functioning – *M* (s.d.)	97.34 (18.20)	108.11 (14.29)	$t(136.39)=-4.052$, $P<0.001$
Range	59–138	72–140	
Parental education level – median (range)	6 (4–7)	6 (2–7)	$P=0.794$
Karyotype		N/A	
47,XXX	26		
47,XXY	39		
47,XYY	10		
Recruitment strategy – *n* (%)			
Information-seeking parents	38 (50.7%)		
Prospective follow-up	25 (33.3%)		
Clinically referred	12 (16.0%)		

For children aged 1.0–2.0, the Cognitive Composite score from the Bayley-3 (Bayley, 2006) was used as global intellectual functioning; for children aged 3.0 to 7–11, the estimated Full Scale IQ score from the short version of the WPPSI-III (Wechsler, 2002) was used as global intellectual functioning. Both scores have a mean of 100 and s.d. of 15.
SCT, sex chromosome trisomies.

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47,XXY (48.7%, $n = 19$) received testosterone replacement therapy at any given time in their development. Parental education level was assessed according to the Hollingshead criteria and ranged from category 1 (no formal education) to 7 (graduate professional training) (23). When the child was raised by two parents (96% of the children in the current sample), the educational level was averaged over both parents. Parental education level was comparable over research groups, as well as age (also see Table 1).

Global intellectual functioning

Global intellectual functioning (GIF) was assessed with the Bayley Scales of Infant and Toddler Development (NSCT = 21, Ncontrol = 21, (24)) in children aged 1–2 years, and the short-version of the Wechsler Preschool and Primary Scale of Intelligence third edition (NSCT = 54, Ncontrol = 60, WPPSI-III (25)) in children aged 3 years or older. GIF scores for two children in the SCT group were missing. There was a significant difference in average full-scale intelligence scores between the SCT and control group, $t(136.39) = -4.052$, $P < .001$. Although both groups had a point mean within the average range (e.g. intelligence scores that fall between 90 and 110 are considered average), the SCT group scored significantly lower ($M = 97.34$, s.d. = 18.20) than the control group ($M = 108.11$, s.d. = 14.29).

Ethics and procedure of the assessment

Both the Ethical Committee of the Leiden University Medical Center in the Netherlands and the Colorado Multiple Institutional Review Board in the United States approved the TRIXY Early Childhood Study. Researchers from Leiden University supervised the 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 cm below the suprasternal notch) and the bottom left of the ribs (10 cm above the bottom of the rib cage). Physiological arousal in terms of heart rate was recorded continuously during baseline and locked box task with AcqKnowledge (version 5.0.2, BIOPAC Systems Inc., Goleta, CA, USA). 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 (26). Motion artifacts were visually identified and excluded from the data. Heart rate data (beats per minute: b.p.m) were summarized in 30-s epochs in concordance with the behavioral data. To establish a baseline heart rate, children watched a 3-min video of a fish tank, which has been shown to be an adequate measure of resting state (27). Heart rate (in b.p.m) over the course of the video was analyzed in epochs of 30 s each and the epoch in which children had the lowest heart rate was identified as representing the resting state. This was done on a group level, for the control group and the SCT group separately.

Behavioral responses to frustration

The locked box task from the Laboratory Temperament Assessment Battery (Lab-TAB (28)) was selected to elicit physiological and behavioral 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 min 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 min (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

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followed the Lab-TAB manual (see Fig. 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 (1–2 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 soothe 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.

Data from the locked box were analyzed in 30-s epochs. Of the total of 180 s (3 min), the first 30 s 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 min ($n = 72$ 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.

Videos of the locked box task were coded and categorized in 10-s epochs (with sound on) for emotion regulation strategies (as described in (29)). In total, 14 emotion regulation strategies were coded in 10-s intervals as either present or absent (scored as 1 or 0). These 14 regulation strategies were assessed independently which means that more than 1 strategy can occur in the same 10-s interval. Strategies were grouped into three categories and their average inter-rater reliability (IRR; expressed in Cohen's kappa) were (i) constructive strategies (consisting of strategy behaviors such as goal-directed behaviors, orienting to experimenter or parent, and social support seeking); k = 0.90, (ii) venting strategies (vocal venting, self-soothing, and self-speech); k = 0.86, and (iii) avoidance strategies (avoidance, distraction, and alternate strategies); k = 0.78. Four strategies (disruptive behavior, physical venting, staring, and other-directed comfort-seeking) occurred too infrequently to be included in subsequent behavioral composites or analyses. IRR was assessed using a two-way mixed, absolute agreement intra-class correlation model (30). Six trained independent coders scored all recorded videos and IRR was monitored continuously in regular consensus meetings. Discrepancies were discussed within the team to obtain a final consensus score. Efforts were made to ensure coders were as blind as possible to the group identity of the child (SCT vs controls). However, because the control group only consisted of Dutch-speaking children, videos including children and researchers who spoke (American) English could be easily identified as SCT.

Statistical analyses

As preliminary analyses, to examine whether certain SCT group characteristics were relevant to emotional processing, three separate multivariate analysis of variances were performed with recruitment site, karyotype, and recruitment strategy as independent variables and the two main outcome parameters (including peak arousal response and three emotion regulation strategies) as dependent variables.

To establish that the locked box task was successful in eliciting physiological arousal (= emotional distress), a GLM-repeated measures analysis was performed with the between-subject factor group (SCT, control) and the within-subjects factor Task (30 s baseline heart rate, 90 s frustration, and 60 s 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 from the baseline heart rate to reflect individual arousal response.

To answer the main research question, a multivariate analysis of covariance (MANCOVA) with group (SCT,

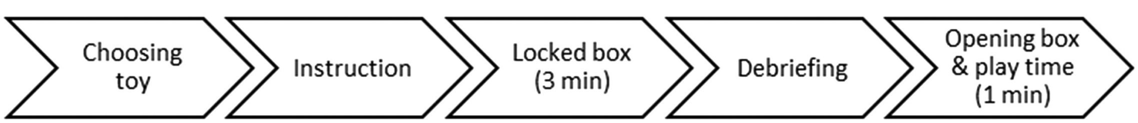

Figure 1
Timeline locked box task (Lab-TAB (28)).

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control) as fixed factor and regulation strategies (constructive, venting, and avoidance) as dependent variables was performed. Peak arousal response and general intellectual functioning were included as covariates to exclude any interference from individual arousability or general cognitive ability during the frustrating task. The moderating effect of age was assessed using PROCESS, a bootstrapping, nonparametric resampling procedure (31). Bootstrapping analysis with 5000 resamples was done to test for a significant moderating effect using the SPSS macro developed by (31). Outcome variables and moderator variable (i.e. child's age) were centered, and 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 CI for the moderator effect does not include zero. For correlation analyses, Pearson's product–moment correlation coefficient was used. The level of significance was set at $P = 0.05$. For all significant effects, Cohen's *d* and η^2 addressed effect size (0.2 = small effect; 0.5 = medium effect; 0.8 = strong effect).

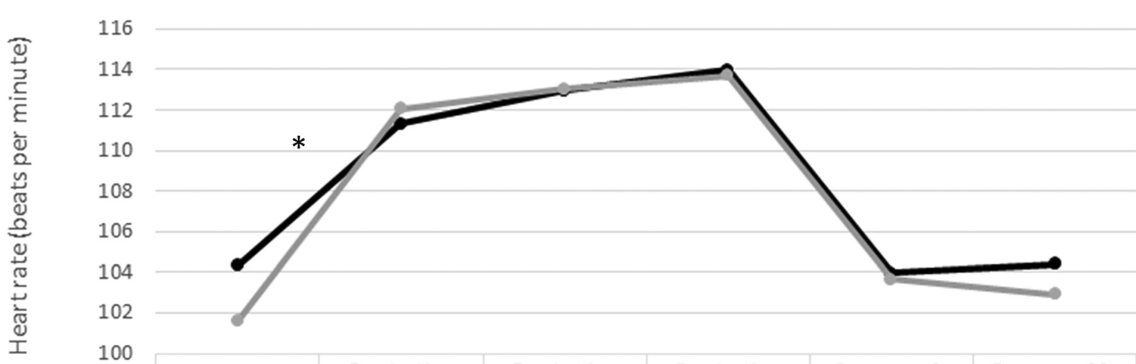
Results

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 physiological arousal 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 = 0.108, $F(4,70) = 2.120$, $P = 0.087$). In addition, which karyotype a child carried (XXX, XXY, and XYY) had no significant influence on the main outcome parameters (Pillai's trace = 0.058, $F(8,140) = 0.522$, $P = 0.838$). 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 = 0.028, $F(8,140) = 0.245$, P = 0.981). 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 physiological arousal (e.g. emotional distress). First, in terms of baseline heart rate, there was no significant difference between children with SCT (*M* 104.32, s.d. 17.27) and children from the control group (*M* 101.67, s.d. 14.10) ($t(154) = 1.050$, $P = 0.295$). 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 ($F(5,149) = 57.105$, $P < 0.001$, ηp^2 = 0.657), no main effect for Group ($F(1,101) = .059$, $P = 0.808$), and no interaction effect ($F(5,149) = 1.623$,



	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 s from the frustrating task were excluded from the analysis to allow for the build-up of frustration.

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$P = 0.157$). These results showed no significant difference in the pattern of arousal response across groups during the locked box task (Fig. 2). Thus, the locked box task was successful in evoking a physiological 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 × Group effect from baseline to the frustration phase ($F(1,153) = 6.586$, $P = 0.011$, $\eta p^2 = 0.041$), 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 a resting state during recovery.

Emotion regulation strategies

The main research objective was to examine the presence and variety of 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 and general intellectual functioning were included as covariates in a MANCOVA to account for individual differences in arousability and general cognitive ability, with the three emotion regulation 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 ($F(3,148) = 7.342$, $P < 0.001$, $\eta p^2 = 0.130$) and Group ($F(3,148) = 3.574$, $P = 0.016$, $\eta p^2 = 0.068$) during the locked box task. There was no main effect on general intellectual functioning ($F(3,148) = 0.678$, $P = 0.567$). When

Table 2 Descriptives and MANCOVA test results for emotion regulation strategies.

	SCT	Control		
	M (S.D.)	M (S.D.)	*F*	*P*
Avoidance	0.62 (0.80)	0.65 (0.80)	0.146	0.703
Venting	1.15 (1.17)	1.49 (1.45)	1.829	0.178
Constructive	2.33 (1.10)	2.62 (0.92)	4.139	**0.044**

SCT, sex chromosome trisomies.
Bold indicates statistical significance, $P < 0.05$.

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 and general cognitive abilities (Fig. 3). For venting or avoidance strategies, there were no significant group differences (Table 2).

To display how individual arousability relates to behavioral outcomes in the different groups, Fig. 4 shows a scatterplot of peak arousal responses and mean constructive strategies for each individual. An examination of this plot shows that there is great variation in children's arousability to a frustration-inducing event, even within the separate research groups.

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 the child's age × group was found for avoidance strategies ($b = -0.17$, S.E. $= 0.06$, $t = -2.70$, $P = 0.008$, 95% CI $= -0.29$ and -0.05). As shown in Fig. 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 ($b = -0.07$, S.E. $= 0.11$, $t = -0.61$, $P = 0.542$, 95% CI $= -0.29$, 0.15) or constructive strategies ($b = 0.01$, S.E. $= 0.09$, $t = 0.09$, $P = 0.931$, 95% CI $= -0.16$, 0.18), see Fig. 5 for a visual representation.

Discussion

The present study examined emotion regulation processes in young children with an SCT compared to controls when faced with a challenging situation. The results show that while children with SCT experienced a significant increase in physiological arousal (similar to controls) when blocked in achieving a desired toy, their behavioral response did not follow accordingly. While controlling for individual arousability and general intellectual functioning, 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 United States),

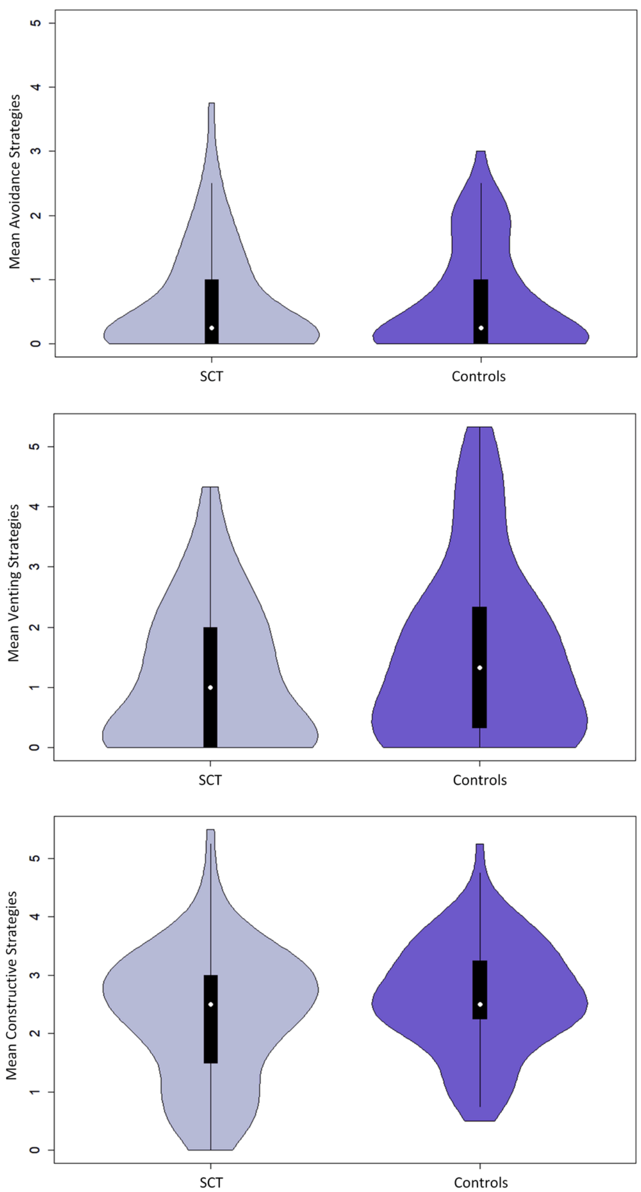

Figure 3
Violin plots of emotion regulation strategies across research groups (sex chromosome trisomies (SCT) and controls).

and recruitment strategies, suggesting that emotion regulation is an area of concern in the development of all children with SCT. Finally, albeit the SCT group had significantly lower average IQ scores than the controls (with mean points still in the average range), a lower IQ was not related to more emotion regulation problems. This indicates that the risk for emotion regulation problems in SCT can be present irrespective of differences in cognitive abilities.

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 on average less emotion regulation strategies that can be considered constructive. Differences between individuals with SCT existed as well, with a subgroup showing an adequate display of constructive behavior and a subgroup showing a more limited range of behavior. Constructive strategies represent behavioral responses as goal-directed actions and support-seeking behavior, in order to achieve a goal at hand. Emotion regulation, by definition, is the ability to organize behavior that could lead to a decrease (or an increase) of negative (or positive) emotions in order to meet the demands of the environment (7). 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 thus limited. The display of other emotion regulation strategies, such as avoiding and venting behavior, was on average not significantly different compared to controls. However, individual differences in the display of behavior were also observed, with some children with SCT showing more avoidance and venting behavior than others (Fig. 3).

Furthermore, another key result of the current study is that with older age, children with SCT tend to rely longer on certain forms of regulation, such as avoidance. Avoiding (displeasant situations) is one of the earliest and automatic forms of emotion regulation, which gradually decreases in use starting at around the age of 18–24 months alongside the emergence of other types of regulation strategies (32). This shift from automatic to volitional forms of regulation

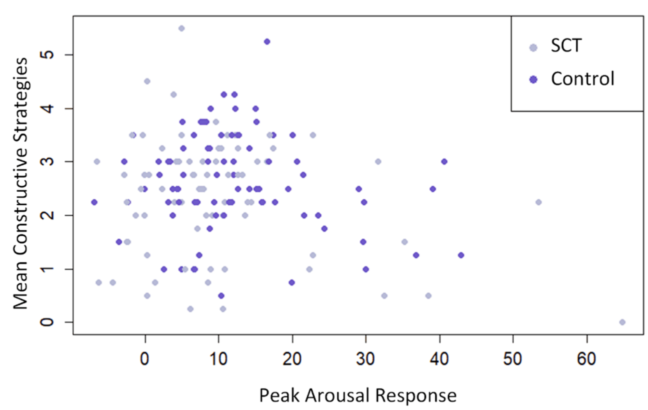

Figure 4
Scatterplot of peak arousal response and mean constructive strategies across research groups (sex chromosome trisomies (SCT) and controls).

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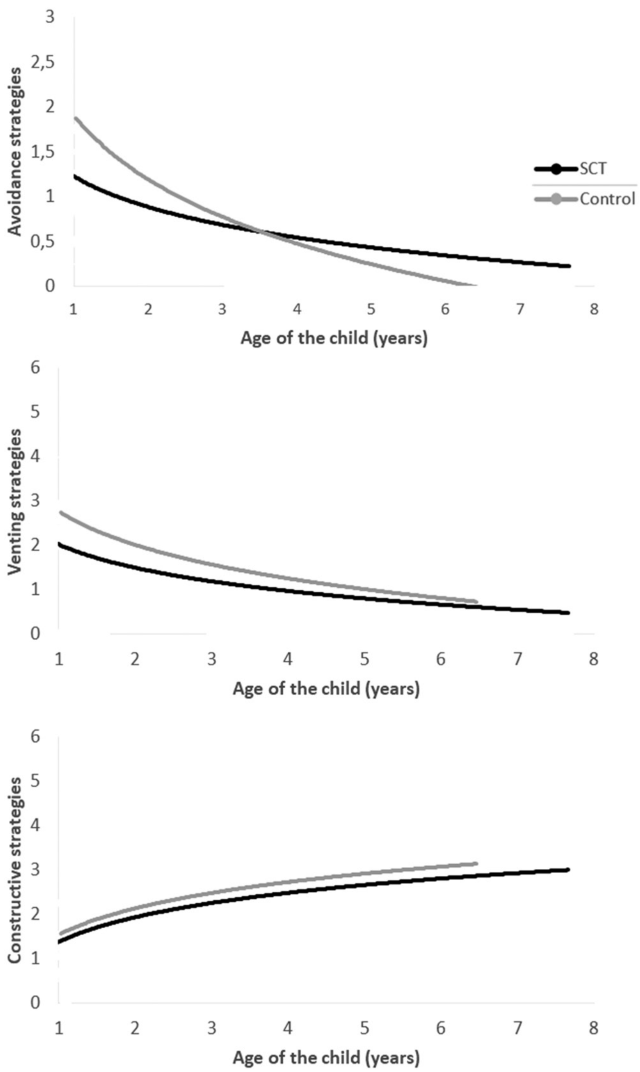

Figure 5
Trajectory lines of child's age by mean emotion regulation strategies across research groups (SCT and controls).

is amongst others associated with the developing (pre) frontal cortical networks during this age period, which at the same time sets the stage for the development of other cognitive functions, including executive functions (33). Taken together with the fact that the genes on X and Y chromosome are densely involved in brain development (34), our results suggest that emotion regulation difficulties might be anchored into the 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. An 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 (35, 36, 37). This suggests that no single 'perfect' emotion regulation strategy exists and that rather the variety in strategies, thus the ability to choose from strategies to adapt your behavior to difficult situations is truly important for good emotional health.

The current findings fit with behavioral observations of emotion regulation difficulties in daily life, found in children with SCT already from the age of 3 years old (38, 39). It is also in line with findings in adults with SCT, which showed atypical emotion regulation strategies in men with Klinefelter (14, 16), including difficulties with verbalizing their emotions and higher indices of avoidance, distraction seeking, and passive regulation strategies. Different to the literature is that we found that our sample of children with SCT had a similar arousal response to the frustration-inducing event compared to controls. Other studies found significant differences when compared to controls, such as increased arousal responses that correlate with empathic behavior in men with 47,XXY compared to controls (15) as well as blunted arousal responses in young children with SCT (22). Differences in these findings might relate to the nature of the stressor (e.g. social, non-social, neutral) and the context in which the arousal is measured (40). These inconclusive results highlight the importance of further investigation of emotional processing in individuals with SCT.

Taken together, our findings indicate that individuals with SCT can be vulnerable in their emotional development, but that not all aspects of emotion regulation are equally impacted. Given that emotion regulation is essential for daily life functioning and an important developmental task in early childhood, our results suggest that individuals with SCT can face challenges in dealing with day-to-day conflicts that require children to cope with their emotions adaptively, from an early age. Successful emotion regulation in preschool years is associated with social competency, school engagement, and academic performance, in early school years (41). On the other hand, emotion regulation is also considered an important process in the etiology and maintenance of different forms of psychopathology (42). It is therefore not surprising that emotion regulation has been acknowledged as a transdiagnostic mechanism in mental health (43). 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 (44). From existing literature, it is known that the SCT population is at significantly increased risk for these types of mental health problems (3). 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.

In addition to understanding gene–brain pathways from a theoretical point of view, these results are also highly relevant to individuals affected by SCT and the professionals working with them and their families. The early signs of emotion regulation dysfunction inform us that children with SCT can 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 early emotion regulation skills through observation and adult (parent)–child interactions and their development is also influenced by the emotional climate in the family (45). 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 incorporate 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 (46) or Affect Regulation Training in adolescents and adults (47). However, research is needed to establish effectiveness in the SCT population. 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 (48) showed that self-management training, which included emotion regulation techniques, led to improvements in emotional stability and self-regulation in adolescents and adults with 47,XXY. Also promising is the study of Bouw and colleagues (49) 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 of emotion regulation is essential given it allows for the implementation of early (preventive) strategies, which have the potential to influence child development toward more optimal outcomes (50).

The study also had some limitations. First, coders of regulation behaviors were only semi-blind to the group identity (SCT vs control) of the children, which could have biased the results. Second, the current design did not allow for the investigation of interactive dynamics between regulation strategies and subsequent changes in physiological 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 the developmental impact of the extra X or Y chromosome over time, as well as its relation to neurodevelopmental difficulties and mental health problems. With regards to directions for future research, it would be relevant to examine the link between emotion regulation and its predictive value in terms of psychopathology later in life. Emotion regulation 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 and childrearing behavior (45). Including all relevant factors and their link to potential outcomes 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. Finally, this study did not examine the potential effect of early testosterone treatment on behavioral outcomes in children with 47,XXY. Although treatment with testosterone is considered an evidence-based practice to improve the physical implications of a micropenis, the evidence for the potential benefits of early testosterone on (neuro) developmental outcomes in infants with Klinefelter syndrome is still limited (51). We support the initiative of Aksglaede and colleagues (51) who call for a randomized and placebo-controlled trial with an adequately powered cohort sample: one of which is currently underway (PI Davis, NCT03325647).

In sum, the results of this study have shown that young children with SCT are limited in their use of emotion regulation strategies, compared to controls, which could impact their developmental outcomes. These results suggest that even at an early age individuals with SCT show difficulties in self-regulatory processes, vital for adaptive day-to-day functioning. Emotion regulation can thus be

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seen as a valid candidate as an underlying mechanism in explaining the heterogeneity and variabilities in psychopathology and mental health problems so often experienced by the SCT population. Future studies are needed to examine developmental pathways into psychopathology and the predictive value of emotion regulation in these trajectories. The current findings on emotion regulation difficulties provide essential information for those involved in care for individuals with an additional X and Y chromosome and can help develop specific tools for early and preventive intervention.

Declaration of interest
The authors report no conflicts of interest.

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References

1 Berglund A, Viuff MH, Skakkebæk A, Chang S, Stochholm K & Gravholt CH. Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: a nationwide cohort study. *Orphanet Journal of Rare Diseases* 2019 **14** 16. (https://doi.org/10.1186/s13023-018-0976-2)
2 Groth KA, Skakkebæk A, Høst C, Gravholt CH & Bojesen A. Clinical review: Klinefelter syndrome—a clinical update. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 20–30. (https://doi.org/10.1210/jc.2012-2382)
3 van Rijn S. A review of neurocognitive functioning and risk for psychopathology in sex chromosome trisomy (47,XXY, 47,XXX, 47,XYY). *Current Opinion in Psychiatry* 2019 **32** 79–84. (https://doi.org/10.1097/YCO.0000000000000471)
4 Visootsak J & Graham Jr JM. Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. *Developmental Disabilities Research Reviews* 2009 **15** 328–332. (https://doi.org/10.1002/ddrr.76)
5 van Rijn S, Stockmann L, Borghgraef M, Bruining H, van Ravenswaaij-Arts C, Govaerts L, Hansson K & Swaab H. The social behavioral phenotype in boys and girls with an extra X chromosome (Klinefelter syndrome and trisomy X): a comparison with autism spectrum disorder. *Journal of Autism and Developmental Disorders* 2014 **44** 310–320. (https://doi.org/10.1007/s10803-013-1860-5)
6 Tartaglia N, Cordeiro L, Howell S, Wilson R & Janusz J. The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). *Pediatric Endocrinology Reviews* 2010 **8**(Supplement 1) 151–159.
7 Gross JJ *Handbook of Emotion Regulation*. New York, NY, USA: Guilford Publications, 2013.
8 Denham SA, Blair KA, DeMulder E, Levitas J, Sawyer K, Auerbach–Major S & Queenan P. Preschool emotional competence: pathway to social competence? *Child Development* 2003 **74** 238–256. (https://doi.org/10.1111/1467-8624.00533)
9 Thompson RA. Emotion regulation: a theme in search of definition. *Monographs of the Society for Research in Child Development* 1994 **59** 25–52. (https://doi.org/10.2307/1166137)
10 Blair C & Razza RP. Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development* 2007 **78** 647–663. (https://doi.org/10.1111/j.1467-8624.2007.01019.x)
11 Eisenberg N, Valiente C & Eggum ND. Self-regulation and school readiness. *Early Education and Development* 2010 **21** 681–698. (https://doi.org/10.1080/10409289.2010.497451)
12 Olson SL, Sameroff AJ, Kerr DCR, Lopez NL & Wellman HM. Developmental foundations of externalizing problems in young children: the role of effortful control. *Development and Psychopathology* 2005 **17** 25–45. (https://doi.org/10.1017/s0954579405050029)
13 Tracy JL. An evolutionary approach to understanding distinct emotions. *Emotion Review* 2014 **6** 308–312. (https://doi.org/10.1177/1754073914534478)
14 van Rijn S & Swaab H. Emotion regulation in adults with Klinefelter syndrome (47,XXY): neurocognitive underpinnings and associations with mental health problems. *Journal of Clinical Psychology* 2020 **76** 228–238. (https://doi.org/10.1002/jclp.22871)
15 van Rijn S, Barendse M, van Goozen S & Swaab H. Social attention, affective arousal and empathy in men with Klinefelter syndrome (47,XXY): evidence from eyetracking and skin conductance. *PLoS One* 2014 **9** e84721. (https://doi.org/10.1371/journal.pone.0084721)
16 Van Rijn S, Swaab H, Aleman A & Kahn RS. X chromosomal effects on social cognitive processing and emotion regulation: a study with Klinefelter men (47,XXY). *Schizophrenia Research* 2006 **84** 194–203. (https://doi.org/10.1016/j.schres.2006.02.020)
17 Tartaglia N, Howell S, Davis S, Kowal K, Tanda T, Brown M, Boada C, Alston A, Crawford L, Thompson T, *et al.* Early neurodevelopmental and medical profile in children with sex chromosome trisomies: background for the prospective eXtraordinarY babies study to identify early risk factors and targets for intervention. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 2020 **184** 428–443. (https://doi.org/10.1002/ajmg.c.31807)
18 Urbanus E, Swaab H, Tartaglia N, Cordeiro L & van Rijn S. The behavioral profile of children aged 1–5 years with sex chromosome trisomy (47,XXX, 47,XXY, 47,XYY). *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 2020 **184** 444–455. (https://doi.org/10.1002/ajmg.c.31788)
19 Crockenberg SC & Leerkes EM. Infant and maternal behaviors regulate infant reactivity to novelty at 6 months. *Developmental Psychology* 2004 **40** 1123–1132. (https://doi.org/10.1037/0012-1649.40.6.1123)
20 Posner MI & Rothbart MK. Developing mechanisms of self-regulation. *Development and Psychopathology* 2000 **12** 427–441. (https://doi.org/10.1017/s0954579400003096)
21 Blair C & Ursache A. A bidirectional model of executive functions and self-regulation. In: KD Vohs & RF Baumeister, Eds. *Handbook of Self-Regulation: Research, Theory, and Applications*. New York, NY, USA: The Guilford Press, 2011.
22 Kuiper KC, Swaab H, Tartaglia NR, Cordeiro L & van Rijn S. Emotional reactivity and expressivity in young children with sex chromosome trisomies: evidence from psychophysiological and observational data. *Child Neuropsychology* 2023 **29** 569–587. (https://doi.org/10.1080/09297049.2022.2102161)
23 Hollingshead ADB. *Four Factor Index of Social Status*. New Haven, CT, USA: Yale University Press, 1975.

24 Bayley N. *Bayley Scales of Infant and Toddler Development* 3rd ed. San Antonio, TX, USA: Harcourt Assessment, 2006.

25 Wechsler D. *WPPSI-III Technical and Interpretative Manual*. San Antonio, TX, USA: The Psychological Corporation, 2002.

26 Sjak-Shie EE. *PhysioData Toolbox (Version 0.5.0)*. Leiden, the Netherlands, 2020. (available at: https://physiodatatoolbox.leidenuniv.nl)

27 Piferi RL, Kline KA, Younger J & Lawler KA. An alternative approach for achieving cardiovascular baseline: viewing an aquatic video. *International Journal of Psychophysiology* 2000 **37** 207–217. (https://doi.org/10.1016/s0167-8760(00)00102-1)

28 Goldsmith HH, Reilly J & Lemery KS. *The Laboratory Temperament Assessment Battery: Preschool Version* (Technical Manual). Madison, WI, USA: University of Wisconsin, 1999.

29 Jahromi LB, Meek SE & Ober-Reynolds S. Emotion regulation in the context of frustration in children with high functioning autism and their typical peers. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* 2012 **53** 1250–1258. (https://doi.org/10.1111/j.1469-7610.2012.02560.x)

30 Hallgren KA. Computing inter-rater reliability for observational data: an overview and tutorial. *Tutorials in Quantitative Methods for Psychology* 2012 **8** 23–34. (https://doi.org/10.20982/tqmp.08.1.p023)

31 Hayes AF. *PROCESS: A Versatile Computational Tool for Observed Variable Mediation, Moderation, and Conditional Process Modeling*. Lawrence, KS, USA: University of Kansas, 2012.

32 Harman C, Rothbart MK & Posner MI. Distress and attention interactions in early. *Motivation and Emotion* 1997 **21** 27.

33 Ursache A, Blair C, Stifter C, Voegtline K & Family Life Project Investigators. Emotional reactivity and regulation in infancy interact to predict executive functioning in early childhood. *Developmental Psychology* 2013 **49** 127–137. (https://doi.org/10.1037/a0027728)

34 Zechner U, Wilda M, Kehrer-Sawatzki H, Vogel W, Fundele R & Hameister H. A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution? *Trends in Genetics* 2001 **17** 697–701. (https://doi.org/10.1016/s0168-9525(01)02446-5)

35 Schäfer JÖ, Naumann E, Holmes EA, Tuschen-Caffier B & Samson AC. Emotion regulation strategies in depressive and anxiety symptoms in youth: a meta-analytic review. *Journal of Youth and Adolescence* 2017 **46** 261–276. (https://doi.org/10.1007/s10964-016-0585-0)

36 Cracco E, Van Durme K & Braet C. Validation of the FEEL-KJ: an instrument to measure emotion regulation strategies in children and adolescents. *PLoS One* 2015 **10** e0137080. (https://doi.org/10.1371/journal.pone.0137080)

37 Braet C, Theuwis L, Van Durme K, Vandewalle J, Vandevivere E, Wante L, Moens E, Verbeken S & Goossens L. Emotion regulation in children with emotional problems. *Cognitive Therapy and Research* 2014 **38** 493–504. (https://doi.org/10.1007/s10608-014-9616-x)

38 Lee NR, Wallace GL, Clasen LS, Lenroot RK, Blumenthal JD, White SL, Celano MJ & Giedd JN. Executive function in young males with Klinefelter (XXY) syndrome with and without comorbid attention-deficit/hyperactivity disorder. *Journal of the International Neuropsychological Society* 2011 **17** 522–530. (https://doi.org/10.1017/S1355617711000312)

39 Kuiper KC, Swaab H, Tartaglia N, van Buggenhout G, Wouters C & van Rijn S. The developmental impact of sex chromosome trisomies on emerging executive functions in young children: evidence from neurocognitive tests and daily life skills. *Genes, Brain, and Behavior* 2022 **21** e12811. (https://doi.org/10.1111/gbb.12811)

40 Stifter CA, Fox NA & Porges SW. Facial expressivity and vagal tone in 5-and 10-month-old infants. *Infant Behavior and Development* 1989 **12** 127–137. (https://doi.org/10.1016/0163-6383(89)90001-5)

41 Robson DA, Allen MS & Howard SJ. Self-regulation in childhood as a predictor of future outcomes: A meta-analytic review. *Psychological Bulletin* 2020 **146** 324–354. (https://doi.org/10.1037/bul0000227)

42 Aldao A, Nolen-Hoeksema S & Schweizer S. Emotion-regulation strategies across psychopathology: a meta-analytic review. *Clinical Psychology Review* 2010 **30** 217–237. (https://doi.org/10.1016/j.cpr.2009.11.004)

43 Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C & Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry* 2010 **167** 748–751. (https://doi.org/10.1176/appi.ajp.2010.09091379)

44 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Washington, DC, USA: American Psychiatric Association, 2013.

45 Morris AS, Silk JS, Steinberg L, Myers SS & Robinson LR. The role of the family context in the development of emotion regulation. *Social Development* 2007 **16** 361–388. (https://doi.org/10.1111/j.1467-9507.2007.00389.x)

46 Braet C & Berking M. Emotieregulatietraining bij kinderen en adolescenten. In: C Braet & M Berking, Eds. Houten: Bohn Stafleu van Loghum, 2019. (https://doi.org/10.1007/978-90-368-2308-1)

47 Berking M & Whitley B. Development of the "affect regulation training" (ART) program BT - affect regulation training: a practitioners' manual. In: M Berking & B Whitley, Eds. New York, NY: Springer, 2014. (https://doi.org/10.1007/978-1-4939-1022-9_6)

48 Martin F, van Rijn S, Bierman M & Swaab H. Social management training in males with 47,XXY (Klinefelter syndrome): a pilot study of a neurocognitive-behavioral treatment targeting social, emotional, and behavioral problems. *American Journal on Intellectual and Developmental Disabilities* 2021 **126** 1–13. (https://doi.org/10.1352/1944-7558-126.1.1)

49 Bouw N, Swaab H & van Rijn S. Early preventive intervention for young children with sex chromosome trisomies (XXX, XXY, XYY): supporting social cognitive development using a neurocognitive training program targeting facial emotion understanding. *Frontiers in Psychiatry* 2022 **13** 807793. (https://doi.org/10.3389/fpsyt.2022.807793)

50 Guralnick MJ. Why early intervention works: A systems perspective. *Infants and Young Children* 2011 **24** 6–28. (https://doi.org/10.1097/IYC.0b013e3182002cfe)

51 Aksglaede L, Davis SM, Ross JL & Juul A. Minipuberty in Klinefelter syndrome: current status and future directions. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 2020 **184** 320–326. (https://doi.org/10.1002/ajmg.c.31794)

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