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

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Summary and general discussion

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One in every 650 to 1000 children has a genetic condition known as a sex chromosome trisomy (SCT), indicating that they are born with three sex chromosomes instead of the typical number of two (Berglund et al., 2019). Karyotypes that results from SCT are 47,XXX (also known as Trisomy X), 47,XXY (also known as Klinefelter's syndrome), and 47,XYY. Individuals with SCT are at increased risk for psychopathology, referring to social, emotional, and behavioral problems (Geschwind et al., 2000; Ross et al., 2012; Tartaglia et al., 2010; van Rijn et al., 2008). By considering behavior on a continuum ranging from adaptive to non-adaptive, having significant behavioral problems can tremendously impact adaptive day-to-day functioning to such an extent that these behaviors can also be classified as symptoms of psychiatric classifications (according to the DSM-5, APA, 2013). For individuals with SCT, an increased risk for psychiatric classifications has been described (van Rijn, 2019), including affective disorders, social-communicative disorders, and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Around 25% of the SCT population is at clinical risk and thus experience a significant impact of the additional X or Y chromosome on their mental well-being and day-to-day functioning.

To understand how the extra sex chromosome impacts development and contributes to daily life outcomes, a neurocognitive perspective can provide insight in how differences in information processing contribute to psychopathology. In other words, how neurocognitive functioning may serve as an underlying and possible driving mechanism between genes, brain, and behavior. Thus far, studies have shown that a significant fraction of genes on the X chromosome are associated with brain development and functioning (Zechner et al., 2001). Furthermore, structural and functional differences in the brain have been identified in individuals with SCT compared to the general population (Steinman et al., 2009; Warling et al., 2020). In addition, impairments in neurocognitive functioning in SCT are described in adolescence and adulthood. These include differences compared to the general population in the area of intelligence, language, executive functioning, and social cognition (for a review, see van Rijn, 2019). Studies on neurocognition in early childhood, before the age of 8 years old, are scarcely available (Urbanus, van Rijn, et al., 2020). Because most neurocognitive functions start to develop in early childhood, a developmental approach is of key importance here. Deviations from typical neurocognitive development could pinpoint at-risk markers in development in children with SCT and potentially indicate a suboptimal process of brain maturation (Urbanus, van Rijn, et al., 2020). Within this dissertation, the goal

was to identify early developmental risks in young children with SCT, with a specific focus on neurocognitive skills essential to adequate social and emotional adaptation, namely self-regulation. The regulation of thoughts, emotions, and behavior in a social context is a vital factor when it comes to daily life functioning and therefore an interesting neurocognitive candidate to study in relation to psychopathology. This knowledge would increase our understanding of neurodevelopmental pathways into later psychopathology and uncover specific targets for early and preventive intervention.

The study of early development in children with SCT becomes more relevant every day: With the increasing use of non invasive prenatal testing worldwide, the number of children who are prenatally diagnosed with SCT are expected to increase (Samango-Sprouse et al., 2017). This has two important implications. First, it highlights the urgent need for more updated knowledge on the development of children with SCT in order to guide clinical care. This knowledge would inform clinicians and parents on the potential developmental impact of SCT and help develop neurocognitive intervention tools. Second, it allows for the unique opportunity to prospectively study these children before any severe developmental problems or delays unfold and provide input for a high-risk model to examine early neurocognitive factors in relation to later psychopathology.

Whilst the somatic profile of individuals with SCT has received increasing scientific interest over the last decade (Pieters et al., 2011), the behavior and neurocognitive development of young children with SCT remains poorly understood (Urbanus, van Rijn, et al., 2020). To enhance our understanding of early development of children with SCT and how differences in behavior and neurocognitive functioning contributes to later psychopathology, the TRIXY Early Childhood Study was initiated. Through means of extensive international and national cooperation, the TRIXY Early Childhood Study was able to include a uniquely large sample of young children with SCT to capture a broad range of developmental outcomes in this population and compare them with age-matched sample of typically developing children. The general aim of the TRIXY Early Childhood Study is to examine behavioral and neurocognitive mechanisms that are not only known to be important in typical childhood development but also identified areas of vulnerability in individuals with SCT. Unraveling differences in neurocognitive functioning and behavior would help us understand the different pathways into later psychopathology, but would also identify vulnerable areas of development suitable for early and/or preventive intervention.

The studies in this dissertation specifically focused on one area of vulnerability: self-regulation. Self-regulation refers to an interrelated set of skills

needed to regulate our emotions, thoughts, impulses, and behavior. Several aspects of self-regulation develop at an accelerated pace in early childhood (Blair & Diamond, 2008), partly due to brain maturation (Posner & Rothbart, 2000), highlighting both its usefulness and relevance when studying at-risk neurocognitive pathways in the young developing child. Moreover, self-regulation has been identified as an important transdiagnostic factor in the development of psychopathology in the general population (Romer et al., 2021) and has significant relevance to daily functioning and quality of life (Blair & Diamond, 2008). Being able to regulate your emotions, thoughts, and behavior promotes positive adjustment and adaptation in daily (social) life, with the latter often being a challenge for individuals with SCT, who are typically described as having emotional, behavioral, and social difficulties in adolescence and adulthood. The central aim of this dissertation was to provide a better neurocognitive understanding of early self-regulatory skills in young children with SCT by using a comprehensive approach. Sensitive and direct measures of self-regulation were used and included not only measures of what can be observed and tested directly in terms of behavior and neurocognition but also included measures of more fundamental processes such as physiological responses, that are able to represent the arousal component of emotion regulation. These measures collectively have the ability to identify how (deviations in) information processing influence and shape behavioral responses in order to function adequately.

This dissertation focused on how children with SCT regulate their emotions, thoughts, and behavior, as expressed in behavioral regulation (symptoms of ADHD), cognitive regulation (executive functions), and emotion regulation (arousal, expression, and coping behavior) in a sensitive period of development. The total sample described in this dissertation consists of 107 children with SCT, between the ages of 12 months and 7 years old, that were compared to 102 age-matched typically developing peers. Children with SCT were recruited with the help of clinical genetic departments, pediatricians, and national advocacy or support groups, in the Netherlands as well as in Denver, USA. The SCT group consisted of 33 girls with 47,XXX, 50 boys with 47,XXY, and 24 boys with 47,XYY. As part of the longitudinal design of the study, children were assessed either at home or at a University lab during an initial baseline assessment and a follow-up assessment 12 months later (with a subgroup also having a 1-month post-intervention assessment). The experimental studies described in this dissertation only include data collected at baseline. During assessment, several aspects of self-regulation were measured. At the behavioral level, parent-reported data on attention and behavioral problems (ADHD-symptoms) was assessed, along with observational data of emotion regulation

strategies and emotional expression. At the level of neurocognitive functioning, both test performances on executive function tasks as well as parental report of executive functioning in daily life was assessed. At the level of psychophysiology, arousal during emotion-evoking situations was assessed using heart rate data as an indicator of emotional reactivity. To examine the developmental impact, age was a significant factor of interest in all studies. This focus on early childhood was crucial to better understand the developmental impact of SCT in young children and for pinpointing targets to serve as markers for preventive and early intervention.

Taken together, the results in this dissertation reveal that children with SCT are a significant risk for self-regulatory difficulties, that appear to be more pronounced with increasing age. Early signs of self-regulation problems were found at a behavioral level, expressed in more symptoms of inattentive behavior (as seen in ADHD-symptomatology) in children with SCT (**Chapter 2**). Although these problems were present as early as 12 months old, older children with SCT show more pronounced inattentive behavior. To adequately regulate behavior, thoughts, and emotions, executive functions are essential neurocognitive skills. However, children with SCT have less strongly developed executive functions to rely on, even with average intelligence levels (**Chapter 3**). Again, older children with SCT show more pronounced but also broader problems in the area of executive functioning. Part of adequate self-regulation are also those skills involved in emotion perception and the regulation of emotions. On a physiological level, children with SCT show a more blunted arousal response (in terms of heart rate) to a stress-evoking event and need more time to recover from this event, compared to their peers (**Chapter 4**). Also, they display significant less expression of negative emotions during stress than their peers. Moreover, their level of arousal was less predictive of a congruent emotional expression: The overlap between arousal and expression was significantly lower in children with SCT. Furthermore, when confronted with a frustration task, children with SCT show a more limited range of behavioral coping strategies and, with increasing age, tended to rely longer on emotionally "immature" regulation strategies (**Chapter 5**). Together, these studies indicate a significant impact of SCT on early development in terms of self-regulation. However, self-regulation is not the only important neurocognitive building block in early childhood that appears vulnerable in SCT. The review (**Chapter 6**) showed that in addition to differences in self-regulation, children with SCT are vulnerable on numerous important neurodevelopmental domains, including language, communication, and social cognition.

Below, the results of the five studies are summarized in more detail, followed by a general discussion of the main conclusions, implications, directions for future research, and a summary of the main findings.

Main Findings

Attention and Behavioral Regulation (ADHD-Symptoms)

The study in **chapter 2** addressed to what extent young children with SCT are able to regulate their actions in daily life, by examining behavioral psychiatric symptoms. The most salient markers of impaired self-regulation to study in early childhood are those behavioral symptoms associated with Attention-Deficit Hyperactivity Disorder (ADHD): a neurodevelopment disorder characterized by severe symptoms of inattentiveness, hyperactivity, and impulsivity that interfere with daily functioning and development (DSM-5: APA, 2013). Rather than considering ADHD as an all-or-none phenomenon (e.g., classify these children as meeting diagnostic criteria for ADHD or not), the present study examined variation in ADHD symptoms as a key factor of interest to provide a more sensitive measure of early regulation deficiencies in young children. We used a sensitive, well-known, and widely used instrument (the SWAN rating scale) that was able to capture the full gradient of attentional behaviors reflected by symptoms of ADHD in daily life as reported by their parents. The results of this study showed that, on average, the level of ADHD symptoms in SCT was higher than in the general population sample in the full 1-to-6-year age range (with medium effect size). More specifically, children with SCT had more behavioral challenges in the domain of inattention reported by their parents (with large effect size), indicating significant difficulties with regulating their attention. Differences with control peers were already evident for the youngest age-group (1-2-year-olds), but also present in the 3-4-year-olds and 5-to-6 year-olds. Furthermore, inattentive ADHD symptoms increased with age for children with SCT, whilst for controls ADHD symptoms were not related to age and appeared to present relatively similar across ages. From a clinical perspective, 24% of the children with SCT had scores in the clinical range on parent-report, indicating the severity of ADHD symptoms and the increased risk for ADHD symptomatology in the SCT population. Levels of ADHD symptoms were largely similar across karyotypes, although boys with an extra Y chromosome showed more and broader impairments than children with an extra X chromosome. In addition to inattention difficulties, boys with 47,XYY also exhibited hyperactivity and impulsivity. Ascertainment bias (how children enrolled in the study) and country of recruitment (whether children were tested in the Netherlands or in the United States of America) were not relevant to the increased risk of ADHD symptoms, underlining the robustness of these findings.

These results suggest that self-regulatory difficulties already exist in very young children with SCT, pointing to a significant neurodevelopmental risk

from toddlerhood onward. Given the fact that a significant fraction of the genes on the sex chromosomes are involved in brain development, this elevated risk for behavioral difficulties may be one of the first signs that the child's genetic makeup has impacted the brain's development and, more specifically, the brain areas that are important for self-regulation. This elevated risk for self-regulation in terms of ADHD-symptoms we found in young children corresponds to what has been found in older children, adolescents, and adults with SCT (van Rijn, 2019): in these samples, estimates of significantly elevated clinical levels of ADHD symptoms fall around 35% for 47,XXY (with a range of 27-42%); 49% for 47,XXX (with a range of 27 52%); and 69% for 47,XYY (with a range of 62-76%), with inattentive symptoms being most common.

Cognitive Regulation (Executive Functions)

The study reported in **Chapter 3** focused on the development of neurocognitive skills essential to self-regulation: executive functions. In early childhood, children start to develop the ability to act purposefully and goal-directed, which is supported by the emerging development of executive functions during this period. Executive functions are interrelated neurocognitive skills essential to learn, cope, and manage daily life (Diamond, 2013) and thus of vital importance to support adequate self-regulation (e.g., to regulate your emotions, thoughts, and behavior). Several executive functions are attention, inhibition, monitoring, flexibility, working memory, planning, and fluency (Anderson, 2001).

To investigate the development of emerging executive functions in children with SCT, we compared the performance on several executive function tasks and parental report on daily life executive function behavior of children with SCT to that of a population based sample. Results showed that impairments in executive functions were significantly more prevalent in SCT than in controls and already present from the age of 3 years old. Specific impairments were found in the domain of verbal executive functions and working memory (with medium effect sizes), in addition to broader and more pronounced impairments in older children with SCT. Children with SCT aged 5 to 7 years showed difficulties with global executive functions, verbal fluency, cognitive flexibility, emotional control, working memory, and planning and organizing (with medium to large effect sizes). In addition to general group effects, the results of the study also showed that for some executive functions, there was an interaction (group by age) effect. Whereas older children in the control group showed improved planning and organizing behaviors with increasing age, children with SCT continued to struggle in this domain and did not improve with increasing age. In addition, we found that impairments in executive functions were present across the broad range of intelligence levels. Thus,

difficulties with executive functions can be part of the neurocognitive profile of children with SCT, and was not only limited to those children with a below average intelligence.

Although impairments in executive functions have been described in school-aged children, adolescents, and adults with SCT (Janusz et al., 2020; Lee et al., 2015; Ross et al., 2008, 2009; Samango-Sprouse et al., 2018; van Rijn & Swaab, 2015), this study is the first to show that there is a developmental impact of SCT on emerging executive functions before the age of 7 years and that children with SCT are at significant risk for difficulties with executive functions already in early childhood. This increased risk in children with SCT indicates that their ability to show purposeful, goal-directed, and problem-solving behavior can be affected, from as early as 3 years old. The impact for these children is significant, given that preschool executive functions are vital for school readiness (Blair & Razza, 2007), academic success (Gathercole et al., 2004), and psychological well-being in general (Kusche et al., 1993). Our results suggest that emerging executive functions could be one of the key components in explaining the variability as well as the increased risk for psychopathology in this genetically at-risk group. This is further supported by evidence from other studies in individuals with SCT that have linked impairments in executive functions with social-emotional and behavioral problems (Skakkebæk et al., 2017), psychotic symptoms (van Rijn et al., 2009), and neurodevelopmental disorders, such as ADHD symptoms (Lee et al., 2011) and ASD symptoms (van Rijn et al., 2012).

Emotion Regulation (Physiological Arousal, Expressivity, and Coping Strategies)

In addition to executive function skills that help to regulate behavior, children also need to process emotional information and regulate their emotions. The manifestation of emotions and its regulation includes multiple biological, cognitive, and behavioral systems, which can be assessed by examining physiological changes and behavioral responses as indicators of these systems (Tracy, 2014). In studies described in **Chapters 4 and 5** examine the interplay between the reactivity of the autonomous nervous system (physiological changes in terms of arousal) and behavioral responses in children with SCT, during different emotion-evoking situations.

The study reported in **Chapter 4** examined how children with SCT process emotions during a stress-evoking event (e.g., toy that unexpectedly approaches the child and makes threatening sounds), by collecting both physiological (heart rate) and observational data (expression of negative emotion). By studying both parameters with sensitive and objective techniques, the study aimed to

identify differences in emotional processing compared to controls. Firstly, the study identified different reactivity and recovery patterns for children with SCT. More specifically, children with SCT showed a significantly lower arousal response (in terms of heart rate) following a stress-evoking event. This indicates that children with SCT show a more blunted response in response to a stressful event. Furthermore, the results showed that even when the stressful event had ended, the recovery of the physiological system to its original baseline state took longer in children with SCT compared to controls. To compare, typically developing children showed an immediate physiological response and were able to recover quickly to their original baseline state when the event had ended. In addition to these differences in emotional arousal, we found that children with SCT showed less expression of emotion in their face or body during the stressful event. Furthermore, there was less overlap between the physiological and behavioral components of the emotion response. Children with SCT showed a significantly lower concordance between emotional arousal and expressivity compared to controls.

In addition to how children with SCT experience emotionally evoking events, the study reported in **Chapter 5** examined what young children with SCT do in terms of the regulation of emotions: how do they shape their behavior when faced with challenges? To what degree are these children able to adjust their behavior accordingly so that they can acquire and accomplish their goals, despite arising emotions? We investigated what the behavioral strategies are of children with SCT during a frustration-evoking event (e.g., locked-box with desirable toy). The results show that whilst children with SCT are similarly frustrated by the situation as their peers (displayed by similar physiological changes), they show a diminished behavioral response to the event. Structured behavioral observations revealed significant differences between groups in the use of constructive emotion regulation strategies: children with SCT show less problem-solving strategies in the face of frustration than their typically developing peers. An interesting developmental effect was also found; whereas the use of avoidance strategies tends to decline with age in typically developing children, this was significantly less so in children with SCT. Thus, these results suggest 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 and emotionally "immature" emotion regulation strategies with increasing age.

The results of the studies reported in **Chapter 4 and 5** show that differences in emotion processing and emotion regulation are already part of the early developmental profile of young children with SCT. To date, no other studies

have examined these self-regulation processes this early in the life of children with SCT. By combining novel, state-of-the-art, and sensitive techniques we were able to provide insights in the fundamental mechanisms of how young children with SCT perceive, process, and regulate emotions. This is especially relevant, given that these processes are traditionally challenging to study in young children (Bölte et al., 2016), for example with more traditional pen-to-paper tasks that require cognitive and language responses: skills that are yet developing in early childhood.

The results of the current studies are of additive value to the literature on emotion regulation in individuals with SCT. Most studies have focused on behavioral measures and questionnaire data and have shown that ineffective emotion regulation strategies are typical to adolescents and adults with SCT and include behaviors such as emotional outbursts, depressive symptoms, and increased anxiety (Tartaglia et al., 2010; van Rijn & Swaab, 2015). Our results also match with other studies that found deviations in emotional expressivity, including difficulties in expressing negative emotions to others (van Rijn et al., 2008), regulating their emotions (van Rijn & Swaab, 2020), and identifying and verbalizing their emotions (Van Rijn et al., 2006). However, only three other studies to date focused on the physiological indices of emotional reactivity similar to our studies, with discordant results. To illustrate, one showed increased affective arousal in response to viewing emotion-evoking visual images (van Rijn, Barendse, et al., 2014), one showed similar arousal responses to sensory stimuli, and the third found a blunted affective arousal response to evoking social stimuli in young children with SCT (Urbanus et al., n.d.). 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 (Stifter et al., 1989). These inconclusive results highlight the importance of further investigation of emotional processing in individuals with SCT.

Neurocognitive Building Blocks in Early Childhood (TRIXY Early Childhood Study)

To fully understand the early developmental profile of children with SCT, it is also important to examine their development in a broader context, rather to focus on one domain specifically. Many other factors are important to childhood development, including language, communication, social cognition, and symptoms of ASD. The review in **Chapter 6** aims to provide an overview of this and includes a description of the collective results from the TRIXY Early Childhood study. Whereas the experimental studies described in this dissertation show that several aspects of self-regulation are impacted in children with SCT, the results described in the review show that it is not a

singular vulnerable domain of development. The results of the collective TRIXY Early Childhood study show that in addition to self-regulatory problems, impairments in social cognition, language, and communication are also part of the behavioral and neurocognitive profile of young children with SCT. Interestingly, in this review we also addressed the initial evidence and potential use of identifying neurocognitive problems, such as social cognition, to implement an early preventive intervention to positively support development in this population. These collective results highlight the importance of a comprehensive and inclusive approach when studying genetic conditions such as SCT.

Conclusions

In sum, the studies included in this dissertation show that children with SCT are vulnerable in their ability to self-regulate. By implementing a neurocognitive approach to the study of the development of children with SCT by using sensitive, state-of-the-art methods and measures, we found that having an extra X or Y chromosome impacts the development of these children on multiple levels of functioning. Not only did we find impaired psychophysiological responses of self-regulation, including a blunted arousal response, we also found individual differences in cognitive skills important for self-regulation: executive functions. Furthermore, the effect of impaired self-regulation was found on the emotional and behavioral level of functioning and included differences in the ability to regulate attention (as reflected in high levels of ADHD-symptoms) as well as diminished emotional expressivity and inefficient use of regulation strategies. Furthermore, in most of the studies, a developmental impact of SCT was found: differences in functioning with typically developing peers were present as early as at 12 months old and increasing and more pronounced differences with typical developing peers were found with increasing age. Despite variation in karyotype (XXX, XXY, and XYY), recruitment strategy (i.e., the reason for enrollment in the study), and timing of diagnosis (prenatal or postnatal), differences between the SCT and control group remained present indicating that we found a robust at-risk neurocognitive profile in this population.

Combined, these studies show clear indications that the self-regulation abilities of children with SCT can be impacted, already from an early age. Because the ability to self-regulate is of significant relevance to daily life functioning and adaptation (Blair & Diamond, 2008), we found substantial evidence in our research studies that self-regulation (expressed in

ADHD-symptoms, executive function problems, and emotion regulation problems) is a vulnerable domain in individuals with SCT. Thus, self-regulation can be considered a key underlying mechanism that can contribute to the increased risk for psychopathology in SCT. To illustrate how early self-regulatory skills may contribute to later social, emotional, and behavioral problems, we provide an overview of our lessons learned and how they interact as well as influence the development in young children with SCT.

First, the blunted physiological arousal response we found (**Chapter 4**) indicates that children with SCT are impacted in their ability to rely on their innate system to signal situations as emotionally relevant. As a result, children can miss relevant situations and thus opportunities to interact with their environment (Gross, 2013). This is imperative in early childhood, because being able to interact with your environment is essential to learn that emotion-evoking events can induce emotional stress, but also that this stress can be regulated effectively and successfully (Beeghly & Tronick, 2011). Second, on a neurocognitive level, we found that the executive functions are vulnerable in children with SCT (**Chapter 3**), indicating that these children can be more limited in guiding their thoughts, emotions, and behaviors towards an adaptive response. In other words, they experience more difficulty in organizing their behavior in such a way that it enables them to make adaptive choices in accordance with their goals and to also consider the feelings and actions of others. This has a significant impact for future development, especially given that executive functioning in young children is an essential precursor for the development of social skills (Hughes & Leekam, 2004). Thus, children with SCT might be dually impacted: not only might they experience more difficulty in relying on their internal compass (e.g., emotional reactivity), their cognitive skills to adequately shape emotional experiences, thoughts, and behavior may also be less developed as well. Three, as a potential result of these impaired processes, children with SCT might have more difficulty shaping adaptive behavioral responses (e.g., experiencing emotional outbursts, depressive symptoms, and social-communication problems), as is reflected in a diminished use of emotion regulation strategies (**Chapter 5**), diminished emotional expressions (**Chapter 4**), and increased symptoms of psychopathology, including ADHD (**Chapter 2**).

The fact that these studies found self-regulation difficulties in addition to other neurocognitive skills such as language, communication, and social cognition as early as 12 months old (**Chapter 6**) indicates that the impact of the X and Y chromosome on development is likely associated with a suboptimal brain development and broad maturation processes in individuals with SCT. This is not surprising, given that a significant fraction of genes on the X

chromosome are associated with brain development and functioning (Zechner et al., 2001). The vulnerabilities in the neurocognitive domain of young children with SCT will undoubtedly have a significant impact on their day-to-day-functioning and future development and even more so, should these vulnerabilities co-occur. Hypothetically, children with SCT who are impaired in their ability to interpret emotional expressions in other people's faces (e.g., the skill to recognize emotions, part of social cognition), might experience more difficulty in interpreting these expressions and understand social cues and interactions with others. This would be even more challenging when their ability to focus their attention on important cues is impacted as well. Combining this with limited options to shape your behavior in a goal-directed manner including considerations about the feelings and actions of others, our social world probably is experienced like a complex and challenging environment to grow-up in.

Clinical Implications

Not only did these studies enhance our knowledge of early development in young children with SCT, they also identified at-risk markers in development on multiple levels of functioning which in turn help shape tailored-made interventions. Specific to the self-regulation results presented in this dissertation, we learned that 1) children with SCT are less able to rely on their internal, emotional compass, 2) that this internal response is less predictive of a behavioral response (display of emotions or coping strategies), 3) children with SCT show more difficulty in cognitively regulating of their emotions, thoughts, and behavior (top-down regulation), and 4) children with SCT tend to rely longer on inefficient, emotionally immature behavior regulation strategies in emotionally-evoking situations. Awareness of these self-regulatory skills and the difficulties children with SCT might experience may be meaningful in when providing psychoeducation and intervention strategies. Parents and clinicians may need to 1) help verbalize and address emotionally relevant situations to the child (i.e., signal situation as relevant by functioning as an external compass), 2) understand that the display of emotions of behavior might not be the same as the internal experience of the emotion of the child, 3) help improve the cognitive skills, including executive functions and language, to help shape an adaptive response in a cognitive manner as well as 4) help shape and teach alternative behavioral strategies in order to cope with emotionally challenging situations. The results of these studies illustrate the usefulness of a neurocognitive perspective in SCT, both empirically and clinically.

The knowledge provided in this thesis is essential to improve (prenatal) genetic counseling as well as clinical care in terms of diagnostics and treatment. Since increases in diagnosis rate is to be expected due to increasing access to NIPT worldwide, an increasing number of parents learn of the genetic condition of their child during prenatal testing (Samango-Sprouse et al., 2017). Our results contribute to the growing knowledge on the development of children with SCT, essential to adequately inform parents and health care professionals on the full gradient of potential outcomes associated with having an extra X or Y chromosome. For children that are diagnosed, the current results highlight that integrating a developmental perspective in diagnostics and treatment is key. Even though these results show that children with SCT show certain neuro-cognitive difficulties at certain periods in time *on a group level*, the cognitive profile of an individual child with SCT can still largely vary, also from time to time. Thus, having a genetic condition per se does not reliably predict the future outcomes and perspective for an individual child. Even more, our studies indicate that skills may appear age-appropriate at one age in development, they may potentially grow into a greater delay later in development, the so called "growing into deficit"-phenomenon, (Rourke et al., 1983)). Therefore, (repeated) individual clinical neuropsychological assessment of important neurocognitive skills (including self-regulation, executive functioning, language, communication, social cognition) is highly advised. Children with SCT should preferably be seen at crucial moments in development (developmental milestones) and/or when problems arise. As a clinician, being aware of the variability and increased risk in neurocognitive functioning, even when intelligence levels are in average range, could increase the use of evidence-based interventions that are tailored-made to individual impairments as well as their strengths. Ideally, these interventions would also consider the somatic, psychological, and environmental (family and school) factors as well. Therefore, close collaboration with other disciplines involved in the clinical care for individuals with SCT, such as neurologists, endocrinologists, physical therapists, occupational therapists, pediatricians, language or speech therapists, and (neuro)psychologists, is highly encouraged (Tartaglia et al., 2015). Both in the Netherlands and in the state of Colorado in the United States of America, such a collaboration has been formalized in centers of expertise for individuals with a trisomy of the X and Y chromosomes (TRIXY Center of Expertise and eXtraordinarY Kids Program). In these centers, different professionals with expertise on SCT join together to facilitate and improve health care of individuals with SCT.

Future Directions

In future work, investigating the developmental pathways from early childhood into school-age, adolescence, and adulthood is important to further determine the predictive value of neurocognitive skills as well as its effectiveness as targets for intervention. It will be imperative that future research incorporates a longitudinal design to validate the age-dependent effects found cross-sectionally in this thesis. When it comes to interventions, we know of only one neurocognitive intervention (pilot) that has been systematically examined in young children with SCT (Bouw, Swaab, & van Rijn, 2022), with promising results showing that an intensive parent-child training of emotion recognition skills can increase social cognitive skills in children with SCT. Future research should further explore whether early (and/or preventive) neurocognitive training could minimize the developmental impact of SCT on daily life outcomes. Elaborating on this hypothesis, future research should look for existing interventions that focus on training a specific neurocognitive skill (such as "Transporters" used in (Bouw, Swaab, & van Rijn, 2022)) as well a designing SCT-specific interventions (such as a social self-management training (Martin et al., 2020)).

Future studies should also examine the underlying dynamics between the several neurocognitive vulnerabilities found in children with SCT. For example whether a cumulative risk is at play (e.g., additive effect of risk factors) or whether the interplay between specific factors is more important. A cumulative risk approach would offer a method for investigating how risk factors operate in the context of one another to influence child outcomes (Appleyard et al., 2005) and could thus provide important guidelines on the timing of early and preventive interventions.

Finally, to enhance our understanding of potential outcomes in order to improve clinical care, the study of protective factors and strengths of both the child and its environment would be essential too. The research presented in this dissertation shows that the area of emotional control and regulation is a distinct area of vulnerability in children with SCT. However, when it comes to emotion regulation, many familiar factors are known to influence the development of emotion-regulation skills of typically developing children (A. S. Morris et al., 2007). Amongst those are parenting skills and behaviors related to emotions. Through their parenting skills, parents react to the emotions of the child that can influence the emotion regulation skills of the child (Eisenberg et al., 1998). These reactions can be positive (e.g., validating, rewarding) as well as negative (e.g., punishing, denying or down-playing emotions). In addition, parental characteristics such as their own emotion regulation skills, mental

well-being, and familial (psychiatric) history, are viewed to be important factors in the development of childhood emotion-regulation as well (A. S. Morris et al., 2007). Interesting, emotion regulation skills of the child has been identified as a mediator between parenting behavior and externalizing behavior in typically developing children (Eisenberg, Gershoff, et al., 2001). It would be interesting to examine how parenting skills and familial factors interplay with the neurocognitive profiles and other characteristics of children with SCT in future studies, both directionally as well as bi-directionally.

Summary of the Main Findings

In this thesis, various neurocognitive and behavioral components involved in self-regulation were explored in a large international cohort of young children with SCT during a critical period of development (1 to 7 year old). Following the neurocognitive perspective that information processing deficits can contribute to psychopathology, this dissertation focused on three important interrelated elements of self-regulation: behavioral regulation, cognitive regulation (in terms of executive functioning), and emotion regulation.

- By combining sensitive and innovative techniques, such as reactivity of the autonomous nervous system, with structured observations and cognitive tests, specific vulnerabilities in different levels of self-regulation (as expressed in behavioral, cognitive, and emotional responses) can be identified in children with SCT. These findings are essential to guide clinical care in terms of early assessment and treatment, but also vital to improve genetical counseling on the developmental profile of these children.
- On the behavioral level, children with SCT show more symptoms of ADHD such as inattentiveness in daily life compared to typically developing peers. Albeit not all children with SCT meet full diagnostic criteria for ADHD, many children will present ADHD-like behaviors throughout early childhood. On a cognitive level, children with SCT show impairments in their ability to regulate their thoughts and behaviors, in terms of executive functioning. Specific vulnerabilities were found in the area of working memory, cognitive flexibility, verbal fluency, and planning. Other areas of executive functions appeared to be intact, such as inhibition and self-monitoring. On the emotional level, it was found that several processes involved with emotions, including reactivity, responsivity, expressivity, and regulation, appears different in children with SCT. When faced with stress, children with SCT have a less sensitive arousal system (expressed in a blunted physiological response), show less emotional expression than can be expected based on

age, and show a more limited range of regulatory behaviors that would otherwise be helpful in coping with stressful situations.

- Emotional responses in children with SCT that can be directly observed in behavior (e.g., facial or bodily expressions) may not necessarily reflect a child's level of arousal to these emotions. The connection between the external display (emotions) and the internal arousal response (in terms of heart rate as a measure of physiological arousal) is significantly less strong in children with SCT, compared to their typically developing peers. It is important that parents and professionals working with children with SCT are aware of the potential discrepancies between these two and that it may require a different approach in stimulating the development of emotion regulation skills in these children.
- Studying early development in children with SCT showed that differences in self-regulatory skills compared to typically developing peers can be identified as early as 12 months of age. It also showed that with increasing age, problems in the area of self-regulation may become more pronounced, warranting a developmental approach both in the study of this genetic condition as well as in clinical care. It is possible that children with SCT show age-appropriate neurocognitive skills at a certain age, but may present serious developmental vulnerabilities at a later age: Continuous monitoring of (neurocognitive) development should thus be considered standard care in children with SCT.
- A neurocognitive approach that examines the underlying building blocks of behavior is helpful in understanding the nature of behavioral problems and individual differences in maladaptive behavior of children with SCT. The impact of the X and Y chromosome on development is likely associated with a suboptimal brain development and broad maturation processes in individuals with SCT, influencing the neurocognitive functioning of the brain that contributes to cognitive, social-emotional, and behavioral problems.

In sum, whilst having an additional X and Y chromosome does not reliably predict an individual's cognitive, emotional, and behavioral outcome, children with SCT evidently are at risk for vulnerabilities in self-regulation that appear more pronounced with increasing age. A developmental neurocognitive perspective is key in increasing our knowledge of gene-brain-behavior pathways in children with SCT as well as advancing clinical care in terms of diagnostics and treatment. Self-regulation amongst other neurocognitive functions may serve as a valuable target for early, tailor-made interventions to minimize the risk for psychopathology later in life and improving quality of life of individuals with SCT.