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

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General introduction

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Sex chromosome trisomies (SCT) are one of the most common chromosomal aneuploidies in humans (Hong & Reiss, 2014) with an estimated prevalence around 1 in 650 to 1,000 live births (Berglund et al., 2019; Bojesen et al., 2003; Groth et al., 2013; Morris et al., 2008). Individuals with SCT have an increased risk for psychopathology, which refers to social, emotional, cognitive, and behavioral problems (Giltay & Maiburg, 2010; Groth et al., 2013; Tartaglia et al., 2010). By viewing 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 the behavioral problems 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). However, not all individuals with SCT are equally impacted and variability in outcome is rather rule than exception. To understand this heterogeneity in outcomes and how the extra sex chromosome impacts development, it may be helpful to implement a neurocognitive perspective. Individual differences in neurocognition (e.g., information processing skills anchored in brain functioning) could help explain individual differences in outcomes and henceforth the increased risk for psychopathology (Anderson, 2001). Within this dissertation, the aim is to identify early neurocognitive risk factors in young children with SCT, with a specific focus on those skills crucial to social, emotional, and behavioral adaptation. The regulation of thoughts, emotions, and behavior in the context of others, in other words *self-regulation*, is a tremendous influential factor when it comes to daily life functioning and therefore an interesting candidate to study in relation to psychopathology.

The fact that SCT can be diagnosed as early as pregnancy has important additive value in increasing our understanding of underlying mechanisms related to psychopathology. Studying genetic populations from an early age provides an unique opportunity to examine at-risk development prospectively before psychopathology actually enfolds. These "neurogenetic" studies include a bottom-up approach that may provide insight in those neurocognitive building blocks essential to childhood development to explain how individual differences in early development could lead to psychopathology later in life (Reiss & Dant, 2003). It complements traditional psychopathology research (top-down approach), where specific neurocognitive profiles are identified in individuals diagnosed with a neurodevelopmental disorder (classified according

to the DSM-5), such as ASD and ADHD. Increasing knowledge of developmental pathways in children with SCT would thus not benefit only individuals with SCT and their families, but also other individuals that suffer from neuro-developmental problems. The study of SCT would serve as a 'high risk model' to understand the etiology of psychopathology and to pinpoint targets for early preventive support (Beauchaine, 2009), which would also sharpen our knowledge on gene-brain-behavior pathways in neurodevelopmental disorders.

The TRIXY Early Childhood Study

This dissertation and its included studies are part of a larger study, The TRIXY Early Childhood Study, that investigates neurocognitive mechanisms (e.g., language, social cognition, and self-regulation) in young children with SCT in order to explain the increased risk for psychopathology. One of the key objectives is to link biomarkers and neurocognition to daily life functioning by using sensitive, state-of-the-art measures (e.g., early neurocognitive performance tests, eye tracking, physiology). Furthermore, it evaluates the effectiveness of intervention tools targeted at stimulating neurocognitive development and thereby potentially reducing the risk for later psychopathology. The TRIXY Early Childhood Study includes a large international cohort of children with SCT (n > 100) between the ages of 1 to 7 years old, for which data was collected on their development at different timepoints (including a 1 year follow-up) and compared to data of peers from the general population (n > 100). Children with SCT and their parents were recruited through the Centre of Expertise for Trisomy of the X and Y chromosomes (TRIXY) in the Netherlands and the eXtraordinarY Kids Clinic in Developmental Pediatrics at the Children's Hospital Colorado (CHCO) in the United States of America (USA). How families came to learn of the study was recorded to correct for potential recruitment bias. This is important whilst studying genetic conditions, because studies need to include enough participants to cover the full range of potential outcomes and not only those who learned upon the diagnosis because of developmental difficulties, e.g. introducing potential bias in results (Prasad & James, 2009). The design of the TRIXY study, that included predominantly prenatally diagnosed children, aimed to tackle this and allowed for the unique and prospective investigation of an at-risk development before psychopathology enfolds.

General Background on Chromosomes and SCT

To understand the genetic background of children with SCT, a short description of typical genetics in humans is needed. Typically, humans are born with 22 pairs of chromosomes numbered from 1 to 22 along with 1 pair of sex chromosomes (X or Y chromosomes) adding up to a total of 46 chromosomes.

A female carries two X chromosomes (46,XX) and a man usually carries one X and one Y chromosome (also noted as 46,XY).In males, the X chromosome always originates from the egg cell of the mother. The sex of the baby is determined by the sex chromosome transmitted in the sperm cell of the father. That cell can contain either an X or a Y chromosome. If the sperm contains the X chromosome, the embryo will carry a female karyotype (46,XX) and if the sperm contains the Y chromosome, the embryo will carry a male karyotype (46,XY). In the case of chromosomal aneuploidies (i.e., an atypical amount of chromosomes), a chromosomal pair includes more than two chromosomes. The presence of three chromosomes is called a trisomy. Whereas other chromosomal trisomies are usually associated with severe medical, cognitive, and functional impairments, SCT have typically more mild phenotypical outcomes. Remarkably, SCT are significantly less known in the general population and by clinicians, although it has a higher prevalence rate than other chromosomal trisomies, such as Down's syndrome (a trisomy of the 21st chromosomes). SCT has an estimated prevalence around 1 in 500 to 1,000 live births (Berglund et al., 2019), whereas Down's syndrome has a prevalence of 1 in 800 (Bittles et al., 2007). Despite its high prevalence, many individuals with SCT experience a significant delay in diagnosis or even non-diagnosis throughout life. The estimated percentage of individuals that remain undiagnosed ranges from 75% to 88% (Berglund et al., 2019; Bojesen et al., 2003). Potentially related to this high non-diagnosis rate are the mild, variable, and mostly non-specific physical features, including minimal facial dysmorphisms, tall stature, and abnormal muscle tone (hypotonia)(Tartaglia et al., 2020).

The trisomy of the sex chromosomes is a *de novo mutation* and caused by random errors in cell division (Maiburg et al., 2012). Karyotypes that result from SCT are 47,XXY (Klinefelter's syndrome) and 47,XYY (XYY syndrome) in males, and 47,XXX (Trisomy X syndrome) in females. Trisomy karyotypes include 47 chromosomes (instead of the typical 46 chromosomes) and thus lead to the genetic notation of 47,XXY, 47,XXX and 47,XYY (see Figure 1 for the visual representation). Other more rare variants of additional chromosomes include karyotypes that have more than one additional chromosomes (for example 48,XXYY or 48,XXXY). In this dissertation, the focus is on sex chromosomes trisomies (SCT).

A Neurocognitive Perspective on SCT

How a genetic condition such as sex chromosomal trisomy impacts daily life functioning is determined by many different factors and would include the somatic, cognitive, and psychosocial experiences that interact together to influence development (Anderson, Northam, & Wrennall, 2019). The research

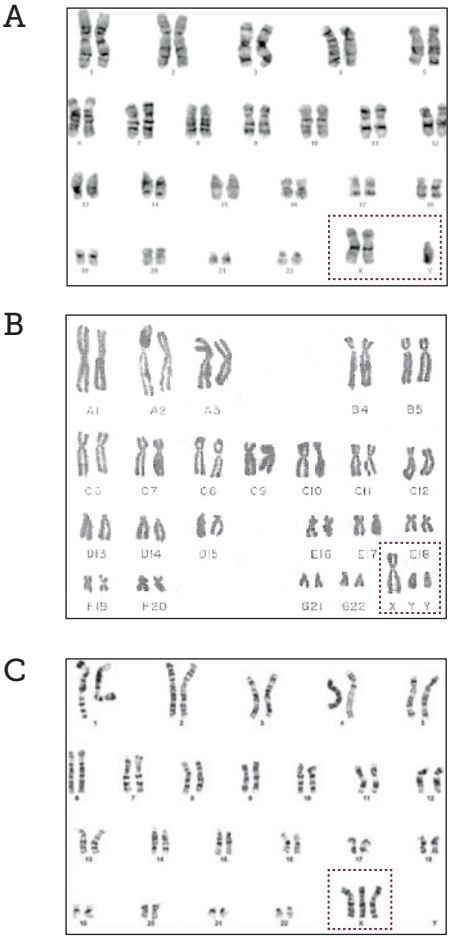

Figure 1 Example Karyotypes of Sex Chromosome Trisomies

Note. A: Karyotype of 47,XXY (Nagvenkar et al., 2005); B: Karyotype showing 47,XYY (Sandberg et al., 1963); C: Karyotype of 47,XXX (Kanaka-Gantenbein et al., 2004).

on SCT has traditionally focused on examining the somatic and physical features, with only a small proportion of the studies (25%) looking at social, emotional, and behavioral problems (Pieters et al., 2011). Even fewer studies examined neurocognitive outcomes in SCT, which is somewhat surprising, given that a significant fraction of genes on the sex chromosomes are associated with brain development and functioning (Zechner et al., 2001), suggesting a link between sex chromosomal aneuploidies and neurocognitive outcomes.

A neurocognitive approach could be relevant in explaining the link between the genetic make-up of children with SCT and the increased behavioral problems observed in daily life. A useful bottom-up approach model to describe how genetics might interact with environmental factors to shape behavioral outcomes is the brain-behavior model (Figure 2). An individual's genetic make-up is reflected in both the architecture of the brain as well as the functioning of the brain. As a result of both architecture and functioning of the brain, neurocognitive functions are developed and reflect the ability to process information. In turn, the complex interplay of multiple neurocognitive functions shape behavior, suggesting that neurocognitive factors can be viewed as building blocks for behavioral outcomes. Finally, environmental factors can influence all levels of the model, acting as either facilitative factors or barriers (Swaab et al., 2011).

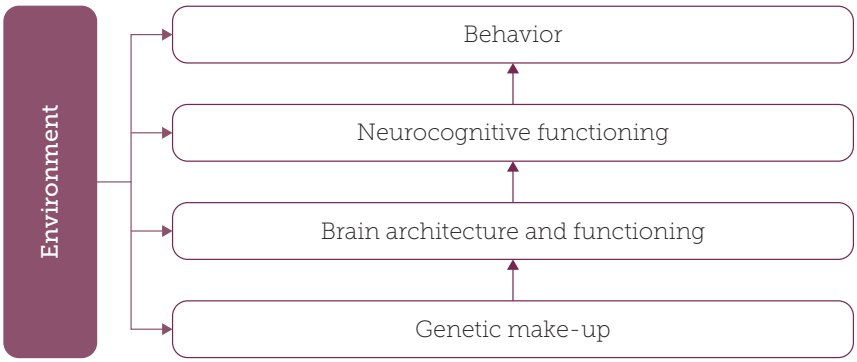

Figure 2 The Brain-Behavior Pathway Model (Swaab et al., 2011)

Thus, as a result of (the complex interplay between) neurocognitive deficits, observable behavioral problems may arise. In addition, these problems can also be clustered based on a set of symptoms as a psychiatric classification according to diagnostic manuals, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association [APA], 2013). For example, the inability to maintain your attention (neurocognitive deficit) would be observed in daily life as the inability to finish homework and fail the accompanying test (behavioral problem). For some children, these neurocognitive deficits and behavioral problems will significantly impact their day-to-day life to such an extent that a psychiatric classification also applies, for example severe symptoms of inattentiveness, hyperactivity, and impulsivity that are also part

of the criteria for Attention-Deficit Hyperactivity Disorder (ADHD) according to the DSM-5 (APA, 2013).

Reflecting on the existing literature, multiple levels of the brain-behavior pathway model seem to be impacted in SCT. Studies already confirmed that brain differences and dysfunction are likely part of the SCT profile. For example, neuroimaging studies showed that brain architecture and functioning appears different in individuals with SCT compared to peers from the general population (Steinman et al., 2009, Warling et al., 2020). Especially relevant are those studies that found differences in areas of the brain known to be involved in processing social and emotion information, including the amygdala, the insula, the fusiform gyrus, and the superior temporal sulcus (van Rijn, Swaab, et al., 2012). In addition, neurocognitive differences are identified in the area of general intellectual functioning (albeit at the lower end of the typical range), social cognition, executive functioning, and language in school-aged children, adolescents, and adults with SCT (for a review on this topic, see van Rijn, 2019). Far less is known about the early development of neurocognitive skills in children with SCT (Urbanus, van Rijn, et al., 2020), but this type of research is a relatively new but booming field. Part of the trend is the generic interest in examining neurocognitive profiles in relation to psychopathology and psychiatric conditions as well as newly developed techniques to measure neurocognition early in life (Kavanaugh et al., 2020). To conclude, a neurocognitive perspective on SCT (linking information processing deficits in the brain to behavioral outcomes) would be considered highly relevant when trying to understand developmental pathways into psychopathology.

Self-Regulation

One of the key neurocognitive functions to study in early childhood is that of self-regulation. **Self-regulation** refers to regulation of thoughts, emotions, attention, behavior, and impulses in order to meet goals and adequately respond to the environment (Blair & Diamond, 2008). Self-regulatory skills are of great importance with regards to daily functioning and quality of life, given that optimal self-regulation promotes positive adjustment and adaptation, as reflected in positive relationships, productivity, achievement, and a positive sense of self (Blair & Diamond, 2008). From a developmental perspective, studies have shown that self-regulation is associated with important long-term outcomes such as mental health (Moffitt et al., 2011), social competence (Bradley & Corwyn, 2013, 2007), and academic achievement (Eisenberg et al., 2010; Vazsonyi & Huang, 2010), showing that self-regulation is a vital skill to be acquired throughout childhood and adolescence. In fact, self-regulation is considered a transdiagnostic feature of psychopathology (Romer et al., 2021). In early

childhood, impairments in the regulation of thoughts, emotions, and behavior are associated to adverse developmental outcomes, including internalizing and externalizing behavior problems (Kostyrka-Allchorne et al., 2020; Lemery-Chalfant et al., 2008).

The central aim of this dissertation was to explore neurocognitive aspects of self-regulation by combining new, sensitive, and direct measures in a large cohort of young children with SCT during a critical period of development, to determine how children with SCT perceive, process, experience, express, and cope with challenging situations. This dissertation focuses on three important interrelated elements of self-regulation: behavioral regulation, cognitive regulation (in terms of executive functioning), and emotion regulation.

Regulation of Behavior

Being able to regulate your feelings and actions is an important part of social and adaptive functioning: It enables us to make good choices in accordance with our goals, but also to consider the feelings and actions of others around us and adjust our behavior accordingly. Self-regulation is precisely the reason why we are able to finish an important assignment for school or job, even when other activities are tempting. It is also the reason why we stop and think when a friend asks our opinion on their clothes. However, having difficulty regulating your actions can result in behavior that is maladaptive or socially inappropriate, for example unable to resist binge-watching your favorite Netflix show and failing to finish your assignment, or commenting on how ugly the clothes are without considering your friend's feelings. When these instances of poor self-regulation occur too frequently, it can significantly impact someone's ability to function in day-to-day social, academic, and occupational situations during lifetime. Thus, impaired self-regulation can result in behavior problems representing symptoms of many psychiatric/mental disorders (American Psychiatric Association, 2013). With this in mind, studying these types of symptoms have the potential to inform us on the development of self-regulation and its difficulties in early childhood.

The most salient markers of impaired self-regulation to study in early childhood are those behavioral symptoms associated with ADHD: a neurodevelopment disorder characterized by severe symptoms of inattentiveness, hyperactivity, and impulsivity that interfere with daily functioning and development (DSM-5: APA, 2013). In addition, ADHD-symptoms are an ideal candidate to study in children with SCT as a marker for self-regulation, given elevated clinical levels of ADHD-symptoms are present across all three karyotypes and across the broad age-range from school-age to adulthood (van Rijn, 2019). Information on early childhood (before the age of 6) is however not

yet available. To be specific, within the TRIXY Early Childhood Study, we are not interested in classifying these young children with SCT as having ADHD or not. In contrast, ADHD symptoms are viewed as a continuous measure to examine the type and variety in self-regulatory skills in early childhood. In other words: The presence and variety of ADHD symptoms would reflect individual differences (or deficits) in self-regulatory skills.

Regulation of Cognition (Executive Function)

Another important component of self-regulation is the cognitive ability to act purposefully and goal-directed, which is supported by our executive functions. The term *executive functions* (EF) refers to a set of interrelated neurocognitive skills essential to learn, cope, and manage daily life (Diamond, 2013). Several components can be identified, including attention, inhibition, monitoring, flexibility, working memory, planning, and fluency (Anderson, 2001). Proper executive functions are crucial when it comes to positive childhood development: executive functions promote mental and physical health; predict success in school and in life; and support cognitive, social, and psychological development (Diamond, 2013). On the other hand, impairments across executive functions are involved in many neurodevelopmental disorders, including ADHD (Diamond, 2005), ASD (Demetriou et al., 2018), and intellectual disabilities (Lee et al., 2015).

Until now, studies that have examined executive functions in individuals with an extra X or Y chromosome showed reduced executive function performance compared to population-based controls (for review see Urbanus et al., 2020 and Van Rijn, 2019). Children with SCT show more impairments across executive functions, including attention, inhibition, mental flexibility, working memory, and planning/problem solving (Janusz et al., 2020; Lee et al., 2015; Ross et al., 2008, 2009; Samango-Sprouse et al., 2018; van Rijn & Swaab, 2015). Furthermore, these impairments have been linked to increased externalizing behavior problems (van Rijn & Swaab, 2015), increased social difficulties (Skakkebæk et al., 2017) as well as increased symptoms of ASD (van Rijn et al., 2012), psychotic symptoms such as disorganized thought (Van Rijn et al., 2009), and ADHD symptoms (Lee et al., 2011). These studies show that early differences in neurocognition can have predictive value to later psychopathology in SCT, highlighting the importance of early investigation of skills yet in development. To date, no other studies have examined early emerging executive functions in young children with SCT, especially none that have used age-sensitive neurocognitive assessments in addition to behavioral report data. Our study will be the first to do so.

Regulation of Emotions

The final component important to self-regulation is the ability to regulate our emotions. **Emotion regulation** refers to all processes that influence the occurrence, intensity, duration, and expression of emotions (Gross, 2013). 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 challenging situations (action-oriented) (Thompson, 1994). It is thus not surprising that the increasing ability to regulate emotions in childhood is associated with adaptive outcomes in multiple domains, including school readiness (Blair & Razza, 2007), better social skills (Eisenberg et al., 2010), and fewer externalizing problems (Olson et al., 2005).

Emotion regulation manifests in multiple biological, cognitive, and behavioral systems and includes amongst others physiological changes and behavioral responses (Tracy, 2014). Emotions serve a signaling function in which they highlight events as relevant or irrelevant to an individual and help to identify which situations are attention-compelling (and which are not). This signaling function can be assessed by measuring the physiological arousal response, also known as emotional reactivity or affective arousal (Gross, 2013). Events that are signaled as relevant (e.g., a barking dog) will activate the autonomic nervous system (Sapolsky, 2004), including the sympathetic nervous system (SNS) that stimulates increased respiratory rate and heart rate and prepares the body both physiologically and behaviorally to act (e.g., run away or freeze; Porges & Furman, 2011). Having sufficient emotional reactivity (SNS activity) is related to greater self-soothing, more attentional control, and greater capacity for social engagement (Blair & Peters, 2003; Calkins et al., 2002; Calkins & Keane, 2004). On the other hand, inadequate emotional reactivity has been linked to both childhood externalizing and internalizing behavior problems (Beauchaine, 2001; Boyce et al., 2001), linking physiological arousal to psychopathology.

By signaling the demands of the environment, emotional reactivity enables the coordination of behavioral responses that facilitates adaptive behavior (Gross, 2013). Behavioral responses can include the expression of emotions as well as the enactment of regulation strategies. The first, expression of emotions, serves an important social and communicative function (Greenberg, 2004). The display of (facial) emotions can elicit behavior in others which subsequently influences the ongoing interaction. For example, showing fear can elicit others to approach for help, whereas showing anger can signal others to avoid and withdraw (Marsh et al., 2005). In young children, the frequency and intensity of emotional expressivity has been linked to the quality of social relationships (Diaz et al., 2017; Eisenberg et al., 1993) and the child's feelings of social competence (Waiden & Field, 1990). Individual differences in the expression of

negative emotions also relate to externalizing problem behavior in typical developing children (Eisenberg et al., 2001), highlighting that the amount and intensity of emotion expressivity will likely have differential effects on person-situation interactions and thus influence social and emotional functioning.

In addition to emotion expressivity, emotion regulation strategies also facilitates adaptive social and emotional functioning. The availability and the variety of emotion regulation strategies is essential to adequately influence the occurrence of emotions and to cope with the intensity, duration, and expression of emotions (Gross, 2013): it is a sign of psychological flexibility when someone is able to choose from different behavioral options in order to cope with a challenging situation. However, it is not only the expression of emotion nor behavioral opportunities that aid self-regulation. For adequate psychosocial functioning, a concordant system of matching emotional internal and external processes is key. When the overt display of emotions matches the internal arousal response (e.g., emotional concordance), it informs the environment on the internal state of the child which enables others to adequately responds to a child's needs (Robinson et al., 1997). Discordance however can significantly hinder the engagement of the environment and confuse others about actual internal states (Mauss et al., 2011) provided that the decision of a caregiver to engage or retreat from interaction with the child depends on the child's display of emotion (Denham, 1998). Thus, emotional expressivity and the concordance with the physiological arousal response is of key importance in terms of adaptive social and communicative functioning and relevant when studying neurocognitive aspects of self-regulation.

Studies so far showed that adolescents and adults with SCT can have difficulties in multiple areas of emotion regulation, including physiological reactivity and behavioral responses. For example, emotional reactivity (expressed in skin conductance levels) was overall increased in adult men with 47,XXY in response to emotion evoking social situations on video (van Rijn, Barendse, et al., 2014). This is in line with self-reported experience of emotion, where men with 47,XXY typically describe themselves as being more easily aroused by emotion-evoking situations than peers (van Rijn et al., 2006). Adult men with 47,XXY also report more use of atypical behavioral strategies, including increased expression of emotions, avoiding, distraction seeking, and passive regulation (van Rijn & Swaab, 2020). Furthermore, the effect of emotion dysregulation on daily life is also present: emotional outbursts (Visootsak & Graham Jr, 2009), anxiety symptoms (van Rijn, Stockmann, et al., 2014), and depressive symptoms (Tartaglia et al., 2010) are commonly present in SCT in the full age range from school-aged children to adulthood. Studies on emotions in individuals with SCT mainly included behavior (self-reported) questionnaire data

and only two other studies so far have examined direct psychophysiological indices (Urbanus et al., n.d.; van Rijn, Barendse, et al., 2014). Furthermore, concordance between emotional constructs has not yet been studied in individuals with SCT, let alone in early childhood.

The Importance of Examining Self-Regulation in Early Childhood

Previous studies that examined self-regulation in the SCT population included school-aged children, adolescents, and adults. There have been very limited systematic studies on neurocognition (including self-regulation) in early childhood, specifically before 6 years of age. However, the preschool period (the period between 3 and 6 years of age) is of particular interest when it comes to self-regulation, given that several aspects that contribute to good self-regulation develop at an accelerated pace in the preschool years (Blair & Ursache, 2011; Zelazo et al., 2008). This acceleration is partly due to increased connectivity between neural networks in the brain within this period (Posner & Rothbart, 2000), as well as changes at the contextual level (social experience (Carlson, 2005)) and other cognitive abilities (increasing memory capacity, increasing language abilities and accelerated information processing (Hale, 1990)). Additional processes that support this development are increased physical and behavioral skills. As such, self-regulation in infancy and early childhood can be seen as a crucial developmental milestone to be achieved (Blair & Ursache, 2011).

Studying this important window in child development in individuals with SCT may help to understand the impact of an extra X or Y chromosome on the developing brain. Studies that examine typical brain development in childhood show clear indications that the childhood brain is extremely plastic (Andersen, 2003), suggesting that children might be more susceptible for intervention during this period of time (so-called window of opportunity). Examining how neurocognitive skills emerge during this time period could reveal disturbances in brain maturation in children with SCT that are indicative of an at-risk development. The earliest ground work of neuropsychology from A.R. Luria (1963) proceeds this notion, considering that the various stages of mental development encountered as children mature can be seen as a unique opportunity to study how neurocognitive processes develop (Horton, 1987). Thus, information on how children (at risk) develop could guide future research and clinicians in developing and implementing early preventive, neuro-cognition targeted interventions in this population, in order to minimize the impact of the extra sex chromosome on development.

Clinical Implications

The study of early development of children with SCT becomes more relevant every day, especially given that the number of prenatally identified sex chromosomal aneuploidies is increasing exponentially (Howard-Bath et al., 2018). Amongst other things, this increase stems from technological advances in prenatal testing that led to the introduction of noninvasive testing (NIPT): a screening that isolates cell-free fetal DNA in maternal blood to detect chromosomal aneuploidies during pregnancy (Carlson & Vora, 2017). In more than 60 countries, NIPT is available to all mothers, regardless of age or risk level, that request prenatal testing to identify fetal abnormalities (Allyse et al., 2015). Upon disclosure of a genetic condition during prenatal testing, the majority of parents experience a certain amount of stress, most often related to the uncertainty of the child's prognosis or opportunities for early preventive intervention (Dinc & Terzioglu, 2006; Jaramillo et al., 2018). To accurately address questions parents may have and to minimize stress burden of parenting a child with a genetic condition, there is a clinical need for updated knowledge on the development of children with SCT (see Box 1 for two clinical vignettes). This knowledge is not only essential to improve genetic counseling, but also to guide clinical care in terms of early assessment and treatment to minimize the impact of the additional X and Y chromosome on development.

Box 1 Clinical Vignettes of Sex Chromosome Trisomies

A) Questions during prenatal testing. It is Tuesday morning and my first client is an expecting female and her partner, 20 weeks into the pregnancy. Last week, they received the results of their non-invasive prenatal screening: They are expecting a girl with Trisomy X. The screening results will need to be verified with other testing, but the soon to be parents were instructed to consult with the TRIXY center of expertise to be the upmost prepared. Both partners are anxious: what does it all mean? Is their daughter going to be "extra feminine"? Will she have learning difficulties? Can she go to a regular elementary school or will she need additional support? Will she have friends? Will she have children of her own? What can they expect as parents, will it be different raising a child with this syndrome? They have already Googled the syndrome and websites state that many girls with Trisomy X have ADHD, will their daughter have that as well? Is it like Down's syndrome?

B) Clinical assessment and treatment. Parents registered their 5-year-old son Arthur with TRIXY Center of Expertise because of concerns about his cognitive and social-emotional development. Arthur was diagnosed with XYY-syndrome at the age of 4. From a young age, parents felt that Arthur was developing differently and have sought help and guidance from different professionals, but not satisfactorily. Parents would like to have a clear overview of Arthur's development, given that some aspects of his development seem delayed while other aspects appear age appropriate. They wonder what the relation is with XYY. In addition, suggestions regarding treatment and specific support for Arthur are requested. Furthermore, parents are concerned about Arthur's education, they would like suggestions on whether he can stay at the current school (special education for children with language and communication disorders).

Aims and Outline of this Dissertation

The central aim of the current dissertation is to study neurocognitive aspects of self-regulation in young children with SCT, in terms of behavioral regulation, cognitive regulation, and emotion regulation. The studies presented in this dissertation are part of a larger longitudinal study, the TRIXY Early Childhood Study, and its participants are children with SCT, aged between 1 and 7 years old, recruited from the Netherlands (and surrounding countries) and Denver, Colorado in the United States of America, who are compared to typically developing children from the general population.

Figure 3 provides a visual overview of the neurocognitive domains that were studied in relation to self-regulation in children with SCT in the current dissertation. The first study (**Chapter 2, ♥**) addresses the question whether difficulties with self-regulation are already present in young children with SCT, using parent-reported behavioral data. This study investigates the presence, variety and severity of ADHD symptoms as markers of difficulties in the regulation of thoughts, emotions, attention, behavior, and impulses in daily life behavior (behavioral regulation). **Chapter 3** (♠) focuses on (precursors of) executive functions: the neurocognitive skills essential to act purposefully and show goal-directed behavior (cognitive regulation). By using a combination of cognitive performance data and parental behavioral report data, this study aims to provide insight in emerging executive functions in young children

with SCT and its presentation across different ages. In **Chapter 4** (♦), we examine self-regulation in terms of emotional reactivity and expressivity of children with SCT in response to a laboratory controlled situation designed to induce stress (emotion regulation). Next to physiological arousal (in terms of heart rate), facial and bodily expressions of emotions were coded to study the overlap between the internal experience and the outside display of emotions. In **Chapter 5** (♣), we assess the use and variety of emotion regulation strategies during a frustration-inducing paradigm, whilst controlling for individual reactivity (physiological arousal). In addition, the developmental impact of SCT on emotion regulation strategies is examined here as well. In **Chapter 6**, the results of aforementioned studies are discussed and related to other key neurocognitive domains, including language, communication, and social cognition, that were also assessed during the TRIXY Early Childhood Study. These combined data provide essential insights in the link between neuro-cognition and psychopathology and pinpoint neurocognitive targets for early, preventive interventions. Finally, **Chapter 7** summarizes the findings, conclusions, and implications of these studies as well as its limitations, and directions for future research are provided.

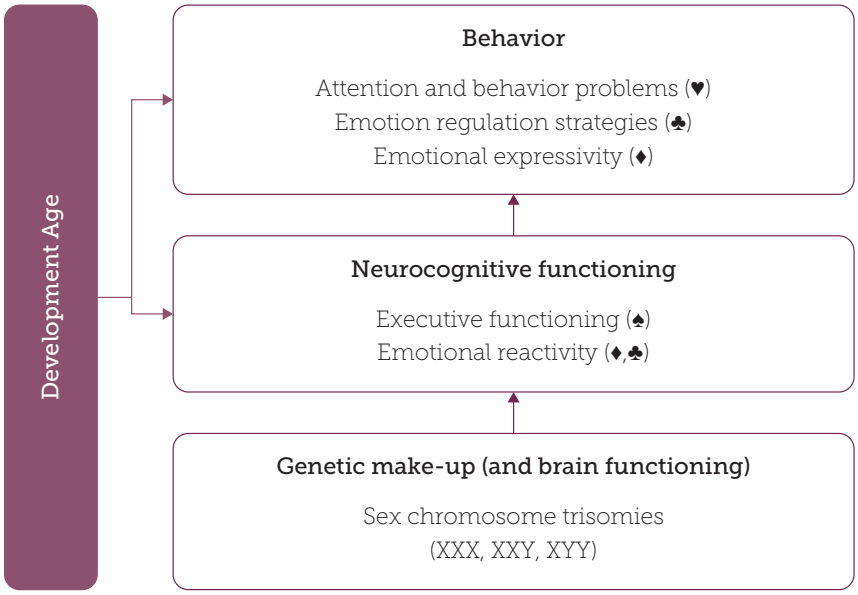

Figure 3 Visuel Overview of the Neurocognitive Domains in relation to Early Self-Regulation Skills that were Studies in the Current Dissertation