Social communication in young children with sex chromosome trisomy: neurocognitive building blocks of behavioral outcomes

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Chapter 1

General Introduction

To gain a better understanding of neurodevelopmental problems, researchers traditionally have focused on individuals with a behavioral diagnosis, such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD), to search for neurocognitive mechanisms underpinning behavioral outcomes. This approach has provided essential knowledge about the etiology of neurodevelopmental problems, however there are two major drawbacks. First, although individuals may have the same behavioral diagnosis, the underlying pathways leading to this diagnosis can be diverse. This makes it difficult to draw conclusions concerning causality. Second, neurodevelopmental impact can only be diagnosed in behavioral outcomes once a clinical behavioral classification is made, which typically is preceded by a cascade of neurodevelopmental problems leading towards the diagnosis and incorporates environmental influences as well. For example, the mean age at diagnosis for ASD is 43 months (van 't Hof et al., 2021), and ADHD is typically diagnosed between 7-9 years of age (Kessler et al., 2007). Due to this 'delay', knowledge about the early development of individuals with behavioral disorders is often based on retrospective information. As a consequence, critical windows of opportunity to intervene might have been missed.

Over the last decades, researchers have started to use a complementary approach to study neurobehavioral phenotypes to learn about neurodevelopmental mechanisms; namely by studying populations with neurobehavioral phenotypes associated with a clear genetic cause. This *neurogenetic approach* can give valuable insight in which factors can explain or predict adverse outcomes (Reiss & Dant, 2003). Knowledge on neurobehavioral phenotypes associated with genetic disorders is necessary to ultimately understand and identify individual patterns of development (Baumgardner et al., 1994; Sroufe & Rutter, 1984). As many genetic disorders can be detected prenatally, this presents the opportunity to study developmental pathways prospectively. Results and implications from studies including individuals with genetic disorders will not only benefit individuals with the genetic disorder but can also serve as a model of behavioral and cognitive conditions that affect individuals in the absence of a genetic disorder (Reiss et al., 2000).

A genetic disorder that could serve as a model for identification of neurodevelopmental mechanisms driving the increased risk for neurobehavioral problems and psychopathology should – preferably – meet certain criteria: 1) The genetic disorder should not be rare, 2) Global intellectual functioning should not be (severely) impaired as this would hinder drawing conclusions, 3) Prenatal or early diagnosis is possible, providing the opportunity to prospectively investigate the early developmental impact, and 4) The genetic disorder has a clear link with neurodevelopmental problems and/or psychopathology.

Sex chromosome trisomy (SCT) is a class of genetic disorders that meets these criteria. Typically, humans are born with 46 chromosomes: 22 pairs of autosomes and two sex chromosomes (XX in females and XY in males), resulting in a 46,XX or 46,XY karyotype. Due to a *de novo* non-disjunction during early cell division, the genetic make-up can contain an extra X or Y chromosome. This leads to a 47,XXY (Klinefelter syndrome) or 47,XYY (XYY syndrome) chromosomal pattern in males, and a 47,XXX (Trisomy X syndrome) in females. Regarding the four criteria mentioned above, SCT meets these criteria as: 1) SCT is one of the most common genetic duplications in humans with an estimated prevalence ranging from

1:650-1:1000 live births, 2) Although slightly lowered, global intellectual functioning is typically within the normal ranges, 3) SCT can be diagnosed prenatally, and 4) The X and Y chromosomes play an important role in neurodevelopment and the prevalence of neurodevelopmental disorders is increased in the SCT population.

Taken together, SCT could serve as a valuable model to study neurocognitive mechanisms driving neurodevelopmental problems and increased risk for psychopathology. Within the next paragraphs of this introduction, we will provide a short overview of the knowledge on SCT. Next, the importance of the X and Y chromosomes for neurodevelopment will be discussed. Third, from a bottom-up perspective, we will look into how SCT can inform us about mechanisms driving neurodevelopmental risk, with a specific focus on the communication domain as a building block for neurobehavioral outcomes. Lastly, the importance of studying young children will be illustrated before the aims and outlines of the dissertation will be discussed.

Trisomy of the X or Y Chromosomes

Within the literature, the vast majority of studies on SCT have focused on physical and medical consequences. For example, individuals with SCT are known to have a tall stature after puberty, hypotonia or low muscle tone is common, and infertility is found in males with an extra X (for a review see Tartaglia et al., 2020). Studies focusing on neurocognitive or behavioral outcomes, however, are rare and especially knowledge of early development is lacking. Before 1970, only a handful of studies investigated SCT, as genetic testing was reserved for individuals with severe physical dysmorphisms and/or psychological problems. Therefore, only severe cases were included in clinical descriptions of individuals with SCT. From the 1970's to 1990's seven research sites across the United States, Canada, and Europe used newborn screening protocols to identify children with X or Y chromosomal variations. The core knowledge of how SCT impacts neurocognitive and behavioral outcomes is based on these birth cohort studies (for a summary see Robinson et al., 1990). Identified children were followed until young adulthood, providing unbiased and prospective information on how SCT impacts development. Although these studies provide valuable information, most of these studies had a descriptive nature. In addition, the strength of the conclusions of these studies was limited by the size of the included samples, subsequently also limiting the opportunity to explore potential moderating variables, such as the impact of an extra X versus an extra Y.

Although SCT is a relatively common genetic variation which can be diagnosed before birth, historically only about 10% of individuals received the diagnosis before adolescence (Abramsky & Chapple, 1997; Bojesen et al., 2003). There are several possible explanations for this underdiagnosis. For example, the physical consequences of SCT can be relatively subtle and the impact of SCT on neurocognitive and behavioral outcomes is variable. These subtle physical characteristics and variability in symptoms do not often prompt genetic testing. Consequently, individuals may be treated for symptoms without knowledge of the underlying genetic condition. Due to advances in the technology to detect genetic variations in unborn children over the past years (e.g., non-invasive methods such as the screening of maternal blood), an exponential increase of prenatally diagnosed individuals with SCT is expected. To better serve the SCT population, more in-depth knowledge of the neurocognitive and behavioral

consequences of an extra sex chromosome is warranted and the advances in prenatal screening methods provide the opportunity to study children from a young age.

The Importance of the X and Y Chromosomes for Neurodevelopment

The X chromosome plays an important role in typical brain development and in the development of human intelligence (Johnson et al., 2009). The frequency of genes that affect general cognitive ability is 3.5 times higher on the X chromosome compared to any of the autosome genes, which makes the X chromosome disproportionally important for cognitive ability (Zechner et al., 2001). Genes on the Y chromosome have also been identified to play a role in brain development, independent from the X chromosome (Berletch et al., 2015). The gene density on the X chromosome is much higher than on the Y chromosome; the X chromosome contains approximately 800-900 coding genes, whereas the Y chromosome contains approximately 60-70 coding genes (ensembl.org; see Figure 1). To maintain relative equivalence in gene dosage between males with a 46,XY chromosomal pattern and females with a 46,XX chromosomal pattern, only one X chromosome is typically activated in females. Approximately 15% of the genes located on the X chromosome however, 'escape' inactivation (Carrel & Willard, 2005), these genes are then expressed in excess. In addition, there are genes on the Y chromosome that have identical homologous regions on the X chromosome, for example the X-chromosomal pseudoautosomal regions that escape inactivation in females are also present on the Y chromosome (see Figure 1). These genes that are located on both the X and Y chromosome, for example neuroligin, may play a significant role in the etiology of autism and other communication disorders (Bishop & Scerif, 2011). The importance of the X and Y chromosomes for neurodevelopment and the link between the X and Y chromosomes in combination with the risk for psychopathology make the X and Y chromosomes interesting candidates to study how genetic make-up in interaction with the environment can lead to behavioral outcomes.

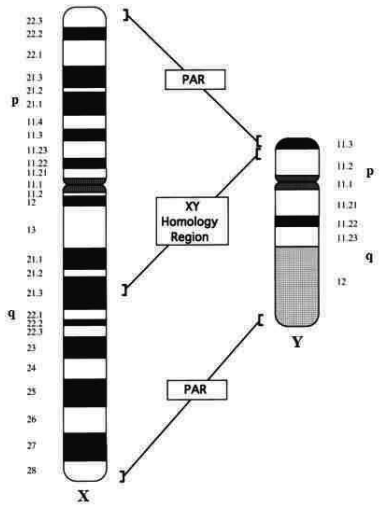

Figure 1. The X and Y chromosomes. Figure adapted from Mumm et al. (1997)

How SCT Can Inform Us About Mechanisms Driving Neurodevelopmental Risk

A valuable model to describe how genetic make-up in interaction with environmental factors can lead to behavioral outcomes, is the brain behavioral model (Figure 2). This model uses a bottom-up approach to explain how an individual's genetic make-up is reflected in both the architecture of the brain and the functioning of the brain. Neurocognitive functions are the expression of the architecture and functioning of the brain and reflect the ability to process information. A complex interplay of multiple neurocognitive functions results in behavior, thus, neurocognitive functions are the building blocks for behavioral outcomes. Environmental factors can influence all levels of the model (Swaab et al., 2011).

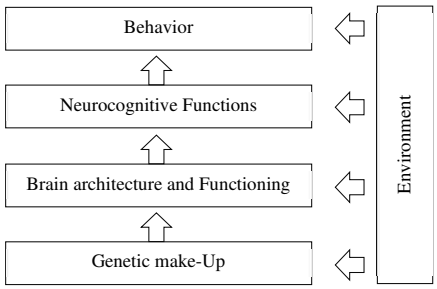

Figure 2. The brain behavioral model from a bottom-up approach

Starting at the bottom when applying the brain behavioral model to SCT, the genetic make-up, or the presence of an extra X or Y chromosome, causes an excess of expression of genes that are important for neural development and related neurocognitive functions (Lenroot et al., 2014; Raznahan et al., 2016). Consequently, the brain behavioral model indicates that the presence of the extra X or Y chromosome impacts the development of the brain.

Neuroimaging studies have researched the effect of SCT on both the structure or architecture of the brain and on brain functioning. Regarding structural effects, studies show that the presence of an extra X or Y chromosome has both convergent and dissociable effects on the anatomy of the brain. Overall, it appears that an extra X chromosome in males and females leads to a decreased total brain volume, whereas the presence of an extra Y chromosome in males leads to an increased total brain volume (Bryant et al., 2012; Raznahan et al., 2016). In addition to an impacted overall brain volume, multiple studies have reported thinning in the (lateral) temporal and frontal brain regions, including subcortical structures such as the amygdala, insula, hippocampus, and cingulate gyrus (Giedd et al., 2007; Lenroot et al., 2014; Lentini et al., 2013; Nadig et al., 2018; Patwardhan et al., 2002; Warling et al., 2020). Researchers have reported mixed results regarding the occipital and parietal regions of the brain; some researchers indicate that these regions are affected as well (Warling et al., 2020), whereas others find that these regions are preserved (Giedd et al., 2007; Lenroot et al., 2014). The effects of SCT on brain functioning have been studied to a lesser extent, and studies mostly included only males with XXY. In addition, studies used different designs, different functional imaging techniques, and included participants from various ages, limiting the ability to compare outcomes. A few studies have investigated language lateralization, and mixed results ranging

from no differences to altered lateralization have been reported (van Rijn et al., 2008; Wallentin et al., 2016; Wilson & Bishop, 2018). Two studies have investigated amygdala activation during exposure to facial expressions and both report contrasting results, ranging from reduced amygdala activation to a tendency for increased amygdala activation (Brandenburg-Goddard et al., 2014; van Rijn et al., 2012). Lastly, one study reported no differences in frontal brain activity when presented with a Stroop task (Wallentin et al., 2016). Although studies have not yet provided evidence to support a direct link between the affected brain regions and neurocognitive functioning in individuals with SCT (Skakkebaek et al., 2020), it is likely that the neurocognitive difficulties experienced by this population are anchored in the brain.

Due to the impact of the X and Y chromosomes on multiple brain regions, several information processing functions can be affected, leading to a range of neurocognitive difficulties encompassing various domains of functioning. It is important to identify neurocognitive strengths and weaknesses in this genetic population, and to link this profile of strengths and weaknesses to behavioral outcomes to learn about underlying neurocognitive mechanisms that drive these outcomes.

At the top level of the brain behavioral model, the behavioral level, an increased risk for neurodevelopmental disorders has been reported. For example, estimates of the prevalence of ASD range from 18-30% in children with SCT (Van Rijn, 2019) versus 0.6% in the general population (Elsabbagh et al., 2012). For ADHD, 25-43% of the children with SCT meets the diagnostic criteria (Van Rijn, 2019), versus 7.2% in the general population (Thomas et al., 2015). Higher rates for other forms of psychopathology have been reported as well. For example, the risk for schizophrenia and bipolar disorder has been estimated to be three to four times higher for individuals with SCT (Bardsley et al., 2013; Cederlöf et al., 2014; Wigby et al., 2016). Lastly, studies have hinted at an increased risk for depression and anxiety disorders, in particular in individuals with an extra X chromosome (for an overview see Green et al., 2019).

Taken together, the presence of an extra X or Y chromosome impacts the brain, which subsequently impacts the neurocognitive functions that act as building blocks for behavioral outcomes. By gaining knowledge of these neurocognitive underpinnings of behavior, diagnostic assessment and treatment may improve, not only for the SCT population but ultimately for the general population as well as this knowledge could help focus on relevant domains of individual functioning in assessment. Furthermore, identifying which neurocognitive building blocks are important for specific behavioral outcomes is essential as focusing on specific targets for intervention may mitigate developmental impact by enabling more tailored mental health care.

Building Blocks for Neurobehavioral Outcomes in the Domain of Communication

Neurobehavioral outcomes in the SCT population are diverse. Knowledge of which neurocognitive building blocks are associated with specific behavioral outcomes is essential. Although neurocognitive vulnerabilities have been identified on several domains, the focus of this dissertation will be on the communication domain. Within the next paragraphs we will

discuss the concept of communication, the importance of communicative abilities in relation to the risk for psychopathology, and the importance of studying communication in the SCT population.

Communication is the process of information exchange between individuals, reflecting a person's ideas, thoughts, feelings, needs, or desires. There are different kinds of modalities someone can use to communicate, including verbal communication, written communication, and the use of gestures (Levey, 2019). Communication is an active process involving the exchange of information between a sender and a receiver; the sender transmits or encodes information that the receiver decodes to comprehend or understand (Owens Jr., 2011). Within the communication domain, several components can be identified. These include speech, language, the use of paralinguistic cues such as intonation and volume, and the use of nonlinguistic cues such as facial expression and posture (Levey, 2019). The degree to which someone is successful in communicating, measured by the appropriateness and effectiveness of sending and receiving messages, is called communicative competence (Hymes, 1972).

The development of communication starts before children are born. When babies are around 24 weeks gestational age, they can hear sounds and they familiarize with voices they hear often. After birth, communication develops further. Although the human brain is prewired for communication, early learning is of great importance and the social basis for communicative development starts within the mother-child dyad. Babies are typically fascinated by faces and voices, showing a marked preference for faces over inanimate objects. When children are only one month old, they will respond to their mothers' vocalizations by making eye contact and following direction of gaze. Within the first months of life, babies continue to learn, for example by paying attention to what they hear and observe in their surroundings. During this time, babies communicate by crying, using different types and intensities of cries to express different needs. Around 4-6 months, babies start to communicate with more vocalizations and babbling. Accompanied by improving motor skills such as the ability to sit and later crawl, children gain the ability to further explore the world. Desired objects or people can be too far away and, in addition to babbling, children communicate their intentions by the use of gestures, such as showing or pointing. By the age of one, most children start to understand the meaning of words and create a verbal understanding. Around 18 months most children start to use spoken language themselves. The number of words a child understands (i.e., receptive vocabulary) and the number of words a child uses (i.e., expressive vocabulary) expands tremendously in a short time period. On average, children have an expressive vocabulary of 20 words around 18 months, which increases to 200-300 words at 24 months, and 2000 words at the age of 5 years (Owens Jr., 2011). In addition, children start to create sentences, combining two words between the ages of 1 and 2 years, and combining three to four words around the age of 3 years. Over the years, sentences will contain more words and become more grammatically complex (i.e., development of syntax), around 7-8 years, most children are able to use complex sentence structures (Simms, 2007). Conversational skills, such as turn taking or maintaining a topic, are refined during the school years. Although at a slower pace, language and communication skills will continue to develop during late childhood, adolescence, and adulthood.

In addition to the development of verbal communication skills, other communicative functions, such as nonverbal communication and conversational skills, continue to develop as well, in particular during social interaction. During social interactions, spoken messages are often accompanied by nonverbal communicative cues, such as facial expression, intonation, or prosody. These nonverbal communicative cues help convey a speaker's intentions or help the receiver to understand the meaning, furthering communicative competence.

Communicative competence is fundamental to successfully participate in society (Rickheit et al., 2008). It is a foundation skill for life and an important building block for many other aspects of life, including social interaction, reflecting on one's own behavior, and behavioral regulation. Language and communication are crucial for further cognitive and social development (Simms, 2007). For that reason, it is not surprising that difficulties with communication are associated with adverse behavioral outcomes and neurodevelopmental problems (Gallagher, 1999).

Within the SCT population, difficulties with language are considered one of the most distinctive traits. Studies have reported language and communication difficulties in as many as 80% of included individuals (Boada et al., 2009; Leggett et al., 2010; Robinson et al., 1983). It should be noted that the method of examining what would be considered as 'difficulty' varies between studies. When reporting outcomes, studies often do not only include specific language and communication measures, but other measures as well. These include, but are not limited to, speech assessments, verbal intelligence, and school reports. In addition, within this percentage, rates of individuals that have received speech- or language therapy, or with language-based learning problems have been included as well. Based on the current literature however, there are two main gaps in the knowledge of language and communication development in SCT. First, the focus of studies investigating language outcomes has been on school-aged children, adolescents, and/or adults. Only a handful of studies – often including only small samples – has included young children. Second, studies that have included specific language outcomes have primarily focused on structural language, including the form and content of language, whereas the impact of SCT on the use of language in a social context and on the broader communication domain has been understudied.

Importance of Studying Communication in Early Child Development

As communication starts to develop from a very young age and develops rapidly in the first years of life (Simms, 2007) and as difficulties with communication at an early age can be a precursor for later neurodevelopmental problems, it is striking that there is little knowledge of the early language and communicative development of children with SCT.

This lack of knowledge of the communicative development of young children in combination with the expected increase in prenatal diagnoses stresses the importance of research in this area. Knowledge about early development could help pinpoint which communicative abilities are vulnerable; for example, if there are difficulties in the communication domain that extend past the recognized risk for structural language difficulties that have been reported in older individuals. In addition to pinpointing vulnerabilities, the opportunity to study a group of children with a clear genetic disorder from birth offers the

unique ability to investigate developmental pathways and possible underlying mechanisms for later outcomes. For example, knowledge about the early development could help identify precursors and early markers for later adverse outcomes, such as behaviors associated with ASD, ADHD, or other psychopathology. By studying these abilities from a developmental perspective, windows of opportunity to support development could be identified. This is not only informative for individuals with SCT but could also increase the understanding of development and developmental risk in the general population. Lastly, this knowledge is needed for clinical purposes; to further inform parents, genetic counselors, pediatricians, developmental psychologists, and all other involved parties on the range of outcomes associated with SCT. Important questions that need to be answered include What are developmental strengths and weaknesses? Which domains are important to monitor? Which abilities could be important targets for early support or intervention?

Thus, we are in need of more knowledge on the early development of children with SCT. Knowledge of these early communicative abilities will help determine which abilities could serve as important targets for early treatment and intervention that could potentially influence the developmental trajectory of young children with SCT in a positive manner.

TRIXY Early Childhood Study

The TRIXY Early Childhood Study is a longitudinal study that was developed to identify neurodevelopmental risks in young children with an extra X or Y chromosome. One of the aims of the study is to gain understanding of the early development of language and communication abilities. The TRIXY Early Childhood Study is based at the TRIXY Center of Expertise in Leiden, the Netherlands, with multiple national and international recruitment and testing sites, including the eXtraordinarY Kids Clinic, Children's Hospital Colorado. Participants in the study are children between 1-7 years old (SCT or control) and their primary caregiver.

Children with SCT were recruited with the help of clinical genetic departments, pediatricians, and national advocacy or support groups in the Netherlands, Colorado USA, and Belgium. For all children in the SCT group, presence of the trisomy ($\geq$ 80% of the cells) was confirmed by requesting the karyotyping outcomes performed by academic hospitals. Children within the same age-range were recruited in the Western parts of the Netherlands to take part as a control group. Due to ethical reasons, genetic screening was not performed in the control group. However, based on the SCT prevalence, the risk of including a child with SCT in the control group was considered minimal and acceptable. All included children and their primary caregiver had to understand Dutch or English. Children with a history of traumatic brain injury, severely impaired hearing or sight, neurological illness, or colorblindness were excluded from the study.

Within the longitudinal design of the TRIXY Early Childhood Study, children were seen during an initial baseline assessment and a follow-up took place approximately 12 months later. Children in the SCT group were included regardless of SCT karyotype (XXX, XXY, XYY), time of diagnosis (prenatal, postnatal), or ascertainment site (i.e., the reason for enrollment in the study). Not selecting on these factors allowed us to determine if specific subgroups of children with SCT have an added risk for unfavorable outcomes. Within each paper, via

preliminary analyses or specific research questions we consider the question if SCT karyotype, time of diagnosis, and ascertainment bias are relevant factors for the interpretation of the results.

In total, 209 children where included: 107 children with SCT and 102 age-matched population controls. At recruitment the age of the children ranged from 11 months to 7 years and 8 months. Within the SCT group, 33 girls with XXX, 50 boys with XXY, and 24 boys with XYY were included. Seventy-two children had a prenatal diagnosis (67%). Reasons for enrollment in the study ('ascertainment bias') were categorized into one of three categories: 'Prospective follow-up', including children with a prenatal diagnosis who are actively followed over time (51%), 'information seeking', including families who want to learn more about their child's condition, but without specific concerns of their child's development (30%), or 'clinically referred cases', including children receiving professional help or from families with specific developmental concerns (19%). Within the control group 58 girls and 44 boys were included.

Aims and Outline of this Dissertation

The central aim of this dissertation is to study early language abilities of young children with SCT within the broader communication domain and to prospectively investigate the relationship between communication and behavioral outcomes. More specifically, within this dissertation we aim to gain knowledge of the behavioral profile, structural language abilities, pragmatic language abilities, and attention and responses to short communicative interactions, to understand mechanisms that may help explain developmental risk and behavioral outcome and to identify targets for early interventions.

Previous studies indicate that individuals with SCT have an elevated risk for serious behavioral difficulties. It is possible that early signs of these behavioral difficulties emerge when children are younger; the developing brain could give more insight on when psychopathology emerges and how it unfolds (Andersen, 2003). Studies including young children, however, are scarce whereas this knowledge is particularly important to identify children who are at risk for more serious neurodevelopmental disorders as early in life as possible and to help reduce the risk for behavioral dysfunction later in life. In **Chapter 2** we assess the profile of 1-year-old, 2-3-year-old, and 4-5-year-old children with SCT on the following behavioral outcomes: Affective problems, anxiety, pervasive developmental problems, attention deficit problems, oppositional defiant problems, and social-emotional functioning. In addition to knowledge of behavioral outcomes, it is important to focus on neurocognitive underpinnings of behavior, as behavioral problems may arise as a consequence of different information processing deficits. Therefore, evidence for impairments in the domains of global intellectual functioning, language, executive functioning, and social cognition are evaluated through a narrative review in **Chapter 3**, with a focus on early development. Within the next chapters of this dissertation, the focus will be on the domain of language and communication as possible building blocks for behavioral outcomes.

Earlier studies including school-aged children, adolescents, and/or adults indicate that a high percentage (70-80%) of individuals with SCT experiences some form of language difficulty (Boada et al., 2009; Leggett et al., 2010; Robinson et al., 1983). Less is known

however, about the first few years of language development, which is striking as language develops rapidly at this age due to significant brain growth. For that reason, this developmental perspective is included in chapters 4, 5, and 6. In **Chapter 4** we focus on language abilities of children with SCT between 1-6 years; a time when several important milestones within child development occur. The time between the ages of 1 to 6 years comprises the period where children rely mostly on nonverbal communication to the period where children begin to use words and finally to a period where children start learning more complex forms of language. With various language measurements the use of gestures, early vocabulary, receptive semantics, expressive semantics, syntax, and phonological processing skills are evaluated at different developmental stages. In addition to the 'structural language measures' related to the *form* and *content* of language that were evaluated in **Chapter 4**, the *use* of language in a social context or pragmatic language is also an important factor in social interaction and communication. In **Chapter 5** we evaluate if the presence of an extra X or Y not only affects structural language, but also pragmatic language. In other words, the question whether there is a broader communication deficit, that extends past the structural language difficulties is addressed. Secondly, in **Chapter 5** we explore if structural and pragmatic language abilities serve as building blocks for behavioral outcomes one year later and we aim to identify targets for early intervention in the communication domain. In **Chapter 6** we further explore the broader communicative abilities of young children with SCT. With eye tracking and physiological arousal measures we objectively assess how children respond to short communicative interactions. Several questions are addressed; which information do children attend to and which information do they miss? Does the direction of gaze during the interaction play a role in this? Do children modulate their arousal levels in reaction to different communicational demands? How do these broader communicative skills relate to structural language abilities? To evaluate to what degree social orientation and physiological arousal levels are related to real-life social behavior and to gain insight in underpinnings of social behavior, we included a group of typically developing children aged 3-7 years in **Chapter 7**. In this chapter, we explore how social orientation as measured with eye tracking relates to daily life behavior. Finally, in **Chapter 8** the conclusions and implications of the studies are summarized and discussed, and directions for future research are presented.

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