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

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Chapter 8

Summary and Discussion

A *neurogenetic approach* can further our understanding of how neurocognitive mechanisms serve as building blocks for neurodevelopmental outcomes. By studying populations with neurobehavioral phenotypes associated with genetic disorders, ultimately individual 'at risk' patterns of development can be identified. Sex chromosome trisomy (SCT), a genetic disorder caused by the presence of an extra X or Y chromosome, is an interesting candidate for studying neurobehavioral phenotypes for several reasons. First, with a prevalence of 1:650 to 1:1000 live births, SCT is not rare, but one of the most common genetic duplications in humans. Second, in contrast to many other genetic disorders, global intellectual functioning in individuals with SCT is often within the normal range, thus interpretation of results is not limited. Third, SCT can be diagnosed prenatally, providing the opportunity to study development early and prospectively. Lastly, the X and Y chromosomes have not only been identified to play a role in neurodevelopment, but the prevalence of neurodevelopmental disorders such as ASD and ADHD is increased in individuals with SCT as well, indicating that SCT can be an important model to further our understanding of mechanisms that contribute to psychopathology.

So far, the majority of studies on SCT have focused on physical and medical consequences of the extra chromosome. Studies looking into the neurocognitive profile are more scarce. Thus, more studies are needed that look into the neurocognitive strengths and weaknesses of this population and how these strengths and weaknesses are related to behavioral outcomes. Within these studies, developmental impact should be taken into account for two reasons. First, early neurocognitive functioning can be a precursor for later development. As SCT can be diagnosed prenatally, early developmental impact can be investigated, providing the opportunity to learn more about the early pathways to psychopathology. Second, as (precursors of) neurocognitive functions start to develop early in life due to rapid brain development, the brain is more susceptible to interventions early in life; there are certain moments or *windows of opportunity* to alter the developmental pathway.

The studies in this dissertation aimed to gain more knowledge of the early development of young children with SCT within the behavioral, language, and communication domains. In addition, studies in this dissertation aimed to prospectively investigate the relationship between communication and behavioral outcomes, or in other words, to identify building blocks of behavioral outcomes. All studies were conducted in young children within the 1-7 year age-range.

When looking at the early presentation of behavioral outcomes – considering the risk for psychopathology in later development – the results in this thesis reveal a higher incidence of behavioral problems in young children with SCT. Further examining age-specific behavioral profiles illustrate that some behavioral outcomes, such as social-emotional difficulties can already be present in very young children (1-year of age), with other behavioral problems gradually emerging in older age groups. Also, the developmental pathway of some of the behavioral outcomes – although examined cross-sectionally rather than longitudinally – appears to be different in children with SCT compared to their peers **(Chapter 2)**. Four neurocognitive domains were identified as possible underpinnings of behavioral outcomes, namely global intellectual functioning, social cognition, executive functioning, and language and communication **(Chapter 3)**. Moreover, as language has been described as one of the core

neurocognitive vulnerabilities in the SCT population, knowing that language and communication are foundation skills that are needed for many other neurocognitive functions, and as difficulties with language and communication are associated with adverse behavioral outcomes and neurodevelopmental problems, the focus of this dissertation was on the language and communication domain. The results of **Chapter 4, 5, and 6** illustrate that language and communication difficulties can already be seen in very young children with SCT and that multiple communicative functions are vulnerable. Language difficulties can already be present before children start to use spoken words to communicate (**Chapter 4**), and communicative difficulties extend past structural language, as the use of language in a social setting (i.e., pragmatic language; **Chapter 5**) and social orientation and arousal modulation during communicative interaction also appeared to be affected **(Chapter 6)**. In addition, language and communication outcomes were relevant in predicting a variety of behavioral outcomes over time **(Chapter 4**) and attention to socially relevant cues, such as the eyes or mouth of an on-screen partner, was related to both concurrent and future language ability in very young children with SCT **(Chapter 6)**. Lastly, social orientation and arousal modulation were related to real-life social behavior in children from a population sample (**Chapter 7**), illustrating that these early functions are meaningful for daily life functioning. Taken together, early communicative abilities are associated with behavioral outcomes, therefore early monitoring of these abilities is important as early childhood may be an important time to positively influence further development.

Within the next paragraphs, the main findings of these studies are summarized and discussed. Finally, a general discussion, implications of the findings, and suggestions for future research will conclude this dissertation.

Summary

The Behavioral Profile of Young Children with SCT

The study presented in **Chapter 2** aimed to describe the early behavioral profile of young children with SCT and to identify if the presentation of the behavioral profile was age dependent. When including children between the ages of 1-5 years, higher incidences of social-emotional functioning problems, affective behavior problems, and pervasive developmental problems were reported in the SCT group compared to the control group. Risk assessment showed high variability within the SCT group; some children showed no behavioral problems, whereas others showed behavioral problems at a clinical level. Compared to the control group, children with SCT more often had a clinical or 'at-risk' score for social-emotional problems (40%), affective problems (11%), anxiety problems (16%), and pervasive developmental problems (38%). Further exploring behavioral outcomes in three age groups revealed age-dependent behavioral profiles. In 1-year-old children with SCT, difficulties with social-emotional functioning could already be present, and elevated scores were persistent across the 1–5-year-old age range. Affective and pervasive developmental behaviors were seen in 3-year-olds, and more prominent in 4-5-year-olds. Anxiety, attention deficit, and oppositional defiant behaviors were seen in 4-5-year-olds. Moreover, the development of affective, pervasive developmental, and oppositional defiant behaviors – although examined cross-sectionally rather than longitudinally – was different for children with SCT compared to the control group. Social-emotional problems however, appeared to be more stable and persistent within the entire

age range. Taken together, these results show that children with SCT are at risk for suboptimal behavioral development from a young age; a risk that appears to increase and expand across behavioral domains with increasing age.

Identifying Neurocognitive Domains as Building Blocks for Behavior

Through a narrative review of the literature, possible neurocognitive underpinnings of behavioral vulnerability were identified in **Chapter 3.** Evidence for cognitive impairment in the domains of global intellectual functioning, language development, executive functioning, and social cognition was evaluated. The aim of this narrative review was two-fold: First, to review existing literature to identify gaps in research that should be explored further and second to identify risk-factors that could serve as a potential target for support and intervention. Earlier reviews have focused on the development of individuals with SCT over the lifespan, primarily during adolescence and adulthood. Therefore, the focus of this review was on early development.

The results of this narrative review illustrate the need for studies in young children, in particular longitudinal studies to follow the developmental trajectory over time. Within the global intellectual functioning domain outcomes vary greatly, ranging from impaired to above average. Taking the results of eight studies together, global intellectual functioning of children with SCT is estimated to be in the average to low-average range. Within the language domain, language difficulties have been identified in young children and appear to be persistent. Taking results of five studies together, effect sizes indicated high clinical significance (i.e., Cohen's d > 1.00), stressing the importance of early detection and support of this domain. Within the executive functioning domain, outcomes were variable depending on the assessed function. Taking the results of five studies together, effect sizes ranged from low to high clinical significance. Finally, on the social cognition domain, taking results from six studies together, results indicated medium to high clinical significance.

To conclude, the results of this narrative review illustrate a significant gap in research focusing on the early developmental impact of SCT. Nonetheless, the existing literature hints that the presence of an extra X or Y chromosome impacts neurocognitive functioning. Knowledge of early development on these domains should be expanded to improve clinical care and to help identify targets for early support and intervention programs.

Early Language and Communication Abilities of Children with SCT

As language has been identified as a vulnerable neurocognitive domain in individuals with SCT, language and communication skills develop early in life, and language and communication are important for other neurocognitive functions, three studies in this dissertation focused on the early language and communication abilities of children with SCT. The study presented in **Chapter 4** aimed to identify language abilities in children with SCT at different developmental stages within the 1–6-year age range and to describe the variability of language development with clinical classifications. Regarding the language abilities at different developmental stages, our results showed that, compared to an age-matched control group, one-year-old children with SCT produce and understand fewer words, and have poorer receptive and expressive semantic skills. The three- to four-year-old children with SCT in our sample have similar receptive semantic and receptive syntactic language skills compared to children in the control group, but poorer expressive semantic skills. Lastly, in the five- to six-year-old children with SCT, we found poorer receptive semantic, expressive semantic, and receptive syntactic language skills.

Regarding the clinical classifications, our results showed much variability in language abilities, with rates of clinically relevant difficulties ranging from 12 to 50%. Odds ratio indicated that the risk of language difficulties was 2-7 times higher in the SCT group, depending on the language function. The study presented in **Chapter 5** further investigated how children use language in social settings (i.e., pragmatic language). Our results showed that children with SCT between the ages of 3–7 years experience more difficulties with all three investigated aspects of pragmatic language: Nonverbal communication, conversational routines, and requesting, giving, and responding to information. These difficulties were not only present in children with structural language problems but appeared to be a more common characteristic within the SCT group. Also, we found that the risk of having inadequate pragmatic language abilities was 23 times higher in the SCT group compared to the population sample. Lastly, the study presented in **Chapter 6** aimed to increase knowledge of how young children with SCT respond to short periods of communicative interactions with a dynamic eye tracking paradigm and physiological arousal measures. Our results indicate that children with SCT aged 1-7 years orient less to social aspects during communicative interactions, in particular to the eyes of the on-screen communicative partner. In addition, the group of children with SCT did not modulate their arousal levels in reaction to different situational demands (i.e., a change in gaze direction). Results of this study hint that children with SCT may experience difficulties with social communication that extend past the risk for early language delays.

Taking these results together, results of these studies add to the growing body of literature on language and communication difficulties in the SCT population. More importantly, these studies expand this knowledge by specifically focusing on young children, by examining specific language outcomes, and by exploring skills in the broader communication domain. As our results show that language and communication difficulties are present across early developmental stages and various skills within this domain are affected, it is likely that these difficulties are anchored in early brain development.

Associations between Language, Communication, and Behavior – Concurrent and Future Outcomes

In three studies, we further looked into associations between language, communication, and behavior and aimed to unravel which language and communication functions possibly serve as building blocks for behavioral outcomes and to gain knowledge of associations between language, communication, and behavior. In **Chapter 6** we investigated the relation between social orientation towards the face, eyes, and mouth of an on-screen communicative partner and both concurrent and future receptive and expressive language abilities. Our results showed that in one-year-old children with SCT both concurrent and future language skills on the receptive and expressive domain were positively correlated to time spent looking at the mouth. These results illustrate that social orientation and language are intertwined at a very young age. The results presented in **Chapter 7** aimed to evaluate to what degree social orientation and arousal modulation in response to social stimuli are associated with real-life social behaviors of young children from a population sample. Results of this study illustrate that social orientation, in particular attention to eyes, is related to real-life social behaviors such as initiation of social interaction, initiation of behavioral request, social awareness, social cognition, and overall social adaptive ability. The ‘social load’ of the paradigms played a role; the paradigm with the highest social load (i.e., a paradigm with social interaction) was related to more real-life behavioral outcomes than paradigms with lower social loads (i.e., paradigms with one person

or several persons without interaction). In addition, a strong physiological arousal response was associated with less social orientation to the eyes and subsequently with less social awareness in real life. Lastly, the results presented in **Chapter 5** illustrate the relevance of structural and pragmatic language on later behavioral outcomes. Poorer pragmatic and structural language abilities were predictive of more attention deficit problems, more pervasive developmental problems, and more social-emotional problems one year later. Poorer pragmatic language was also predictive of more affective problems and more oppositional defiant problems. Thus, pragmatic language in particular was predictive of a broad range of outcomes; social communicative abilities can serve as an early sign of later behavioral problems and may also help explain the variance in neurobehavioral outcomes.

Taking the results of these studies together, these results hint at a broader communication deficit in children with SCT that encompasses several tools that are needed to navigate the social world and that at least some of these communicative tools act as building blocks for later neurobehavioral outcomes.

General Discussion

The central aim of this dissertation was to gain knowledge of early language abilities of young children within the broader communication domain and to prospectively investigate the relationship between language, communication, and behavioral outcomes. From the studies included in this dissertation, four main conclusions can be drawn.

Conclusion 1: Communication Difficulties that Extend Language Vulnerabilities

Language is a vulnerable cognitive domain in children with SCT, but children with SCT may experience difficulties with communication that extend language abilities. Several language and communicative functions may be involved, including functions regarding the form and content of language, the use of language as a social tool, and the ability to rely on a 'social compass' which is needed to navigate social communicative interactions. Both comprehension (i.e., receptive abilities) and production (i.e., expressive abilities) can be affected. Language plays an important role in cognitive and social development (Simms, 2007), and is required to communicate one's needs, thoughts, and emotions. Language and communication are also needed for learning, reflecting on experiences, and to understand the world around us. As language and communication are intertwined with many other functions, compromised language and communication abilities could have severe consequences for the development of other neurocognitive functions and behavioral outcomes, consequently also affecting one's ability to participate in society or one's experienced quality of life.

Conclusion 2: Language and Communication as Building Blocks for Neurobehavioral Risk

Already at a young age, children with SCT have an increased risk for a range of neurobehavioral problems. This finding adds to the growing body of literature that individuals with SCT have an elevated risk for serious behavioral problems. Behavioral problems have been negatively associated with many other outcomes, such as daily life functioning, social competence, school performance, and peer acceptance (de Lijster et al., 2019). Also, behavioral problems during early childhood could be predictive of later psychopathology (Goodwin et al., 2004; Ormel et al., 2015; Roza et al., 2003). This illustrates the importance to further unravel which mechanisms underly this neurobehavioral risk and signal these 'at-risk' developmental trajectories. By targeting these mechanisms early on, this could hopefully reduce the risk of

more serious psychopathology in later life. Studies included in this dissertation illustrate that language and communication are neurocognitive building blocks that – at least in part – may drive, or present as early markers of, this increased risk. Vulnerable language and communicative abilities could lead to, or precede, various adverse behavioral outcomes; this stresses the importance to look into preventive support and to study if improving language and communication could also positively impact behavioral outcomes.

Conclusion 3: A Developmental Perspective is Key

A developmental perspective is key to understand the impact of SCT on both neurocognitive and behavioral outcomes. The studies presented in **Chapters 2, 4, 5, and 6** all included young children with SCT to increase our knowledge of the early development of this group. The majority of previous studies focused on school-age children, adolescents, and/or adults; thus, the results of the studies included in this dissertation fill an important gap in knowledge. In addition, increasing our understanding of the development and the developmental risk of language and communication in the SCT population could not only help to better serve the SCT population, but may also serve as a model to understand 'at-risk' pathways in general child development. In contrast to studies including children with a behavioral diagnosis, where early development can only be studied retrospectively, studying a group of children with a genetic diagnosis provides a unique opportunity to prospectively study the early markers and pathways of an 'at risk' development, such as seen in the earliest forms of communicative development.

To improve our understanding of early development, age was included as a factor to interpret results either by studying outcomes in specific age ranges or by investigating the developmental pathway of outcomes based on cross-sectional data. Results from **Chapters 2, 4, 5, and 6** illustrate that children with SCT have an increased risk for social-emotional problems, even as young as one-year-olds. In addition, in the communication and language domain, children with SCT may understand and use less words, may experience difficulties with other semantic abilities, and may rely less on tools such as social orientation and arousal modulation during interactions. In 3–4-year-old children, affective and pervasive developmental problems become more apparent, in addition to the social-emotional problems. In the language and communication domain, children may experience difficulties with expressive semantics, with using language in a social setting, and in using social tools during interaction. Finally, in children aged 5-7 years, children with SCT have an increased risk for social-emotional, affective, anxiety, pervasive developmental, attention deficit, and oppositional defiant problems. In the language and communication domain, receptive and expressive semantic skills, syntactic abilities, and pragmatic language may be affected, as well as social orientation and arousal modulation.

Our findings illustrate that language and communication abilities can already be affected from a young age. Results from neuroimaging studies suggest that brain anatomy and function may be impacted by the presence of an extra X or Y chromosome (Brandenburg-Goddard et al., 2014; Bryant et al., 2012; Giedd et al., 2007; Lenroot et al., 2014; Lentini et al., 2013; Nadig et al., 2018; Patwardhan et al., 2002; Raznahan et al., 2016; van Rijn et al., 2008; van Rijn et al., 2012; Warling et al., 2020). The early impact of SCT on language and communication abilities combined with the results of neuroimaging studies fit with the idea that these difficulties are anchored in early brain development. In the first years of life the brain develops rapidly; not only does the volume of the brain more than double within this time period, structural and functional networks increase tremendously as well. Although the brain continues

to mature, this occurs at a much slower pace compared to the development during early childhood (Gilmore et al., 2018). Due to this rapid brain development in the early years of life, the brain is more susceptible and early timing of interventions may help modify suboptimal development to a greater extent than later in development. As the risk for suboptimal development in children with SCT is present early in life *and* as for some functions this risk appears to increase and expand when children get older, this stresses the importance of early monitoring and interventions that could possibly influence the developmental trajectory of children with SCT in a positive manner.

Conclusion 4: Robust Vulnerabilities

Our studies did not find evidence that specific SCT characteristics such as karyotype, time of diagnosis, or ascertainment bias (i.e., the reason for participation in the study) play a significant role in explaining outcomes. In **Chapters 2, 4, 5, and 6,** we explored if these characteristics impacted results. Regarding the SCT karyotypes there were some differences in behavioral profiles when comparing children in the SCT group with their same-sex peers (i.e., XXX vs XX, XXY vs XY, XYY vs XY), but affective and social-emotional problems appeared to be persistent across variants. Our results did not indicate differences in the language and communication abilities of girls with an extra X, boys with an extra X, or boys with an extra Y. Regarding time of diagnosis, the behavioral profile of children with a postnatal diagnosis was more severely affected, which was expected as genetic testing may have been conducted due to behavioral problems. Social emotional problems, however, were also present in children with a prenatal diagnosis. Our results did not indicate differences in the language and communication abilities of children with a prenatal diagnosis versus children with a postnatal diagnosis. Lastly, language and communication abilities and behavioral profiles were not different between children who enrolled into the study as part of the prospective follow-up, information seeking, or clinically referred group. Taken together, the presence of an extra X or Y chromosome by itself has a greater impact on language, communication, social-emotional, and behavioral outcomes than specific SCT characteristics, such as karyotype, time of diagnosis, or ascertainment bias; the vulnerabilities identified in our studies appear to be robust within the SCT group.

Clinical Implications

Results of this dissertation illustrate that as a group, children with SCT have an increased vulnerability for both adverse behavioral outcomes and language and communication difficulties. However, the results also indicate that both behavioral outcomes and language and communication abilities are highly variable in children with SCT; some children may be severely affected where others are less affected or may not noticeably differ from peers. It should be noted that the results presented in this dissertation represent the average group of children with SCT, whereas all children are unique, and every child develops at his or her own pace. Based on the results of this dissertation, three clinical implications can be drawn.

Implication 1: Importance of Early Monitoring and Identification

We stress the importance of monitoring the broader communication domain in addition to language in routine clinical care and stress the early identification of adverse behavioral outcomes. When a child does not meet the age-appropriate milestones, standard neuropsychological screening is advised rather than a ‘wait and see’ approach. The standard for neuropsychological screening should be comprehensive, for example also including the earliest

stages of nonverbal communication and social aspects of communication. The developmental trajectory should be monitored closely as language and communication develop rapidly at a young age and the risk for adverse behavioral outcomes seems to increase when children get older.

Implication 2: Importance of Early Preventive Support or Intervention

Developing communication and language skills is an important task for young children and difficulties in the acquisition of these skills can have an impact on many other outcomes. Results from this dissertation identified social communication as an important marker for a range of neurobehavioral outcomes and strong associations between language and social orientation at a very young age, both concurrently and one year later were found. These findings stress the importance to provide preventive support or to intervene as early as possible. Early development is an important window of opportunity in which effective intervention can be crucial to ensure positive social and academic outcomes in later life (Kaiser & Roberts, 2011). It is important to investigate the effectiveness of existing evidence-based support and intervention programs for children with SCT, and if these programs do not suffice, to develop programs tailored to the specific needs of children with SCT.

Implication 3: Importance of Informing Professionals and Parents

Professionals should be aware of the possible impact of SCT, the role of 'expert' should not fall onto the parents' shoulders (Richardson et al., 2021). It is important that professionals such as genetic counselors, pediatricians, developmental psychologists, speech-and language pathologists, and physical therapists stay up to date on the knowledge of genetical conditions such as SCT.

Professionals should be aware of the wide variability in outcomes and should have knowledge of which domains to monitor even more closely at certain developmental stages. Professionals should also inform parents of this variability in outcomes when their child receives the diagnosis. Parents in turn, can provide valuable information to professionals: Parents' concerns are an important marker for early detection of neurocognitive or behavioral problems (Glascoe & Dworking, 1995).

Professionals should inform parents about early opportunities to stimulate development that parents can easily implement themselves. For example, to stimulate the language development of a child, parents are advised to read books with their child. This is a general recommendation that is important for all children but could possibly be crucial for children with an increased vulnerability for language difficulties, such as children with SCT. Furthermore, it is important that professionals provide parents with knowledge and tools how to support their child's *individual* needs so parents can create a safe and sensitive environment for their child to develop.

Strengths and Limitations

Language and communication are vulnerable neurocognitive domains in children with SCT that may be important to signal 'at-risk' developmental trajectories and can – at least in part – explain neurobehavioral outcomes. Unfortunately, the number of studies that have investigated neurocognitive and neurobehavioral functioning in SCT, especially in young children, is limited. The studies included in this manuscript were designed to gain knowledge in these domains. A major strength of the studies included in this manuscript was the sample; we were

able to include a large international sample of young children with SCT and because of this large sample size, we were able to look into age-specific outcomes and the influence of SCT characteristics such as karyotype, time of diagnosis, and ascertainment bias. In addition, the availability of behavioral outcomes one year later allowed us to predict behavioral outcomes over time. There were, however, also limitations to this study. In our study, we included children into two protocols: A protocol for one-year-old children and a protocol for children aged 3-7 years. In order to prevent mixing of these protocols within one individual child, two-year-old children were not represented in the study. Also, some measures were age-specific, therefore children of a certain age had to be excluded for some analyses. Lastly, recruitment bias will always lead to variance in the SCT phenotype, where some difficulties may be overestimated, and others may be underestimated. By including children with SCT regardless of time of diagnosis and reason for enrollment, we have attempted to reduce this bias. However, as not all families with a child with SCT opt to enroll in scientific studies and genetic testing may not always be performed, it cannot be excluded that the described outcomes are not fully representative for the total population of children with SCT.

Recommendations for Future Research

Based on the results of the studies included in this manuscript, there are a number of directions we recommend for future research.

First, as language and communication develop rapidly in the first years of life, we recommend expanding the age range and to study outcomes over a longer period of time. As children with SCT can be diagnosed prenatally, monitoring would preferably take place soon after birth. By studying development of neurocognitive functions across a longer time span and by projecting outcomes over a longer time period, the understanding of different pathways and factors that drive or moderate these pathways could increase.

Second, more knowledge is needed to gain insight into the overall neurocognitive profile of children with SCT and how neurocognitive functions relate to behavioral outcomes. This includes other functions in the language and communication domain but based on vulnerabilities that have been identified in older cohorts with SCT, more knowledge of early social cognitive functioning and executive functioning in young children with SCT is also warranted. In addition, studies that investigate how these neurocognitive functions relate to behavioral outcomes or to each other are scarce. It is possible that vulnerabilities on neurocognitive functions and behavioral difficulties may be due to deficits in metacognitive control functions. An example of such a function is self-directed speech. Self-directed speech emerges in the toddler years; toddlers will talk to themselves out-loud (i.e., overt). Gradually, this progresses to more covert speech, for example children will whisper to themselves, especially when performing a difficult task. Finally, self-directed speech will take on the form of inner speech (Mulvihill et al., 2020). Studies have shown than impaired self-directed speech can result in significant cognitive and behavioral impairments in both typically and atypically developing children and adults (Alderson-Day & Fernyhough, 2015; Whitehouse et al., 2006). Studies including children with neurodevelopmental disorders, for example developmental language disorder, ASD, and ADHD have suggested atypical development of self-directed speech (for an overview see Mulvihill et al., 2020). Due to the increased prevalence of neurodevelopmental disorders and the increased risk of neurocognitive difficulties, it could be of interest to study the concept of self-directed speech in individuals with SCT as well.

Third, development of children is dynamic; there is a complex relation between environmental and interpersonal factors, neurocognitive functions, and behavioral outcomes. More knowledge is needed about the impact of environmental and interpersonal factors. For example, language richness of the environment may serve as a risk- or protective factor in the development of language and communication. Interpersonal factors, for example services a child received and at what age may also impact later outcomes. This also includes the effect of testosterone replacement therapy. Effects of these environmental and interpersonal factors on neurocognitive and behavioral outcomes should be explored further.

Lastly, the effectiveness of existing intervention programs should be evaluated for children with SCT. Results from studies included in this dissertation show that social communicative abilities in particular are an important marker to identify children at risk for unfavorable outcomes, which could possibly also be related to risk for more severe psychopathology later in life. Interventions that are used in other populations, for example in children with autism spectrum disorder or with specific language impairment, and that target this neurocognitive building block could also be of interest for children with SCT. If existing intervention programs are not appropriate or do not exist, specific interventions tailored to the needs of children with SCT should be developed.

Conclusions

The studies included in this dissertation demonstrate that children with SCT have an increased vulnerability for adverse neurobehavioral outcomes and an increased risk for neurocognitive difficulties in the language and communication domain, starting from a young age. This risk for language and communication difficulties and vulnerability for adverse neurobehavioral outcomes may increase when children get older. Moreover, these neurocognitive functions appear to serve as early markers of at-risk pathways with unfavorable neurobehavioral outcomes. These results come with important clinical implications for the SCT population and will ideally fuel the implementation of early monitoring, and implementation and development of preventive support and intervention. Lastly, studying underlying mechanisms of adverse outcomes via a *neurogenetic* approach furthers our understanding of brain-behavior relationships in general.