Archives of Clinical Neuropsychology, 2023, **00**, 1–16
https://doi.org/10.1093/arclin/acad088
Original Empirical Article

OXFORD

Social Communication in Young Children With Sex Chromosome Trisomy (XXY, XXX, XYY): A Study With Eye Tracking and Heart Rate Measures

Evelien Urbanus[1,2,3], Hanna Swaab[1,2], Nicole Tartaglia[4,5], Sophie van Rijn[1,2,*]

[1]Department of Clinical Neurodevelopmental Sciences, Leiden University, Leiden, The Netherlands
[2]TRIXY Center of Expertise, Leiden University Treatment and Expertise Centre (LUBEC), Leiden, The Netherlands
[3]Department of Clinical, Neuro, and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[4]eXtraordinarY Kids Clinic, Developmental Pediatrics, Children's Hospital Colorado, Aurora, CO, USA
[5]Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

*Corresponding author at: Department of Clinical Neurodevelopmental Sciences, Leiden University, Wassenaarseweg 51, 2333 AK, Leiden, The Netherlands.
Tel.: +31 71 527 1846. *E-mail address:* srijn@fsw.leidenuniv.nl (S. van Rijn).

ABSTRACT

Objective: Children with sex chromosome trisomy (SCT) have an increased risk for suboptimal development. Difficulties with language are frequently reported, start from a very young age, and encompass various domains. This cross-sectional study examined social orientation with eye tracking and physiological arousal responses to gain more knowledge on how children perceive and respond to communicative bids and evaluated the associations between social orientation and language outcomes, concurrently and 1 year later.

Method: In total, 107 children with SCT (33 XXX, 50 XXY, and 24 XYY) and 102 controls (58 girls and 44 boys) aged between 1 and 7 years were included. Assessments took place in the USA and Western Europe. A communicative bids eye tracking paradigm, physiological arousal measures, and receptive and expressive language outcomes were used.

Results: Compared to controls, children with SCT showed reduced attention to the face and eyes of the on-screen interaction partner and reduced physiological arousal sensitivity in response to direct versus averted gaze. In addition, social orientation to the mouth was related to concurrent receptive and expressive language abilities in 1-year-old children with SCT.

Conclusions: Children with SCT may experience difficulties with social communication that extend past the well-recognized risk for early language delays. These difficulties may underlie social–behavioral problems that have been described in the SCT population and are an important target for early monitoring and support.

Keywords: Sex chromosome trisomy; Early development; Eye tracking; Physiological arousal; Social orientation; Language and communication

INTRODUCTION

Due to a de novo error in early cell division, approximately 1:650–1:1,000 children are born with an extra X or Y chromosome or sex chromosome trisomy (SCT; Berglund et al., 2019; Groth et al., 2013). An extra X chromosome leads to a 47,XXX karyotype in women or to a 47,XXY karyotype in men, whereas an extra Y chromosome in men leads to a 47,XYY karyotype. This high prevalence makes SCT one of the most common genetic disorders in humans (Hong & Reiss, 2014). The SCT can be detected before birth, resulting in a relatively unique opportunity to study the effects of an extra sex chromosome on the neurocognitive and behavioral development from an early age. Genes that are located on both the X and Y chromosomes play an important role in the neural development (Raznahan et al., 2016). Subsequently, children with SCT have an increased risk for suboptimal neurodevelopment, with studies reporting higher incidences of neurodevelopmental disorders (for a review, see Van Rijn, 2019) and neurocognitive difficulties (for a review, see Urbanus et al., 2019) compared to population samples.

Difficulties with language are frequently reported in individuals with SCT. Studies on language outcomes have shown compromised language abilities in children as young as 8 months old (Zampini et al., 2020). Difficulties with language can already be noted in the preverbal stage (e.g., use of communicative gestures), and these appear to cover a wide range of language abilities, including but not limited to semantic language, syntax, and pragmatic language (Bishop et al., 2011; Ross et al., 2008, 2009; St John et al., 2019; Urbanus, Swaab, Tartaglia, Boada, et al., 2021; Urbanus, Swaab, Tartaglia, Stumpel, et al., 2021; Zampini et al., 2017, 2018, 2020). As these language difficulties can already be apparent at a very young age and multiple language abilities appear to be affected, these difficulties are likely anchored in early brain maturation. Considering the importance of language in social communication, it is thought that language

Received: February 3, 2023. **Revised:** September 22, 2023. **Accepted:** September 25, 2023

difficulties may help explain the social–behavioral difficulties that have been observed in the SCT population. However, there is more to social communication than language alone. To understand the social world around us, for example, to understand another individual's intent, humans rely on broader communicative skills in addition to language skills. Examples of these broader communicative skills include attending to social cues in a social situation or the ability to adapt to internal or external demands. For example, when attending to social cues in a social situation, the expression of emotion and the direction to which a person is looking to convey important information. Similarly, the ability to adapt to internal or external demands during a social encounter, for example, by modulating the level of arousal someone experiences, provides the opportunity to take in important social information. The current study was designed to gain insight into the broader communicative skills of young children with SCT by examining social attention and modulation of arousal to situational demands.

The first skill of interest in this study is social attention. Humans show a natural preference to look at faces and face-like stimuli over nonsocial stimuli, a phenomenon that can already be observed in very young children (Frazier Norbury et al., 2009). Social attention can be divided into three constructs (Dawson et al., 2004): Social orienting (i.e., the ability to direct one's attention to another person, spontaneously or when requested; Guillon et al., 2014), joint attention (i.e., the capacity to share attention with others in a coordinated way; Nation & Penny, 2008), and attending to the distress and emotions of others (i.e., the ability to understand and communicate about emotional states and desires; Sigman et al., 1992). These three constructs are crucial in early development; children with impaired social attention may experience difficulties with understanding the social world around them, which may result in compromised development of adaptive social behaviors. This study will focus on social orientation, more specifically, the ability to spontaneously attend to the face of an on-screen communicative partner.

Within the SCT population, only a handful of studies assessed social orientation abilities in individuals with SCT. For example, in a previous study from this research group, which included children from the same population, children with SCT showed reduced attention to the faces and eyes of two people engaged in a social plot in addition to less accurate joint attention skills (Bouw et al., 2021). Studies on XXY adolescents and adults showed diminished attention to the eyes while watching affective clips (Van Rijn et al., 2014) or static pictures of facial expressions (Van Rijn, 2015). In addition, adolescents and adults with XXY showed a reduced tendency to focus on the eyes when presented with faces (Van Rijn, 2015). Social orientation shows great individual variability, ranging from children who easily tune into others to children who have significant difficulties in navigating the social world. Taken together, there is some evidence that individuals with SCT show deviant social orientation skills. To get a better picture of how children engage in social interactions and respond to a communicative partner, more research is warranted.

The second skill of interest in this study is the modulation of arousal to situational demands. Modulation of arousal reflects someone's ability to attend and react in an appropriate matter to environmental or situational demands (Roberts et al., 2008), for example, cognitive demands (e.g., decision-making or concentration), sensory demands (e.g., loud noises or bright lights), or social demands (e.g., engaging with unfamiliar people or eye contact). The arousal system is driven by the complex and interactive functioning of the autonomic nervous system (ANS). Together with other neurophysiological and neuroanatomical processes, the ANS is considered as a primary behavioral regulator (Porges, 2001). The ANS consists of a sympathetic branch, which is involved in stress and activity, and a parasympathetic branch, which promotes calm and vegetative activities. Through constant monitoring and adjustment of the two branches, the ANS enables the body to respond to internal and external demands (Levenson, 2014). One's ability to attend and react in an appropriate manner differs from person to person. When someone experiences difficulties with modulating arousal levels, this could lead to the development of behavioral and emotional problems (Lydon et al., 2016). If someone experiences too much arousal, for example, this can lead to a feeling of being overwhelmed or anxiousness, which subsequently could lead to diminished social participation. Alternatively, experiencing too little arousal could lead to less motivation to participate, resulting in a diminished focus on others during social encounters (Lydon et al., 2016). Taken together, although the optimal level of arousal differs from person to person, both hyper- and hypoarousal have consequences for social engagement.

Within the SCT population, literature on arousal responses is scarce. One study showed increased affective autonomic response levels as measured with skin conductance in adults with XXY when looking at empathy-evoking stimuli (Van Rijn et al., 2014). A second study indicated that adult men with Klinefelter report higher levels of emotional arousal in emotion-evoking situations compared to men from the general population (Van Rijn et al., 2006). Lastly, a study from this research group, including the same cohort of children as the current study, found a blunted but prolonged emotional reaction to a nonsocial stressor (i.e., unpredictable mechanical toy approach) in young children with SCT (Kuiper et al., 2022). Taken together, there are only a few studies investigating the arousal response of individuals with SCT; more importantly, to our knowledge, there are no studies that have investigated the physiological arousal responses in children specifically in reaction to social stimuli. As physiological arousal is important to navigate the social world, getting more knowledge on the arousal response in young children with SCT is important.

In the current study, we were interested in the impact of gaze direction during social interaction, as both social orientation and modulation of arousal can be affected by the direction of gaze. The direction of someone's gaze is of importance as it can signal approach-avoidance tendencies (Adams Jr. & Kleck, 2005); a direct gaze of another person indicates that attention is directed at the viewer and that there is an intent to communicate, whereas the direction of attention or the intention of an averted gaze is less clear. Typically, developing infants already show sensitivity to the deviations in eye gaze direction from a young age, with more attention to the eyes of a person when in direct eye contact in contrast to looking away (Symons et al., 1998). Gaze behavior provides children with clues to either approach or withdraw from the other person, which helps them regulate emotional experiences and control internal states (Doherty-Sneddon et al., 2002); thus, eye contact or direct gaze can affect the physiological arousal (Kleinke, 1986). Studies have found greater arousal responses, such as skin conductance responses and pupil dilation, when under direct rather than averted gaze (for a review, see Hietanen, 2018). There is some evidence that typically developing children are more sensitive to gaze direction (i.e., faster in detecting direct gaze than averted gaze) compared to children with neurodevelopmental disorders. For example, children with autism spectrum disorder (ASD) may not always differentiate between gaze direction (for a review see Frischen et al., 2007). When studying a group of children with an increased risk for suboptimal neurodevelopment and neurodevelopmental disorders, it is important to investigate this sensitivity to the direction of gaze.

When studying the sensitivity to the direction of gaze, it is important to take age into account. Although infants show a strong preference for faces and face-like stimuli (Frazier Norbury et al., 2009) and a strikingly strong sensitivity to eye gaze from birth (Farroni et al., 2002), social orientation significantly develops in the first years of life. This development of social orientation can be attributed to the maturation of brain areas involved in the processing of social information; collectively, these brain areas are referred to as the “social brain network” (Adolphs, 2003). For example, at the age of 4 months, children show enhanced processing of faces with direct gaze compared to averted gaze (Farroni et al., 2007); this sensitivity to direct gaze results in deeper processing of the face. The ability to determine whether an adult is making eye contact or where an adult is looking is a construct that further develops in the first years of life (Doherty & Anderson, 1999), and by the age of 7 years, children activate similar brain regions in the social brain network to adults when they analyze gaze direction (Mosconi et al., 2005). To get a full picture of the social orientation skills in children with SCT, children aged 1–7 years were included. This age period was chosen as this is a time when several important social cognitive skills develop, including the time when children start labeling what they perceive in the social environment to a time when higher-order functions, such as Theory of Mind, are typically well established. In other words, this age range was chosen as it reflects a period in which there is a significant growth of the social brain network (Grossmann & Johnson, 2007; Soto-Icaza et al., 2015).

Lastly, spontaneous visual attention to socially relevant information is related to real-life social behaviors (Van Rijn et al., 2018) and plays an important role in language acquisition and development (Mundy & Neal, 2000). The ability to orient to the face of another individual can help children learn about speech sounds, facilitating early vocabulary learning (Hillairet de Boisferon et al., 2018). Also, the ability to orientate to the relevant aspects of a social scene can reflect a child’s sensitivity to picking up relevant (nonverbal) communicative cues. Focus on the mouth while looking at someone who is speaking indicates that a child scans the scene for communicative-relevant information (Tenenbaum et al., 2015). In typically developing children, there is a developmental change within the social orientation to faces. This starts with a period of predominant orientation toward the eyes, followed by an increased focus on the mouth during language learning, and lastly a decrease of orienting to the mouth with a simultaneous increase in looking to the eyes (Frank et al., 2012). Studies in typically developing children, children with diagnosed neurodevelopmental disorders such as ASD, and children “at-risk” for neurodevelopmental disorders (e.g., due to shared genetics, such as having a sibling with a diagnosis of autism) have found relations between the time children attend to the eyes or mouth of another person and both concurrent and longitudinal language outcomes in young children (e.g., Elsabbagh et al., 2014; Habayeb et al., 2021; Stagg et al., 2014; Tenenbaum et al., 2014; Tenenbaum et al., 2015; Wagner et al., 2018; Young et al., 2009), clearly demonstrating the importance of attention to social cues in early life for later language outcomes. As language is a vulnerable domain in children with SCT, it is important to explore if these social orientation abilities are related to the language outcome.

This study has two main aims, namely to assess the social orientation patterns during short communicative interactions or “bids” with eye tracking to determine which information children attend to and what information children may miss and to assess the arousal response during these communicative bids, to determine how the ANS responds. Regarding the first aim, the primary focus will be on the difference of attention for social versus nonsocial aspects of the visual scene (Aim 1a) and within social aspects specifically on the time spent looking at the eyes and mouth of the communicative partner (Aim 1b). Regarding the second aim, the focus lies on the similarities or differences in response to a direct or averted gaze (i.e., the sensitivity to differences in gaze direction). As the heart rate (HR) varies due to the influence and interaction of both the sympathetic (preparing the body for action—heightened responsiveness) and parasympathetic (preparing the body for rest—lowered responsiveness) activities of the ANS, the HR was chosen as a fitting physiological index to answer this question. For both aims, we were interested in several outcomes, which were investigated per aim (i.e., Aims 1a, 1b, and 2). First, we expected that children with SCT would show deviant social orientation (i.e., different social orientation patterns) and deviant arousal responses in reaction to communicative bids compared to controls. Therefore, we compared the SCT group with the control group. Second, the impact of the direction of gaze during the bid (i.e., direct vs. averted gaze) was investigated. Third, we investigated if the impact of the gaze differed for the SCT and the control group. Lastly, we exploratively investigated the impact of specific SCT karyotypes on the results of Aims 1a, 1b, and 2; as there is limited research that included all three karyotypes, we had no a priori expectations.

On top of these two main aims, we had two additional aims. As social orientation plays an important role in language acquisition and development and language is a vulnerable domain in children with SCT, our third aim was to investigate to what degree time spent looking at social aspects of the scene (i.e., the face, eyes, and mouth) is associated with the language outcomes, both concurrently and 1 year later. Finally, because of the rapid development of social skills in early childhood, we were interested to see if there were developmental effects of viewing patterns toward the eyes and mouth and modulation of arousal responses between the control and SCT groups. Therefore, our fourth aim

Table 1. Descriptive statistics SCT versus control and SCT karyotypes

	SCT	Control	*p* (SCT vs. Control)	XXX	XXY	XYY	SCT comparisons[e]
N	107	102		33	50	24	
Age (years)	3.68 (1.94)	3.61 (1.62)	.751	4.26 (1.74)	3.25 (1.93)	3.80 (2.05)	0.062
Range	1.00–7.66	1.03–6.46		1.06–7.17	1.00–7.59	1.07–7.66	
GIF[a]	96.58 (17.63)	105.70 (14.34)	<.001	94.69 (16.33)	99.48 (17.73)	92.86 (19.00)	0.275
Range	55–138	72–140		60–122	55–138	59–125	
VIQ[b]	96.36 (18.41)	109.66 (17.25)	<.001	91.65 (15.08)	102.23 (18.96)	92.67 (20.80)	0.097
Range	57–139	69–145		65–120	74–139	57–127	
PIQ[b]	96.48 (17.16)	106.35 (14.56)	<.001	92.33 (16.44)	100.58 (16.28)	95.92 (19.70)	0.238
Range	61–140	74–137		61–120	65–140	63–124	
SES[c]	5.92 (0.94)	5.43 (1.40)	.003	5.91 (1.03)	6.06 (0.88)	5.67 (0.90)	0.239
Range	3.50–7.00	2.00–7.00		3.50–7.00	4.00–7.00	3.50–7.00	
Ascertainment bias[d] (A/B/C)				11/12/10	28/15/7	16/3/5	0.063
Time of diagnosis (prenatal/postnatal)				20/13	35/15	16/8	0.675

Notes: Scores represent means (SD). Abbreviations: SCT = sex chromosome trisomy; GIF = global intellectual functioning/IQ; VIQ = verbal intelligence; PIQ = performance intelligence; SES = social economic status. [a]Data for six children with SCT were incomplete (one XXX, two XXY, three XYY). [b]VIQ and PIQ were only available for 3–7-year-old children. [c]Data for one child with SCT were not available; Classified according to the criteria of Hollingshead: (0) No formal education; (1) Less than seventh grade; (2) Junior high school; (3) Partial high school; (4) High school graduate; (5) Partial college or specialized training; (6) Standard college/university graduation; (7) Graduate/professional training. [d]A = Active prospective follow-up; B = Information-seeking parents; C = Clinically referred cases. [e]SCT comparisons: XXX versus XXY versus XYY.

was to investigate if there is diminished social orientation and modulation of arousal response, and if so, is this diminished throughout the 1–7-year age range, or whether this emerges at a certain age.

MATERIALS AND METHODS

Editorial Policies and Ethical Considerations

This study was approved by the Ethical Committee of Leiden University Medical Center, the Netherlands, and the Colorado Multiple Institutional Review Board in CO, USA. Written informed consent according to the declaration of Helsinki was obtained after describing the study to the parent(s) of the child.

Participants

The present study is part of a larger ongoing project (TRIXYEarlyChildhoodStudy) at Leiden University. The TRIXY Early Childhood Study is a longitudinal study with an initial baseline and a 1-year follow-up assessment, which aims to identify the neurodevelopmental risk in young children with an extra X or Y chromosome. In total, 107 children with SCT (33 XXX girls, 50 XXY boys, and 24 XYY boys) and 102 controls (58 girls and 44 boys) were included. Ages at enrollment ranged from 1.00 to 7.66; years; mean age did not differ between the SCT ($M = 3.68$, $SD = 1.94$) and control group ($M = 3.61$, $SD = 1.62$; $p = .751$; see Table 1 for descriptive statistics).

Within the SCT group, 71 children received a prenatal diagnosis of SCT as a result of prenatal screening or screening, for example, due to advanced maternal age. Children who received a postnatal diagnosis ($N = 36$) received a diagnosis of SCT due to a developmental delay ($N = 15$), physical, growth problems, or both ($N = 12$) or medical concerns ($N = 9$). In addition to the time of diagnosis, the reason families enrolled in the study was monitored (i.e., ascertainment bias). Three subgroups were identified: "Active prospective follow-up" (51.4% of the SCT group), "Information seeking parents" (28.0% of the SCT group), and "Clinically referred cases" (20.6%) of the SCT group. Distributions at the time of diagnosis and ascertainment bias were similar between the three SCT karyotypes (see Table 1.).

Recruitment took place in the Netherlands, Belgium, and CO, USA. Children with SCT were recruited with the help of clinical genetic departments, pediatricians, and national support and advocacy groups. Children in the control group were recruited with the help of public institutions (e.g., public daycare centers and primary schools) and via the civil registry. Recruitment of the control group took place in the western parts of the Netherlands. Assessments took place at a range of (inter)national testing sites, including the Trisomy of the X and Y (TRIXY) Expert Center in the Netherlands and the eXtraordinarY Kids Clinic in Developmental Pediatrics at Children's Hospital Colorado.

For both the SCT as well as the control groups, the following exclusion criteria applied: a history of traumatic brain injury, severely impaired hearing or sight, neurological illness, or colorblindness. Specifically for the control group, children with a previous diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) were excluded. In addition, as an inclusion criterion for both groups, both the child and the (primary) parent or caregiver had to speak Dutch or English. All children had normal or corrected-to-normal vision. Specific to the SCT group, children were included if the trisomy was present in at least 80% of the cells, as confirmed by standard karyotyping. Due to ethical reasons, genetic screening was not performed in the control group.

However, based on the prevalence of SCT, the risk of including a child with SCT in the control group was considered to be minimal and acceptable.

Global intellectual functioning (GIF) was assessed with the Bayley Scales of Infant and Toddler Development (third edition; Bayley, 2006), the Wechsler Preschool and Primary Scale of Intelligence (third edition; Wechsler, 2002), or the Wechsler Nonverbal Scale of Ability (Wechsler & Naglieri, 2006). On average, GIF was lower in the SCT ($M = 96.58$, $SD = 17.63$) than in the control group ($M = 105.70$, $SD = 14.34$; $p < .001$). As a proxy for social economic status (SES), parents were asked to report the highest level of completed education. If two caregivers were present (96.2%), SES was computed as the average of both caregivers. The Hollingshead criteria were used to account for the differences in educational systems between countries (Hollingshead, 1975). On average, SES was higher in the SCT group ($M = 5.92$, $SD = 0.94$) than in the control group ($M = 5.43$, $SD = 1.40$; $p = .003$). Children recruited in the USA were White (88.1%), Black or African American (3.4%), Asian (3.4%), or "unknown" (5.1%). Information on race or ethnicity in the sample recruited in Western Europe was not available. Autism symptoms were assessed in a subsample of children with SCT approximately 12 months after the initial visit ($N = 53$). The Autism Development Interview-Revised (ADI-R; Rutter et al., 2003) assesses autism symptoms in the domains of social interaction, communication, and restricted and repetitive behaviors/interests. According to the ADI-R, 24% of the children in our subsample met the diagnostic criteria for an ASD diagnosis.

Descriptive statistics for age, GIF, and SES for the SCT versus the control group and between the SCT karyotypes can be found in Table 1.

Procedure

Assessments took place in either a quiet room at the university or at home. As assessments took place at various sites (Belgium, the Netherlands, and CO, USA), the test setup and research protocol were identical on all sites. Researchers from the Dutch site were responsible for project and data management (i.e., training and supervision of researchers and processing and scoring of data).

Language assessments were administered in either Dutch or English. All tests were administered according to the standardized procedure as specified in the instrument's manual. Neurocognitive assessments, including the assessment of receptive and expressive language, took place before the eye tracking and physiology assessments to get the child acquainted with the examiner and testing location. For the eye tracking (Tobii) and physiology (BIOPAC) assessments, the laptop with the eye tracker was placed on an adaptable table to adjust to the height of the child. The table was placed in a small tent to minimize diversions. The child was seated in a comfortable car seat at approximately 65-cm viewing distance, which is within the ideal range for recording according to the Tobii eye tracking manual. Recording electrodes were placed on the child in the presence of the parent. For the electrode to properly attach to the skin, and for the child to get used to the feeling of the electrodes, there was a 5- to 10-min break before the eye tracking and physiological recording in which the child watched a short movie. One electrode was placed 10 cm below the suprasternal notch, and a second electrode was placed 10 cm above the bottom of the rib cage on the right side of the child. A ground electrode was included by simultaneously recording the electrodermal activity (not included in the current study).

Before the paradigm was shown, a 5-point calibration procedure was conducted. We used qualitative estimates during this procedure, which are in line with the Tobii Studio manual. Successful calibration was defined as a maximum calibration error of 1° for individual calibration points (i.e., <1 cm at a distance of 65 cm from the eye tracker). The video clips were shown in a fixed order, all preceded by an attention grabber (i.e., a moving picture of an animal shown on a black background, accompanied by a sound). First, a 3-min resting clip was shown to assess the baseline autonomic response levels. During this time, children looked at the fish in an aquarium. Next, the communicative bids paradigm was shown, with a 30-s resting clip showing a ball and a slide in between the two conditions (see "communicative bids paradigm" below). The researcher sat on the left of the child and controlled the Tobii via a remote keyboard. A second researcher controlled the BIOPAC. All physiology equipment was placed outside the sight of the child. Children were instructed to sit quietly and watch the video clips.

Instruments

Communicative bids paradigm

The communicative bids paradigm consisted of two dynamic video clips of 30 s each. Dynamic video clips were used, as the ecological validity is higher for dynamic video clips rather than for static pictures. In both video clips, children were shown a scene of naturalistic caregiver interaction: a female actress in the middle of the screen, with two objects (a piano and a farm) positioned on the left and right of the actress. The actress alternated between a neutral facial expression or a smile and tried to engage the viewer by waving and using simple universal sounds (e.g., "hi" and "oh") throughout the 30-s time frame of the video clips. The use of more complex language (e.g., sentences) during a communicative bid might be a confounding factor, where children do not necessarily attend to the social aspects of a scene naturally but rather attend to the eyes or mouth of the communicator as a response to hearing language (Brooks & Meltzoff, 2005). For that reason, only simple speech sounds were used in the paradigm of this study. In the first video clip, the actress looked directly at the child (direct gaze condition), whereas in the second video clip, the actress was facing sideways—looking toward a point at the right of the child (averted gaze condition). See Fig. 1 for a still of the dynamic video clips.

Eye tracking: apparatus

Eye gaze data was collected with a Tobii X2-60 eye tracking device, which records the X and Y coordinates of the position of the eye using a corneal reflection technique (Tobii Technology AB, Danderyd, Sweden). Stimuli were shown on a 15.6-inch laptop with a resolution of 1,920 × 1,080 pixels. A sampling frequency of 60 Hz was used.

Eye tracking: processing procedure

Gaze data were processed with Tobii studio version 3.4.8. The Tobii I-VT fixation filter was used for defining visual fixations.

Fig. 1. Communicative bids paradigm: direct gaze direction (left) and averted gaze direction (right).

This filter controls for the validity of the raw data, thus only including valid data (Olsen, 2012). The I-VT Threshold filter was set to define the minimum fixation duration to 60 ms, with a velocity threshold of 30°/s. Data were considered to be valid and were included in the analyses if one or both eyes had a valid reading according to the Tobii validity criteria.

Areas of interest (AOI) included the total screen, objects, face, eyes, and mouth of the actress and were drawn with the "dynamic AOI" tool in the Tobii studio. An extended region of 1 cm surrounding the AOI was included to create sufficiently large AOIs, as large AOIs are more robust to noise and reliably capture gaze fixations (Hessels et al., 2016). There was no overlap between the objects and face AOI nor between the eyes and mouth AOI; the eyes and mouth AOI were part of the face AOI. The visual angles were as follows for the directed and averted conditions, respectively: 29.73° × 16.98° ("total screen"), 7.93° × 6.52° or 7.93° × 6.34° ("piano"), 7.05° × 6.70° or 7.05° × 6.52° ("farm"), 8.37° × 6.61° or 8.19° × 6.17° ("face"), 1.76° × 4.42° or 1.76° × 4.06° ("eyes"), and 1.76° × 3.53° or 1.59° × 3.09° ("mouth").

To evaluate the percentage of valid data, the proportion scores were computed by dividing each child's "total visit duration screen" by 30 (i.e., the duration of the clip) and multiplying by 100. This was done for the direct and averted gaze video clips separately, and this "proportion attention to the screen" reflects the percentage of valid data per condition. Next, the percentage of time a child fixated on the objects, face, eyes, and mouth was calculated by dividing the "total fixation duration for that AOI" by the computed "proportion attention to the screen" and multiplying by 100. This "proportion per AOI" thus reflects the time a child fixated on an AOI, given the time they attended to the screen. The main interests in this study were the total time children attended to the screen, the time children spent looking at social versus nonsocial aspects of the scene, and the time children spent looking at the eyes versus the mouth of the actress.

Due to technical issues or fatigue of the child, data for the eye tracking paradigm were missing for 21 children (10%; $N_{SCT} = 17$). As an indication of the reliability of the data, the total proportion of time children spent looking at the screen (for the direct gaze and averted gaze direction separately) was screened for children who did not contribute sufficient data (30% which equals 10 s). For 14 children (6.7%; $N_{SCT} = 9$) the data for one or both gaze directions were deemed insufficient, and these children were discarded from the analyses. Thus, in total, 35 children were not included in "any" of the analyses and 174 children (81 SCT and 93 controls) did complete the eye tracking paradigm with sufficient data. Data of these 174 children were only included in the analyses if the calculated *Z*-scores lay within a specified range. These *Z*-scores were calculated for each of the AOI for the SCT and control groups separately. Filters were used to exclude children with *Z*-scores that deviated more than 3 *SD* from the mean. To maximize the power, this was done separately for each analysis; consequently, the *N* differed slightly between the analyses. An overview of the number of children included per analysis can be found in Fig. 2.

As an indication of overall attention to the paradigm, attention to the screen collapsed for gaze direction was used. On average, children attended to the video 90.4% of the time the videos were displayed. An independent samples *t*-test indicated similar attention to the screen between the SCT (89.4%) and control groups (91.3%, $p = .245$).

Physiology: apparatus

The HR was used as an indicator of arousal levels. The HR data were collected with AcqKnowledge (version 5.0.2; BIOPAC Systems Inc.). Recordings were acquired with an Electrocardiogram amplifier (ECG100C) and a BIOPAC data acquisition system (MP150 Windows) at a sampling rate of 1,000 Hz. The HR was recorded simultaneously with the eye tracking data. The physiological equipment was synchronized with the Tobii software, with markers representing the start of the video clips.

Physiology: processing procedure

The HR data were processed with PhysioData Toolbox v0.5 (Sjak-Shie, 2019). Recorded data were manually inspected by detecting the R peaks. With visual identifications, motion artifacts were identified and excluded from the data.

For the physiological data, the first 30 s of the baseline clip were considered as the "baseline autonomic response level." There was no significant difference in the average baseline HR between the SCT group ($M = 102.27$, $SD = 16.22$) and the control group ($M = 101.93$, $SD = 13.92$). There were, however, significant differences between the three SCT karyotypes, with a higher baseline HR in the XXY compared to the XXX and XYY groups, and the latter not being significantly different. To account for these differences, delta (Δ) scores were computed.

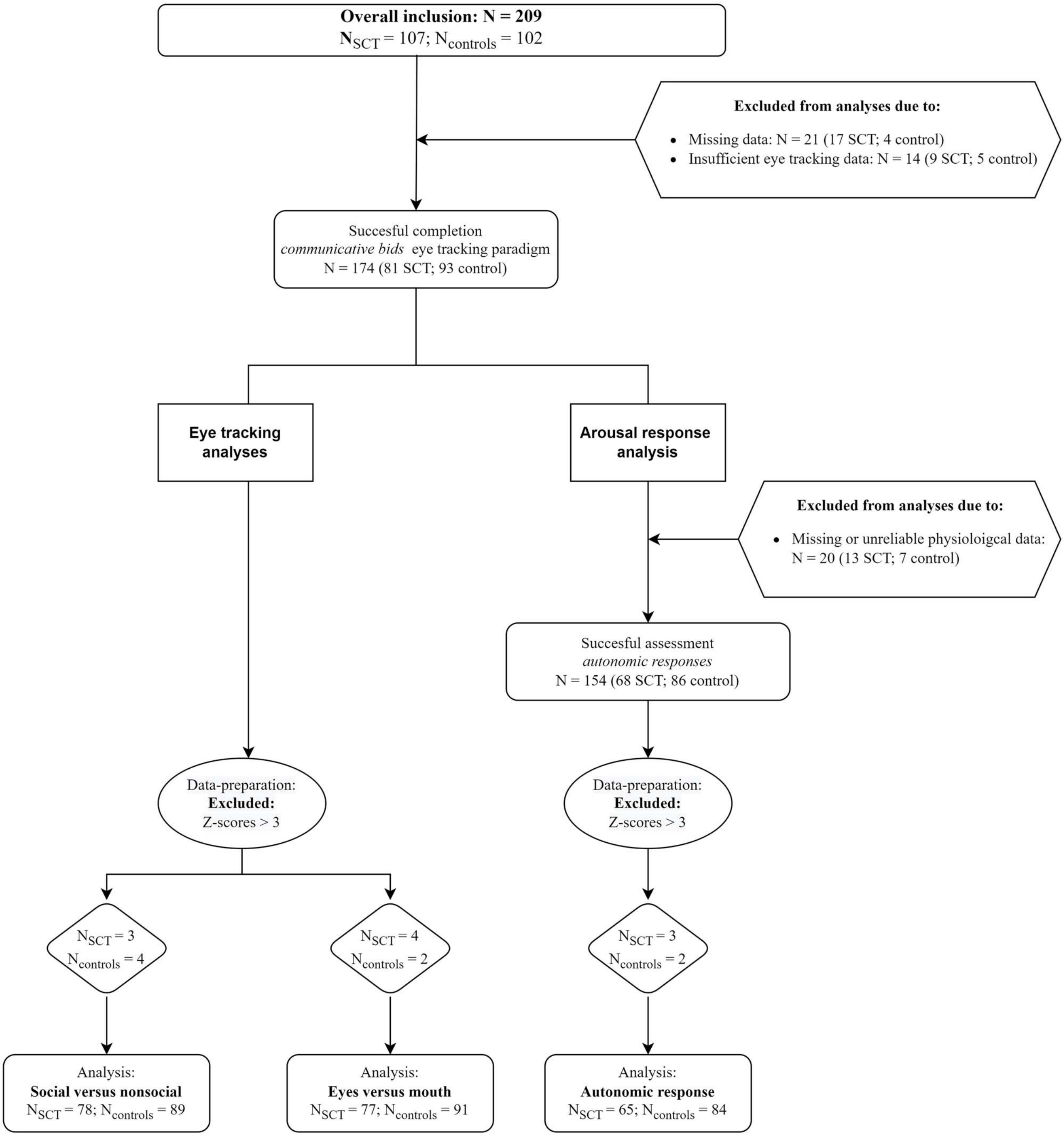

Fig. 2. Flowchart of eye tracking and physiology data processing: In total, 209 children were included in the study, of whom 174 completed the eye tracking paradigm. Further exclusion criteria were applied for the eye tracking and arousal response analyses, as shown on the left (eye tracking) and right (arousal response) sides of the flowchart. The total number of included children varied per analysis due to the specific exclusion criteria for each analysis.

To examine the dynamics within the 30-s duration of the video clips, HR data collected during the communicative bids eye tracking paradigm were summarized in three 10-s epochs. Delta HR score (ΔHR-score) was computed by subtracting the baseline HR from the HR for each epoch.

Children who had missing data or low reliability on the eye tracking measures were excluded from the arousal analyses as well ($N = 35$). In addition, children with unreliable physiology data, for example, due to a large number of motion artifacts or malfunctioning hardware, or children who had no (reliable) baseline HR data were excluded ($N = 20$). For the remaining 154 children (68 SCT and 86 controls), *Z*-scores were requested for the six 10-s epochs for the SCT and control groups separately. Filters were used to exclude children with *Z*-scores that deviated more than 3 *SD* from the mean. As with the eye tracking analyses, this was done separately for each analysis to maximize the power, therefore the N slightly differed between the analyses. An overview of the number of children included per analysis can be found in Fig. 2.

First, to evaluate the effectivity of the paradigm in triggering the arousal system, the effect of the direct and averted gaze directions over time was assessed in the control group only. A repeated measures ANOVA with gaze direction (direct vs. averted) and time (ΔHR-scores in three epochs) revealed a significant interaction effect between gaze direction and time ($p < .001$). Paired samples t-test per epoch (e.g., direct 1 vs. averted 1) revealed that the arousal response in the control group differed between the direct and averted gaze directions in the first epoch (10 s, $p < .001$), but not in the remaining epochs (p ranging from .332 to .475). This illustrates that children in the control group have a different initial arousal response to the direct versus averted gaze direction; in other words, there is sensitivity for gaze direction in the first stages of a communicative bid. To assess the arousal response in children with SCT in this sensitive time window, the ΔHR-scores for the first epochs for the direct and the averted gaze direction will be included in the analyses.

Receptive and expressive semantic language skills

In 1-year-old children, the semantic language skills were assessed with the Bayley Scales of Infant and Toddler Development—Language scale (Bayley, 2006). This scale consists of separate subtests for the receptive and expressive semantic skills. In the receptive subtest, depending on the age of the child, pre-verbal behavior, ability to identify objects and pictures, and understanding of verbal messages were assessed. In the expressive subtest, depending on the age of the child, pre-verbal communication and the ability to name objects and pictures were assessed.

In children aged 3 years and older, receptive semantic skills were assessed with the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1997, 2005). The PPVT assesses the child's listening comprehension of spoken words, where the child must identify the picture (out of four pictures) that is orally presented by the researcher. Expressive semantic skills were assessed with the Expressive Vocabulary subtest of the Clinical Evaluation of Language Fundamentals Preschool edition (CELF-P; Wiig et al., 2004, 2012). The CELF-P Expressive Vocabulary subtest assesses the child's ability to label people, objects, and actions based on colored images.

Follow-up language outcomes in combination with baseline eye tracking data were available only for a subset of the children ($N_{SCT} = 55$, $N_{controls} = 60$), with follow-up assessments taking place 46–61 weeks after the initial assessment ($M = 53$, $SD = 2.24$). The high number of missing data was largely due to the worldwide COVID-19 pandemic, where families were unable to participate or assessments had to be postponed (i.e., took place >18 months after baseline; $N = 56$). Missing data at follow-up were further due to invalid baseline eye tracking data ($N = 21$), or other reasons ($N = 17$). Participant demographics (i.e., age, GIF, and SES) did not differ between children who did versus children who did not participate in the follow-up assessment (p ranged from .105 to .975).

Statistical Analyses

Data were analyzed with the Statistical Package for the Social Sciences version 25. Several parametric and nonparametric tests were used. The level of significance was set at $p \leq .05$ for multivariate tests. For the other main outcomes (i.e., age effects, associations with language outcomes, and SCT karyotypes), the level of significance was set at $p \leq .001$; a more stringent significance level was used for these tests to account for the use of multiple tests and to minimize the chance of reporting a significant effect when none truly exists. Effect sizes were calculated with partial η^2 and interpreted according to the guidelines by Cohen (1988), with partial η^2 0.01 considered as small, partial η^2 0.06 considered as medium, and partial η^2 0.14 considered as large.

Preliminary analyses

As there were significant differences in IQ and SES between the SCT and control groups, correlations were calculated between these variables, three global eye tracking outcome measures (screen, face, and objects collapsed for gaze direction), and ΔHR-scores for the initial 10 s (direct and averted gaze direction). No significant correlations were found (see Supplementary material online, Table S1). Therefore, IQ and SES were not included in further analyses regarding eye tracking outcomes or physiological outcomes. Also, to account for the potential effect of (severe) social difficulties (i.e., children who scored above the cut-off on the ADI-R), an independent t-test was used to test for differences in the three global eye tracking outcome measures and ΔHR-scores. No significant differences were found (p ranged from .248 to .941), therefore, autism symptomatology was not included in further analyses. Third, as not all children were included in the eye tracking and physiological arousal analyses, demographic variables (i.e., age, GIF, and SES) were compared between included and excluded children. No significant differences were found (p ranged from .097 to .249). Lastly, to account for possible differences based on sex, boys and girls in the control group were compared on the three global eye tracking outcome measures (screen, face, and objects) and ΔHR-scores. No significant differences were found (p ranged from .090 to .599), therefore all controls were collapsed into one control group. As sex-dependent effects were also not expected in the SCT group, SCT karyotypes were compared directly.

Lastly, to assess the impact of SCT characteristics (i.e., time of diagnosis, ascertainment bias, and research site), exploratory analyses—nonparametric Kruskal–Wallis tests or MAN(C)OVA, depending on sample sizes and comparability of age between groups—were run for the time spent looking at the face and eyes (collapsed for gaze direction) and arousal response sensitivity to gaze direction. Within these comparisons, the created subgroups did not differ in the distribution of karyotypes, time of diagnosis, and ascertainment bias (when applicable). When comparing subgroups that differed in age, age was included as a covariate in the analysis. No significant differences were found for any of the SCT characteristics on time spent looking at the face, time spent looking at the eyes, or sensitivity to gaze direction. Therefore, these SCT characteristics were not included as covariates in any subsequent analyses.

All outcomes can be found in Supplementary materials (see Supplementary material online, Table S2).

Research questions

To investigate the social orientation patterns and arousal response during the communicative bids paradigm (Aims 1a, 1b, and 2), repeated measures MANOVA was used to compare the outcomes. If there was unequal variance–covariance (i.e., Box's M $p < .05$), Pillai's trace was used to interpret the effect. Significant interaction effects were followed by within-group paired samples *t*-tests, and significant multivariate main effects were followed by univariate tests. Descriptive statistics (mean, min, max for the SCT and control group separately) can be found in the Supplementary material online, Table S3).

To investigate the associations with language (Aim 3), correlations were calculated between the eye tracking outcomes and both concurrent and future language outcomes. To account for the use of different tests on children of different ages (i.e., 1-year-old and 3–7-year-old children), correlations were calculated for these age groups separately and separately for the SCT and control groups. To account for the initial language level (i.e., concurrent language), partial correlations were used to assess the associations between eye tracking outcomes and future language outcomes.

To investigate the developmental effects (Aim 4), PROCESS moderation analyses were used (Hayes, 2017). The interaction effect between the research group and either the time spent looking at the eyes or mouth or arousal levels were examined.

RESULTS

Social Orientation Patterns With Eye Tracking—Attention to Social Versus Nonsocial Information (Aim 1a)

In total, 78 children in the SCT group and 89 children in the control group were included in the social versus nonsocial analysis. The proportion of time that children spent looking at social (i.e., the face of the actress) versus nonsocial (i.e., objects on the sides of the actress) aspects of the scene was analyzed for the factor "gaze direction" (direct vs. averted), with research group (SCT vs. control) as a between-subjects variable. The repeated measures MANOVA showed a significant main multivariate effect of research group, Wilks' Lambda = 0.95, $F(2,164) = 4.46$, $p = .020$, partial $\eta^2 = 0.05$, and a significant main multivariate effect of gaze direction, Wilks' Lambda = 0.95, $F(2,164) = 4.27$, $p = .016$, partial $\eta^2 = 0.05$. The interaction effect of research group × gaze direction was not significant, Wilks' Lambda = 0.99, $F(2,164) = 0.80$, $p = .451$, partial $\eta^2 = 0.01$. The significant main effects were further analyzed with univariate tests.

Regarding the main effect of gaze direction (direct vs. averted), univariate tests for objects showed that children, regardless of research group, spent proportionally more time looking at the objects in the direct gaze direction (EMM = 11.52, SE = 0.73) compared to the averted gaze direction (EMM = 9.71, SE = 0.58), $p = .012$, partial $\eta^2 = 0.04$, indicating a small effect. No differences between the gaze directions were found for the time spent looking at the face, $p = .511$. Regarding the main effect of research group, results showed that, regardless of gaze direction, children with SCT spent proportionally less time looking at the face (EMM = 47.39, SE = 2.10) than the children in the control group (EMM = 55.27, SE = 1.96), $p = .007$, partial $\eta^2 = 0.04$, indicating a small effect. No significant differences between the children with SCT and the control group were found for the time spent looking at objects ($p = .362$).

To evaluate if the significant deviations in the SCT group in terms of the overall looking time toward the face (irrespective of gaze direction) was affected by a specific SCT karyotype, a nonparametric Kruskal–Wallis test was used for a more in-depth analysis within the SCT group. No significant subgroup effects were found ($H(2) = 2.42$, $p = .090$); indicating that there were no significant differences in the attention to faces between the three karyotypes (XXX, XXY, and XYY).

Taken together, these results indicate that both children with SCT and controls do not seem to differentiate between the gaze directions (direct vs. averted) when looking at a face, but children in both groups do tend to look more at objects during a direct compared to an averted communicative bid. In addition, compared to controls, children with SCT are less inclined to fixate on the face during a communicative bid, but they attend equally to nonsocial objects. This diminished attention to the face appears to be irrespective of SCT karyotype.

Social Orientation Patterns With Eye Tracking—Eyes Versus Mouth (Aim 1b)

In total, 77 children in the SCT group and 91 children in the control group were included in the eyes versus mouth analysis. The proportion of time children spent looking at the eyes versus the mouth was analyzed for the two gaze directions (direct vs. averted), with research group (SCT vs. control) as a between-subjects variable. The repeated measures MANOVA showed a significant main multivariate effect of research group, Pillai's Trace = 0.04, $F(2,165) = 3.79$, $p = .025$, partial $\eta^2 = 0.04$, and a significant main multivariate effect of gaze direction, Pillai's Trace = 0.10, $F(2,165) = 9.12$, $p < .001$, partial $\eta^2 = 0.10$. The interaction effect of research group × gaze direction was not significant, Pillai's Trace = 0.01, $F(2,165) = 0.63$, $p = .537$, partial $\eta^2 = 0.01$. The significant main effects were further analyzed with univariate tests.

Regarding the main effect of gaze direction (direct vs. averted), univariate tests for attention to the mouth showed that children, regardless of research group, spent proportionally more time looking at the mouth of the actress in the direct gaze direction (EMM = 16.13, SE = 1.18) compared to the averted gaze direction (EMM = 13.13, SE = 1.10), $p < .001$. Partial $\eta^2 = 0.07$, indicating a moderate effect. There was no effect of the gaze direction on the time spent looking at the eyes of the actress, $p = .110$. Regarding the main effect of research group, results showed that, regardless of gaze direction, children with SCT spent proportionally less time looking at the eyes (EMM = 18.40, SE = 1.95) than the children in the control group (EMM = 23.94, SE = 1.79), $p = .038$. Partial $\eta^2 = 0.03$, indicating a small effect. No significant differences between the children with SCT and the control group were found for the time spent looking at the mouth of the actress ($p = .418$).

To evaluate if the significant deviations in the SCT group in terms of the overall looking time toward the eyes (irrespective of gaze direction) was affected by specific SCT karyotype, a nonparametric Kruskal–Wallis test was used for a more

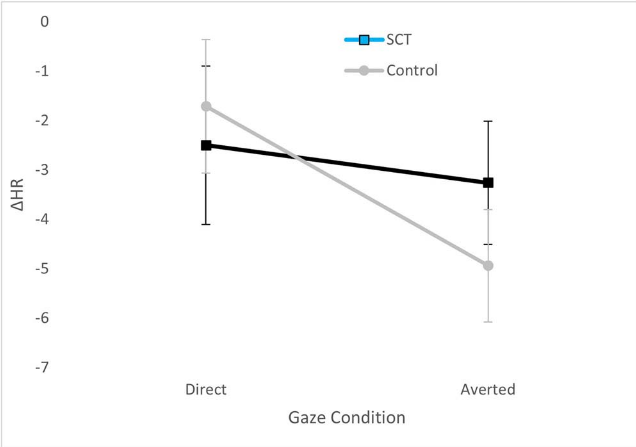

Fig. 3. Sensitivity to the direction of eye gaze in the SCT and control groups (mean scores and margins of error).

in-depth analysis within the SCT group. No significant differences were found ($H(2) = 1.03$, $p = .596$), indicating that there were no significant differences in the attention to eyes between the three karyotypes (XXX, XYY, and XYY).

Taken together, these results indicate that both children with SCT and controls do not differentiate between the gaze directions (direct vs. averted) when looking at eyes, but they do tend to look more at the mouth during a direct compared to an averted communicative bid. In addition, compared to controls, children with SCT are less inclined to fixate on the eyes during communicative bids, but they attend equally to the mouth. This diminished attention to the eyes appears to be irrespective of SCT karyotype.

Arousal Response With HR (Aim 2)

In total, 65 children in the SCT group and 84 children in the control group were included in the analysis. The ΔHR-levels within the two gaze directions (direct vs. averted) were included as a within-subjects variable, with research group (SCT vs. control) as a between-subjects variable. The repeated measures MANOVA showed a significant research group × gaze direction interaction effect, Wilks' Lambda = 0.96, $F(1,147) = 5.89$, $p = .016$, partial $\eta^2 = 0.04$.

The significant interaction effect was further explored with post hoc paired samples t-tests. Children in the control group showed a stronger initial response to the averted gaze direction (ΔHR = −4.94. *SD* = 5.34) compared to the direct gaze direction (ΔHR = −1.71, *SD* = 6.31). However, a different pattern was found in the SCT group. In contrast to the control group, the paired samples t-test did not indicate a difference in the initial arousal response to the gaze direction in children with SCT, $t(64) = 1.09$, $p = .281$; children with SCT responded similarly to the averted gaze direction (ΔHR = −3.26, *SD* = 5.14) and the direct gaze condition (ΔHR = −2.50, *SD* = 6.61). A visualization can be found in Fig. 3.

To evaluate if the significant deviations in the SCT group in terms of this reduced arousal sensitivity was affected by a specific SCT karyotype, a nonparametric Kruskal–Wallis test was used for a more in-depth analysis within the SCT group. A $\Delta HR_{sensitivity}$ score was calculated by subtracting the ΔHR in the averted gaze direction from the ΔHR in the direct gaze direction (first epoch only), where a higher score indicates more sensitivity to gaze direction. With a nonparametric Kruskal–Wallis test, gaze direction sensitivity was compared between the three karyotypes (XXX, XXY, and XYY). No significant differences were found ($H(2) = 0.28$, $p = .869$), indicating that there are no differences in the sensitivity to gaze direction between the three karyotypes.

Collectively, these results indicate that, compared to controls, the arousal system of children with SCT appears to be less sensitive to the gaze direction. These findings appear to be irrespective of the SCT karyotype.

Attention to the Eyes and Mouth: Associations With Language Outcomes (Aim 3)

Correlations were calculated between the proportion of time children spent looking at an AOI (face, eyes, and mouth) and both concurrent and future language skills (i.e., at 1-year follow-up). Correlations were calculated for the SCT and control groups separately in two age groups (1-year-olds and 3–7-year-olds). Correlations for future language skills were corrected for concurrent language skills.

In the 1-year-old SCT group, a significant correlation was found between looking at the mouth and both receptive and expressive concurrent language scores ($r_{receptive} = .66$, $p < .001$, $r_{expressive} = .65$, $p = .001$); 1-year-old children with SCT who attended more to the mouth of the actress had significantly better concurrent receptive and expressive semantic skills.

No significant correlations were found for future language skills in the 1-year-old SCT group for any of the language outcomes in the 3–7-year-old SCT group, the 1-year-old control group, or the 3–7-year-old control group. Correlations for both the SCT and control groups can be found in Table 2.

Developmental Effects (Aim 4)

The effect of age on the fixation to the eyes and mouth and sensitivity to the differences in gaze direction was explored with PROCESS analyses. For fixation to the eyes and mouth, data were collapsed for the direct and averted gaze directions as previous analyses showed no significant research group × gaze direction interactions. For sensitivity, the $\Delta HR_{sensitivity}$ score was used, with higher scores indicating more sensitivity. In all analyses, research group (SCT and control) was included as an independent variable, age as moderator, and time spent looking at the mouth, eyes, or sensitivity as the dependent variable.

The PROCESS analyses did not yield significant group-by-age interactions for any of the outcome variables. This indicates that differences between children with SCT and controls in time spent looking at the eyes ($t(164) = 0.57$, $p = .570$), time spent looking at the mouth ($t(164) = -0.87$, $p = .384$), or arousal response sensitivity ($t(145) = 1.61$, $p = .110$) are stable across the 1–7 year age range. Visualizations of these results can be found in Supplementary materials (see Supplementary material online, Fig. S1).

DISCUSSION

It is important to gain more knowledge on the broader communicative skills of young children with SCT. Assessments to

Table 2. (Partial) correlations between social orientation and language (concurrent and at 1-year-follow-up) in children with SCT and controls

				1-year-olds				3–7-year-olds		
			N	Face	Eyes	Mouth	*N*	Face	Eyes	Mouth
SCT	Concurrent	RSS	22	0.19	−0.36	0.66**	50	0.12	−0.00	0.06
		ESS		0.21	−0.45	0.65*	51	0.06	0.12	−0.11
	Follow-up[a]	RSS	13	−0.44	−0.47	−0.02	27	0.05	0.23	−0.06
		ESS		−0.22	−0.54	0.32	28	0.02	0.01	−0.00
Control	Concurrent	RSS	24	0.27	0.28	−0.05	62	−0.09	0.05	−0.21
		ESS		0.22	0.24	−0.05	63	−0.16	−0.08	−0.14
	Follow-up[a]	RSS	15	0.14	−0.36	0.25	32	−0.11	−0.35	−0.21
		ESS		0.01	−0.09	−0.09		0.26	0.12	0.13

Notes: RSS = receptive semantic skills; ESS = expressive semantic skills. $^{*}p = .001$. $^{**}p < .001$ (two-sided). [a]Follow-up correlations are partial correlations corrected for concurrent (baseline) language scores.

pinpoint strengths and weaknesses in the overall communicative domain will result in knowledge that could be used for early detection of the broad spectrum of verbal and nonverbal communicative problems and ultimately for the development of tailored and comprehensive intervention programs that focus on the broad spectrum of communication skills. If building blocks in the domain of communication, such as social orientation and arousal regulation, are not adequate in children with SCT, this can have consequences for both the amount and quality of social interactions. Eventually, this could lead to a negative feedback loop, where the social learning opportunities are limited due to inadequate skills. As children with SCT have an increased risk for unfavorable behavioral outcomes, it is important to gain more insight into the early communicative skills of these children. The current study aimed to increase the knowledge of how young children with SCT respond to short periods of communicative interactions (i.e., communicative "bids"). Overall, this study shows that children with SCT appear to attend less to the face, and specifically, the eyes of another person during communicative bids and that the arousal system of children with SCT appears to be less sensitive to differences in gaze directions. In addition, social orientation toward the mouth was correlated to concurrent and future language outcomes at 1-year follow-up in children with SCT.

This study used a dynamic eye tracking paradigm, with an actress that smiles and uses simple speech sounds rather than more complex language to study responses to communicative bids in an ecologically valid way. Previous studies have shown that language and communicative development are among the most affected neurocognitive outcomes in individuals with SCT (e.g., Boada et al., 2009; Urbanus et al., 2019). Diminished social attention already present very early in life may play a significant role in this. This study shows that young children with SCT orient less to social aspects during communicative interactions (i.e., the face). However, this does not seem to be due to increased attention toward objects. Further exploring this reduced attention to social aspects showed that children with SCT orient less to the eyes of another person, however, orientation to the mouth did not differ from controls. This is particularly striking, as attention to the mouth is believed to be adaptive for language learning, and it could be expected that children with SCT, for whom language is a vulnerable domain, would show deviances in looking toward the mouth. Social orientation was modulated by the gaze direction in a similar way to the control group; in other words, children with SCT do not appear to differ in sensitivity to the direction of eye gaze while watching a social scene such as a communicative bid. Taken together, it appears that children with SCT experience difficulties orienting toward social aspects of a scene. This reduced attention may play a role in picking up social signs that are important for an adequate communicative competence. Sensitivity to these social signs, such as eye gaze, is important as it may lead to a heightened receptive state for the upcoming information (Csibra & Gergely, 2009) and to a better understanding of, for example, another person's mental state (Farroni et al., 2002). In other words, the ability to orient to social aspects of a social scene facilitates neurocognitive development. As some children with SCT appear to have difficulties with attending to social cues, this could play a role in the increased risk for neurocognitive and neurobehavioral difficulties that are reported in this population (e.g., Urbanus et al., 2019; Van Rijn, 2019).

When looking at the arousal system, and more specifically to evaluate if children with SCT are able to adapt to situational demands (i.e., direct vs. averted gaze), we observed a different pattern compared to the control group. In the control group, the level of arousal was dependent on the direction of gaze during the communicative bids; in other words, children in the control group modulated their arousal response to the situation. However, this sensitivity to gaze direction, or arousal modulation, was not observed in the SCT group. Based on the results of this study, it can be suggested that the arousal system of children with SCT may respond differently than that of typically developing children. This could imply that children with SCT can depend less on their arousal system as a social "compass" during social interactions. As Porges' theory (2001) states that autonomic responses are an adaptive biobehavioral response strategy to various challenges and that the range of social behavior is limited by the physiological state, this diminished opportunity to rely on a social compass may have consequences for how these children respond and behave during social interactions. It is important to further explore the arousal responses in social situations to gain a better understanding of how the arousal response relates to the outcomes in children with SCT.

In addition to the SCT group as a whole, the role of SCT-specific characteristics was also explored, including SCT karyotype (XXX, XXY, and XYY), time of diagnosis, ascertainment bias, and research site. For none of the studied outcomes of interest (i.e., attention to the face, the eyes, and arousal sensitivity), an effect of these SCT characteristics was found. This suggests that the observed vulnerabilities in social orientation and arousal modulation may represent a rather "stable" vulnerability associated with the genetic variation. It should be noted, however, that results represent the "average" group of children with SCT and that there is always variability in outcomes, where some children are vulnerable, whereas other children will not differ from the control group.

Looking at the eyes and mouth of someone during social interactions may be affected by the age of the child; younger children may focus more on the mouth during language learning, whereas this preferential looking might gradually shift to a preference for looking at the eyes. Also, sensitivity to the differences in gaze directions might differ between younger and older children. For these reasons, the effect of age on group differences in looking times and sensitivity in arousal levels were explored further. No interaction effects were found for either time spent on looking at the eyes, time spent on looking at the mouth, or sensitivity in arousal modulation. These results indicate that, although there might be differences between groups (i.e., children with SCT look less at the eyes), children with SCT do not appear to deviate from the control group more when they get older. This implies a persistent vulnerability across the entire 1–7-year age range, which is not likely the result of learning experiences, but rather a vulnerability in information processing, characteristic of individuals with SCT.

Relations between looking behaviors and language outcomes, both concurrent and 1 year later were explored as well. Within the SCT group, significant correlations were found with both concurrent receptive and concurrent expressive language skills and attention toward the mouth in the youngest age group only; 1-year-old children with SCT with better receptive and/or expressive language abilities looked more at the mouth of the actress. No significant correlations were found for future language skills in this age group, for the 3–7-year-old children with SCT, or the control group. Our results are in part in line with previous studies that found positive correlations between the time spent on looking at the mouth and language skills in young typically developing children or children with neurodevelopmental disorders such as ASD (e.g., Habayeb et al., 2021; Stagg et al., 2014; Tenenbaum et al., 2014, 2015; Young et al., 2009). The strong associations found between language skills and looking at the mouth in young children with SCT illustrate that social orientation and language are intertwined at a very young age. It should be noted, however, that no causal conclusions can be drawn; it remains unclear if more orientation to the mouth is beneficial for language or if children with better language abilities are more able to scan for socially relevant aspects, thus if better language abilities are beneficial for social orientation.

Several factors could contribute to our finding that looking behavior is associated with the language outcome in the youngest age group only, for example, age or developmental effects and the choice of used instruments. For example, when children get older, the variability in cognitive ability gets more pronounced due to the differences in previous experiences and environmental factors, contributing to a wider range of cognitive functioning. As there is also a great variability in both looking behavior and language outcomes, with the latter become also more pronounced in older children (Urbanus, Swaab, Tartaglia, Boada, et al., 2021). In children with SCT, this variability may mask the correlations in the older age group. In addition, with increasing age, typically developing children show a developmental change in orientation to the eyes versus the mouth (Frank et al., 2012). As a result, attention to specific areas of the face may contribute to language learning during specific developmental stages. Our findings fit with the proposition that, with increasing age, attention to the mouth becomes less important for language learning and that, at a certain age, children may have passed this point (Tenenbaum et al., 2014). Lastly, it is possible that correlations were not found in the older age group due to the choices in language tests. Although all used language instruments are reliable and valid tests for receptive and expressive semantic skills, the instruments used in the older age group only capture one specific aspect of semantic language, namely receptive and expressive vocabulary. Not vocabulary, but other aspects of language, for example, pragmatic language skills, may be associated with looking behaviors instead.

When taking the results from the eye tracking and arousal together, the results of this study hint at a reduced ability to understand and/or respond to the social-communicative demands in the environment. In other words, children with SCT might have a broader communication deficit. If children with SCT are less able to adapt to situational demands, this might explain why children with SCT also experience difficulties with language and other aspects of communication (Ross et al., 2008, 2009; St John et al., 2019; Urbanus, Swaab, Tartaglia, Boada, et al., 2021; Urbanus, Swaab, Tartaglia, Stumpel, et al., 2021; Zampini et al., 2018, 2020) and why there are increased reports of social difficulties and social–emotional behavioral problems (Freilinger et al., 2018; Hong & Reiss, 2014; Urbanus et al., 2020; Visootsak & Graham Jr., 2009). This study illustrates that nonverbal communication, which is needed to navigate social communicative interactions, consists of several important aspects and that children with SCT may experience difficulties with at least some of these aspects in areas of social attention and arousal responses.

This study comes with important clinical and scientific implications. Results of this study suggest that the presence of an extra X or Y chromosome may affect the systems involved in social communication, not merely language systems. This is in line with neuroimaging studies that demonstrate the impact of an extra sex chromosome on cortical regions that are part of the "social brain" (e.g., Raznahan et al., 2016). It is recommended that future studies and clinicians take into account the broader domain of communication in addition to structural language outcomes in children with SCT. This should be done from a young age, as both orientation difficulties and reduced arousal modulation were found irrespective of age. In addition, as language develops rapidly at a young age, language difficulties are already present in very young children with SCT, and language and social orientation are highly correlated in young children, results from this study point to an important window of opportunity to target social orientation and language in young children with SCT.

A relative strength of this study was that a large international sample of young children with SCT was included. Within this diverse group, no effect of recruitment site, time of diagnosis, or ascertainment bias was found, indicating that the included sample may be an adequate representation of the population of diagnosed children with SCT. It should be noted that, although there were significant differences in the IQ and SES between the control and SCT groups, IQ and SES were not significantly correlated with our main parameters of interest. This is in line with previous work (Van Rijn et al., 2018), illustrating that the use of eye tracking is a reliable measure to assess the group differences regardless of the level of functioning.

In addition to strengths, some limitations of this study should also be noted. Although eye tracking allows for an ecologically valid way to study looking behaviors, and we used a naturalistic situation, children might respond differently to watching a video as compared to a real-life situation. Although we found reduced attention to the eyes in the SCT group while watching a video clip, we cannot conclude that these children also show reduced attention to the eyes in daily interactions. Also, both the effect of age and the effect of SCT karyotype were assessed separately. Due to the sample sizes, we were not able to look at age-dependent effects within SCT karyotypes, which is an important direction for future studies. Largely due to the worldwide COVID pandemic, we were unable to assess language 1 year after the baseline assessment for some children. Lastly, it should be noted that social norms and what is considered socially appropriate behavior may differ between cultures. For example, in some cultures, maintaining eye contact is considered to be appropriate, whereas in other cultures, this may be considered to be impolite. Similarly, even though language tests were administered in the child's native language and only validated instruments were used, it cannot be excluded that there may be subtle differences between the different versions of the test. Although our findings did not indicate an impact of the inclusion of multiple research sites, it is important to note that native language and culture are interesting factors to keep in mind in international studies. Nonetheless, we strongly recommend more international collaboration to include large cohorts to get a full picture of the neurocognitive and behavioral outcomes of young children with SCT.

Language is a vulnerable domain in children with SCT and language difficulties may become worse when children get older due to the differences in task demands, a phenomenon known as "growing into deficit." As our results indicated strong associations between looking at the mouth and concurrent receptive and expressive language skills in very young children, these results should be replicated in larger cohorts, also including younger children, to pinpoint if better language leads to better orientation or vice versa. As language and social orientation appear to be intertwined specifically at this young age, this could be an important developmental period to target these skills. In addition, within this study, we only looked at the relation between semantic language, and in the older children, only vocabulary and social orientation, whereas other aspects of language, such as syntax or pragmatic language, might also be related to social orientation, particularly in older children (Çetinçelik et al., 2021). As this is one of the first studies on social orientation and autonomic responses in children with SCT, more research is needed. For example, in our paradigm, only simple speech sounds were included, as the use of more complex language might affect how and why children look at, for example, the mouth of the speaker (Brooks & Meltzoff, 2005). However, to fully assess the impact of language on social orientation and to assess the relation between social orientation and language outcomes, future studies could include video clips with different levels of language (e.g., no language, simple speech, and more complex language) to see if the level of language indeed affects how children perceive a social scene. In addition, it would be of interest to examine if the social orientation patterns are predictive of initial autonomic response modulation. Also, in line with Porges' theory (2001), it would be of interest to examine if and how social orientation and autonomic response modulation are predictive of the social–behavioral problems and psychopathology in this group. Although our results did not indicate the differences in average attention to the screen, face, or objects between children who scored below or above the cut-off for ASD diagnostic criteria, it would be of interest to study if the orientation patterns at a young age can predict which children have a greater risk for social difficulties and possibly ASD. Lastly, results showed a diminished arousal modulation, and even though overall arousal levels are relevant and interesting, it does not inform us about the type of emotions that are experienced.

CONCLUSION

To conclude, this study suggests that young children with SCT may have reduced orientation to social cues in response to social communication. In addition, the arousal system of children with SCT may be less sensitive to social cues. Finally, social orientation was related to both concurrent and longitudinal language outcomes. Taken together, these results suggest a potential direction for future work of targeting social communication to support the development of young children with SCT.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

FUNDING

This work was supported by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (grant/award number to SvR: 016.165.397). Work in CO was partially supported by infrastructure of NIH/NCATS Colorado CTSA grant number UL1 TR002535. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors thank the families that participated in our study, the research assistant, and students for their help with data collection and processing, and in particular, Daniëlle Bos for her contributions to the processing of the eye tracking paradigm.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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