The Impact of Sex Chromosome Trisomies (XXX, XXY, XYY) on Social Attention and Affect Recognition: A Cross-Sectional Eye Tracking Study

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Research

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Abstract

Background

About 1:650–1000 children are born with an extra X or Y chromosome (47,XXX; 47,XXY; 47,XYY), which results in a Sex Chromosome Trisomy (SCT). This international cross-sectional study was designed to investigate social attention and affect recognition during early life of children with SCT, with the aim to find indicators for support and treatment.

Methods

A group of 101 children with SCT (aged 1–7 years old; M_{age}= 3.7 years) was included in this study, as well as a population-based sample of 98 children without SCT (M_{age}= 3.7). Social attention was measured using an eye tracking method that quantifies first fixations and fixation durations on eyes of static faces and fixation durations on social information (eyes, faces) in a dynamic paradigm (with two conditions: single face and multiple faces). Affect recognition was measured using the subtest Affect Recognition of the NEPSY-II neuropsychological test battery. Recruitment and assessment took place in the Netherlands and the United States.

Results

Eyetracking results reveal that children with SCT show lower proportions fixation duration on social information already from the age of three years, compared to children without SCT. Also, impairments in the clinical range for affect recognition were found (32.2% of the SCT group scored in the well below average range); these difficulties increase with age.

Conclusions

These results highlight the importance to further explore the development of social cognition skills of children with SCT in a longitudinal design, the monitoring of affect recognition skills, and the implementation of (preventive) interventions aiming to support the development of social attention and affect recognition.

Background

About 1:650 - 1000 children are born with an extra X or Y chromosome, which results in the chromosomal patterns 47,XXY (Klinefelter Syndrome, KS), 47,XXX (Trisomy X or Triple X) or 47,XYY (XYY Syndrome), as compared to the typical 46,XY or 46,XX karyotype in boys and girls. These sex chromosome trisomies (SCT) are caused by a spontaneous nondisjunction of the X or Y chromosome during early cell division, and often not diagnosed (Boyd et al., 2011, Berglund et al., 2019). SCT is being increasingly identified during pregnancy with recent technical advances of non-invasive prenatal screening (i.e. the introduction of the noninvasive prenatal screening test, NIPT). Therefore the opportunity is present to gain insight in the developmental pathways and mechanisms that underlie developmental risks of very young children with SCT, an area of research that has not received much attention so far.

There is wide phenotypic variability among individuals with SCT, with an increased risk of somatic, neurodevelopmental, educational, behavioral, and psychological difficulties during development and in their adult life (Tartaglia et al., 2015). Neurodevelopmental challenges in childhood and adolescence include impairments in language development, social cognition, and executive functioning. Global intellectual functioning within SCT is variable, ranging from impaired to above average, mean intellectual functioning is in the average to low-average range (Urbanus et al., 2020). However, many studies only include adolescents and adults with SCT, and a majority focus on the somatic phenotype (Pieters et al., 2011). Social (cognitive) functioning of individuals with SCT has recently received more attention. Although the social phenotype is variable and varies widely within the SCT group, there is increasing recognition that individuals with SCT have an increased risk for social anxiety, difficulties with social interactions and social adjustment, and impairments in social cognitive abilities (Urbanus et al., 2020, Van Rijn et al., 2014, Van Rijn, 2019). Interestingly, neuroimaging studies in individuals with SCT have shown that the X and Y chromosomes convergently impact brain networks involved in higher-order social cognition (see for a review: Hong & Reiss, 2014). A current study comparing the impact of the extra X- and Y-chromosome on cortical anatomy contribute to our understanding of neural mechanisms that underlie vulnerabilities of individuals with SCT on social cognitive domain, as it was shown that the presence of an extra X- or Y-chromosome effects the maturation of brain areas within the ‘social brain’ network (Raznahan, A., Lee, N. R., Greenstein, D., Wallace, G. L., Blumenthal, J. D., Clasen, L. S., & Giedd, J. N., 2016).

Insights in the development of social cognition help to understand vulnerabilities in social functioning (as described in the SOCIAL model: Beauchamp & Anderson, 2010). Social cognition is defined as the ability to perceive, and understand social signals, and to adequately react in social interactions (Crick & Dodge,1994). These social processing skills are largely independent of other cognitive abilities, such as language, intelligence, and attention (Pinkham et al., 2003). A recent review of the scarce literature on SCT in children (Urbanus et al., 2019) suggests that (although these abilities are not yet fully matured), the development of social cognition, assessed by parent-report and performance-based tests, is already found to be affected from age eight years and older, but was not studied in younger age groups.

Social cognitive functioning results from the dynamic and complex development of brain functions in the first years of life. Depending on genetic factors (such as SCT) and environmental influences, brain areas involved in perceiving and understanding social information mature, and facilitate social cognitive functioning. Difficulties with social cognition impact how children perceive and interact with their environment, which is affected in a broad range of psychopathology, including Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and language disorders, children with SCT show higher percentages of these behavior classifications, compared to their peers (for a review see: Van Rijn, 2019). To gain more insight in to the brain-behavior dynamics it is important to investigate age dependent risk factors during the early development of social cognitive skills. Since social impairments have a great impact on everyday life, an objective study of social cognitive abilities during early development of children with SCT is warranted, and could contribute to the identification of indicators for (preventive) support and treatment.

Social situations are rich in providing large amounts of information that need to be processed simultaneously. These situations trigger social cognitive mechanisms in individuals to select information to be able to respond adequately. Central to this selective cognitive processing of social relevant stimuli is the automatic and spontaneous visual orientation, which is referred to as social attention. Faces are especially important in the social context, as they provide a wealth of socially relevant information, and are therefore important in successful social interactions and adaptive functioning. Already from birth, newborns show an automatic orientation to faces, and highly prefer to attend to face-like patterns (Johnson, 2005b), for a review on eye tracking studies, see Reynolds & Roth, 2018). Studies have shown that eyetracking is a suitable technique to assess developmental changes in different aspects of social attention in young children. Attention to social cues, as measured with eyetracking, is found to be strongly related to the ability to learn from social signals and to develop everyday social behavior (Frank et al., 2019). Even more than other facial characteristics, the eye region is the source of information most used to understand the mental and emotional states of others, and to which we most attend (Itier & Batty, 2009). In young children (and people in general) the preference to orient to social stimuli is largely automatic, and requires little effort (Langton et al., 2000). However, the conscious recognition of emotions on faces of others needs more processing time and other higher-order (neuro)cognitive skills are involved (such as language abilities, Adolphs, 2001). The recognition of affective facial expressions gives the opportunity to detect the emotional states of others, and is therefore important during social interactions (Grossmann & Johnson, 2007). It is believed that impairments in social cognition (such as spontaneous visual orienting toward social cues and face affect recognition) may be one of the key mechanisms underlying social behavioral difficulties found in individuals with SCT (e.g. Van Rijn, 2019).

Indeed, there is evidence that individuals with SCT have attend in a different way to social cues, as compared to individuals without SCT. Eyetracking research in adult men with 47,XXY, and in boys and girls with an extra X-chromosome (47,XXX and 47,XXY) showed shorter fixation durations to eyes as compared to boys and girls without an extra X-chromosome, and no typical tendency to first fixate on the eyes, both during the scanning of static facial expressions (Van Rijn, 2015), and during dynamic presentation of faces in movie clips (Van Rijn et al., 2014). Studies also show that boys and adults with 47,XXY have difficulty with the recognition of facial emotions (Samango-Sprouse et al., 2018, Van Rijn et al., 2018). School-aged children and adolescents with an extra X-chromosome (47,XXX, 47,XXY) also showed impairments in identifying angry facial expressions (Van Rijn et al., 2014). However, to the best of our knowledge, there have been no studies investigating whether these different processes of facial social features and impairments in the recognition of facial expressions also exist in very young children with SCT, and are also present in individuals with 47,XYY. For that reason, the main question of the present study is whether difficulties with social attention and affect recognition are already present very early in life.

Studies of reduced and deferred attention to key social emotional features in young children with other genetic syndromes, as compared to children without genetic variations (e.g. fragile X syndrome, Farzin et al., 2009) and ASD (for reviews: Guillon et al., 2014, Chita-Tegmark, 2016) suggest that differences with typically developing groups in processing social cues are partially determined by the nature of the task stimuli. In order to assess the nuances of social attention in the current study, three considerations were taken into account while constructing the eye tracking paradigms. First, we studied various outcome measures: the basic ability to orient to social stimuli when confronted with a face, and the choice of focal area when presented with social stimuli for a longer period of time. Second, we studied social attention abilities in both static and dynamic paradigms, since it was found that individuals at risk of showing impairments with social attention perform relatively well compared to typically developing peers in tasks that use only static social stimuli, contrasted to tasks with dynamic social stimuli (see for example (Freeth et al., 2010). Last, we used paradigms with both single and multiple faces, as it has been found that social content and complexity of the stimuli is a significant predictor of social attention difficulties and severity of impairments in social adaptation and communication (see for example (Speer et al., 2019).

To summarize, school-age children, adolescents and adults with SCT are at risk of developing difficulties in social cognitive abilities. More specifically, they show differences in directing their attention to socially important cues as compared to individuals without SCT, and impairments in the recognition of facial affect expressions. Unfortunately, studies investigating the early onset and development of these parameters in very young children with SCT do not exist. A thorough investigation of social attention and facial affect recognition skills during different stages of early development could give more insight in the early markers and developmental pathways leading to social and communication difficulties later in life, and has the potential to provide targets for (preventive) support or intervention. In this study we aimed to provide in this. Our research questions were: First, if children with SCT show differences with processing social information as compared to children without SCT, i.e. attend less to socially relevant cues when looking at static faces, and dynamic social scenes. As we were particularly interested in the role of age, we investigated social attention in different age groups (1-2 years old, 3-4.9 years old, 5-7.5 year old). Second, we aimed to investigate whether young children with SCT have difficulties with affect recognition skills compared to their typically developing peers, in different age groups (3-4.9 years old, 5-7.5 years old). For all outcome measures, we investigated the moderating effect of age x group (SCT vs. children without SCT). Lastly, we investigated the role of research site, recruitment bias, and the role of karyotype on social attention and affect recognition. Although many factors are involved in presentation of the SCT phenotype, such as timing of diagnosis, the aim of the current study was to contribute to the understanding of the early phenotype by focusing on the impact of age on social attention and affect recognition, which has remained underexposed so far.

Methods

Participants

The present study is part of a larger ongoing longitudinal study (the TRIXY Early Childhood Study - Leiden the Netherlands), which includes children with SCT and typically developing children aged 1-7,5 years. The TRIXY Early Childhood Study aims to identify neurodevelopmental risk in young children with an extra X or Y chromosome. A group of 100 children with SCT (range 1-7 years old, M_{age}= 3.69, SD = 1.91) was included in this study, as well as a population-based group of 98 children without SCT (42 boys, M_{age}= 3.66, SD = 1.62). Mean age did not significantly differ between groups (t (196) = 0.11, p = .913). The SCT group consisted of 34 girls with 47,XXX (34%), 45 boys with 47,XXY (45%) and 21 boys with 47, XYY (21%). In order to investigate social attention and affect recognition outcomes in different developmental stages in early childhood, the participants were divided in three age groups: children one and two years old (n = 61, M_{age} = 1.47 years, SD_{age} = 0.33, 32 SCT (6 47,XXX, 18 47,XXY, 8 47,XYY), 29 without SCT), children three and four years old (n = 83, M_{age} = 3.88, SD_{age} = 0.58, 40 SCT (13 47,XXX, 19 47,XXY, 8 47,XYY), 43 without SCT), and children five, six and seven years old (n = 54, M_{age} = 5.86, SD_{age} = 0.67, 28 SCT (15 47,XXX, 8 47,XXY, 5 47,XYY), 26 without SCT). To test if the frequencies of SCT types differed across age groups, a χ^2 test was conducted, an no differences were observed (χ^2 (4) = 8.40, p = .078).

Recruitment and assessment took place at two sites: the Trisomy of the X and Y chromosomes (TRIXY) Expert Center the Netherlands, and the eXtraordinary Kids Clinic in Developmental Pediatrics at Children's Hospital Colorado/University of Colorado in the USA. Children in the SCT group were recruited with the help of clinical genetics departments (from the Netherlands, Colorado, and Belgium), as well as through patient-advocacy groups and social media postings. For the SCT group, recruitment bias was assessed, three subgroups were identified: (1) 'Active prospective follow-up', which included families who were actively followed after prenatal diagnosis (51% of the SCT group), (2) 'Information seeking parents', which included families who were actively looking for more information about SCT without having specific concerns about the behavior of their child (29% of the SCT group), and (3) 'Clinically referred cases', which included families seeking professional help based on specific concerns about their child's development (20% of the SCT group).

The diagnosis of SCT was defined by trisomy in at least 80% of the cells, which was confirmed in the study by standard karyotyping. Sixty-seven children were diagnosed prenatally (65.3%, 20 girls with XXX, 32 boys with XXY, 15 boys with XYY), and 33 children postnatally (34.7%, 14 girls with XXX, 13 boys with XXY, 6 boys with XYY). 24 out of 45 boys with 47,XXY received testosterone treatment (53.3%).

Children without SCT were recruited from the western part of the Netherlands, and approached with information brochures about the study. All participants were Dutch (The Netherlands) or English (USA) speaking, had normal or corrected-to-normal vision, and did not have an history of traumatic brain injury. For ethical reasons, children without SCT were not subjected to genetic screening, as these children were meant to be a representation of the general population. As the prevalence of SCT is ~1 in 1000, the risk of having one or more children with SCT in group children without SCT was considered minimal and acceptable.

Eye tracking paradigms

Social attention to eyes. The Static Facial Emotions paradigm consisted of 16 static photographs of cross-cultural actors with an equal distribution of two facial emotions (happy and angry), and of male and female actors (see Figure 1). The photographs were taken from the Karolinska Directed Emotional Faces (KDEF, (Lundqvist et al., 1998). These KDEF pictures have no background, and actors have no visible beards, mustaches, earrings, eyeglasses, or make-up. The photographs were presented to the child, displayed at the center of the screen, in a counterbalanced order. The child was exposed to each picture for 3 s., with a 2 s. inter-item interval during which a attention grabber (i.e. a picture of a toy or animal, together with a sound to grab the child's attention), was presented in one of the four corners of the screen, to prevent for the automatic response to fixate at the center of the screen.

Social attention and social load. The Dynamic Social Information eyetracking paradigm consisted of two natural and dynamic conditions: single face (SF) and multiple faces (MF). Six blocks were included (3 single face, 3 multiple faces) of 15 s. each. The total time of the stimulus set was 90 s. The blocks were presented in an alternate order (i.e. single, multiple, single, multiple, single, multiple). In each block, a video clip was presented to the child. In the single face condition, one face of a child was on the screen, in the multiple faces condition, two or more faces were on the screen (child-child or child-adult). The video clips consisted of subjects with different cultural background, and were extracted from the TV broadcasted series 'Baby Einstein' (Kids2, 2015, see Figure 1). The videos were accompanied by unsynchronized classical instrumental music, and no speech was involved. As this task did not involve language and used age-appropriate stimuli, it was considered to be appropriate for participants in all countries. In a group of non-clinical young children aged 3-7 years, this eye tracking paradigm was found to be significantly predictive of real-life social behaviors, and independent of age, IQ, or gender (Van Rijn et al., 2019).

Eye tracking equipment and procedures

Gaze data within specific areas of interest (AOIs) was collected using the Tobii X2-60 eye tracker (Tobii Technology AB, Danderyd, Sweden), which records the X and Y coordinates of the child's eye position at 60 Hz by using corneal reflection techniques. The computer with eye tracker was placed on a table adapted to the height of the seat, and the child was seated in a car seat at 65 cm viewing distance. A 5-point calibration procedure was used, with successful calibration defined as a maximum calibration error of 1 degree for individual calibration points (i.e. < 1 cm at a distance of 65 cm from the eyetracker). After the calibration procedure, the child was instructed to watch the movie clips and pictures on the computer. The two eye tracking paradigms started with an attention grabber (e.g. a moving picture of an animal, shown on a black background and accompanied by a sound) to direct the attention of the child to the screen.

Only gaze data points with validity code '0' (indicating that high quality data of both eyes was collected) were included in the analysis. Gaze data was processed using Tobii Studio (version 3.2.1), using the Tobii Identification by Velocity Threshold (I-VT) fixation filter. This filter controls for validity of the raw eyetracking data making sure only valid data were used (Olsen, 2012). The 'Dynamic AOI' tool was used to draw AOIs, drawn with a one centimeter margin, to ensure that the AOIs were sufficiently large outside the defining contours to reliably capture the gaze fixation (Hessels et al., 2016). In the Static Facial Emotions paradigm, AOIs were grouped into the category eyes, and for the whole screen, first fixations within the eye AOI, and total fixation duration within the eye AOI were measured, in order to study social attention to eyes. In the Dynamic Social Information paradigm, dynamic AOIs were grouped into the following categories: face and eyes, and for the whole screen, total fixation duration within AOIs were measured in two conditions: Single Face condition (low social load) and Multiple Face condition (high social load). In order to evaluate the amount of nonvalid eye tracking data, the total visit duration toward the whole screen was calculated, divided by the duration of the clip, multiplied by 100, reflecting the percentage of valid data collected during each of the eye tracking tests. For both paradigms, proportions fixation duration were calculated by taking the total fixation duration within the AOI, divided by the total visit duration toward the whole screen of the individual child, multiplied by 100, reflecting the percentage of time children were attending to an AOI. In the facial emotion paradigm, proportions first fixations within the AOI eyes were calculated by taking the number of photographs where participants fixated first on the eyes, divided by the total number of photographs (max = 16).

NEPSY Affect recognition

The Affect Recognition subtest of the Developmental NEuroPSYchological Assessment, second edition (NEPSY-II neuropsychological test battery, Korkman et al., 2007) was designed to assess children's ability to discriminate among common facial emotions from photographs of children, and used in this study to measure task performance of affect recognition skills. The task has been normed with typically developing children aged 3-16 years old, and was administrated in a subsample of the study sample with the age of 3 years and older (n = 138). During the task, participants are required to match faces of different children with different cultural backgrounds who show the same emotional expressions (happy, sad, angry, disgust, fear and neutral). The participant indicates if two expressions are the same or different, determines which two faces have similar expressions, or identifies two children with expressions that match a third child's face. The total raw score range is between 1 and 25, with higher scores reflecting a better ability to recognize facial expressions. Besides raw scores, percentile scores as compared to norms from the general population can be calculated. Dependent upon the spoken language of the child, the Dutch or English norms were used. Percentile scores were labeled as being in the average range (percentile score > 25), the borderline range (11 < percentile score > 25), the below expected level (3 < percentile score > 10), and the well below expected level (percentile score ≤ 2).

Cognitive assessment

To measure global level of intelligence and language three tests were administrated. The Bayley III (subscale cognitive scale (Bayley-III: Bayley Scales of infant and toddler development., 2009) was administered to children with the age of 1-2 years old. In the older children four subtests of the Wechsler Preschool and Primary Scales of Intelligence, 3rd edition (WPPSI-III) were used to estimate global level of intelligence (children aged 3 years: Block Design, Receptive Vocabulary, Information, Object Assembly, children aged 4 years and older: Block Design, Matrix Reasoning, Vocabulary, and Similarities, (Wechsler, 2002). The Peabody Picture Vocabulary Test (PPVT, Dunn & Dunn, 1997) was used to measure receptive language level in children aged 3 years and older.

Study procedures

Assessment took place at various sites (Colorado USA and the Netherlands) either in a quiet room at the University or at home. To standardize the testing environment, the testing set-up and research protocols were identical at all sites. Researchers from Leiden University were responsible for project and data-management (i.e., training and supervision of researchers processing and scoring of data). Administration of cognitive assessment and the NEPSY was performed on a table by trained child psychologists or psychometrists in Dutch or English (dependent on the first language of the child). The eye tracking procedure took place during a separate appointment, within one week after the NEPSY administration. The laptop with the eye tracker was placed in a small tent to standardize the testing environment, and to control for lighting conditions. The child was seated in a car seat in front of the eye tracker. The examiner was seated beside the child (directing Tobii Studio with a remote keyboard) and started the calibration procedure. Eye tracking paradigms were shown in a fixed order (single/multiple faces, facial emotions). Parents were allowed to stay in the room (out of sight) and were asked not to communicate with their child during the procedure.

Data analyses

Statistical Package for the Social Science (SPSS) version 25 was used for statistical analyses. A χ^2 test was used to compare the distribution of karyotypes within the three age groups. Pearson's correlation analyses were used to measure the association between main outcome variables (i.e. social attention and affect recognition) and global cognitive functioning and receptive language abilities. For group wise (SCT vs. children without SCT) comparisons of proportions first fixations, proportions duration fixation within the AOIs in the three age groups, and affect recognition skills in two age groups (M)ANOVAs were used. Pillai's trace was used to assess the multivariate effect. Significant multivariate effects were post-hoc analyzed with univariate ANOVAs to determine the locus of the multivariate effect. The moderating effect of age on social attention and affect recognition outcomes between the SCT and typically developing group was assessed using PROCESS, a bootstrapping, nonparametric resampling procedure (Hayes, 2009). Bootstrapping analysis with 5000 resamples was done to test for a significant moderating effect using the SPSS macro developed by Hayes (2017). Outcome variables and moderator variable (i.e. child's age) were centered. In this analysis, the moderation effect is significant if the 95% bias corrected confidence interval for the moderator effect does not include zero. Influence of karyotype accounting for the effect of age was tested by an MANCOVA. (M)ANOVAs were used to investigate differences between recruitment groups, and influence of research sites was analyzed with independent t-tests. Statistical analyses were performed one-tailed (SCT vs. children without SCT) or two-tailed (influence of karyotype/recruitment bias/research site), and level of significance was set at $p < .05$. In case of significant differences, Cohen's d or partial η2 were used to calculate effect sizes.

Results

Eyetracking: data quality

Social attention to eyes. The Static Facial Emotions paradigm was successfully completed by 181 children (eighteen children were not able to complete the task due to technical issues or fatigue of the child). Valid data were ensured by screening attention to the screen on a stimulus to stimulus basis, and stimuli of <30% attended were omitted from calculation of the average looking time for each individual child. After screening, the total proportion valid on-screen visit duration (averaged across conditions) was 83.3% and did not significantly differ between children with and without SCT, t(179) = -1.10, p = .272. Proportion first fixation and proportion fixation duration to eyes were not correlated to global cognitive functioning (respectively: r = .119, p = .114, r = .143, p = .058). See Table 1 for descriptive statistics for all outcome measures in the SCT and typically developing group.

Social attention and social load. The Dynamic Social Information paradigm was successfully completed by 188 children (eleven children were not able to complete the task due to technical issues or fatigue of the child). Total proportion valid on-screen visit duration (averaged across conditions) was 83.4 % and did not significantly differ between children with and without SCT, t(186) = -0.10, p = .921. Proportion fixation duration to eyes and faces in the Single Face condition were not correlated to global cognitive functioning (AOI face in Single Face condition: r = .062, p = .403, AOI eyes in Single Face condition: r = .104, p = .161) Similar, proportion fixation duration to faces in Multiple Faces condition was not correlated with global cognitive functioning: r = .111, p = .135). However, proportion fixation duration to eyes in the Multiple Faces condition was related to global intellectual functioning, r = .169, p = .022. See Table 1 for descriptive statistics for all outcome measures in the SCT and typically developing group.

Social attention to eyes: age dependent group differences

Proportions of first fixations on eyes. Age dependent SCT vs. typically developing group differences in first tendency to look at eyes were analyzed, when presented with static photographs of faces. Three separate ANOVAs in the three age groups were carried out with two groups (SCT vs. children without SCT) on proportions of faces where participants first fixated on the eyes. No significant effects of group (SCT vs. children without SCT) were found in the 1-2 years-old group (F(1,49 = 0.169, p = .342), and the 3-5 years old group (F(1,74) = 0.479, p = .246). A borderline group effect (SCT vs. children without SCT) was found in the 5-7 years old group (F(1,52) = 2.288, p = .068). See Table 2 for *M,* and *SDs.*

To test for a moderating effect of child's age on proportions of first fixations on eyes between children with and without SCT, bias-corrected bootstrapping analyses (PROCESS) were conducted. No significant moderation effect of child's age was found (b = 0.01, *SE =* 0.02, t = 0.57, p =.571, 95% CI [-0.03, 0.05]).

Proportions of fixations duration on eyes. Age dependent SCT vs. typically developing group differences in social attention were analyzed, when presented with static faces: three separate ANOVAs with two groups (SCT vs. children without SCT) were carried out on proportions of fixation duration to eyes. In the 1-2 years-old age group, no significant effect of group (SCT vs. children without SCT) was found on the proportions of fixation duration, F(1,49) = 0.771, p = .192. Also, in the 3-5 years-olds, no significant effect of group (SCT vs. children without SCT) was found on the proportions of fixation duration, F(1,74) = 0.314, p = .289. However, in the 5-7 year-olds, a significant effect of group (SCT vs. children without SCT) was found on the proportions of fixations duration for the AOI eyes (F(1,51) = 4.925, p = .016, η_p^2= .09): the SCT group spent less time fixating on eyes, compared to their typically developing peers. See Table 2 for *M* and *SDs.*

Bias-corrected bootstrapping analyses (PROCESS) were conducted to test for a moderating effect of child's age on proportions of fixation durations on eyes between children with and without SCT. A trend towards significance was found: b = 0.03, *SE =* 0.02, t = 1.78, p =.077, 95% CI [-0.003, 0.06].

Social attention and social load: age dependent group differences

Proportions of fixation duration on eyes and faces. Within each age group, differences in social attention with one single face (low social load, Single Face condition) and multiple faces (high social load, Multiple Faces condition) were analyzed with three separate MANOVAs, using Pillai's trace. Descriptive statistics can be found in Table 3. In the 1-2 year-olds, there was no significant effect of group (SCT vs. children without SCT) on the proportions of fixation duration for the AOIs in both the SF and MF condition, F(4,52) = 0.439, p = .390. In the 3-5 year-old age group, a significant effect of group (SCT vs. children without SCT) was found, F(4,72) = 2.782, p = .017, η_p^2 = .13. Post-hoc ANOVA tests on the outcome variables revealed a significant group effect with a medium effect size on the proportions of fixation duration for AOI face in the SF condition such that the SCT group spent less time fixating on the face when compared to their typically developing peers. In the 5-7 year-olds, a significant effect of group was found (SCT vs. children without SCT), F(4,49) = 2.165, p = .044, η_p^2= .15. Post-hoc ANOVA tests on the outcome variables revealed significant group effects on the proportions of fixation duration for AOI face and AOI eyes in the MF condition with a medium effect size, revealing that the SCT group spent less time fixating on faces and eyes, when compared to children without SCT.

To test for a moderating effect of child's age on proportions fixation duration for the AOIs face and eyes in both conditions (Single Face/Multiple Faces) between children with and without SCT, bias-corrected bootstrapping analyses (PROCESS) were conducted. No moderating effect of age was found on the difference between the SCT group and children without SCT for the AOIs face and eyes in both conditions. See Table 3 for exact b-, t-, and p-values.

Facial Affect recognition: age dependent group differences

The NEPSY Affection recognition task was administered only in the group of children aged 3 years and older (n = 138). Eight children were not able to finish the NEPSY Affect recognition task (total n = 130, 61 SCT (26 children with 47, XXX, 26 children with 47, XXY, 9 children with 47,XYY), 69 without SCT). Affect recognition scores were not correlated to global cognitive functioning (r = .162, p = .071), but were correlated to respective language skills (r = .604, p <.001). See Table 1 for descriptive statistics of all outcome variables for both the SCT and typically developing group.

Within the two age groups (3-5, 5-7), differences in affect recognition were analyzed with two separate ANOVAs. Differences between the SCT group and their typically developing peers were found in both age group, see Table 4 for exact *M, SD*s, p-values, and effect sizes. When evaluating scores normalized for age, for affect recognition in the SCT group 54.2% scored in the average level, 5.1% in the borderline range, 8.5% scored in the below expected level, and 32.2% in the well below expected level.

Bias-corrected bootstrapping analyses (PROCESS) were conducted to test for a moderating effect of child's age on the difference in affect recognition skills between children with and without SCT. There was a significant moderation effect of child's age (b = 1.96, *SE* = 0.51, *t* = 4.09, *p* <.001, 95% CI [1.01, 2.91]), revealing that the difference on affect recognition skills between the SCT group and their typically developing peers increases with age (not in favor of children with SCT). R^2 = .61, indicating that this model explained 61% of the variance in affect recognition skills. The significant effect of group on affect recognition skills remains, even when receptive language skills were added as covariate (b = 1.47, *SE* = 0.51, *p* = .005, 95% CI [0.45, 2.48], R^2 = .62). See Figure 2 for a graphical representation of affect recognition and age in the SCT group and the typically developing group.

Karyotype differences within the SCT group

In order to investigate the influence of various karyotypes on social attention and affect recognition taking into account the effect of age, MANCOVAs were carried out with main effect of karyotype (XXX vs. XXY vs. XYY), and age as covariate. No differences between karyotypes were found for all eyetracking outcome measures. A significant difference between karyotypes was found for affect recognition (XXY < XXX), when age was accounted for and kept constant. See Table 5 for Estimated Marginal Means, and *p*-values, post-hoc effects and effect sizes.

Recruitment bias within the SCT group

Within the SCT group we tested with MANOVA for differences on social attention and ANOVA for difference on affect recognition between the three recruitment groups (A: prospective follow-up, B: information seeking parents, and C: clinically referred cases group). Differences between recruitment groups were only analyzed in the study measures in which a difference was found between children with and without SCT. There were no significant differences for study outcomes between the recruitment groups (except for proportions fixation duration on faces in the dynamic social information paradigm, single faces). See Table 6 for means, exact *p*-values, post-hoc effects and effect sizes.

The role of research site

To control for the potential impact of research site on outcomes of the study, the data of the two research sites were compared. Comparing the outcome measures in the SCT group between both research sites (the Netherlands vs. USA), revealed a consistent pattern of results, indicating that none of the eye movement measures showed significant differences between research sites (see Table 7). However, a significant difference between research sites was found for affect recognition skills: children in the USA had lower affect recognition scores (*M*=13.11, *SD*=4.81), compared to children in the Netherlands (*M*=10.65, *SD*=3.90, *p* =.037, Cohen's *d* = 0.56).

Discussion

This study aimed to investigate age dependent social attention and affect recognition vulnerabilities in very young children with sex chromosome trisomies (SCT) aged 1-7.5 years. Key outcomes of the study include differences in automatically orienting and holding attention to socially important information between children with and without SCT, suggesting that young children with SCT are less inclined to automatically orient towards social information. These difficulties with attending to social information were most pronounced in children aged three years and older, and when the social load of stimuli was high. Also affect recognition impairments were found, with on average 32.2% of the group children with SCT scored in the well below expected range.

First of all, we explored with the help of eyetracking measures attention to eyes on static faces, and attention to eyes and faces in dynamic social scenes with low (i.e. single face) and high social load (i.e. multiple faces). Age specific analyses showed that 1-2 years old children with SCT showed no different tendency to initially fixate on the eyes, when presented with a face. Also, when presented with dynamic social interactions, the results revealed no differences in social attention between 1-2 years-olds with and without SCT (i.e. displayed no shorter fixation duration to eyes nor to face). However, in the 3-5 year-old group we did find differences between the children with SCT and typically developing children: children with SCT were less inclined to fixate their attention on faces when looking at dynamic social stimuli with a single face, although percentages of first fixation to the eye region of static faces were similar to 3-5 year-olds without SCT. These results suggest that children with SCT aged 3-5 years assess static facial emotions as fast as their typically developing peers, but are less consistent in their choice of focal area when presented with dynamic social stimuli with one single face.

Moreover, 5-7 year-olds with SCT showed lower fixation duration on eyes compared to typically developing children, when presented with static faces. In addition, children with SCT aged 5-7 years-old fixated less on socially important information (both faces and eyes) when presented with dynamic social stimuli with multiple faces. This pattern of findings among 5-7 year-olds with SCT shows that impairments of attention to social stimuli occur as a function of the amount of social information: if the load of socially relevant and dynamic information is high (multiple faces), children with SCT deviate their attention from central and important social information (i.e. eyes and faces).

Taken together, these eyetracking results reveal that children with SCT generally are less inclined to automatically orient their attention at relevant social-emotional information (i.e. eyes and faces), compared to typically developing children from preschool age on. Research has shown that typically developing children preferentially attend to social stimuli, beginning as early as infancy. Furthermore, high social content typically increases attention of children towards the eyes and faces (Birmingham et al., 2008). However, our results suggest that, on average, very young children with SCT, on average, have difficulties with attention to social cues, with more impairments when presented with high social load as compared to low social load, and more impairments in children of older age, as compared with their typically developing peers.

Reduced attention to socially meaningful and complex stimuli already during early development, and more pronounced social attention deficits if the amount of social information is high, may have substantial impact on the fundamentals of social learning. Reduced social attention may lead to limited quantitative and qualitative opportunities to acquire social knowledge in children with SCT, and to learn from (complex) social interactions (Mundy & Neal, 2001). Attending to another person's face and eyes allows typically developing children to have rich social experiences that are crucial for the development of social and communicative abilities, such as joint attention, language acquisition, and face or affect recognition (Gliga & Csibra, 2007). Consequently, avoidance of the eyes and faces of others may have a broad impact on the complex maturation of social (cognitive) abilities, which are built upon basic social-perceptual information. Earlier studies also reported social attention deficits in adult men with an extra X-chromosome (Van Rijn et al., 2014, Van Rijn, 2015). These adult studies might represent the cumulative effects of long-term atypical attention to socially important information, whereas the results of the current study suggest a developmental pathway in which profiles of impairments are emerging during early childhood.

Although such longitudinal relations between social attention and more complex social processing abilities not being assessed in this study, we did investigate age dependent affect recognition skills in very young children with SCT, between the ages of 3-7.5 years. First, a difference was found for affect recognition abilities between children with and without SCT from the age of 3 years old, indicating deficits in young children with SCT. Next, when age was considered, analyses revealed a moderating effect of age. This effect was independent of receptive language skills. Although the current study had a cross-sectional design, the moderating effect of age on affect recognition skills indicated that as the age of children increases, the difference between children with SCT and their typically developing peers enlarges, with more difficulties in older children with SCT. Earlier studies also found impairments with affect recognition in school-aged children and adolescents with SCT, in both parent report of individuals with SCT (Ross et al., 2012, Cordeiro et al., 2012, Van Rijn et al., 2014) and direct assessment of individuals with an extra X-chromosome (Van Rijn et al., 2018, Samango-Sprouse et al., 2018, Van Rijn et al., 2014). Percentages of young children with SCT that scored in the clinical range in the current study (32.8% on average) are comparable with earlier research in older individuals with an extra X-chromosome, and add to the literature that clinically significant deficits already arise early in development, and can also be found in boys with 47,XYY.

A difference between research sites was found for affect recognition abilities in children with SCT, which may suggest that cultural and social factors can be related to emotional processing. Although we acknowledge that cultural differences may contribute to some of the variance in the outcome, we are confident that this is not relevant for the systematic group differences between the SCT and typically developing group that we found in the current study. Further research could study the influence of ethnicity, cultural differences, and family environment on affect recognition abilities in children with SCT. As no differences between research sites were found for study outcomes measured with eyetracking methods, we suggest to use eyetracking methods in international studies aimed to measure the influence of culture on emotion processing.

When exploring the influence of specific karyotype (XXX, XXY, XYY) on social attention and affect recognition, accounting for the effect of age, results showed that for the majority of social cognitive measures no significant differences between the karyotypes were found. However, for affect recognition boys with 47,XXY showed the be more vulnerable as compared to some of the other SCT karyotypes (see Table 5). These results suggest that although social attention and affect recognition were impaired in all karyotypes and older children with SCT had more difficulties than younger children, boys with XXY may be more vulnerable in their ability to recognize facial affects than other SCT karyotypes.

The phenomenon of an increasing deviation of abilities compared to typical developing peers as found in the current study for affect recognition skills (but not for social attention), is often seen during the development of children with genetic syndromes and neurodevelopmental disorders. This concept is referred to as 'growing into deficit' (Rourke et al., 2007, Sprong, 2008). Effects of chromosomal trisomies often become more apparent later on in development, when a child is faced with developmental tasks and when compromised development of the brain leads to an increasing discrepancy with the age-required norms. It is therefore important that affect recognition skills are included in standard neuropsychological assessment from the age of three years old, in addition to assessments of language and learning difficulties, to allow for close monitoring in children with SCT. Sensitive developmental periods also serve as key windows of opportunity, and early implementation of (preventive) support and intervention programs on social attention and affect recognition skills have the potential to reduce risk for social and communication impairments, and to optimize quality of life.

Regarding possible bias of recruitment on the outcomes variables, affect recognition and social attention (except for one social attention parameter) were not dependent on recruitment strategy, i.e. prospective follow-up group, information seeking parents group, or clinically referred cases group. These findings suggests that the outcomes of this study are representative for this group of diagnosed children with SCT as a whole. However, it remains unsure to what degree the findings in this study can be generalized to those who have SCT, but remain undiagnosed (see for example: Berglund et al. (2019) for estimated proportions of underdiagnosing in SCT).

Limitations of the current study include the cross-sectional design that limits cause-effect conclusions. Future studies should focus on the longitudinal development of social attention in children with SCT, and the impact of altered attention to social information on affect recognition and other social (cognitive) functions (e.g. Theory of Mind). In this study, we only focused on social attention to faces with affective expressions of basic emotions, as these convey a high load of social information, more so than neutral faces. Based on our findings, it would be interesting to learn more about the impact of SCT on the scanning of faces in general. Future research should also address the questions whether intervention programs targeting the early development of affect recognition skills are effective in improving these skills and if so, whether interventions lead to improved social behavioral outcomes. As it was beyond the scope of this study to investigate the influence of testosterone treatment in boys with 47,XXY, future studies with suitable designs (e.g. Randomized Control Trials) should study these parameters in relation to general social cognitive functioning in children with SCT.

Conclusion

In conclusion, the overall results of this study indicate that young children with SCT (on average) have difficulties automatically orienting their attention and holding their attention to socially important information, especially when social load of stimuli is high. Social attention difficulties were found in children with SCT aged 3 and older. In addition, impairments in facial affect recognition skills were found, with 32.8% of the SCT children scoring in the clinical range. This calls for a focus on the monitoring of social cognitive functioning from an early age onwards in SCT. *These findings also* highlight the importance of further exploring the developmental pathway of social attention in children with SCT in studies with a longitudinal design that allows for more understanding of the predictive value of these social cognitive skills for social behavioral difficulties and psychopathology, and the implementation of (preventive) early interventions aiming to support social cognition, to positively influence developmental outcomes in children with SCT.

Abbreviations

SCT = Sex Chromosome Trisomies; AOI = Area of Interest

Declarations

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Ethical approval and consent to participate

This study was approved by the Ethical Committee of Leiden University Medical Center, the Netherlands, and the Colorado Multiple Institutional Review Board (COMIRB) in Colorado, USA. Signed informed consent was obtained from the parents of all participating children, according to the declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the present study are not publicly available due to confidentiality constraints within our ethical approvals.

Authors' contributions

N.B.: design, recruitment of participants, acquisition of data, analysis, interpretation of the data, drafting. H.S.: conception, design, and final-approval of the manuscript. N.T.: recruitment of participants, and final-approval of the manuscript. L.C.: recruitment of participants, acquisition of the data, revising the article, and final-approval of the manuscript. S. van R.: conception, design, interpretation of the data, and final-approval of the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Tables

Table 1. *Descriptive statistics for SCT and TD group.*

	Age group	*N*	Missing	Condition	SCT		TD	
					Min-Max	*M (SD)*	Min-Max	*M (SD)*
Cognitive development *Norm score, Bayley-III*	1-2 year	60	1		80-125	100.39 (12.18)	72-129	99.48 (14.32)
Total IQ *WPPSI-III*	3-7 years	131	7		55-138	95.48 (19.88)	72-140	109.01 (13.27)
Receptive language *Standard score, PPVT-III*	3-7 years	135	3		65-129	99.26 (14.94)	74-133	108.67 (12.44)
Social Attention to eyes *Proportions first fixations*	1-7 years	181	18		.00 - .1.00	.58 (.24)	.00 - .1.00	.63 (.27)
Social Attention to eyes *Proportions fixation duration*	1-7 years	181	18		.00 - .69	.32 (.17)	.00 - .73	.35 (.20)
Social Attention: social load *Proportions fixation duration*	1-7 years	188	11	SF: face	.01-.79	.46 (.17)	.04 - .83	.51 (.19)
				SF: eyes	.00 - .59	.21 (.13)	.00 -.61	.23 (.15)
				MF: faces	.04 - .79	.51 (.16)	.04 -.80	.57 (.19)
				MF: eyes	.00 - .45	.14 (.11)	.00 - .57	.18 (.13)
Affect recognition *Raw score, NEPSY-II*	3-7 years	130	8		1-23	12.07 (4.58)	1-23	13.64 (4.86)

Notes: SCT = Sex Chromosome Trisomy, TD = Typically Developing, SF = single face, MF = multiple faces.

Table 2. *Social attention to eyes (proportions first fixations, proportions fixation durations) on static photographs in three age groups.*

	Phases of development											
	-	**1, 2 years old** (*n* = 51: 24 SCT, 27 TD)			**3, 4 years old** (*n* = 76: 34 SCT, 42 TD)			**5, 6, 7 years old** (*n* = 54: 28 SCT, 26 TD)				
Social attention to eyes	**AOI**	SCT *M (SD)*	TD *M (SD)*	*p*-value	SCT *M (SD)*	TD *M (SD)*	*p*-value	SCT *M (SD)*	TD *M (SD)*	*p*-value	Post-hoc effect	Effect size (η_p^2)
Proportion first fixation	Eyes	.51 (.26)	.53 (.26)	.342	.60 (.24)	.65 (.29)	.246	.62 (.23)	.71 (.22)	.068		
Proportion fixation durations	Eyes	.35 (.19)	.30 (.22)	.192	.35 (.17)	.38 (.20)	.289	.28 (.14)	.38 (.17)	.016	SCT < TD	.09

Notes: SCT = Sex Chromosome Trisomies, TD = Typically Developing.

Table 3. *Social attention and social load: proportions fixation duration on eyes and faces in two conditions (low social load - single face, high social load - multiples face): outcomes in three age groups and moderated effect of age.*

	Phases of development															**Interaction effect (age x group)**			
	-	**1,2 years old** (*N* = 57: 30 SCT, 27 TD)			**3,4 years old** (*N* = 77: 35 SCT, 42 TD)					**5,6,7 years old** (*N* = 54: 28 SCT, 26 TD)									
	AOI	SCT *M (SD)*	TD *M (SD)*	*p*-value	SCT *M (SD)*	TD *M (SD)*	*p*-value	Post-hoc effect	Effect size (part. η^2)	SCT *M (SD)*	TD *M (SD)*	*p*-value	Post-hoc effect	Effect size (η_p^2)	b	se	*t*	[illegible]
Single Face	**Face**	.52 (.17)	.57 (.21)	.132	.45 (.16)	.54 (.16)	.009	SCT < TD	.07	.40 (.16)	.40 (.15)	.458			-.02	.01	-1.23	[illegible]
	Eyes	.20 (.14)	.20 (.16)	.474	.22 (.14)	.26 (.15)	.142			.20 (.12)	.22 (.10)	.225			.005	.01	0.45	[illegible]
Multiple Faces	**Faces**	.56 (.15)	.60 (.21)	.172	.53 (.14)	.57 (.18)	.124			.43 (.18)	.52 (.17)	.029	SCT < TD	.07	.002	.01	0.14	[illegible]
	Eyes	.13 (.11)	.13 (.13)	.437	.16 (.12)	.20 (.13)	.074			.14 (.09)	.19 (.13)	.033	SCT < TD	.06	.01	.01	1.09	[illegible]

Notes: SCT = Sex Chromosome Trisomies, TD = Typically Developing, AOI = Area of Interest

Table 4. *Affect recognition in SCT vs. TD group and age groups.*

	Phases of development									
	3, 4 years old (*n* = 76: 33 SCT, 43 TD)					**5, 6, 7 years old** (*n* = 54: 28 SCT, 24 TD)				
	SCT *M (SD)*	TD *M (SD)*	*p*-value	Post-hoc effect	Effect size (part. η^2)	SCT *M (SD)*	TD *M (SD)*	*p*-value	Post-hoc effect	Effect size (η_p^2)
Affect recognition scores	9.30 (3.25)	10.65 (3.18)	.037	SCT < TD	.04	15.32 (3.71)	18.58 (2.56)	<.001	SCT < TD	.21

Notes: SCT = Sex Chromosome Trisomies, TD = Typically Developing.

Table 5. *Differences between karyotypes on social attention and affect recognition accounted for age (EMM (SE)).*

			47,XXX	47,XXY	47,XYY	*p*-value	Post-hoc effect	Effect size (η_p^2)
Social Attention	**Condition**	**AOI**	*n* = 30	*n* = 41	*n* = 15			
Social Attention to eyes *Proportions first fixations*		Eyes	.60 (.05)	.69 (.05)	.49 (.08)	.074		
Social Attention to eyes *Proportions fixation duration*		Eyes	.29 (.03)	.40 (.03)	.30 (.05)	.056		
Social attention: social load *Proportions fixation duration*	Single Faces	Faces	.46(.03)	.45 (.03)	.40 (.05)	.547		
		Eyes	.22 (.03)	.25 (.03)	.17 (.04)	.284		
	Multiple Faces	Faces	.51 (.03)	.51 (.03)	.40 (.06)	.223		
		Eyes	.17 (.02)	.18 (.02)	.09 (.04)	.107		
NEPSY Affect Recognition			*n* = 28	*n* = 19	*n* = 14			
Raw score			13.56 (.67)	10.55 (.69)	11.98 (1.12)	.011	XXY<XXX	.14

Notes: EMM = Estimated Marginal Means, AOI = Area of Interest.

Table 6. *Differences in social attention and affect recognition across SCT recruitment groups* (*M, SD*).

			Prospective follow-up (A)	Information seeking parents (B)	Clinically referred cases (C)	*p*-value	Post-hoc effect	Effect size (η_p^2)
Social Attention	**Condition**	**AOI**	*n* = 41	*n* = 25	*n* = 18			
Social Attention to eyes *Proportions fixation duration*		Eyes	.32 (.17)	.35 (.19)	.33 (.15)	.851		
Social Attention and social load *Proportions fixation duration*	Single Faces	Faces	.42 (.17)	.52 (.15)	.44 (.14)	.032	A < B	0.12
	Multiple Faces	Faces	.47 (.18)	.57 (.14)	.51 (.14)	.080		
		Eyes	.12 (.11)	.18 (.12)	.16 (.10)	.117		
Affect Recognition			*n* = 28	*n* = 19	*n* = 14			
Raw scores			11.14 (4.55)	12.21 (4.69)	13.71 (4.30)	.229		

Notes: SCT = Sex Chromosome Trisomy, AOI = Area of Interest

Table 7. *Impact of research site on social attention and affect recognition in the SCT group.*

	Condition	The Netherlands *M (SD)*	USA *M (SD)*	*t*-value	*p*-value
Social Attention to eyes *Proportions first fixations*		.61 (.22)	.55 (.26)	1.05	.296
Social Attention to eyes *Proportions fixation duration*		.32 (.16)	.32 (.19)	0.14	.887
Social Attention: social load *Proportions fixation duration*	SF: face	.43 (.16)	.48 (.17)	1.46	.147
	SF: eyes	.21 (.13)	.20 (.13)	0.22	.823
	MF: faces	.50 (.18)	.52 (.15)	0.61	.545
	MF: eyes	.15 (.11)	.13 (.10)	0.92	.361
Affect Recognition *Raw scores*		13.11 (.4.81)	10.65 (3.90)	2.14	.037

Figures

Figure 1

Examples of photographs in the Static facial emotions paradigm: (1) happy face, (2) angry face (taken from KDEF, Lundqvist et al. 1998), and screenshots of videoclips in the Dynamic social information paradigm: (3) single face, (4) multiple faces.

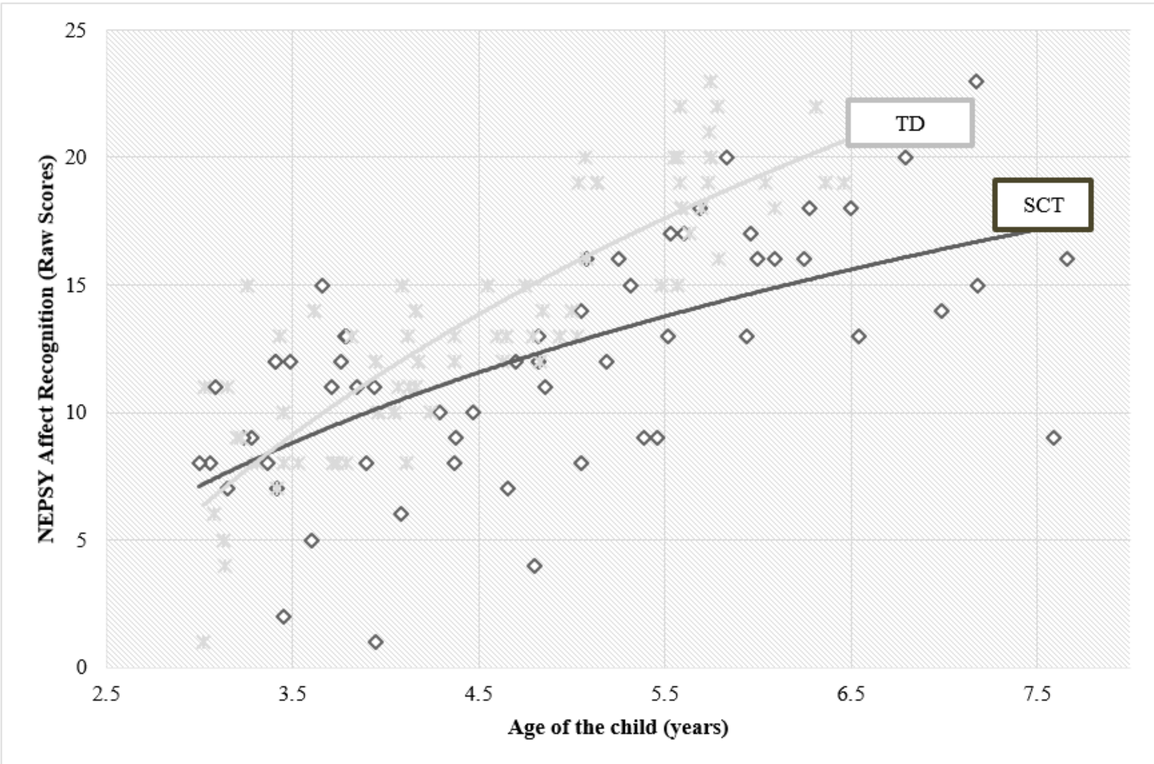

Figure 2

Affect recognition and age in young children with Sex Chromosome Trisomies (SCT) and typically developing peers (TD).