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Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: a comparison with autism spectrum disorder

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Individuals with an extra X chromosome are at increased risk for autism symptoms. This study is the first to assess theory of mind and facial affect labeling in children with an extra X chromosome. Forty-six children with an extra X chromosome (29 boys with Klinefelter syndrome and 17 girls with Trisomy X), 56 children with autism spectrum disorder (ASD) and 88 non-clinical controls, aged 9–18 years, were included. Similar to children with ASD, children with an extra X chromosome showed significant impairments in social cognition. Regression analyses showed that different cognitive functions predicted social cognitive skills in the extra X and ASD groups. The social cognitive deficits were similar for boys and girls with an extra X chromosome, and not specific for a subgroup with high Autism Diagnostic Interview Revised autism scores. Thus, children with an extra X chromosome show social cognitive deficits, which may contribute to social dysfunction, not only in children showing a developmental pattern that is 'typical' for autism but also in those showing mild or late presenting autism symptoms. Our findings may also help explain variance in type of social deficit: children may show similar social difficulties, but these may arise as a consequence of different underlying information processing deficits.

Keywords: Autism, facial expressions, Klinefelter, theory of mind, Trisomy X

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Our understanding of gene–brain–behavior pathways underlying severe social dysfunctioning in childhood is almost exclusively derived from studies in autism spectrum disorders (ASDs). The autism spectrum refers to a heterogeneous group of individuals who share difficulties in social competence, communication problems and rigid behaviors. In the search for specific, different pathways to social dysfunctioning early in life, we may expand our scope to children with severe social difficulties because of a genetic disorder. Starting at the genotype, rather than the behavioral phenotype, may provide unique insights in mechanisms of social development, beyond what we have learned from studies on ASD. One of the genetic syndromes of interest is the group of children with an extra X chromosome, known as 'Klinefelter syndrome' in boys (47,XXY chromosomal pattern) and 'Trisomy X' in girls (47,XXX chromosomal pattern). Approximately 1–2 in 1000 children are born with an extra X chromosome.

The reported social behavioral difficulties in individuals with an extra X chromosome include shyness, social withdrawal, social anxiety, social immaturity, difficulties in peer relationships, social impulsivity, communication difficulties, reduced social assertiveness and difficulties with 'being sensitive and responsive to the feelings and rights of others' (Bender *et al.* 1999; Bishop *et al.* 2011; Boone *et al.* 2001; Geschwind & Dykens 2004; Harmon *et al.* 1998; Ratcliffe 1999; Ratcliffe *et al.* 1991; van Rijn *et al.* 2006, 2008; Robinson *et al.* 1991; Stewart *et al.* 1991; Tartaglia *et al.* 2010a, 2010b; Visootsak & Graham 2009; van 't Wout *et al.* 2009). The severity of social difficulties is illustrated by an overall level of autism traits that may be up to 2.2 standard deviations (SDs) above mean in a non-clinical group (van Rijn *et al.* 2008). From a dichotomous point of view, a reported 11–27% of the individuals score above clinical threshold for ASD (Bishop *et al.* 2011; Bruining *et al.* 2009; Cordeiro *et al.* 2012; van Rijn *et al.* 2014; Ross *et al.* 2012).

In order to gain more insight in the gene–brain-behavior relations, it is important to dissect neurocognitive dysfunctions that mediate between the genetic level and the behavioral level. The risks in social development call for the study of cognitive functions involved in social information processing. The importance of social cognition is also stressed in the SOCIAL model of Beauchamp and Anderson (2010), which offers a neuropsychological framework for the underlying mechanisms of social functioning. There are three reports on social cognition in individuals with an extra X chromosome, which show difficulties in reading social signals from others such as facial expressions (van Rijn *et al.* 2006), gaze direction (van 't Wout *et al.* 2009) and tone of voice (van Rijn *et al.* 2007). However, all the three studies included

adult men; so far, there are no studies on social cognition in children with an extra X, and there are no studies on social cognition in girls or women with an extra X chromosome. This study aims to provide in this and focuses on theory of mind (ToM) and facial affect recognition, i.e. core aspects of social cognition (Adolphs 2003), in boys and girls with an extra X chromosome, when compared with children with ASD. We also assessed to what degree cognitive functions in areas of language, gestalt closure, face processing, intellectual functioning and executive functioning contribute to ToM, in order to address the question whether deficits in attributing mental states are related to different or similar information processing impairments in children with an extra X and children with ASD.

Methods

Participants

In total, 46 children (29 boys and 17 girls) with an extra X chromosome, 56 children (45 boys and 11 girls) with an ASD and 88 non-clinical controls (41 boys and 47 girls) participated in this study. The participants were 9–18 years old. The group of children with an extra X chromosome consisted of two subgroups. The first group included children from those families that were actively followed up after prenatal diagnosis with the help of clinical genetics departments. These departments of academic medical centers in the Netherlands and Belgium screened their databases for families who had received a prenatal diagnosis of Klinefelter syndrome or Trisomy X. Individuals in this group were considered 'prenatal follow-up' cases and constituted 48.9% of the extra X group. The second group included children from those families that were actively seeking information about the condition of their child (recruited through support groups and calls for participants) and those who were seeking help for developmental problems (recruited through pediatricians, psychologists, psychiatrists, clinical genetics departments). These were considered 'referred' cases and constituted 51.1% of the total extra X group. Diagnosis of Klinefelter syndrome and Trisomy X was confirmed by standard karyotyping, all had non-mosaic kayotypes. In the group of boys, 23.9% used testosterone supplements.

The ASD group was recruited from a child psychiatric outpatient department (Centrum Autisme Rivierduinen), serving a large region in the Netherlands. All children with ASD were classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association 1994) and were high functioning. The clinical procedures for diagnosis of ASD included questionnaires for parents, an interview with parents, developmental history and family history, information from treating physicians and extensive expert clinical observations. Consensus regarding the diagnostic classification of ASD had to be reached by board-certified child psychiatrists (with experience in the field of autism) and by a consensus meeting with a multidisciplinary team. Five out of 56 children with ASD were receiving psychopharmacological treatment.

Controls from the general population were recruited from schools distributed across the western part of the Netherlands. Children in the control group were screened for psychopathology: none scored in the clinical range (≥70) on the Childhood Behavior Checklist (CBCL) (Achenbach 1991). Inclusion criteria for all the participants were Dutch as the primary language and an age between 9 and 18 years. Exclusion criteria were a recent history of substance abuse, intellectual disability (<60 IQ points) and neurological conditions. After providing a complete description of the study to the subjects and to their parents, we obtained written informed consent according to the Declaration of Helsinki. The study was approved by the Ethical Committee of Leiden University Medical Center, the Netherlands.

A chi-squared test indicated a significant difference (at $P < 0.001$) in the sex distributions between the groups: this could be attributed to a lower number of girls in the ASD group than in the other groups. Multivariate analysis of variance (MANOVA) with the fixed factor group (control, XXY, ASD) and the dependent variables age, IQ and parental education showed no significant main effect of group for age and parental education. However, there was a main effect of group for IQ ($F_{2,187} = 23.0$, $P < 0.001$). *Post hoc* least significant difference tests indicated that this was driven by a significantly lower mean IQ in the extra X group when compared with both the control and the ASD group. Table 1 provides an overview of these variables.

Autism symptoms: ADI-R

The Autism Diagnostic Interview Revised (ADI-R) is a structured parent-report interview and widely recognized as the gold standard for validating a clinical diagnosis of autism (Le Couteur *et al.* 2003). The ADI-R is based on DSM-IV and International Classification of Diseases and Related Health Problems (ICD-10) diagnostic criteria for autism and generates algorithm scores for each of the three subdomains of autistic symptomatology: (1) qualitative impairments in reciprocal social behavior (2) deficits in language development and (3) restricted range of interest and/or stereotypic behaviors. For each domain, a cut-off score is provided, above which a child meets the clinical criterion. We used the diagnostic algorithm, which is based on the (retrospective) functioning at age 4–5 years.

Social cognition

The Social Cognitive Skills Test (SCST) was used to assess ToM (Coleman *et al.* 2008; Van Manen *et al.* 2009). Psychometric properties of the SCST have been rated by the COTAN (Dutch Committee on Tests and Testing) as satisfactory with regard to reliability and validity, the internal consistency is $\alpha = 0.96$ and test–retest reliability is $r = 0.82$. The SCST consists of seven cartoon stories, which are visually presented together with a verbal description of what can be seen in the cartoon. For each story, eight different questions are formulated, which correspond to four developmental social cognitive levels that increase in complexity. See Table 2 for an overview of these levels.

Facial affect identification was assessed using the Karolinska Directed Emotional Faces (KDEF) set, which contains 4900 pictures (562 × 762 pixels) of facial expressions of male and female amateur actors, aged between 20 and 30 years of age. No beards, mustaches, earrings or eyeglasses, or makeup are visible. We used 144 face forward pictures displaying either angry, afraid, disgusted or sad expressions, digitally presented using EPRIME software, version 2.0. There were four subtests of 36 trials each; 18 pictures of the target emotion and 18 pictures of other emotions. In each trial, one picture was presented. Participants were asked to identify whether the target emotion was present, using the mouse buttons to respond with 'yes' or 'no'. Participants were asked to work as fast and as accurate as possible. The task was self-paced, with an intertrial interval of 1000 milliseconds. Accuracy (percentage correct) and reaction times (ms) were registered.

Cognitive predictors of social cognition

Intellectual functioning

IQ was assessed using the subtests Blockdesign and Vocabulary of the of the Dutch adaptations of the Wechsler Intelligence Scales for Children (Wechsler 2003), i.e. V-BD short form. The V-BD short form is often used to estimate full-scale IQ (FSIQ) according to the algorithm [2.9 × (sum of normed scores) + 42] (Campbell 1998). The V-BD short form correlates highly with FSIQ ($r = 0.88$) (Hererragraf *et al.* 1996), and has been found valid for the estimation of intelligence, with a good reliability ($r = 0.91$) and validity (0.82) (Campbell 1998).

Language

To specifically assess expressive language skills, the 'Formulated Sentences' subtest of the Clinical Evaluation of Language Fundamentals (CELF) was used (Semel *et al.* 2003). Receptive language skills

Table 1: Group characteristics (mean, SD) of the non-clinical controls, children with an extra X chromosome and children with ASD

	N (boys/girls)	Age (years)	IQ	Receptive language (percentage)	Expressive language (scaled scores)	Parental education (*scale 1–5)
Controls	88 (41/47)	11.7 (2.7)	102.6 (13.3)	93.8 (5.9)	11.1 (2.8)	2.1 (0.7)
Extra X	46 (29/17)	12.8 (3.0)	84.15 (13.6)	85.2 (15.5)	5.8 (3.5)	2.2 (0.6)
ASD	56 (45/11)	12.0 (2.2)	102.3 (20.5)	93.7 (10.3)	9.9 (3.5)	2.4 (0.4)

*Ranges from 1 (primary school) to 5 (university).

Table 2: The eight subscales of the Social Cognitive Skills Test, corresponding to four levels of perspective taking with increasing complexity

Egocentric role taking	Identifying	Identifying and labeling perspectives of others and oneself
	Discriminating	Judging whether two or more observable perspectives are similar or dissimilar, without having to label those verbally
Subjective role taking	Differentiating	Understanding that two or more persons in similar or dissimilar situations do not necessarily have identical perspectives
	Comparing	Determining and labeling discrepancies and similarities between observable perspectives of different persons in the same situation
Self-reflective role taking	Perspective taking	Taking the position of another person and inferring the perspective of that person
	Relating	Relating to at least two other perspectives
Mutual role taking	Coordinating	Taking a third person's position
	Discounting	Taking one's own perspective, and taking that of others into account at the same time

were measured using the subtest 'Comprehension of Implicit Sentences' of the Dutch assessment battery 'Language Tests for Children' ('Taaltest voor Kinderen') (Van Bon 1982).

Executive functioning

The Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville 1999) has proven to be helpful in defining neurocognitive deficit profiles in different clinical and non-clinical populations (Rommelse *et al.* 2008; Serra *et al.* 2003), and several studies have demonstrated satisfactory psychometric properties of ANT paradigms (for a review, see De Sonneville 2005). Also, neuroimaging studies have shown that performance on neuropsychological tests of the ANT correlates with white matter density in the brain (Schuitema *et al.* 2013). Stimuli were presented on the computer screen and participants respond by pressing the mouse buttons with the index fingers or by using the mouse as a tracking device. To verify that subjects understand the instructions and are able to meet task demands, each subtest is preceded by illustration trials and practice trials. We used the subtests ' Shifting Set Visual' (number of errors) to measure inhibition and mental flexibility, 'Sustained Attention-Dots' to measure sustained attention regulation (tempo fluctuation) and 'Spatial Temporal Sequencing' (number of identified targets in correct order, backwards) to measure visual working memory.

Two subtests of CELF (Semel *et al.* 2003) were also used: the subtest 'Digit span' to measure verbal working memory and 'Word Associations' to measure verbal fluency.

Face processing

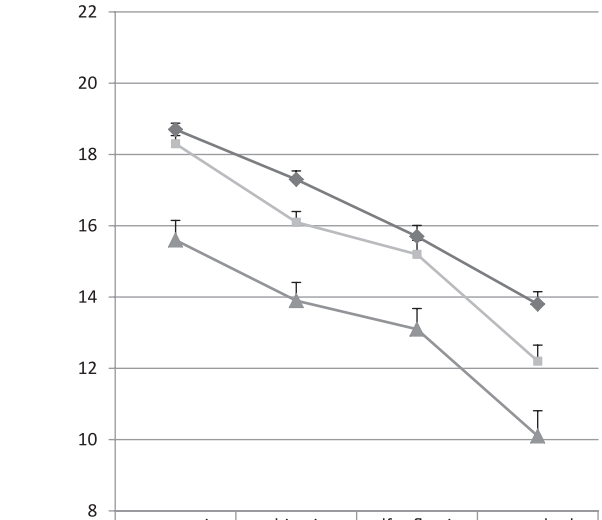
The face processing task from the ANT program (see above) measures the capacity to visually match faces based on color photographs. A neutral target face is presented for 2500, and after 500 milliseconds, it is followed by a display set of four neutral faces, which remain on the screen until the child presses a key indicating 'yes' (the target face was present in the display set) or 'no' (the display set did not contain the target face). The task consists of 40 trials in half of which the target set contained the target face (target trials) and in half of which the target face was absent. Dependent measures are speed (mean reaction time) and accuracy (number of errors).

Gestalt closure

This subtest of the Kaufman Assessment Battery for Children (K-ABC) (Kaufman & Kaufman 1983) measures perceptual closure and perceptual inference, part–whole relationships (synthesis) and perceptual organization skills. Children are shown 25 partially completed inkblot drawings and are asked to name or describe what is pictured. The test is preceded by a practice trial.

Statistical analyses

For analysis of the ToM task, multivariate analysis of covariance (MANCOVA; covaried for IQ, receptive and expressive language) was used with the fixed factor 'group' and accuracy for the eight ToM subscales as dependent variables. For analysis of the facial affect recognition task, we used GLM repeated measures, which allowed us to test for interaction with specific emotion types. In this analysis, 'IQ' was used as a covariate, 'group' as the between-subjects factor, and 'accuracy in recognizing the four emotions' as the within-subjects factor. We used separate MANCOVAS, repeated measures analysis and analyses of covariance (ANCOVAS) for various group comparisons, in order to be able to test for specific group differences while covarying for other variables. For group comparisons within the extra X group, we used MANCOVA (covaried for IQ, receptive and expressive language), with the between-subjects factor 'group' (control, extra X) and 'sex' (boy, girl), 'ADI subtype' (ADI–, ADI+) or 'ascertainment' (referred, prenatal follow-up). To assess underlying cognitive mechanisms of ToM for the clinical groups seperately, we used two linear regression analyses (forward) with total SCST score as the dependent variable and scores on the other cognitive tests as independent variables, i.e. IQ, gestalt closure, face processing, facial affect recognition, receptive language, expressive language, verbal fluency, inhibition, mental flexibility, sustained attention, visual working memory and verbal working memory. For correlation analysis, Pearson's r was used. Level of significance was set at $P = 0.05$.



	egocentric role taking	subjective role taking	self reflective role taking	mutual role taking
Control	18.7	17.3	15.7	13.8
ASD	18.3	16.1	15.2	12.2
Extra X	15.6	13.9	13.1	10.1

Figure 1: Mean scores (and SEs) for each of the four ToM levels in the Social Cognitive Skills Test, for the control group, ASD group and extra X group.

Results

Autism symptoms: ADI-R

We were not able to conduct the ADI interview with parents of five children in the extra X group. A comparison of ADI-R scores in the extra X group and ASD group has been previously published, for more information, refer to van Rijn *et al.* (2014). In the ASD group, all children scored above cut-off on two or three domains. In this study, we used the ADI-R data merely to split up the extra X group into two subgroups based on ADI-R scores: a subgroup with above cut-off scores on 0 or 1 domain, and a subgroup with above cut-off scores on 2 or 3 domains of the ADI-R (i.e. similar to the ASD group). There were 22 children in the first group, referred to as the ADI− group, and there were 19 children in the second group, referred to as the ADI+ group. The subgroups did not significantly differ in mean age ($P = 0.57$), mean IQ ($P = 0.24$) and sex distribution ($P = 0.78$).

Theory of mind

Data from two children in the control group, three children in the extra X group and one child in the ASD group were incomplete and left out of analysis. Means and standard errors (SEs) are provided in Fig. 1.

ToM: extra X group vs. controls

Multivariate analysis of covariance (covaried for IQ, receptive and expressive language) with the fixed factor 'group' (control, extra X) and the four ToM levels of dependent variables showed a main multivariate effect of group ($F_{4,122} = 7.8$, $P < 0.001$). There was no significant main effect of the covariate IQ. However, there were significant main effects of the covariates expressive language ($F_{4,122} = 3.9$, $P = 0.005$) and receptive language ($F_{4,122} = 2.7$, $P = 0.03$). Univariate effects of group were significant for all the four ToM levels: egocentric role taking ($F_{1,125} = 16.78$, $P < 0.001$), subjective role taking ($F_{1,125} = 21.4$, $P < 0.001$), self-reflective role taking ($F_{1,125} = 7.3$, $P = 0.008$) and mutual role taking ($F_{1,125} = 9.3$, $P = 0.003$). In others words, the extra X group showed an impairment in ToM, independent of the level of intellectual functioning, receptive and expressive language.

Table 3: Mean percentage hits and SEs in identifying facial expressions in the control group, extra X group and ASD group

	Control	Extra X	ASD
% hits sadness	79.1 (1.7)	72.7 (2.6)	75.7 (2.2)
% hits anger	77.5 (1.5)	70.7 (2.5)*	77.3 (2.0)
% hits fear	62.6 (1.8)	64.0 (2.9)	62.7 (2.4)
% hits disgust	81.4 (1.7)	76.1 (2.6)	78.3 (2.3)

*Significantly different from controls.

ToM: ASD group vs. controls

Multivariate analysis of covariance (covaried for IQ, receptive and expressive language) with the fixed factor 'group' (control, ASD) and the four ToM levels of dependent variables showed a main multivariate effect of group ($F_{4,136} = 2.9$, $P = 0.02$). Although there was no significant main effect of covariates IQ or expressive language, there was a significant main effect of the covariate receptive language ($F_{4,136} = 4.1$, $P < 0.001$). Univariate effects of group were significant for the ToM levels 'subjective role taking' ($F_{1,139} = 8.5$, $P = 0.004$) and 'mutual role taking' ($F_{1,139} = 6.6$, $P = 0.01$). In other words, the ASD group showed an impairment in ToM, independent of the level of intellectual functioning, receptive and expressive language.

ToM: extra X group vs. ASD group

Multivariate analysis of covariance (covaried for IQ, receptive and expressive language) with the fixed factor 'group' (extra X, ASD) and the four ToM levels as dependent variables showed no significant main multivariate effect of group ($P = 0.10$). There were no significant main effects of the covariates IQ or expressive language. However, there was a significant main effect of the covariate receptive language ($F_{4,90} = 6.2$, $P < 0.001$). In other words, there were no significant differences between children with an extra X and children with ASD in mean ToM scores.

Facial affect identification

Data from six children in the ASD group were incomplete or showed registration errors and were left out of analysis. Data on accuracy are presented in Table 3, and data on reaction time are presented in Table 4.

Table 4: Mean reaction times (RT) and SEs in identifying facial expressions in the control group, extra X group and ASD group

	Control	Extra X	ASD
RT (milliseconds) sadness	1166 (43)	1190 (73)	1267 (58)
RT (milliseconds) anger	1170 (45)	1154 (81)	1317 (60)*
RT (milliseconds) fear	1346 (50)	1346 (96)	1433 (66)
RT (milliseconds) disgust	1094 (35)	1148 (136)	1189 (46)

*Significantly different from controls.

Facial affect identification: extra X group vs. controls

Repeated measures analyses, covaried for IQ, with the between-subjects factor 'group' (control, extra X) and accuracy in recognizing the four emotions as within-subjects factor, showed a significant main effect of emotion ($F_{3,131} = 3.1$, $P = 0.03$), no significant main effect of IQ and no significant main effect of group. However, there was a significant emotion by group interaction ($F_{1,133} = 4.2$, $P = 0.04$), indicating group effects for specific emotions. *Post hoc* ANCOVA showed that this interaction was driven by a significant effect of group on accuracy in identifying angry faces ($F_{1,131} = 4.5$, $P = 0.03$), with lower scores in the extra X group. The effect size in terms of Cohen's d was 0.33, and partial η^2 was 0.03.

Repeated measures analyses, covaried for IQ, with the between-subjects factor 'group' (control, extra X) and reaction times in recognizing the four emotions as within-subjects factors, showed no significant main effects or interactions.

Facial affect identification: ASD group vs. controls

Repeated measures analyses, covaried for IQ, with the between-subjects factor 'group' (control, ASD) and accuracy in recognizing the four emotions as within-subjects factor, showed no significant main effects or interactions.

Repeated measures analyses, covaried for IQ, with the between-subjects factor 'group' (control, ASD) and reaction times in recognizing the four emotions as within-subjects factors, showed a borderline significant main effect of emotion ($F_{3,133} = 2.4$, $P = 0.06$), no significant main effect of IQ and a borderline significant main effect of group ($F_{1,135} = 3.5$, $P = 0.06$). *Post hoc* ANCOVA showed that this main effect was driven by a significant effect of group on reaction times in identifying angry faces ($F_{1,135} = 3.8$, $P = 0.05$), with longer reaction times in the ASD group. The effect size in terms of Cohen's d was 0.35, and partial η^2 was 0.03.

Social cognition in boys vs. girls with an extra X chromosome

We performed a separate analysis to assess whether there were any differences in social cognitive performance between boys and girls with an extra X chromosome. We entered total ToM score as well as accuracy and reaction times in the facial affect labeling task in MANCOVA (covaried for IQ, receptive and expressive language), with the between-subjects factor 'group' (control, extra X) and 'sex' (boy and girl). This showed a main effect of group ($F_{11,109} = 4.6$, $P < 0.001$), but, central to this research question, no significant main effect of sex ($F_{11,109} = 0.76$, $P = 0.67$) or group by sex interactions ($F_{11,109} = 1.2$, $P = 0.26$). Regarding the covariates, there was a significant main effect of language comprehension ($F_{11,109} = 4.5$, $P < 0.001$), but no significant main effects of IQ or expressive language. Taken together, social cognitive performance was similar in boys and girls with an extra X chromosome.

Social cognition within the extra X group: the role of early autism symptoms

Multivariate analysis of variance with the fixed factor 'group' (ADI−, ADI+) and scores on the four ToM subscales as dependent variables did not show a significant main multivariate effect of group ($P = 0.25$) and, related to this, none of the univariate group effects on specific ToM subscales were significant. As for the facial expression recognition task, repeated measures analyses with the between-subjects factor 'group' (ADI−, ADI+) and the within-subjects factors either reaction times or accuracy scores showed no significant main effects of group ($P = 0.39$ and $P = 0.52$, respectively) or group by emotion interactions ($P = 0.23$ and $P = 0.09$, respectively). In sum, there were no differences in ToM abilities or emotion recognition skills between the ADI− and ADI+ group.

Social cognition within the extra X group: referred and prenatal follow-up cases

Multivariate analysis of variance with the fixed factor 'ascertainment' (referred, prenatal follow-up) and scores on the eight ToM subscales as dependent variables did not show a significant main multivariate effect of group ($P = 0.18$) and, related to this, none of the univariate group effects on specific ToM subscales were significant. As for the facial expression recognition task, repeated measures analyses with the between-subjects factor 'ascertainment' (referred, prenatal follow-up) and the within-subjects factors either reaction times or accuracy scores showed no significant main effects of group ($P = 0.27$ and $P = 0.35$, respectively) or group by emotion interactions ($P = 0.43$ and $P = 0.46$, respectively). In sum, there were no differences in ToM abilities or emotion recognition skills between the referred and prenatal follow-up cases.

Social cognition: underlying cognitive mechanisms

Using additional data on cognitive functioning in several domains, we had to exclude 10 children in the extra X group and 4 children in the ASD group because of missing scores. For the extra group and the ASD group separately, linear regression analysis was performed with total ToM score (SCVT) as the dependent variable and the other cognitive scores as independent variables, i.e. IQ, gestalt closure, face processing, facial affect recognition, receptive language, expressive language, verbal fluency, inhibition, mental flexibility, sustained attention, visual working memory and verbal working memory. In the extra X group, this yielded a significant model, $F_{1,35} = 14.2$, $P = 0.001$, in which sustained attention regulation was the single significant predictor, $\beta = -0.53$, $t = -3.8$, $P = 0.001$. More stable attention regulation predicted better ToM performance, and explained 27% of the variance in ToM ability. In the ASD group, this

also resulted in a significant model, $F_{3,49} = 32.0$, $P < 0.001$, which included three significant predictors: receptive language $\beta = 0.54$, $t = 5.9$, $P < 0.001$, verbal fluency $\beta = 0.29$, $t = 3.2$, $P < 0.003$ and face processing $\beta = -0.23$, $t = -2.5$, $P = 0.01$. Better performance in these areas predicted better ToM performance. Together, these three predictors explained 64% of the variance in ToM ability.

Discussion

The aim of this study was to assess several aspects of social cognition, i.e. ToM and facial affect recognition, in boys and girls with an extra X chromosome when compared with typically developing children and children with ASD, and to assess whether deficits in ToM are related to different or similar information processing deficits.

First, the children with an extra X chromosome showed significant impairments in ToM when compared with the typically developing children, with performance not different from children with ASD. This impairment in ToM was independent of level of intellectual functioning, receptive and expressive language. These findings suggest that many children with an extra X chromosome have difficulties in ToM. Impaired ToM may result in social difficulties as ToM is needed to understand emotions of others, infer intentions of others, predict the impact of your behavior on others, understand the perspectives of others and predict their behavior, and respond according to social conventions. Considering there were no significant differences in ToM scores between the ASD group and the extra X group, findings suggest that the extra X group may have ToM deficits as severe as a high-functioning ASD group. However, we cannot exclude that other, more lower functioning or more severely affected, children with ASD might have more severe ToM difficulties. Indeed, data from Coleman *et al.* (2008), who used the same ToM test, showed somewhat lower scores in their group of children with ASD.

Although both the extra X group and the ASD group showed deficits in attributing mental states, there were substantial differences in the cognitive functions contributing to these deficits. Although the degree to which ToM depends on domain specific processes that are exclusively devoted to ToM computations or upon domain general processes that also serve other cognitive functions is still a considerable debate in the literature (Apperly *et al.* 2005), there is evidence showing that cognitive functions such as language (Astington & Jenkins 1999; Garfield *et al.* 2001; Milligan *et al.* 2007), visual perception (Gopnik *et al.* 1994) and executive functions such as inhibition and working memory (Dennis *et al.* 2009) are related to ToM abilities. In this study, using SCST, we found that mentalizing abilities in children with ASD were significantly predicted by language comprehension, verbal fluency and the ability to process facial features. Thus, ToM deficits are primarily accompanied by impairments in receptive and expressive communication and social cue processing. In contrast, mentalizing abilities in the extra X group were significantly predicted by executive attentional abilities, i.e. the ability to regulate attentional control by focusing on relevant information and ignoring irrelevant information. Obviously, the reported cognitive mechanisms could not explain all variance in ToM abilities (27% in the extra X group and 64% in the ASD group), suggesting that other, possibly more domain specific, deficits may also be present. Thus, both children with ASD and children with an extra X chromosome have difficulties in mentalizing, but these difficulties may be related to a different set of cognitive dysfunctions.

This study also showed difficulties in facial affect recognition in children with an extra X chromosome when compared with typically developing children. This deficit was specifically found in identifying angry facial expressions. The children with ASD also showed impairments in identifying facial expressions when compared with the typically developing group, which was, similar to the extra X group, driven by more difficulties in identifying angry facial expressions. As deficits were reflected in lower accuracy scores in the extra X group, but reflected in longer reaction times in the ASD group, we did not directly compare these two groups. In the extra X group and ASD group, impairments were independent of level of intellectual functioning. The finding that the children with an extra X chromosome were specifically impaired in labeling angry facial expressions lines up with a study in adult men with an extra X chromosome showing deficits in identifying angry facial expressions (van Rijn *et al.* 2006). It would be interesting in future studies to further explore why specifically angry faces are most difficult to label. These difficulties may contribute to problems in social interactions, as such non-verbal cues may convey crucial information about the emotional state of the sender. Various studies have revealed significant relationships between facial affect recognition performance and social functioning (Hooker & Park 2002).

In this study, social cognitive performance children with an extra X chromosome was not dependent on recruitment strategy (i.e. prenatal follow-up cases or referred cases), which suggests that our findings are representative for this group of diagnosed children as a whole. In the Netherlands, the standard clinical guidelines are that women above the age of 36 are offered prenatal screening at no additional cost. As this group was traced with the help of the clinical departments where karyotyping was performed 8–19 years ago, this group may represent a broad spectrum of outcomes. Although referred cases were also included, there was no systematic difference in social cognitive outcome detected by our study, which paralells our earlier findings on social behavior (van Rijn *et al.* 2014).

Another factor we addressed in understanding social cognitive impairments in the extra X group was sex differences. This study showed that girls and boys with an extra X chromosome could not be differentiated in ToM ability and facial affect identification skills. An earlier report based on this cohort (van Rijn *et al.* 2014) showed that there were no sex differences in levels of autism traits and symptoms, which is in line with the present findings. One could speculate that the shared social cognitive and social behavioral phenotype in boys and girls with an extra X chromosome could be (partly) attributed to shared genetic mechanisms. We hope that our findings stimulate future genetic studies on this issue.

In order to assess whether social cognitive impairments in children with an extra X chromosome were driven by a subgroup showing high levels of autism symptoms, we compared performance in the ToM task and facial affect identification task between those who showed high vs. low levels of autism symptoms. Because we used the diagnostic algorithm which is based on behavior at age 4–5, this allowed us to identify a subgroup with prominent autism symptoms already at a young age, similar to the ASD group in this study. Comparing performance in the ToM task and the facial affect identification task showed that there were no significant differences between children with an extra X chromosome, showing low or high levels of early autism symptoms. Thus, the social cognitive deficits were not specific for a subgroup with high levels of typical autism symptoms, but present in the extra X group as a whole. This suggests that ToM and facial affect recognition is not exclusively impaired in children with ASD, but that other children may have social cognitive deficits as well, including children with an extra X chromosome who do not show the typical autism phenotype. Social cognitive impairments are part of the phenotype of children with an extra X chromosome, and such deficits may contribute to social dysfunction irrespective of whether children show a developmental pattern that is 'typical' for autism. Thus, children who are characterized by subclinical levels of autism traits, children who display autism symptoms later in development or children who show social dysfunction that is atypical for ASD may also show social cognitive impairments. Such social cognitive deficits could not be present without consequences for social behavior. Indeed, other findings in this cohort (van Rijn *et al.* 2014) showed that children with an extra X chromosome, who do not show the typical autism phenotype in terms of quantity, quality and developmental trajectory of social developmental problems, do show significant social behavioral problems, increased levels of autism traits and high levels of social anxiety at 9–18 years of age.

This study also had some limitations that should be mentioned. Because the ASD group did not have an even distribution of girls and boys (with few girls), we were not able to assess gender-specific findings within the ASD group. Also, the age range was relatively broad, from 9 to 18 years, which made it difficult to perform detailed analyses of specific development effects. There was also a limited selection of social cognitive tests, and it would be interesting to also investigate other aspects of social cognition such as emotional prosody, pragmatic language and eye gaze following. Furthermore, the ASD group was a high-functioning group, and therefore does not reflect the full spectrum of level of functioning within the population of children with ASD. Nonetheless, our findings indicate that regardless of high levels of intellectual functioning, social cognition is affected in these children, underscoring the relevance of the findings in the ASD group.

The finding of social cognitive impairments calls for more attention to social cognitive development in children with an extra X chromosome. Considering the substantial risk for social dysfunction and the high proportion of children that have social cognitive deficits, routine assessment of social cognitive functioning as part of neuropsychological screening is warranted, also taking into account a potential variety in cognitive impairments contributing to ToM deficits. Our findings may also help in identifying new targets for treatment and intervention. Interventions aimed at supporting language development are typically part of treatment in neuropsychological settings. We hope that our findings stimulate the development or implementation of interventions that are focused on social cognitive deficits. Currently available interventions aimed at improving labeling of facial expressions or ToM, which have been developed for children with ASDs, might also benefit children with an extra X chromosome. However, based on the evidence we found for different types of cognitive deficits contributing to ToM impairments, we cannot exclude that the effect of intervention may vary dependent on the broader profile of cognitive deficits. Future studies addressing effectiveness in children with an extra X chromosome are warranted.

There are also theoretical implications, based on the insights in pathways to psychopathology that are obtained by studying genetically defined disorders rather than behaviorally defined disorders. By studying children with an extra X chromosome, we may learn about the mechanisms of social cognition in relation to behavioral problems and psychopathology, beyond what is typical for children with ASD. First, it may be important to consider vulnerability for autism in children with an extra X chromosome in terms of a continuum of various autism traits that may present in various developmental stages. This variability helps in gaining insight in the factors that drive this risk. Our findings tentatively suggest that the reported social cognition deficits may be necessary, but possibly not sufficient, to cause a 'typical autism phenotype' in children with an extra X chromosome. Obviously, social–emotional development entails more than ToM or facial affect recognition. To illustrate, these are 'cognitive' aspects of social information processing, whereas social adaptation also involves emotional resonance and affective empathy. Besides this, other cognitive functions might contribute to a typical ASD phenotype as well, such as central coherence deficits. Thus, it is likely a broad profile of cognitive, social and emotional dysfunctions that lead to the typical autism phenotype, and one should focus on profiles rather than single neuropsychological deficits. Also, some deficits, such as social cognitive deficits, may not be specific for ASD but can be found in other conditions as well, not only sex chromosome disorders but, for example, also psychotic disorders (Bora & Pantelis 2013) and attention deficit hyperactivity disorder (Miranda-Casas *et al.* 2013).

Second, our data suggest that mentalizing deficits may be related to a different set of cognitive dysfunctions in children with ASD and children with an extra X chromosome. The relevance of this finding is also illustrated in a recent neuroimaging study, in which we found differences in neural processing during social cognitive processing in children with an extra X chromosome when compared with children with ASD (Brandenburg-Goddard *et al.* 2014). This functional MRI study showed frontal deficits in the extra X group in contrast to amygdala deficits in the ASD group. Although speculative, this finding fits very well with the current findings of frontally mediated executive attentional deficits predicting

ToM deficits in the extra X group and face processing deficits (in addition to language impairments) predicting ToM deficits in the ASD group. These findings illustrate the importance of understanding the underlying mechanisms of social cognition and social behavior, and may also help explain variance in type of social deficit within the autism spectrum. Children may show similar social difficulties, but these may arise as a consequence of different underlying information processing deficits.

In conclusion, this study showed that having an extra X chromosome may impact cognitive development in the area of social information processing and illustrated that taking a neuropsychological perspective may significantly contribute to understanding risk for developmental psychopathology.

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