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ORIGINAL ARTICLE

The nature of social cognitive deficits in children and adults with Klinefelter syndrome (47,XXY)

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Abstract

About 1 in 650 boys are born with an extra X chromosome (47,XXY or Klinefelter syndrome). 47,XXY is associated with vulnerabilities in socio-emotional development. This study was designed to assess types of cognitive deficits in individuals with 47,XXY that may contribute to social-emotional dysfunction, and to evaluate the nature of such deficits at various levels: ranging from basic visuospatial processing deficits, impairments in face recognition (FR), to emotion expression impairments. A total of 70 boys and men with 47,XXY, aged 8 to 60 years old, participated in the study. The subtests feature identification, FR and identification of facial emotions of the Amsterdam Neuropsychological Tasks were used. Level of intellectual functioning was assessed with the child and adult versions of the Wechsler Intelligence Scales. Reaction time data showed that in the 47,XXY group, 17% had difficulties in visuospatial processing (no social load), 26% had difficulties with FR (medium social load) and an even higher number of 33% had difficulties with facial expressions of emotions (high-social load). Information processing impairments increased as a function of "social load" of the stimuli, independent of intellectual functioning. Taken together, our data suggest that on average individuals with XXY may have more difficulties in information processing when "social load" increases, suggesting a specific difficulty in the higher-order labeling and interpretation of social cues, which cannot be explained by more basic visuospatial perceptual skills. Considering the increased risk for social cognitive impairments, routine assessment of social cognitive functioning as part of neuropsychological screening is warranted.

KEYWORDS

cognition, emotions, facial expressions, Klinefelter syndrome, sex chromosome aneuploidies, sex chromosome variations, social cognition, visual processing, X chromosome, XXY

1 | INTRODUCTION

The understanding of neurocognitive mechanisms driving social dysfunction is a major area of research in the field of autism spectrum disorders (ASD), a behaviorally defined psychiatric condition. A large number of studies have been devoted to identifying how individuals with ASD process faces and facial expressions of emotions, as a means of identifying neurocognitive factors that contribute to problems in social interactions. However, much less research is carried out in populations with genetic conditions associated with impaired social functioning. It is important to also study genetic syndromes as

these are more clearly delineated, that is, genetically defined, rather than by a constellation of behavioral symptoms that are subject to change over time. This may help advance our understanding of the different mechanisms and pathways to social behavioral difficulties in general, not limited to the specific population of individuals with ASD, which typically by definition have some type of social cognitive impairment as part of the diagnostic classification. Genetic syndromes such as XXY provide an opportunity to understand social difficulties in a broader context, independent of behavioral classifications.

One of the genetic conditions of interest in this regard is Klinefelter syndrome, which is defined by the presence of an extra X

chromosome in boys and men (47,XXY). This syndrome is relatively common, as newborn screening studies have shown rates of 1 in 650 live-born boys with this condition.¹ Research has shown that although outcome is variable and many boys and men remain undiagnosed, there is a substantial risk for social dysfunction. Boys and men with XXY have been described as shy, unassertive, withdrawn, impulsive and anxious in social contexts. In terms of the proportion of boys and men with XXY struggling with social functioning, a study in 60 boys and girls with an extra X chromosome showed that about 66% had experienced problems in social interactions and social communication at age 4 to 5 (as assessed with the Autism Diagnostic Interview, Los Angeles, CA, USA) and 45% had scores in the “mild/moderate” or “severe” range of the Social Responsiveness Scale.² The degree of social dysfunction was similar for boys (XXY) vs girls (XXX), and similar for prenatally diagnosed vs referred cases. In another study, about 42% of 20 boys with XXY were found to have significant deficits in either reciprocal social interactions or social communication as assessed with the Autism Diagnostic Interview.³ In a larger study, about 47% of 102 boys with XXY scored in the “mild/moderate” or “severe” range of the Social Responsiveness Scale.⁴ These numbers show that this population is at risk for social dysfunction in childhood, adolescence and adulthood.

Because of the impact of social impairments on daily life functioning and outcome in life, including the detrimental effects in terms of limited social support networks, problems in school, difficulties in getting and maintaining jobs and forming close relationships, studies examining the neurocognitive factors that may help explain social dysfunction in XXY are warranted. Especially since such knowledge is helpful in designing cognitive-behavioral interventions or training, which are currently lacking for individuals with this syndrome. Even although there is a limited understanding of mechanisms underlying the difficulties in social adaptation, recent studies have revealed that individuals with XXY may have social cognitive difficulties. Social cognition refers to the ability to perceive, understand and express social signals. To illustrate, many boys with XXY have difficulties with theory of mind (ToM), referring to the attribution of mental states, intentions and emotions to others.⁵ Also, XXY has been associated with difficulties in reading social signals from social gaze direction,⁶ affective tone of voice⁷ and facial expressions.^{5,8} Two recent eyetracking studies showed that men with XXY attended less to faces, and had a reduced tendency to first look at the eyes of others.^{9,10}

Successful social interaction and adaptive functioning in social context heavily relies on the abilities to process information from faces. During any encounter, it is crucial to be able to quickly “read” faces of others, based on which one can organize social responses. These skills are anchored in early brain development, as infants are capable of abstracting direction of gaze, facial gestures and expressions of emotion within the first year of life already.¹¹ Individuals typically have extraordinary skills in perceptual processing of faces: considering that all faces are perceptually similar in terms of their features (eyes, nose, mouth) and configuration (position of the eyes, nose, mouth), face processing heavily relies on visual perception and faces require the finest visual discrimination skills as compared with all categories of objects.¹² Therefore, it is important to assess the type of cognitive deficits in individuals with 47,XXY that may

contribute to their social dysfunction, and to evaluate the nature of such deficits at various levels, ranging from basic visuospatial processing deficits and impairments in face recognition (FR), to emotion expression impairments. This study was designed to provide in this.

2 | MATERIAL AND METHODS

In the present study, about 70 boys and men with 47,XXY participated. The participants were 8 to 60 years old, with a mean age of 31.2 (SD = 16.5) years. Participants were recruited from clinical genetics departments, support groups, health clinics and patient conferences. With regard to timing of diagnosis, 23.9% had a prenatal diagnosis and 76.1% had a postnatal diagnosis. Assessments took place at the University Medical Center Utrecht or Leiden University. Informed consent was obtained from participants and/or parents or caretakers.

The assessment protocol was approved by the Dutch Central Committee on Research Involving Human Subjects and the study was conducted according to the Declaration of Helsinki of the World Medical Association (WMA). Assessments were carried out by an experienced neuropsychologist.

2.1 | Measures

Intellectual functioning (full scale IQ; FSIQ) was assessed using the Dutch version of the Wechsler Intelligence Scales for Children (WISC)-III¹³ or the adult scale¹⁴ for individuals older than 16 years. In 9 cases, information about intelligence was missing.

Visuospatial information processing, FR and identification of facial expressions of emotion were assessed using 3 tasks from the Amsterdam Neuropsychological Tasks (ANT) program.¹⁵ Test-retest reliability and validity of this computerized assessment battery are satisfactory and have extensively been described elsewhere.^{16,17} All tasks are self-paced and presented in a fixed order, as described below. Prior to each task, the participant receives a standard verbal instruction, including display of visual material (signals). Preceding the actual test, the participant is given a practice session to ensure that the task is understood and to familiarize him or her with the task. The participant is instructed to respond as fast and accurately as possible. A brief description is provided below; for more details, including examples of signals and timing between signals, see, for example, De Sonnevle et al.¹⁸ For all tasks, mean reaction time of correct responses and number of errors were registered: both speed and accuracy were used as parameter reflecting information processing deficits.

2.1.1 | Feature identification

This pattern recognition task assesses speed and accuracy of processing abstract visuospatial information. Subjects were asked to detect a predefined target pattern (a 3 × 3 matrix consisting of 9 squares of which 3 were red and 6 were white) in a signal consisting of 4 patterns with the locations of the red squares varying. The subject was asked to press the “yes”-key when the pattern was present (40 trials) and the “no”-key when the pattern was not present (40 trials). Processing of these abstract patterns does not require any social

cognitive skill, and therefore this task is considered as having “no social load”.

2.1.2 | Face recognition

This task assesses speed and accuracy of recognizing (neutral) faces. From a set of 20 pictures of different persons (boys, girls, men and women) a probe, the face to be recognized, is presented on a monitor for 2.5 seconds prior to the imperative signal, which consists of 4 digitized high-quality color photos of human faces. Gender and age category (children, adults) of signal and probe always match. The subject was asked to press the “yes”-key when the probe was present in the signal (20 trials) and the “no”-key when the pattern was not present (20 trials). Faces are also visuospatial patterns, but some degree of social cognitive skills is needed to perform this task. Therefore, this task is considered to have a “medium social load”.

2.1.3 | Identification of facial emotions

This task assesses speed and accuracy of recognizing facial emotions by asking the participants to judge whether a face on a picture shows a specific (target) emotion (“yes”-key) or a different emotion (“no”-key). The total stimulus set consisted of 32 pictures from 4 different adult persons, each showing the 8 emotions: happiness, sadness, anger, fear, disgust, surprise, shame and contempt. The task consists of 8 parts of 40 trials in which half of the trials contain the target emotion, whereas in the other half a random selection of the other emotions is presented. Four task parts were administered to measure the recognition of happiness, sadness, anger and fear, respectively. Performance on this task depends heavily on social cognitive skills, therefore this task is considered to have a “high-social load”.

Because we used the feature identification (FI) and FR test in addition to the identification of facial emotions (IFE) test, we were able to disentangle the different cognitive components that may underlie social cognition problems. The 3 subtests have a similar design/set-up (in terms of type of motor responses, practice trials, visual presentation, computerized testing and similar outcome parameters), yet the subtests differ in type of stimuli that need to be processed. By comparing performance differences across subtests, we were able to evaluate if performance is dependent on degree of “social load,” with the pattern recognition test having no social load, the FR test having medium social load and the facial emotion recognition test having high-social load. This set of 3 tasks has been frequently and successfully used to identify cognitive skill deficits in subjects with attention deficit hyperactivity disorder,¹⁹ ASD²⁰⁻²⁴ and schizophrenia.^{25,26}

2.2 | Statistical analyses

Main outcome parameters for analyses are z-scores, which are automatically computed by means of nonlinear regression functions that describe the relation between test age and raw scores of task performance. These regression functions, intrinsically implemented in the ANT program, are based on norm samples consisting of 3750 (FI), 3420 (FR) and 4580 (IFE) typically developing subjects,¹⁷ and are therefore considered to be reliable estimates of performance level.

Prior to analysis, the z-scores for the 4 emotion recognition subtests were averaged across emotion type. Results were examined for extreme values. Tests of homogeneity of variance and normality were performed and assumptions were met.

Two repeated-measures analyses of variance (RM-ANOVA) were run with pattern, face and facial emotion recognition as levels of the within-subject (WS) factor task, using a repeated contrast (patterns vs faces vs facial emotions), with speed and accuracy of performance as dependent variables, respectively. To determine whether mean performance of the participants differed from the norm, that is, z-scores differed from zero, the intercept test of the ANOVAs was used. Furthermore, a significant WS factor effect actually reflects a significant interaction, that is, implies that differences in performance level between the group and the norm depends on the task that is performed. Using repeated contrasts it can be determined which task(s) discriminate(s) the participants from the norm and thus it can be tested if performance is dependent on social load of the stimuli. For all analyses, α was set to .05.

As speed of processing visuospatial patterns and accuracy of processing facial emotions appeared to be correlated with full-scale intelligence (FSIQ), it was decided to investigate the contribution of intelligence to the observed findings, by rerunning the RM-ANOVAs after adding IQ as a covariate.

3 | RESULTS

The FSIQ of the participants ($N = 61$) was 89.4 ($SD = 14.1$, range 56-120), verbal IQ was 87.9 ($SD = 14.6$, range 53-121) and performance IQ was 93.7 ($SD = 13.6$, range 58-123). Intelligence correlated with task performance, that is, lower intelligence was associated with slower speed of pattern recognition and lower accuracy of face and facial emotion recognition (see Table 1).

3.1 | Visuospatial information processing, FR and identification of facial expressions of emotion

Speed and accuracy of processing were not significantly correlated in pattern recognition ($r = -.054$, $P = .66$), FR ($r = .044$, $P = .71$) and emotion recognition ($r = -.120$, $P = .32$). This absence of a speed-accuracy trade-off indicates that these 2 performance indices may be interpreted independently. On average, participants were slower [$F_{(1,69)} = 47.083$, $P < .0001$, $\eta_p^2 = .406$] and less accurate [$F_{(1,69)} = 13.343$, $P = .001$, $\eta_p^2 = .162$] than the norm.

TABLE 1 Pearson correlations task performance with intelligence, * $P < .05$, ** $P < .01$

		FSIQ	VIQ	PIQ
Pattern recognition	Speed	.358**	.342**	.312**
	Accuracy	.123	.002	.266*
FR	Speed	-.043	-.030	-.126
	Accuracy	.390**	.344**	.376**
Facial emotion recognition	Speed	.121	.200	.017
	Accuracy	.456**	.420**	.422**

Standardized means of total group performances on all tasks of visual information processing are presented in Figure 1.

Crucial to our aim, the effect of the WS factor Task was significant for speed [$F_{(2,138)} = 17.458$, $P < .0001$, $\eta_p^2 = .202$] and for accuracy [$F_{(2,138)} = 4.142$, $P = .018$, $\eta_p^2 = .057$]. The repeated WS-subject contrasts revealed significant effects for speed of pattern vs FR [$F_{(1,69)} = 7.134$, $P = .009$, $\eta_p^2 = .094$] and face vs facial emotion recognition [$F_{(1,69)} = 13.121$, $P = .001$, $\eta_p^2 = .160$], indicating that differences from the norm increased when “social load” of stimuli increased (see Figure 1).

The repeated WS-subject contrasts for accuracy of processing revealed a nonsignificant effect for patterns vs faces [$F_{(1,69)} = .035$, $P = .853$], but a significant effect for faces vs facial emotions [$F_{(1,69)} = 5.020$, $P = .018$, $\eta_p^2 = .078$], reflecting that differences in accuracy with the norm are only present when “social load” is highest, that is, when facial emotions have to be recognized.

To investigate the influence of intelligence, the repeated-measures analyses of variance was repeated with IQ and age (child, adult) as a covariate. This did not change the significance of the results, indicating that the observed effects of WS factor task, and related WS-subject contrasts, were independent of IQ or age.

In order to obtain a more clinical impression of the performances, the percentage of participants that demonstrated (mildly or severely) impaired performance was computed. This was based on criteria of Lezak,²⁷ with mild impairments defined as $1.3 < z < 2$, and severe impairments defined as $z > 2$. Reaction time data showed that 17.1% of the XXY group had impaired performance in pattern recognition, 25.7% had impaired performance in FR and 32.9% had impaired performance in facial emotion recognition. Accuracy data showed that 8.9% of the XXY group had impaired performance in pattern recognition, 12.8% had impaired performance in FR and 12.9% had impaired performance in facial emotion recognition.

4 | DISCUSSION

The aim of this study was to assess vulnerability for social cognitive deficits in boys and men with 47,XXY, and to evaluate the nature of such deficits at various levels, ranging from basic visuospatial processing deficits and impairments in FR, to impairments in interpreting facial expressions of emotion. Our findings show that in the group of boys and men with 47,XXY information processing impairments increase as a function of “social load”: the more socially relevant information needs to be processed, the more difficulties boys and men with 47,XXY have. This effect was independent of level of intellectual functioning.

The deficit in social cognition was also evident in the number of individuals with 47,XXY with significant difficulties as expressed in scores in the mildly or severely impaired range. Although only 17% had difficulties in visuospatial processing, 26% had difficulties with FR and even higher number of 33% had difficulties with facial expressions of emotions. Information processing difficulties were largely expressed in longer reaction times. This indicated that many boys and men with 47,XXY need more time to identify facial expressions, and the absence of a speed-accuracy trade-off suggests additive effects so that more time does not lead to improved performance. Taken

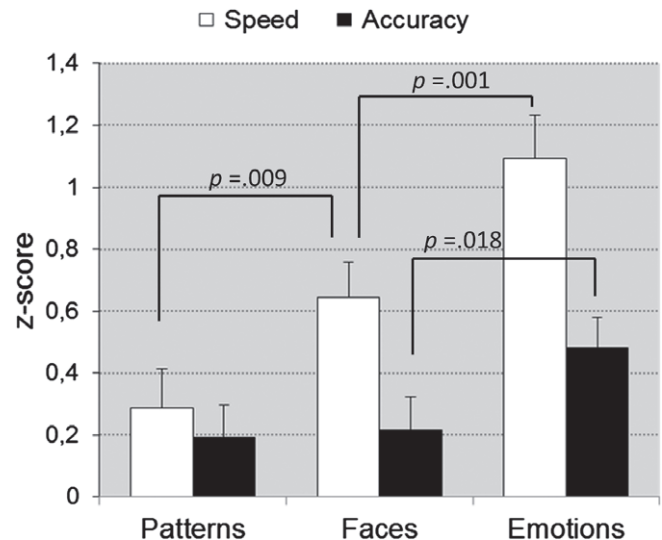


FIGURE 1 Speed and accuracy of processing visuospatial patterns, faces and facial emotions, expressed in z-scores (\pm SEM). Positive z-scores indicate poorer performance compared with the norm

together, our data suggest that on average individuals with XXY may have disproportionate difficulties in information processing when “social load” increases, pointing to a specific vulnerability and difficulty in the higher-order labeling and interpretation of social cues,²⁸ which cannot be explained by more basic visuospatial perceptual skills.

Our findings fit with an earlier study⁵ showing that social cognition as expressed in the ability to understand emotions, thoughts and intentions of others, also referred to as ToM, was related to higher-order cognitive skills in boys and girls with an extra X chromosome. Our findings of specific social cognitive impairments at the level of emotion understanding and social interpretation also fit with earlier neurocognitive studies in which impairments in the interpretation of facial expressions of emotion (using others tests) were found in boys⁵ and adults⁸ with 47,XXY. Social cognition may be among the key areas of vulnerability in 47,XXY, which is also supported by a recent MRI study²⁹ comparing brain architecture of a large number of individuals with X and Y chromosome duplications. In this study an algorithm was used to identify brain areas that show abnormalities across a range of sex chromosome aneuploidies (XX, XY, XXX, XXY, XYY, XXYY, XXXXY) irrespective of the exact combination of X and Y chromosomes. This revealed that X and Y chromosomes exert convergent dosage effects on the proportional size of cortical systems involved in socio-communicative and socio-emotional functioning. In other words, especially higher-order brain areas crucial for social information processing are influenced by the extra X and Y chromosomes, which may help explain social cognitive and social behavioral difficulties in the sex chromosome aneuploidy population.

Social cognitive impairments are not specific for the XXY group: social cognitive deficits have been found in many different conditions. Therefore, the current findings may also have broader implications. At the same time, the exact nature of social cognitive deficits may also be different across different populations, which poses an interesting avenue for research. For example, using the exact same test battery, a comparison of the ability to recognize patterns, faces

and emotions yielded somewhat different results in a population of individuals with a psychiatric condition (schizophrenia).²⁶ Similar to the current study, difficulties in emotions recognition were most pronounced. However, in contrast to the findings in the XXY group, individuals with schizophrenia did show deficits in pattern recognition, suggesting that more fundamental impairments in visuospatial processing are present as well. Another example of the importance of studying specificity of information processing impairments is a recent study⁵ showing that ToM abilities were best predicted by degree of executive functioning impairments in the XXY group, rather than IQ, language skills, gestalt closure or FR skills. This was in contrast to a group of children with ASD, in which ToM performance was best predicted by receptive language skills, verbal fluency and FR. Knowledge about the specific underlying mechanisms of social difficulties in XXY, and how these may be different or similar to other conditions, may have implications for implementing (existing or new) interventions targeted at alleviating social behavioral problems in XXY. Paradigms in which specific types of cognitive deficits can be disentangled, such as the paradigm in this study, can be helpful in this. Future studies might rely on such paradigms to directly compare pathways to social dysfunction across different genetically defined and/or behaviorally defined conditions. It would also be interesting to assess such underlying mechanisms of social cognition in other sex chromosome aneuploidies, as social deficits have also been found in 45,X, 47,XXY and 48,XXYY.^{30–32}

The cognitive data in this study were all normscores, which means that performance of each individual with 47,XXY was compared with age-matched normdata from the general population. The ANT program produces a continuum of age-specific normscores for the (based on population sample of 3750–4580 individuals for the tests that were used) rather than age-bins. Because, we used normscores, the findings have automatically been corrected for developmental effects. However, a weakness of the study was that the group reflected a rather broad age range; from age 8 years to 60 years. Future studies, preferably with a longitudinal design, are needed to address developmental dynamics of social cognitive impairments and the predictive value of social cognitive impairments for socio-emotional development and related risk for psychopathology. Another weakness of the study was that it remains unclear to what degree findings can be generalized to the total population of individuals with XXY. First, participants in this study were recruited using mixed strategies (through clinical genetics departments, support groups, health clinics and patient conferences). Second, with regard to timing of diagnosis, 23.9% had a prenatal diagnosis and 76.1% had a postnatal diagnosis. Although a range of subgroups was included, replication of the findings in studies with other samples is warranted.

The finding of specific social cognitive impairments calls for a clinical focus on social cognitive functioning in children and adults with an extra X chromosome. Considering the increased risk for social dysfunction and the social cognitive vulnerabilities that have been identified, routine assessment of social cognitive functioning as part of neuropsychological screening is warranted. Our findings may also help in identifying new targets for intervention and treatment. Currently, cognitive-behavioral interventions are often aimed at language

development and learning problems in children with 47,XXY. We hope that our findings stimulate the development or implementation of interventions that target social cognitive development.

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