# Chapter 4

## X Chromosomal effects on social cognitive processing and emotion regulation: a study with Klinefelter men (47,XXY)

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**Abstract**

Studying Klinefelter syndrome (47,XXY), a genetically defined disorder characterized by the presence of an additional X chromosome, can reveal insights into genotype-phenotype associations. Increased vulnerability to psychiatric disorders characterised by difficulties in social interactions, such as schizophrenia and autism, has been reported for this population. The reported social difficulties in 47,XXY men may arise as a consequence of impairments in the processing of social and emotional information. The present study is the first investigation of social-emotional information processing in this X-chromosomal disorder.

32 Klinefelter men and 26 men from the general population, with the groups matched for age, educational level and I.Q., participated in the study. Several tasks were included, reflecting aspects of social-emotional information processing on levels of perception, experience and expression: labeling of facial expressions of emotion, emotion-cognition interactions in decision making and emotion regulation, that refers to subjective experience and identification of emotional arousal as well as verbal expression of emotions.

A discrepancy between cognitive appraisal of emotions and emotional arousal was observed in Klinefelter syndrome. Taken together, Klinefelter men seem less accurate in perception of socio-emotional cues such as angry facial expressions, they are less able to identify and verbalize their emotions, but experience increased levels of emotional arousal, in comparison to the general population. Besides describing the social-emotional phenotype of this X-chromosomal disorder, the present data may prove to be an important contribution to the development of more general models describing pathways to neuropsychiatric disorders characterized by social cognitive disturbances.

## Introduction

Studying genetically defined syndromes can reveal insights into gene-brain-behavior mechanisms. This may lead to a better understanding of complex psychiatric diseases, such as schizophrenia. In this regard, an interesting genetic condition that has been associated with an increased vulnerability to schizophrenia, is Klinefelter syndrome (Bojesen et al., 2006; L.E. DeLisi et al., 1994; L. E. DeLisi et al., 2005; Kunugi et al., 1999; van Rijn et al., in press).

Klinefelter syndrome is characterised by the presence of an additional X chromosome in men. The 47,XXY chromosomal pattern has been associated with a variety of physical and neuropsychological abnormalities (Lanfranco et al., 2004). For example, infertility, lowered testosterone levels and language disabilities have been reported. At a behavioral level, Klinefelter men have been reported to have difficulties in social functioning and have been described as being introvert, anxious, impulsive, quiet, subassertive and socially withdrawn (D. H. Geschwind et al., 2000a). Socially inappropriate behavior as well as anti-social behavior have also been documented (Gotz et al., 1999; Ratcliffe, 1999).

Social difficulties in Klinefelter syndrome may be dismissed as a consequence of daily life struggles associated with the disorder, but they may also arise from deficits in social cognitive processing. Social cognitive processing, i.e. the ability to perceive, understand and express social signals, covers aspects of intelligence other than general cognitive abilities such as language and attention, that have an independent contribution to social functioning (Amy E. Pinkham et al., 2003). In the general population, social competence seems to be under substantial genetic control (Scourfield et al., 1999).

Findings from MRI studies showing structural abnormalities of brain regions that form part of a neural network subserving social cognition and emotion call for a more thorough investigation of social cognitive processing in Klinefelter syndrome. For example, volume reductions of the amygdala, insula, anterior cingulate and superior temporal gyrus, all of which have been shown to play an important role in social cognition and emotion, have been observed in this syndrome (Shen et al., 2004).

Social cognitive processing is thought to mediate between the molecular, genetic level and the behavioral, or even clinical, level and thereby may provide insight into gene-brain-behavior linkages underlying psychopathology (Van Rijn et al., 2005). Interestingly, as Klinefelter syndrome has been associated with increased levels of schizophrenia spectrum pathology and autistic features (L.E. DeLisi et al., 1994; L. E. DeLisi et al., 2005; Gillberg, 1995; Swaab et al., in prep.;

van Rijn et al., in press), studying social cognitive processing in Klinefelter syndrome may prove to be an important contribution to the development of more general models describing pathways to neuropsychiatric disorders characterized by social cognitive disturbances (Van Rijn et al., 2005).

The present study is, to the best of our knowledge, the first investigation of social cognitive processing in a large sample of Klinefelter men. Therefore, a broad range of aspects of social cognitive processing was investigated. Several tasks were included, reflecting aspects of social cognitive processing on levels of perception, experience and expression: labeling of facial expressions of emotion, emotion-cognition interactions in decision making and emotion regulation, that refers to subjective experience and identification of emotional arousal as well as verbal expression of emotions. The tasks in this study have been used in previous studies of social cognitive processing in schizophrenia and/or autism, and for all tasks neural correlates have been defined (A. Aleman, in press; R. Gur et al., 2002a; Sanfey et al., 2003).

## Methods

Subjects

32 Men with Klinefelter syndrome (mean age 38.8, SD 8.3) were studied. The participants were recruited from the Dutch Klinefelter Association, and were not selected for psychological, behavioral or cognitive abnormalities. Diagnosis of Klinefelter syndrome was confirmed by karyotyping, using standard procedures. In this group, 28 men were treated with testosterone supplements, with a mean age of treatment onset of 26.2 years (SD 7.9).

26 Male controls from the general population (mean age 35.2, SD 9.1) were included in the study. They were recruited using advertisements in local newspapers or were drawn from an already existing database in our department. There were no significant differences in age ($F(1,50)=2.4$, $p=0.12$) and years of education ($F(1,56)=0.4$, $p=0.52$) between the groups. None of the control subjects had a history of psychiatric illness as confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998).

Exclusion criteria for both Klinefelter men and controls were neurological conditions or history of head injury with loss of consciousness, recent history of substance abuse and mental retardation. After complete description of the study to the subjects, written informed consent was obtained.

Intellectual ability

*Raven's Advanced Progressive Matrices (short form)*

This test is commonly accepted as a measure of general intelligence and has been shown to correlate with a number of standardized intelligence tests (Lezak, 1995; Raven et al., 1993). Subjects are shown 12 pictures of matrices (i.e., related patterns), each of which is a figural design with a part removed. The subject must choose the correct missing part from eight options.

*National Adult Reading Test (NART)*

Since Klinefelter syndrome has been associated with verbal deficits, we included a measure of reading skills in addition to general I.Q. The Dutch translation of the NART (Nelson, 1982; Schmand et al., 1991) provides an estimate of verbal IQ and is based on the high correlation between reading ability, specifically of irregular words, with intelligence in the normal population. The test is composed of a list of 50 irregular words (i.e., pronunciation does not follow the normal phonetic rules) printed in order of increasing difficulty. Subjects are required to read these words aloud, and, on the basis of the number of errors made in pronunciation a reliable estimate of WAIS-R IQ can be calculated (Willshire et al., 1991).

General cognition

*General face recognition*

The Benton and Van Allen Test of Facial Recognition, Short Form (Benton & Van Allen, 1973), comprises a series of sheets containing a single photographed target face to be matched to a set of six face photographs. In the first six trials, the identical face has to be selected out of six options. In the remaining six trials, three different views (changed in orientation or lighting conditions compared to the target photograph) have to be discriminated from three incorrect alternatives. All faces are physically similar, not showing glasses or hair.

Social cognitive processing

*Facial Affect Recognition*

This task is a measure of explicit facial affect recognition of degraded faces, that has been used in earlier studies on emotion processing (van 't Wout et al., 2004). Photographs of four different actors, two male and two female, were used (Frigerio et al., 2002). Sixty-four trials were presented, consisting of 16 face presentations in each of four conditions: angry, happy, fearful and neutral. In each condition, 8 trials displayed 100% emotional intensity and the other 8 trials

displayed 75% emotional intensity. All photographs of the faces were passed through a filter that reduced visual contrast by 30%, in order to avoid local- and stimulate global processing. Subjects were asked to indicate the expression of each emotion by clicking with the mouse on one of the four emotion labels depicted on the computer screen. They were asked to work as accurately and rapidly as possible.

*Emotion in decision making*

The Ultimatum Game is an extensively studied paradigm originating from the field of strategic decision-making. It provides a measure of cognition-emotion interactions in strategic decision making, by inducing conflict between acceptance (cognitive motive) and rejection (emotional motive) of unfair financial offers (Sanfey et al., 2003).

In the Ultimatum Game two players were given the opportunity to split fictitious a sum of money, ?5. A fictitious proposer (20 times another person and 20 times the computer) made an offer as to how this money should be split between the two. The responder (participant) could either accept or reject this offer. If it was accepted, the money was split as proposed, but if the responder rejected the offer, then neither player received anything. In either event, the next offer appeared. 20 times the money was fairly split (5,00 versus 5,00) and in another 20 rounds the offer was unfair. There were three different unfair offers, i.e. twice 9,00 versus 1,00; twice 8,00 versus 2,- and once 7,00 versus 3,00. This resulted in a total of 40 rounds. The different offers (fair, unfair, human, computer) were assigned in a random order.

*Emotion regulation*

Alexithymia refers to a personality trait implying an inability or reduction to identify, experience, describe and reflect on one's own emotions (Lane et al., 1997; Sifneos, 1973).

We used the Bermond-Vorst Alexithymia Questionnaire to measure alexithymia, i.e. emotion-regulation (Morera et al., 2005; Vorst & Bermond, 2001). The BVAQ has good psychometric properties, and consists of five subscales: *Emotionalizing*: the degree to which someone is emotionally aroused by emotion inducing events. *Fantasizing*: the degree to which someone in inclined to fantasize, imagine, daydream, etc. *Identifying*: the degree to which one is able to define one's arousal states. *Analyzing*: the degree to which one seeks out explanations of one's own emotional reactions. *Verbalizing*: the degree to which one is able or inclined to describe or communicate about one's own

emotional reactions. Each of the subscales consists of eight items. Answers are scored on a 5-point scale (1=certainly does not apply to me, up to 5=certainly applies to me). The calculated scores were substracted from 50, resulting in lower scores reflecting lower capacity or performance.The latter three BVAQ-subscales have substantial overlap (correlation of .80) with the more widely used Toronto Alexithymia Scale 20 (TAS-20) (Bagby et al., 1994). However, the BVAQ also includes two measures of emotional experience, fantasizing and emotionalizing, which form part of the original definition of Alexithymia introduced by Sifneos (Sifneos, 1973).

Statistical analyses

Separate t-tests were conducted on the demographic data, Raven's Advanced Progressive Matrices, NART and the Benton and Van Allen test of Facial Recognition.

Data of the social cognitive tasks were analyzed using GLM repeated measures analysis, with a fixed factor Group (Klinefelter and control) and a variable factor reflecting the conditions within the tasks. When the multivariate tests indicated significant differences, the differences were analyzed with subsequent post-hoc ANOVA's. When potential confounding variables (i.e. general face recognition and intellectual ability) differed between the groups, then these were included as a covariate in the analysis. Alpha was set at 0.05.

## Results

Intellectual ability

Mean score on the Raven's Advanced Progressive Matrices was not significantly different between the groups ($t(1,55)=1.0$, $p=0.32$). Mean scores were 107.2 (SD 14.2) and 110.4 (SD 8.6) for the Klinefelter group and control group respectively.

On the NART, mean score of the Klinefelter men did not significantly differ from controls ($t(1,54)=1.78$, $p=0.08$). Mean score in de Klinefelter group was 103.5 (SD 9.8), for the control group it was 108.0 (SD 9.1).

General cognition

*General face recognition*

In general, no ceiling effects were observed in the Benton and van Allen test. Mean percentage of correct responses was 76.25 % and 80.0 % in the Klinefelter and control group respectively. No group differences were present

in general face recognition performance, t(1,55)= 1.83, p=0.07. Mean number of correct responses was 21.35 (SD 2.3) for Klinefelter men and 22.42 (SD 2.0) for control participants.

Social cognitive processing

*Facial Affect Recognition*

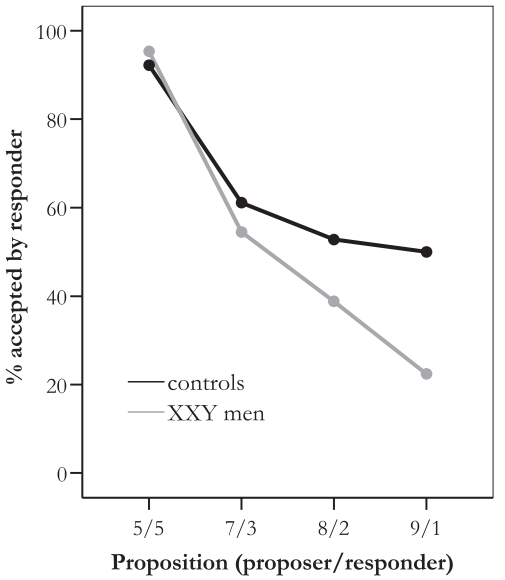
In general, performance on degraded facial affect recognition was well beyond chance level for each emotion. In the control group percentage correct was 84.4 for neutral faces, 89.7 for happy faces, 60.6 for fearful faces and 78.6 for angry faces. Percentage correct in the Klinefelter sample was 75.8 for neutral faces, 91.7 for happy faces, 58.8 for fearful faces and 67.7 for angry faces.

A GLM repeated measures analysis showed an interaction between Group (Klinefelter, control) and Emotional Expression (neutral, fear, anger, happy), F(1,53)=3.11, p=0.03. Post-hoc ANOVA's demonstrated a significant difference between the groups in the recognition of anger, F(1,55)=5.98, p=0.018, i.e. Klinefelter men were less accurate as compared to control subjects (mean number correct responses: 10.8 and 12.6 respectively). This deficit appeared not to depend on intensity of the emotional expressions, as group differences were present in both the 75% anger condition (F(1,55)=4.57, p=0.037) and the 100% anger condition (F(1,55)=4.79, p=0.033). There was no specific bias of Klinefelter men in type of errors when erroneously labeling anger. A GLM repeated measures analysis with factor Group (Klinefelter, control) and factor error-type (% happy, fear and neutral with error anger) demonstrated no group differences in the error pattern, F(2,48)=0.73, p=0.48.

*Emotion in decision-making*

Although the UItimatum Game was not performed by 8 of the controls and 3 of the Klinefelter men, exclusion of these subjects did not affect matching of the groups on age, years of education, verbal I.Q and performal I.Q. A significant (within-subjects contrasts) interaction between Group and Percentage accepted offers was observed when the Ultimatum Game was played with a human proposer (F(1,45)=6.45, p=0.015). Post-hoc ANOVA's demonstrated a significant difference between the groups in the proportion accepted offers in the most unfair (9/1) condition (F(1,45)=5.93, p=0.019), i.e. Klinefelter men rejected significantly more offers compared to control subjects. Results are presented in figure 1. No significant differences between the groups were observed when the Ultimatum Game was played with a computer.

**Figure 1**
When the Ultimatum game was played with a human proposer, Klinefelter males rejected significantly more offers compared to control subjects in the most unfair (€9:€1) condition.




*Emotion regulation*
A significant interaction was observed between Group and the alexithymia dimensions ($F(1,54)=6.32$, $p<0.001$). Klinefelter men showed increased scores compared to controls, indicating more problems, on the subscales *Identifying* ($F(1,54)=8.18$, $p=0.006$) and *Verbalizing* ($F(1,54)=4.73$, $p=0.034$). In addition, lower scores on the subscale *Emotionalizing* ($F(1,54)=10.88$, $p=0.002$) were observed in the Klinefelter group, indicating that Klinefelter men are more easily emotionally aroused. See table 1 for mean scores and standard deviations.

**Table 1**
In the Alexithymia questionnaire, Klinefelter males reported significantly more difficulties (i.e. higher scores) in *identifying* as well as in *verbalizing* their emotions and reported to be more easily emotionally aroused as indicated by lower scores on the subscale *emotionalizing* (*p<.05).

| Dimensions of Alexithymia | Controls (mean, SD) | Klinefelter men (mean, SD) |
|---|---|---|
| Verbalizing emotions | 20.2 (6.2) | 24.6 (8.3) * |
| Fantasizing | 24.6 (8.2) | 21.1 (8.0) |
| Identifying emotions | 15.6 (4.0) | 20.2 (7.0) * |
| Emotionalizing | 26.2 (6.3) | 20.7 (5.9) * |
| Analyzing emotions | 18.6 (6.1) | 19.2 (7.7) |

## Conclusion

The current study investigated various aspects of social cognitive processing and emotion regulation in Klinefelter syndrome, a genetic disorder characterized by an XXY chromosomal pattern. Our findings suggest disturbances in perception, experience and expression of social cognitive information in this population. Specific deficits in perception of facial expressions of anger were observed. Abnormal experience of emotions in Klinefelter men was suggested by both explicit and implicit measures. Klinefelter men explicitly reported increased emotional arousal in response to emotion-inducing events and were more influenced by their emotions in a strategic decision making game. Difficulties in identification and expression of one's own emotions were also found in this group, as indicated by the alexithymia measures. Taken together, Klinefelter men seem less accurate in perception of social-emotional cues, experience increased levels of emotional arousal, but are less able to identify and verbalize the emotions they experience, in comparison to the general population.

These deficits in social cognition may explain, in part, the social difficulties that have been described in Klinefelter syndrome. First, we found Klinefelter men to be impaired in recognizing facial expressions of anger, independent of the intensity of the emotional expression. Misperception of angry facial expressions may contribute to problems in social interactions, as non-verbal signals 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 (Christine Hooker & Park, 2002).

Regarding the experience of emotions, Klinefelter men rejected more often unfair financial offers from human proposers as compared to the control group in the Ultimatum game. This pattern of performance is shown to reflect the influence of emotion, in response to the offer being unfair, on strategic decision making (Sanfey et al., 2003). A recent fMRI study has shown that rejection of unfair offers could be significantly predicted on the basis of insular activity (Sanfey et al., 2003), a brain region involved in processing emotions such as disgust (Wicker et al., 2003), and monitoring of the internal milieu, for example arousal (Augustine, 1996). In line with this, a recent study revealed that autonomic, emotional arousal, as measured by skin conductance activity, is higher for unfair offers and associated with the rejection of unfair offers in this particular paradigm (van 't Wout et al., in press). Interestingly, in Klinefelter syndrome, structural abnormalities of the insula and amygdala have been

reported which may, in part, contribute to this pattern of performance indicating increased emotional arousal (Shen et al., 2004).

Autistic adults, like Klinefelter men, also accept very little in this paradigm and it has been proposed that impairments in reading intentions and beliefs from others play a role in rejecting unfair offers (Camerer, 2003). Although speculative, our finding that Klinefelter men only rejected more offers when proposed by a human individual, and not when proposed by a computer, tentatively suggests that Klinefelter men have problems in reading intentions of other people. The present results support our hypothesis that *social* cognition in Klinefelter syndrome is disturbed, which is expressed predominantly in social contexts such as interpersonal relations. The hypothesis regarding theory of mind capabilites in Klinefelter syndrome should be tested in future research.

Besides this implicit emotional task, increased emotional experience was also observed in an explicit, self-report measure of emotional experience, i.e. the alexithymia questionnaire. Klinefelter men reported increased emotional arousal in response to emotion-inducing events, as indicated by the subscale 'emotionalizing' in the Alexithymia questionnaire. In contrast to apparent *hyperfunctional* emotional -experience and -reactivity, identifying and verbalizing these emotions appears to be *hypofunctional* in Klinefelter syndrome. The latter finding can be considered as a possible risk factor for both medical and psychiatric disorders (Bagby & Taylor, 1997). Interestingly, the specific alexithymia profile observed in Klinefelter syndrome has recently also been described for schizophrenia patients and their relatives, indicating that it may be an expression of the genetic vulnerability for the disease (van 't Wout et al., in prep.). The finding that alexithymia seems to be under considerable genetic control fits this picture (Valera & Berenbaum, 2001).

Recently, a model has been proposed that can explain the two seemingly contradictory features in schizophrenia that we also find in Klinefelter syndrome; deficits in perception and experience on the one hand and increased emotional arousal on the other hand (A. Aleman & Kahn, 2005a). This neuroanatomical model describes amygdala dysfunctions that arise from structural abnormalities of the amygdala in combination with an imbalance in dopamine systems, with specific effects on intra-amygdaloid processing. Indeed, Klinefelter syndrome, as well as other populations at increased risk for schizophrenia, has been associated with structural abnormalities of the amygdala (Van Rijn et al., 2005). Interestingly, such a dissociation between cognitive appraisal of emotions on the one hand and autonomic, emotional arousal on the other hand has also been reported for females with Turner

syndrome, characterised by X monosomy (45,X) and a 200-fold increased risk for autism. Turner syndrome subjects display (left amygdala mediated) impairments in labeling of facial expressions of both anger and fear, while their (right amygdala mediated) somatic responses are enhanced in reponse to emotional faces (D. Skuse et al., 2005). Thus, X-linked genes seem important for functional integration of autonomic, emotional arousal with cognitive appraisal of emotions.

Altogether, the present study reveals the behavioral/functional consequences of a compromised neural network for social cognitive processing. A central issue concerns the degree to which these disturbances in social cognitive processing are related to the X chromosomal abnormality. Evidently, neural and behavioral phenotypes in Klinefelter syndrome can all be traced back to the additional X chromosome. In this regard, studies with individuals with Turner syndrome (45,X) may provide some insight. In one of these studies, a dosage-sensitive locus on the X chromosome has been identified that directs development of the amygdala (Good et al., 2003). As in Klinefelter syndrome, individuals with Turner syndrome have social adjustment problems and poor social skills (Lesniak-Karpiak et al., 1999; Mazzocco et al., 1998). These parallels in brain architecture and socio-behavioral phenotype support the idea that (mal)development of this area in Klinefelter syndrome may indeed be under control of genes on the X chromosome.

Unfortunately, the exact pathway from X chromosome abnormalities to social cognitive impairments in Klinefelter syndrome remains unclear. One of the issues deserving attention is the role of abnormal testosterone levels in Klinefelter syndrome, which become apparent in puberty. It is thought that during development circulating gonadal hormones can modify brain structure and -function of target areas. As shown by animal studies, one of the major target areas of testosterone is the amygdala (Simerly et al., 1990). However, the relation between testosterone levels and behavior is complex; timing of exposure, sensitivity to testosterone reflected in androgen receptor density and modulation by environmental factors are important determinants in the behavioral effects of testosterone (Craig et al., 2004). Furthermore, gonadal hormones may be one of many mechanisms by which sex chromosomes exert their influence on brain development. Recent animal studies have pointed to direct, non-hormonal, effects of sex-chromosomes on brain maturation (Dewing et al., 2003).

Reports of increased levels of schizophrenia spectrum pathology and autistic features in Klinefelter men point to a role of the X chromosome in

psychiatric disorders with predominant social cognitive impairments (L.E. DeLisi et al., 1994; L. E. DeLisi et al., 2005; Gillberg, 1995; Swaab et al., in prep.; van Rijn et al., in press; Van Rijn et al., 2005). Although speculative, X-related disturbances in social cognitive processing may be one of many pathways to psychiatric disorders such as schizophrenia and autism. As these disorders are more common in males compared to females (A. Aleman et al., 2003; D. H. Skuse, 2000), it will be interesting in future studies to investigate if and how the widely described sex differences in social cognition can be related to genes on the X chromosome and whether such genes are implicated in these psychiatric disorders (S. Baron-Cohen et al., 2005; Scourfield et al., 1997). Also, more studies are needed to explore the role of testosterone in social cognitive impairments in Klinefelter syndrome as well as autism and schizophrenia, especially since there are findings pointing to abnormal testosterone levels in these latter disorders (S. Baron-Cohen et al., 2005; Goyal et al., 2004).

In a recent review it has been argued that the amygdala abnormalities seen in schizophrenia may be an X-linked endophenotype that can account for the social cognitive processing deficits observed in patients and their relatives (Van Rijn et al., 2005). Also, it has been proposed that dysfunctional neural circuits underlying social cognitive impairments in autism may be phenotypes of X-linked genes, that may be sexually dimorphic in expression (S. Baron-Cohen et al., 2005; D. Skuse, 2003). Support for this hypothesis also comes from a review of all chromosomal studies in autism suggesting that the X chromosome, chromosome 15 and 17 are the most consistently reported chromosomes to show abnormalities in the field of autism spectrum disorders (S Baron-Cohen, 2004).

A crucial question is how Klinefelter syndrome may serve as a model for investigating the potential role of X-linked genes for susceptibility to mental disorders, most notably schizophrenia. In contrast to schizophrenia, the genetic pathology underlying deficits in Klinefelter syndrome is known. Common endophenotypes that are shared by both disorders, such as deficits in social cognition, point to a role of the X chromosome in social cognitive dysfunction in the schizophrenia spectrum. Subsequently, one can narrow the search for genetic pathology involved in schizophrenia, with the hypothesis that genes on the X chromosome may code for abnormal social cognition in schizophrenia. Other possibilities may be to compare and study genetic pathology of subgroups of Klinefelter men: with low versus high levels of schizophrenia spectrum pathology, or poor versus relatively spared social cognition. This might lead us to more specific underlying genetic mechanisms such as genomic

imprinting or degree of X inactivation. Of course, these strategies apply to all endophenotypes that are shared by schizophrenia, which is clinically defined, and Klinefelter syndrome, which is genetically defined.

Finally, we are aware of some limitations of the present study. As many men with Klinefelter syndrome remain undiagnosed (Bojesen et al., 2003), our sample may not be completely representative. In spite of this, the present findings describe social cognitive deficits, that may have important implications for daily life functioning, in at least a specific population of Klinefelter men.
In summary, the disturbances in perception, experience and expression of social cognitive information that were observed in Klinefelter men may explain the social difficulties that have been reported in this syndrome. Besides describing the social cognitive phenotype of this specific genetic disorder, the present data encourage the development of a general model describing gene-brain-behavior pathways underlying neuropsychiatric disorders characterized by social cognitive disturbances.

**References**

Aleman, A. (in press). Feelings you can't imagine: Towards a cognitive neuroscience of alexithymia. Trends in Cognitive Sciences.

Aleman, A., & Kahn, R. S. (2005). Strange feelings: Do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Progress in Neurobiology, in press.

Aleman, A., Kahn, R. S., & Selten, J. P. (2003). Sex differences in the risk of schizophrenia: Evidence from meta-analysis. Archives of General Psychiatry, 60(6), 565-571.

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. Brain Research Reviews, 22(3), 229-244.

Bagby, R. M., & Taylor, G. J. (1997). Affect dysregulation and alexithymia. In G. J. Taylor, R. M. Bagby & J. D. A. Parker (Eds.), Disorders of affect regulation: Alexithymia in medical and psychiatric illness. UK: Cambridge University Press.

Bagby, R. M., Taylor, G. J., & Parker, J. D. A. (1994). The 20-item toronto-alexithymia-scale.2. Convergent, discriminant, and concurrent validity. Journal of Psychosomatic Research, 38(1), 33-40.

Baron-Cohen, S. (2004). The cognitive neuroscience of autism. J Neurol Neurosurg Psychiatry, 75(7), 945-948.

Baron-Cohen, S., Knickmeyer, R. C., & Belmonte, M. K. (2005). Sex differences in the brain: Implications for explaining autism. Science, 310(5749), 819-823.

Benton, A. L., & Van Allen, M. W. (1973). Test of face recognition manual (number 287 ed.). Department of Neurology, Iowa, USA: Neurosensory Center Publication.

Bojesen, A., Juul, S., Birkebaek, N. H., & Gravholt, C. H. (2006). Morbidity in klinefelter syndrome; a danish register study based on hospital discharge diagnoses. J Clin Endocrinol Metab.

Bojesen, A., Juul, S., & Gravholt, C. H. (2003). Prenatal and postnatal prevalence of klinefelter syndrome: A national registry study. The Journal of Clinical Endocrinology and Metabolism, 88(2), 622-626.

Camerer, C. F. (2003). Psychology and economics: Enhanced: Strategizing in the brain. Science, 300(5626), 1673-1675.

Craig, I. W., Harper, E., & Loat, C. S. (2004). The genetic basis for sex differences in human behaviour: Role of the sex chromosomes. Annals of Human Genetics, 68, 269-284.

DeLisi, L. E., Friedrich, U., Wahlstrom, J., Boccio_Smith, A., Forsman, A., Eklund, K., et al. (1994). Schizophrenia and sex chromosome anomalies. Schizophrenia Bulletin, 20(3), 495-505.

DeLisi, L. E., Maurizio, A. M., Svetina, C., Ardekani, B., Szulc, K., Nierenberg, J., et al. (2005). Klinefelter's syndrome (xxy) as a genetic model for psychotic disorders. Am J Med Genet B Neuropsychiatr Genet, 135(1), 15-23.

Dewing, P., Shi, T., Horvath, S., & Vilain, E. (2003). Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. Molecular Brain Research, 118(1-2), 82-90.

Frigerio, E., Burt, D. M., Montagne, B., Murray, L. K., & Perrett, D. I. (2002). Facial affect perception in alcoholics. Psychiatry Research, 113(1-2), 161-171.

Geschwind, D. H., Boone, K. B., Miller, B. L., & Swerdloff, R. S. (2000). Neurobehavioral phenotype of klinefelter syndrome. Mental Retardation and Developmental Disabilities Research Reviews, 6(2), 107-116.

Gillberg, C. (1995). Specific syndromes not otherwise referred to. In G. Christopher (Ed.), Clinical child neuropsychiatry (pp. 185-267). Cambridge, U.K.: Cambridge University Press.

Good, C. D., Lawrence, K., Thomas, N. S., Price, C. J., Ashburner, J., Friston, K. J., et al. (2003). Dosage-sensitive x-linked locus influences the development of amygdala and orbitofrontal cortex, and fear recognition in humans. Brain, 126(11), 2431-2446.

Gotz, M. J., Johnstone, E. C., & Ratcliffe, S. G. (1999). Criminality and antisocial behaviour in unselected men with sex chromosome abnormalities. Psychological Medicine, 29(4), 953-962.

Goyal, R. O., Sagar, R., Ammini, A. C., Khurana, M. L., & Alias, A. G. (2004). Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann N Y Acad Sci, 1032, 291-294.

Gur, R., Schroeder, L., Turner, T., McGrath, C., Chan, R., Turetsky, B., et al. (2002). Brain activation during facial emotion processing. Neuroimage, 16(3 Pt 1), 651.

Hooker, C., & Park, S. (2002). Emotion processing and its relationship to social functioning in schizophrenia patients. Psychiatry Research, 112(1), 41-50.

Kunugi, H., Lee, K. B., & Nanko, S. (1999). Cytogenetic findings in 250 schizophrenics: Evidence confirming an excess of the x chromosome aneuploidies and pericentric inversion of chromosome 9. Schizophr Res, 40(1), 43-47.

Lane, R. D., Ahern, G. L., Schwartz, G. E., & Kaszniak, A. W. (1997). Is alexithymia the emotional equivalent of blindsight? Biol Psychiatry, 42(9), 834-844.

Lanfranco, F., Kamischke, A., Zitzmann, M., & Nieschlag, P. E. (2004). Klinefelter's syndrome. The Lancet, 364(9430), 273-283.

Lesniak-Karpiak, K., Mazzocco, M. M., Lanham, D. C., & Denckla, M. B. (1999). Behavioral assessment of social skills in children with turner syndrome or fragile x. Archives of Clinical Neuropsychology, 14(8), 767-767.

Lezak, M. D. (1995). Neuropsychological assessment (third ed.). New York: Oxford University Press.

Mazzocco, M. M. M., Baumgardner, T., Freund, L. S., & Reiss, A. L. (1998). Social functioning among girls with fragile x or turner syndrome and their sisters. Journal of Autism and Developmental Disorders, 28(6), 509-517.

Morera, O. F., Culhane, S. E., Watson, P. J., & Skewes, M. C. (2005). Assessing the reliability and validity of the bermond-vorst alexithymia questionnaire among u.S. Anglo and u.S. Hispanic samples. Journal of Psychosomatic Research, 58(3), 289-298.

Nelson, H. E. (1982). National adult reading test (nart), manual. Windsor, Bershire, UK: NFER-Nelson.

Pinkham, A. E., Penn, D. L., Perkins, D. O., & Lieberman, J. (2003). Implications for the neural basis of social cognition for the study of schizophrenia. American Journal of Psychiatry, 160(5), 815-824.

Ratcliffe, S. (1999). Long-term outcome in children of sex chromosome abnormalities. Archives of Disease in Childhood, 80(2), 192-195.

Raven, J. C., Raven, J., & Court, J. H. (1993). Manual for raven's progressive matrices and vocabulary scales. Oxford: Oxford Psychologist Press.

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2003). The neural basis of economic decision-making in the ultimatum game. Science, 300(5626), 1755-1758.

Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). [the dutch reading test for adults: A measure of premorbid intelligence level]. Tijdschrift voor Gerontologie en Geriatrie, 22(1), 15-19.

Scourfield, J., Martin, N., Lewis, G., & McGuffin, P. (1999). Heritability of social cognitive skills in children and adolescents. British Journal of Psychiatry, 175, 559-564.

Scourfield, J., McGuffin, P., & Thapar, A. (1997). Genes and social skills. Bioessays: News and Reviews in Molecular, Cellular and Developmental Biology, 19(12), 1125-1127.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The mini-international neuropsychiatric interview (m.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. Journal of Clinical Psychiatry, 59 Suppl 20, 22-33;quiz 34-57.

Shen, D., Liu, D., Liu, H., Clasen, L., Giedd, J., & Davatzikos, C. (2004). Automated morphometric study of brain variation in xxy males. NeuroImage, 23(2), 648-653.

Sifneos, P. E. (1973). The prevalence of 'alexithymic' characteristics in psychosomatic patients. Psychotherapy and Psychosomatics, 22(2), 255-262.

Simerly, R. B., Chang, C., Muramatsu, M., & Swanson, L. W. (1990). Distribution of androgen and estrogen-receptor messenger rna-containing cells in the rat-brain - an insitu hybridization study. Journal of Comparative Neurology, 294(1), 76-95.

Skuse, D. (2003). X-linked genes and the neural basis of social cognition. Autism: Neural Basis and Treatment Possibilities, Novartis Foundation Symposium, 251, 84-98.

Skuse, D., Morris, J. S., & Dolan, R. J. (2005). Functional dissociation of amygdala-modulated arousal and cognitive appraisal, in turner syndrome. Brain, 128(Pt 9), 2084-2096.

Skuse, D. H. (2000). Imprinting, the x-chromosome, and the male brain: Explaining sex differences in the liability to autism. Pediatric Research, 47(1), 9-16.

Swaab, H., Cohen-Kettenis, P. T., & Van Engeland, H. (in prep.). Social dysfunction in boys with klinefelter syndrome.

Valera, E. M., & Berenbaum, H. (2001). A twin study of alexithymia. Psychotherapy and Psychosomatics, 70(5), 239-246.

van 't Wout, M., Aleman, A., Bermond, B., & Kahn, R. (in prep.). No words for feelings: Alexithymia in schizophrenia patients and first degree relatives.

van 't Wout, M., Aleman, A., Kessels, R. P., Laroi, F., & Kahn, R. S. (2004). Emotional processing in a non-clinical psychosis-prone sample. Schizophrenia Research, 68(2-3), 271-281.

van 't Wout, M., Kahn, R., Sanfey, A. G., & Aleman, A. (in press). Affective state and decision-making in the ultimatum game. Experimental Brain Research.

van Rijn, S., Aleman, A., Swaab, H., & Kahn, R. (in press). 47,xxy karyotype and schizophrenia spectrum pathology. British Journal of Psychiatry.

Van Rijn, S., Aleman, A., Swaab, H., & Kahn, R. S. (2005). Neurobiology of emotion and high risk for schizophrenia: Role of the amygdala and the x-chromosome. Neuroscience and Biobehavioral Reviews, 29(3), 385-397.

Vorst, H. C. M., & Bermond, B. (2001). Validity and reliability of the bermond-vorst alexithymia questionnaire. Personality and Individual Differences, 30(3), 413-434.

Wicker, B., Keysers, C., Plailly, J., Royet, J. P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in my insula: The common neural basis of seeing and feeling disgust. Neuron, 40(3), 655-664.

Willshire, D., Kinsella, G., & Prior, M. (1991). Estimating wais-r iq from the national adult reading test - a cross-validation. Journal of Clinical and Experimental Neuropsychology, 13(2), 204-216.