Chapter 10

Functional neuroimaging evidence for abnormal brain activation during social perception in a sex chromosomal disorder (Klinefelter syndrome, 47XXY)

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Abstract

Klinefelter syndome is a sex chromosomal disorder (47, XXY) that may help us to unravel genotype-phenotype relations. The XXY karyotype has been associated with behavioral problems in the social domain and deficits in social cognition have been observed. Here we used functional MRI to reveal the neural correlates of social perception in XXY men.

Eigtheen healthy men and thirteen XXY men were scanned during social evaluation of faces. In an event-related design, we measured activation in a neural network comprising the amygdala, insula, superior temporal sulcus (STS) and fusiform gyrus during judgments of faces with regard to trustworthiness. Judging faces as untrustworthy was associated with less activation in each of the four brain areas in XXY men as compared to men from the general population. To our knowledge, this is the first study of brain mechanisms underlying social perception in Klinefelter syndrome. Reduced engagement of brain areas important for social perception may explain some of the deficits in social cognition and in social behavior that have been observed in XXY men. Our findings suggest a link between the X chromosome and abnormal development of the neural networks involved in social perception in Klinefelter syndrome. Besides revealing a neural basis for social dysfunctions in this specific genetic disorder, the data show that Klinefelter syndrome may serve as a model for studying the genetic basis of disturbances in the development of social cognition, which are considered core abnormalities in severe psychiatric disorders such as autism and schizophrenia.

Introduction

Genetic disorders associated with specific deficits in brain development and cognition may help us to unravel genotype-phenotype relations. One such disorder is Klinefelter syndrome, defined by the presence of an extra X chromosome in men (47,XXY). Unlike many other X chromosomal disorders, XXY men do not display general intellectual deficits, which allows the study of specific cognitive abilities and their neural mechanisms without the confound of a general intellectual deficit.

Many boys and men with Klinefelter syndrome suffer from behavioral problems in the social domain, such as social withdrawal, social anxiety, shyness, impulsivity and inappropriate social behavior (Boone et al., 2001; Geschwind et al., 2000; Ratcliffe, 1999). Data on cognitive mechanisms that may underlie the impaired social adaptation in XXY men is scarce. It is generally thought that the social difficulties, particularly those regarding communication are attributable to the verbal disabilites that have been found consistently in Klinefelter syndrome (see Samango-Sprouse, 2001). However, other deficits, such as abnormal facial affect recognition, that were also observed in XXY men (Van Rijn et al., 2006b) may play an equally important role in explaining some of the social problems in Klinefelter syndrome.

Compared to what is known about the cognitive deficits that may contribute to social difficulties in Klinefelter syndrome, much less is known about the neural mechanisms that are involved. Interestingly, abnormalities in structural development of brain regions important for processing social information in XXY men are suggested by structural Magnetic Resonance Imaging (MRI) finding volume reductions the amygdala, insula, anterior cingulate and superior temporal gyrus in XXY men (DeLisi et al., 2005; Patwardhan et al., 2002; Shen et al., 2004). As Klinefelter syndrome is defined by the presence of an additional X chromosome, the structural abnormalities may result from genetic mechanisms involving the X chromosome. Support for the importance of the X chromosome for both structural and functional development of neural networks subserving social cognition is provided by neuroimaging studies with females with Turner syndrome, another X chromosomal disorder that is characterised by the presence of only one X chromosome in females (the X0 karyotype). X monosomy has been associated with abnormalities of the amygdala, superior temporal gyrus and -sulcus, anterior cingulate, orbitofrontal cortex and insula, which are brain regions involved in processing social information (Kesler et al., 2003; Kesler et al., 2004; Molko et al., 2004; Murphy et al., 1997; Skuse et al., 2005).

Although reductions in volume of brain areas important for social cognitive processing have been found in XXY men, it remains unclear whether and to what degree these neural networks are dysfunctional. In this study, we investigated the effects of an additional X chromosome on functioning of key brain regions involved in social perception (Adolphs, 2001). To our knowledge, this is the first study of functional brain mechanisms underlying social perception in Klinefelter syndrome. Using functional Magnetic Resonance Imaging (fMRI) we measured activity in a neural network including the amygdala, fusiform face area, insula and superior temporal sulcus during trustworthiness evaluations of faces. These regions were selected based on their involvement in trustworthiness evaluations in the general population (Winston et al., 2002).

The presence of dysfunctions in neural networks underlying social cognition in men with the XXY karyotype may have several potential implications. First, it would provide a neural basis for the social cognitive dysfunctions that have been observed in men with Klinefelter syndrome. Second, it would suggest that the X chromosome may play an important role in the development of some of the brain areas subserving social cognition in Klinefelter syndrome and possibly also in the general population. Third, we might speculate that the X chromosome plays a role in some of the brain abnormalities associated with social cognitive dysfunction in other disorders, such as autism and schizophrenia, which are more prevalent in men.

Methods

Subjects

Thirteen XXY men (mean age 39.0, SD 10.3) and 18 control men from the general population (mean age 32.2, SD 9.4) participated in the fMRI study. XXY men were recruited via the Dutch Klinefelter Association, and were not selected for psychological, behavioral or cognitive abnormalities. Diagnosis of Klinefelter syndrome was confirmed by genetic analysis (i.e. karyotyping) using standard procedures. Of the 13 XXY men, 11 were treated with testosterone supplements (mean age of treatment onset of 23.4, SD 6.8 years). Data on intellectual abilities as measured with the WAIS-III were available in our database for 11 XXY men (data on intelligence were collected within one year of the fMRI session). Mean general intelligence in these XXY men was 94.4 (SD 14.35), with a score of 96.3 (SD 14.9) for verbal intelligence and 93.7 (SD 12.0) for performance intelligence. There were no significant differences in age

(t(1,29)=3.5, p=0.07) or years of education between the groups (Klinefelter group 14.9 (SD 2.1), control group 15.9 (SD1.8), t(1,29)=1.29, p=0.18). 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 (which was approved by the local ethical board) to the subjects, written informed consent was obtained according to the declaration of Helsinki.

Social judgment task

In the MRI scanner subjects completed a task (adapted from Winston et. al.) that involved judgments based on facial appearance. Subjects were presented with 16 task blocks of 45 s., in which every 3 s. a face was presented, alternated with rest periods of 45 s., during which a fixation cross was presented. Neural correlates of both explicit social evaluations as well implicit, indirect attention to social signals from faces was measured. In the explicit condition (eight task blocks) a trustworthiness judgment was required, i.e. untrustworthy or trustworthy. In the implicit condition (eight task blocks) an age judgment was required, i.e. older or younger than 30 years. Explicit and implicit task blocks were alternated. Decisions were indicated by button presses. Each face was presented once.

Scans

Functional scans were aquired with a Phillips ACS-NT 1.5-T clinical scanner, using a blood-oxygen-level dependent sensitive (BOLD), gradient-echo echoplanar T2*-weighted sequence, with the following parameter settings: echo time 40 ms; repetition time 76 ms; flip angle 90 degrees; field of view 192 x 192 x 99 mm. Each volume comprised 33 x 2.2 mm axial scans with 3-mm in-plane resolution, and volumes were continuously acquired every 2.5 s in an interleaved fashion (bottom slice first). Each run was preceded by 6 'dummy' scans (which were not used in further analyses) to allow for T1 equilibration effects. Finally, a T1 weighted structural image was acquired.

Regions of interest

Regions of interest (ROI's) were selected based on the findings in the fMRI study of Winston et al. (2002), showing that the amygdala, insula, fusiform gyrus and superior temporal sulcus (STS) are key brain regions involved in judging trustworthiness from faces. Using the WFU Pickatlas tool for SPM (Maldjian et al., 2003), ROI's for the fusiform area, insula and STS were formed based on the talairach atlas (in MNI space) and a ROI for the amygdala was formed based on the AAL atlas (in MNI space). Size of the ROI's was 162 voxels for the amygdala, 1029 voxels for the fusiform gyrus, 1436 voxels for the insula and 3872 voxels for the STS.

fMRI analysis

Functional MRI data preprocessing and analysis was done using SPM2 (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk). After slice-timing correction, all functional scans were registered to the last volume of the last block and coregistered to the anatomical scan. Next, all functional images were registered to an MNI standard brain, to enable group-wise comparisons. All volumes were then smoothed with a 6 mm full-width half-maximum isotropic Gaussian kernel. Time series were high-pass filtered with a cut-off of 128 sec. to remove low frequency signal changes.

In this event-related design, brain activity maps were obtained by analysing the fMRI scans categorised according to individual judgments of trustworthiness and age. For each subject, a statistical map (i.e. t-map) was obtained from a general linear model regression analysis using a factor matrix that contained a regressor modeling the onsets of faces that were judged to be untrustworthy, a regressor modeling the onsets of faces that were judged to be trustworthy and a regressor which modeled the onsets of faces that were judged during the age condition.

First, a whole brain analysis was performed (for the groups seperately) on activation related to trustworthiness decisions (all faces) versus baseline. P value was set at 0.001, uncorrected, with an extend threshold of 10 voxels. Second, significant activation in each region of interest was determined in each voxel by applying a statistical treshold. The threshold corresponded to a p value of 0.05, FWE-corrected for multiple comparisons and resulted in the control group to a t-value of 3.70 for the amygdala, 4.80 for the fusiform gyrus, 5.22 for the insula and 5.73 for the STS. To enhance the interpretability of the within-group activation patterns, the thresholds that we applied in the XXY group were identical to those in the control group. Note however, that group differences in

brain activation were explicitly tested in two-sample T-tests. Several averaged contrasts maps were creasted for both groups, namely: trustworthy minus base-line, untrustworthy minus base-line and untrustworthy minus trustworthy. The averaged contrast maps for each group (XXY men and controls) were subsequently entered in a two-sample t-test and differential task activation was defined as differential activation above a significance threshold of $P<0.001$, uncorrected.

Results

Behavioral

A repeated measures analysis indicated no significant interactions between group and trustworthiness judgments ($F1,29)=0.03$, $p=0.87$). Within each group, no significant differences between the mean number of decisions of 'trustworthy' and 'untrustworthy' were observed, as indicated by paired sample t-tests ($t(1,12)=1.21$, $p=0.25$ for XXY men and $t(1,17)=1.70$, $p=0.11$ for controls).

Neural activations associated with judging trustworthiness of faces

Results of the whole-brain analysis are presented in table 1 for controls and table 2 for XXY men. With regard to our regions of interest, within-group analyses indicated significant activation in the fusiform gyrus in both groups when faces were judged *trustworthy* compared to baseline. In the control group the t value was above threshold in 68 voxels (t max.=7.9; x,y,z= -39, -69, -21), whereas in the XXY group this was 17 voxels (t max.=8.2, x,y,z= 45, -57, -24). Indeed, a subsequent two-sample t-test indicated slightly, but significantly, more activation in the fusiform gyrus in controls as compared to XXY men (1 voxel, t max.=3.6, $p<0.001$, x,y,z= 30, -60, -15). No significant activation in the amygdala, STS or insula was observed in both groups. The crucial comparison was the difference in brain activation between the groups when faces were judged *untrustworthy* (versus baseline). Again, within group analyses of activation in our ROI's indicated significant activation in the fusiform gyrus in the control group (62 voxels, t max.=7.8; x,y,z= 39, -69, -18) and the XXY group (1 voxel, t=4.9; x,y,z= 45, -57, -24). In addition, significant activation in the amygdala (bilaterally) was observed in the control group (16 voxels, t max.=4.2; x,y,z= 21,-3,-18), but not in the XXY group. A two sample t-test not only showed significantly more activation in the fusiform gyrus (17 voxels, t max.=4.7,

p<0.001, x,y,z= -30, -33, -24), including the fusiform face area (FFA, see Grill-Spector et al., 2004 for coordinates), but also in the left amygdala (3 voxels, t max.=4.77, p<0.001, x,y,z=-21, 3, -18) in the control group as compared to the XXY group. In addition, small but significant group differences were observed in the insula (1 voxels, t max.=3.6, p=0.001, x,y,z= 27, 12, -21), with reduced activation in the XXY group.

Neural activations associated with judging age of faces

When judging the age of the presented faces, significant activation (as compared to baseline) in ROI's important for social perception was observed in both groups. In controls, significant activation in the fusiform gyrus (143 voxels, t max.=10.2, x,y,z=-39, -48, -24), insula (12 voxels, t max.=6.6, x,y,z= -33, 18, 9) and amygdala (2 voxels, t max.=4.9, x,y,z= 21, -3, -12) was observed. In XXY men, significant activation was found in the fusiform gyrus (30 voxels, t max.=7.8, x,y,z= 42, -54, -21) and slight activation in the insula (1 voxel, t=6.1, x,y,z= -39, 12, 15) and amygdala (1 voxel, t=3.9, x,y,z= -24, -3, -27), but not in the STS. A two-sample t-test showed that activation in the fusiform gyrus (11 voxels, t max.= 4.3, p<0.001, x,y,z= -30, -66, -15) and STS (12 voxels, t max.= 4.05, p<0.001, x,y,z= -45, -54, 12), but not in the insula or amygdala, was significantly stronger in in the control group than in the XXY group.

Table 1
Areas with significant activation associated with trustworthiness judgments of faces in controls as indicated by a whole-brain analysis.

Region	Max. t value	Max. z value	Nr. of voxels	x,y,z peak activation
Middle occipital gyrus	8.99	5.39	528	-48, -78, -12
Lingual gyrus (region includes fusiform gyrus)	8.47	5.23	1704	-3, -75, 0
Inferior frontal gyrus	7.19	4.81	234	48, 6, 36
	6.85	4.68	81	30, 30, -3
	4.75	3.74	17	51, 36, -6
Medial frontal gyrus	6.88	4.69	90	-6, 6, 48
Insula	6.53	4.56	61	-33, 21, 0
Cingulate gyrus	6.53	4.56	18	9, 24, 30
Caudate nucleus	6.11	4.38	21	-12, 9, 3
Thalamus	6.04	4.36	77	18, -24, 12
	5.11	3.92	38	-6, -18, 9
Parahippocampal gyrus	5.75	4.23	23	-15, -3, 15
Middle frontal gyrus	5.27	4.00	26	36, 42, 27
	5.04	3.89	10	42, 42, 15
Amygdala	4.89	3.81	14	18, -6, -18
Cerebellum	4.38	3.54	11	24, 9, -9

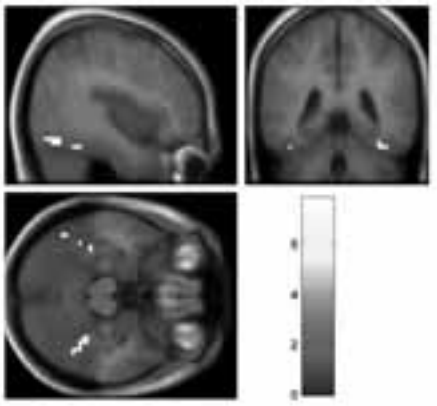
Table 2
Areas with significant activation associated with trustworthiness judgments of faces in XXY men as indicated by a whole-brain analysis.

Region	Max. t value	Max. z value	Nr. of voxels	X,y,z peak activation
Cuneus (occipital)	9.80	5.05	17	21, -93, 18
Fusiform gyrus	8.93	4.86	64	45, -57, -24
	5.28	3.73	26	33, -75, -18
Lingual gyrus	6.21	4.08	63	12, -87, -3
Cerebellum	6.15	4.06	14	-18, -81, -21
	4.96	3.59	16	-42, -57, -27
Middle frontal gyrus	6.05	4.02	17	-39, 45, 12

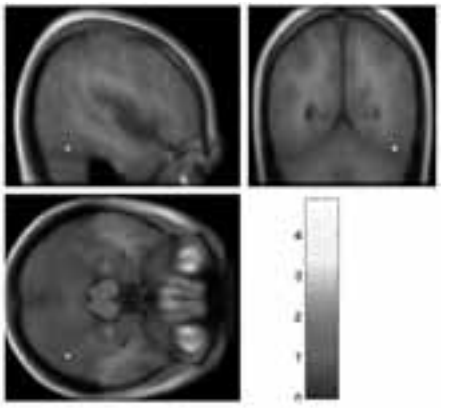
Figure 1

T-maps showing voxels in the fusiform gyrus and amygdala with a t-value above threshold ($p<0.05$, FWE corrected for multiple comparisons) during untrustworthy judgments of faces in the control group and XXY group. 1A) Significant activation in the fusiform gyrus, including the fusiform face area, in control men (62 voxels, maximal voxel (x,y,z) 39,-69,-18, T=7.8). 1B) Significant activation in the fusiform gyrus in XXY men (1 voxel, (x,y,z) 45, -57, -24, T=4.9). 1C) Significant activation in the amygdala in control men (16 voxels, maximal voxel (x,y,z) 21,-3,-18, T=4.2). No significant activation in the amygdala was observed in XXY men.

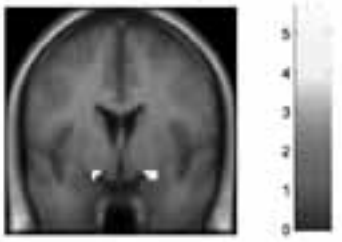
Two-sample t-tests confirmed that the XXY group had significantly less activation in the fusiform gyrus (including the fusiform face area) (17 voxels, t max.=4.7, $p<0.001$, x,y,z= -30, -33, -24) and amygdala (3 voxels, t max.=4.8, $p<0.001$, x,y,z=-21, 3, -18). In addition, small group differences were observed in the the insula (1 voxels, t max.=3.6, $p=0.001$, x,y,z= 27, 12, -21), with reduced activation in the XXY group.



1A. Fusiform gyrus activation in control men



1B. Fusiform gyrus activation in XXY men



1C. Amygdala activation in control men

Discussion

This fMRI study examined brain activation patterns underlying social evaluation of faces in men with an extra X chromosome (XXY chromosomal pattern). Compared to men from the general population, evaluation of faces as untrustworthy was associated with decreased activation in the amygdala, insula and fusiform face area, which are key neural structures subserving social perception. In addition, we observed small, but significant, group differences in brain activation in the insula, with lower activation in XXY men. When faces were evaluated with regard to age, during which faces may be implicitly screened for social significance as shown by Winston et al. (2002), we again observed less activation in the fusiform gyrus and insula, but not in the STS and amygdala, in XXY men as compared to men from the general population.

The finding of decreased involvement of brain areas that process socio-emotional signals in XXY men provides, for the first time, a putative neural explanation for the reported social cognitive deficits (Van Rijn et al., 2006b) in Klinefelter syndrome. Using an event-related design, brain activation was analysed according to subjective evaluation of untrustworthiness. Because the distribution of trustworthiness decisions was not different between XXY men and controls, we may assume that differences in brain activation patterns did not reflect differences in behavioral performance. Therefore, our findings of less activation in the amygdala and fusiform face area during untrustworthy faces in XXY men as compared to men from the general population, can be interpreted as abnormal functioning of these brain areas in Klinefelter syndrome.

The amygdala plays a central role in the neural circuit subserving social cognition, as indicated by the high density of incoming and outgoing projections to other brain regions (Aggleton, 2000). The amygdala is especially known for its engagement in screening information for emotional and social significance, especially threat-related information (Amaral, 2003; Phelps, 2006). As emotional expressions on faces provide a crucial source of information needed for decoding social and emotional signals, the amygdala generally activates in response to facial expressions, especially to angry or fearful faces (Adolphs, 2001; Haxby et al., 2002; Phan et al., 2002). Indeed, in men from the general population, we observed in this study significant activation in the amygdala when judging faces as untrustworthy as well as an increase in amygdala activation during untrustworthy- as compared to trustworthy decisions. In contrast, no significant activation in the amygdala was seen in de XXY group when judging trustworthiness of faces. Interestingly, the functional abnormalities of the amygdala in XXY men as found in this study are in line

with volume reductions of this area that have been observed in structural MRI studies in Klinefelter syndrome (Patwardhan et al., 2002; Shen et al., 2004).

One of the areas that receives input from the amygdala is the fusiform gyrus, which includes the 'fusiform face area' (FFA) (Puce et al., 1996). This area appears to be important for visual processing of the structural, static properties of faces, which are used to determine personal identity (Adolphs, 2001; Haxby et al., 2000). It has been shown that activation in the fusiform gyrus can be modulated by activation in the amygdala (Morris et al., 1998). Increasing threat-related social significance as processed in the amygdala may elicit re-allocation of attentional resources to allow detailed visual analysis of a socially significant stimulus. We speculate that lower levels of activation in the fusiform face area during judgment of faces as untrustworthy might, in part, result from reduced activation in the amygdala.

The insula is another brain area that is closely connected to the amygdala and is thought to be subject to attentional modulation by the amygdala (Adolphs et al., 2006). This somatosensory area is important for monitoring and organizing physiological (autonomic) changes in the internal milieu, as is seen in response to emotion-inducing stimuli (Damasio et al., 2000). It appears to be especially involved in mediating affective responses to aversive, including disgust-related, incoming information (Adolphs, 2002; Phillips et al., 2003a). The latter is consistent with a role of this region in judging faces as untrustworthy. XXY men displayed less activation associated with (un)trustworthiness in the insula as compared to controls. Significantly, the functional abnormalities of this region as found in this study are in line with structural abnormalities, i.e. smaller volumes, of the insula that have been reported for XXY men (Shen et al., 2004).

It has been shown by Winston et al. (2002) that not only during trustworthiness judgments, but also during evaluation of faces with regard to age, the fusiform face area, amygdala and insula are active. This suggests that faces may be automatically screened for social significance. Indeed, in controls we observed activation in these areas during age-judgments of faces. Similar to the trustworthiness condition, XXY men displayed less activation in the insula and fusiform gyrus during age-evaluations as compared to control men. However, no significant group-differences were present in activation in the amygdala, suggesting that even though explicit screening for social relevance by the amygdala seems to be diminished in Klinefelter syndrome, implicit screening for social relevance may be intact.

Our observations of disturbed development of some regions in a neural network supporting social cognition in XXY men may have several implications. First, abnormal engagement of a neural network subserving social perception may underlie some of the social cognitive dysfunctions and impaired social adaptation that have been described in XXY men (Van Rijn et al., 2006b). In other words, it provides a neuro-anatomical basis for the social behavioral phenotype in Klinefelter syndrome. Second, we can extrapolate from these findings that the X chromosome may play an important role in the development of some of the brain areas subserving social cognition. This is also supported by findings of abnormal development of brain areas involved in social cognitive processing in Turner syndrome, another X chromosomal disorder that is characterised by the presence of only one X chromosome in females (i.e. the X0 karyotype) (Mazzocco et al., 1998; McCauley et al., 2006; Ross et al., 2000). Similar to XXY men, individuals with X monosomy display impairments in social cognition, such as facial affect recognition (Lawrence et al., 2003; McCauley et al., 1987). Interestingly, imaging studies have revealed structural and functional abnormalities in the amygdala and insula in females with Turner syndrome, regions that we also found to be abnormal in XXY men (Molko et al., 2004; Murphy et al., 1997; Skuse et al., 2005). Although speculative, involvement of one of the sex chromosomes in the development of social cognitive abilities would also be in line with the observed sex differences in social cognitive skills in the general population, with performance of men generally somewhat lower than that of women (Hall, 1984; Hampson et al., 2006; McClure, 2000). Third, we might consider a role the X chromosome in some aspects of social cognitive dysfunction and underlying neuroanatomical abnormalities in other disorders, such as autism or schizophrenia. Deviant social behavior and impairments in social cognitive functions are considered core abnormalities in these neurodevelopmental disorders (Abdi et al., 2004; Corrigan et al., 2001; Fein et al., 1986). Neuroimaging studies have consistently shown abnormalities of the amygdala, insula and fusiform face area in both autism and schizophrenia (Grelotti et al., 2002; Phillips et al., 2003b; Quintana et al., 2003). Interestingly, these disorders are more prevalent in men. The reported risk ratio for men to develop schizophrenia relative to women is 1.42 (Aleman et al., 2003), while autism is diagnosed approximately four times more often in boys than in girls (Volkmar et al., 1993). This fact has led others to propose that dysfunctional neural circuits underlying social cognitive impairments in autism may be related to genes on the X chromosome, that are differentially expressed in men and women (Baron-Cohen et al., 2005; Skuse,

2000). Interestingly, a study on sex differences in social perception in schizophrenia has shown that the female superiority in reading social signals from faces seems not to be affected by schizophrenia, in contrast to males with the disorder who perform significantly worse as compared to healthy men (Scholten et al., 2005).

Both Turner syndrome and Klinefelter syndrome have been associated with increased symptoms and personality traits that resemble features from the autism- or schizophrenia spectrum. The estimated risk of autism spectrum disorders may be several times higher in women with X-monosomy (3 %) as compared to women from the general population (0.01 %) (Creswell et al., 1999). In Klinefelter syndrome, we observed increased levels of autism traits, schizotypal personality traits and schizophrenia-like symptoms (Van Rijn et al., 2006a; Van Rijn et al., submitted). In addition, a survey of hospital admissions and discharge diagnoses has indicated a significantly increased relative risk of being hospitalized with psychoses (hazard ratio of 4.97) for men with Klinefelter syndrome (Bojesen et al., 2006). In turn, there is suggestive evidence that prevalence of the XXY karyoype in the male schizophrenia population may be several times higher as compared to the prevalence of Klinefelter syndrome in the general population (DeLisi et al., 1994; Kunugi et al., 1999). Although speculative, observations of increased autism- or schizophrenia spectrum pathology in Turner syndrome and Klinefelter syndrome fit with the hypothesis that the X chromosome may play a role in some of the developmental abnormalities of the neural structures for social information processing, such as the amygdala, insula or fusiform face area, in autism or schizophrenia.

In sum, this study has revealed reduced engagement of the amygdala, insula and fusiform face area during social perception in XXY men as compared to men from the general population. Compromised function of these areas may underlie some of the deficits in social cognition and social behavior that have been observed in XXY men. In addition, as Klinefelter syndrome is defined by an X chromosomal abnormality, our findings suggest a link between one of the sex chromosomes and development of some of the neural regions supporting social cognition. In addition to revealing a neural basis for social dysfunctions in this specific disorder, our data suggest that Klinefelter syndrome may serve as a more general model for studying the genetic basis of developmental abnormalities in social cognition. This may be particularly relevant since these deficits are considered core abnormalities in severe psychiatric disorders such as autism and schizophrenia.

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