Chapter 11

General discussion

Social cognitive capacities are crucial for flexible navigation through a social world. The severe impact of impaired social cognition is illustrated by disorders such as autism or schizophrenia. In these neurodevelopmental disorders, social cognition is among the core domains of deficits (Corrigan et al., 2001; Fein et al., 1986). The importance of social cognitive capacities in coping with the social world and related mental well-being has called for a search into the origins of social cognition on the level of cognition, neurobiology and genes.

Klinefelter syndrome is an X chromosomal disorder known for social dysfunction and specific deficits in brain development and cognition, which can help us to unravel genotype-phenotype relations that are relevant for social behavior. Klinefelter syndrome might be used as a model for disorders of social behavior to reveal insight into involvement of the X chromosome in social cognitive pathways to psychopathology which may be more difficult to uncover by studying heterogeneous, behaviorally defined populations (Reiss, 2000; Reiss et al., 2000).

In the present thesis, we investigated the effects of an extra X chromosome on social cognition and the underlying neural basis. Besides providing insight into the cognitive and neural basis of social dysfunctions in this specific genetic disorder, another aim of the present thesis was to explore whether Klinefelter syndrome may serve as a model for social cognitive disturbances in autism or schizophrenia. We have focused on socially deviant behavior in adult XXY men on a behavioral, cognitive and neuroanatomical level and reviewed evidence for autism and schizophrenia spectrum traits, social dysfunction, social cognitive disabilites and underlying dysfunctional neural mechanisms in XXY men.

Social behavior and psychopathology

As described in **chapter two** and **three**, we assessed social difficulties, reflected in frequency of participation in social interactions and distress during these interactions, as well as vulnerability to disorders of social behavior, such as autism and schizophrenia, in XXY men. Vulnerability to neurodevelopmental disorders associated with difficulties in social adaptation was investigated from a dimensional, symptom oriented perspective, rather than a dichotomal, all-or-none, approach. Dimensional measures allow quantification of a number of traits associated with the autism or schizophrenia spectrum. In addition, we used a measure of schizophrenia symptoms to quantify symptoms at a clinical level. Measures of social behavior and psychopathology in XXY men were compared to those of men from the general population.

Men with Klinefelter syndrome reported to less often engage in social behavior and to experience more distress during social interactions as compared to men from the general population. In addition, XXY men displayed significantly increased levels of schizophrenia spectrum traits and symptoms as compared to controls. Scores were higher on all traits, with effect sizes (cohen's d) of 1.43 for the negative dimension (for example constricted affect and social anxiety), 1.31 for the positive dimension (for example referential thinking and delusional atmosphere) and 1.81 for the disorganized dimension (vague/overinclusive speech and eccentric behavior). Also on a clinical level, higher levels of schizophrenia symptoms were observed in XXY men, with effect sizes of 1.60 for negative symptoms, 1.45 for positive symptoms and 1.66 for general psychopathology. These findings provide evidence for increased vulnerability to schizophrenia psychopathology in Klinefelter syndrome and are in agreement with reports of increased prevalence of the XXY karyotype among schizophrenia populations (DeLisi et al., 1994; Kunugi et al., 1999) and a survey of hospital admissions and discharge diagnoses that 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). Similarly, levels of autism traits, such as impaired social skills, communication, imagination, attention switching and increased attention to details, were all higher in XXY men as compared to controls. This is the first report of increased levels of autism traits in Klinefelter syndrome.

These findings suggest that men with Klinefelter syndrome less often engage in social behavior and experience more distress during social interactions as compared to men from the general population. Our findings of difficulties in coping with social situations in XXY men, especially the high levels of distress during social interactions, are consistent with reports of social anxiety, social withdrawal and shyness in individuals with the XXY karyotype (Bender et al., 1999; Ratcliffe, 1999). Difficulties in social adjustment have mostly been reported for children or adolescents with Klinefelter syndrome. Our data suggest that social difficulties may persist into adulthood, with social distress more prominent than a general reduction in engagement in social behavior.

The high levels of autism traits and schizotypal traits in XXY men that were observed across all dimensions of the autism and schizophrenia phenotype, suggest that some aspects of the XXY phenotype parallel the phenotype that characterizes individuals at increased risk for autism or schizophrenia. For example, biological relatives of subjects with these disorders also display increased levels of schizotypal- or autism traits (Bishop et al., 2004; Vollema et

al., 2002). This hypothesis is in agreement with the concept of 'broad phenotypes' of autism or schizophrenia, which refers to mild features of the clinical autism- or schizophrenia phenotype that are seen in biological (i.e. genetically related) relatives of individuals with these disorders (Bailey et al., 1998; Bishop et al., 2004; Gottesman et al., 2003; Jablensky, 2006).

Thus, mild features of the autism or schizophrenia phenotype may not only be found in genetically related relatives of individuals with these disorders, but also in men with an extra X chromosome.

Social cognition

Next, we investigated the effects of an extra X chromosome on social cognition and explored whether social cognitive dysfunction in Klinefelter syndrome may be an underlying cognitive mechanism contributing to difficulties in coping with social environments as reflected in social distress and increased autism or schizophrenia traits. Several aspects of social cognitive processing were assesed at the level of perception, experience and expression, namely: labeling of facial expressions of emotion, emotion-cognition interactions in decision making, automatic processing of social cues such as gaze direction and implied biological motion, discriminating emotions in tone-of-voice, and emotion regulation, i.e. subjective experience and identification of emotional arousal as well as verbal expression of emotions.

Perception

As described in **chapter four**, we found XXY men to be impaired in recognizing facial expressions of anger, independent of the intensity of the emotional expression. This deficit was not attributable to a generalized impairment in analyzing faces, as performance in a face identity matching task was intact. Misperception of angry facial expressions may contribute to difficulties in social interactions, as non-verbal signals can convey crucial information about the emotional state of the sender. Various studies have revealed significant relationships between facial affect recognition performance and social functioning (Hooker et al., 2002).

The XXY group not only displayed deficits in processing social signals in the visual domain, but also in the auditory domain. Besides facial expressions of emotions, affective prosody in speech is also important for understanding intentions of others, because variations in tone of voice, such as intonation and loudness, provide information about the emotional state of the speaker. In social exchange, it is not only important to understand the content of words and

sentences, i.e. what is said, but it may even be more crucial to consider the (social) context of words and sentences, i.e. how it is said. Lesion- and fMRI studies indicate that whereas the left hemisphere is specialized for processing linguistic (semantic) information, the right hemipshere may be specialized for analyzing pragmatic aspects of language, such as understanding metaphors, irony, discourse, indirect requests and analyzing emotional prosody. In **chapter six**, we provided evidence for a causal involvement of the right hemisphere, more specifically the fronto-parietal operculum, in processing affective prosodic information in individuals from the general population. Applying inhibitory Transcranial Magnetic Stimulation (TMS) to the right hemisphere temporarily disrupted recognition of emotions in prosodic cues in speech, but not semantic (linguistic) cues. These findings extend an earlier study of Vingerhoets et al. (Vingerhoets et al., 2003) who have measured blood flow velocity (BFV) with functional transcranial doppler ultrasonography (fTCD) to study the contribution of the right and left hemisphere to the detection of emotion in prosody versus semantics of spoken language using this particular task. During detection of emotion in semantics they observed a significant left-hemispheric lateralization of BFV. This lateralization effect disappeared when attention was shifted to discriminating emotion in prosody, due to a rise in right hemispheric BFV. Our findings provide evidence that the right hemisphere is not only associated with, but also causally involved in emotional prosody.

As described in **chapter seven**, discrimination of emotions in prosodic cues was impaired in XXY men. Although recognizing emotions in semantic cues was also impaired in the XXY group, which is in line with the typical left hemisphere mediated language dysfunctions in Klinefelter syndrome, recognizing emotions in prosody, a pragmatic, right hemisphere mediated aspect of language, was more affected. Difficulties in picking up pragmatic communicative cues in conversation might have an impact on how well XXY men cope with social situations, as these aspects of language are important for understanding interpersonal intentions and responding to those in an appropriate way.

Another important underlying characteristic of successful social interaction is the ability to quickly and automatically process basic elements of a social signal such as direction of gaze, head orientation and body postures (Frith et al., 1999; Jellema et al., 2005). These cues can give clues about someone's intentions, goals and believes (Perrett, 1999). It is suggested that the ability to process these basic social cues automatically is a prerequisite for establishing successful social interactions and communication (Frith and Frith, 1999). We have shown

(**chapter five**) that in contrast to men from the general population, XXY men have difficulties in automatically attending to, and process, basic social cues such as gaze direction and implied biological motion. Reduced availability of basic social information may contribute to more widespread effects on ('upstream'-) higher-order social cognitive processing. Although speculative, this reduced sensitivity to basic elements of a social signal might, in part, explain social awkwardness and reduced social intuition and which have been described in XXY men. We not only compared performance of XXY men with matched controls, but we were also able to include patients with schizophrenia as well as biological relatives of schizophrenia patients. Interestingly, performance in processing these social cues was indistinguishable between Klinefelter men and schizophrenia patients. Moreover, performance of biological relatives of schizophrenia patients resembled the lack of sensitivity to social cues observed in schizophrenia patients and XXY men, albeit to a lesser extent, indicating that it may be an expression of genetic vulnerability for the disease.

Experience and expression

Not only perception, but also disturbances in experience and expression of emotions were observed in XXY men (**chapter four**). 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; van 't Wout et al., 2006). 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. Alexithymia is 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). In contrast to apparent *hyperfunctional* emotional -experience and -reactivity, identifying and verbalizing one's own emotions appeared to be *hypofunctional* in Klinefelter syndrome. This dissociation has been termed type II alexithymia, which contrasts with type I alexithymia (a general reduction in processing emotions). This emotion regulation profile of increased experience but decreased expression of emotions can be considered as a possible risk factor for both medical and psychiatric disorders (Bagby et al., 1997).

Taken together, Klinefelter men seem less accurate in perception of social signals, both from facial expressions and tone-of-voice, and have reduced automatic attention to basic social cues, such as gaze direction and implied

biological motion. Moreover, they are less able to identify and verbally describe their emotions, but experience increased levels of emotional arousal, in comparison to men from the general population. Although it has been suggested in the literature that the reported deficits in typical left hemisphere mediated language functions largely explain social dysfunction in XXY men, the present thesis identified dysfunctions in processing social signals, emotions and right hemisphere mediated pragmatic language as mechanisms that may also contribute to social dysfunction and related mental well-being.

Social cognition: neural basis

Language

As it has been proposed that language impairments, with language being a crucial part of social communication, may contribute to the observed difficulties in social functioning in Klinefelter men (Samango-Sprouse, 2001), we studied the neural basis of language processing in XXY men. Although language impairments in Klinefelter syndrome are well-documented, and are not restricted to the typical left hemisphere language deficits but also include right hemisphere language dysfunctions as pointed out in the present thesis, underlying neural mechanisms are not well understood (Geschwind et al., 2000). One possible neural mechanism involved in the verbal disabilities in Klinefelter syndrome that we investigated was abnormal hemispheric involvement in language processing.

By using functional Magnetic Resonance Imaging (fMRI) we were able to assess lateralization of activation in specific brain areas during language processing in XXY men (**chapter eight**). By measuring the relative contribution of the right and left hemisphere in each individual it was shown that language activity in the brain was indeed less lateralized in the XXY group as compared to control men. Loss of asymmetric processing of language was due to increased activity in the right hemisphere rather than reduced activity in the left hemisphere. Analysis of functional asymmetry within different language regions indicated that loss of functional asymmetry in the superior temporal gyrus (STG) was the most prominent contributor to reduced language laterality in XXY men. This regional loss of language laterality was highly correlated with the degree of disorganization (vague or overinclusive speech and odd/eccentric behavior) in the XXY group. This is consistent with studies finding structural (Matsumoto et al., 2001; Menon et al., 1995; Rajarethinam et al., 2000; Rossi et al., 1994; Shenton et al., 1992) and functional (Kircher et al., 2002) abnormalities

of the STG to be related to disorganization symptoms such as thought disorder in schizophrenia.

Social perception

The present thesis revealed that not only some aspects of language but also perception of social signals, another core function within the domain of social cognition, may be disturbed in XXY men. We explored the effects of an extra X chromosome on the neural basis of social cognition and reviewed structural neuroimaging findings in Klinefelter syndrome, as well as investigated neural networks supporting social perception in XXY men using functional neuroimaging.

The amygdala seems to play a central role in social perception and is especially known for its engagement in screening information for emotional and social significance (Amaral, 2003; Phelps, 2006). In **chapter nine** we have reviewed evidence for structural abnormalities of the amygdala in Klinefelter syndrome based on findings in the literature. Findings were compared to what is known of abnormalities of the amygdala in populations with increased vulnerability to schizophrenia: individuals from the general population displaying subclinical signs of schizophrenia and biological relatives of schizophrenia patients who may carry a genetic predisposition for the disorder. Reductions in volume of the amygdala were found to be present both in Klinefelter syndrome and the populations at high risk for schizophrenia, i.e. across the spectrum of schizophrenia spectrum vulnerability. Morphological abnormalities of the amygdala provide a putative neuro-anatomical basis for the deficits in social perception, such as impaired facial affect recognition, that we have observed in XXY men. In addition, the fact that amygdala abnormalities are not only consistently reported in patients with schizophrenia (Breier et al., 1992; Bryant et al., 1999; Gur et al., 2000; Hulshoff-Pol et al., 2001; Lawrie et al., 2003; Wright et al., 2000) but are also observed in populations with an increased liability for schizophrenia is of considerable importance. Abnormalities of the amygdala in the schizophrenia spectrum may be neurodevelopmental in origin and might reflect a genetic vulnerability for the disease rather than being the consequence of antipsychotic medication, hospitalisation and neurotoxic effects of psychosis.

Structural abnormalities of the amygdala in Klinefelter syndrome suggest abnormal functioning of this brain area, possibly extending to a neural network for social perception this region is part of. By using fMRI we were able to study functioning of such a neural network during social evaluation of faces

(**chapter ten**). We measured brain activity during trustworthiness evaluations of faces, with special interest in the amygdala, fusiform face area, superior temporal gyrus and insula. These regions are highly interconnected brain regions involved in social perception. We selected those regions based on their involvement in trustworthiness evaluations of faces in the general population (Winston et al., 2002). Activity in the amygdala during trustworthiness evaluation of faces may represent screening of social relevance and especially threat. Involvement of the fusiform face area may indicate processing of the structural, static properties of faces that are used for identification. Activation in the superior temporal sulcus may reflect efforts to detect goals and intentions based on eye-gaze and other signals in faces. Finally, insula activity may represent monitoring and organizing physiological (autonomic) changes in the internal milieu in response to the degree of trustworthiness of faces.

As predicted, we observed less involvement of region in this key neural network subserving social cognition during untrustworthy faces as compared to controls. Significantly lower levels of activation were observed in the amygdala, insula and fusiform face area in XXY men as compared to controls. The findings of less involvement of key brain areas in processing socio-emotional signals in XXY men offer, for the first time, insight into the neural basis of social cognition in Klinefelter syndrome. Abnormal engagement of a neural network subserving social perception may contribute to social cognitive dysfunctions and impaired social adaptation that have been described for men with Klinefelter syndrome.

Taken together, we observed reduced hemispheric specialization for language and less engagement of a neural network processing social information in XXY men. These findings, for the first time, may provide a neural explanation for some of the social cognitive impairments in Klinefelter syndrome.

The X chromosome and social cognition

As Klinefelter syndrome is defined by an X chromosomal abnormality, our findings suggest that the X chromosome plays a role in the development of some aspects of social cognition and neural mechanisms involved in social information processing in Klinefelter syndrome. Additional support for a putative role of the X chromosome in the development of social information processing is derived from observations of social dysfunction and social cognitive disabilites in Turner syndrome (45,X0), another X chromosomal disorder characterised by a partial or complete absense of one of the X

chromosomes in females (Mazzocco et al., 1998; McCauley et al., 2006; Ross et al., 2000). Similar to XXY men, individuals with X monosomy display impairments in facial affect recognition (Lawrence et al., 2003b; McCauley et al., 1987). Also, deficits in gaze direction processing and impairments in judging mental states from eyes have been reported (Elgar et al., 2002; Lawrence et al., 2003a). Difficulties in picking up social signals are not only observed in the visual domain, but also in the auditory domain. Comparable to men with the XXY pattern, women with one X chromsome display impairments in decoding emotions from tone of voice, i.e. emotional prosody (Ross et al., 1995).

Similar to XXY men, abnormal development of brain regions that are part of a neural network supporting social cognition have been observed in 45,X0 females. These include the amygdala, superior temporal sulcus and -gyrus, anterior cingulate, orbitofrontal cortex and insula (Kesler et al., 2003; Kesler et al., 2004; Molko et al., 2004; Murphy et al., 1997; Skuse et al., 2005). Specifically interesting is a functional neuroimaging study with Turner females revealing a loss of correlation between activation in the left amygdala and left fusiform gyrus underlying impairments in labeling of facial expressions of both anger and fear, while right amygdala mediated somatic responses were enhanced in reponse to emotional faces (Skuse et al., 2005). This finding is in line with our observation of a dissociation between reduced cognitive labeling of emotions and increased emotional arousability in XXY men.

The extra X chromosome may also affect neural systems involved in language processing. Genetic mechanisms involving the X chromosome may influence the development of hemispheric specialization for language, as reduced language lateralization was observed in XXY men using fMRI. A putative link between the X chromosome and reduced language lateralization is in line with a proposed role of the X chromosome in the development of asymmetry in the brain. It is thought that a pseudo-autosomal region on the X chromosome is involved in abnormal development of brain asymmetry in XXY men, as indicated by increased left-handedness and neuropsychological evidence of anomalous hemispheric dominance (Geschwind et al., 1998). Interestingly, also in Turner syndrome (45,X0) reduced lateralization of verbal information processing has been reported, which supports the hypothesis that the X chromosome may be important for the development of hemispheric specialization for verbal information (Netley et al., 1982).

However, the exact genetic mechanism that leads to the XXY phenotype remains unclear. In healthy females, who have two X chromosomes, certain genes on the X chromosome are inactivated, while others escape inactivation. In

Klinefelter syndrome, genes on the X chromosome that that escape inactivation and have a homologue on the Y chromosome and, may be overexpressed. Is has been proposed that phenotype in Klinefelter syndrome, at a neural, cognitive and behavioral level, might originate from overexpression of such genes (Crow, 1988; DeLisi et al., 2005; Geschwind et al., 2000). Alternatively, genomic imprinting may play a role. Genomic imprinting refers to differential expression of a gene, dependent of the parental origin of that gene. It has been shown that Turner females with a maternally derived X chromosome display more impairments in social skills as compared to those with the X chromosome from the father (Skuse et al., 1997). The authors proposed an X-chromosomal locus for social cognition, which is imprinted and not expressed by the maternally derived X chromosome. In Klinefelter syndrome, the extra X chromosome is derived from the mother in over half of the cases (Thomas et al., 2003). A recent study has pointed to putative imprinting effects in 54 XXY men. Impairments in speech and motor development were more often found in subjects with a paternal (extra) X chromosome as compared to those with a maternal (extra) X chromosome (Stemkens et al., 2006). Taken together, abnormal expression of genes on the X chromosome in Klinefelter syndrome may affect development of the brain resulting in social, emotional and language dysfunctions. Although speculative, an involvement of sex chromosomes in socio-emotional brain functions would be in line with the observed sex differences in social cognitive skills in the general population, with performance of men generally somewhat below that of women (Hall, 1984; Hampson et al., 2006; McClure, 2000; Montagne et al., 2005). However, the exact genetic mechanisms that lead to the XXY phenotype, which may for example include overexpression, abnormal inactivation, genomic imprinting or gene-gene interactions, are as yet unclear. Future genetic studies are needed to identify candidate genetic mechanisms involving the X chromosome that can explain the social cognitive deficits in XXY men, sex differences in social cognition in the general population and the male preponderance in disorders of social cognition.

The role of testosterone deficits

The degree to which the observed cognitive and neurobiological deficits in XXY men represent the effects of testosterone- deficits that become apparent in puberty and subsequent testosterone supplementation, is unclear. The relationship between testosterone levels and brain development is complex; timing of exposure, sensitivity to testosterone reflected in androgen receptor density and modulation by environmental factors are important determinants in

the effects of testosterone (Craig et al., 2004). Although speculative, abnormal testosterone levels might be part of the mechanism by which X chromosomal abnormalities lead to disturbances in development of neural systems supporting social cognition. However, 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).

Although speculative, support for the hypothesis that brain function and cognition in XXY men may represent the effects of X chromosomal genetic pathology rather than low testosterone levels by itself, comes from individuals with X chromosomal aneuploidies that are not associated with low testosterone levels. For example, although females with the XXX karyotype show typical hormone levels, they do display impairments in the language domain and have decreased social adjustment (Bender et al., 1999; Harmon et al., 1998). Interestingly, there have been reports of increased psychopathology, such as conduct disorders and affective disorders, in XXX females (Harmon et al., 1998).

Furthermore, there is no evidence for an effect of testosterone supplementation on language lateralization. A recent longitudinal study dealing with the effects of testosterone treatment on language lateralization in transsexuals showed that language laterality is highly stable and not affected by hormonal interventions (Sommer et al., in prep). Also, testosterone levels by itself seem not enough to, for example, explain the amygdala abnormalities in individuals with sex chromosome aneuploidies. Although females with Turner syndrome, who are missing one X-chromosome, are also characterised by a reduction in testosterone levels (Hojbjerg Gravholt et al., 1999), these patients show an increase in amygdala volume rather than a reduction (Kesler et al., 2004). Although speculative, differences in amygdala volume between Turner and Klinefelter patients might be stronger related to the number of X-chromosomes, which differentiates the two groups, than to testosterone levels, which are reduced in both syndromes. Alternatively, abnormal testosterone levels may result from X-chromosome linked amygdala abnormalities, since it has been shown that the amygdala is involved in the production of testosterone (Banczerowski et al., 2003).

In conclusion, the exact nature of the effects of testosterone deficits and testosterone supplementation on development of social cognition and neural substrates in Klinefelter syndrome remains unclear.

Potential implications for the study of autism and schizophrenia

Our findings may have potential implications for the study of neurodevelopmental disorders associated with impaired social adaptation. We might consider a role of genetic mechanisms involving the X chromosome in some aspects of social cognitive dysfunction and underlying neuroanatomical abnormalities in the autism or schizophrenia spectrum. Tentative support for this hypothesis comes from observations of increased autism spectrum psychopathology in Turner syndrome and both autism and schizophrenia spectrum traits in Klinefelter syndrome. The estimated risk for 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., 2006; Van Rijn et al., in preparation). 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).

The increased levels of autism- and schizotypal traits that we observed in XXY men parallel the schizotypal or autism-like features that characterize individuals at increased risk for autism or schizophrenia. Biological relatives of individuals with autism or schizophrenia also display increased levels of traits or mild features of the disorder (Bishop et al., 2004; Vollema et al., 2002). Based on twin studies, it has been suggested that the typical clinical phenotype of autism or schizophrenia as seen in subjects with these disorders and the broader subclinical phenotypes (i.e. autism or schizotypal traits) as seen in biological relatives, may share a genetic origin (Rutter, 2000; Torgersen et al., 2002). Although speculative, this might suggest that the X chromosome may play a role in the etiology of some of the traits that are part of the broad autism or schizophrenia spectrum.

Difficulties in the domains of language, social adaptation and emotion are thought be among the core abnormalities in autism and schizophrenia (Aleman et al., 2005; Crow, 2004; Fein et al., 1986). Some of the social cognitive impairments in individuals with autism or schizophrenia resemble our findings in men with Klinefelter syndrome. I will now discuss parallels between XXY

men and individuals with autism or schizophrenia with regard to socio-emotional processing and language.

Socio-emotional processing

Our studies in Klinefelter syndrome indicated that XXY men have difficulties in analyzing emotional expressions on faces. A body of research has demonstrated that individuals with autism or schizophrenia also have difficulties in analyzing social cues from faces and hence are less able to use this crucial source of information in social interactions (Pinkham et al., 2006; Sigman et al., 2004). These deficits are not only present in decoding of basic emotions (Gross, 2004; Kohler et al., 2004), but also observed when complex social evaluations of faces are required (Adolphs et al., 2001; Hall et al., 2004). In one of our studies we were able to compare social information processing abilities in XXY men with schizophrenia patients and relatives of schizophrenia patients. Interestingly, performance in a task which measured the degree to which social cues (such as direction of gaze and implied biological motion) are processed automatically, was indistinguishable between XXY men and patients with schizophrenia. Biological relatives of schizophrenia patients were also impaired, although to a lesser extent, suggesting that this deficit may be expressed to different degrees across a schizophrenia vulnerability continuum. However, this social cognitive deficit seems not confined to the schizophrenia spectrum. Individuals from the autism spectrum also display reduced automatization in attending to social cues, such as gaze direction and implied biological motion, as measured with the same task as we used (Jellema et al., 2004).

Not only in perception of socio-emotional signals, also at the level of experience and expression of emotions some parallels between XXY men and individuals with autism or schizophrenia are present. Cognitive processing of one's own emotions, which is neccessary for regulation of emotions, also seems to be impaired in these neurodevelopmental disorders. Specifically, deficits in identifying and describing one's own emotions have been reported for individuals with autism or schizophrenia, and also in male biological relatives of schizophrenia patients. (Hill et al., 2004; van 't Wout et al., 2007). Increased emotional experience of emotions is also seen in patients with schizophrenia and their male biological relatives (van 't Wout et al., 2007). The presence of such disturbances in emotional processing in biological relatives of patients with schizophrenia, who share part of their genes, suggests that this may be part of the genetic vulnerability for the disease and possibly be expressed to different degrees across the phenotypic continuum of schizophrenia. The finding that

alexithymia seems to be under considerable genetic control fits this picture (Valera et al., 2001).

Not only our observations in Klinefelter syndrome at the level of cognition, also our findings at the level of neural mechanisms involved in social behavior might be extrapolated to other disorders. If we focus on structural and functional abnormalities of brain regions that are part of a neural network supporting social cognitive functions, some similarities among individuals with autism or schizophrenia and XXY men can be observed. Structural neuroimaging findings that we reviewed suggest that morphological abnormalities of the amygdala might not only be present in individuals with schizophrenia, but may also be an endophenotype both in Klinefelter syndrome and in individuals at increased risk for schizophrenia (because they have a family member suffering from the disease or display subclinical signs of the disease). We might extrapolate from these findings that in patients with schizophrenia and individuals at increased risk for schizophrenia, the observed structural abnormalities of the amygdala might in part originate from genetic mechanisms involving the X chromosome. This endophenotype may also be present in other psychiatric disorders, for example autism, which has also been associated with structural abnormalities of the amygdala (Brambilla et al., 2003; Palmen et al., 2004).

The observed functional abnormalities of the amygdala, fusiform face area and insula in Klinefelter syndrome, also show some resemblence with neuroimaging findings in autism and schizophrenia. Functional MRI studies have situated social cognitive deficits in schizophrenia in a neural network that includes, besides other brain regions, the amygdala, fusiform face area and insula (Phillips et al., 2003; Quintana et al., 2003). Functional abnormalities in these regions have also been reported for individuals with an autism spectrum disorder. Reduced involvement of the amygdala in processing social information has been widely reported and is thought to be among the core neurodevelopmental abnormalities in autism (Baron-Cohen et al., 2000). It has been proposed that amygdala deficits may be related to reduced activation of the fusiform face area in response to faces, which has consistently been observed in autism spectrum disorders (Grelotti et al., 2002).

Language

As language is a crucial part of social communication, it has been proposed that the well documented language impairments in Klinefelter syndrome may contribute to the observed difficulties in social functioning. The reported

language disabilities include impairments in both language production and perception and indicate compromised language functions that are typically associated with the left hemisphere (Samango-Sprouse, 2001). However, data in this thesis suggest that XXY may also have impairments in decoding emotional prosody, which is a pragmatic aspects of language lateralized to the right hemisphere. Deficits in decoding emotional prosody may also play an important role in social behavioral dysfunction in Klinefelter syndrome. In the search for determinants of impaired social communication in autism, impairments in the perception of pragmatic aspects of language, such as emotional prosody, have also been revealed (Lindner et al., 2006). Similarly, in schizophrenia, understanding pragmatic language appears to be affected (Mitchell et al., 2005) and difficulties in analyzing emotional cues in tone of voice have been observed (Edwards et al., 2002). It has even been argued that, at least for language and communication, right hemispheric functions are more affected than those mediated by the left hemisphere in schizophrenia (Ross et al., 2001).

One possible neural mechanism that may underlie language disorders in Klinefelter syndrome is reduced lateralization of language in the brain. Reduced hemispheric specialization for language may contribute to disorders of language and communication that we not only see in men with the XXY karyotype, but also in patients with schizophrenia or autism. Recent studies have suggested that autism spectrum disorders may be associated with abnormal development of hemispheric specialization for language. A magnetoencephalogram (MEG) study has revealed increasing rightward language dominance with age in autistic children in contrast to normally developing children, who display an increasing leftward lateralization (Flagg et al., 2005). The importance of gaining insight into the genetic and neural basis of language lateralization is also illustrated by findings in schizophrenia patients. Reduced cerebral asymmetry and, more specifically, loss of language lateralization is considered to be among the core developmental brain abnormalities underlying schizophrenia symptoms (Bhati, 2005; Crow, 2004). A range of language laterality studies in schizophrenia have supported this (Artiges et al., 2000; Dollfus et al., 2005; Kircher et al., 2002; Sommer et al., 2001a; Weiss et al., 2006). One of these studies not only assessed the degree of lateralization, but also examined whether this was secondary to increased right hemisphere activation or decreased left hemisphere activation (Sommer et al., 2001b). Similar to what we observed in Klinefelter men, decreased lateralization of language in schizophrenia patients was due to increased activity in the right hemisphere, rather than decreased activity in the left hemisphere. For schizophrenia, it has been suggested that deficits in typical

right hemispheric language functions, such as in processing emotional prosody, might arise as a consequence of a shift from left hemisphere dominance to more bilateral control of language processing (Mitchell et al., 2005). The hypothesis that reduced language lateralization may also be an endophenotype in the 'broad' schizophrenia spectrum is tentitavely supported by our findings in XXY men suggesting that reduced language lateralization in the superior temporal gyrus is associated with increased schizotypal traits related to disorganization of thought and language, such as vague or overinclusive speech and odd or eccentric behavior.

Although speculative, similarities between XXY men and individuals from the autism- or schizophrenia spectrum suggest that we might consider a role of the X chomosome in some of the neurobiological and social cognitive abnormalities that are present in these neurodevelopmental disorders. This hypothesis fits with the notion that genetic factors in autism or schizophrenia might operate on components of the disorders, rather than the syndrome as a whole (Gottesman et al., 2003; Jablensky, 2006; Rutter, 2000). It has recently been suggested that some of the relations between genotypes and endophenotypes in schizophrenia may not be specific nor confined to one disorder (Weiser et al., 2005). Weiser et al. (2005) proposed that studying endophenotypes at the level of cognitive, emotional and social functioning in other disorders may help elucidating the etiology of schizophrenia and psychiatric morbidity as a whole.

Sex chromosomal effects on brain development and cognition may be especially relevant for the study of autism and schizophrenia because of the male preponderance in these psychiatric disorders. Schizophrenia is diagnosed approximately 1.5 times and autism spectrum disorders approximately 4 times more often in males than in females (Aleman et al., 2003; Volkmar et al., 1993). Observations that males are more often affected have 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). Studies focused at the genetic underpinnings of abnormal language lateralization in schizophrenia have also suggested abnormal expression of a X-Y homologous genetic locus directing development of brain asymmetry (Crow, 2004). Crow proposes that such a gene would underlie the observed sex differences in language abilities, handedness, relative rates of hemispheric growth and both ages of onset and prevalence of schizophrenia.

Taken together, the extra X chromosome in Klinefelter syndrome may play a role in abnormal development of some of the brain mechanisms involved in language, emotion and social behavior, which are considered core domains of disabilities in autism and schizophrenia. Although speculative, studying X-linked genetic mechanisms in Klinefelter syndrome might help us understand pathways from genes to psychopathology in the autism- and schizophrenia spectrum.

Concluding remarks and future perspectives

This thesis has presented Klinefelter syndrome as a genetic disorder that may advance our understanding of the biological basis of social cognition, i.e. human capacities that are crucial for adapting to complex social environments. As severe difficulties in social adaptation have been described for neurodevelopmental disorders such as autism or schizophrenia, our findings may also have potential implications for understanding some of the gene-brain-behavior pathways to such forms of psychopathology. Relevance for the study of neurodevelopmental psychiatric disorders is also illustrated by reports suggesting an increased risk for psychopathology in men with Klinefelter syndrome and our observations of increased autism- and schizotypal traits, as well as schizophrenia symptoms, in these men. However, clinical research is needed to more precisely define the vulnerability to autism and schizophrenia in Klinefelter syndrome in a larger and more representative sample in epidemiological terms. The effects of testosterone treatment on the cognitive and neural development in Klinefelter syndrome may be investigated in longitudinal studies during adolescence. Also, developmental studies in Klinefelter syndrome may reveal whether impaired social cognitive functioning is also present in early infancy, before testosterone deficits become apparent. Future genetic studies are warranted to help us understand the mechanisms by which an extra X chromosome affects brain development and cognition in Klinefelter syndrome. In addition, an interesting issue for genetic research concerns the interactions between X chromosomal genetic pathology and environmental factors, such as stress, that may interactively direct brain development, social cognitive abilities and mental well-being. Also, there is a need for studies in which neural and cognitive endophenotypes related to social behavior are directly compared between individuals with autism or schizophrenia and individuals with Klinefelter syndrome. Although speculative, putative overlap in endophenotypes between Klinefelter syndrome and these neurodevelopmental disorders might point to a common genetic origin on the X chromosome.

Besides revealing a putative neural and cognitive basis for social dysfunctions in this specific genetic disorder, the present thesis shows that Klinefelter syndrome may serve as a more general 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.

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