Summary

Humans are equipped with affective and cognitive capacities that allow them to deal with a complex and dynamic social world. Although social signals can be processed automatically and quickly, in many situations the social significance of expressions, actions, and experiences is not fixed, and depends upon cognitive computations to extract meaning. As a consequence, social skills largely rely on social cognitive capacities that are needed to make sense of the incoming socially relevant information.

The severe impact of impaired social cognition is illustrated by disorders such as autism or schizophrenia. Autism spectrum disorders and schizophrenia share some characteristics, both clinical phenomena pertaining to affect, communication and social insight (Abdi et al., 2004; Frith, 1992; Goldstein et al., 2002; Konstantareas et al., 2001; Rumsey et al., 1986) as well as cognitive dysfunctions in the domain of social information processing, language and emotion (Abdi et al., 2004; Frith, 1992; Pilowsky et al., 2000; Rumsey 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. These pathways 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 associated with the XXY karyotype, the 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 autism or schizophrenia was investigated from a dimensional, symptom oriented perspective, rather than a dichotomal, all-or-none, approach.

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, scores were higher on traits accross all dimensions of the autism- and schizophrenia phenotype. Also on a clinical level, higher levels of schizophrenia symptoms were observed in XXY men.

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 participation in social interactions. The high levels of autism traits and schizotypal traits in XXY men suggest that some aspects of the XXY phenotype parallel the phenotype that characterizes individuals at increased risk for autism or schizophrenia. This hypothesis fits 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. Findings in this thesis suggest that 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 explored various aspects of social cognitive functioning in Klinefelter syndrome. Deficits in social cognition might contribute to the difficulties in coping with social environments as reflected in increased social distress and increased autism or schizophrenia traits.

Klinefelter men appeared less accurate in perception of socio-emotional signals. 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. The XXY group not only displayed deficits in processing social cues in the visual domain, but also in the auditory domain. Besides facial expressions of emotions, af fective prosody (tone of voice) in speech is also important for understanding intentions of others, because variations in tone of voice provide information about the emotional state of the speaker. Lesion- and MRI studies have suggested that in contrast to linguistic information, which is largely lateralized to the left hemisphere, pragmatic aspects of language, such as emotional prosody, are lateralized to the right hemisphere. Indeed, by using Transcranial Magnetic Stimulation (**chapter six**), we provided evidence for a causal involvement of the right hemisphere in processing affective prosodic information in individuals from the general population. As described in **chapter seven**, recognition 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 was more affected.

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). We have shown (**chapter five**) that in contrast to men from the general population, XXY men have difficulties in automatically attending to, and processing, basic social cues such as gaze direction and implied biological motion. 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.

Not only perception, but also disturbances in experience and expression of emotions were observed in XXY men (**chapter four**). XXY men were less able to identify and verbally describe their emotions, but reported to experience increased levels of emotional arousal, in comparison to men from the general population. Increased emotional experience as reported by XXY men fitted with our observation that XXY men more often rejected financial offers in a strategic decision game (**chapter four**). Their pattern of performance in this game suggested an increased influence of emotions on strategic decision making.

It has been proposed that the reported deficits in typical left hemisphere mediated language functions, such as understanding and finding words, largely explain social dysfunction in XXY men. However, the present thesis has pointed to dysfunctions in processing affective facial expressions, decoding affective tone of voice, emotion regulation and automatic processing of basic social cues (such as gaze direction and implied biological motion), which may also contribute to social dysfunction and related mental well-being.

Social cognition: neural basis

As it is thought 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 (**chapter eight**). 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. 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. Loss of functional asymmetry in the superior temporal gyrus (STG) was the most prominent contributor to reduced language laterality in XXY men. This regional reduction of language laterality was highly correlated with the degree of disorganization (vague or overinclusive speech and odd/eccentric behavior) in the XXY group. These findings fit with a proposed role of the X chromosome in development of asymmetry in the brain. In addition, these data suggest that reduced language lateralization might underlie disorders of thought and language in Klinefelter syndrome.

We also explored the effects of an extra X chromosome on the neural basis of social perception and reviewed structural neuroimaging findings in Klinefelter syndrome, as well as investigated neural networks supporting social perception in XXY men using functional neuroimaging. Because the amygdala plays a crucial role in social perception and social behavior, we reviewed evidence for structural abnormalities of the amygdala in Klinefelter syndrome based on findings in the literature (**chapter nine**). Findings were compared to what is known of abnormalities of the amygdala in populations with increased vulnerability to schizophrenia, namely: 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 broad spectrum of vulnerability for schizophrenia psychopathology. These findings suggest that abnormal development of the amygdala may be an endophenotype that is not only present in patients with the clinical schizophrenia phenotype, but also in individuals displaying traits from the broad (milder) schizophrenia phenotype.

Structural abnormalities of the amygdala in Klinefelter syndrome suggest abnormal functioning of this brain area, possibly extending to a neural network for social perception. 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. In the XXY group, we observed signifianctly lower levels of activation in the amygdala, insula and fusiform face area during untrustworthy faces as compared to controls. The amygdala is escpecially involved in screening the environment for threat signals en has strong connections with the insula, which is involved in emotional arousal and experience, and fusiform face area, which is involved in analyzing the structural properties of faces in detail. These findings, for the first time, may provide a neural explanation for some of the impairments in social cognition 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 may play 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). Also in Turner syndrome, abnormalities in brain regions important for social cognition have been found. 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).

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, as indicated by increased left-handedness and neuropsychological evidence of anomalous hemispheric dominance in Klinefelter syndrome (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.

Taken together, the X chromosome might play an important role in the development of brain regions that support social social perception and language processing. However, the exact genetic mechanisms that lead to the XXY phenotype are as yet unclear. Such mechanisms might include overexpression or abnormal inactivation of genes on the X chromosome, genomic imprinting or complex gene-gene interactions.

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). 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). Indeed, females with the XXX karyotype display impairments in the language domain and have decreased social adjustment, in the face of typical hormone levels (Bender et al., 1999; Harmon et al., 1998).

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 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. 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 phenotype, i.e. autism or schizotypal traits, 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 impairments socio-emotional processing and language that are found in individuals with autism or schizophrenia resemble our findings in men with Klinefelter syndrome. Paralells are also observed at the level of neural networks that support social perception and language. 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). 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.

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.

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