Chapter 1

General introduction

Social cognition

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 cognitive capacities that are needed to make sense of the incoming socially relevant information (Pinkham et al., 2006).

The cognitive skills required to adapt to our social environment are encompassed in the term social cognition, which has been defined as 'all cognitive processes underlying interaction with conspecifics' or 'the ability to perceive, process en appropriately respond to social signals'. Examples of socio-emotional processes that are included in this 'umbrella' term are perception of faces, decoding affective expressions in faces, decoding social signals from voices and body postures, attribution of mental states (believes, desires and intentions) to others, empathy and regulation of emotions.

Social cognitive capacities appear to be relatively independent from other aspects of intelligence, such as memory or planning. Support for this idea comes from observations of selective impairments in social behavior together with normal general intelligence as is seen after damage to the frontal cortex in the brain (Anderson et al., 1999; Fine et al., 2001). In turn, individuals with William's syndrome are characterized by below-normal intelligence, but are described as 'hypersocial' (Jones et al., 2000). Dissociations between social cognitive abilities and general cognitive capacities have led to the idea that these functions can be dissociated at the neural level and that specific regions devoted to social cognition exist (Adolphs, 2001).

The neural basis of social cognition

Social cognitive capacities rely on neural networks in the brain that include regions specifically dedicated to processing social information as well as regions that are generally involved in complex perceptual or cognitive computations. A body of research has pointed to a set of strongly interconnected key areas in the brain, which are tuned to processing socio-emotional information. The amygdala seems to play a central role as indicated by the high density of incoming and outgoing projections to other brain regions. The amygdala is especially known for its automatic 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 (Adolphs, 2001; Haxby et al., 2002; Phan et al., 2002). A region within the fusiform gyrus, the 'fusiform face area', seems to be specifically tuned to faces. This area appears important for processing the structural, static properties of faces, which are used to determine personal identity (Adolphs, 2001; Haxby et al., 2000). Another region is the insula, which is important for monitoring and organizing physiological (autonomic) changes in the internal milieu, as is seen in reponse to emotion inducing stimuli (Damasio et al., 2000). It is involved in mediating affective responses to emotional incoming information (Adolphs, 2002; Phillips et al., 2003). It is shown that the superior temporal sulcus (STS) is implicated in processing socially salient 'motion' information, such as gaze direction, goal-directed movements and biological motion. It contributes to the detection of other people's goals and intentions and is involved in mentalizing (Frith et al., 1999; Pelphrey et al., 2006; Zilbovicius et al., 2006). The medial prefrontal cortex also plays a role in the detection of intentions as it seems active during mentalizing; that is, attributing mental states, goals and believes to others (Adolphs, 2001; Ochsner, 2004). This region, especially the ventromedial part, also appears to be important for regulation of affective states and behavior (Phillips et al., 2003). Another region that is important for regulation of social behavior is the orbital frontal cortex, which is involved in representation of reward value and ways in which this representation guides social behavior (Phillips et al., 2003). The ventral part of the anterior cingulate gyrus plays a role in emotional and social behavior by integrating sensory, motivational and cognitive information (Bush et al., 2000). This region has been associated with response selection, decision making and volitional behavior.

In sum, a network of brain regions prominently involved in social cognition includes the amygdala, fusiform face area, insula, superior temporal sulcus, medial prefrontal cortex, orbital frontal cortex and anterior cingulate.

Genetic factors in social cognition

Individual variance in social cognitive competence is for a substantial part attributable to genetic factors, as indicated by twin studies. For social cognitive skills, a heritability of 68% has been reported, with shared environment accounting for only a minor part of the variance (5%) (Scourfield et al., 1999). In line with this study, an estimated 60% of the individual variation in understanding the minds, i.e. believes, intentions and goals, of other individuals, seems to be due to genetic factors (Hughes et al., 1999). Shared environment

accounted for only 7% in that study. There is also evidence that social reciprocal behavior is highly heritable in the general population (Constantino et al., 2003a; Constantino et al., 2000). For monozygotic twin boys (who share 100 % of their genes) an 'inter-twin' correlation of 0.73 has been observed for impaired social reciprocal behavior. For dizygotic twin boys (who share on average 50 % of their genes), the intertwin correlation was 0.37.

Socially deviant behavior

Social cognitive competence appears to be a good predictor of social behavior and adaptation. Severe difficulties in social adaptation, accompanied by a detachment from reality and preoccupation with inner thoughts and feelings, have been described for individuals with an autism spectrum disorder or schizophrenia (Bleuler, 1911; Kanner, 1943). For the diagnostic criteria of schizophrenia and autism according to the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders -fourth edition (1994), see box I and II. Autism spectrum disorders and schizophrenia are neurodevelopmental disorders with a considerable genetic component, as estimated heritability is around 80% for schizophrenia (Gottesman, 1991) and 90% for autism (Santangelo et al., 2005). Both autism and schizophrenia are more prevalent in men. A meta-analysis has reported a risk ratio of 1.42 for men to develop schizophrenia relative to women (Aleman et al., 2003), while autism spectrum disorders are diagnosed approximately four times more often in boys than in girls (Volkmar et al., 1993).

Autism spectrum disorders and schizophrenia share some characteristics, such as 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). Note that clinical criteria (box II.F.) state that 'if there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month'. Although they are distinct disorders, with the onset of autistic disorders in childhood while schizophrenia is typically diagnosed in late adolescence/early adulthood (DeLisi, 1992; Minshew, 1996), autism spectrum disorders and schizophrenia share social cognitive dysfunctions, including aspects of language and emotion (Abdi et al., 2004; Frith, 1992; Pilowsky et al., 2000; Rumsey et al., 1986).

Box I.

DSM-IV criteria for autism

Autistic disorder

I A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)

- **A.** qualitative impairment in social interaction, as manifested by at least two of the following:
  1. marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
  2. failure to develop peer relationships appropriate to developmental level
  3. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
  4. lack of social or emotional reciprocity (note: in the description, it gives the following as examples: not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or "mechanical" aids)
- **B.** qualitative impairments in communication as manifested by at least one of the following:
  1. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
  2. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
  3. stereotyped and repetitive use of language or idiosyncratic language
  4. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
- **C.** restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:
  1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
  2. apparently inflexible adherence to specific, nonfunctional routines or rituals
  3. stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
  4. persistent preoccupation with parts of objects

II Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

- **A.** social interaction
- **B.** language as used in social communication
- **C.** symbolic or imaginative play

III The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

Box II.

DSM-IV criteria for schizophrenia

Schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g., frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms, i.e., affective flattening, alogia, or avolition

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved before the onset. (Or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (i.e., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either 1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Schizophrenia

Among the clinical manifestations of schizophrenia, significant impairments in social functioning have been consistently reported. Social isolation, impairments in social competence (Penn et al., 1996), deterioration in interpersonal close relationships (Poole et al., 2000), communication-deficits and interpersonal oddity (Hooker et al., 2002) are recognized as characteristics frequently displayed by patients suffering from schizophrenia. Social cognitive impairments have been widely described for these patients, such as impairments in gaze-interpretation, reading of affective facial expressions, picking up emotional signals in tone of voice and the ability to infer and interpret intentions, knowledge and believes of others, as measured in theory-of-mind (mentalizing) tasks (Corcoran et al., 1995; Corrigan et al., 2001; Doody et al., 1998; Edwards et al., 2002; Mazza et al., 2001; Penn et al., 1997; Sarfati et al., 1997).

Deficits in social perception appear to play an important role in social dysfunctioning of schizophrenia patients. General cognitive skills seem to explain between 20% to 60% of the variance in social outcome (Green et al., 2000). It has been suggested that social cognitive performance may help to, partly, explain the remaining 40% to 80%. Indeed, it has been shown that social cognitive capacities can explain significantly more variance (26 %) in social functioning in these patients as compared to general cognitive abilities (15 %) (Pinkham et al., 2006), which is comparable to a report of mentalizing abilities explaining 27 % of the variance in social behavioral problems in schizophrenia patients (Brune, 2003). In line with this, another study revealed that the ability to mentalize (realize that others may have different thoughts, feelings or goals) is among the best cognitive predictors of global social functioning in schizophrenia patients (Roncone et al., 2002).

Autism spectrum

Disabilities in the social domain are considered as the primary symptoms in the autism spectrum (Fein et al., 1986). A triad of impairments is characteristic of this spectrum: atypical development in reciprocal social interactions, atypical communication, and restricted, stereotyped and repetitive behaviors.

The impairments in social interactions can for example take form of difficulties in forming friendships, a lack of social motivation, misinterpretation in communicative intent of others and difficulties in understanding socio-emotional signs and social nuances (Wing et al., 1979). Research devoted to identifying the social cognitive deficits that may contribute to social dysfunction

in the autism spectrum, has revealed abnormalities in eye-gaze processing, interpreting language in social contexts, mentalizing ('theory of mind') abilities and identifying social signals from faces, voices and body postures (Buitelaar et al., 1999; Klin et al., 2002; Ozonoff et al., 1996; Rutherford et al., 2002; Sasson, 2006; Tager-Flusberg, 1999).

The importance of social cognitive capacities in coping with the social world and related mental well-being calls for a search into the origins of social cognition on the level of cognition, neurobiology and genes. Although it is widely acknowledged that there is a genetic basis to the neural and cognitive abnormalities seen in schizophrenia and autism, defining the underlying genetic factors directing these aberrations appears to be a difficult task (Norton et al., 2006).

Factors that complicate the search for genetic origins of socially deviant behavior

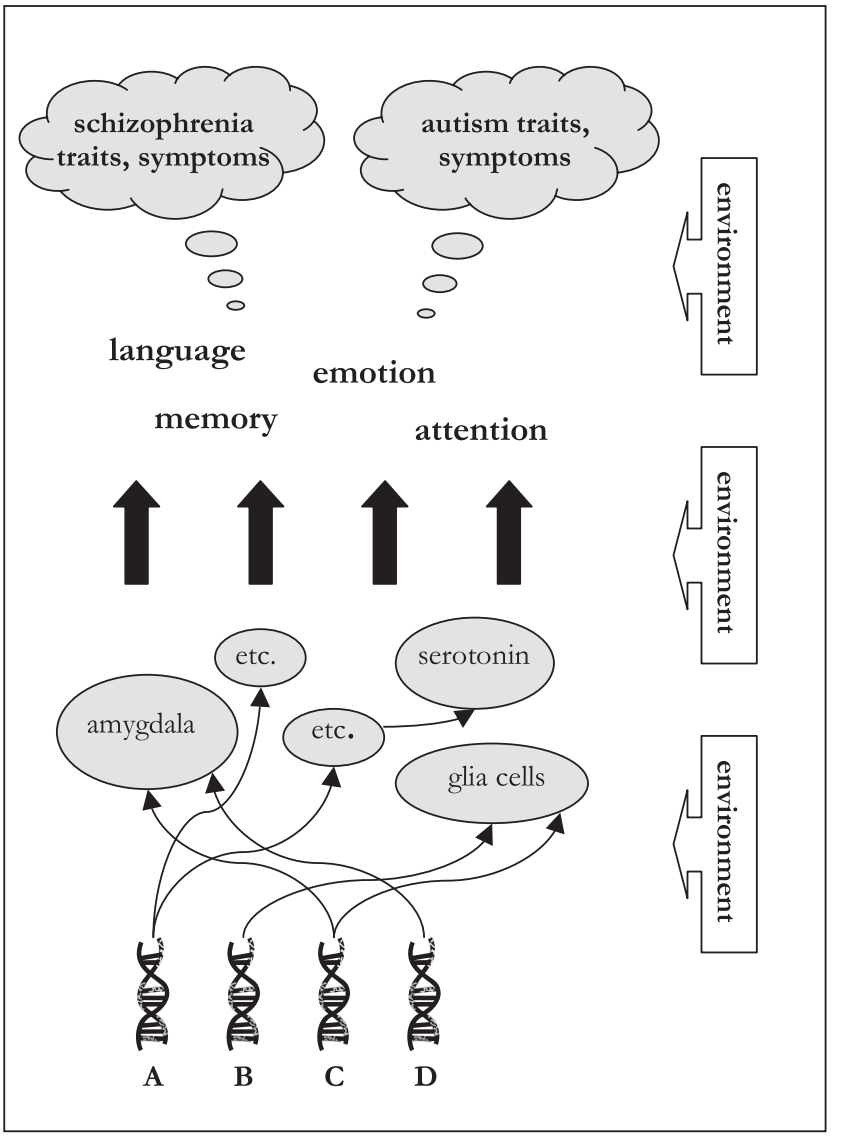
1. Genetic mechanisms are complex

The relations between genes and final phenotypes in behavior are complex. Many forces determine the unique phenotypic expression of an individual's genetic make-up. Genes can have dynamic interactions with environmental factors. These environmental influences not only encompass things as life events, nutrition, aging, and chance, but also endogenous factors such as genes that regulate expression of other genes (epigenetics). Moreover, genes may predispose an individual to be exposed to certain environmental influences, i.e. genotype-environment correlations are present (for a review on gene-environment interactions see (Gottesman et al., 2005). Another reason why the relation between genes and behavior is complex, is that gene expression is dynamic over time. Genes can be turned on and off or can take on different roles during various stages of development (Gottesman et al., 2005).

It is a long road from genotype to final phenotype and many intermediary mechanisms are involved, which are referred to as endophenotypes (see figure 1) (Gottesman et al., 2003). For a behavioral phenotype these intermediary endophenotypes can for example be neurobiological (brain structure) or cognitive (brain function) in nature. The closer a (endo-) phenotype to the genotype is, the less 'noise' from interaction with environmental factors. In case of the brain, these also include biochemical interactions and dynamic

interactions between circuits of cells. Because of this complexity, it has been a difficult challenge to identify gene-brain-behavior pathways leading to social adaptation. In the field of abnormal and non-adaptive behavior in the social domain, such as is seen in psychiatric disorders like autism and schizophrenia, identification of etiological pathways to psychopathology has been hampered by the distant relation between clinical features (the 'molar' level) and genetic abnormalities (the 'molecular' level) together with a lack of knowledge of intermediary mechanisms in the genotype-phenotype pathway (Bearden et al., 2004; Gottesman et al., 2003).

Figure 1
Traits and symptoms from the schizophrenia or autism spectrum may arise from an interplay among various genetic and environmental (including epigenetic) forces, that interactively affect brain development and associated cognitive capacities along the genotype-phenotype pathway. Adversities in brain development or cognitive abilities underlying social behavior are considered as endophenotypes (vulnerability markers) that may be shared by autism and schizophrenia.



2. Behavioral phenotypes are heterogeneous

Genotype-environment interactions allow maximum adaptability to our environment and lead to a heterogeneity in behavioral phenotypes. As a result, behavioral phenotypes may be limited in their use for identifying etiological pathways, including biological and genetic underpinnings, to psychopathology (Gottesman et al., 2003) Despite the presence of standardized criteria (DSM-IV) allowing reliable diagnostic classification of mental disorders based on observed behavior, self-reported symptoms and course, disorders such as autism and schizophrenia are heterogeneous clinical phenomena. (Bearden et al., 2004; Caspi et al., 2006; Jablensky, 2006). Variation in phenotypic expression across development, i.e. temporal inconsistency, as well as individual differences in exposure to medication or other treatments, may result in additional heterogeneity in clinical populations (Jablensky, 2006).

Not only variance at the behavioral or clinical level, but also variance on a genetic level is implicated in the phenotypic variation of brain disorders such as autism or schizophrenia. It is thought that these disorders have a polygenetic origin, i.e. many genes are involved rather than one single gene (Jablensky, 2006; Risch et al., 1999).

The continuum approach

The select set of genes that we carry can direct the development of very complex phenotypes such as is seen in brain structure, brain function and behavior, because of a 'pleiotropic' design; many genes, in different combinations, affect a phenotype. Together with a variety of environmental forces, a spectrum of variation in brain structure, -function and behavior is produced in the general population. These distributions tend to take form of a bell curve, with the majority of individuals represented in the small range around the mean and only a small part of the population in the extremes. Indeed, plots of social competence in the general population appear to be bell curved distributions (Constantino et al., 2003a; Constantino et al., 2000).

Individuals with severe impairments in the social domain, as is seen in autism and schizophrenia, are found at the far end of the spectrum of social abilities. Because of the many factors (genetic or environmental) involved in development of the disorders, variation in phenotypic expression is likely to be distributed along a spectrum. Only in the case of a single factor, such as a single gene, one would expect the distribution to be truly dichotomous giving rise to all-or-none phenomena (Johns et al., 2001).

Phenomena that are part of the clinical phenotype of autism or schizophrenia may be quantitatively distributed along a continuum, rather than being all-or-none, dichotomous disease entities (Johns et al., 2001; Krabbendam et al., 2004). In this view, a clinical definition of autism or schizophrenia may represent only a small part of the total phenotypic continuum, which is not necessarily clinical in nature.

It has been proposed that autism is a 'social brain disorder' that reflects the extreme of a bell-shaped distribution of variation in autism traits, including social competence, in the population (Baron-Cohen et al., 2001; Constantino et al., 2003b; Spiker et al., 2002). Considering the male disadvantage in social cognitive abilities in the general population, the 'extreme male brain theory of autism' postulates that autism represents the male end of a sexually-dimorphic social cognitive continuum (Baron-Cohen, 2002). Similarly, it has been proposed that psychotic or schizophrenia-like traits are distributed along a continuum of severity that ranges from complete absence of schizophrenia-like traits to a severity that is seen in individuals with schizophrenia (Lenzenweger, 1994). For example, some individuals from the general population have magical ideas, whereas individuals with schizophrenia may have severe delusions impacting their behavior and functioning in society (Mullen, 2003). Also, subtle, subclinical signs that parallel the symptoms of the illness may be present in healthy individuals. These signs may be manifested as various schizotypal personality traits, such as unusual perceptual experiences, excentric and desorganized speech and behavior, suspiciousness and social isolation. Subclinical signs may in some individuals progress to symptoms of schizophrenia. In fact, a number of schizotypal traits partially predict schizophrenia at long term follow-up in subjects diagnosed with Schizotypal Personality Disorder (DSM III) (Fenton et al., 1989). Also, the following schizotypal traits in young relatives of patients predict progression to schizophrenia in the following dimensions: social withdrawal, psychotic symptoms and socio-emotional dysfunction (Miller et al., 2002).

The observation that several different personality traits and disorders tend to cluster among biological relatives of individuals suffering from schizophrenia has lead to the hypothesis that a there is spectrum of related phenotypes that includes schizophrenia, as well as less severe phenotypes such as schizotypal personality disorder (DSM IV) and schizotaxia (Cadenhead et al., 2002; Jablensky, 2006; Meehl, 1989; Vollema et al., 1995). Several studies have reported cognitive and neuroanatomical abnormalities in individuals with schizotypal personality disorder that resemble those found in schizophrenia

patients, although the deviations are to a lesser degree (Cadenhead et al., 2002; Siever et al., 2004). The term schizotaxia is proposed to reflect a genetically determined defect in integration in the brain, predisposing to schizophrenia. In this view, only a minority of individuals with this defect decompensate to the point of being diagnosed with schizophrenia based on DSM-IV criteria (Faraone et al., 2001; Meehl, 1989). Also for autism, the concept of a 'broader phenotype' has been introduced to describe the mild features of the clinical autism phenotype that are seen in biological (i.e. genetically related) relatives of individuals with this disorder (Bailey et al., 1998; Bishop et al., 2004). 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) that are seen in biological relatives, may share a genetic origin (Rutter, 2000; Torgersen et al., 2002).

Relevance of studying genetic disorders

Genetic disorders associated with specific deficits in brain development and cognition may help us to unravel genotype-phenotype relations. Starting at the level of the genotype instead of the phenotype, reversing the typical line of research, may be a complementary approach. Specific genetic conditions may be used as models of cognitive or behavioral disorders and provide insights into neurodevelopmental pathways that may be more difficult to uncover by studying heteregeneous, behaviorally defined populations (Reiss, 2000; Reiss et al., 2000). As such, studying individuals with a genetic abnormality who display social cognitive abnormalities and hence difficulties in coping with social situations may help us understand the mechanisms involved in social behavior. It may especially be useful for understanding etiological pathways to autism- or schizophrenia psychopathology.

Klinefelter (47,XXY) syndrome

One genetic disorder that is associated with abnormal brain development and behavior is Klinefelter syndrome, defined by the presence of an extra X chromosome in males (47,XXY). Klinefelter syndrome is the most common sex chromosomal disorder (Wesner et al., 1973), affecting approximately 1 in 700 males (Bojesen et al., 2003). This sex chromosomal aneuploidy results in a variety of phenotypes including hypogonadism, androgen deficiency and infertility (Lanfranco et al., 2004). Cognitive and behavioral dysfunctions in Klinefelter syndrome have generally been under-appreciated relative to

endocrinological and physical features. Although the primary focus in research has been on reproductive dysfunction of these patients, there is an awareness of behavioral and cognitive abnormalities (Boone et al., 2001; Geschwind et al., 2000b). The most prominent behavioral problems in men with Klinefelter syndrome are found in the social domain, such as social withdrawal, social anxiety, shyness, impulsivity and inappropriate or anti-social behavior (Bender et al., 1999; Geschwind et al., 2000a; Ratcliffe, 1999). In early adulthood they report having few or no friends, little energy and initiative, few or no sparetime interests and poor relations with siblings and parents (Nielsen et al., 1980).

The literature on cognitive mechanisms that may underlie impaired social adaptation in XXY men is scarce. It has been proposed that difficulties in social interactions, and specifically those related to communication, are largely attributable to disabilities in the language domain in Klinefelter syndrome (Rovet et al., 1996). The reported verbal 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). For example, Klinefelter boys or men display disabilities in reading, articulation, phonemic processing, spelling, language expression, verbal memory, language comprehension, understanding words, finding words and verbally expressing their thoughts, all resulting in a verbal IQ that is somewhat lower than their performance IQ (Boone et al., 2001; Geschwind et al., 2000a; Money, 1993).

Compared to what is known about the cognitive mechanisms that contribute to social incompetence in Klinefelter syndrome, even much less is known about the neural mechanisms that are involved. Resting state cerebral blood flow patterns, as measured with SPECT, seem more symmetrical in XXY men as compared to men from the general population (Itti et al., 2003). Higher resting state blood flow in the right hemisphere in men with the XXY karyotype has been related to language impairments. Specific language dysfunctions have also been associated with morphological abnormalities of the temporal lobe (Itti et al., 2006). Furthermore, structural Magnetic Resonance Imaging (sMRI) studies with XXY men have indicated volume reductions in regions that are part of a neural network supporting social cognition, such as the amygdala, insula, anterior cingulate and superior temporal gyrus (DeLisi et al., 2005; Patwardhan et al., 2002; Patwardhan et al., 2000; Shen et al., 2004). The difficulties in social adaptation together with the structural brain abnormalities associated with the XXY karyotype suggest that a genetic mechanism involving genes on the X chromosome might lead to disturbances in development of social cognition in XXY men.

Difficulties in coping with the social world may be reflective of an increased vulnerability to traits and symptoms from the autism or schizophrenia spectrum. Indeed, there is some suggestive evidence for a link between the XXY karyotype and increased psychopathology from the schizophrenia spectrum. The importance of investigation into the cognitive and behavioral phenotypical manifestations of Klinefelter syndrome as a means of understanding a predisposition to schizophrenia, is shown by epidemiological studies reporting an increased incidence of XXY karyotypes in schizophrenia. The prevalence of the XXY karyotype in the general population is 0.1-0.2% (Bojesen et al., 2003). There is suggestive evidence that prevalence of the XXY karyoype in the male schizophrenia population may be 1.6 %, which is several times higher (DeLisi et al., 1994; Kunugi et al., 1999). However, these studies involved relatively small sample sizes (N=60 and N=120) in epidemiological terms and some studies have been unable to replicate these findings (Mors et al., 2001; Toyota et al., 2001). In turn, early studies have indicated an increased risk for schizophrenia and psychotic illnesses among Klinefelter men (Lishman, 1998). A review of mental hospital surveys pointed to a threefold increase in Klinefelter patients compared to the general population, which was mainly due to 'psychotic illnesses of a schizophrenic nature' (Forssman, 1970). Another study showed that 7% of the Klinefelter patients in the psychiatric literature had psychoses with paranoid delusions and 6% suffered from schizophrenia (Nielsen et al., 1969). Recently, 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 addition, several case reports of Klinefelter men suffering from schizophrenia or psychosis have been described in the literature (Dervaux et al., 2002; Michielsen et al., 2001; Ong et al., 1995; Roy, 1981; Warwick et al., 2003).

Present thesis

Studying socio-emotional information processing in XXY men at a neuropsychological level as well as neurobiological level might reveal a cognitive and neural basis for the difficulties in interpersonal relations and social 'awkwardness' that have been described. Because the XXY chromosomal pattern appears to be associated with difficulties in the social domain, Klinefelter syndrome might also prove to be a useful model for studying gene-brain-behavior pathways to socially deviant behavior and associated traits from the autism- or schizophrenia spectrum. Importantly, not only is the XXY

population narrowly defined by the presence of an extra X chromosome, individuals with the XXY pattern are generally not mentally retarded (in contrast to many other X chromosomal disorders) which allows the study of specific cognitive disabilities, and underlying neural mechanisms, without the confound of general intellectual decline.

In this thesis, I will focus on socially deviant behavior in adult XXY men on a behavioral, cognitive and neuroanatomical level. In **chapter two,** we aim to refine the social behavioral phenotype in XXY men. We will examine frequency of social behavior and distress during social interactions in men with the XXY karyotype. In addition, we will assess the degree to which features of the autism phenotype, as expressed in autism traits, are present in XXY men. In **chapter three,** we will explore evidence for increased schizophrenia spectrum pathology in XXY men. We will report on clinical measures of schizophrenia symptoms as well as measures of schizotypal personality traits.

I will continue with four chapters that deal with social cognitive abilities in XXY men. In **chapter four** we will examine socio-emotional processing in Klinefelter syndrome. Several domains of social cognition will be discussed, reflecting aspects of social-emotional information processing on levels of perception, experience and expression: labeling of facial expressions of emotion, emotion-cognition interactions in decision making and emotion regulation, that refers to subjective experience and identification of emotional arousal as well as verbal expression of emotions. **Chapter five** focuses on 'social intuition' in XXY men. The ability to quickly and automatically process basic social cues, such as gaze direction and implied biological motion, is thought to be a prerequisite for establishing successful social interactions and especially for construing a sense of 'social intuition'. We report on the extent to which social cues are processed effortlessly and implicitly in three different groups characterized by the presence of traits or symptoms from the schizophrenia spectrum, i.e. patients with schizophrenia, first-degree relatives of patients with schizophrenia and individuals with Klinefelter syndrome (47,XXY). Performance in those groups will be compared to matched controls from the general population. In **chapter six,** we test the hypothesis of the importance of the right hemisphere for specific pragmatic aspects of language in individuals from the general population. We will examine the effects of transcranial magnetic stimulation (TMS) over the right hemisphere on detection of emotions in tone of voice, a pragmatic aspect of language, in contrast to discrimination of emotions in verbal content, a semantic aspect of language

which has been associated with the left hemisphere. **Chapter seven** describes a first exploration of evidence for such pragmatic language impairments in in Klinefelter syndrome. By assessing the ability to discriminate emotions in speech we are able to examine the capacity to perceive and understand social signals in the auditory modality. We will contrast perception of emotional prosody (tone of voice), which is a pragmatic aspect of language thought to be lateralized to the right hemisphere, with perception of emotions in verbal content, which is lateralized to the left hemisphere.

The following three chapters deal with neuroanatomical mechanisms that may underlie social cognitive capacities in Klinefelter syndrome. In **chapter eight,** a possible neural mechanism underlying language disabilites in XXY men is explored. By using fMRI we are able to reveal the effects of an extra X chromosome on lateralization of neural activation during language processing. This technique allows us to identify functional asymmetries in specific brain regions as well as to determine whether reduced lateralization, if found, is secondary to decreased function of the left- or increased activity in the right hemisphere. We will explore the relation between loss of language lateralization and mental functioning in these men, with special interest in clinical phenomena of disorganization of thought and language.

As the amygdala is considered as a key brain area in socio-emotional processing, in **chapter nine** I will review evidence for structural abnormalities of the amygdala in Klinefelter syndrome based on findings in the literature. Findings will be 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. Not only volume of the amygdala, also functioning of the amygdala will be considered. **Chapter ten** deals with findings from a funtional MRI study (fMRI) focused on the neural mechanisms underlying social cognition in XXY men. In this chapter the functional contributions of a neural circuit comprising the amygdala, insula, fusiform gyrus and superior temporal gyrus, to social judgements of faces will be discussed.

Finally, in **chapter eleven,** I will evaluate all the presented evidence regarding social behavior, autism and schizophrenia spectrum traits, social cognitive disabilities and underlying neural mechanisms in XXY men. Besides describing the social cognitive phenotype at the level of behavior, cognition and brain structure and -function of this X chromosomal disorder, I will discuss the

potential implications of a link between the X chromosome and disturbances in development of social cognition and underlying neural networks for understanding gene-brain-behavior pathways to neuropsychiatric disorders such as autism or schizophrenia.

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