Chapter 9

Neurobiology of emotion and high risk for schizophrenia: Role of the amygdala and the X chromosome

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Abstract

Abnormalities in emotion processing and in structure of the amygdala have consistently been documented in schizophrenia. A major question is whether amygdala abnormalities reflect a genetic vulnerability for the disease.

In the present paper, we reviewed Magnetic Resonance Imaging (MRI) studies that reported amygdala measures in several high risk populations: subjects from the general population with subclinical schizophrenia symptoms and relatives of schizophrenia patients. In addition, we reviewed the evidence regarding Klinefelter syndrome (characterised by an additional X chromosome), which has also been related to an increased risk for schizophrenia.

Overall, the evidence points to structural abnormalities of the amygdala in individuals at increased risk for schizophrenia. Although the genetic basis of amygdala deficits remains unclear, abnormalities (of genes) on the X chromosome might play a role as suggested by the evidence from individuals with sex chromosome aneuploidies. We propose that amygdala abnormalities are an endophenotype in schizophrenia and may account for subtle emotional processing deficits that have been described in these high risk groups.

Introduction

There is ample evidence that the amygdala plays a central role in emotional information processing (Aggleton, 2000; Aggleton et al., 2000; Baxter et al., 2002). The amygdala appears to be important, among other functions, for evaluation of the emotional valence of stimuli in the very early phases of sensory processing, linkage of perceptual representation to emotional memories, and regulation of autonomic responses (Aggleton, 2000; Aggleton et al., 2000). In humans, the amygdala appears to be especially important for processing of emotional information in a social context. Facial affect recognition, for example, is shown to depend on the integrity of the amygdala (Adolphs et al., 1994; Adolphs et al., 1999; Calder et al., 1996; Gur et al., 2002a; Morris et al., 1998; Young et al., 1995). Not only is the amygdala involved in processing information about basic facial emotions, but also about complex social judgements, such as trustworthiness judgements of faces (Adolphs, 2002).

Schizophrenia is a serious psychiatric disorder characterised by positive symptoms, reflecting the presence of abnormal behavior such as delusions and hallucinations, and negative symptoms, representing the absence of normal behavior. Besides impairments in the cognitive domain (Aleman et al., 1999; Heinrichs et al., 1998), individuals with schizophrenia show deficits in emotion processing, as indicated by a markedly reduced ability to perceive, process and express facial emotions (Mandal et al., 1998; Morrison et al., 1988; Mueser et al., 1996; Streit et al., 2001). These difficulties have a major impact on social dysfunction in these patients (Edwards et al., 2002). Deficits in facial affect recognition, for example, have been associated with dysregulation of social behaviours and deterioration of interpersonal relations in schizophrenia (Mueser et al., 1996; Poole et al., 2000).

Although a broad range of brain regions seems to be affected in patients with schizophrenia, structural and functional MRI (Magnetic Resonance Imaging) studies have suggested that abnormalities in the amygdala may account for deficits in emotional processing. Structural MRI studies have shown reduced volume and reduced gray matter density of the amygdala in these patients (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). Recent fMRI-studies with schizophrenia patients have shown less functional activation of this structure in response to emotional salient stimuli, such as faces (Gur et al., 2002b; Schneider et al., 1998; Taylor et al., 2002). As revealed by a review of studies focused at facial affect recognition in schizophrenia (Mandal et al., 1998), recognition of facial

expressions of fear and anger seems to be specifically impaired in this illness. These patterns of emotion processing deficits parallel those found in both humans and primates with damage to the amygdala; the processing of fear and anger is an almost invariable consequence of amygdala lesions (Skuse et al., 2003). Not only the recognition of basic facial emotions, also creation of complex social judgements such as trustworthiness of faces, which involves the amygdala as evidenced by functional neuroimaging- as well as focal brain lesion studies, appears to be impaired in schizophrenia (Hall et al., 2004). More support for dysfunction of the amygdala in schizophrenia comes from impairments of patients in aversive conditional avoidance learning (Hofer et al., 2001; Kosmidis et al., 1999), in which the amygdala is critically involved (Maren, 2003).

Evidence for a specific contribution of morphological abnormalities of the amygdala to deficient emotional processing in schizophrenia is given by a study showing that volume of the amygdala can significantly predict performance in an emotional learning task in schizophrenia (Exner et al., In Press). Besides specific contributions to behavioral impairments, effects of amygdala abnormalities may also extend to a clinical level in schizophrenia. Processing of emotional faces is impaired in schizophrenia and associated with problems in social behavior (Hooker et al., 2002). Social dysfunction is one of the hallmarks of schizophrenia and social impairments are often already present before actual onset of the disease (Pinkham et al., 2003), which underlines the importance of studying neural networks, with a key role for the amygdala, that underlie social cognition in schizophrenia.

Interestingly, it has been argued that in schizophrenia early amygdala damage can lead to dysfunction in other brain areas (Grossberg, 2000), for example prefrontal regions. Indeed, using an animal model for neurodevelopmental psychopathological disorders it has been shown that amygdala lesions early in life can result in a restricted pattern of innervation of the prefrontal cortex later in adulthood (Bouwmeester et al., 2002).

Although emotion deficits in schizophrenia have been widely reported, the degree to which these deficits are present in individuals with a genetic vulnerability for the disease has received less attention. Therefore, we will address the issue whether abnormalities of the amygdala form part of the liability to schizophrenia. We will review evidence of amygdala dysfunction with regard to several distinct populations who are at risk for schizophrenia; subjects from the general population with subclinical schizophrenia symptoms and relatives of schizophrenia patients. Furthermore, we review the evidence

regarding individuals with Klinefelter syndrome, characterised by an additional X chromosome and cognitive and emotional deficits that parallel those associated with schizophrenia. Klinefelter Syndrome has also been related to an increased risk of schizophrenia (Lishman, 1998).

The study of these individuals with an increased risk for developing the illness is important for several reasons. First, these studies may help distinguish the latent abnormalities that are related to genetic vulnerability of the illness apart from the illness itself, because in these studies no confounding effects of hospitalisation, antipsychotic drug treatment and potential neurotoxic consequences of psychosis are present. Second, these studies may lead to the identification of biobehavioural markers of the illness, which are important for genetic research because these markers may be more reliable and valid descriptors of a vulnerability to schizophrenia compared to the clinical, DSM-IV-based, phenotypes.

High risk paradigm

There is a general consensus that both environmental- and genetic factors underlie the structural and functional brain abnormalities found in schizophrenia (Hirsch et al., 2003). The genetic predisposition to schizophrenia can be expressed in a variety of manifestations, ranging from mild schizotypal personality traits to severe schizophrenia, as reflected in a schizophrenia phenotype continuum (Faraone et al., 1995; Johns et al., 2001; Keefe et al., 1991; Lenzenweger, 1994). Accordingly, neurobiological markers of a predisposition to schizophrenia are not only present in schizophrenia patients, but to some degree also in healthy individuals carrying a vulnerability for the disease. One reason why it may be interesting to focus on structural brain abnormalities in these individuals, is that brain volumes are highly heritable. To illustrate, several twin-studies have reported heritabilities of 0.94 (Bartley et al., 1997), 0.92 (Carmelli et al., 1998) and 0.90 (Baare et al., 2001) for total brain volume.

Table 1. lists characteristics and findings of studies into structural amygdala abnormalities in high-risk groups, which are discussed in the present review.

Table 1.
Overview of Magnetic Resonance Imaging (MRI) studies that compared amygdala or AHC measures between healthy controls and the following populations who are at risk for schizophrenia; relatives of schizophrenia patients, subjects from the general population with subclinical symptoms and individuals suffering from Klinefelter syndrome (characterised by an additional X chromosome).

Authors	High risk group	Method	Findings
Hendren et al. 1995	Children with mild symptoms (n= 20) Healthy controls (n=12)	MRI, ROI analysis	Volume reduction left and right amygdala left < right
Yeo et al. 1997	Children with mild symptoms (n=20) Healthy controls (n=20)	MRI, ROI analysis	Volume reduction left and right amygdala Reductions more prominent in children with mild symptoms and developmental delay
Keshavan et al. 1997	Adolescent relatives (n=11) Healthy controls (n=12)	MRI, ROI analysis	Volume reduction left amygdala
Seidman et al. 1997	Adult relatives (n=6) Healthy controls (n=11)	MRI, ROI analysis	Volume reduction right amygdala
Marcelis et al. 2003	Adult relatives (n=32) Schizophrenia patients (n=31) Healthy controls (n=27)	MRI, VBM analysis	Reduced grey matter density in amygdala in patients, not in relatives (but no significant differences between patients and relatives either)
Staal et al. 2000	Adult relatives (n=32) Schizophrenia patients (n=32) Healthy controls (n=32)	MRI, ROI analysis	No differences in amygdala volumes between patients, controls and relatives
Seidman et al. 1999	Adult relatives (n=28) Healthy controls (n=26)	MRI, ROI analysis	Volume reduction AHC
Lawrie et al. 2001	Adolescent relatives (n=147) Schizophrenia patients (n=34) Healthy controls (n=36)	MRI, ROI analysis	Reduction AHC volume patients < high risk < controls
Keshavan et al. 2002	Adolescent relatives (n=17) Healthy controls (n=22)	MRI, ROI analysis	Volume reduction anterior AHC, increased leftward asymmetry in AHC
Schreiber et al. 1999	Adolescent relatives (n=15) Healthy controls (n=15)	MRI, ROI analysis	Volume reduction right amygdala, smaller right to left ratio in amygdala
O'Driscoll et al. 2001	Adult relatives (n=20) Healthy controls (n=20)	MRI, ROI analysis	Volume reduction left and right amygdala-anterior-hippocampus
Steel et al. 2002	Adult obligate carriers (n=6) Nonaffected/noncarriers (n=6) Schizophrenia patients (n=6)	MRI, ROI analysis	Volume reduction AHC complex in obligate carriers and schizophrenia patients patients = obligate carriers < nonaffected/noncarriers
Warwick et al. 1999	Adult klinefelter patients (n=10) Healthy controls (n=25)	MRI, ROI analysis	No differences in AHC volume
Patwardhan et al. 2002	Adult Klinefelter patients (n=10) Healthy male controls (n=10) Healthy female controls (n=10)	MRI, ROI analysis	Volume reduction amygdala healthy females = Klinefelter patients < healthy males
Shen et al. 2004	Adolescent Klinefelter patients (n=34) Adolescent healthy controls (n=62)	MRI, VBM analysis	Volume reduction right amygdala

MRI: Magnetic Resonance Imaging, ROI: region of interest, VBM: voxel based morphometry, AHC: amygdala hippocampal complex

Subclinical signs in the general population

One approach to investigate vulnerability to schizophrenia is to identify subtle, subclinical signs in healthy individuals that parallel the symptoms of the illness. These signs, often manifested as various schizotypal personality traits, have been suggested to be continuously distributed in the general population (Aleman et al., 2001; Claridge et al., 1996; Jessimer et al., 1997; Johns et al., 2001). Examples of schizotypal traits are referential and magical thinking, suspiciousness and social isolation.

Subclinical signs may in some individuals progress to symptoms of schizophrenia. In fact, the abovementioned schizotypal traits partially predict schizophrenia at long term follow-up in subjects diagnosed with Schizotypal Personality Disorder (DSM III) (Fenton et al., 1989). Also, 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).

Subclinical signs in the general population: abnormalities of the amygdala

Some of the structural neuroimaging studies have relied on clinical criteria when defining vulnerability for the disease. Hendren and colleagues (Hendren et al., 1995) have examined amygdala volumes of twelve children between 8 and 12 years, who displayed mild symptoms of (early-onset) schizophrenia and/or schizotypal personality disorder. When compared to twelve age-, sex- and socio-economic status- paired matched controls, a significant reduction in amygdala volume was present in the symptomatic group. Measurements were adjusted for the effects of age and total brain volume. Group differences were more prominent for the left than the right amygdala, a finding that has also been reported in studies with chronic schizophrenia patients (Rossi et al., 1994; Shenton et al., 2001).

Yeo and al. (Yeo et al., 1997) have been able to partially replicate this result in a group of twenty children, aged 9 to 12, characterised by schizophrenia-like symptoms, but who did not meet all the diagnostic criteria for schizophrenia. Again, compared to paired matched controls, a reduction in the amygdala volume was found using MRI, but no differences between the right and left amygdala were present. When the symptomatic group was split up in children with and without a history of developmental delay in motor or language function, a comparison of volumetric measurements showed a significantly smaller amygdala volume in the group who did have a history of developmental

delay. All measurements were controlled for age and total brain volume. As the authors noted, these results point to a possible role of the amygdala in the neural development of schizophrenia.

Thus, already in pre-adolescence schizophrenia-like symptoms may be associated with abnormalities in the development of the amygdala. Functions of the amygdala may become more relevant with age, since it is important for recognizing and learning the emotional, and possibly survival-related, meaning of stimuli in the environment and producing appropriate behavioural responses. Indeed, findings from structural MRI studies suggest that there is an age- and gender related increase in amygdala volume during childhood and adolescence (Giedd et al., 1996; Sowell et al., 1998). We speculate that the behavioural effects of dysmaturations of the amygdala may become apparent as high risk children approach adolescence, a period in which maturational processes are dynamic and strengthening of neural connections between the amygdala and for example frontal areas take place ((Benes, 1998; Walker et al., 2002). Although the degree to which these dysmaturations are a direct expression of a genetic predisposition to schizophrenia remains unclear, the parallels in symptoms between these children and schizophrenia patients indicate that they also may share genetic pathology.

Relatives

Sharing a substantial amount of genes, relatives of patients suffering from schizophrenia are at increased risk for the disease, with the risk increasing with the degree of kinship (Gottesman, 1991). Schizophrenia as well as schizotypal traits are more often identified in relatives of patients suffering from schizophrenia when compared to the general population (Kendler et al., 1995; Kety et al., 1994; Kremen et al., 1998; Vollema et al., 2002; Yaralian et al., 2000). When rates of schizotypal personality traits are substantially increased, criteria for Schizotypal Personality Disorder (SPD) may be met. Whereas the prevalence of this disorder is 3% in the general population, 10 to 15% of the relatives suffer from SPD.

But even in the absence of schizophrenia-like symptoms or schizotypal personality traits, biological relatives of schizophrenia patients are at substantial risk for a range of biobehavioral and neurobiological abnormalities that are related to a genetic vulnerability (McDonald et al., 2002; Seidman et al., 1997; Seidman et al., 1999; Staal et al., 2000). In addition, healthy relatives of patients show abnormalities at a neuropsychological level that parallel the deficits seen in schizophrenia patients, although they are more subtle (Sitskoorn et al., 2003).

All in all, relatives of schizophrenia patients provide an opportunity for studying amygdala abnormalities as a neurobiological marker of the disease.

Relatives: abnormalities of the amygdala

The most widely used approach to identify liability to schizophrenia is to establish the genetic risk of subjects based on a family tree describing affected and unaffected family members. In some family trees unaffected family members have been further specified in obligate carriers, subjects having transmitted schizophrenia while remaining healthy themselves, and non-carriers who have not passed any pathological genes on to their offspring. Besides adolescents with a familial risk for schizophrenia, adult relatives of patients have also been subject of investigation. Several studies have been able to show amygdala- or amygdala-hippocampal-complex (AHC) abnormalities in individuals at familial risk.

Amygdala measurements

An MRI study conducted by Keshavan et al. (Keshavan et al., 1997) included eleven high-risk adolescents, aged 12 to 18, who had a parent suffering from schizophrenia. Neither the high-risk adolescents, nor the healthy controls had a history of psychotic disorders. After correction for whole brain volumes, offspring of patients were characterised by reduced left amygdala volume.

One of the first studies that systematically examined brain volumes in adult relatives of patients compared 6 female relatives with 11 controls (Seidman et al., 1997). None of the subjects had suffered from psychosis or schizophrenia spectrum disorders. Among a range of brain volume abnormalities, a mean reduction of the right amygdala was present in the relatives group. Although this reduction was present in spite of the small sample size, no correction for multiple comparisons had been included. When the sample size was extended to 28 relatives, both male and female, and 26 controls, the volume reduction of the amygdala was not statistically significant. However, the amygdala-hippocampal complex as a whole appeared to be significantly reduced in relatives (Seidman et al., 1999).

The apparent inconsistencies in their results might be related to heterogeneity in their sample. As proposed by the authors, schizophrenia may arise from a single pool of environmental and genetic factors in which small effects of the individual factors can add up to result in a vulnerability for the disease. As a consequence, relatives may be characterised by different, probably partially overlapping, sets of vulnerability markers. One way to deal with this

heterogeneity is to select large sample sizes. Their sample of 28 relatives was further extended to 45 and factor analysis, a psychometric approach, was employed. Although no main effects were present for the left and right amygdala combined, the left amygdala, among other brain regions, contributed to the only factor that discriminated relatives from controls (Faraone et al., 2003). This reduction in left amygdala volume is consistent with findings from Keshavan as described above (Keshavan et al., 1997).

There are imaging studies, however, in which no reduction of the amygdala in relatives has been shown. A recent MRI study used computational morphometry to compare grey matter densities on a clustered-voxel basis in 31 schizophrenia patients, 32 relatives and 27 healthy controls (Marcelis et al., 2003). Grey matter density deficits in the amygdala were present in patients, but not in relatives, when compared to controls. However, grey matter density in the amygdala did not significantly differ between relatives and patients, making it difficult to interpret the findings in this study regarding amygdala abnormalities in relatives. In study by Staal et al. (Staal et al., 2000), 16 schizophrenia patients were compared to their healthy siblings and 16 healthy control subjects. Amygdala volume did not differ between the healthy siblings and controls. However, compared to healthy controls, schizophrenia patients did not show a reduction of the amygdala, which makes it difficult to draw conclusions from this study regarding amygdala abnormalities as a vulnerability marker in healthy siblings.

Amygdala-hippocampal complex (AHC) measurements

Because the amygdala is notoriously difficult to measure reliably (Brierley et al., 2002), several studies try to solve the problem by measuring the amygdala and hippocampus as a whole; the amygdala-hippocampal complex (AHC). Some studies divide the AHC in a posterior and anterior portion, with the latter portion representing the amygdala.

As part of the Edinburgh High Risk Study (EHRS), a series of MRI studies by Lawrie and colleagues have explored abnormalities of the amygdala-hippocampal complex as an expression of a genetic liability to schizophrenia. First, they have compared AHC volumes of 100 adolescents characterised by two or more affected relatives, with 20 first episode schizophrenia patients and 30 healthy controls (Lawrie et al., 1999). AHC volume in the high-risk group appeared to be midway between that of healthy controls and first episode patients, with the latter group showing the smallest mean AHC volume. When the high risk sample was extended to 147 subjects, and compared to 34 first

episode patients and 36 healthy controls, the same pattern of results appeared (Lawrie et al., 2001). Although AHC volumes in the high risk group were not related to the number of affected relatives which may reflect a measure of genetic liability, this gradient in AHC volume provides evidence for the idea that AHC abnormalities in schizophrenia are largely genetically mediated. The findings were only partially replicated when using automated Voxel Based Morphometry (VBM), allowing comparisons of grey matter densities, instead of volumetric Region of Interest (ROI) measurements. Although patients did show a reduction in grey matter density in the amygdala when compared to controls, differences in amygdala volume between healthy controls and high risk subjects disappeared when this VBM analysis was applied to the dataset of the Edinburgh High Risk Study (Job et al., 2003).

In the Edinburgh High Risk Study, abnormalities in AHC complex were not related to the presence of psychotic symptoms in the high risk group. A subgroup of 28% of the high risk adolescents characterized by psychotic symptoms did not differ in mean AHC volume from the high risk adolescents without psychotic symptoms. This finding underlines that AHC abnormalities may reflect an underlying genetic vulnerability to schizophrenia, and may not predict the presence or development of psychotic symptoms which in turn may be triggered by environmental factors and/or other neurodevelopmental processes.

This hypothesis is supported by findings in a two-year follow-up study (Lawrie et al., 2003), which was included allowing investigation of the relation between symptom development and brain volume changes. 20 Healthy subjects and 66 high-risk adolescents were re-scanned and symptoms were re-evaluated. No significant time by group interaction was present for the AHC, meaning that change in AHC volume over time did not differ between high risk adolescents and controls. When comparing high-risk subjects displaying symptoms at follow-up with high-risk adolescents without symptoms, no significant time by group interaction was found for the AHC. This finding has been replicated in a longitudinal imaging study focused at the amygdala as a separate region. Adolescents at high-risk for development of psychosis showed no differences in gray-matter volume of the amygdala between those who subsequently developed a psychotic illness (n=23) and those who did not (n=52) (Pantelis et al., 2003).

Other investigators have also performed measurements of AHC volumes in adolescent relatives of schizophrenia patients. Schreiber et al., for example, focused at brain abnormalities in offspring of schizophrenia patients. 15 High-

risk adolescents and 15 controls were between 11 and 19 years of age, and individually matched for age, sex, education and social background. A mean volume reduction of the right AHC was present in high-risk adolescents. In addition, they were characterized by a smaller right-to-left ratio of the AHC when compared to controls (Schreiber et al., 1999).

Keshavan et al. included seventeen high risk adolescents (offspring) in their MRI study and were able to demonstrate volume reductions of about 25% in the left anterior amygdala-hippocampal complex (AHC) (Keshavan et al., 2002). This anterior part of the AHC largely comprises the amygdala. Significant reductions in the right anterior AHC were also present although not as prominent as in the left hemisphere, indicating an increased leftward asymmetry of the anterior AHC.

Another study in which the AHC was split up in an anterior and posterior part focused at adult individuals at familial risk for schizophrenia. O'Driscoll et al. (O'Driscoll et al., 2001) have compared AHC volumes of 20 first-degree relatives with 20 healthy controls using MRI. All subjects were between 18 and 50 years and were similar on demographic variables. None of the subjects had a history of any DSM axis I disorder or met the criteria for Schizotypal Personality Disorder. The area of the amygdala-hippocampal complex was divided in two regions of interest; the amygdala-anterior hippocampus and the posterior hippocampus. Relatives showed a volume reduction of the left- as well as right amygdala-anterior hippocampus, which comprises the amygdala, the pres hippocampus and the anterior portion of the subiculum.

Although the risk of relatives for developing schizophrenia is increased, only a subgroup will actually carry pathological genes. More evidence for a genetic loading of amygdala abnormalities in schizophrenia comes from experimental designs with multiple affected families in which affected subjects, non-carriers (no affected offspring) and obligate carriers (affected offspring) are identified. In addition to an increase in power, such a design allows a clear separation of the contribution of pathological genes from the effects of the illness itself.

In the Edinburgh High Risk Study, sib-ships in high risk families were identified including one affected, one non-affected/non-carrier and one non-affected/carrier (obligate carrier) familymember (Steel et al., 2002). AHC volumes (right and left combined) in subjects with schizophrenia and obligate carriers were significantly smaller when compared to non-affected/non-carriers, which implies a genetic contribution in AHC pathology in schizophrenia. Thus, although AHC abnormalities were not related to a genetic liability index as

measured by the number of affected relatives and whether these are first-degree or second degree relatives, carriers of pathological genes do show reductions of the AHC. Because cortical changes in relatives were not found, the authors concluded that in a framework of complex genetic mechanisms it could be possible that some vulnerability genes, in this case causing AHC abnormalities, are inherited by obligate carriers, whereas other vulnerability genes, responsible for cortical changes for example, are not.

In summary, both adolescents and adult relatives of schizophrenia patients show abnormalities of the amygdala, either measured as the amygdala region exclusively or as part of the amygdala-hippocampal-complex. Since these relatives share a substantial amount of genes with an affected family member, a shared genetic pathology may account for these amygdala abnormalities. The finding that AHC volumes in obligate carriers of pathological genes are similar to AHC volumes in patients, but different from non-affected/non-carriers supports this hypothesis. AHC volumes in relatives seem not to be related to the presence of symptoms. Because AHC abnormalities are thought to reflect a genetic liability for schizophrenia and not the actual expression of the illness (Steel et al., 2002), this is not unexpected.

Klinefelter syndrome

One interesting neurodevelopmental disorder that has been associated with an increased risk for schizophrenia is Klinefelter Syndrome, a genetic disorder characterised by sex chromosome abnormalities. Klinefelter patients have an additional X chromosome, leading to the XXY karyotype. Although the primary focus in clinical studies on Klinefelter Syndrome has been on reproductive dysfunction of these patients, there is an awareness of behavioral and cognitive abnormalities, including socio-emotional disturbances (Boone et al., 2001; Geschwind et al., 2000; Simpson et al., 2003; Swaab et al., submitted). 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 Klinefelter Syndrome in the general population is 0.1-0.2% (Bojesen et al., 2003). The prevalence of Klinefelter Syndrome in the schizophrenia population is 1.6 %, which is several times higher (DeLisi et al., 1994; Kunugi et al., 1999). In turn, early studies have indicated an increased risk for schizophrenia and psychotic illnesses among Klinefelter patients (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). In addition, Klinefelter syndrome has recently been associated with high levels of schizophrenia spectrum pathology (van Rijn et al., submitted). Compared to 26 healthy males, a group of 26 Klinefelter patients were characterised by elevated levels of schizophrenia symptoms as well as schizotypal traits. Effect sizes, the difference between the groups expressed in standard deviations, in this study paralleled those reported for patients suffering from schizophrenia. From the 26 Klinefelter males, 7 individuals (27%) met diagnostic criteria for a psychotic disorder.

Studying Klinefelter patients present an opportunity to investigate whether amygdala abnormalities can be associated with a predisposition to schizophrenia. An additional advantage over studying relatives is the knowledge of the precise genetic aetiology of Klinefelter syndrome in contrast to what is known of the genetic pathology in schizophrenia.

Klinefelter syndrome: abnormalities of the amygdala

Although AHC abnormalities were not found in an explorative MRI study with Klinefelter patients (Warwick et al., 1999), specific amygdala reductions were present in an MRI study focusing at temporal lobe structures in Klinefelter patients (Patwardhan et al., 2002). 10 XXY males were recruited from a cohort newborns screened for sex chromosome abnormalities and compared to 10 individually matched healthy males and healthy 10 females. Approximately half of the patients had been exposed to testosterone supplements. Amygdala volumes of Klinefelter patients were comparable to those of healthy females. Interestingly, Klinefelter patients suffering from schizophrenia show several parallels with females suffering from schizophrenia; similar ages of onset that differ from male schizophrenia patients and a predominance of positive symptoms over negative symptoms (Pinabel et al., 1997). In an important study, using voxel-based morphometry, Shan et al. observed pronounced volume reductions of the right amygdala in 34 subjects with Klinefelter syndrome (mean age 12.6 years) compared to 62 healthy matched controls (Shen et al., 2004). Compared to previous findings documented in the literature, findings from this study provide a better spatial localization of the affected regions (other affected regions are the insula, cingulate, hippocampus, temporal gyri and occipital gyri).

X-linked genes appear to be involved in the functional as well as structural development of the amygdala (Good et al., 2003). Several studies have shown amygdala volume to be inversely correlated with the number of X chromosomes (Goldstein et al., 2001; Good et al., 2003). For example, males (46,XY) have larger amygdalae than females (46,XX). Patients suffering from Turner syndrome (45,X), who are characterised by a partial or complete deletion of the X chromosome, have even larger amygdala volumes when compared to healthy males. On a behavioural level, these patients are impaired in facial affect recognition while showing normal configural processing (Lawrence et al., 2003). This deficit in emotion recognition appears to be most pronounced for fear, a finding that parallels data from studies with schizophrenia patients (Kohler et al., 2003).

Although speculative, the idea that amygdala abnormalities in schizophrenia may somehow be related to X chromosomes deserves further investigation. Especially in the light of sex-differences in the onset and course of the disease.

Conclusion and discussion

The present review explored whether an increased risk for schizophrenia is associated with structural abnormalities of the amygdala. Structural neuroimaging studies with three distinct populations at risk for schizophrenia have provided indications that reductions in amygdala volume indeed may be associated with an increased risk for schizophrenia. First, individuals from the general population with subclinical signs of schizophrenia show reductions in amygdala volume. Second, volume reductions of the amygdala and amygdala-hippocampal-complex (AHC) have been found in relatives of schizophrenia patients. Third, Klinefelter patients, characterised by an XXY chromosomal pattern, also show reduced amygdala volumes.

The fact that amygdala abnormalities, which have consistently been 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), are also observed in high risk populations, is of considerable importance. Since volume reductions of the amygdala seem to be present already in pre-adolescents with subclinical signs of the illness, abnormalities of the amygdala in schizophrenia might have a developmental origin. Indications that these amygdala abnormalities are an expression of a genetic predisposition to schizophrenia are primarily derived from studies with healthy relatives of patients, who besides sharing genes also share amygdala or AHC abnormalities. Consequently, abnormalities of the amygdala or AHC might belong to the

endophenotype of schizophrenia, a concept which is introduced to refer to brain structures or cognitive functions that mediate between the molecular, genetic level and the molar, clinical level of the disease (Gottesman et al., 2003). This would imply that antipsychotic medication, hospitalisation and neurotoxic effects of psychosis may not fully account for volume reductions of the amygdala in schizophrenia, since reductions have been found in subjects with an increased risk for the disease, but who did not have a history of pharmacological treatment, psychosis or hospitalisation. This is supported by an imaging study with medication-naive schizophrenia patients, who show volume reductions of the amygdala (Joyal et al., 2003). In the same study, neither duration of illness, nor symptom severity correlated with amygdala volume.

Amygdala abnormalities may be one of many endophenotypes in schizophrenia, each one being an expression of a particular genetic pathology (Gottesman et al., 2003). Although most attempts to link the general schizophrenia phenotype to aberrations of the X chromosome have produced contradictory results (DeLisi, 1997; DeLisi et al., 2000), recent genome screens have pointed to a possible locus on the X chromosome (Paterson, 1999). However, in these studies the magnitude of the effects regarding the X chromosome is smaller than the most positive loci. We argue that amygdala abnormalities, a specific phenotype, in schizophrenia might be related to X-linked genetic pathology. Support for this idea comes from studies with individuals suffering from X chromosome abnormalities. For example, individuals with Klinefelter syndrome (47,XXY), who have almost an approximately ten-fold increased risk for schizophrenia when compared to the healthy population, show reductions in amygdala volume. Furthermore, support for the hypothesis that amygdala abnormalities may be directed by genes on the X–chromosome, comes from a study with subjects with X chromosome abnormalities, showing that a dosage sensitive genetic locus on the X chromosome appears to play a key role in the functional and structural development of the amygdala (Good et al., 2003). In addition, several lines of research have indicated that the number of X chromosomes is inversely correlated with amygdala volume (Goldstein et al., 2001; Good et al., 2003). For example, males (46,XY) have larger amygdalae than females (46,XX). Males and females do not only differ at the level of X chromosomes and amygdala volumes, at a clinical level gender differences are also present. A recent meta-analysis of 38 studies that reported sex-specific incidences of schizophrenia has provided evidence for a sex difference in the risk for developing schizophrenia (Aleman et al., 2003; Phillips et al., 2004). The reported risk ratio for males to

develop schizophrenia relative to females was 1.42 (95% CI 1.30–1.56). In addition, a meta-analysis on sex differences in deficit schizophrenia (which involves larger emotional deficits) even reported a ratio of 1.7 (Roy et al., 2001). Males not only suffer more often from schizophrenia when compared to females, men also appear to have an earlier age of onset and a more severe course of the illness (Gur et al., 1996). Interestingly, Klinefelter patients suffering from schizophrenia show several parallels with women suffering from schizophrenia; similar ages of onset, later than male schizophrenia patients, and a predominance of positive symptoms over negative symptoms (Pinabel et al., 1997).

X chromosome abnormalities may co-direct amygdala volumes partly through abnormal testosterone levels, because sex of the gonads that produce gonadal hormones is determined by genes on the sex chromosomes (Arnold et al., 2004). However, testosterone levels by itself seem not enough to explain the amygdala abnormalities in individuals with sex chromosome aneuploidies. For example, 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). Differences in amygdala volume between Turner and Klinefelter patients appear to 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, although the amygdala, testosterone levels and X chromosomes appear to strongly inter-related, the exact nature of the relationship still remains unclear.

We propose that in schizophrenia, X-linked genetic pathology, either directly or indirectly via testosterone, might result in a endophenotype characterised by amygdala abnormalities. Amygdala abnormalities as an endophenotype of putatively X-linked pathology may not be specific for schizophrenia. 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). Interestingly, in autism males (46, XY) are affected four-fold more often than females (46, XX). Moreover, females suffering from Turner syndrome (45,X), who are missing one X chromosome, have a 200-fold increased risk of autism (Creswell et al., 1999). These findings support the idea that amygdala

abnormalities in autism may be linked to the X chromosome. If we in turn focus at psychiatric disorders characterised by X-linked genetic pathology, abnormalities of the amygdala have been consistently reported. Not only in the population of Klinefelter patients who are at increased risk for schizophrenia, also in Turner syndrome (complete or partial deletion of X chromosome) and Fragile X syndrome (mutations on X chromosome) abnormalities of the amygdala have been observed (Good et al., 2003; Hessl et al., 2004; Kesler et al., 2004). In contrast to Klinefelter Syndrome, these disorders have been associated with an increase in amygdala volume (Good et al., 2003; Hessl et al., 2004). Interestingly, it has been reported that Turner syndrome occurs approximately three-fold more frequently in schizophrenic females when compared to the general female population (Prior et al., 2000). Thus, amygdala abnormalities as an endophenotype may be present in several psychiatric disorders. This review has provided support that schizophrenia is one of these disorders. In addition, we propose that individuals with Klinefelter Syndrome, associated with X chromosome abnormalities, share this endophenotype with schizophrenia.

A clinically relevant question that arises from these speculations would be: How may amygdala abnormalities at an endophenotypical level extend to a phenotypical, behavioural level? Since the amygdala is strongly involved in emotion processing and appears to be part of a neural network underlying social cognition, one would expect emotional-and social difficulties to be present in the populations that have been described here. A review of the literature tentatively supports this idea. As observed in schizophrenia patients, relatives of patients show deficits in facial affect recognition, although they are more subtle (Toomey et al., 1999). Amygdala abnormalities as an endophenotype may result in behavioural deficits which, again, need not necessarily be specific for schizophrenia. In Autism and Turner Syndrome, deficits in facial affect recognition and impairments in social cognition have been reported (Baron-Cohen et al., 2000; Good et al., 2003; Klin et al., 2002; Lawrence et al., 2003). Interestingly, parallel to schizophrenia patients and amygdala damaged patients, individuals with autism and Turner syndrome show selective impairments in the recognition of facial expressions of fear (Howard et al., 2000; Lawrence et al., 2003).

Regarding high risk populations, there is a shortage of behavioural studies focused at emotion processing. Recently, our department has shown a range of emotional processing abnormalities in a non-clinical psychosis-prone sample (van 't Wout et al., 2004). In this population, unusual perceptual experiences, a positive schizotypal trait, correlated with more problems in identifying

emotions. Verbalizing and analysing emotions, as well as emotional arousability, correlated with constricted affect, a negative schizotypal trait.

Future research should investigate the functional consequences of amygdala abnormalities in genetically predisposed subjects using functional MRI and behavioural measurements. Specific effects of normal brain maturation, illness and medication on the amygdala should be examined in these subjects in longitudinal designs. Twin studies or designs in which multiplex families are included and obligate carriers are identified will provide unique opportunities for disentangling genetic from environmental effects on the development of schizophrenia.

It should be noted that several limitations have become apparent in the present review of studies. A number of limitations associated with structural measurement of the amygdala may contribute to the heterogeneity in findings in MRI-studies focused at high-risk populations. The amygdala is located in proximity of the nasal cavity, which may lead to an increase of MRI susceptibility artefacts. In addition, low scan resolution and limited number of slices through the amygdala make it more difficult to reliably estimate its volume and separate it from the hippocampus. Future studies should follow the guidelines given by Brierley et al. (Brierley et al., 2002; David et al., 2002) in order to enhance methodological rigor. In addition, in several MRI studies reported in this paper, the amygdala is measured as part of a complex (AHC) and not as a separate region of interest, which is a major limitation. However, although the amygdala and the hippocampus are anatomically dissociable, the AHC may be perceived as a unitary complex at some level, since they sustain functions that pertain to emotion processing (Phillips et al., 2003). The hippocampus has direct connections with the amygdala and plays a key role in context modulation of emotional behaviour (Davidson et al., 2000). Finally, the range of MRI studies focused at populations at high risk for developing schizophrenia is somewhat limited and not all studies find amygdala abnormalities. However, the majority of studies are indicative of a role of the amygdala or AHC abnormalities.

In summary, this review focused at structural abnormalities of the amygdala in various populations a high risk for developing schizophrenia. Studies with individuals from the general population showing subclinical signs of the illness and studies with relatives of schizophrenia patients indicate that amygdala abnormalities may form part of the genetic predisposition to schizophrenia. Amygdala abnormalities may be one of the endophenotypes in schizophrenia and might be X chromosome linked, as suggested by converging evidence from

individuals with X chromosome abnormalities. We therefore suggest that amygdala abnormalities might be an X-linked endophenotype in psychiatric disorders, especially in schizophrenia and populations at high risk for schizophrenia, and may account for emotional en social processing deficits that have been described in these populations.

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