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Review

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

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Summary

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.

Keywords: Amygdala; Schizophrenia; High Risk; Endophenotypes; Neurobiological Markers; X-Chromosome

Contents

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1. Introduction

There is ample evidence that the amygdala plays a central role in emotional information processing (Aggleton and Young, 2000; Baxter and Murray, 2002; Aggleton, 2000). 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 and Young, 2000; Aggleton, 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 (Gur et al., 2002a; Morris et al., 1998; Young et al., 1995; Adolphs et al., 1999; Adolphs et al., 1994; Calder et al., 1996). 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, (Heinrichs and Zakzanis, 1998; Aleman et al., 1999) 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 C). 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 and Park, 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