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Progress in Neurobiology 77 (2005) 283–298

progress in Neurobiology

www.elsevier.com/locate/pneurobio

Strange feelings: Do amygdala abnormalities dysregulate the emotional brain in schizophrenia?

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Received 29 April 2005; received in revised form 2 November 2005; accepted 9 November 2005

Abstract

Schizophrenia is widely regarded to be a neurocognitive disorder, i.e. a dysfunction of the neural and cognitive systems subserving thinking and reasoning, memory, language, attention and perception. However, although cognitive dysfunction is certainly a cardinal feature of schizophrenia, we argue that dysfunction of emotional brain systems may be even more important in understanding the disorder. Indeed, in recent years research on the emotional aspects of schizophrenia is accumulating at a high rate. Here, we review the available evidence regarding behavioral and neural manifestations of abnormal emotional systems in schizophrenia. This evidence comes from patient studies using tasks of emotion recognition, emotional expression and emotional experience. Furthermore, studies of schizophrenia patients using structural MRI have demonstrated volume reductions of the amygdala, a key structure of the emotional brain. Finally, functional fMRI studies have revealed an attenuated response of the amygdala to emotional stimuli as compared to neutral stimuli. Beyond demonstrating that dysfunction of the emotional brain is a hallmark of schizophrenia, we propose a model that integrates previous neural accounts of emotional abnormalities in schizophrenia, and specifies a neural basis for differential emotional correlates of positive and negative symptoms. Specifically, a lesion to the amygdala in combination with reduced interconnectivity with the prefrontal cortex is hypothesized to give rise to reduced emotional expression (affective flattening) and emotion recognition deficits. In contrast, an imbalance in dopamine systems may underlie increased anxiety and autonomic arousal, and the assignment of emotional salience to insignificant stimuli, associated with psychosis. We also hypothesize that the central and basolateral nuclei of the amygdala may contribute differentially to these abnormalities.

Keywords: Schizophrenia; Amygdala abnormalities; fMRI

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Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; DA, dopamine; CeA, central nucleus of the amygdala; BLA, basolateral nucleus of the amygdala

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0301-0082/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2005.11.005

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1. Introduction

Schizophrenia is a complex and variable psychiatric disorder characterized by cognitive, social and emotional impairment, and by psychotic symptoms such as delusions and hallucinations (Mueser and McGurk, 2004). Psychotic symptoms refer to the loss of contact with reality, and involve delusions (fixed, false beliefs), hallucinations (aberrant, false perceptions) or bizarre behaviors. Negative symptoms are deficit states in which basic emotional and behavioral processes are diminished or absent. Examples include blunted or flat affect, as evidenced by reduced emotional expression in the face or voice, apathy and anhedonia. Negative symptoms are more pervasive than psychotic symptoms and are strongly related to social dysfunction. Finally, the cognitive deficits concern deficits in attention, memory and executive functions such as planning of behavior, set shifting ability and problem solving. Other, similar, classifications of symptoms characteristic of schizophrenia have been proposed, such as the three statistical clusters identified by Liddle (1987), who distinguished between the psychomotor syndrome (poverty of speech, flattened affect, and decreased spontaneous movement), the disorganization syndrome (formal thought disorder and inappropriate affect) and the reality distortion syndrome (delusions and hallucinations). The lifetime prevalence of schizophrenia is about 1% (Jablensky, 2003), and the incidence is higher in men than in women (Aleman et al., 2003). The combined social and economic costs of schizophrenia are very high, placing it among the world's top ten causes of disability (Mueser and McGurk, 2004).

The prevalent view on the nature of schizophrenia is that it is a neurocognitive disorder, i.e. a dysfunction of the neural and cognitive systems subserving thinking and reasoning, memory, language, attention and perception (Elvevag and Goldberg, 2000; Frith, 1992; Minzenberg et al., 2002; Green, 1998; Andreasen, 1999). Indeed, quantitative reviews have documented large effect sizes for the difference between patients with schizophrenia and healthy comparison subjects on a range of cognitive tests, with probably the largest effect size for memory functioning (Heinrichs and Zakzanis, 1998; Aleman et al., 1999). These cognitive deficits have been observed in first-episode patients, are stable and wide-ranging, and are present, albeit to a lesser extent, in non-psychotic relatives (Hoff and Kremen, 2002; Sitskoorn et al., 2004). However, although cognitive dysfunction is certainly a cardinal feature of schizophrenia, we argue that emotional dysfunction may be as important. In making this distinction between emotion and cognition, we assume that emotion and cognition are best thought of as separate but interacting mental functions mediated by separate but interacting brain systems (LeDoux, 1995; Zajonc, 2000). According to LeDoux (1995), empirical findings that are consistent with this assumption concern the fact that (1) the emotional significance of stimuli and the perceptual representation and significance of an object are processed by different brain areas, (2) the emotional meaning of a stimulus can be appraised before the perceptual systems have fully processed the stimulus, (3) brain systems involved in storage and retrieval of emotional information are different from those involved in storage and retrieval of cognitive representations of the same stimuli, (4) systems that perform emotional appraisals are directly connected with systems involved in the control of emotional responses, whereas this connection between cognitive processing and response control systems is not so tightly coupled, and therefore allows a larger degree of flexibility, and (5) the strong coupling of emotional appraisal systems with response control systems leads to the activation of bodily sensations which form part of the conscious experience of emotion, whereas bodily sensations are not typically involved in cognitive processing. Indeed, emotional expression, perception and experience are regarded to be part of the broader construct of ''social cognition'', which refers to information processing underlying social interaction, and which can be dissociated from nonsocial cognitive processes such as memory and general problem solving (Pinkham et al., 2003).

Although emotional dysfunction has been regarded a hallmark of schizophrenia since the early days of schizophrenia research (Bleuler, 1911), this is largely neglected in contemporary neurocognitive accounts of the disorder. Notably, Bleuler (1911) considered affective symptoms to belong to the primary symptoms of schizophrenia. Interestingly, he suggested that the affective disturbances could be either part of the underlying disease process or, alternatively, psychological reactions to the illness. Thus, he left open the question whether emotional disturbances belong to cause or effect. As schizophrenia research was in its infancy, no firm conclusions on this issue could be reached in Bleulers time. Over the past decades, researchers and clinicians have mainly adapted the viewpoint that emotional disturbance is a reaction to the illness, as is evidenced by the fact that schizophrenia is considered to be a ''non-affective'' psychosis, in contrast to bipolar disorder, which is considered an ''affective'' psychosis by the two most influential diagnostic classification systems, DSM-IV-TR (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992). In the present article, we describe recent theoretical proposals and integrate the growing body of evidence in favour of the former position, that emotional disturbances and dysfunction of the corresponding brain circuits may be at the core of schizophrenia (cf. Ciompi, 1998). More specifically, the putative role of amygdala abnormalities in dysregulating the emotional brain will be discussed.