Psychiatry Research: Neuroimaging 221 (2014) 195–203

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Evidence for altered amygdala activation in schizophrenia in an adaptive emotion recognition task

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ARTICLE INFO

Article history:
Received 18 December 2012
Received in revised form
29 June 2013
Accepted 3 December 2013
Available online 10 December 2013

Keywords:
Social cognition
Functional magnetic resonance imaging
Negative bias
Facial affect recognition

ABSTRACT

Deficits in social cognition seem to present an intermediate phenotype for schizophrenia, and are known to be associated with an altered amygdala response to faces. However, current results are heterogeneous with respect to whether this altered amygdala response in schizophrenia is hypoactive or hyperactive in nature. The present study used functional magnetic resonance imaging to investigate emotion-specific amygdala activation in schizophrenia using a novel adaptive emotion recognition paradigm. Participants comprised 11 schizophrenia outpatients and 16 healthy controls who viewed face stimuli expressing emotions of anger, fear, happiness, and disgust, as well as neutral expressions. The adaptive emotion recognition approach allows the assessment of group differences in both emotion recognition performance and associated neuronal activity while also ensuring a comparable number of correctly recognized emotions between groups. Schizophrenia participants were slower and had a negative bias in emotion recognition. In addition, they showed reduced differential activation during recognition of emotional compared with neutral expressions. Correlation analyses revealed an association of a negative bias with amygdala activation for neutral facial expressions that was specific to the patient group. We replicated previous findings of affected emotion recognition in schizophrenia. Furthermore, we demonstrated that altered amygdala activation in the patient group was associated with the occurrence of a negative bias. These results provide further evidence for impaired social cognition in schizophrenia and point to a central role of the amygdala in negative misperceptions of facial stimuli in schizophrenia.

1. Introduction

Patients with schizophrenia suffer from severe deficits in social cognition. These social cognitions, as defined by Brothers (1990), refer to the processing of information that leads to accurate perception of the dispositions and intentions of others. One important social cognitive function is emotion recognition, which is a necessary prerequisite for the understanding of others' intentions (Mier et al., 2010a). It has been shown that deficits in emotion and mental state recognition in schizophrenia are related to psychopathology and can affect quality of life and social outcome (Brüne, 2005; Couture et al., 2006). On the neuronal level, these deficits are reflected in atypical activation of the amygdala, which is one of the core structures used in the processing of social stimuli (Adolphs and Spezio, 2006). While many studies have demonstrated atypical amygdala functioning in schizophrenia, results are mixed with respect to whether the amygdala is hyporesponsive (Li et al., 2010) or hyperresponsive (Holt et al., 2006a; Mier et al., 2010b) towards social stimuli.

Emotion recognition deficits in schizophrenia have been documented for decades (for reviews, see Edwards et al., 2002; Kohler et al., 2010). However, these deficits occur not only in periods of acute psychosis (Malik et al., 2010) and chronic schizophrenia (Mueser et al., 1996), but also in subjects at high risk of schizophrenia (Amminger et al., 2012) and in relatives of schizophrenia patients (Erol et al., 2010). Hence, it has been recently postulated that aberrant social cognition can be viewed as an intermediate phenotype of schizophrenia (Derntl and Habel, 2011).

While findings from behavioral studies of schizophrenia clearly point to deficits in social cognition, results from studies investigating the neurobiological correlates of social cognition, and particularly emotion recognition in schizophrenia, are rather mixed (although it should be mentioned that findings from behavioral studies also differ with regard to which emotions are most difficult to recognize for schizophrenia patients) (e.g., Kohler et al., 2003; Silver et al., 2009). Meta-analyses point to the amygdala as the structure that shows the most systematic differences between schizophrenia patients and healthy controls during emotion recognition

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http://dx.doi.org/10.1016/j.pscychresns.2013.12.001

(Li et al., 2010; Anticevic et al., 2012; Taylor et al., 2012). However, while most of the early studies found *hypo*activation of the amygdala and other structures in schizophrenia (see meta-analyses by Li et al., 2010; Anticevic et al., 2012; Taylor et al., 2012; Delvecchio et al., 2013), more recently a growing number of studies in schizophrenia have reported *hyper*activation of several emotion-related brain areas, including the amygdala (Holt et al., 2006a; Seiferth et al., 2008; Mier et al., 2010b). Such heterogeneity of results (concerning hypoactivity versus hyperactivity of the amygdala) might be due to methodological differences between the studies, including (but not limited to) the emotions that have to be recognized, as well as the subsequent analysis of task effects.

First of all, there is evidence that hypoactivation in response to emotional expressions in schizophrenia occurs only for specific types of emotions. While most of the studies examining general emotion recognition abilities found *hypo*activation (Li et al., 2010), studies comparing activation in response to neutral facial expressions found *hyper*activation of the amygdala in schizophrenia patients (Holt et al., 2006a; Mier et al., 2010b). Going along with findings of hyperactivation of the amygdala in the processing of neutral facial expressions, several studies demonstrated altered salience attribution to neutral stimuli in schizophrenia (Holt et al., 2006b), as well as a negative bias (Premkumar et al., 2008); that is, patients are more likely than healthy control subjects to perceive negative emotions in neutral facial expressions. Hall and colleagues (Hall et al., 2008) demonstrated amygdala hypoactivation in a sample of schizophrenia patients in response to fearful faces, but only when contrasting the activation with activation in response to neutral facial expressions. These results by Hall and colleagues are in agreement with a recent meta-analysis by Anticevic and colleagues (Anticevic et al., 2012), showing amygdala hypoactivity for negative emotions in schizophrenia, when activation was contrasted with neutral emotions. Hence, there seems to be a difference in the processing of emotional and neutral facial expressions between schizophrenia patients and healthy controls, suggesting that a separate investigation of brain response to neutral and emotional facial expressions in schizophrenia might be beneficial (Mier et al., 2010b).

Two additional factors that have important implications for the strength of brain activation are task difficulty and task motivation. It has been demonstrated that low performance in working memory tasks is associated with decreased activation of prefrontal areas (Callicott et al., 2003; Van Snellenberg et al., 2006). Comparable evidence can be found for emotional processing. Hempel and colleagues showed that activation in prefrontal areas increases when emotion recognition is more difficult (Hempel et al., 2003). These prefrontal areas in turn have a modulatory influence on the amygdala (Stein et al., 2007a), and it was shown that when a task has a higher cognitive demand, task-irrelevant emotional stimuli have a weaker effect on amygdala activation (Pessoa et al., 2005; Jasinska et al., 2012), and that amygdala activation is stronger when emotion processing is less explicit (Hariri et al., 2000). Similar to these results, we demonstrated reduced amygdala activation in schizophrenia patients with increasing task demand and decreasing performance in a social-cognitive task (Mier et al., 2010b). Moreover, a motivational deficit, associated with reduced activation in the ventral striatum has been repeatedly demonstrated in schizophrenia (Esslinger et al., 2012; Nielsen et al., 2012; Gradin et al., 2013). Hence, there is evidence that task difficulty and motivation can have an indirect or even a direct influence on activation of limbic structures. Since patients with schizophrenia are impaired in emotion recognition, i.e., the task is more difficult for them, one could assume that this impairment is also reflected in reduced amygdala activation. Hence, in attempts to determine whether schizophrenia is associated with altered amygdala activation during emotion recognition, comparable task difficulty has to be established for the patients and the control group. In other words, differences in task difficulty between groups have to be avoided because they could lead to altered amygdala activation in various ways that are not necessarily caused by a biological emotion recognition deficit.

Here, we present a study that tests the ability to recognize positive and negative emotions, as well as neutral facial expressions, in schizophrenia, using an adaptive emotion recognition paradigm. An adaptive design has the advantage that the intensity of the to-be-recognized emotion is adjusted to each subject's ability to recognize emotions, allowing for comparable levels of subjective difficulty (in terms of the number of correct responses) between subjects and groups. By adjusting the task difficulty based on subject ability, we can also avoid confounds in brain activation that are due to performance differences between groups. We hypothesized that in comparison to a healthy control group, schizophrenia patients would have prolonged reaction times and show a necessity for higher emotional intensities for accurate emotion recognition, as well as a negative bias. In addition, we hypothesized that we would find amygdala hyperactivation in schizophrenia subjects for the recognition of neutral facial expressions, but not for the recognition of emotional expressions. Lastly, we hypothesized that the strength of amygdala activation for neutral facial expressions would be correlated with the amount of negative bias.

2. Methods

2.1. Subjects

Participants comprised 12 schizophrenia outpatients and 16 healthy control subjects. One schizophrenia patient was excluded from analyses because he recognized none of the faces with a fearful expression correctly. Groups were matched for age, gender, fluid and crystalline intelligence, and education. With the exception of one left-handed patient, all participants were right-handed. All participants (*as well as all facial stimuli for the emotion recognition task*) were Caucasian. Healthy controls were excluded if they indicated having a current or lifetime psychiatric disorder, as assessed with the German screening interview MINI-DIPS (Margraf, 1994). Moreover, control subjects were also excluded if they reported having any first degree relatives with a psychiatric disorder (self-report). All patients met criteria for a DSM-IV diagnosis of schizophrenia and were on stable doses of antipsychotic medication. To assess current schizophrenic psychopathology in the patient group, Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) were applied by an experienced clinical psychologist (D.M.). Patients were low on positive symptoms, as well as on negative symptoms. Table 1 presents demographic information, chlorpromazine-equivalent antipsychotic dosage (Andreasen et al., 2010; Gardner et al., 2010), and psychopathology (see Supplementary Table 1 for detailed information on medication for each of the patients). All subjects fulfilled inclusion criteria for magnetic resonance imaging. Before participation, written informed consent was acquired from all subjects. The study was approved by the local ethics board of the University of Giessen, School of Medicine, and conducted in agreement with the declaration of Helsinki.

2.2. Stimuli

Facial stimuli with neutral, angry, happy, fearful, or disgusted expressions were presented. To generate facial stimuli with graded emotional intensities, pictures from eight people (four females) were subjected to a morphing procedure. A morphing program was used to prepare pictures with 20%, 40%, 60%, and 80% intensity of the emotion by superimposing the neutral expression of each person with their emotional expression, resulting in one neutral picture for each person and five pictures (the original emotion and four generated ones) for each of the emotions. Next, these pictures were shown to 93 university students for emotion recognition (Mier et al., 2010a). Based on their ratings, five intensity levels of the emotions (20%, 40%, 60%, 80%, and 100%) were reproduced (which were not necessarily identical to the grading of the morphing program). These stimuli were used to adjust the difficulty of emotion recognition to achieve comparable average recognition rates for all subjects. The aim of this process was not to create fine-tuned stimuli with which, for example, an emotion-detection threshold could be defined, but rather to generate enough stimuli that varied in difficulty to apply an adaptive emotion recognition task.