The nature of emotional abnormalities in schizophrenia

Evidence from patients and high-risk individuals

De aard van de emotionele stoornissen bij schizofrenie
(met een samenvatting in het Nederlands)

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Stemmen

Is het van onder het water
dat de stem spreekt,
van onder het spiegelwater
dat zonder gezicht
alleen maar weerkaatst
wat is?
Is het de stem van de zee
die ik hoor, de zee
die brengt en haalt
bruist en buldert
tegen rotsen schreeuwt
het strand bekruipt

  is het de zee
  of hoor ik de stem van mijn bloed
  het rode schreeuwen
  van mijn hart?

Is het van achter de heuvels
dat ik stemmen hoor, of
in het gehuil van spelonken
in het weerkaatsen van wanhoop
tegen bergen

  of hoor ik het gieren van angst
  door mijn darmen
  het groeien van noodlot
  in mijn maag?

Hoor ik de stem van het vuur
het vreten van vlammen
het blakeren van hout

of is het de stem
van de eeuwige veenbrand
in mijn onderbuik
die om brandstof roept
naar adem snakt?

Is het een stem in de wind
die ik hoor, de wind,
die soms buldert
dan weer fluistert
om daken giert
door bladeren gruizelt

of is het mijn eigen adem,
mijn adem, mijn eigen stem?

Jan Vijn voor Mascha

Voor al mijn ouders

General Introduction

Chapter 1

Emotional abnormalities in schizophrenia

Schizophrenia

Schizophrenia is a psychiatric disorder that affects about one out of 100 people, with symptoms generally emerging in early adulthood. According to the DSM-IV, schizophrenia is characterized by psychotic symptoms, such as hallucinations, delusions, bizarre behavior or speech and negative symptoms such as flattening of affect (American Psychiatric Association, 1994). Psychotic symptoms such as hallucinations and delusions are regarded as particularly characteristic for schizophrenia, although they may also occur in other psychiatric disorders. Besides these psychotic symptoms, which are often treatable with antipsychotic medication, people with schizophrenia experience negative symptoms (social withdrawal, affective flattening, apathy, alogia) and cognitive disturbances, e.g. memory dysfunction, attention problems, and emotional dysfunction. It are mainly these latter problems that cause that the majority of people with schizophrenia are unable to built up a social network, career and romantic relationships, making it one of the most invalidating psychiatric disease.

The genetic contribution to schizophrenia has been recognized for decades (Hirsch and Weinberger, 2003). Whereas schizophrenia affects about 1% of the general population the incidence of developing schizophrenia is up to ten times higher for siblings and even 50% for monozygotic twins of patients with schizophrenia (Gottesman, 1991). This suggests that although genetic factors play a role, other, environmental factors are crucial for the development of schizophrenia. Diathesis-stress models proposed that the expression of a biological schizophrenia vulnerability was influenced by exposure to stress (Rosenthal, 1970). Although there is little evidence that patients with schizophrenia have been exposed to higher levels of stress than the general population, there is a relationship between stressful events and severity of schizophrenia symptoms (Norman and Malla, 1993b; 1993a). This suggests that patients with schizophrenia are more responsive to psychosocial stress. Recent research supports this theory that some patients with schizophrenia show a higher sensitivity to stress (Myin-Germeys et al., 2002). Moreover, this increased reactivity to stress has also been observed in first-degree relatives of patients albeit to a lesser extent (Myin-Germeys et al., 2001).

A growing number of studies consider psychosis as a continuum with normal functioning at one end and abnormal functioning (psychosis) at the other end (Claridge, 1997; Johns and van Os, 2001; Verdoux and van Os, 2002). In accordance with this view, Johns and van Os (2001) have reviewed evidence indicating that psychotic signs, often called schizotypal signs or schizotypal traits, are present in healthy people to a certain extent. Schizotypy refers to the personality trait of experiencing 'psychotic' symptoms (Claridge, 1997) and schizotypy may be conceptualized as a predisposition to schizophrenia at the level of the organization of the personality (Meehl, 1989; Vollema

and van den Bosch, 1995). Such schizotypal traits, e.g., referential thinking and odd or eccentric behavior have been hypothesized to be normally distributed in the non-clinical population (Chapman et al., 1976).

The schizophrenia spectrum phenotype hypothesis suggests that deficits cardinal for schizophrenia could also be observed in biological first-degree relatives of patients, although these deficits are usually less pronounced. This has been confirmed for neuropsychological dysfunction (Sitskoorn et al., 2004). Also, with respect to social-emotional information processing some previous research demonstrated that relatives of patients with schizophrenia show subtle deficits in aspects of social cognition (Toomey et al., 1999; Loughland et al., 2004). When abnormal emotion processing is observed in these high-risk groups these abnormalities could not be due to the effects of illness per se or its treatment as high-risk individuals are not clinically psychotic and have not been treated by antipsychotic medication for this. In this regard, the investigation of emotion processing in high-risk individuals enables the study of deficits related to schizophrenia without confounding influences. In that way, results can validate the observed results in patients. Second, emotion-processing deficits observed in high-risk individuals may reflect at least in part a vulnerability to schizophrenia. This search for measures that reflect the genetic predisposition to schizophrenia, also called endophenotypes, can provide more specific and simpler clues to the genetic underpinnings of schizophrenia (Gottesman and Gould, 2003).

Emotional processing in schizophrenia

Although there is abundant research on memory and attention deficits in schizophrenia (Heinrichs and Zakzanis, 1998; Aleman et al., 1999), the amount of studies that identify and describe the emotional deficits in schizophrenia are relatively small. This may seem contradictory as from the early days of describing and classifying schizophrenia symptoms, emotional disturbances are regarded as cardinal symptoms (Bleuler, 1911; Kraepelin, 1919). Kreapelin, however, also stressed the cognitive component of schizophrenia as the very term "dementia praecox" testifies, and the success of neuropsychology in identifying large differences between patients and control subjects on a range of neuropsychological tests, led several researchers to proclaim impaired cognition to be at the core of the disorder (Elvevag and Goldberg, 2000; Heinrichs, 2005). Another reason for the paucity of research on emotional disturbances might be the lack of appropriate methods and techniques for studying emotion.

Emotion and emotion processing is a broad term and includes different aspects. For instance, a distinction can be made between the perception, expression and experience of emotions. The neural basis of emotion processing includes also different

brain structures, such as the amygdala, frontal cortex (medial prefrontal cortex and orbitofrontal cortex), insula and cingulate cortex (LeDoux, 1995; Davidson and Irwin, 1999; Dolan, 2002; Phan et al., 2002). It has been proposed by Phillips et al. (2003a) that a ventral system, including the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, and prefrontal cortex, is important for the identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses. A second, dorsal system includes the hippocampus, dorsal anterior cingulate gyrus, and prefrontal cortex, for the effortful regulation of affective states and subsequent behavior. In schizophrenia specific structural and functional abnormalities of these neural systems are associated with specific positive symptoms and negative symptoms (Phillips et al., 2003b). Moreover, a growing body of research supports abnormalities in the amygdala and prefrontal cortex and other emotional structures in schizophrenia (Schneider et al., 1998; Gur et al., 2002b; Hempel et al., 2003; Phillips et al., 2003b; Takahashi et al., 2004).

Thus, over the past few decades, the possibility that individuals with schizophrenia may be disturbed in their expression, experience and perception of emotions expressed by other people has received increasing attention. However, it is still unclear which emotion processes are disturbed in schizophrenia. A recent review summarized that patients with schizophrenia show deficits in emotion perception, emotional experience and behavior with an emphasis on negative emotions (c.f. Shayegan and Stahl, 2005). Indeed, studies that investigated emotion processing in schizophrenia generally support the idea that emotion processing, such as facial affect processing or to a lesser extent affective prosody is deficient in schizophrenia (Leentjens et al., 1998; Edwards et al., 2001; Kohler et al., 2003). These findings are in line with early observations that emotional abnormalities of schizophrenia depend on reduced emotional abilities. However, this mainly concerns emotional perception, i.e. the recognizing and labeling emotional expressions or utterances. There are a number of studies that suggest that not all emotion processes are diminished. For instance, although patients with schizophrenia are associated with a reduced ability to express emotions, patients report comparable levels of experiencing positive and negative emotions as controls (Kring et al., 1993; Kring and Neale, 1996). Moreover, Kring and Neale (1996) showed that patients with schizophrenia exhibited greater skin conductance reactivity to emotional films than controls. Thus a disjunction among emotional processing domains might be present in schizophrenia. Further evidence for such as disjunction was recently discussed by Aleman and Kahn (2005), who proposed dysfunctional amygdala circuits as a putative neurobiological substrate for a specific patterns of emotional abnormalities in schizophrenia.

Emotion perception in schizophrenia

The perception of emotions in schizophrenia has frequently been examined with tasks measuring the recognition, labeling and matching of faces expressing different emotions. In recent years various reviews on facial affect recognition in schizophrenia have been published. The first review covers the period through 1986 and concludes that although deficits in emotion recognition are observed there is no consensus about the nature of the deficits (Morrison et al., 1988). A later review published by Mandal et al. (1998) concluded that schizophrenia patients, despite a general impairment of perception or expression of facial emotions, might have specific deficits in the processing of negative emotions compared to positive emotions. Another extensive review by Edwards et al. (2002) also covers important methodological issues in facial affect recognition research and affective prosody in schizophrenia. From this review it was concluded that although individuals with schizophrenia experience problems in the perception of emotional information, the specificity, extent and nature of these deficits is unclear. Secondly, deficits in the recognition of negative affect, such as fear and anger appear most often disturbed in schizophrenia, which is in line with the previous review of Mandal et al. (1998). The most recent review comes from Kohler and Brennan (2004), who concluded that schizophrenia patients may be particularly impaired in the recognition of fear, show abnormal visual fixation upon scanning of facial features (Phillips and David, 1997) and exhibit abnormal amygdala activation when processing emotional faces (Phillips et al., 1999; Gur et al., 2002b). In addition, this review also mentions the finding of schizophrenia-like emotional abnormalities in healthy high-risk populations, such as first-degree relatives of patients with schizophrenia (c.f. van Rijn et al., 2005). For instance, abnormal visual scanning (Phillips and David, 1998; Loughland et al., 2004) and abnormal affect perception (Kee et al., 2004) extends to relatives of patients with schizophrenia. Moreover, biological first-degree relatives of patients demonstrate volume reductions similar (albeit smaller in magnitude) to those observed in patients with schizophrenia, including volume reductions of parts of the emotional brain, such as reduced bilateral amygdala-hippocampal region (Seidman et al., 1997; Seidman et al., 1999; Seidman et al., 2002; Seidman et al., 2003; van Rijn et al., 2005). The investigation of these high-risk groups is appealing as high-risk populations enable to study deficits that may be related to vulnerability for schizophrenia without confounding environmental influences such as hospitalization, medication and psychopathology.

Even though studies have reported facial affect recognition deficits in schizophrenia, controversy exists as to whether this impairment represents a specific *emotion* recognition deficit, a general *face* processing deficit (Johnston et al., 2001) or

reflects other cognitive problems, such as attentional problems (Combs and Gouvier, 2004). However, there is some evidence for a specific emotion-processing deficit in schizophrenia that consists of poorer performance in tasks of facial emotion recognition than in general faces processing tasks. In addition, there are several studies that report specific deficits in the recognition of negative emotions compared to positive emotions (cf. Mandal et al., 1998).

Expression of emotions in schizophrenia

With respect to the expression of emotions, schizophrenia has been associated with reduced or diminished expression of emotions. This is also present in the classification of negative symptoms of schizophrenia that reflect a reduction of normal (emotional) behavior, in particular a flattening of affect and emotional and social withdrawal or affective unresponsiveness (Kay et al., 1987; American Psychiatric Association, 1994). Studies that investigated emotional expressiveness in patients with schizophrenia have videotaped patients while they were watching affect-eliciting stimuli. These studies showed that patients with schizophrenia were facially less emotionally expressive compared to control participants (Berenbaum and Oltmanns, 1992; Kring et al., 1993; Dworkin et al., 1996; Kring and Neale, 1996). Similar results were found when facial expressiveness was measured with electromyography (EMG), that is, patients showed reduced facial expressiveness to happy films (Mattes et al., 1995). However, more recent research demonstrated that facial reactions in schizophrenic patients assessed via EMG in response to pictures of facial expressions exhibited greater reactivity of facial muscles than did nonpatient controls (Kring et al., 1999). In addition, Earnst et al. (1996) demonstrated that although schizophrenia patients showed less observable facial expressiveness to emotional films, they showed greater EMG activity to emotional films. With regard to functional outcome, Cohen et al. (2005) reported that patients with schizophrenia who show a diminished emotionality have poorer social functioning. However, there appeared to be a discrepancy between self-reported levels of emotionality and patients' emotionality rated by trained observers.

Emotional experience in schizophrenia

Besides difficulties in the expression of emotions, the inability to experience emotions is also regarded as a characteristic negative symptom of schizophrenia. With regard to the inability to experience positive emotions or pleasure, this has been called anhedonia (Meehl, 1962). Research on anhedonia is complicated as it is a subjective experience, in contrast to affective flattening that can be objectively assessed. Recent research that investigated the subjective experience of emotions asked patients during the day how

strong and which emotions were felt. Results showed that more intense negative emotions were reported, whereas for the positive emotions, less intensity was reported in schizophrenia patients compared to control participants (Myin-Germeys et al., 2000). Moreover, the experience of negative emotions, in particular anxiety even seems to precede the onset of psychotic symptoms like hallucinations (Delespaul et al., 2002). However, Aghevli et al. (2003) showed that emotional experience in schizophrenia patients seems normal compared to controls. Furthermore, using mood induction patients with schizophrenia and first-degree relatives of patients reported comparable levels of mood induction as control participants. Nevertheless, patients with schizophrenia and relatives of patients showed reduced amygdala activation during negative mood induction (Habel et al., 2004).

This thesis

The present thesis will focus upon the nature of emotion-processing deficits in schizophrenia, as well as in individuals at risk for schizophrenia and how emotive information influences other cognitive functions, such as memory, attention and goal-directed behavior in schizophrenia or high-risk individuals. Currently, the prevalent idea is that emotion processing is generally deficient in schizophrenia (Leentjens et al., 1998; Edwards et al., 2001; Kohler et al., 2003). Thus, the emphasis is solely on reductions or impairments. However, as noted above, there are some studies that argue for a more complex pattern of emotional abnormalities in schizophrenia. More specifically, patients with schizophrenia show deficits in the perception and expression of emotions together with intact, or even heightened experience of emotions (Kring et al., 1993; Kring and Neale, 1996; Aleman and Kahn, 2005). In this thesis, different aspects of emotion processing, i.e. perception, expression, experience and psychophysiological responses to emotive material will be investigated in schizophrenia and individuals at high risk for developing schizophrenia. The research that will be described in this thesis concentrates in particular on the investigation of disjunctions between different emotional processes and the influence of abnormal emotion processing on other cognitive functions. For instance, a disjunction will be made between the automatic allocation of attention to threatening information versus more elaborative processing of emotional information. Additionally, the ability to express as well as experience emotions will be investigated, along with autonomic indices of emotional reactivity. The investigation and acknowledgement that not all emotional processing aspects might be deficient in schizophrenia is important for the development and implication of specific treatment strategies.

Outline and aims of the studies

The nature of emotion processing deficits in schizophrenia

The first research question of this thesis is to define the nature of the emotion perception deficits in schizophrenia in more detail. In *chapter 2* the central issue is whether emotion perception processing is overall disturbed in schizophrenia or whether a distinction can be made between incidental, automatic processing of facial affect (i.e. gender decision of affective faces) and more elaborative, controlled perception of facial affect (i.e. the labeling of emotional faces). There is reason to believe that the automatic processing of affective stimuli is less affected than the controlled processing of facial affect (Kohler et al., 2003; Suslow et al., 2003a; Rossell, 2004). Furthermore, it is suggested that brain areas associated with automatic and controlled processing of emotive stimuli differ. *Chapter 3* will deal with the question whether certain patient characteristics, like negative or positive symptoms are associated with facial affect processing performance of specific emotions. This is a relevant question since schizophrenia is a heterogeneous disorder and it has been proposed that differences in results on facial affect processing are due to the investigation of heterogeneous patient samples. On the basis of the literature we predict that especially males (Scholten et al., 2005) and patients with negative symptoms (Gaebel and Wölwer, 1992; Schneider et al., 1995; Kohler et al., 2000a) show errors in facial affect recognition.

Chapter 4 describes a study that investigates the interference of threat-related information in object-location memory using highly symbolic stimuli. To our knowledge this is the first investigation of spatial memory for affective information in schizophrenia. This is of importance, as in every-day life, emotional signals are bound to spatial locations, and the latter information is of significant relevance for undertaking action. In *chapter 5*, emotional arousal as measured with skin conductance activity in response to affective faces is investigated. These psychophysiological responses to affective stimuli are, besides emotional perception, expression and experience, important components of emotional processing (Lang, 1984). Skin conductance activity is mediated through the autonomic system and is suggested to reflect emotional arousal (Bouscein, 1992).

Emotional abnormalities in individuals at high-risk for schizophrenia

This thesis furthermore addresses the question whether emotional abnormalities are also present in individuals who are at high-risk for developing schizophrenia or psychosis. In *chapter 6* aspects of emotion regulation as measured with an alexithymia questionnaire will be investigated in patients with schizophrenia, healthy siblings of patients with schizophrenia and healthy control participants. Alexithymia is a multidimensional construct that refers to personality traits relating to inabilities or severe reductions in

identifying, describing and communicating feelings, difficulties in differentiating feelings from bodily sensations, and diminished affect-related fantasy (Sifneos, 1973; Sifneos et al., 1977). The presence of alexithymic tendencies could be hypothesized in schizophrenia and siblings of patients, because schizophrenia is typically associated with deficits in emotion expression that could also observed in relatives. In *chapter 7* emotion processing, including emotion perception, expression and experience will be investigated in individuals with an increased risk for psychosis, in particular hallucinations.

Chapter 8 describes a study in which patients with schizophrenia and siblings of patients are compared on the explicit processing of biological relevant social cues, i.e. the evaluation of trustworthiness of faces. *Chapter 9* describes a study in which different groups on the schizophrenia spectrum are compared on the automatic, effortless processing of simple social cues including gaze direction and implied biological motion towards or away from conspecifics. As the automatic, effortless processing of social cues is thought to underlie optimal social cognition and social functioning (Frith and Frith, 1999), deficits in the processing of social cues might contribute to problems in social functioning in schizophrenia.

Emotions, goal-directed behavior and high-risk for schizophrenia

In the third part of this thesis aspects associated with strategic decision-making, i.e. goal-directed behavior and emotional state will be investigated. Although traditional economic models typically regard decision-making as a rational, cognitive process, recent approaches incorporate the idea that emotions and their physiological components may play an important role in decision-making (Bechara et al., 1997; Camerer, 2003). For example, in a recent fMRI study, Sanfey et al. (2003) reported that activation of the anterior insula, a brain area implicated in aversive emotions, such as disgust (Phillips et al., 1997), was related to decision-making performance and that this activation reflected negative emotional responses. At the same time, activity in the dorsolateral prefrontal cortex was observed when people made a choice, possibly reflecting cognitive control or goal maintenance (Sanfey et al., 2003).

In *chapter 10* the role of emotions in strategic decision-making is further investigated. Specifically, physiological emotional responses as measured with skin conductance activity were related to decisions including unfairness. *Chapter 11* describes a study in which the causal contribution of the dorsolateral prefrontal cortex for decision-making strategy is demonstrated using repetitive Transcranial Magnetic Stimulation (rTMS) in the same decision-making paradigm as used in *chapter 10*. (r)TMS delivers short magnetic pulses that penetrate the skull and disrupt neural processing in a non-invasive, reversible way (Walsh and Pascual-Leone, 2003). If the dorsolateral prefrontal cortex

guides goal-directed behavior by optimizing decision strategy on the basis of prior choices (Barraclough et al., 2004), neural interference by rTMS must cause behavioral interference with the present strategy.

Chapter 12 will go into abnormal decision-making behavior on the basis of emotions in a genetically high-risk group for schizophrenia, i.e. siblings of patients with schizophrenia. A recent neurobiological model of emotional abnormalities in schizophrenia suggests that an anatomical lesion of the basolateral nucleus of the amygdala, together with an imbalance in dopamine systems will result in aberrant emotional reactivity (Aleman and Kahn, 2005). Consistent with this, previous studies showed an increased interference of emotive information on cognition in patients as well as siblings of patients (Docherty et al., 1998). On the basis of this model it can be hypothesized that the increase of emotional arousal by the amygdala will override normal goal-directed behavior mediated through the prefrontal cortex, resulting in more rejections of unfair offers by siblings compared to control participants in strategic decision-making.

Finally, *chapter 13* provides a summary and discussion of the main findings of this thesis.

The nature of emotion processing deficits in schizophrenia

Chapter 2

Exploring the nature of facial affect processing deficits in schizophrenia

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Psychiatry Research; in press.

Abstract

Schizophrenia has been associated with deficits in facial affect processing, especially negative emotions. However, the exact nature of the deficit remains unclear. The aim of the present study was to investigate whether schizophrenia patients have problems in automatic allocation of attention as well as in controlled evaluation of facial affect. 37 Patients with schizophrenia were compared with 41 control subjects on incidental facial affect processing (gender decision of faces with a fearful, angry, happy, disgusted and neutral expression) and degraded facial affect labeling (labeling of fearful, angry, happy and neutral faces). The groups were matched on estimates of verbal and performance intelligence (National Adult Reading Test; Raven's Matrices), general face recognition ability (Benton Face Recognition) and other demographic variables. The results showed that patients with schizophrenia as well as control subjects demonstrate the normal threat-related interference during incidental facial affect processing. Conversely, on controlled evaluation patients were specifically worse in the labeling of fearful faces. In particular, patients with high levels of negative symptoms may be characterized by deficits in labeling fear. We suggest that patients with schizophrenia show no evidence of deficits in the automatic allocation of attention resources to fearful (threat-indicating) faces, but have a deficit in the controlled processing of facial emotions that may be specific for fearful faces.

Introduction

From the first descriptions of schizophrenia the apparent emotional disturbances, such as emotional flattening or blunted affect are regarded as a core deficit of schizophrenia (Bleuler, 1911). In addition, more recent research demonstrated deficits in the processing of emotional material including faces, pictures, verbal information and other symbolic emotive information in schizophrenia (Edwards et al., 2001; Edwards et al., 2002; van 't Wout et al., in press). Indeed, the deficits in facial affect recognition are one of the main findings of the last decade and are now widely acknowledged (Schneider et al., 1995; Mueser et al., 1996; Wölwer et al., 1996; Addington and Addington, 1998; Habel et al., 2000; Kohler et al., 2000a; Penn et al., 2000; Pinkham et al., 2003). Moreover, a growing body of research indicates that the emotion processing deficits in schizophrenia are stronger for the recognition of negative facial affect (Mandal et al., 1998; Edwards et al., 2002; Kohler et al., 2003), such as fearful faces (Gaebel and Wölwer, 1992; Archer et al., 1994). These facial affect-processing deficits may be linked to amygdala disturbances in schizophrenia. The amygdala, as a key area for the processing of negative emotional information (Morris et al., 1996) seems deficient both structurally and functional in schizophrenia, which might result in emotion processing deficits (Gur et al., 2002b).

Yet, the exact nature of the facial emotion-processing deficit in schizophrenia remains unclear. Currently, the prevalent idea seems to be that schizophrenia patients have general deficits in emotional processing (Shayegan and Stahl, 2005). That is, no differentiation is made between different processes or components, with the exception of valence, i.e. the recognition of negative emotions has been reported to be more affected than positive emotions (Mandal et al., 1998). However, automatic and controlled evaluative processing of affect have been distinguished as important components of emotional processing (LeDoux, 1996; Cunningham et al., 2003). Automatic processes are thought to be primarily involved in the generation of quick evaluative judgments. For instance, valence detection on a positive-negative dimension is an automatic evaluative process often used in priming paradigms (Hermans et al., 1994; Rossell et al., 2001; Klauer and Musch, 2003). In turn, controlled processes are involved in processing more complex information, such as explicit emotion recognition or labeling (Gorno-Tempini et al., 2001; Winston et al., 2003). Notably, there is also evidence for a differential neural basis for these two distinct kinds of emotional processing. Whereas automatic emotional processing of facial expressions has been shown to depend primarily on right hemispheric resources (Hartikainen et al., 2000) including the right amygdala (Markowitsch, 1998; Gläscher and Adolphs, 2003), the labeling of facial emotions has been shown to depend on the left hemisphere (Young et al., 1993; Stone et al., 1996). To our knowledge, the difference

between automatic and controlled facial affect processing has not yet been contrasted in a single study.

Previous research on automatic processing of schizophrenia resulted in mixed findings. For instance, schizophrenia patients employed abnormal visual scan paths when viewing faces (Phillips and David, 1997). In addition, patients with schizophrenia showed a reduced left perceptual bias in response to emotional faces (Gooding et al., 2001). On the other hand, Hoschel and Irle (2001) reported stronger emotional priming in schizophrenia when primed with an unpleasant face, reflecting a stronger influence of automatically processed emotional stimuli on judgments. These findings were extended by Suslow et al. (2003a) who demonstrated that in an affective priming task schizophrenia patients were more sensitive to subliminal negative facial affect than controls and perceive positive facial affect as aversive or unpleasant. In addition, Suslow et al. (2005) showed in a sequential affective priming task based on faces that schizophrenia patients without affective negative symptoms showed comparable priming effects as controls, whereas patients suffering from flat affect or anhedonia manifested only a prime effect due to negative facial valence. Finally, Kring et al. (1999) used electromyography to measure facial responsivity to affective faces and found that schizophrenia patients showed greater corrugator reactivity than healthy controls. Moreover, support for augmented automatic affect processing in schizophrenia comes from studies that demonstrated the presence of a threat-related bias, i.e. a predisposition for threatening stimuli already present in the early stages of processing, in people with persecutory delusions (Blackwood et al., 2001). This is consistent with a recent model of emotion processing in schizophrenia (Aleman and Kahn, 2005), in which a neural basis was proposed for the paradox of impaired explicit emotion perception and expression in the face of normal or heightened levels of emotional reactivity. Following this line of reasoning patients with schizophrenia could show normal or increased automatic attention to facial affect, but show deficits in controlled processing. However, to our knowledge there are no studies that investigate both processes together in schizophrenia on a behavioral level.

The aim of the present study was to further investigate the nature of the facial affect processing deficits in schizophrenia by examining incidental attention allocation processes, i.e. Stroop-like interference of facial affect and controlled evaluation of facial affect. Automatic allocation of attention to facial affect (Vuilleumier, 2005) was tested with an incidental facial affect-processing task in which participants made a gender judgment concerning affective faces. We hypothesized that patients with schizophrenia would show a normal incidental processing of threat-related facial affect, i.e. expected interference for fearful faces compared to neutral faces. Controlled evaluation of facial affect was measured using degraded, low-pass filtered pictures of affective faces with

different emotional intensities since low spatial frequency faces might convey global information for coarse emotional recognition. We hypothesized that schizophrenia would be associated with difficulties in the labeling of threat-related faces, in particular fearful faces (Edwards et al., 2001).

Both involuntary attention allocation to faces and controlled evaluation of facial affect were tested in a highly educated, stable patient sample with low levels of symptomatology to eliminate confounding effects, such as acute phase of the illness or severe symptoms to the maximum.

Methods

Participants

37 Patients with a DSM-IV diagnosis of schizophrenia from the University Medical Center Utrecht participated in the study. Diagnosis of schizophrenia was confirmed by using a standardized interview, the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) that was administered by a psychiatrist. Patients were also screened for affective disorders, i.e. depression and mania, substance-related disorders by the CASH. Most patients were diagnosed with paranoid type of schizophrenia (n=26). One patient was diagnosed with disorganized type of schizophrenia, one with catatonic type of schizophrenia, one with residual type of schizophrenia, one with schizoaffective type of schizophrenia, five undifferentiated type of schizophrenia and two with schizophreniform disorder. Most patients were clinically stable. Ten patients were inpatients and 27 were outpatients. Symptoms were rated independently by two trained raters with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Once a year, PANSS raters attend interrater reliability meetings given by a qualified neuropsychologist. 33 Patients used antipsychotic medication and of these patients nine also used other medications (paroxetine; citalopram; lithium; valproate; oxazepam; temazepam), one patient only used antidepressants, 4 patients did not receive medication due to remission of symptoms. Clinical and demographic characteristics of the groups are listed in Table 1.

41 Healthy control subjects were drawn from the general population by advertisements in local newspapers and were paid for their participation. Inclusion criteria for both patients and healthy controls were age between 18-65 years and physically healthy. Exclusion criteria were neurological conditions or history of head injury with loss of consciousness, recent history of substance abuse and mental retardation. None of the control subjects had a history of psychiatric illness confirmed with the Mini International

Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1997). Control subjects were recruited to match the patient sample with respect to age, sex and educational level.

In addition, neuropsychological tests were administered to match the patient sample and control sample on an estimation of IQ, and general face processing. The Dutch translation of the National Adult Reading Test, NART (Nelson, 1982; Schmand et al., 1991) and the Raven's Advanced Progressive Matrices, Short Form were used as an estimate of respectively verbal and nonverbal IQ (Raven et al., 1993; Lezak, 1995). To control for general face processing the Benton and Van Allen Test of Facial Recognition, Short Form (Benton et al., 1983) was used. A trained psychologist carried out neuropsychological testing. Separate t-tests demonstrated that patients did not differ from control subjects in age, years of education or parental education, male:female ratio, estimates of IQ and general face processing. The local ethics committee approved the study according to the Declaration of Helsinki and all subjects provided written informed consent after the procedure had been fully explained. Testing was done in a quiet room at the University Medical Center Utrecht and presentation of the tests was fixed to eliminate possible order effects.

Automatic processing of facial affect

In this face perception task, standardized Ekman and Friesen photographs of faces with emotional expressions (Ekman and Friesen, 1976) were presented using e-prime software version 1.1 (Psychology Software Tools, 1996-2002). Angry, fearful, disgusted, happy and neutral emotional expressions were included. In total 80 trails, 16 trails for each emotion were included. Half of the faces were male and the other half were female. Five trails of each emotion were used as practice trials, resulting in 15 trials for each emotion type. The ratio male:female faces were 8:7 for angry faces; 7:8 for fearful faces; 7:8 for disgusted faces, 8:7 for happy faces and 7:8 for neutral faces. Each picture was presented 400 ms and the subject had to judge, as fast as possible the sex of the person to which the face belonged (male/female). Two highlighted buttons on the keyboard were used to answer. The task was performed bimanually using the two index fingers of the left and right hand. Subjects were instructed to 'work as quickly as possible, but do not sacrifice accuracy for speed'. Subjects first completed 5 practice trials. Outlier latencies, i.e. very fast responses (ms $<$ 400 ms) and very slow responses (ms $>$ 900 ms or individual mean ms $\pm$ 3 times the standard deviation) were excluded from analyses (less than 2% was excluded in this way.

Table 1. Clinical, demographic and neuropsychological characteristics of 37 patients with schizophrenia and 41 healthy control subjects. PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

	Schizophrenia patients	Control subjects	
	Mean (SD)	Mean (SD)	P
Age (years)	32.19 (9.05)	30.95 (8.48)	0.54
Sex (male/female)	24/13	28/13	0.75
Education (years)	15.53 (2.50)	15.24 (2.49)	0.63
Parental education (years)	14.81 (2.45)	13.44 (3.70)	0.09
Verbal IQ	106.29 (8.07)	109.10 (9.61)	0.18
Non-verbal IQ	103.76 (14.22)	108.85 (12.19)	0.10
General Face Processing (errors)	5.29 (1.99)	4.49 (1.89)	0.07
Duration of illness (years)	9.62 (9.08)		
Age of onset (years)	22.30 (5.14)		
Positive scale PANSS	11.81 (3.99)		
Negative scale PANSS	12.43 (3.88)		
General psychopathology PANSS	24.78 (5.26)		
Neuroleptic dosage (CPZ equivalent)	293.21 (322.87)		

CPZ: Chlorpromazine equivalent

P: Between-groups comparisons with Student's *t*-tests, except Sex analyzed with non-parametric Mann-Whitney *U* test, $df = 76$

Controlled evaluation of facial affect

This was a forced-choice facial affect labeling of degraded faces (van 't Wout et al., 2004). Photographs of four different actors, two male and two female were used from the set of faces developed and used by Frigerio et al. (2002). Sixty-four trials were presented on a computer screen. The 64 trials consisted of 16 face presentations in each of four conditions: angry, happy, fearful and neutral. In each condition, 8 trials displayed 100% emotional intensity and the other 8 trials displayed 75% emotional intensity as created from a morph. All photographs of the faces were passed through a filter that reduced visual contrast by 30% (van 't Wout et al., 2004). See Figure 1 for an example of the

stimulus used. Subjects were asked to indicate the expression of each face by forced-choice with button press (F1 to F4) or mouse. The labels ('angry', 'happy', etc.) were presented at the bottom of the screen to remind subjects of the different categories. Subjects were asked to work as accurate as possible, no time limit was given.

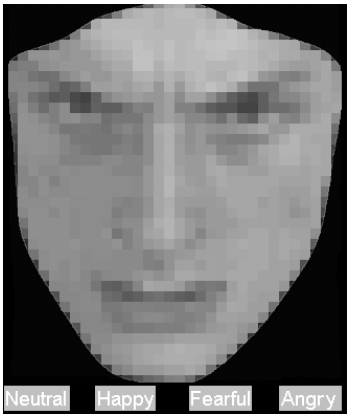

Figure 1. Example of stimulus (angry) used in the controlled evaluation of facial affect task.

Statistical analysis

The data was analyzed with SPSS, version 11.5 (SPSS, 2002). In the automatic facial affect processing task we used a within-subjects design to examine a main effect of Emotion Expression (reaction times and number of errors for happy, fearful, angry, disgusted, neutral faces). Furthermore, we were interested whether there was an interaction between Emotion Expression and Group (patients, controls) to examine if this emotional interference differed for the two groups. In addition, we performed planned post-hoc paired t-tests to further investigate the emotional interference. Behavioral data (number of errors only) of the controlled evaluation of affect task were analyzed by MANOVA including the different emotions, as we were only interested in between group differences. Moreover, error-patterns and the effect of emotional intensity (100% or 75%) were investigated. Correlations between automatic and controlled facial affect processing and the PANSS, duration of illness and neuropsychological task performance were analyzed by Pearson's correlation coefficients. Alpha level was set at 0.05, two-tailed.

Results

Automatic processing of facial affect

Percentage of correct (gender judgments) for emotional faces was 86.5% for the patient sample and 89.7% for the control sample, for non-emotional faces this was 87% and 87.8% for respectively patients and control subjects. These differences were not significant. Both groups had longer mean reaction times (ms) for emotional faces than for neutral faces (Table 2). A within-subject ANOVA demonstrated that there was a main effect of Emotion Expression (neutral, fearful, anger, happy, disgust), $F(4,73)=5.36$, $P=0.001$. Specifically, paired sample *t*-test showed that patients as well as control subjects demonstrated interference of fearful faces compared to neutral faces, respectively $t=2.88$, $df=36$, $P=0.007$ and $t=3.12$, $df=40$ $P=0.003$. This demonstrates that more time was needed to make a gender decision when it concerned emotional faces compared to neutral faces. However, there was no interaction between Emotional Expression and Group (patient or control), $F(4,73)=0.49$, $P=0.74$, demonstrating that the emotional interference in gender judgment was the same in patients and controls. In addition, there was no between group difference on the gender decision task, $F(1,76)=0.62$, $P=0.43$. However, a correlation between reaction times on the gender decision task and general face processing approached significance ($r=0.31$, $p=0.06$), we performed a supplementary interaction Group*Emotion Expression analysis with performance on the Benton Face Recognition test as covariate, $F(4,72)=0.33$, $P=0.85$. With respect to number of errors, there was no interaction between Emotional Expression and Group, $F(4,73)=1.93$, $P=0.12$ or between group difference, $F(1,76)=0.55$, $P=0.46$.

Table 2. Mean reaction times in milliseconds (SD) and number of errors (SD) for the different affective faces in the automatic evaluation of facial affect patients and control subjects.

Facial affect	Schizophrenia patients (N=37)		Control subjects (N=41)	
	RT	Errors	RT	Errors
Neutral faces	184.8 (135)	1.95 (3.1)	169.5 (103)	1.83 (2.5)
Happy faces	191.8 (135)	1.81 (3.3)	175.6 (121)	1.39 (2.5)
Disgusted faces	200.9 (138)	1.22 (3.5)	179.7 (115)	1.24 (2.3)
Angry faces	199.8 (135)	2.19 (3.3)	170.3 (102)	1.22 (1.9)
Fearful faces	216.1 (146)	2.92 (2.6)	190.9 (110)	2.29 (2.5)

Automatic processing of facial affect, psychopathology and neuropsychological performance

There were no significant correlations between the positive, negative or general psychopathology subscale of the PANSS and reaction times or errors on automatic facial affect processing. Duration of illness correlated significantly with reaction times of gender decision in the automatic facial affect processing task, i.e. fearful faces r= 0.37, P=0.03, angry faces r= 0.44, P=0.009, disgusted faces r=0.49, P=0.003, happy faces r= 0.39, P=0.024 and neutral faces r=0.43, P=0.012. There were no significant correlations between reaction times or errors on automatic facial affect processing and estimated verbal IQ (NART) and performance IQ (Raven's Advanced Progressive Matrices).

Controlled evaluation of facial affect

In general, performance on degraded facial affect labeling was well above chance level for each emotion; see Figure 2 for percentage correct for the different emotions. A MANOVA showed a significant multivariate effect of Group (across emotion types), $F(4,73)=2.98$, P=0.03. More specifically, the groups differed in the labeling of fear $F(1,76)=9.06$, P=0.004, i.e. patients made more errors than control subjects. There was no correlation between errors in labeling fear and the chlorpromazine-equivalent, r=0.15, P=0.39. Both patients and control subjects tended to erroneously label fearful faces as 'neutral' (83.38% for patients and 89.14% for control subjects). No differences in error pattern between patients and control subjects were observed, $F(2,75)=1.05$, P=0.35.

We also examined whether patients with schizophrenia benefit to the same extent as healthy control subjects from increased intensity of emotion by including the variable Emotional Intensity (100% or 75% emotional intensity) into the model. Both patients and control subjects were better in the labeling of 100% intensity emotions than of 75% intensity emotions ($F(1,76)=104.78$, $P<0.0001$). Patients did not differ significantly from control subjects, $F(1,76)=0.03$, P=0.87. There were no significant correlations between general face recognition as measured with the Benton Facial Recognition and errors in labeling affective faces.

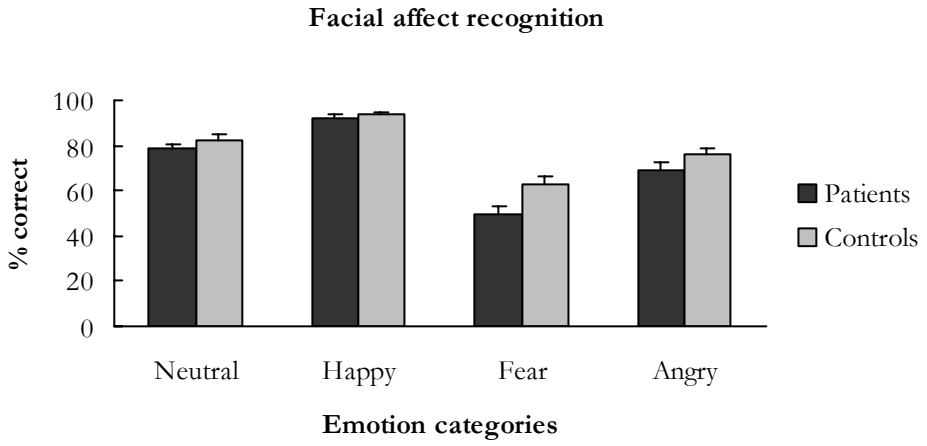

Figure 2. Mean percentage correct and standard error on the degraded facial affect recognition task for the different emotions for patients with schizophrenia and healthy control subjects, *p=0.004 investigated with MANOVA, df=76.

Controlled evaluation of facial affect, psychopathology and neuropsychological performance

Errors in the labeling of fear were positively correlated with severity of negative symptoms as measured with the PANSS, r=0.39, P=0.02. There were no significant correlations between errors in labeling of the other affective faces and severity of positive symptoms or general psychopathology of the PANSS. There were no significant correlations between errors in labeling facial affect and duration of illness. Nor were there any significant correlations between errors in labeling of affective faces and estimated verbal IQ as measured with the NART or performance IQ as measured with the Raven Advanced Progressive Matrices.

Discussion

In the present study we investigated the automatic allocation of attention and controlled evaluation of facial affect in schizophrenia. Regarding the automatic processing of facial affect, results revealed that patients as well as control subjects demonstrated the expected interference of fearful faces, i.e. longer reaction times to make a gender decision in fearful faces compared to neutral faces. Patients with schizophrenia did not differ from control participants on automatic attention allocation to fearful, i.e. threat-related faces, suggesting that the automatic attention towards facial threat is comparable in patients with

schizophrenia and control participants. This is consistent with previous research that demonstrated behaviorally normal automatic processing of emotive information (Gur et al., 2002b; Suslow et al., 2003b; Rossell, 2004). However, compared to affective words (Suslow et al., 2003b; Rossell, 2004) are faces a biological more relevant stimulus schizophrenia might be specifically associated with abnormalities in the automatic processing of facial affect. For instance, Hoschel and Irle (2001) and Suslow et al. (2003a) reported stronger negative emotional priming using negative facial expressions as primes in schizophrenia patients compared to controls. In addition, Suslow et al. (2005) showed in a sequential affective priming task based on faces that schizophrenia patients without affective negative symptoms showed comparable priming effects as controls, whereas patients suffering from flat affect or anhedonia manifested only a prime effect due to negative facial valence. Moreover, we found that patients with longer illness duration were generally slower on the automatic processing of facial affect, which is in line with studies that report that chronic patients with longer illness duration perform worse on cognitive tasks (Kucharska-Pietura et al., 2005).

With respect to controlled evaluation, patients with schizophrenia had particular difficulties in the labeling of fearful faces compared to control subjects. This deficit in labeling faces was not related to chlorpromazine dosage of medication used by patients. Although patients made more errors in the labeling of fear, there was not a deviant bias in error pattern, i.e. both patients and control subjects mistook fear for neutral when making errors. This suggests that normal errors are made to a greater extent. Furthermore, impaired fear labeling was positively correlated with severity of negative symptoms, thereby replicating that schizophrenia patients with more severe negative symptoms are more impaired in facial affect processing (Schneider et al., 1995; Sachs et al., 2004). The finding of problems in the labeling of fear in particular, corroborates studies that reported emotion-specific deficits in the recognition of fearful faces (Gaebel and Wölwer, 1992; Archer et al., 1994; Edwards et al., 2001). Thus, the deficit in the labeling of facial affect even in a highly educated and stable group of patients suggests that impairments in the labeling of facial affect are a core deficit of schizophrenia and could be emotion specific. However, it is important to note that in the facial affect labeling task we used posed facial expressions as stimuli instead of genuine facial expressions. Previous research demonstrated that paranoid patients (most of our patients included are diagnosed with paranoid schizophrenia) appear only disturbed in recognizing posed facial expression (LaRusso, 1978), but at the same time appear more accurate in the recognition of genuine facial expressions (Davis and Gibson, 2000).

Taken together, the present study demonstrates that patients show intact automatic allocation attention to threat-related faces, but disturbed labeling of fearful

faces. This suggests that the emotional stimulus is initially processed by the cognitive and affective system, but patients are unable to categorize these emotional cues. In other words, the intact automatic allocation of attention towards threat-related information, i.e. fearful faces calls for action, but the patient is unable to label or explicitly classify this facial expression of others. Thus, the information may not reach a more elaborate processing stage, involving the verbal labeling of this emotional percept. This could ultimately hamper effective emotion regulation, which involves verbalizing of emotions (Lane et al., 1996; Taylor et al., 1997) and may have important clinical implications. The present results may also have implications for treatment strategies. In particular, emotion training in which verbal labels are explicitly associated with facial emotion cues could have beneficial effects. Given that patients show normal attending towards emotional information, a selective impairment of labeling facial affect might be trainable. For instance, Frommann et al. (2003) and Silver et al. (2004) reported improvements in affect recognition after training in patients schizophrenia. However, emotion training is a complex issue and it is not known whether emotion-training intervention generalize to social behavior to reduce social isolation. Although emotion training may sound beneficial, more knowledge about the precise nature and etiology of emotional disturbances in schizophrenia in needed.

It is important to note that there is an ongoing debate in the literature whether schizophrenia can be associated with a general face-processing deficit (Archer et al., 1992), a facial *affect*-processing deficit (Borod et al., 1993) or an emotion-specific facial affect-processing deficit. This is a difficult issue as emotion-specific deficits might be due to the psychometric property of negative affect, i.e. fearful faces being more difficult to recognize than happy faces (Johnston et al., 2001; Edwards et al., 2002). On the basis of the present results we suggest that our findings support a general labeling problem of facial affect in schizophrenia, which will be most pronounced for fearful faces. However, an emotion specific deficit in processing fearful faces might also exist in schizophrenia and further research including different psychiatric groups is needed to draw conclusion about this issue.

A second aspect of this study that should be mentioned is that due to the different dependent variables of the automatic and controlled facial affect processing tasks, i.e. reaction times versus number of errors, it was not possible to directly compare both tasks statistically. Although this might be a limitation of this study, it is inherent to the tasks used to measure these processes (Knight and Silverstein, 2001). A last limitation might be the included patients of the experimental group. We selected a patient sample that is highly educated and demonstrated low symptomatology to reduce confounding effects of disturbances in cognitive function on the measures of facial affect processing.

As a consequence, the present findings on automatic and controlled facial affect processing might not generalize to other, more typical schizophrenia patient groups.

In sum, our findings demonstrate that patients with schizophrenia do process and attend to threatening information, but have difficulties in the labeling of fearful faces. This is particularly pronounced in patients with high levels of negative symptoms. Future research should establish whether such as pattern of normal or higher attentional sensitivity to threat-related information on an automatic level, but impairments of threat processing on a more controlled level is related to patients' social functioning.

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Chapter 3

Fearful faces in schizophrenia: the relationship between patient characteristics and facial affect recognition

Mascha van 't Wout, Annemiek van Dijke, André Aleman, Roy.P.C. Kessels, Wietske Pijpers, René S. Kahn. Fearful faces in schizophrenia: the relationship between patient characteristics and facial affect recognition.

Submitted for publication.

Abstract

Although schizophrenia has often been associated with deficits in facial affect recognition, it is debated whether the recognition of specific emotions is affected and if these facial affect-processing deficits are related to symptomatology. The purpose of the present study was to explore the specificity of facial affect processing in relation with different patient characteristics. 64 Patients with a DSM-IV diagnosis of schizophrenia were assessed with a computerized test of degraded facial affect recognition. Linear regression analysis showed that in particular negative symptoms and male sex were associated with worse recognition of fearful faces. Furthermore, diagnosis of non-paranoid schizophrenia and later age of onset were associated with worse recognition of neutral faces. Findings are explained in the light of a neuroanatomical dysfunction accounting for both negative symptoms such as reduced emotional expression and social-emotional dysfunction for which males are more vulnerable than females.

Introduction

A growing body of research provides abundant evidence for deficits in emotion recognition in schizophrenia compared to healthy controls (Kohler and Brennan, 2004). Although emotion processing deficits appear to extend to a wide range of different domains, such as recognition of prosody (Edwards et al., 2001) and the processing of symbolic objects (van 't Wout et al., in press), the most striking deficits are reported in the recognition of facial affect (Edwards et al., 2002). Moreover, deficits in affect recognition might contribute to social isolation, hamper independent living and negatively affect professional functioning in schizophrenia (Mueser et al., 1996; Poole et al., 2000; Hooker and Park, 2002; Kee et al., 2003). In addition, Pollice et al. (2002) demonstrated that comprehension of other people's mental states, recent illness onset, good verbal fluency and low levels of schizophrenia symptomatology were among the best predictors of global social functioning.

Even though numerous studies have reported facial affect recognition deficits in schizophrenia, research resulted in mixed findings. Moreover, it is commonly agreed upon that schizophrenia is a heterogeneous disease. Hence, differences in symptomatology and other patient characteristics may account for the diversity of findings on facial affect processing deficits. This is illustrated by research demonstrating a relationship between poor performance on emotion recognition and schizophrenia symptoms, in particular negative symptoms (Gaebel and Wölwer, 1992; Schneider et al., 1995; Kohler et al., 2000a). In addition, other studies have demonstrated differences in emotion processing between acute and chronic patients (Penn et al., 2000), paranoid and non-paranoid patients (Kline et al., 1992; Lewis and Garver, 1995; Phillips et al., 1999; Davis and Gibson, 2000) and male and female patients (Scholten et al., 2005). In turn, others did not find an association between characteristics of schizophrenia illness and emotion processing (Salem et al., 1996; Wölwer et al., 1996; Addington and Addington, 1998; Silver and Shlomo, 2001).

Despite the above-mentioned research on the relationship between clinical variables and facial affect processing, there are no studies that investigate the role of different patient characteristics simultaneously on facial affect processing. However, different patient characteristics may influence one another resulting in more extreme dysfunction. For instance, Gur et al. (1996) demonstrated specific interactions between age, sex and symptoms in schizophrenia, i.e. although aging was associated with increased severity of negative symptoms, women showed a reduction in negative symptoms. Taken together, examining the influence of illness characteristics on emotion processing is important, since it can help us to gain more insight in the precise nature of the emotion

recognition deficit and give consensus about (clinical) aspects that contribute to facial affect processing deficits.

The aim of the present study was to investigate whether particular patient characteristics could be associated with recognition of specific affective faces. Patient characteristics that were included are positive and negative symptoms and general psychopathology as measured with the Postive and Negative Syndrome Scale (Kay et al., 1987), illness duration, age of illness onset, type of mediation, schizophrenia diagnostic subtype and sex. We hypothesized that recognition performance of negative emotional expressions is related to negative symptoms, male sex and non-paranoid schizophrenia. With respect to previous research that investigated the relationship between facial affect processing and symptoms, this study is the first to examine different patient characteristics simultaneously in one model as predictors of facial affect recognition. Furthermore, this is the first study that investigates whether specific emotional expressions are particular related to patient characteristics.

Methods

Participants

64 Patients with schizophrenia (49 men, 15 women) participated in the present study. 44 Patients were recruited from the University Medical Center Utrecht and 20 patients were recruited from the DeltaBouman Hospital Rotterdam. Most of the patients were in remission at the time of the study and half of the patients were inpatients. Diagnosis of schizophrenia was confirmed using the Comprehensive Assessment Symptoms and History (CASH) (Andreasen et al., 1992). All patients were clinically stable and 60 patients received medication at time of the study. Symptoms were rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) independently by two trained raters. Table 1 lists the demographic and clinical characteristics of the patient sample. Exclusion criteria were neurological conditions affecting the central nervous system, a history of head injury with loss of consciousness, recent history of substance abuse and mental retardation. The local ethics committee approved the study and all subjects provided written informed consent after the procedure had been fully explained, according to the Declaration of Helsinki.

Table 1. Demographic and clinical characteristic of 57 patients with schizophrenia.

Characteristics	Total mean (SD), range
Age (in years)*	32.28 (9.06), range: 19-57
Sex (men/women)	49/15
Positive PANSS	13.50 (5.89), range: 7-34
Negative PANSS	13.28 (4.74), range: 7-34
General psychopathology PANSS	27.22 (6.87), range: 17-48
Schizophrenia subtype (paranoid/non-paranoid)	39/25
Duration of illness (in years)	9.72 (8.14), range: 1-38
Onset of illness (age in years)	22.56 (5.81), range: 16-42
Medication (number of patients)	
Antipsychotic medication	Clozapine (23); Risperidone (9); Olanzapine (6); Quetiapine (2); Sulpiride (1); Bromperidole (1); Pimozide (2); chloorprotixeen (1); zuclopentixol (1)
Antidepressant medication	Paroxetine (2); Citalopram (2)
Mood stabilizers	Lithium (1); Valproate (2)
Benzodiazepines	Oxazepam (3); Temazepam (1); Lorazepam (3)

* Due to multicollinearity with onset of illness (age in years) this variable was not included in the linear regression model.

Degraded facial affect recognition

This is a forced-choice facial affect labeling task of degraded faces (van 't Wout et al., 2004). Photographs of four different actors, two male and two female were used from the set of faces developed and used by Frigerio et al. (2002). 64 Trials were presented on a computer screen and consisted of 16 face presentations in each of four conditions: angry, happy, fearful and neutral. In each condition, 8 trials displayed 100% emotional intensity and the other 8 trials displayed 75% emotional intensity as created from a morph. All photographs of the faces were passed through a filter that reduced visual contrast by 30% (van 't Wout et al., 2004). See Figure 1 for an example of the stimulus used. Subjects were asked to indicate the expression of each face by forced-choice with button press (F1 to F4) or by mouse. The labels ('angry', 'sad', etc.) were also presented at the bottom of the screen to remind subjects of the different categories. Subjects were asked to work as accurate as possible, no time limit was given.

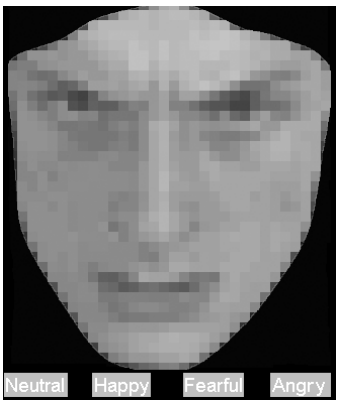

Figure 1. Image display of the degraded facial affect recognition task (angry).

Results

Performance on degraded facial affect recognition

92.0% of faces were correctly identified as happy, 78.4% of neutral faces were correctly identified as neutral, 69.3% was correctly identified as angry and 49.8% of fearful faces were correctly identified as such. A GLM repeated measures of within-subject contrast with the different emotions as within-subjects variables revealed that performance for the different affective facial expressions was significant, $F(3,61)=106.35$, $p<0.0001$, demonstrating that patients made the most errors in the recognition of fearful faces.

Relationship between clinical variables and degraded facial affect recognition

Linear regression analyses with number of errors on the different emotions as dependent variables and clinical variables as independent associates were performed. Schizophrenia symptom dimensions (positive, negative and general psychopathology score) as measured with the PANSS, illness onset (in years), illness duration (in years), medication (type: antipsychotic, antidepressant, other or combinations), schizophrenia subtype (paranoid:non-paranoid) and sex (male:female) were included as independent variables. See Table 2 for R^2, standardized beta for the different models.

Patients with more negative symptoms made more errors in recognizing fearful faces ($p=0.047$) and male patients made more errors in the recognition of fearful faces than female patients ($p=0.027$). Severity of negative symptoms is related to fewer errors in recognizing neutral faces ($p=0.01$). Moreover, non-paranoid patients made more errors in the recognition of neutral faces than paranoid patients ($p=0.039$). There was no effect of the associates on the ability to recognize happy faces or angry faces.

Table 2. R^2 and standardized beta (95% CI) for each model, i.e. errors in emotion recognition.

Predictor	Neutral R^2=0.37	Fearful R^2=0.29	Angry R^2=0.08	Happy R^2=0.09
Positive symptoms (PANSS)	0.33 (-0.05-0.39)	-0.26 (-0.35-0.08)	0.25 (-0.13-0.38)	0.42 (-0.02-0.26)
Negative symptoms (PANSS)	**-0.34** (-0.43--0.02)	**0.36** (0.02-0.43)	-0.11 (-0.32-0.17)	0.01 (-0.13-0.14)
General psychopathology (PANSS)	0.15 (-0.15-0.28)	0.11 (-0.17-0.26)	-0.05 (-0.27-0.23)	-0.47 (-0.25-0.02)
Illness duration (years)	-0.05 (-0.12-0.08)	0.23 (-0.02-0.19)	-0.03 (-0.13-0.11)	0.09 (-0.05-0.08)
Age of onset (years)	**0.33** (0.04-0.32)	0.19 (-0.04-0.23)	0.04 (-0.14-0.19)	0.08 (-0.06-0.11)
Diagnosis (paranoid: non-paranoid)	**-0.29** (-3.52--0.20)	0.11 (-0.99-2.28)	-0.17 (-3.04-0.85)	-0.19 (-1.70-0.39)
Medication	0.06 (-0.39-0.69)	-0.11 (-0.79-0.29)	-0.05 (-0.76-0.53)	-0.04 (-0.40-0.30)
Sex (male: female)	0.16 (-0.61-3.06)	**0.29** (0.18-3.81)	0.14 (-1.12-3.19)	0.06 (-0.94-1.39)

Bold= $p<0.05$

Discussion

The aim of the present study was to investigate whether particular patient characteristic are associated with the recognition of specific facial expressions in patients with schizophrenia. Our findings show that patients with more negative symptoms made more errors in recognizing fearful faces, but not in recognizing angry and happy faces. This result of a specific association between negative symptoms and fear recognition extends previous research demonstrating a relationship between severity of negative symptoms and poorer facial affect recognition as a whole (Schneider et al., 1995; Mandal et al., 1999; Kohler et al., 2000a; Sachs et al., 2004; Martin et al., 2005). Furthermore, our results showed that men with schizophrenia perform worse in the recognition of fearful faces compared to women with schizophrenia. This corroborates previous studies demonstrating that women typically outperform men in the recognition of emotions in general (Erwin et al., 1992; Thayer and Johnsen, 2000; Montagne et al., 2005) and in negative emotion in specific (McClure, 2000). Indeed, a recent study demonstrated that

men with schizophrenia compared to control men and women have difficulties in the recognition of negative facial affect (Scholten et al., 2005).

The findings that patients with more negative symptoms made more errors in recognizing fearful faces as well as the finding that men with schizophrenia perform worse in the recognition of fearful faces can be explained by abnormalities in brain areas important for emotion processing in schizophrenia. The amygdala and other structures, such as the (medial) prefrontal cortex, insula and cingulate cortex are important for emotion processing (Phan et al., 2002). However, the amygdala seems to be especially involved in the processing of fearful faces (Morris et al., 1996). In schizophrenia, neuroimaging studies demonstrated that both the amygdala and medial prefrontal cortex are less active during facial affect processing and these abnormalities are related to emotion processing (Takahashi et al., 2004). Moreover, Anderson et al. (2002) reported that reductions in gray matter in the temporal lobe were specifically observed in patients with predominately negative symptoms. Indeed, deficits in fear recognition reported in schizophrenia parallels findings in amygdala damaged patients (Adolphs et al., 1994) and negative symptoms, such as a flattening of affect have also been demonstrated in amygdala damaged patients (Scoville et al., 1953; Lee et al., 1988). Volume reductions of the amygdala in schizophrenia might result in a disturbance of the normal sex specific orbitofrontal to amygdala volume ratio (Gur et al., 2004), which explains normal sex differences in emotion processing (Gur et al., 2002a). This disturbed orbitofrontal to amygdala volume ratio is also related to negative symptoms in schizophrenia (Gur et al., 2004). These findings suggest that negative symptoms like reduced emotional expression and social-emotional dysfunction may share a common neuroanatomical basis for which males are more vulnerable than females. Recent neurobiological models of emotion abnormalities in schizophrenia indeed suggest that a specific lesion of the amygdala might lead to reduced signals to the prefrontal cortex, resulting in a loss of active emotion response, i.e. perception and expression of emotions (Grossberg, 2000; Aleman and Kahn, 2005).

Finally, we observed that non-paranoid patients are worse in the recognition of neutral faces compared to paranoid patients. It should be noted however that neutral faces could appear cold (Ekman and Rosenberg, 1997) and for this reason mild happiness is often used in facial affect recognition paradigms that include neutral as a condition (Morris et al., 1996; Phillips et al., 1997; Phillips et al., 1999). Nonetheless, our findings are in line with previous research demonstrating worse performance in non-paranoid patients compared to paranoid patients on facial affect processing (Kline et al., 1992; Lewis and Garver, 1995; Phillips et al., 1999). Moreover, Phillips et al. (1999) demonstrated that non-paranoid patients compared to paranoid patient failed to activate brain areas that are

normally associated with the perception of emotions. In addition, patients with a later age of illness onset were worse in the recognition of neutral faces. Speculatively, these patients had a longer prodromal phase or duration of untreated psychosis, which has been related to social and emotional disturbances (Hafner et al., 1995; Gourzis et al., 2002). The finding of fewer errors in recognizing neutral faces by patients with more negative symptoms might be due to a response bias of attributing no emotions to faces and in that way also more often correctly identifying neutral.

From a clinical viewpoint the present study can be regarded as an attempt to specify a group of patients that could have the most benefit from emotion recognition training. Emotion training appears to have beneficial effects in schizophrenia (Frommann et al., 2003); (Silver et al., 2004). However, training programs are costly and probably not all patients will benefit from it. From the present study it can be concluded that especially male, non-paranoid patients with predominately negative symptoms and a later illness onset are worse in the recognition of specific emotions. Thus, emotion training in this specific group of patients could lead to the most positive results. However, our patient sample is not severely ill as is reflected by low PANSS scores. As a consequence, the relationship between negative symptoms and fear recognition and the lack of associations with other symptoms in this group might not generalize to other, more typical schizophrenia groups.

Overall, this is the first study that included different patient characteristics simultaneously as predictors for facial affect recognition performance in one model. Results demonstrated that in particular severity of negative symptoms and being male are associated with worse recognition of fearful faces. In addition, the diagnosis of non-paranoid schizophrenia and later illness onset are associated with worse recognition of neutral faces. These findings suggest that negative symptoms like reduced emotional expression and social-emotional dysfunction may share a common neuroanatomical dysfunction for which males are more vulnerable than females.

Chapter 4

Object-location memory in schizophrenia: interference of symbolic threatening content

Mascha van 't Wout, André Aleman, Roy P.C. Kessels, René S. Kahn. Object-location memory in schizophrenia: interference of symbolic threatening content.

Cognitive Neuropsychiatry; in press.

Abstract

Monitoring environmental stimuli for their emotional relevance is inherently associated with spatial processing. In schizophrenia, deficits in spatial working memory on the one hand, and abnormal emotion processing on the other hand, have been documented, but these have not been related to one another. In the present study, we investigated whether a specific aspect of spatial memory, i.e. object-location memory, is impaired in patients with schizophrenia. Moreover, we hypothesized that symbolic threatening content of the objects would interfere with spatial processing in patients with schizophrenia but not in healthy controls. Spatial memory for symbolic pictorial stimuli was assessed in 40 patients with schizophrenia compared to 41 healthy matched control participants using an object relocation task. Patients with schizophrenia performed worse in relocating objects, independent of overall intellectual ability. More specifically, patients were particularly worse in the relocation of objects with a symbolic threatening content. These results suggest that a threatening semantic emotional content of schematic stimuli can interfere with spatial processing in schizophrenia. We hypothesize that a disproportional influence of the amygdala on other brain areas, such as the hippocampus, might underlie this specific emotional interference.

Introduction

In schizophrenia, profound deficits in cognitive functioning have been consistently documented (Heinrichs and Zakzanis, 1998; Aleman et al., 1999), which cannot be explained by medication effects (Aleman and de Haan, 2000). Additionally, impairments in spatial working memory have also been reported in schizophrenia (Park and Holzman, 1992; Carter et al., 1996; Fleming et al., 1997; Keefe et al., 1997; McGrath et al., 2001; Cameron et al., 2003). Park and Holzman (1992) demonstrated that patients with schizophrenia show deficits on an oculomotor and haptic spatial delayed-response task independent of non-spatial working memory and sensory control tasks. This suggests that patients with schizophrenia are less able to maintain visuospatial representations. Consistent with this finding, Fleming et al. (1997) also reported marked deficits in spatial working memory in schizophrenia in the presence of intact perceptual abilities.

A specific aspect of spatial memory concerns object location. Object-location memory concerns knowledge of the exact position of objects and their relative relationship with each other (Kessels et al., 2001). Although spatial working memory has been investigated in schizophrenia, object-location memory has not. The investigation of location-memory is of value as it enables identification, classification, and location of items used in everyday life (cf. Milner et al., 1997). Importantly, deficits in location-memory may contribute to the difficulties with activities of daily living observed in schizophrenia.

With regard to the neural basis of spatial memory and object-location memory, the temporal lobes have been shown to play a crucial role. More specifically, the hippocampal formation is important for memory, in particular, the encoding of information, and receives input from the parahippocampal region. Intact functioning of the parahippocampal region is crucial for spatial memory (Bohbot et al., 1998; Kessels et al., 2001). Interestingly, a reduction in volume in the (para)hippocampal region has been reported in schizophrenia (Wright et al., 2000; Seidman et al., 2003), which might account for the deficits in spatial memory observed in schizophrenia.

In addition to cognitive dysfunction, emotional dysfunction is increasingly recognized as a core feature of schizophrenia (Lane, 2003). This emotional dysfunction includes disturbances in the expression of emotions and perception of affective information and may contribute to social isolation, hamper independent living and negatively affect professional functioning and community functioning (Poole et al., 2000; Hooker and Park, 2002; Kee et al., 2003). More specifically, behavioral research has shown deficits in facial affect recognition (Schneider et al., 1995; Mueser et al., 1996; Wölwer et al., 1996; Addington and Addington, 1998; Habel et al., 2000; Kohler et al., 2000a; Penn et al., 2000), particularly in the processing of threat-related faces and potentially threatening

social scenes (Phillips et al., 2000; Green et al., 2003). It is important to note that affective disturbance in schizophrenia does not only pertain to reduced levels of emotional expression, but may also concern increased levels of emotional arousal, e.g., raised anxiety levels (Kring and Neale, 1996; Delespaul et al., 2002).

In recent years, neural models of schizophrenia have been advanced that hypothesize an imbalance between the amygdala and other brain areas (Grace, 2000; Grossberg, 2000). Specifically, Grace (2000) hypothesized an increased influence of the amygdala on cortical areas resulting from a disruption of cortical regulation of subcortical systems in schizophrenia. As the emotional relevance of information is processed through the amygdala (Morris et al., 1996), such overactivation of the amygdala could lead to the signalling of actual threat where there is none. According to the model proposed by Grace (2000), in these circumstances, the amygdala overrides hippocampal circuits, thus inhibiting the processing of historical and contextual information, and giving priority to emotional processing. A behavioral prediction might be that presentation of threat-related information might disrupt performance on a spatial task, relative to neutral information. Because the monitoring of environmental stimuli for their emotional relevance is inherently associated with spatial processing, the study of spatial memory for emotional stimuli in patients with schizophrenia might indirectly test this hypothesis.

To the best of our knowledge object-location memory and, more specifically the influence of affective information on object-location memory in schizophrenia have not been investigated yet. The aim of the present study was twofold. First, we tested the hypothesis that patients with schizophrenia show a specific deficit in their memory for locations of objects after controlling for overall intellectual ability. Second, we tested the hypothesis that patients with schizophrenia show a threat-related interference in object location memory. We hypothesized that there will be no threat-related interference in healthy comparison participants as the stimuli are highly symbolic and non-arousing and will therefore not serve as a distractor in healthy participants.

Object-location memory was measured with the emotional object relocation task, an adapted version of Object Relocation (Kessels et al., 1999). Participants had to remember the location of schematic drawings of everyday objects (icons) presented on a computer screen. The stimuli concerned threatening, neutral, positive and obsessive-compulsive disorder-related symbolic information (the latter three were considered as non-threatening). Subsequently, participants were asked to relocate these icons in an empty frame as accurately as possible.

Methods

Participants

Forty patients with a diagnosis of schizophrenia were recruited from the University Medical Center Utrecht. All patients fulfilled the DSM-IV criteria for schizophrenia as confirmed with the Comprehensive Assessment of Symptoms and History, CASH (Andreasen et al., 1992). Patients were clinically stable and 37 of the patients received medication at time of the study. Of patients, 24 received only atypical antipsychotics (clozapine, risperidone, olanzapine and quetiapine) and 13 patients also received other medication, such as classic antipsychotics, antidepressant, mood stabilisators and benzodiazepines. Symptoms were rated with the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987). The clinical characteristics of the patient sample are listed in Table 1.

Forty-one non-psychiatric healthy control participants were drawn from the general population by advertisements in local newspapers and through an institute for volunteers. Inclusion criteria for both patients and healthy control participants were age between 18-65 years and physically healthy. Exclusion criteria for all participants were neurological conditions or history of head injury with loss of consciousness, recent history of alcohol and substance abuse and mental retardation. None of the control participants had a history of psychiatric illness confirmed with the Mini International Neuropsychiatric Interview Plus, MINI (Sheehan et al., 1998). Control participants were recruited to match the patient sample with respect to age, gender, handedness, and educational level. The demographic characteristics of the patient and healthy control sample are listed in Table 2. The study was approved by the local ethics committee (METC) and all participants provided written informed consent after the procedure had been fully explained and prior to testing.

Intellectual ability

Two tests were used to index intellectual function. The first test was the Dutch translation of the National Adult Reading Test (NART) (Nelson, 1982; Schmand et al., 1991). The NART provides an estimate of verbal IQ based on the high correlation between reading ability, specifically of irregular words, with intelligence in the normal population. The test is composed of a list of 50 irregular words (i.e., pronunciation does not follow the normal phonetic rules) printed in order of increasing difficulty. Participants are required to read these words aloud, and, on the basis of the number of errors made in pronunciation a reliable estimate of WAIS-R IQ can be calculated (Willshire et al., 1991).

In addition, we examined with the Raven's Advanced Progressive Matrices a reliable and valid measure of nonverbal reasoning (Lezak, 1995). This test consists of 12

pictures of matrices (i.e. related patterns), each of which is a figural design with a part removed. Participants must choose the correct missing past from eight options. On the basis of the number of errors made by participants an estimate of performance IQ can be calculated.

Table 1. Clinical characteristics of 40 patients with schizophrenia.

Clinical charactersitic	Mean (S.D.)
Duration of illness in years	8.14 (6.6.7)
Age of onset in years	23.09 (6.22)
Positive scale PANSS	11.48 (3.58)
Negative scale PANSS	12.58 (3.71)
General psychopathology PANSS	25.0 (5.29)
Medication (number of patients)	
Antipsychotics	Clozapine (17); Risperidone (5); Olanzapine (10); Quetiapine (2); Sulpiride (1); Bromperidol (1); Pimozide (1)
Antidepressants	Paroxetine (2); Fluoxetine (2); Citalopram (3)
Mood stabilisators	Lithium (1); Valproate (1)
Benzodiazepines	Oxazepam (3); Temazepam (1); Alprazolam (1)

Table 2. Demographic characteristics of 40 patients with schizophrenia and 41 healthy control participants.

	Schizophrenia patients	Control subjects	
	Mean (SD)	Mean (SD)	P
Age (years)	31.53 (7.71)	31.41 (9.17)	0.95
Gender (male/female)	26/14	26/15	0.88
Education in years	15.0 (2.81)	14.73 (2.58)	0.68
Handedness (right/left/ambidextrous)	37/2/1	37/3/1	0.77

Object Relocation

The emotional memory task is an adapted version from Kessels et al. (1999) and is a measure of spatial memory for affective objects. The test consisted of three trials and in each trial, 8 different icons of everyday objects were presented. The icons were categorised into four affective types: neutral (e.g., tree, house), threatening (e.g., skull, danger signal), obsessive-compulsive disorder (OCD)-related (e.g., toilet, towels) and positive (e.g., smiley). For the main analysis, threatening icons were contrasted with the other icons (non-threatening). The obsessive-compulsive disorder-related icons were chosen to serve as control stimuli as they have a threatening emotional meaning for a different psychiatric disorder, namely obsessive-compulsive disorder (OCD) (Wilhelm et al., 1996). However, these icons are not expected to be threatening to schizophrenia patients. The icons for the emotional memory task were selected on the basis of valence ratings of 20 persons with formal psychological training and 2 ratings from experienced clinicians. Only icons with unanimous ratings were included as stimuli.

In each trail the icons were displayed for 12 seconds in different locations within a 180 x 180 mm frame on a computer screen. Participants were placed before the computer screen at approximately 90 cm. After 12 seconds encoding, the frame would re-appear empty with the eight icons presented in a horizontal line above the frame, see Figure 1. Participants had to relocate the icons to their original position by using the touch-sensitive computer monitor. No time limit was present during the relocation of the icons and participants were allowed to make corrections. After their confirmation of the relocation, the next trail was presented. Participants were told to try to relocate the icons to the original position as accurately as possible. The absolute deviation in millimeters between the original and relocated position was computed for each of the stimulus types. The procedure for this is explained in more detail in Kessels et al. (1999).

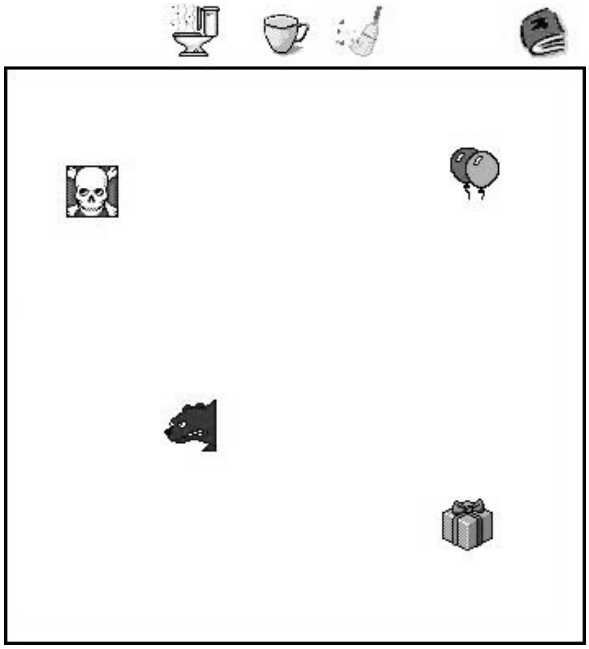

Figure 1. Example of an image display in Object Relocation (actual size 18x18 cm).

Results

Intellectual ability

On the Dutch translation of the NART patients and control participants had a mean estimated IQ of 105.08 (SD 8.89) and 107.39 (SD 9.51), respectively. The calculated IQ of Raven's Advanced Progressive Matrices was 98.63 (SD 17.22) for patients and 107.60 (SD 12.85) for control participants. T-tests of these measures revealed a significant difference between the groups on estimated IQ by the Raven's Advanced Progressive Matrices ($t=2.60$, $p=0.01$), but no significant group difference on the estimated IQ by the NART ($t=-1.11$, $p=0.27$).

Object relocation

A 2 x 4 within-subjects ANOVA with diagnosis (patient or control participant) as grouping variable and the different affective object types (neutral, positive, threatening and OCD-related) as within subjects variables, demonstrated that overall patients with schizophrenia were less accurate in relocating the icons than control participants, $F(1,79)=15.61$, $MSE=3882.99$, $p<0.0001$. Additionally, patients and control participants differed significantly on intellectual ability as measured with the Raven Advanced

Progressive Matrices, in which patients made more errors. However, the difference in object-location memory remained significant when performance on the Raven Advanced Progressive Matrices was entered as a covariate, F(1,75)=9.78, MSE=3781.09, p=0.003.

With regard to the affective content, the main analysis concerned threatening versus non-threatening icons (which included neutral, positive and OCD-related icons). A 2 x 2 within-subejcts ANOVA with Group (patient versus control participant) and Threat (accuracy of threatening versus non-threatening objects) showed that patients performed significantly worse on the relocation of threatening objects compared to non-threating objects, (F(1,79)=3.88, MSE=600.09, p=0.05), see Figure 2. 2 x 2 within-subjects ANOVAs of the individual affective stimuli categories demonstrated no differences between the two groups in accuracy of neutral objects versus objects with a threatening (F(1,79)=2.63, MSE=743.48, p=0.11), OCD-related (F(1,79)=0.10, MSE=1410.21, p=0.92) or positive (F(1,79)=0.19, MSE=1999.92, p=0.66) content, see Figure 3.

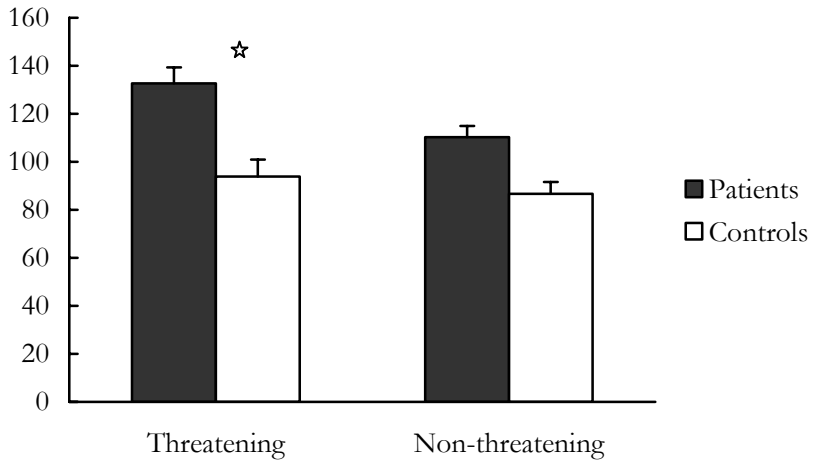

Figure 2. Mean deviations (mm) of relocated objects in the object relocation task on threatening and non-threatening objects for patients with schizophrenia and healthy control participants, *p=0.05.

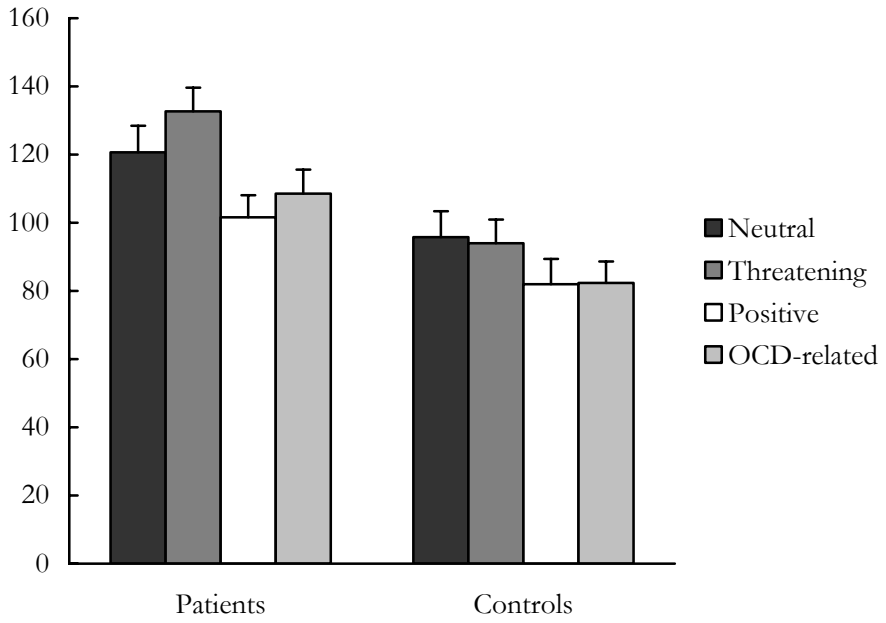

Figure 3. Mean deviation (mm) for relocated objects compared with original position for the different affective objects for patients and control participants.

Discussion

The aim of the present study was to investigate object-location memory in schizophrenia. More specifically, we also investigated whether a symbolic threatening content would interfere with object-location memory in schizophrenia. As hypothesized, patients with schizophrenia performed worse in relocating everyday objects into space, independent of overall intellectual ability. This is in accordance with research that demonstrated spatial working memory deficits in schizophrenia (Park and Holzman, 1992; Keefe et al., 1995; Fleming et al., 1997; Burglen et al., 2004; Leiderman and Strejilevich, 2004).

With regard to the neural basis of spatial memory, involvement of a network comprising the hippocampus, dorsolateral prefrontal and parietal cortex has been demonstrated (McCarthy et al., 1994; McCarthy et al., 1996; Geffen et al., 1997; Moulden et al., 1997; Belger et al., 1998; Carlson et al., 1998; Rolls, 2000). In addition, the importance of the hippocampus in object location memory has been established (Rolls, 2000; Kessels et al., 2001). Research reported that deficits in spatial associate learning were associated with functioning in the frontal lobes and medial temporal regions, including the

hippocampus in schizophrenia (Gruzelier et al., 1988). In a more speculative manner, the present result of a specific deficit in object-location memory in schizophrenia might be consistent with the large body of evidence indicating structural and functional abnormalities of the prefrontal cortex and hippocampus in schizophrenia (Lawrie and Abukmeil, 1998; Wright et al., 2000; Crespo-Facorro et al., 2001; Shenton et al., 2001).

To investigate whether there was more interference in spatial memory due to negative rather than positive or neutral content in schizophrenia, we compared relocation accuracy of threatening objects with non-threatening objects. Our results showed that patients were disproportionally worse in the relocation of threatening objects, in contrast to the healthy control group. These results suggest that schizophrenia can be associated with an increased interference in spatial short-term memory for highly symbolic threatening stimuli as used in the object relocation task. A related issue that deserves attention is the perceived intensity of threat as schizophrenia patients might have experienced these objects as more threatening. Although we do not have these ratings of patients or control subjects, implicit processes of relocating threatening objects as used here are not necessarily accompanied by an increase in overt threat perception. For instance, in anxiety disorder, individuals are usually unaware that they process certain information perceived as threatening in a highly automatic way, therefore making it difficult to control the anxiety (Beck and Clark, 1997).

The increased interference of threatening stimuli in spatial cognition in schizophrenia can be explained by Grace (2000), who hypothesized that a disruption of cortical regulation of subcortical systems may eventually lead to an exaggerated influence of the amygdala on the other brain areas, such as prefrontal cortex and hippocampus. More specifically, the neural model proposed by Grace (2000) assumes that under normal conditions people perform tasks based on past experiences or current context, which is mediated through the hippocampus. However, when a threatening object appears, the brain has to signal whether this potentially threatening object requires action. In such circumstances, the amygdala has an overriding influence over the hippocampus in order to trigger flight behavior. In schizophrenia, the amygdala might become hyperactive due to an imbalance in dopamine systems. Eventually, the processing of the affective connotation of a stimulus (amygdala) may acquire excessive priority, at the cost of contextual or historical information (hippocampus) or a motor plan (prefrontal cortex) (Grace, 2000; 2003). Indeed, schizophrenia has been associated with abnormalities in prefrontal-temporal circuits (Egan and Weinberger, 1997; Shenton et al., 2001; Torrey, 2002), which includes brain areas that are crucial for cognition and emotion. Therefore, the influence of emotion on cognition might be disturbed in schizophrenia.

A limitation of the present study is that our design does not differentiate between problems in either the encoding or the retrieval of threat-related information. Object identification at encoding has been shown to affect object location memory significantly (Kohler et al., 2001) and spatial processing deficits in schizophrenia have also been argued to arise during encoding (Leiderman and Strejilevich, 2004). To investigate whether encoding or retrieval is specifically disturbed in schizophrenia a memory task using both free recall and recognition should be administered. In case of deficits in encoding, patients will demonstrate problems both during recall and recognition. Deficits in retrieval on the other hand will only result in problems during recall with intact recognition of the objects. Although the aim of the present study was to investigate the influence of symbolic threat, future research might investigate object location memory with the use of affective faces (Van Honk et al., 2003; Putman et al., 2004). This will provide insight in the presence of a threat-related bias in object relocation memory when it concerns biologically more relevant stimuli. Additionally, the use of neuroimaging techniques can also further elucidate the neural basis of dysfunctional spatial memory for emotional information in schizophrenia.

To summarize, patients with schizophrenia revealed deficits in object-location memory, independent of overall intellectual ability. This finding corroborates and extends research that demonstrated spatial working memory deficits in schizophrenia (Gruzelier et al., 1988; Park and Holzman, 1992; Fleming et al., 1997) and implicates dysfunctions of prefrontal-hippocampal circuits in schizophrenia. With regard to the interaction between emotion and cognition, schizophrenia can be associated with an increased influence of threatening content on spatial cognition, e.g. object-location memory. We hypothesize that this result might be due to a dysregulation of prefrontal-amygdala circuits in schizophrenia.

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Chapter 5

Threatening faces: impaired autonomic response, but intact cognitive evaluation in schizophrenia

Mascha van 't Wout, André Aleman, René S. Kahn. Threatening faces: impaired autonomic response, but intact cognitive evaluation in schizophrenia.

Manuscript in preparation.

Abstract

The processing of emotional information and in particular affective faces is disturbed in schizophrenia. Still, knowledge of physiological responsivity to affective faces is limited. The aim of this study was to investigate the physiological reactions of schizophrenic patients to affective faces. 27 Patients with schizophrenia were compared with 34 healthy matched controls on skin conductance and subjective evaluations of valence and arousal, while watching happy, angry and fearful faces. Results showed that patients with schizophrenia were specifically impaired to respond autonomically to threat-related faces, i.e. angry and fearful faces in spite of normal cognitive evaluation of valence and arousal of these faces. In addition, autonomic arousal is intact for happy faces, but happy faces are rated less positive and more arousing by patients, which is more pronounced in patients with negative symptoms. These findings support theories that propose a partly distinct, but complementary role in the cognitive evaluation and the autonomic processing of faces. Moreover, we suggest that in schizophrenia especially the autonomic responses to threatening faces are disturbed.

Introduction

There is abundant evidence of emotional disturbances in schizophrenia, such as the expression and perception of emotions. In particular the recognition of negative facial affect seems disturbed (Mandal et al., 1998; Edwards et al., 2002; Kohler and Brennan, 2004). Furthermore, previous studies reported that especially patients with negative symptoms seem poor in the processing of facial affect (Schneider et al., 1995; Kohler et al., 2000a; Baudouin et al., 2002). Taken together, it has been suggested that specific neural pathways subserving emotion processing are affected, and that these pathways might also be implicated in specific symptoms in schizophrenia (Phillips et al., 2003b).

In contrast to this growing body of research demonstrating deficits in the perception and expression of facial affect in schizophrenia, the subjective experience of emotions seems impaired to a lesser extent (Myin-Germeys et al., 2000; Aghevli et al., 2003). This suggests a distinction between deficient expression and perception of emotions and intact experience of emotions. However, emotion processing comprises at least three components: expressive, experiential and physiological (e.g. Lang, 1984). These physiological responses accompanying the processing of affective information can be investigated by measuring skin conductance activity, i.e. sweating on the hand palms. This so-called "emotional sweating" results in an increased skin conductance and is related to activity of centers in the brain important for emotion processing such as the amygdala and prefrontal cortex (Bouscein, 1992). Hence, skin conductance activity is regarded as an indicator of activation of the emotion-processing network and is thought to reflect emotional arousal.

Research about these physiological responses on affective information is however, relatively sparse in schizophrenia, since most studies on skin conductance activity in schizophrenia focused on innocuous stimuli, such as auditory tones. However, previous research measuring skin conductance while watching affective pictures (Hempel et al., 2005) or film clips (Joseph et al., 1992) found no differences between patients with schizophrenia and controls. However, Kring and Neale (1996) reported increased skin conductance responses to film clips in patients compared with controls. In contrast to affective pictures, faces are highly biologically relevant stimuli, as they convey important information about the status and intentions of other people. Williams et al. (2004) demonstrated a higher skin conductance response to neutral and fearful facial expression in schizophrenia compared to controls. However, this study only included fearful and neutral faces, but not angry or happy faces. In addition, autonomic responses and subjective ratings on arousal and valence were not correlated with schizophrenia symptoms. Abnormalities in the ability to respond autonomically and subjectively to *specific* affective facial expressions in schizophrenia might provide insight into the precise

emotional disturbances and gives clues about the neural correlates that are affected in schizophrenia.

The aim of the present study was to investigate autonomic responses measured with skin conductance activity to faces displaying a happy, angry or fearful expression in schizophrenia compared to control participants. Moreover, subjective ratings of valence and arousal of the different facial expressions were measured. In addition, skin conductance activity and subjective ratings of valence and arousal are related to schizophrenia symptomatology. We hypothesize that patients with schizophrenia compared to control subjects show abnormalities in skin conductance response to negative facial expression, i.e. fearful and angry faces. However, we expect that the subjective experience, i.e. ratings of valence and arousal are comparable to control levels. Furthermore, we expect that patients with more negative symptoms especially show abnormal skin conductance activity in response to facial expressions.

Methods

Participants

36 Patients with schizophrenia (24 men, 12 women) from the University Medical Center Utrecht participated in the study. 34 Non-psychiatric control participants (18 men, 16 women) were drawn from the general population by advertisements in local newspapers to match the patient sample on sex (Mann-Whitney $U=528.0$, $Z=-1.16$, $p=0.24$), age ($t=1.63$, $p=0.11$) and education level of the parents ($t=-0.43$, $p=0.54$). The Dutch translation of the National Adult Reading Test (NART) (Schmand et al., 1991) was used as an estimate of verbal IQ (Lezak, 1995), patients and control participants did not differ on the NART ($t=-1.44$, $p=0.16$).

All patients fulfilled the DSM-IV criteria for schizophrenia as confirmed with the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) that was administered by a psychiatrist. Patients were also screened for affective disorders, i.e. depression and mania, substance-related disorders by the CASH. Most patients were diagnosed with paranoid type of schizophrenia (n=25). However, one patient was diagnosed with disorganized type of schizophrenia, one with residual type of schizophrenia, six undifferentiated type of schizophrenia and three with schizophreniform disorder. Most patients were clinically stable and in residual state and five patients were inpatients and 31 were outpatients. Mean duration of psychotic symptoms was 9.44 years (SD 8.01, range 1-24). Age of illness onset was 23.83 years (SD 5.47, range 16-34). 34 patients received antipsychotic medication and six patients used olanzapine, 15 clozapine, five quetiapine, and eight risperdal. One patient used also penfluridol, two patients used

oxazepam and one patient also used diazepam. Symptoms and severity were rated with the Dutch translation of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Mean positive symptoms was 13.68 (SD 4.74, range 7-22), negative symptoms 14.94 (SD 5.81, range 7-29) and general psychopathology 26.31 (SD 6.58, range 17-47).

Inclusion criteria for all participants were age between 18-65 years and physically healthy. Exclusion criteria were neurological conditions or history of head injury with loss of consciousness, recent history of alcohol and substance abuse and mental retardation. None of the control participants had a history of psychiatric illness or use of psychiatric medication confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998). The local ethics committee approved the study and all subjects provided written informed consent after the procedure had been fully explained, according to the Declaration of Helsinki.

Facial affect perception task

Participants sat in front of a computer screen, approximately 90 cm away. Each trial started with the presentation of a fixation point. The duration of this fixation point was variable and could be 10, 15, 20 or 25 seconds and was followed by an image display with a photograph of an affective face. 26 Photographs of faces were taken from the Ekman and Friesen set (Ekman and Friesen, 1976) and in 50% of the faces a male was shown and 50% was a female face. 26 Trials were presented consisting of eight face presentations in each of three conditions: angry, happy and fearful and two practice trials (neutral faces). Each photograph was presented for 10 seconds in which participants were asked to attend carefully to the face. This was followed by an image of a Self-Assessment Manikin (Bradley and Lang, 1994) in which participants rated each face on a nine-point scale on valence (1 very negative, 5 neutral, 9 very positive) and arousal (1 completely calm to 9 very aroused). After participants gave their response, the 10, 15, 20 or 25 second fixation point was presented again. This resulted in a variable intertrial interval of at least 10 seconds. This was chosen to allow skin conductance activity to return to baseline and to reduce possible habituation.

Skin conductance recording

All testing was done in a quiet, dimly lit room at the University Medial Center Utrecht on a computer with a 15-in monitor. While watching the faces, skin conductance level (SCL) was continuously recorded. Skin conductance was recorded using a constant voltage of (0.5 V) with 1-cm^3 AgAg/Cl electrodes attached to the medial phalanx surfaces of the middle and index finger of the non-dominant hand. KY-jelly was used for conductance. Before starting the task two minutes of baseline were recorded, followed by two external

stimuli, a sigh and handclap, in order to ensure a correct attachment and conductance of the electrodes. Values of skin conductance were transformed to microsiemens values using Psylab software (www.psylab.com). Presentation of the pictures was synchronized with the sampling computer. Skin conductance responses occurring 1 to 5 seconds after presentation of the picture were computed. A phasic increase in conductance of more than 0.04 microsiemens was counted as a response. To normalize the data a log transformation was used.

Statistical analysis

The data were analyzed with GLM within-subjects ANOVA with average skin conductance response for the different affective faces as within-subjects factor and Group (patient or control) as between-group factor. Planned post-hoc t-tests were administered to investigate skin conductance activity for the different emotions for the two groups. Subjective ratings of valence and arousal were analyzed with non-parametric Mann-Whitney U tests. Correlations between skin conductance measurements were analyzed by Spearman's correlation coefficients. Alpha level was set at 0.05.

Results

Non-responders, skin conductance level and skin conductance response to physical stimulus

Non-responders were defined as those subjects who failed to elicit a skin conductance response on the sigh, handclap and the first three trials and were excluded from further analysis (16.7% of patients). This resulted in a group of 30 patients with schizophrenia and 34 control participants, see Table 1 for demographic variables of the patient and control group. The difference in amount of non-responders between patients and controls was significant (Mann-Whitney $U=510$, $Z=-2.47$, $p=0.01$), demonstrating that non-responsiveness was more common in the schizophrenia group. Before onset of the actual experiment skin conductance level was measured. Patients and control participants did not differ significantly on skin conductance level, $F(1,62)=2.57$, $p=0.11$. Nor did patients and controls differ in skin conductance response to the physical stimuli: sigh ($F(1,62)=0.16$, $p=0.69$) or handclap ($F(1,62)=3.05$, $p=0.09$).

Table 1. Demographic characteristics of 30 patients with schizophrenia and 34 control subjects.

	Schizophrenia patients	Control subjects	
	Mean (SD)	Mean (SD)	P
Age (years)	31.6 (7.5)	28.6 (8.6)	0.15
Sex (male:female)	20:10	18:16	0.27
Education (years)	14.2 (2.8)	15.3 (2.1)	0.08
Parental education (years)	14.8 (2.6)	14.9 (2.6)	0.77
Estimated verbal IQ	103.0 (9.2)	106.6 (9.0)	0.16

Skin conductance responses to facial expressions

Analysis revealed a main effect of group, $F(1,62)=4.39$, $p=0.04$, suggesting that patients with schizophrenia demonstrated lower skin conductance responses to affective faces compared to controls. No main effect of facial expression was found, $F(2,61)=0.24$, $p=0.79$, suggesting that skin conductance responses did not differ for the three emotions. However, there was a group*facial expression interaction, $F(2,61)=5.05$, $p=0.009$, demonstrating that skin conductance responses for specific affective faces was different for controls and patients. Planned post-hoc t-tests demonstrated that patients with schizophrenia showed specifically lower skin conductance activity in response to angry faces ($t(62)=-3.19$, $p=0.002$) and fearful faces ($t(62)=-2.06$, $p=0.04$), but not to happy faces ($t(62)=-0.65$, $p=0.52$). Figure 1 displays means and standard error of skin conductance activity for the different affective faces.

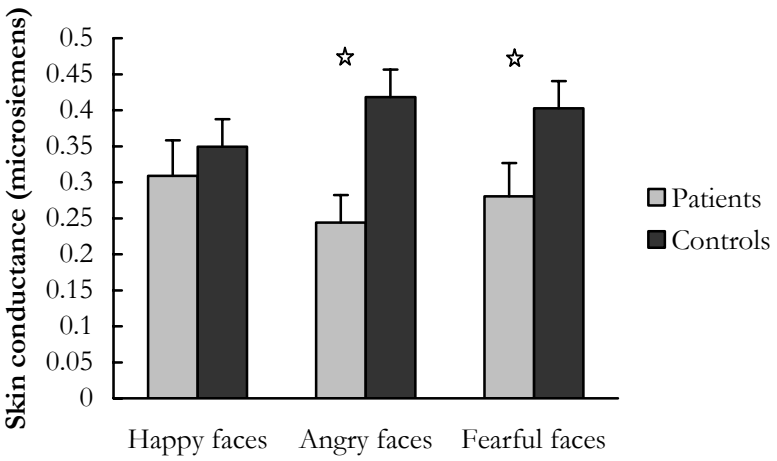

Figure 1. Mean skin conductance response (S.E.) in microsiemens for the different affective faces in 30 patients with schizophrenia and 34 control participants, *p<0.05.

Subjective ratings of valence and arousal of facial affect

A non-parametric analysis of variance, Mann-Whitney U test revealed that patients had significantly lower ratings of valence on happy facial expressions compared to control subjects (Z= -2.43, p=0.015), but patients and controls did not differ on valence ratings of angry (Z=-0.015, p=0.89) and fearful faces (Z=-0.56, p=0.58). Patients demonstrated higher arousal ratings for happy faces compared to control (Z=-2.12, p=0.034), but patients and controls did not differ in arousal ratings of angry (Z=0.06, p=0.96) and fearful faces (Z=-0.26, p=0.79).

Within-subjects, non-parametric Wilcoxon signed-rank tests demonstrated that happy faces were more positively rated than angry faces in both patients (Z=-4.33, p<0.0001) as well as controls (Z=-5.09, p<0.0001). Happy faces were also rated more positive compared to fearful faces in patients (Z=-4.0, p<0.0001) and controls (Z=-5.09, p<0.0001). Angry and fearful faces did not differ on valence ratings in patients (Z=-1.69, p=0.09) and control subjects (Z=-0.19, p=0.84).

With respect to arousal ratings, arousal was higher for angry faces compared to happy faces in patients (Z=-4.03, p<=0.0001) as well as controls (Z=-5.07, p<0.0001). Fearful faces were also rated as more arousing compared to happy faces in patients (Z=-3.97, p<=0.0001) and controls (Z=-5.07p<=0.0001). Angry and fearful faces did not differ on ratings of arousal in patients (arousal Z=-0.25, p=0.80) and control subjects (arousal Z=0.29, p=0.29).

Relationship between schizophrenia symptomatology and skin conductance, valence and arousal

There were no significant correlations between skin conductance activity in response to the different facial expressions and symptoms as measured with the PANSS. A negative correlation was found between subjective valence ratings of happy faces and severity of negative symptoms, spearman's rho=-0.61, p=0.0008 (see Figure 2). Other correlations between symptoms and valence ratings of fearful and angry faces were not statistically significant, nor were there any significant correlations between subjective arousal ratings and symptoms.

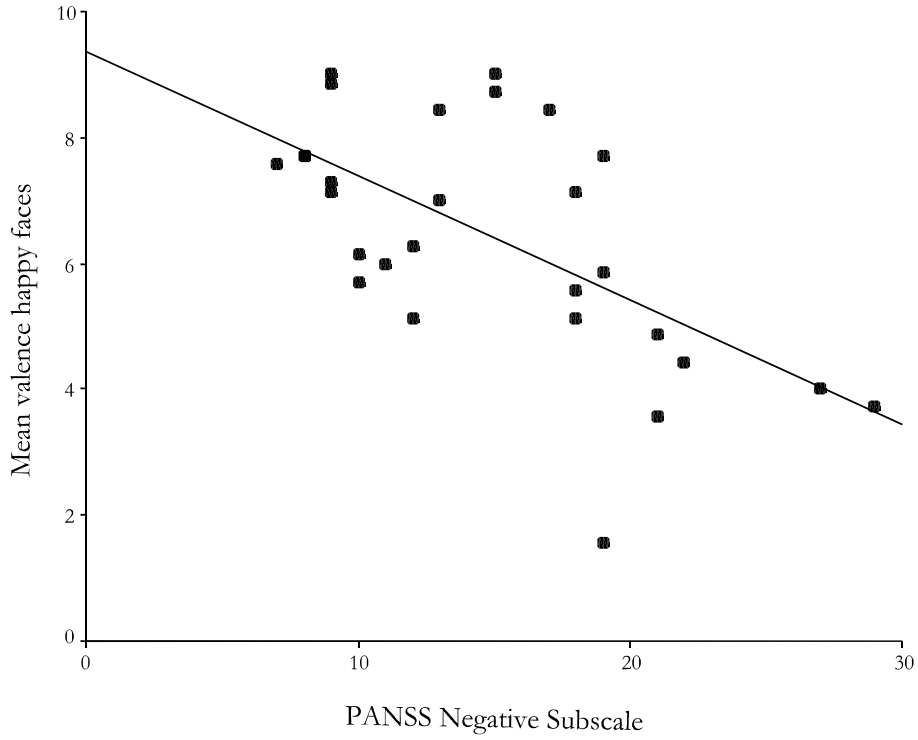

Figure 2. Relationship between negative symptoms as measured with the PANSS and subjective valence ratings of happy faces in 30 patients with schizophrenia.

Discussion

This study investigated the autonomic responses to different affective faces in schizophrenia. Our results showed that patients with schizophrenia specifically displayed lower skin conductance responses to fearful and angry faces in comparison with control subjects, but not in response to happy faces or to the physical stimuli, i.e. handclap and sigh. This specific failure to respond autonomically to threatening faces seems not related to symptoms. Skin conductance responses reflect stimulus-bound activity, such as attentional and affective processing (Bouscein, 1992). Given that skin conductance responses were specifically diminished in response to angry and fearful faces, but not to happy faces or physical stimuli, we suggest that this unresponsiveness indicate problems in the processing of these affective faces instead of attentional deficits.

Furthermore, the low autonomic reactions to angry and fearful faces were not reflected in abnormal subjective evaluation of valence and arousal of these faces and subjective evaluations were quite similar to those of the control subjects. Both patients and controls demonstrated the expected pattern of high positive valence and low arousal for happy faces and low, negative valence and high arousal in angry and fearful faces. However, patients with schizophrenia rated happy faces less positively and more arousing compared to control subjects. Although this might seem at odds with the normal skin conductance responses to happy faces, it suggests that happy facial expressions are nevertheless differentially evaluated. In particular patients with more negative symptoms rated happy faces as less positive. This relationship can be explained by the presence of anhedonia or hypohedonia, which refers to the inability to experience pleasurable or positive emotions and which is suggested to be a trait of schizophrenia (Meehl, 1962). Generally, the confrontation with happy faces induces a positive mood (Schneider et al., 1994). However, inabilities in the experience of positive emotions, or anhedonia in patients with schizophrenia might result in less positive mood induction and a less positive rating after watching happy faces. However, anhedonia is often difficult to distinguish from lack of social interest, avoidance and withdrawal from activity and interpersonal contacts. An alternative explanation is that smiling, in contrast to fearful and angry expressions, is frequently used in social situations. The evaluation of happy faces as less positive and more arousing might be consequently related to problems in social behavior, in particular in patients that are characterized by social and emotional withdrawal.

The absence of skin conductance responses to fearful and angry faces suggests a deficient neural processing of these faces. Most prominent is the role of the amygdala in emotion processing, particularly in the perception of threatening faces (Morris et al., 1996) as well as in the mediation of skin conductance activity (Bouscein, 1992). However, other brain structures, such as the medial prefrontal and orbitofrontal cortex, insula and anterior

cingulate are part of the emotional brain that may mediate skin conductance activity (Bouscein, 1992; Critchley et al., 2000; Phan et al., 2002; Williams et al., 2005). There is abundant evidence for disturbances of the amygdala during emotion processing in schizophrenia (Schneider et al., 1998; Phillips et al., 1999; Gur et al., 2002b; Takahashi et al., 2004), but deficits in the medial prefrontal cortex, insula and cingulate cortex have also been observed in schizophrenia (Hempel et al., 2003; Phillips et al., 2003b; Takahashi et al., 2004). It is thought that the automatic processing of emotive information, here reflected in skin conductance responses to affective faces, is mediated by the amygdala. A deficit of the amygdala might result in deficient neural processing of especially threatening faces. In addition, the subjective ratings of pleasantness and arousal is a more deliberate process thought to be mediated by prefrontal brain areas, such as the dorsal medial prefrontal cortex and anterior cingulate sulcus (Taylor et al., 2003). However, the dissociation between disturbed arousal responses, but intact evaluation of negative, threat-related faces can also be explained by theories that proposed lateralization of the amygdala as reviewed by Baas et al. (2004). For instance, the framework proposed by Gläscher and Adolphs (2003) suggests that the right amygdala is crucial for emotional arousal responses, i.e. skin conductance, whereas the left amygdala is important for the cognitive evaluation of affective information. A specific deficit of the right amygdala might result in abnormal autonomic activity in response to affective threatening faces, in the face of normal subjective evaluation of these faces. This double dissociation within the amygdala has recently been validated in individuals with Turner syndrome, who indeed show dissociation between cognitive appraisal and arousal (Skuse et al., 2005). However, it is still unclear how the autonomic system and more evaluative processing systems interact and these processes might very well be partly independent (Ohman and Birbaumer, 1993; Skuse et al., 2005). Future research should investigate the dissociation of arousal and cognitive evaluation using brain-imaging techniques in more detail.

Our finding of a specific affective hyporesponsivity to threatening faces does not support previous research that demonstrated higher baseline levels and increased reactivity to affective pictures or faces (Kring and Neale, 1996; Williams et al., 2004). Recent studies refined these findings by demonstrating that increased autonomic reactivity is specifically present in patients with high levels of symptoms (Schell et al., 2005; Zahn and Pickar, 2005). The patient sample included in this study demonstrated relatively low levels of symptomatology and most patients were treated by atypcial antipsychotices, in particular clozapine and olanzapine, which could dampen skin conductance activity (Mueck-Weymann et al., 2001). Notwithstanding, we were able to observe reduced skin conductance responses to angry and fearful faces, but not to happy faces or physical stimuli. Hence, the present selective findings are probably not due to medication effects. It

should be noted that the results might be different when other patient samples with different symptoms and medication are investigated and the present result might not generalize to other groups of patients with schizophrenia. In addition, it is yet unclear whether this pattern relates to abnormal perception of affective faces or to social function in schizophrenia. Future research should investigate the relationship between skin conductance activity to emotional information, emotion perception and social behavior.

In sum, schizophrenia can be associated with a specific impairment to respond autonomically to faces that convey an immediate threat towards the observer, in the face of normal cognitive evaluation of valence and arousal of these faces. In addition, the reversed pattern was observed for happy faces, i.e. autonomic arousal was comparable with controls, but happy faces were differentially evaluated on valence and arousal. This is particularly pronounced in patients with high levels of negative symptoms. We conclude that the present findings are supportive of theories that propose a partly distinct, but complementary role in the cognitive evaluation and the autonomic processing of faces. Moreover, we suggest that in schizophrenia especially the autonomic responses to threatening faces are disturbed.

Acknowledgements

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Emotional abnormalities in individuals at high-risk for schizophrenia

Chapter 6

No words for feelings: alexithymia in schizophrenia patients and first-degree relatives

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Abstract

Alexithymia refers to difficulties in emotionalizing, fantasizing, verbalizing, identifying and analyzing emotions. The goal of this study was to investigate features of alexithymia in patients with schizophrenia. In addition, we investigated if alexithymia would be associated with vulnerability to schizophrenia, by studying unaffected first-degree relatives of schizophrenia patients. Furthermore, sex differences were taken into account. 43 Patients with schizophrenia, 32 unaffected siblings and 44 healthy control subjects were compared on the Bermond-Vorst Alexithymia Questionnaire. Results showed that male patients with schizophrenia in particular demonstrated a specific pattern of alexithymia: difficulty identifying and verbalizing emotions, in the face of a higher subjective emotional arousal. Moreover, male siblings showed comparable problems in verbalizing their emotions as male patients. We suggest that these difficulties in aspects underlying affect regulation could account for the deficits in social functioning observed in schizophrenia and could contribute to a greater vulnerability for schizophrenia in particular for males.

Introduction

A growing body of evidence demonstrates emotion disturbances in schizophrenia, including deficits in emotional expression, perception and recognition (Aleman and Kahn, 2005). Schizophrenia is typically regarded a neurocognitive disorder with a genetic component, which suggests that emotional disturbances reflect abnormalities in brain areas important for emotion processing (Phillips et al., 2003b). Indeed, emotion abnormalities observed in schizophrenia even extends to persons at risk for schizophrenia, including relatives of patients with schizophrenia (van Rijn et al., 2005). Interestingly, there appears to be some specificity in these emotion deficits. For instance, the recognition of negative emotions might be in particular deficient and male patients seem especially worse in emotion recognition (Scholten et al., 2005). Although the expression of emotions is impaired in schizophrenia, evidence is accumulating that the subjective emotional experience may not be reduced and that even more intense negative emotions are experienced (Kring et al., 1993; Myin-Germeys et al., 2000; Aghevli et al., 2003). Moreover, levels of emotional arousal, i.e. anxiety seem to precede symptoms such as hallucinations (Delespaul et al., 2002).

The ability to experience and express emotions is crucial for regulating one's own emotions and the ability to maintain interpersonal relationships. Indeed, the use of suppression as emotion regulation strategy is associated with decreased emotional expression and with more negative social consequences compared to other emotion regulation strategies (Gross, 2002; Gross and John, 2003). To describe a relative narrowing in emotional functioning Sifneos (Sifneos, 1973; Sifneos et al., 1977) introduced the term 'alexithymia' from the Greek 'a'=lack, 'lexis'=word, 'thymos'=emotion. Alexithymia is a multidimensional construct that refers to personality traits relating to inabilities or severe reductions in identifying, describing and communicating feelings, difficulties in differentiating feelings from bodily sensations, and diminished affect-related fantasy. In addition, it has been suggested that the conscious experience of feelings is also part of the alexithymia definition as argued by Lane et al. (1997). Based on recent knowledge from neurobiology, Bermond (1995; 1997) has proposed that two forms of alexithymia may be distinguished. One form of alexithymia is characterized by an absence of emotional experience and thus an absence in the expression (verbalization and identification) of emotions, type I alexithymia, which is associated with right hemisphere dysfunction (Larsen et al., 2003). The other form of alexithymia, type II alexithymia, refers to reductions in the expression of emotions in the face of intact or even increased levels of emotional experience and has been associated with corpus callosum abnormalities (Larsen et al., 2003). In addition, alexithymia has been associated with hypofunction in the

cingulate cortex and the insula, which probably result in type I alexithymia (Larsen et al., 2003; Aleman, 2005).

The reduction of expression of emotion as found in alexithymia almost certainly implies a lack of, or dysregulation of emotions (Bagby and Taylor, 1997). Likewise, the impairments in emotion-processing and emotion-regulating capacities underlying alexithymia may be a possible risk factor for a variety of both medical and psychiatric disorders, such as somatization and maybe schizophrenia (Taylor et al., 1997). Previous studies that investigated alexithymia in schizophrenia demonstrated that patients with schizophrenia had more problems in identifying and communicating feelings, which might be in particular true for non-paranoid patients (Stanghellini and Ricca, 1995; Cedro et al., 2001). These studies were limited however, by the fact that no specific syndrome ratings, i.e. positive or negative symptoms were correlated with alexithymia scores. Furthermore, they did not evaluate verbal IQ to control for verbal abilities or sex differences. Any study of alexithymia should take sex differences into account as the incidence and severity of alexithymia have been observed to be higher in men than in women (Lane et al., 1998; Salminen et al., 1999; Vorst and Bermond, 2001). Sex differences have also been reported for incidence, course and outcome of schizophrenia, with higher figures for men (Leung and Chue, 2000; Aleman et al., 2003). Hence, men with schizophrenia could be hypothesized to be especially vulnerable for deficits in affect regulation as compared to women. Finally, the alexithymia construct covers the ability to be aware of emotion arousal and there are no studies that tapped this latter aspect of alexithymia in schizophrenia, although emotional experience might be intact in schizophrenia (Kring et al., 1993; Myin-Germeys et al., 2000; Aghevli et al., 2003).

It is important to realize however, that inabilities in verbalizing emotions or awareness of emotional arousal could also result from confounding factors, such as severe symptomatology or medication use in schizophrenia. In this regard, the investigation of alexithymia in siblings of patients with schizophrenia enables the study of deficits related to schizophrenia without these confounding influences. Moreover, if such deficits are also observed in nonaffected relatives these disturbances reflect at least in part a vulnerability to the illness. In that way, abnormal traits are associated with vulnerability for schizophrenia and not with psychosis or being ill. Thus investigating relatives might increase the understanding about the biological vulnerability to schizophrenia. Indeed, there is evidence that individuals higher on the schizophrenia spectrum show increased awareness of emotional arousal measured with an alexithymia questionnaire (van 't Wout et al., 2004).

The aim of the present study was to investigate aspects of alexithymia in patients with schizophrenia, siblings of patients and healthy matched control subjects with the

Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001). The BVAQ investigates the ability to describe, identify and analyze feelings as well as fantasizing and awareness of emotional arousal. We predicted that individuals with schizophrenia would show more difficulties in verbalizing and identifying their own emotions compared to individuals without schizophrenia, but with intact emotional experience. We hypothesized that on these aspects siblings of patients with schizophrenia would show intermediate results. Usually, non-psychotic relatives manifest abnormalities to a lesser degree than patients with full-blown psychosis, but somewhere intermediate between patients and control participants (Toomey et al., 1999; Staal et al., 2000). With respect to sex differences, we hypothesized that especially male patients and siblings would show the expected pattern of alexithymia.

Methods

Participants and Procedure

43 Patients (19 females; 24 males) with a diagnosis of schizophrenia were recruited from the University Medical Center Utrecht. All patients fulfilled the DSM-IV criteria for schizophrenia as confirmed with the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992), which was administered by a psychiatrist. Patients were also screened for affective disorders, i.e. depression and mania and substance-related disorders by the CASH. Most patients were diagnosed with paranoid type of schizophrenia (n=29). One patient was diagnosed with disorganized type of schizophrenia, one with catatonic type of schizophrenia, two with residual type of schizophrenia, one with schizoaffective type of schizophrenia, six undifferentiated type of schizophrenia and three with schizophreniform disorder. 39 Patients used antipsychotic medication and of these patients nine also used other medications (paroxetine; citalopram; lithium; valproate; oxazepam; temazepam). Most patients were clinically stable. Ten patients were inpatients and 33 were outpatients. Symptoms and severity were rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) by two trained raters.

32 Healthy siblings (19 females; 13 males) of patients with schizophrenia were recruited through advertisements at the Ypsilon website, i.e. a specific website for relatives of patients with schizophrenia and through an already existing database at the University Medical Center Utrecht. The diagnosis of schizophrenia from the affected sibling was confirmed with a CASH interview (Andreasen et al., 1992). However, we were unable to interview 12 affected siblings. None of the siblings had a history of psychiatric illness or

use of psychiatric medication confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998).

44 Non-psychiatric control participants (15 females; 29 males) were drawn from the general population by advertisements in local newspapers and were paid for their participation. Inclusion criteria for all participants were age between 18-60 years and physically healthy. Exclusion criteria were neurological conditions or history of head injury with loss of consciousness, recent history of alcohol and substance abuse, and mental retardation. None of the control participants had a history of psychiatric illness or use of psychiatric medication confirmed with the MINI (Sheehan et al., 1998). Control subjects were recruited to match the patient and sibling sample with respect to age, sex and educational level. See Table 1 for clinical characteristics and demographic data of the investigated groups. The local ethics committee approved the study according to the Declaration of Helsinki and all subjects provided written informed consent after the procedure had been fully explained. Each participant was assigned with a different number to guarantee anonymous processing of the data.

Table 1. Demographic characteristics of the three groups and clinical characteristics of patient group.

Clinical characteristic	Patients (N=34)	Siblings (n=32)	Control subjects (N=44)	p
Age (years)	31.14 (7.30)	34.44 (10.29)	31.98 (9.16)	0.27
Sex (male:female)	24:19	19:13	29:15	0.09
Education (years)	15.31 (2.59)	16.16 (2.02)	14.89 (2.52)	0.08
Duration of illness (years)	9.44(8.01)			
Age of onset (years)	23.84 (8.01)			
Positive scale PANSS	11.69 (4.30)			
Negative scale PANSS	13.05 (4.38)			
General psychopathology PANSS	24.88 (4.74)			

Values are presented as mean ± SD.

Verbal IQ

The Dutch translation of the National Adult Reading Test (NART) (Schmand et al., 1991) was used as an estimate of verbal IQ (Lezak, 1995).

Alexithymia

Alexithymia was measured with the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001). This questionnaire has five separate subscales, (8 items per subscale, four indicative and four contra-indicative) for all alexithymia features as mentioned by Nemiah and Sifneos (1970) and Sifneos (1973), who defined the concept of alexithymia by the following traits: reduced capacities for emotionalizing, fantasizing, identifying emotions, verbalizing emotions and pensé opératoire (Marty and De M'Uzan, 1963) or analyzing emotion. Item examples of respective subscales are: 'When friends around me argue violently, I become emotional'. (*Emotionalizing*; positive) 'Before I fall asleep, I make up all kinds of events, encounters and conversations' (*Fantasizing*; positive). 'When I am distressed, I know whether I am afraid or sad or angry' (*Identifying*; positive). 'I find it difficult to verbally express my feelings' (*Verbalizing*; negative). 'I hardly ever go into my emotions' (*Analyzing*; negative).

There is substantial overlap between the previous more frequently used Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994) and BVAQ on three subscales that measure the ability to identify, verbalize and analyze emotions. The correlation between the sum scores on these three BVAQ subscales and the TAS-20 is high, indicating that these scales measure the same features (Vorst and Bermond, 2001). However, the BVAQ also includes, as mentioned above, subscales for emotionalizing and fantasizing. Like in the TAS-20, BVAQ-items are scored on a 5-point scale (1= certainly does not apply to me, up to 5= certainly applies to me). High scores indicate reductions in the capabilities measured. The BVAQ has good psychometric properties and is a promising instrument for research in clinical groups (Zech et al., 1999; Vorst and Bermond, 2001; Muller et al., 2004; Berthoz and Hill, 2005; Morera et al., 2005).

Statistical Analysis

The NART was analyzed with an analysis of variance (ANOVA). Data of the BVAQ was analyzed with a multivariate analysis of variance (MANOVA) with the BVAQ subscales as dependent variables and Group and Sex as independent variables, resulting in a 5x3x2 design. When an analysis indicated significant differences, the differences were analyzed with subsequent post-hoc Tukey HSD t-tests. Correlations between the PANSS and BVAQ subscales were analyzed by Spearman's rank correlation coefficients. Alpha level was set at 0.05.

Results

Verbal IQ

Mean verbal IQ estimated from NART scores was for the patients 105.56 (9.04), for the siblings 104.65 (8.20) and for the control participants 107.57 (9.09). These differences were not significant, $F(2,116)=1.11$, $p=0.34$.

Alexithymia

There was a significant main effect of Group ($F(10,216)=3.11$, $p=0.001$), Sex ($F(5,109)=8.84$, $p<0.0001$) and a significant Group*Sex interaction ($F(10,216)=2.04$, 0.03). Patients, siblings and control subjects differed significantly on the subscales 'verbalizing' ($F(2,116)=3.86$, $p=0.02$), 'identifying' ($F(2,116)=8.76$, $p=0.0003$) and 'emotionalizing' ($F(2,116)=4.59$, $p=0.01$). In addition, men had more problems than women on 'verbalizing' ($F(1,117)=18.70$, $p<0.001$), 'analyzing' ($F(1,117)=7.98$, $p=0.006$) and 'emotionalizing' ($F(1,117)=20.49$, $p<0.001$). See Table 2 for means (S.D.) for men and women separately for the three groups.

No differences on the BVAQ scales were observed when only females were included in the analyses. However, the same analyses for males revealed significant differences between the groups on 'verbalizing' ($F(2,63)=8.29$, $p=0.001$), 'identifying' ($F(2,63)=6.13$, $p=0.004$), 'emotionalizing' ($F(2,63)=4.93$, $p=0.01$) and 'fantasizing' ($F(2,63)=3.55$, $p=0.035$). Post hoc analyses showed that on 'verbalizing' male patients and male siblings demonstrated similar scores ($p=0.98$). Compared with male control subjects both male patients ($p=0.001$) and male siblings ($p=0.01$) had a higher score on 'verbalizing'. On 'identifying', male patients had a higher score compared to male siblings ($p=0.04$) and male control subjects ($p=0.004$). Male siblings did not differ from control males ($p=0.98$) on 'identifying'. For 'emotionalizing', male patients had a lower score than male siblings ($p=0.02$) and male controls ($p=0.04$). Siblings did not differ from male controls ($p=0.69$) on 'emotionalizing'. On 'fantasizing' patients did differ neither from siblings nor controls, however, male siblings had a higher score compared to control males ($p=0.04$).

Correlation between symptoms and the Bermond-Vorst Alexithymia Questionnaire

Within the patient group there was a positive correlation between severity of negative symptoms as measured with the PANSS and 'identifying', $r=0.31$, $p=0.05$. None of the other PANSS scales correlated significantly with the BVAQ subscales.

Table 2. Means score (S.D.) of the Bermond-Vorst Alexithymia subscales for the three groups, scores separated for males and females.

Alexithymia	Schizophrenia patients (N=43)	Siblings (N=32)	Control subjects (N=44)
Verbalizing	23.37 (6.39)	21.03 (7.42)	19.47 (6.06)
Males	26.46 (5.63)	26.08 (7.44)	19.97 (6.28)
Females	19.47 (5.11)	17.58 (5.18)	18.53 (5.71)
Analyzing	18.05 (6.57)	15.78 (5.13)	16.25 (4.86)
Males	19.71 (6.66)	18.08 (6.08)	16.66 (4.64)
Females	15.95 (5.99)	14.21 (3.79)	15.47 (5.33)
Identifying	19.72 (5.91)	15.59 (5.34)	15.29 (4.87)
Males	20.42 (6.33)	15.62 (5.28)	15.28 (5.13)
Females	18.84 (5.38)	15.58 (5.53)	15.33 (4.48)
Emotionalizing	18.93 (5.10)	20.44 (6.41)	22.36 (4.56)
Males	20.00 (5.02)	24.85 (6.34)	23.48 (4.36)
Females	17.58 (4.99)	17.42 (4.50)	20.20 (4.25)
Fantasizing	23.44 (6.21)	23.69 (7.52)	22.59 (6.78)
Males	24.29 (5.65)	26.85 (7.19)	21.24 (7.03)
Females	22.37 (6.85)	21.53 (7.13)	25.20 (5.59)

Discussion

This study examined aspects of alexithymia in patients with schizophrenia and siblings of patients compared to control subjects. The results revealed that male patients with schizophrenia are characterized by type II alexithymia. That is, male patients with schizophrenia have more problems in verbalizing and identifying their emotions than control subjects, but at the same time they experience higher levels of emotional arousal. These findings regarding the impaired cognitive component of alexithymia (verbalizing and identifying) are consistent with previous research that demonstrated difficulties in identifying and verbalizing emotions in patients with schizophrenia using the TAS-20 (Stanghellini and Ricca, 1995; Cedro et al., 2001). Our replication of this observation is important, as we used a different scale and a different sample of patients than the sample included by Cedro et al. (2001). Moreover, the difficulties in verbalizing and identifying feelings in patients were not due to differences in verbal intelligence between patients and control participants. At the same time, our results for the first time underline the importance of sex differences when investigating alexithymia in schizophrenia, as we only observed significant impairment in men with schizophrenia. Furthermore, we found that

difficulties with identifying one's own emotions correlated with the severity of negative symptoms, like flat affect and emotional-social withdrawal. Although this is in contrast with Todarello et al. (2005) who found no correlation between negative symptoms of schizophrenia and alexithymia, a speculative mechanism underlying this relationship might be that people who are not capable of identifying one's own feelings and thus unable to cope or regulate these feelings, will be more prone to withdraw emotionally and socially. Indeed, Gross (Gross, 2002; Gross and John, 2003) demonstrated that people who use suppression as an emotion regulation strategy experience less positive affect and have a worse social and interpersonal functioning.

Our finding that impairments in cognitive aspects of emotion regulation co-exist with a disposition for higher levels of subjective emotional arousal is novel, however. The higher ratings on the subscale 'emotionalizing' suggest that patients are more easily aroused by emotion-inducing events than healthy control subjects. Such increased emotional reactivity has been reported earlier in reaction to experimentally induced stressful situations, i.e. patients with schizophrenia show greater affective reactivity in speech when discussing negative topics (Cohen and Docherty, 2004). In addition, in daily life stressful situations, schizophrenia patients appear to experience increased levels of negative affect compared to controls (Myin-Germeys et al., 2003).

In this study, alexithymic features were also investigated in siblings of patients with schizophrenia. Results showed that male siblings demonstrated comparable problems in verbalizing their feelings as male patients. In addition, male siblings appeared to fantasize less compared to control participants and patients. Our finding of difficulties in verbalizing one's feelings may thus specifically be related to schizophrenia instead of having a psychiatric disorder as such. Since alexithymic tendencies are considered to be a possible risk factor for medical and psychiatric disorders (Bagby and Taylor, 1997; Kreitler, 2002), especially male siblings might be at increased risk for schizophrenia. Indeed, our results regarding alexithymic features only in male patients and siblings fit with other literature demonstrating that male schizophrenia patients have more severe symptoms, a worse prognosis and outcome compared to female schizophrenia patients (Gur et al., 1996; Leung and Chue, 2000; Aleman et al., 2003; Usall et al., 2003).

Thus, the observed pattern of alexithymic features suggests that male patients with schizophrenia are less able to identify and verbalize the emotions they are experiencing and the latter problems are also present in males at increased risk for schizophrenia. At the same time male patients are more easily mentally aroused by emotion inducing stimuli. Recent research demonstrated that in normal healthy subjects and a clinical sample, difficulties with identifying and verbalizing feelings correlates with high scores on neuroticism (Muller et al., 2004; Morera et al., 2005). This is

understandable as the increase in mental emotional arousal forces people to reflect on, think about their feelings (Laird and Bresler, 1992; Buck, 1993; Damasio, 1999). However, due to restrictions in the ability to verbalize and identify emotions, this reflection will not lead to a better understanding of one's affective state, resulting in more emotional problems instead of reducing such problems (Taylor et al., 1997). As a consequence, problems in affect regulation are inevitable and might contribute to social dysfunction and emotion processing deficits observed in schizophrenia and to a lesser extent in relatives of patients (Toomey et al., 1999; Hooker and Park, 2002; Kee et al., 2004; Loughland et al., 2004). On the basis of the present results we support the development of emotion regulation training for male patients with schizophrenia in particular. Emotion regulation training to recognizing one's own feelings could be helpful and in that way contributing to a reduction in interpersonal problems in male patients (Spitzer et al., 2005). For instance, the 'emotion-focused therapy' proposed by Greenberg (Greenberg, 2002) is focused on how to become aware of one's emotions, to understand their bodily reactions, and to express emotion in ways that are appropriate to the context. This includes coaching patients in learning to describe their feelings in words, which will help them develop problem-solving skills.

Regarding the neuroanatomical basis, the present pattern of alexithymia has mainly been related to corpus callosum deficits or reduced interhemispheric communication and frontal hypoactivation (Larsen et al., 2003). Furthermore, alexithymia has been associated with hypofunction in the cingulate cortex, which is related to affect regulation and perception and the insula, which has been shown to be important for awareness of internal bodily states (see Aleman, 2005 for an overview). Future research should investigate the neuroanatomical basis of alexithymia type II in schizophrenia. In addition, a replication of the present findings is desirable to elucidate a specific relationship between affect regulation difficulties and psychopathology in more severe patients with schizophrenia and whether alexithymia can be regarded as a vulnerability marker for schizophrenia. At last, it should be noted that the BVAQ is a self-report measure of aspects of affect regulation and the presents findings could be strengthened by including an objective measure of affect regulation.

In conclusion, male patients with schizophrenia demonstrated more difficulties in the identification and verbalization of their emotions on the one hand, but reported to be more easily emotionally aroused on the other hand. This pattern is troublesome as patients are aware of being emotionally aroused, but have difficulties in identifying or verbalizing, and hence regulating, their feelings. Interestingly, healthy male siblings of patients with schizophrenia show comparable problems in verbalizing their emotions as patients. We suggest that these difficulties in aspects underlying affect regulation could account for the

deficits in social functioning observed in schizophrenia and could contribute to a greater vulnerability for schizophrenia.

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Chapter 7

Emotional processing in a non-clinical psychosis-prone sample

Mascha van 't Wout, André Aleman, Roy P.C. Kessels, Frank Larøi, René S. Kahn. Emotional processing in a non-clinical psychosis-prone sample.

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Abstract

Symptoms of psychosis have been proposed to form part of a continuous distribution of experiences in the general population, rather than being an all-or-nothing phenomenon. Indeed, schizotypal signs have been reported in subjects from non-clinical samples. Emotional processing has been documented to be deficient in schizophrenia. In the present study, we tested the hypothesis whether putatively psychosis-prone subjects would show abnormalities in emotion processing. Based on the extremes of Launay-Slade Hallucination Scale (LSHS) ratings of 200 undergraduate students, two groups of subjects (total N=40) were selected. All forty participants filled in the Schizotypal Personality Questionnaire (SPQ). We compared both groups on an alexithymia questionnaire and on four behavioral emotional information-processing tasks. Hallucination-proneness was associated with an increased subjective emotional arousal and fantasy-proneness. Although no differences between the high and low group were observed on three behavioral emotion processing tasks, on the affective word-priming task presentation of emotional stimuli was associated with longer reactions times to neutral words in high schizotypal subjects. Also, SPQ scores correlated with several emotion processing tasks. We conclude that these findings lend partial support to the hypothesis of continuity between symptoms characteristic of schizophrenia and psychosis-related phenomena in the normal population.

Introduction

A growing number of studies consider psychosis as a continuum with normal functioning at one end and abnormal functioning (psychosis) at the other end (Claridge, 1997; Johns and van Os, 2001; Verdoux and van Os, 2002). In accordance with this view, Johns and van Os (2001) have reviewed evidence indicating that psychotic signs, often called schizotypal signs or schizotypal traits, are present in healthy people to a certain extent. Schizotypy refers to the personality trait of experiencing 'psychotic' symptoms (Claridge, 1997) and schizotypy may be conceptualized as a predisposition to schizophrenia at the level of the organization of the personality (Meehl, 1989; Vollema and van den Bosch, 1995). Such schizotypal traits, e.g., referential thinking and odd or eccentric behavior have been hypothesized to be normally distributed in the non-clinical population (Chapman et al., 1976).

One of the cardinal dysfunctions associated with schizophrenia concerns processing of emotional information (McKenna, 1994), including disturbances in the expression, experience and perception of emotions. Indeed, Kraepelin (1907) regarded emotional disturbances such as flattened and inappropriate affect to be characteristic of schizophrenia. Although schizophrenia patients inadequately *express* emotions (Berenbaum and Oltmanns, 1992; Knight and Valner, 1993; Kring et al., 1994), Kring and Neale (1996), Kohler et al. (2000b) and Myin-Germeys et al. (2000) suggested that the subjective *experience* of emotion is much less disturbed in schizophrenia.

Sifneos (1973) introduced the term 'alexithymia' to describe abnormalities in affect regulation. More specifically, alexithymia refers to difficulties in recognizing, identifying and describing one's own emotions. Thus, alexithymic individuals have impaired affect regulation (Bagby and Taylor, 1997) and may also show specific inabilities to communicate emotions while the experience of emotion might be intact (Kihlstrom et al., 2000). Cedro et al. (2001) demonstrated that schizophrenic patients have higher scores on an alexithymia questionnaire than healthy controls, i.e. they have more problems in identifying and verbalizing their emotions.

With regard to behavioral measures of emotional processing in schizophrenia deficits in emotion recognition have been found (Edwards et al., 2002). In addition, schizophrenic patients appear to inadequately process facial affect (Addington and Addington, 1998; Streit et al., 2001) and demonstrate a reduced left-perceptual bias in the processing of emotional chimeric faces (Gooding et al., 2001). There might also be a bias towards material with a negative emotional valence, as observed in a study in which hallucinating patients were more sensitive to negative words compared to controls (Johns et al., 2002). Moreover, a recent study (Hoschel and Irle, 2001) reported that negative

emotional expressions yield stronger priming effects in schizophrenia patients compared to control subjects (hyperpriming).

The present study is important for several reasons. First, research on psychosis-prone or schizotypal individuals may help to develop preventive interventions for schizophrenia. Cannon et al. (2002) and McGorry et al. (2002) already showed that early interventions in prodromal schizophrenic patients reduces the risk of early transition to psychosis in young people and possibly reduces the incidence of schizophrenia. Second, the study of non-clinical subjects with schizotypal traits enables researchers to study schizotypal phenomena without the confounding contribution of factors such as medication, duration of illness and severe psychopathology or institutionalization. Third, previous research has concentrated on cognitive dysfunctions that may be associated with psychotic traits in non-clinical samples (Suhr, 1997; Aleman et al., 2000). To our knowledge, the present study is the first to examine emotional processing in such a sample.

The aim of this study was to investigate whether healthy individuals with high positive schizotypy differ from individuals with low positive schizotypy (as screened by the Launey-Slade Hallucination Scale (LSHS)) on measures of subjective and objective emotional information processing tasks. Following the schizophrenia literature positive schizotypal signs could, like positive symptoms in schizophrenia be associated with an attentional bias for negative valenced material, including threat, anger and sadness (Mandal et al., 1999; Phillips et al., 1999). In contrast, negative symptoms of schizophrenia reflect a more generalized and severe emotion-recognition deficit (Schneider et al., 1995; Mandal et al., 1999).

On subjective emotion processing (as measured with an alexithymia questionnaire) we predicted that individuals with positive schizotypal signs would report lower levels of identifying and verbalizing their own emotions compared to individuals without positive schizotypal signs. On the other hand, higher levels of emotionalizing might be expected, as an increase in arousal and anxiety has been associated with occurrence of positive symptoms in schizophrenia (Delespaul et al., 2002). With regard to behavioral emotional information processing we concentrated on verbal and facial affect recognition. On verbal affect recognition tasks we hypothesized that persons with positive schizotypal signs would show an increased sensitivity to emotional material, specifically an attentional bias for material with a negative valence. Thus, greater priming especially for negative valenced words and a reduced Stroop effect in an emotional counting Stroop paradigm for the positive schizotypal persons compared to persons with less schizotypal signs. On facial affect recognition tasks we predicted that persons with positive schizotypal signs would show a reduced left perceptual bias in a chimeric faces task (David

and Cutting, 1990) and more errors in recognizing degraded facial affect (Mandal et al., 1998).

Finally, in a more exploratory analysis, we also included the Schizotypal Personality Questionnaire (SPQ). First, to explore relations between positive schizotypy and the other two dimensions, disorganization and negative schizotypy in a non-clinical sample. Second, to explore the relation between the SPQ subscales and the emotional measures. Given the exploratory nature of this analysis, we only hypothesized that subjects selected for positive schizotypy would also show negative schizotypal signs and emotional processing characteristics associated with negative symptoms. We based this prediction on the fact that positive and negative symptoms generally occur together in patients with schizophrenia (McKenna, 1994). For example, whereas positive symptoms such as hallucinations and delusions occurred in about 70% of a sample of 306 concordant patients with schizophrenia in the International Pilot Study on Schizophrenia (WHO, 1973) , flatness of affect was also found in 66% of the sample (Murray, 1997).

Methods

Participants

Two-hundred undergraduate students from Utrecht University (79 male and 120 female (one student did not specify 'gender'); mean age 20.9 (SD=4.5) completed the revised Launey-Slade Hallucination Scale (LSHS) (Launay and Slade, 1981; Bentall and Slade, 1985; Larøi et al., 2004). Their scores ranged from 0 to 58, mean score: 16.12 (SD=10.1).

From the 200 students, 40 participants were selected for participation in the study. Twenty participants were from the highest and twenty participants were from the lowest quartile (range LSHS scores: 27-49 and 0-8 respectively). For the high LSHS group mean age was 21.65 (SD=2.43) with a male: female ratio of 1:4. The low LSHS group had a mean age of 22,75(SD=3.73) with a male: female ratio of 1:1.5. There were no significant group differences for mean age and gender, $F(1,38) = 1.222$, $p=0.276$ and $F(1,38) = 1.9$, $p=0.176$, respectively. Handedness was measured with the Edinburgh Handedness Inventory (-24 = exclusively left handed, 0 = no preference, 24 = exclusively right handed; (Oldfield, 1971). All participants were right handed except one (mean 19.5, SD=6.9).

Schizotypy questionnaires

Subjects were selected on the basis of either high or low ratings on a measure of positive schizotypy, the LSHS (Vollema and van den Bosch, 1995). The Schizotypal Personality Questionnaire (SPQ), a more comprehensive syndrome-based measure, was used to further characterize the two groups on other schizotypal traits.

The revised LSHS questionnaire consists of 16 questions, including items on sleep-related hallucinatory experiences and visual hallucinations (Larøi et al., 2004). Answers are scored on a 5-point scale (0= certainly does not apply to me, up to 4= certainly applies to me) and a high score on the LSHS indicates proneness towards hallucinations.

The Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) is a 74-item questionnaire with a dichotomous response format (yes or no) and is seen as an indicator of the genetic vulnerability to schizophrenia (Vollema et al., 2002). The items of the schizotypal traits are reduced to three dimensions. Positive schizotypy includes magical ideation, unusual perceptual experiences, delusional atmosphere, referential thinking and suspiciousness. The dimension of negative schizotypy includes the subscales social anxiety, referential thinking, no close friends, constricted affect and suspiciousness. Finally, the disorganization dimension includes the subscales odd speech and odd or eccentric behavior (Vollema et al., 2002). We followed Vollema et al. (2002) in the allocation of the items to the dimensions (see also Table 1).

Subjective and objective emotion measures

Alexithymia questionnaire

The Bermond-Vorst Alexithymia Questionnaire measures personality traits associated with experiencing, verbalizing, fantasizing, identifying and thinking about one's own emotions (BVAQ) (Bermond et al., 1994; Vorst and Bermond, 2001). These traits have been proposed to be essential for affect regulation (Bagby and Taylor, 1997). The BVAQ consists of five subscales:

Emotionalizing: the degree to which someone is emotionally aroused by emotion inducing events. *Fantasizing*: the degree to which someone is inclined to fantasize, imagine, daydream etc. *Identifying*: the degree to which one is able to define one's arousal states. *Analyzing*: the degree to which one seeks out explanations of one's own emotional reactions. *Verbalizing*: the degree to which one is able or inclined to describe or communicate about one's own emotional reactions (cf. Vorst and Bermond, 2001).

Each of the subscales consists of eight items. Answers are scored on a 5-point scale (1= certainly does not apply to me, up to 5= certainly applies to me). High scores are an indication for problems in affect regulation.

Objective measures of emotional information processing.

Affective priming task

All words were selected from Hermans and de Houwer (1994, appendix A). The fifteen words with the highest mean evaluation on affectivity served as positive targets and

primes. The fifteen words with the lowest mean evaluation served as negative targets and primes. Forty-five non-words only served as targets and were letter strings that were pronounceable legally. The Stimulus Onset Asynchrony (SOA) was 250 ms. Priming will rely more on automatic processing when short SOAs are used rather than longer SOAs, which have been associated with more controlled processing (Rossell et al., 2001). Participants had to decide as quickly as possible if a word presented on a computer screen was a real word or a non-word (i.e., lexical decision). Subjects responded by pressing 'N' for a non-word and 'M' for a real word on a keyboard.

Emotional counting Stroop task

This task was adapted from Whalen et al. (1998), and is intended to measure attentional biases (as indexed by increased reaction times) for emotional words. Participants had to decide by button press how many words were presented on a screen. The number of words varied from 1 to 4 and the presentation of these numbers of words was balanced over the conditions. When more than one word was presented, the other words were repetitions of the first word. There were 5 categories of words: neutral; fearful; negative; positive and obsessive-compulsive disorder-related words (Whalen et al., 1998). Word groups did not differ significantly on word length ($F(1,4)=0.414$, $p=0.798$) and word frequency ($F(1,3)=0.138$, $p=0.937$). Each condition consisted of fifteen trials, resulting in a total of 75 trials. Participants were instructed to decide as quickly as possible, and to try to make no mistakes. Subjects pressed 'N' in the case of 1 or 3 words (odd) and 'M' when 2 or 4 words (even) had been presented on the screen.

Emotional chimeric faces task

In this task participants viewed 48 happy-sad chimeric face drawings (David, 1989). These schematic face drawings had a happy expression on the left half and a sad expression on the right half. There were 12 original drawings and 12 mirror images of the original drawings, and both were shown twice. Participants had to tell immediately when they saw the picture whether the face looked sad or happy. Afterwards, they were asked how they felt on a scale ranging from 0 (very sad) to 100 (very happy) and these subjective scores are so-called 'mood ratings'. This task has been shown to reflect the use of the right hemisphere for visuospatial processing and for emotion processing. Healthy subjects show a left perceptual bias when they have to make a judgment of emotion. David and Cutting (1990) reported that schizophrenic patients display a reduction of this bias.

Degraded facial affect recognition task

This task is a measure of facial affect recognition of degraded faces. Photographs of four different actors, two male and two female were used. 64 trials were presented, consisting of 16 face presentations in each of four conditions: angry, happy, fearful and neutral. The photographs of the faces were passed through a filter that reduced visual contrast by 30%. This procedure was adopted in order to increase the difficulty of the task and to enhance the contribution of perceptual expectancies and interpretation. Subjects were asked to indicate the expression of each face with button press (F1 to F4) and were asked to respond as accurately as possible.

Results

Statistical analyses were performed using Statistical Package for the Social Sciences 11.5 (SPSS, 2002). The SPQ and the emotion processing measures for the high and low LSHS groups were compared by analysis of variance (ANOVA). Furthermore, correlations were computed between SPQ scores and objective emotional processing tasks. Alpha was set at 0.05. On request the authors can provide tables with means and SDs for all parameters of each measure.

Group comparisons

Schizotypal Personality Questionnaire

High and low LSHS groups differed significantly on the positive schizotypy dimension as well as the disorganization dimension (both $p<0.001$). When subscales were compared separately, significant differences were observed on, unusual perceptual experiences, magical ideation, delusional atmosphere, referential thinking, odd speech, and odd or eccentric behavior. In which the high LSHS group had higher scores than the low LSHS group (Table 1).

Alexithymia Questionnaire

There was a significant difference between the two groups on the dimensions of 'fantasizing' and 'emotionalizing' of the Alexithymia Questionnaire. The high LSHS group had lower ratings on these dimensions than the low LSHS group ($p<0.05$), which is indicative of higher levels of fantasizing and emotionalizing (Table 2).

Table 1. Means, SDs and ANOVA results of the three-dimensional SPQ model according to Vollema et al. (2002) for both high and low LSHS group.

SPQ-scores	High LSHS	Low LSHS	F(1,38)	P
Positive schizotypy	14.4 (6.83)	6 (4.94)	19.85	<0.0001*
Magical ideation	3.45 (2.52)	1.05 (1.32)	14.22	0.001*
Unusual perceptual experiences	4.25 (2.86)	0.7 (2.09)	20.47	<0.0001*
Delusional atmosphere	1.8 (1.11)	0.9 (0.97)	4.51	0.009*
Referential thinking	3.1 (1.41)	2 (1.75)	4.80	0.035*
Suspiciousness	1.8 (1.88)	1.35 (1.63)	0.65	0.424
Disorganization	8.25 (4.0)	3.6 (3.5)	15.31	<0.0001*
Odd speech	6.20 (3.11)	3.05 (2.98)	10.71	0.002*
Odd or eccentric behavior	2.05 (1.57)	0.55 (1.05)	12.59	0.001*
Negative schizotypy	9.7 (4.3)	7.6 (5.9)	1.65	0.207
Social anxiety	2.55 (1.93)	1.9 (1.83)	1.19	0.282
Referential thinking	3.1 (1.41)	2 (1.75)	4.80	0.035*
No close friends	1.40 (1.23)	1.35 (1.73)	0.01	0.917
Constricted affect	0.85 (0.99)	1 (1.17)	0.19	0.664
Suspiciousness	1.8 (1.88)	1.35 (1.63)	0.65	0.424

*Significant at a $p<0.05$ levels

Table 2. Bermond-Vorst Alexithymia total score and sub-scores for the high and low LSHS group and statistics.

Alexithymia	High LSHS	Low LSHS	F(1,38)	P
Verbalizing	19.35/ 8.52	20.45/ 5.96	0.224	0.639
Fantasizing	14.1/ 5.45	23.9/ 8.69	18.251	<.0001*
Identifying	19/ 5.18	15.7/ 5.55	3.782	0.059
Emotionalizing	17.05/ 5.05	20.55/ 5.13	4.722	0.036*
Analyzing	14.95/ 5.70	16.35/ 5.67	0.607	0.441

*Significant at a $p<0.05$ levels.

Affective priming task

Repeated-measures ANOVA did not reveal significant differences between the groups for affective priming, when the reaction times for the conditions with a positive prime and a positive target were compared to conditions with a neutral prime and a neutral target, F(1,

38)=0.32, p=0.58, nor when conditions with a negative prime and a negative target were compared to conditions with a neutral prime and a neutral target, F(1, 38)=3.12, p=0.09. However, when the conditions with a positive prime and a neutral target were compared to conditions with a neutral prime and a neutral target, a significant Group×Task interaction was observed, F(1, 38)=6.60, p=0.01. The same difference was observed for the negative-neutral versus neutral-neutral comparison, F(1, 38)=5.67, p=0.02. Mean reaction time on the neutral-neutral condition was 757 ms. (SD=110) for the high LSHS group and 782 ms. (SD=232) for the low LSHS group. On average there was a 99 ms. reduction in the low LSHS group due to emotional primes, whereas in the high LSHS groups an increase of 23 ms. was found. This indicates that there was no priming in the high LSHS group.

Emotional counting Stroop task

Analysis revealed no significant differences between high and low LSHS groups on Stroop reaction time for the different word groups.

Chimeric faces task

Due to practical reasons we included fifteen subjects in the high LSHS group and twenty subjects the low LSHS group. Both groups showed the typical left-field bias that has been reported for subjects from the normal population, F(1, 13)=7.75, p=0.02, and F(1, 18)=4.91, p=0.04, for the high and low LSHS groups respectively. There were no significant differences in bias between the high and low LSHS groups. The results remained not significant after compensating for mood ratings, F(1, 32)=2.31, p=0.14. The effect of mood on hemifield bias was significant, F(1, 32)=7.13, p=0.01.

Degraded facial affect recognition task

ANOVA showed no significant differences the number of mistakes made for the two groups.

Correlations between SPQ and emotion measures

Alexithymia questionnaire

Non-parametric Spearman correlation coefficients were computed between the SPQ and BVAQ across the whole sample (N=40). Higher ratings on the positive schizotypy and disorganization dimension correlated with fewer problems on fantasizing (r=-0.41, p=0.009 and r=-0.337, p=0.033 respectively). Additionally, higher ratings on all SPQ dimensions correlated with more problems in identifying emotions, r=0.46, p=0.003 for

the positive dimension; r=0.339, p=0.032 for the disorganization dimension; r=0.404, p=0.01 for the negative dimension.

Regarding the different SPQ subscales, higher ratings on magical ideation, unusual perceptual experiences and odd or eccentric behavior correlated with fewer problems in fantasizing (r=-0.35, r=-0.49, and r=-0.38, respectively, all ps <0.05). Magical ideation also correlated with fewer problems in emotionalizing, r=-0.38, p=0.02. On the other hand, unusual perceptual experiences correlated with more problems in identifying emotions (r=0.48, p=0.002), which was also true for the dimensions delusional atmosphere (r=0.34, p=0.03), odd or eccentric behavior (r=0.40, p=0.01), and no close friends (r=0.41, p=0.009). In addition, the subscale constricted affect correlated with more problems on verbalizing (r=0.66, p=0.001), emotionalizing (r=0.35, p=0.03), and analyzing (r=0.37, p=0.02),).

Affective priming task

There were no associations between affective priming parameters and schizotypy subscales.

Emotional counting Stroop task

The SPQ subscale suspiciousness correlated negatively with reaction times for negative words (r=-0.40, p=0.011), fearful words (r=-0.33, p=0.039), and obsessive-compulsive disorder-related words (r=-0.41, p=0.009). The subscale no close friends correlated positively with reaction times for positive words, r=0.34, p=0.03.

Chimeric faces task

The SPQ subscale delusional atmosphere correlated significantly with a left perceptual bias, r=0.39, p=0.02. The correlation for the dimension of positive schizotypy with left perceptual bias approached significance, r=0.32, p=0.06. Furthermore, there was a significant negative correlation between the SPQ subscale social anxiety and mood rating, r=-0.48, p=0.003.

Degraded facial affect recognition task

The positive schizotypy subscale correlated significantly with errors in classifying angry faces as happy, r=0.53, p=0.0005. Of the subscales, unusual perceptual experiences correlated significantly with erroneously classifying happy faces as angry (r=0.66, p=0.0005), and with erroneously classifying happy faces as fearful (r=0.37, p=0.018). All other correlations were not significant.

Discussion

This study examined the relationship between psychosis-proneness and subjective and objective emotional information processing measures in a non-clinical sample. We observed significantly lower ratings on the 'emotionalizing' and 'fantasizing' subscales of the alexithymia questionnaire in psychosis-prone subjects. This is indicative of an increased sensitivity for emotional arousal in positive schizotypy. An increase in subjective emotional arousal in relation to hallucinations and delusions is compatible with reports by Freeman et al. (2001) and Delespaul et al. (2002), who found associations between distress and anxiety levels and hallucinations. Indeed, Delespaul et al. (2002) reported that subjective anxiety levels rose before the onset of actual hallucinations and are the strongest predictor of hallucination intensity. Moreover, using direct measures of autonomic arousal, higher skin-conductance responsivity to emotional stimuli in schizophrenia patients has been reported (Kring and Neale, 1996). Our findings of both increased sensitivity for emotional affect and increased levels of fantasizing in hallucination-prone subjects are comparable to findings from Larøi et al. (submitted) where both neuroticism and openness to experience were found to be associated with hallucinations in non-clinical subjects. We did not observe lower levels of identifying and verbalizing one's own emotions in the psychosis-prone group. Although these deficits have been associated with schizophrenia, apparently they are not related to hallucination-proneness per se. Such emotional deficits might possibly be more related to other positive or negative symptoms (Schneider et al., 1995; Cedro et al., 2001). Thus, an important finding of the present study is that emotional processing abnormalities associated with positive and negative symptoms are not correlated in psychosis-prone subjects from the general population, although they tend to occur together in schizophrenia.

Regarding behavioral emotion processing tasks, no differences between the high and low LSHS groups were observed, with the exception of the affective word-priming task. Although priming with congruent prime-target pairs (e.g. negative-negative as compared to neutral-neutral) was identical in the two groups, the high LSHS group was negatively primed by emotional words when a neutral target followed either a positive or a negative prime. Therefore, positive schizotypy seems to be associated with difficulties in the activation of an unrelated semantic network after activation of emotional nodes, possibly due to a preoccupation with emotional material. Using a similar lexical decision paradigm, Rossell et al. (2000) demonstrated an inhibition of priming for negatively valenced words in schizophrenic, deluded patients. They suggested that a preoccupation with negative emotional material could be associated with the inhibition of normal semantic associations.

However, our finding was not in line with our initial hypothesis that expected an attentional bias for negative valenced material, i.e. only priming in the congruent or incongruent negative prime conditions. This might be due to the difference in content of the hallucinations experienced by hallucination-prone people and schizophrenic patients. The content of hallucinations experienced by schizophrenic patients is often hostile (Nayani and David, 1996) and might result in a preoccupation with negative valenced information. On the other hand, hallucinations experienced by persons from the normal population are rarely experienced as negative or hostile (Barrett and Caylor, 1998). Mikhailova et al. (1996) found that people with schizotypal personality disorder show poorer recognition of both sad and happy expressions. Moreover, Green et al. (2001) suggested that delusion-prone individuals are delayed when processing angry faces in an affective decision task as a result of a threat-related bias, which captures the attention of delusion-prone subjects and result in longer reaction times.

Psychosis-prone persons as measured with the LSHS differed significantly from non hallucination-prone subjects on the SPQ dimension 'positive schizotypy' and 'disorganization', but not on 'negative schizotypy'. More specifically, hallucination-prone subjects also differed on all other subscales of the positive dimension of the SPQ, with the exception of suspiciousness. This suggests that hallucination-prone subjects from the normal population may also show other psychotic-like phenomena related to schizophrenia, such as magical ideation, delusions and referential thinking. Thus, our results are an extension of Levine et al. (2004) who demonstrated an association between hallucination-proneness and a general vulnerability for psychosis on the Chapman scales Magical Ideation and Perceptual Aberration.

With regard to subjective emotional processing our results indicate that all schizotypy dimensions correlated positively with 'identifying' one's own feelings. This suggests that a higher degree of schizotypal signs might result in more problems in the identification of one's own emotions, which is in line with Cedro et al. (2001). In addition, associations between the SPQ and behavioral emotion processing measures were observed in the emotional counting Stroop task, chimeric faces task and degraded facial affect recognition task. In the Stroop task the subscale suspiciousness correlated negatively with negative valenced words. It might be that persons with a higher score on suspiciousness have a higher sensitivity to threat-related stimuli (Green and Phillips, 2004).

Furthermore, correlations between positive subscales of the SPQ and the chimeric faces task suggested an increased left perceptual bias in subjects with high ratings for positive schizotypy. Although this is contrary to the finding in patients with schizophrenia, who show a reduced left perceptual bias (David and Cutting, 1990), our finding is in accordance with Luh and Gooding (1999) who reported an increased left

perceptual bias in non-clinical subjects selected for positive schizotypy, whereas a reduced left perceptual bias was observed in subjects selected for negative schizotypy.

A limitation of our study is the use of healthy university students. On average, students function at a high level (Chapman et al., 1994) what may account for the absence in differences on the emotion processing tasks between the two groups. Since the tasks used in the present study partially depend on general level of cognitive functioning. Additionally, we suggest that schizotypal individuals with high intellectual capacity might cope better with the problems associated with schizotypy. Romme et al. (1992) reported that hallucinating subjects who could cope with their voices were less often in psychiatric care.

In addition, emotional abnormalities could contribute highly to the severity gradient along the continuum of psychotic experiences from the normal population to patients with schizophrenia and are therefore not expected to be found in non-clinical populations. For example, Honig et al. (1998) reported differences between nonpatient voice-hearers and schizophrenic patients in content, emotional quality and locus of control of the voices. Patients experienced more negative voices, were more afraid of the voices and patients had less control over their voices.

In conclusion, psychosis-proneness is associated with increased self-reported tendency for emotional arousal and increased fantasy-proneness. However, non-clinical hallucination-prone subjects do not show the same pattern of emotional processing deficits as patients with schizophrenia. This conclusion extends findings reported by Cadenhead et al. (1996), who failed to find deficits that were identical or similar to information processing abnormalities characteristic of schizophrenia, e.g. concerning prepulse inhibition, in hallucination-prone subjects from the normal population. On the other hand, we observed some interesting associations between schizotypal traits as measured by the SPQ and alexithymia traits on one hand, and between SPQ subscales and emotional processing biases on the other hand.

Consequently, our findings lend only partial support to the hypothesis of continuity between symptoms characteristic of schizophrenia and psychosis-related phenomena in the normal population. An alternative model concerns the hypothesis of a continuum-threshold, as described by Johns and van Os (2001). They suggested that people develop a full-blown psychosis only when above a certain threshold. As Johns and van Os (2001) illustrated, schizotypal signs might behave like blood pressure in which normal variation exists and is not symptomatic. However, above a certain threshold blood pressure becomes dangerous for other organs. Thus, above critical value schizotypal traits themselves or accumulating independent risk factors might lead to a need for care. According to the diathesis-stress models of schizophrenia stress is such a mediating factor

(Walker and Diforio, 1997). Future research should focus on emotional processing in non-clinical samples that are more closely related to the schizophrenia genotype, e.g. relatives of schizophrenia patients, which will shed more light on the genetic liability for emotional processing impairments associated with schizophrenia.

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Chapter 8

Social judgment of faces in patients with schizophrenia and healthy relatives: behavioral evidence of social brain dysfunction

Daan Baas, Mascha van 't Wout, André Aleman, René S. Kahn. Social judgment of faces in patients with schizophrenia and healthy relatives: behavioral evidence of social brain dysfunction.

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Abstract

To test whether patients with schizophrenia and unaffected first-degree relatives of schizophrenia patients display behavioral signs of social brain dysfunction, in particular the amygdala. Eighteen patients with schizophrenia, twenty-four first-degree unaffected relatives, i.e. siblings and twenty-eight healthy comparison subjects completed a task to assess trustworthiness judgments of faces. A second task was included to control for the general ability to recognize faces. Patients with schizophrenia made more positive trustworthiness judgments of faces, specifically for those that were judged as untrustworthy by healthy comparison subjects. Siblings of schizophrenia patients display the same bias, albeit to a lesser degree. Patients and siblings did not differ from controls in their ability to recognize faces in general. The pattern of more positive trustworthiness judgments parallels the results of studies that involved patients with amygdala dysfunction. Patients with schizophrenia and siblings of schizophrenia patients display an abnormal pattern in social judgment of faces, which is consistent with dysfunction of the social brain, in particular the amygdala.

Introduction

Impaired social information processing is a stable feature in schizophrenia and numerous studies of patients with schizophrenia have reported specific abnormalities in the ability to interpret the beliefs and intentions of others in order to explain and predict their behavior (Pinkham et al., 2003). Others have found impairments in the ability to identify facial and prosodic emotion (Edwards et al., 2001; Pinkham et al., 2003). Because patients with schizophrenia often display poor social skills and frequently misinterpret social cues, their impaired social cognition could cause social isolation, making it one of the most disabling clinical features of the disease (A.P.A., 1994).

Evaluating trustworthiness on the basis of facial appearance of others is an important aspect of social cognition and the ability to adequately process facial appearances is related to better social function in schizophrenia (Hooker and Park, 2002; Pollice et al., 2002). Previous research indicates that both cortical and subcortical brain areas are involved in the processing of social information which underlies trustworthiness judgments (Adolphs et al., 1998). Several lines of evidence suggest an important role for the amygdala in the processing of social information. Firstly, a neuropsychological study of people with bilateral amygdala lesions demonstrated impairments in the ability to make judgments of trustworthiness, i.e. these patients judged faces to be more trustworthy (Adolphs et al., 1998). Additionally, a recent functional neuroimaging study by Winston et al. (2002) reports bilateral engagement of the amygdala and right insula in response to faces that were rated as untrustworthy. In addition, during the explicit judgment of trustworthiness the right superior temporal sulcus (STS) was also activated. Recently, there is a growing body of studies that report dysfunction of the social brain, including the amygdala, insula, cingulate cortex and STS in patients with schizophrenia. Furthermore, supportive evidence for amygdala dysfunction comes from studies that demonstrated hypofunction of the amygdala in response to processing of social-emotional cues, i.e. facial affect in schizophrenia (Schneider et al., 1998; Gur et al., 2002b; Hempel et al., 2003). Moreover, a number of functional studies demonstrated that populations which are at high risk for developing schizophrenia spectrum disorders are characterized by abnormal amygdala activity (see van Rijn et al., 2005 for a review).

Although the precise etiology of schizophrenia is not completely understood, compelling evidence from family, twin and adoption studies suggests that hereditary factors play an important role in its pathogenesis (McGuffin et al., 1995). In combination with environmental factors, a high genetic risk for schizophrenia may variably manifest itself in a schizophrenia "spectrum" phenotype that can range from mild schizotypal traits to severe schizophrenia (Johns and van Os, 2001). This schizophrenia spectrum phenotype suggests that deficits cardinal of schizophrenia could also be observed in

biological first-degree relatives of patients. Indeed, with respect to social information processing previous research demonstrated that relatives of patients with schizophrenia show subtle deficits in aspects of social cognition (Toomey et al., 1999; Loughland et al., 2004). Investigating social information processing in relatives of patients with schizophrenia is a valuable strategy for two reasons. First, high-risk individuals are not clinically psychotic and have not been treated by antipsychotic medication for this. In this regard, the investigation of social processing in high-risk individuals enables the study of deficits related to schizophrenia without confounding influences. In that way, results could validate the observed results in patients. Second, if social-processing deficits are observed in high-risk individuals these disturbances reflect at least in part a vulnerability to schizophrenia.

In this study we used a task that requires subjects to make trustworthiness judgments about faces with a neutral emotional expression to measure social information processing capabilities. The explicit trustworthiness judgments made by patients with schizophrenia and healthy first-degree relatives of schizophrenia patients were compared to those of healthy matched controls. Because trustworthiness judgments require processing of subtle emotional cues and thus place relatively high demands on social information processing, a trustworthiness judgment task is sensitive to subtle differences in social information processing (Adolphs, 2002). We hypothesized that patients with schizophrenia and siblings of patients with schizophrenia would give untrustworthy faces higher trustworthiness ratings than healthy controls would, similar to patients with amygdala lesions (Adolphs et al., 1998).

Methods

Participants

18 Patients with schizophrenia (10 men and 8 women; mean age 30.3, SD=9.1), 24 healthy siblings of patients with schizophrenia (8 men and 16 women; mean age 33.8, SD=9.9) and 28 healthy control subjects (14 men, 14 women; mean age 33.4, SD=8.5) participated in the study. The groups were tested for significant differences in age, sex and intellectual ability (See Results). Intellectual ability was measured with a combination of the Raven Advanced Progressive Matrices test of nonverbal reasoning (Raven et al., 1993; Lezak, 1995) and the Dutch translation of the National Adult Reading Test, NART (Nelson and Willison, 1991), which provides an estimate of performance and verbal intelligence respectively.

We established the presence of psychopathology in patients using the Comprehensive Assessment of Symptoms and History, CASH (Andreasen et al., 1992)

that was administered by a psychiatrist. All patients fulfilled DSM-IV criteria for schizophrenia as measured with the CASH, were clinically stable and received antipsychotic medication. 13 Patients were taking clozapine (mean dose 290 mg/day), two patients were taking olanzapine (mean dose 17.5 mg/day), one patient was taking quetapine (400 mg/day), another was taking risperidone (1 mg/day) and one patient was taking pimozide (4 mg/day). Symptoms were rated independently by two trained raters with the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987). Mean score on positive symptoms was 10.3 (SD 3.2, range 7-18), mean score on negative symptoms was 13.1 (SD 3.8, range 8-21) and mean score on general psychopathology was 22.9 (SD 4.2, range 17-33). Duration of illness was 9.9 (SD 10.3, range 1- 38) and mean age of onset of psychotic symptoms was 22.5 (SD 5.5, range 17- 39).

The absence of psychopathology in healthy siblings and control subjects was confirmed with the Mini International Neuropsychiatric Interview, MINI (Sheehan et al., 1997). The present study was carried out in accordance with the latest version of the Declaration of Helsinki and the study design was reviewed and approved by the local ethics committee. Informed written consent was obtained from all participants after the nature of the procedure had been fully explained.

Trustworthiness evaluation

During an adapted version of a self-paced computerized task (Winston et al., 2002), subjects viewed 120 grayscale frontal photographic images of emotionally neutral faces and made trustworthiness judgments about each individual face on a scale that ranged from 1 (highly untrustworthy), 4 (neutral), to 7 (highly trustworthy). The images were selected from a larger set of images on the basis of trustworthiness and emotional valence ratings given by 36 healthy subjects in a separate pilot study (9 men, 27 women; mean age 21.6, SD=3.3). The images used in the present study cover the full range of trustworthiness ratings. Because a strong correlation was found between perceived trustworthiness and facial expressions of anger and happiness in a previous study (Winston et al., 2002), we selected images that were given low 'anger' and ' happiness' ratings by subjects in our pilot study. Of the images used in the present study, 75 were from the set that Adolphs et al. used in their study of social cognition in patients with bilateral amygdala damage (Adolphs et al., 1998), these images were supplemented with 45 images from the psychological image collection of the psychology department of Stirling University (PICS). We supplemented the original set of images that was used by Adophs et al. (1998) with additional images, because the current set of images is also intended for use in an event-related fMRI study in which many repetitions are needed. Following the trustworthiness judgment task, patients and controls performed the Benton general face

recognition task (Benton et al., 1983), which was included to control for possible abnormalities in the general ability to recognize faces among patients.

Statistical analyses

An Analysis of Variance (ANOVA) with mean Trustworthiness rating as dependent factor and Group (patients, relatives, and controls) as independent factor, followed by appropriate post-hoc univariate tests, was used to test for differences between groups. Following Adolphs et al. (2001), we subsequently divided the set of face-stimuli into a set with the 60 least trustworthy and a set with the 60 most trustworthy faces, according to the trustworthiness ratings of the healthy controls during a second analysis. We then compared mean trustworthiness judgments given by patients, relatives and controls for these groups of stimuli using ANOVAs.

Results

The experimental groups did not differ with regard to possible confounding factors like sex (non-parametric Chi square = 2.36, $p = 0.31$), age ($F(2,67) = 0.87$, $p = 0.42$), or general intellectual ability ($F(2,67) = 2.31$, $p = 0.11$). See Table 1 for estimated intelligence scores.

We found a main effect of experimental group on trustworthiness ratings ($F(2,67) = 3.49$, $p = 0.036$, see Table 1), with trustworthiness ratings of patients ($F(1,44) = 7.89$, $p = 0.007$, see Table 1); and siblings ($F(1,50) = 4.31$, $p = 0.043$, see Table 1) being significantly higher than the ratings of healthy controls. There was no significant difference between patients and controls with regard to their performance on the Benton face-recognition task ($F(1,37) = 0.95$, $p = 0.34$), indicating that patients were generally able to recognize faces. Our second analysis revealed that the trustworthiness ratings of patients differed from those of control subjects mainly when they concerned the least trustworthy faces ($F(1,44) = 8.73$, $p = 0.005$, see Figure 1), but to a lesser extent when they concerned the most trustworthy faces ($F(1,44) = 3.66$, $p = 0.062$). The difference between judgments of controls and siblings shows a similar pattern: there is a stronger trend when their judgments concerned the least trustworthy faces ($F(1,50) = 3.29$, $p = 0.076$) then when they concerned the most trustworthy faces ($F(1,50) = 2.66$, $p = 0.109$).

Table 1. Characteristics of the sample, ratings of trustworthiness of faces and estimated intelligence test scores.

	Schizophrenia patients (N=18)	Siblings (N=24)	Control subjects (N=28)
Trustworthiness ratings	4.4 (0.49), 3.6-5.4	4.3 (0.57), 3.8-5.9	4.0 (0.31), 3.4-4.6
Least trustworthy	4.0 (0.52), 3.2-5.2	3.8 (0.73), 3.1-5.9	3.5 (0.42), 2.6-4.4
Most trustworthy	4.8 (0.57), 4.0-5.6	4.7 (0.63), 3.3-6.3	4.5 (0.34), 4.0-5.5
NART	105 (13.31)	105.8 (5.59)	106.8 (9.83)
Raven	97.7 (15.71)	109.5 (9.68)	106.6 (13.65)

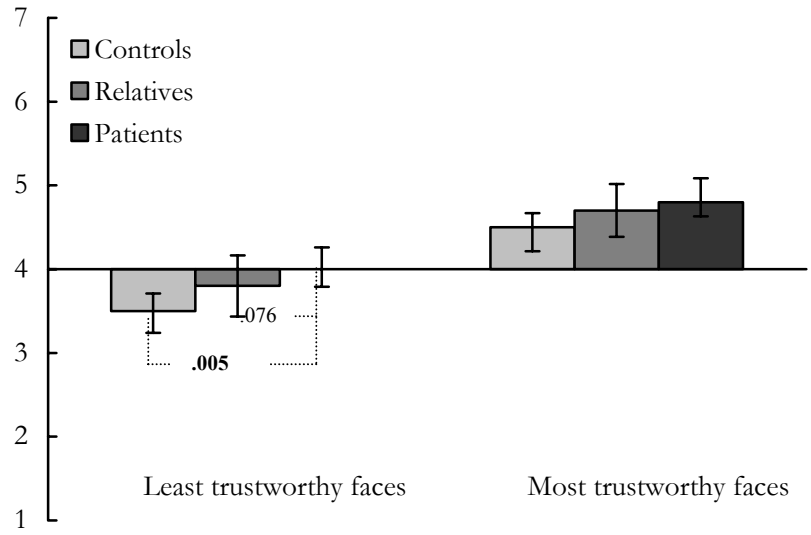

Figure 1. Mean Ratings of trustworthiness of faces (1 = 'highly untrustworthy', 4 is 'neutral', 7 = 'highly trustworthy'). The two bars on the left represent the 60 faces that controls judged to be the least trustworthy. The bars on the right represent the 60 faces that controls judged to be the most trustworthy.

Discussion

The aim of this study was to investigate whether social information processing is affected in patients with schizophrenia and siblings of patients with schizophrenia. To measure social information processing capabilities we used a paradigm that requires subjects to make trustworthiness evaluations about unfamiliar faces with neutral expressions. The main result was that patients with schizophrenia and siblings judge unfamiliar faces to be more trustworthy than healthy control subjects do. It is important to note that these differences in trustworthiness ratings cannot simply be explained by general face recognition, as the patients and siblings did not differ from the control subjects in this regard. Since we found the same pattern of results in the siblings that participated in the study, even though they did not use medication, the findings are not very likely to be attributable to their medication or other confounding variables associated with illness, i.e. schizophrenia. Moreover, these findings suggest that abnormal trustworthiness evaluation at least in part reflect vulnerability for schizophrenia.

As was stated above, we suspect that the abnormalities in social information processing that were found in the present study are the result of abnormal amygdala functionality, a notion that is supported by compelling evidence from previous research. For example, the positive bias in trustworthiness judgments is identical to that reported in patients with bilateral amygdala lesions, albeit with a smaller magnitude (Adolphs et al., 1998). Furthermore, comparable abnormalities in trustworthiness judgments have been demonstrated in autistic subjects (Adolphs et al., 2001), a group in which structural grey matter abnormalities of the amygdala have been reported (Abell et al., 1999). Moreover, our findings are consistent with numerous reports of amygdala volume reduction in schizophrenia patients (Wright et al., 2000; Hulshoff Pol et al., 2001) and populations at risk of developing schizophrenia (Keshavan et al., 1997; Seidman et al., 1997; van Rijn et al., 2005). Furthermore, supportive evidence for amygdala dysfunction comes from studies that demonstrated hypofunction of the amygdala in response to processing of social-emotional cues, i.e. facial affect in schizophrenia (Schneider et al., 1998; Gur et al., 2002b; Hempel et al., 2003).

Also consistent with the findings of Adolphs et al. (2001) was that the difference between trustworthiness judgments of schizophrenic patients and relatives and those of healthy controls was most pronounced when the judgments concerned the least trustworthy faces; a result that provides additional support for the notion that the amygdala, which is part of a fear-danger recognition circuit (LeDoux, 2000), is compromised in patients with schizophrenia. The present findings are in agreement with recent functional neuroimaging research of medicated and unmedicated schizophrenia patients that found reduced activation of the amygdala during evaluation of emotional

stimuli (Williams et al., 2004; Aleman and Kahn, 2005). However, besides the role of the amygdala in the automatic evaluation of trustworthiness, the explicit evaluation of trustworthiness was also related to activation of the superior temporal sulcus (STS) (Winston et al., 2002). In this study we investigated the explicit trustworthiness evaluation of faces. Hence, the present findings might also reflect STS dysfunction in patients with schizophrenia. Indeed, STS dysfunction has been observed in patients with schizophrenia and also in high schizophrenia spectrum groups (Fletcher et al., 1999; Rajarethinam et al., 2000; Shenton et al., 2001; Shen et al., 2004).

Obviously, inaccurate complex social judgments of constructs like trustworthiness can have far-reaching consequences for social functioning. Although no study has yet investigated the functional consequences of impaired trustworthiness evaluation, there is supportive evidence that demonstrate a relationship between social cognition and social functioning (Ihnen et al., 1998; Hooker and Park, 2002; Roncone et al., 2002; Brune, 2005). It is important to point out that besides the perception of subtle social cues, amygdala damage may also influence the display of subtle social cues, as evidenced in a study of amygdala-lesioned rhesus monkeys, who appeared less threatening and more approachable to conspecifics (Emery et al., 2001). Indeed, abnormal trust towards persons judged untrustworthy by healthy people, which we found in the present study, might contribute to the higher rates of victimization (involving financial, psychological or physical abuse) that have been observed in patients with schizophrenia (Brekke et al., 2001).

It is important to note that the presently included patient sample is high functioning and shows low levels of psychopathology. Hence, abnormal trustworthiness evaluation might be more severe in more typical groups of schizophrenia patients characterized by more severe psychopathology. In addition, the present study only investigated the trustworthiness evaluation of neutral faces. However, it would have been interesting to investigate whether this is a specific deficit for trust evaluation or evaluative judgments in general by including age or gender evaluation of faces. Future research should elucidate this possibility.

To conclude, our results show that patients with schizophrenia and siblings of patients with schizophrenia on average judged untrustworthy faces to be more trustworthy then controls did. This suggests that abnormal trustworthiness evaluation is not due to confounding variables associated with schizophrenia, i.e. medication use and hospitalization. Moreover, these findings suggest that abnormal trustworthiness evaluation at least in part reflect vulnerability for schizophrenia. The observed pattern of higher trustworthiness evaluation in patients and siblings is consistent with observations using the same task in patients with amygdala lesions and in autistic subjects. Together with

problems in affect recognition, problems with evaluating trustworthiness could be an important factor that leads to problems in social behavior and possibly, victimization of schizophrenia patients.

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Chapter 9

Insensitivity for social cues in schizophrenia patients, relatives of schizophrenia patients and Klinefelter men (47, XXY)

Mascha van 't Wout, Sophie van Rijn, Tjeerd Jellema, René S. Kahn, André Aleman. Insensitivity for social cues in schizophrenia patients, relatives of schizophrenia patients and Klinefelter men (47, XXY).

Manuscript in preparation.

Abstract

Schizophrenia is characterized by disturbances in social functioning. Central to social functioning is the adequate processing of social cues, such as gaze direction and human biological motion. In the present study we used a new visual illusion measuring the extent in which social cues are processed effortlessly and implicitly in different groups with high schizophrenia spectrum vulnerability, i.e. 28 patients with schizophrenia, 29 siblings of patients with schizophrenia and 29 individuals with Klinefelter syndrome (47,XXY). These groups were compared to 46 matched healthy control subjects. Results indicated that, in contrast to control subjects, patients with schizophrenia showed insensitivity to social cues. This was particularly pronounced in patients with negative symptoms. The reduced influence of social cues was also observed in first-degree relatives of patients with schizophrenia as well as in Klinefelter subjects. We suggest that the insensitivity for social cues is a cognitive aspect of schizophrenia that also appears to be present in people high on schizophrenia spectrum vulnerability. Possibly, these social cue-processing deficits could contribute to impairments in social skills in schizophrenia.

Introduction

The genetic contribution to schizophrenia has been recognized since years (Hirsch and Weinberger, 2003). Whereas schizophrenia affects about 1% of the general population the incidence of developing schizophrenia is up to ten times higher for first-degree relatives of patients with schizophrenia (Gottesman, 1991). In contrast, most people with this genetic vulnerability do not develop schizophrenia. The search for aspects that are apparent in schizophrenia and also observed in individuals at risk for schizophrenia can provide more specific insights into the vulnerability and genetic underpinnings of schizophrenia (Gottesman and Gould, 2003).

One of the cardinal dysfunctions associated with the schizophrenia phenotype concerns disturbances in social functioning (DSM-IV American Psychiatric Association, 1994). Although some researchers have argued that this might be a consequence of severe psychopathology, others demonstrated that social dysfunction is relatively independent of symptomatology (Lenzenweger and Dworkin, 1996). This view is further supported by findings that disturbances in social functioning are already present in early adolescence and often precede the onset of psychosis (Hans et al., 1992; Walker, 1994; Baum and Walker, 1995). An important underlying characteristic of successful social interaction is the ability to quickly process social information (Frith and Frith, 1999). In the last decade, there is a growing body of research demonstrating deficits in the processing of social information in schizophrenia (Pinkham et al., 2003). More specifically, schizophrenia is associated with difficulties in emotion recognition (Edwards et al., 2002; Kohler and Brennan, 2004) and the inability to understand and manipulate other people's behavior in terms of their mental states, also called Theory of Mind (Frith, 1992). Furthermore, schizophrenia patients have difficulties in the recognition of abstract social cues, such as inferences regarding actors' affect and goals (Corrigan and Green, 1993). These deficits seem to be independent of intelligence, i.e. not attributable to a generalized performance deficit (Corrigan, 1994), but are related to negative symptom such as withdrawal (Corrigan et al., 1994) and skills to receive, process, and send social signs (Corrigan and Toomey, 1995). Furthermore, abnormalities in the processing of social-emotional cues have also been observed in relatives of patients with schizophrenia (Toomey et al., 1999; Loughland et al., 2004) and have been associated with higher schizotypy (van 't Wout et al., 2004).

Underlying the ability to recognize social cues is the ability to effortlessly process a number of basic, social cues, such as the other's gaze direction, head orientation and body postures (Jellema and Perrett, 2005). These cues can give clues about someone's intentions, goals and believes (Perrett, 1999). Usually, these basic social cues are practically automatically processed, which is necesarry to continuously infer the meaning of the rapidly changing social signals. Moreover, it is suggested that the ability to process these

social cues automatically is a prerequisite for establishing succesful social relationships (Frith and Frith, 1999), although studies that address the ability to process these simple social cues in schizophrenia are lacking.

In this study we use a new paradigm involving a bias in the judgment of the distance between two agents induced by the automatic processing of social cues conveyed by these agents (Jellema et al., 2004). The social cues consist of the direction of attention and implied goal-directed actions. Typically, these social cues induce the sensation of people (dis-)engaging in social interaction when their gaze or body postures are attended towards (or away from) each other. Therefore, the social cues of gaze direction and implied biological motion used in the present paradigm will result in people judging the persons as closer together compared to reference objects whilst this is not the case objectively.

In addition, we tested two groups high on schizophrenia spectrum vulnerability, siblings of patients and Klinefelter men (47, XXY chromosomal pattern). Siblings of patients have been shown to be at significantly higher risk for the development of schizophrenia (Gottesman, 1991). In addition, Klinefelter syndrome a well-defined genetically syndrome characterized by an extra X-chromosome in males is associated with schizophrenia spectrum vulnerability (van Rijn et al., in press-a) and disturbances in processing social information (van Rijn et al., in press-b). Inclusion of these populations enables the study of deficits related to a genetic vulnerability to schizophrenia without confounding environmental influences as hospitalization, medication and psychopathology. An additional advantage arising from including Klinefelter men regards the precise genetic etiology of this syndrome, in contrast to what is known of the genetic pathology in schizophrenia. This might shed more light on the involvement of the X-chromosome in social cue processing (cf. Skuse et al., 2005).

The aim of the present study was to investigate whether people who share schizophrenia spectrum vulnerability are less sensitive to social cues. To this end we used a social distance judgment task that included two social cues, social attention (gaze direction) and implied biological motion (Jellema et al., 2004). It was hypothesized that patients with schizophrenia would demonstrate difficulties in the automatic processing of social cues compared to control participants, i.e. patients may show no response bias congruent with the direction of the social cues. Furthermore, the relationship between symptomatology and social cue processing is investigated. We predicted that the problems in social cue processing would be especially prevalent in patients with negative symptoms, since patients with negative symptoms are characterized by social-emotional disturbances.

We hypothesized that siblings of patients with schizophrenia as well as Klinefelter men would show a comparable pattern as patients, although to a lesser extent. This would

indicate that deficient processing of social cues form part of the genetic vulnerability to the disease, rather than environmental factors such as medication and potential toxic effects of psychosis and could give more insight in the involvement of the X-chromosome in social processing.

Methods

Participants

33 Patients (23 men, 10 women) with a diagnosis of schizophrenia were recruited at the University Medical Center Utrecht. All patients met the DSM-IV criteria for schizophrenia, as confirmed by the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) administered by a psychiatrist. Patients were also screened for affective disorders, i.e. depression and mania, substance-related disorders by the CASH. Most patients were diagnoses with paranoid schizophrenia (n=22), one with disorganized type, one with residual type, six with undifferentiated type and three with schizophreniform disorder. Most patients were clinically stable and in residual state and four patients were inpatients and 29 were outpatients. Patients were all clinically stable, 31 patients received medication (30 patients only antipsychotics, such as leponex (n=13), quetiapine (n=4), olanzapine (n=6), risperidone (n=8) and one patient also received oxazepam). Symptoms and severity were independently rated by two raters with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Raters were trained by a qualified trainer and followed interrater reliability training every six months. Mean positive symptoms was 14.22 (SD 5.22, range 7-27), negative symptoms 14.84 (SD 5.78, range 7-29) and general psychopathology 26.66 (SD 6.84, range 17-47). Most patients were in remission, residual state and were outpatients (29 outpatients and 4 inpatients). Mean duration of illness was 9.44 years (SD 8.01) and mean age of onset was 23.83 years (SD 5.45).

32 Siblings of patients with schizophrenia (12 men, 20 women) were recruited through advertisements at the Ypsilon website, which is a website dedicated to relatives of patients with schizophrenia. The diagnosis of schizophrenia for the affected sibling was confirmed with a CASH interview (Andreasen et al., 1992). However, due to ethical reasons we were unable to verify the diagnosis of schizophrenia for 12 affected siblings with the CASH interview.

32 Men with Klinefelter syndrome (47,XXY) were studied. The participants were recruited from the Dutch Klinefelter Association, and were not selected for psychological, behavioral or cognitive abnormalities. Diagnosis of Klinefelter syndrome was confirmed by karyotyping, using standard procedures. 50 Non-psychiatric control participants (31

men, 19 women) were drawn from the general population via advertisements in local newspapers.

Inclusion criteria for all participants were age between 18 and 65 years and good physical health. Exclusion criteria were neurological conditions, history of head injury with loss of consciousness, recent history of alcohol and substance abuse, or mental retardation. None of the control participants and siblings had a history of psychiatric illness or use of psychiatric medication confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998). The local ethics committee approved the study and all subjects provided written informed consent after the procedure had been fully explained, according to Declaration of Helsinki. The Dutch translation of the National Adult Reading Test (NART) (Schmand et al., 1991) and Raven's Advanced Progressive Matrices (Raven et al., 1993) were used to match the groups on estimates of verbal and performance intelligence level, respectively (Lezak, 1995).

Social Distance Judgment Task

The Social Distance Judgment Task measures the illusion of de- or increasing distance caused by the automatic processing of social cues (Jellema et al., 2004). It is hypothesized that the perceived distance between the agents will be influenced by the social cues conveyed by the agents, resulting in a response bias paralleling the strength of social cues. Stimuli were pairs of two cartoon figures shown in running postures conveying two different social cues: gaze direction (figures looking away or towards each other) and biological motion (figures running away or towards each other). Head and body of the cartoon figures were pointing in the same direction, or in opposite directions, amounting to a total of four different compositions of cartoon figures, see Figure 1.

A pair of cartoon figures was presented for 3 s, after which a mask of 1 s was shown, followed by a pair of geometrical figures (see Figure 2 for an example of a trial). Except for the catch trials, the distance between the geometrical figures was always the same as the distance between the cartoon figures and three different distances were randomly presented: 2, 3 and 4 cm. In the catch trials the distance between the geometrical figures was different (2 cm) from the distance between the cartoon figures. The catch-trials were used to allow exclusion of those participants from analysis who did not pay proper attention to the task. Participants who made more than two errors in the catch-trials were excluded from the analyses. Participants had to choose one of two possible responses: (1) 'I think the two cartoon figures were closer together than the two geometrical objects', and (2) 'I think the two cartoon figures were further apart than the two geometrical objects'.

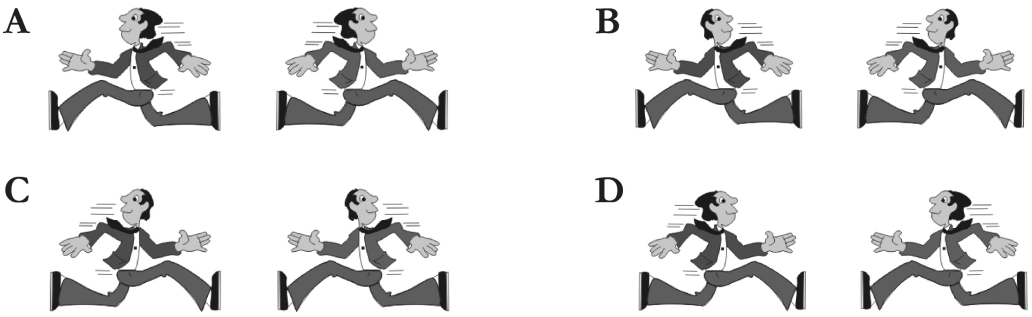

Figure 1. From A to D: increasing strength of social cues leading to underestimation of the distance between the cartoon figures, i.e. the response: 'I think the two cartoon figures were closer together than the two geometrical objects'.

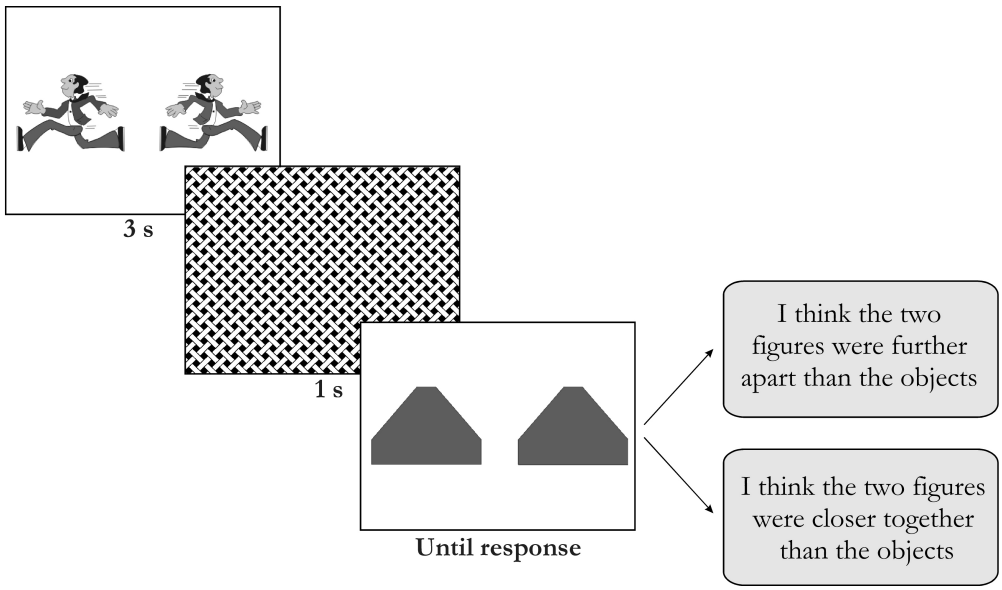

Figure 2. Example of a single trial.

Results

As only males are affected with Klinefelter syndrome, two separate analyses were performed. One for schizophrenia patients and relatives, including both males and females, and one for Klinefelter men, including XXY men and male controls. 5 Patients

with schizophrenia, 3 siblings, 3 Klinefelter men and 4 control participants made more than two errors in the catch-trials and were not included in further analysis.

Social Distance Judgment Task

28 Patients with schizophrenia, 29 siblings of patients with schizophrenia and 46 control participants were included in the analyses, see Table 1 for demographic data. In the control group, a GLM repeated measures test of within subject contrasts with increasing social cue strength as within subjects variable (with 4 strength levels) revealed a significant linear increase in percentage of response 1 ('I think the two figures are closer together than the two geometrical figures'), $F(1,45)=14.27$, $p=0.0005$.

In contrast, percentage response 1 did not change with increasing social cue strength in the patient group, $F(1,27)=0.34$, $p=0.56$. Remarkably, absence of a response bias was also found in the sibling group , $F(1,28)=0.77$, $p=0.39$.

Over the three groups, the sensitivity for social cues differed significantly between patients with schizophrenia, siblings and control subjects, revealed by different patterns of percentage response 1 with increasing strength of social cues, $F(2,100)= 3.79$, $p=0.026$ (Figure 3). Although, the control group differed significanlty from the patient group in senstivity for social cues ($F(1,72)=8.06$, $p=0.006$), the sibling group did not differ from the control group ($F(1,73)=2.21$, $p=0.14$), nor from the patient group ($F(1,55)=1.09$, $p=0.30$). This suggests that performance in patients and to a certain extent also in siblings, was not influenced by automatic social interpretation of the social cues.

Table 1. Demographic data of 28 patients with schizophrenia, 29 siblings of patients with schizophrenia and 46 healthy control participants included in the Social Distance Judgment Task.

Variable	Patients	Siblings	Control subjects	P
Age in years (SD)	32.43 (7.51)	34.62 (10.72)	31.89 (9.19)	0.45
Male:female ratio	18:10	11:18	27:20	0.11
Education in years (SD)	14.29 (2.80)	16.21 (1.93)	14.89 (2.58)	0.01*
Parental education in years (SD)	13.97 (2.98)	14.67 (2.68)	13.20 (2.89)	0.27
NART (SD)	103.56 (8.16)	104.54 (8.11)	107.63 (9.54)	0.13
Raven's (SD)	Not available	109.21 (9.93)	108.40 (13.75)	0.79

* $P<0.05$, Between-groups comparisons with Student's t-tests, except Male:female ratio is analyzed with non-parametric Kruskal Wallis test, df =100

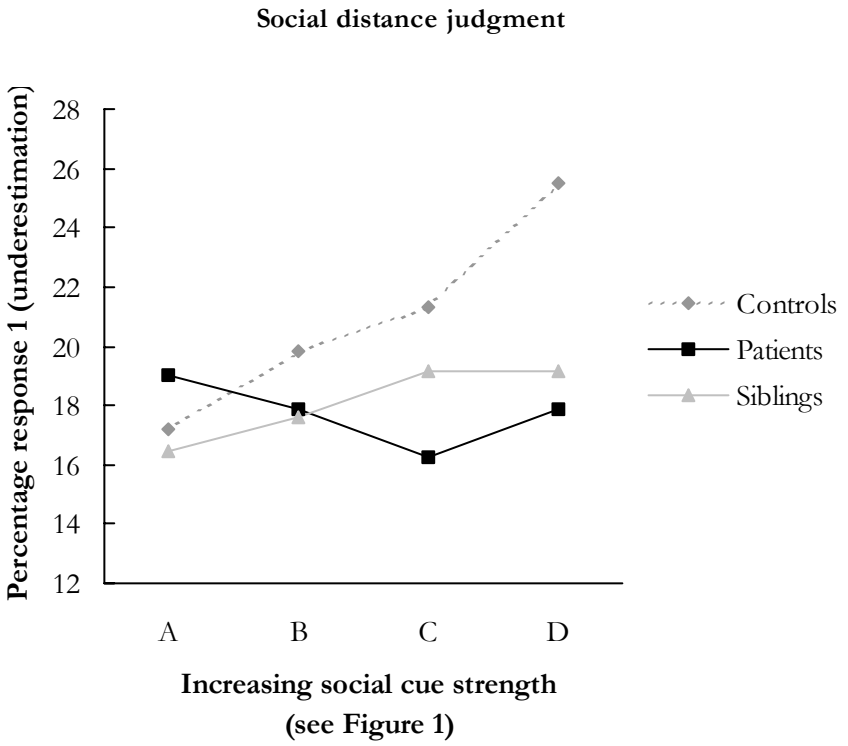

Figure 3. Increasing social cue strength resulted in a linear increase in response 1 ('I think the two cartoon figures were closer together than the two geometrical objects') in healthy control subjects, but not in patients or sibling of patients.

Social distance judgment and symptomatology

There was a significant negative correlation between the response bias due to social cue strength and negative symptoms of schizophrenia as measured with the Positive and Negative Syndrome Scale (PANSS), r=-0.39, p=0.04. This suggests that patients with more negative symptoms are less influenced by social cues. There were no correlations between positive symptoms or general psychopathology as measured with the PANSS and influence of social cues.

Klinefelter men

A group of 29 Klinefelter men was compared to 25 control men, see Table 2 for demographic variables. In the control group, a GLM repeated measures test of within subject contrasts revealed that the social cues did elicit a response bias congruent with the

directions of the social cues. We observed a significant linear increase in underestimations (i.e. increase in percentage response 1) of the perceived distance as strength of the social cues would increase, $F(1,24)=13.54$, $p=0.001$. Sensitivity for social cues differed significantly between the Klinefelter men and controls, as reflected by different patterns of percentage response 1 over the four conditions (group effect in GLM repeated measures of within subject contrasts; $F(1,52)=4.4$, $p=0.04$). Although strength of the social cues increased, percentage response 1 remained at the same level in the Klinefelter group, $F(1,28)=0.001$, $p=0.98$. The absence of a response bias congruent with direction of the social cues indicated that the distance judgment performance in this group was not influenced by social interpretation. Results are presented in Figure 4.

Table 2. Demographic data of 29 Klinefelter men and 25 control men.

Variable	Klinefelter men	Control men	P
Age (in years)	38.07 (8.47)	33.84 (8.90)	0.08
Education (in years)	13.92 (2.65)	14.36 (2.66)	0.56
NART (SD)	102.67 (8.61)	107.20 (10.03)	0.09
Raven's (SD)	107.68 (14.37)	111.71 (9.20)	0.24

P: Between-groups comparisons with Student's t-tests, df =52

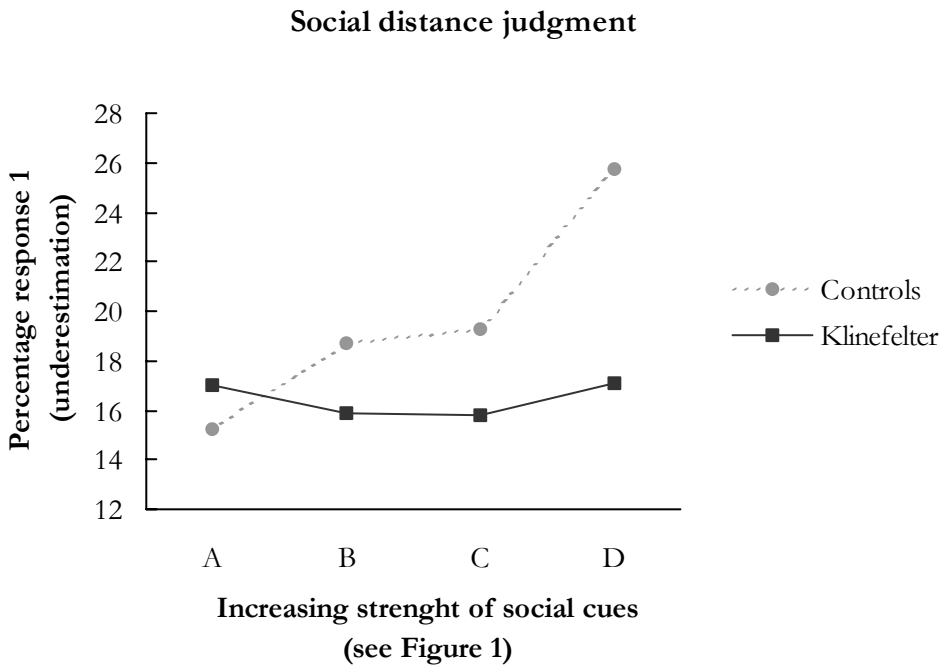

Figure 4. Increasing social cue strength resulted in a linear increase in response 1 ('I think the two cartoon figures were closer together than the two geometrical objects') in healthy control subjects, but not in Klinefelter men.

Discussion

This study allowed the investigation of sensitivity to two simple, basic social cues, i.e. implied biological motion and gaze direction in different groups high on schizophrenia spectrum vulnerability. The main finding was that as strength of the social cues in the stimuli increases, a linear increase in underestimation of the perceived distance was present in healthy controls, but not in schizophrenia patients, siblings of patients and Klinefelter men. This suggests that distance judgment performance in these groups was not influenced by social interpretation. In addition, schizophrenia patients and Klinefelter men showed to be less sensitive to social cues compared to controls. However, the siblings of patients performed between patients and control participants, that is siblings did not differ significantly from either controls or patients.

These results suggest that patients with schizophrenia demonstrated a lack of sensitivity to even basic simple social cues, instead of deficits only in more abstract,

higher-order social cue recognition (Corrigan and Green, 1993). Furthermore, our results showed that especially patients with negative symptoms were insensitive to the influence of the social cues in their judgments. Negative symptoms comprise social and emotional withdrawal and patients with these symptoms typically show problematic social functioning (Dickerson et al., 1996; Van der Does et al., 1996; Dickerson et al., 1999), but also deficits in other social emotional tasks (Schneider et al., 1995; Mandal et al., 1998; Kohler et al., 2000a; Martin et al., 2005). Thus, these results corroborate previous research demonstrating that patients with schizophrenia show deficits in the processing of social information (Pinkham et al., 2003), with more severe impairments in patients with negative symptoms (Corcoran et al., 1995; Mandal et al., 1999; Kohler et al., 2000a; Leitman et al., 2005). However, this study extends previous research in demonstrating deficits in the *effortless* processing of *simple* social cues. The ability to process social cues automatically is important, especially to deduce someone else's intentions, goals and believes (Perrett 1999) and deficits in the automatic processing of these social cue might lead to disturbances in the attribution of mental states to others (Frith and Frith, 1999). Thus, the observed insensitivity to social cues may underly social cognitive deficits, such as Theory of Mind and social dysfunction in schizophrenia. Indeed, a recently published study demonstrates that patients with schizophrenia were impaired in using appropriate language to describe Theory of Mind animations (Russell et al., 2006).

Interestingly, the absence of influence of the social cues on distance judgment extends to individuals high on schizophrenia spectrum vulnerability, i.e. siblings of patients with schizophrenia and Klinefelter men. Based on these findings three important conclusion scan be drawn. First, siblings as well as the Klinefelter men were not clinically psychotic and did not use antipsychotic medication. The lack of sensitivity for social cues could thus not be due to the effects of illness or medication use. In that way, these results validate the observed results in patients. Second, we propose that the observed lack of sensitivity for social cues is related to a genetic vulnerability to schizophrenia. The results showed that there were no differences between patients and siblings in distance judgment, suggesting that siblings resemble patients in an absence of automatic processing of social cues. However, one could also argue that siblings perform normally, as they also did not differ from controls. When taking the between group analysis into account we demonstrated that siblings did not show a linear increase in underestimations, i.e. distance judgment is not influenced by social cues when strength of social cues increase. Thus we interpret our findings in favor of siblings resembling schizophrenia patients albeit to a lesser extent. Moreover, our results mirror and extend previous studies demonstrating impairments in social emotional cue processing in relatives of patients with schizophrenia (Toomey et al., 1999; Loughland et al., 2004), suggesting that insensitivity for social cues

might be regarded as a genetic vulnerability for schizophrenia. Third, additional evidence for a genetic loading on social cue processing comes from the findings in the Klinefelter sample. As this disorder is defined by an X-chromosomal abnormality, impaired cognitive processing of social cues in this group can be regarded as the expression of X-linked genetic pathology. Thus insensitivity to social cues can be regarded as an endophenotype that is shared by schizophrenia patients and Klinefelter men, who are at increased risk for schizophrenia, and this deficit may have a common genetic origin in both syndromes. Furthermore, individuals with autism, who are also characterized by Theory of Mind deficits and social dysfunction, also demonstrate an insensitivity to social cues using this task (Jellema et al., 2004). It has been argued that autism and schizophrenia may have in part a shared genetic origin, possibly on the X-chromosome (van Rijn et al., 2005). Hence, this study gives converging evidence that dysfunction of even basic, typically effortlessly processed social cues forms part of the genetic vulnerability for schizophrenia, in which probably the X-chromosome plays a crucial role.

The neural correlates involved in the processing of biological motion and social attention are the superior temporal gyrus, medial prefrontal cortex and anterior cingulate (Jellema and Perrett, 2005). Both in schizophrenia patients as well as relatives of patients, abnormalities in these regions have been reported (Dolan et al., 1995; Fletcher et al., 1999; Ashton et al., 2000; Rajarethinam et al., 2000; Shenton et al., 2001; Takahashi et al., 2004; Mitelman et al., 2005). Interestingly, structural abnormalities in the anterior cingulate and the superior temporal gyrus have been found in Klinefelter syndrome as well (Shen et al., 2004). Evidence for a role of the X-chromosome in the development of the superior temporal gyrus comes from studies with individuals with X-monosomy, showing that volume of this region is dependent on parental origin of the X-chromosome (Kesler et al., 2003). It is suggested that these neural correlates also underlie Theory of Mind capabilities (Frith and Frith, 1999; Siegal and Varley, 2002). Future studies should relate neural substrates of social cue processing in schizophrenia and relatives together with measures of social functioning. This would elucidate the relationship between the ability to process social cues and social behavior and its underlying brain pathology in schizophrenia and provide more insight into the biological vulnerability to schizophrenia.

In summary, this study allowed the investigation of sensitivity to simple, basic social cues that are usually effortlessly processed, i.e. biological motion and gaze direction in different groups with schizophrenia spectrum vulnerability. Results showed that patients with schizophrenia, sibings of patients with schizophrenia and Klinefelter men (47, XXY) did not process these social cues automatically compared to healthy controls. This was especially the case in patients with more severe negative symptoms, i.e. patients that show additional social emotional disturbances. Hence, social cue processing deficits

seem related to the vulnerability for schizophrenia, instead of illness in general and with a potential involvement of genes on the X-chomosome. These basic social cue processing deficits might underly impairments in other aspects of social cognition and social functioning. Future research should investigate further the relationship between insensitivity to social cues, social functioning and neurobiological substrates in schizophrenia.

Acknowledgements

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Emotions, goal-directed behavior and high-risk for schizophrenia

Chapter 10

Affective state and decision-making in the Ultimatum Game

Mascha van 't Wout, René S. Kahn, Alan G. Sanfey, André Aleman. Affective state and decision-making in the Ultimatum Game.

Experimental Brain Research 2006; 169:564-568.

Abstract

The emerging field of neuroeconomics has provided evidence that emotional as well as cognitive processes may contribute to economic decision-making. Indeed, activation of the anterior insula, a brain area involved in emotional processing, has been shown to predict decision-making in the Ultimatum Game. However, as the insula has also been implicated in other brain functions, converging evidence on the role of emotion in the Ultimatum Game is needed. In the present study, thirty healthy undergraduate students played the Ultimatum Game while their skin conductance responses were measured as an autonomic index of affective state. The results revealed that skin conductance activity was higher for unfair offers and was associated with the rejection of unfair offers in the Ultimatum Game. Interestingly, this pattern was only observed for offers proposed by human conspecifics, but not for offers generated by computers. This provides direct support for economic models that acknowledge the role of emotional brain systems in everyday decision-making.

Introduction

Although traditional economic models typically regard decision-making as a rational, cognitive process, recent approaches incorporate the idea that emotions and their physiological components, bioregulatory signals, may play an important role in decision-making (Bechara et al., 1997; Camerer, 2003). Indeed, in a recent fMRI study, Sanfey et al. (2003) reported that activation of the anterior insula, a brain area implicated in aversive emotions such as disgust (Phillips et al., 1997), was related to performance in a task of decision-making known as the Ultimatum Game. Specifically, activation of the insula was correlated with rejecting unfair financial offers made by other people. The authors suggested that this neural activation reflected negative emotional responses to these unfair offers (Sanfey et al., 2003). However, there has not been a direct test of the hypothesis that a specific measure of emotional arousal is related to decisions in the Ultimatum Game. Therefore, converging evidence on the role of emotion in the Ultimatum Game is needed.

In the Ultimatum Game a sum of money is split between two people, a proposer and a responder. The proposer decides how this money should be split between the two. The responder decides if he or she will either accept or reject this offer. If the responder accepts the offer, the amount of money is split as agreed. However, if the responder rejects it, neither player receives anything. In either event, the game is over. The rational strategy suggested by classical game theory is for the proposer to offer the smallest possible positive share and for the responder to accept in turn. Instead however, proposers tend to offer around 50% of the total, and responders reject about half of offers below 20% of the total (Nowak et al., 2000). Notably, the rejection rates are substantially lower when the proposer is a computer instead of a fellow human being. This suggests that there is something special about an unfair offer from another person (Sanfey et al., 2003).

One possible explanation is that responders experience an unpleasant emotional state in response to these unfair offers and as a consequence 'punish' human proposers by rejecting the offer, thus depriving the proposer of their greater share of the money (Nowak et al., 2000). The present study was designed to test this hypothesis, namely that physiological emotional responses are associated with the receipt and particularly the rejection of unfair offers. To do this, we measured skin conductance activity prior to the decision to accept or reject an offer in the Ultimatum Game. Skin conductance reflects sympathetic tone, and a relationship between changes in phasic response in skin conductance and rejection rates in the Ultimatum Game may well reflect the involvement of the affect arousal system (Bouscein, 1992). Specifically, we hypothesized that higher skin conductance responses would be associated with more rejections for the human

offers in the Ultimatum Game, based on the positive relationship between anterior insula activation and such rejections demonstrated by Sanfey et al. (2003).

Methods

Participants and procedure

Thirty undergraduate students (12 males) participated in the experiment. Mean age was 21.25 years (SD 1.86). The study was conducted in compliance of the Declaration of Helsinki and local ethics committee approval. All participants provided written informed consent after the procedure had been fully explained.

Participants were instructed as to the nature and rules of the Ultimatum Game. Participants acted only in the role of responder in the Ultimatum Game. In the task instructions it was emphasized that the participant's partners in the game would play the game independently of each other, with no collusion. Participants were also told that they would be paid according to their choices in the game.

Participants played 20 rounds, 10 times with a person (a different person in each round) and 10 times with a computer partner, each time dividing 5 euro ($6.50). Of these 20 rounds, the money was fairly split 10 times (2.50 euro to each player) and in another 10 rounds the offer was unfair (in euros: four times 4.50 versus 0.50; four times: 4.00 versus 1.00 and twice 3.50 versus 1.50). The 10 offers from human partners were identical to the 10 offers from the computer. The different offers (fair and unfair from each of human and computer partners) were assigned in a random order. All participants were paid an initial 5 euro for their participation. In addition, participants received 10% of the amount of money that was earned in the Ultimatum Game.

The Ultimatum Game format and description

Participants sat in front of a computer screen, approximately 90 cm away. Each trial started with the presentation of a fixation point. The duration of this fixation point was variable and could be 10, 15, 20 or 25 seconds and was followed by an image display with a picture of the proposer (human face or computer) for 10 seconds. After this, the offer (fair or unfair) was presented for 10 seconds. When a human proposed the offer participants saw: 'Mary gets 4 euro, you get 1 euro' and in a typical computer trial participants saw: 'Computer gets 4 euro, you get 1 euro'. This was followed by a 10 second interval after which participants were able to make their response ('accept' or 'reject') by button press, highlighted on the computer keyboard. After this response, the 10, 15, 20 or 25 second fixation point was presented again. This resulted in a variable intertrial interval of at least 10 seconds. This was chosen to allow skin conductance responses to return to

baseline after gain (acceptance of offer) or no-gain (rejection of offer) and to reduce possible habituation.

Skin conductance recording

All testing was done in a quiet, dimly lit room at the University Medial Center Utrecht on a computer with a 15-in. monitor. While playing the Ultimatum Game, skin conductance level was continuously recorded. Skin conductance was recorded using SC5 24 bit digital skin conductance amplifier applying a constant voltage of 0.5V (Contact Precision Instruments: psychophysiological equipment, London, UK). 8 mm prewired AgAg/Cl electrodes were attached to the medial phalanx surfaces of the middle and index finger of the non-dominant hand. A water-soluble jelly, i.e. KY Jelly (Johnson & Johnson) was used as an electrolyte for conductance. Before starting the Ultimatum Game two minutes of baseline were recorded, followed by two external stimuli, a sigh and handclap, in order to ensure a correct attachment and conductance of the electrodes. Values of skin conductance were transformed to microsiemens values using PSYLAB 7 software for windows (www.psylab.com). Presentation of the offer in the Ultimatum Game and pressing a response key ('reject' or 'accept') was synchronized with the sampling computer. Skin conductance responses occurring 1 to 5 seconds after presentation of the offer were computed. A phasic increase in conductance of more than 0.02 microsiemens was counted as a response. To normalize the data a log transformation was used.

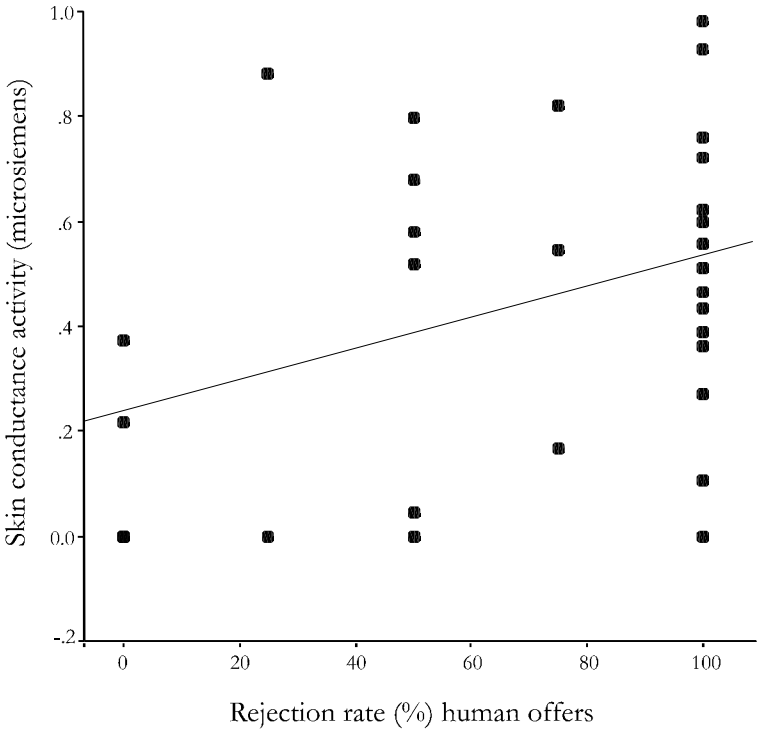
Results

All fair offers were accepted, but this was not the case for unfair offers and acceptance rate decreased as the offers became less fair. Of the unfair offers proposed by humans 56.7% accepted the 3.50:1.50 offer, 41.7% accepted the 4:1 offer and 20.0% accepted the 4.50:0.50 offer. The acceptance rates of the unfair offers proposed by computers were 66.7% for the 3.50:1.50 offer, 53.3% for the 4:1 offer and 38.3% for the 4.50:0.50 offer. Unfair offers proposed by humans were more frequently rejected (60.56%) than unfair offers generated by computers (47.22%), Wilcoxon signed rank test: $t=-2.43$ $df=1$ $p=0.02$ (two-tailed).

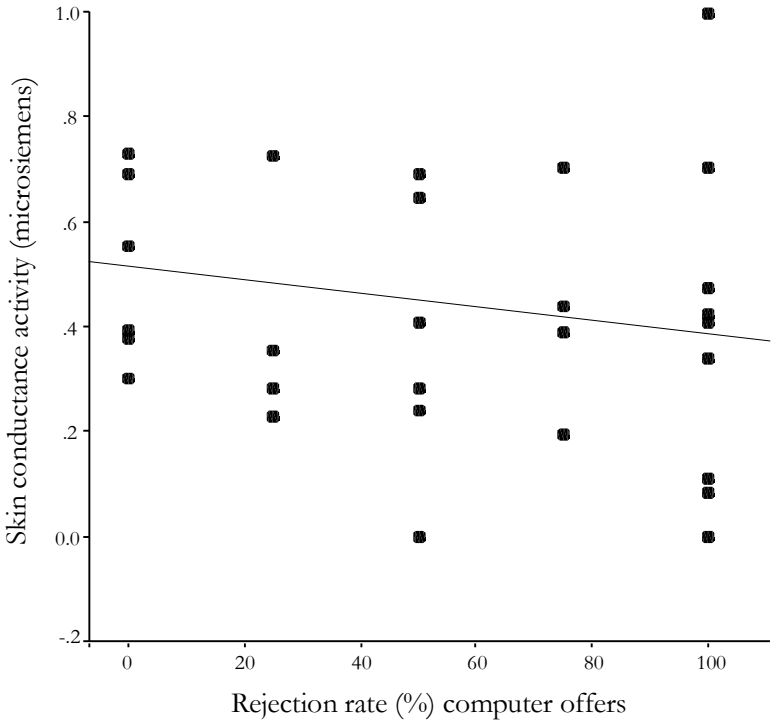
Regarding skin conductance measurements, a repeated measures analysis of skin conductance activity showed an effect of fair versus unfair offers, $F(1,29)=5.08$, $p=0.03$ (two-tailed). This demonstrates that skin conductance responses to unfair offers were significantly higher than responses to fair offers.

To investigate whether emotional arousal would be predictive of decisions made in the Ultimatum Game, we conducted a further analysis. Specifically, we hypothesized

that higher skin conductance responses would be associated with more rejections for the human offers, based on the previously observed positive relationship between anterior insula activation and such rejections (Sanfey et al., 2003). Therefore, following Sanfey et al. (2003), we employed a one-tailed test and focused on the two most unfair offers (4:1 euro; 4.50:0.50 euro). Results showed that skin conductance activity correlated with rejection of unfair offers for human proposers, r=0.35, p=0.03 (see Figure 1A), where higher skin conductance activity was associated with higher rejection rates. This shows that skin conductance activity as a response to the presented offer and prior to the decision is related to the rejection of unfair offers in human proposers. On the contrary, this was not the case for computer proposers, r=-0.18, p=0.17, i.e. rejections of unfair offers proposed by computers were not related to skin conductance activity (see Figure 1B). Figure 2 shows mean skin conductance levels for accepted and rejected offers, across trials.



1A



1B.

Figure 1A. Rejection rates (%) of unfair offers proposed by humans (Beta= 0.35, B=42.39) and Figure 1B Rejection rate (%) of unfair offers proposed by computers (Beta=-0.18, B=-26.03) plotted against skin conductance activity for each participant.

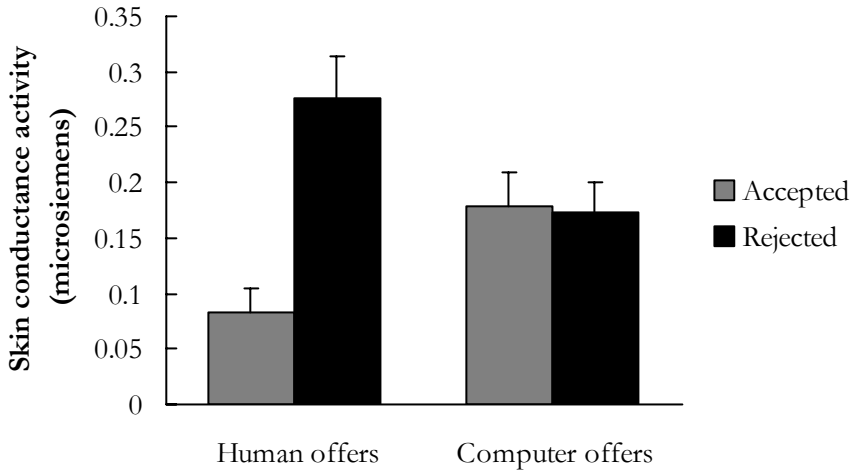


Figure 2. Mean and SE skin conductance activity (in microsiemens) for subsequently accepted and rejected unfair offers.

Discussion

In the present study we investigated whether emotional state, as measured by autonomic reactivity as reflected by skin conductance responses, would be associated with unfair offers and the subsequent rejection of these unfair offers in the Ultimatum Game. Our finding of a significantly higher skin conductance response for unfair offers compared to responses for fair offers, suggests that participants experienced more emotional arousal when confronted with an unfair offer as compared to a fair offer. Moreover, emotional arousal was specifically related to rejections of unfair offers proposed by humans. That is, participants with higher skin conductance activity in response to unfair offers rejected a higher proportion of these offers when they came from human proposers, but not when computer proposers made the offers. This extends earlier findings of a comparable relationship between anterior insula activation and rejection of unfair offers from humans (Sanfey et al., 2003) and research demonstrating a relationship between emotional arousal and advantageous gambling (Bechara et al., 1997).

We replicated the well-documented behavioral pattern of accepting all fair offers and a declining acceptance rate as the offers became progressively less fair (Guth et al., 1982; Bolton and Zwick, 1995; Roth, 1995; Guth et al., 2001; Sanfey et al., 2003). The idea that unfair offers proposed by humans convey more than just inequality is strengthened by

the behavioral observation of overall lower acceptance rates of unfair offers from humans as compared to from computers.

The rejection of unfair offers, and the finding that the most frequent outcome is a fair share, can be explained by social utility theories, that focus on guilt from getting more than others, and envy from getting less, which predicts rejections of low ultimatum offers to reduce envy, and repayment of trust to reduce guilt (Camerer, 2003). Alternative explanations have focused on the human instinct to reciprocate, and the idea that adaptive human behavior emerged from playing repeated "games" in close-knit groups. Hence, "punishing" others for unfair offers in order to keep up social status and reputation will persist even in one-shot games (Nowak et al., 2000). Both of these factors should play a far greater role in unfair offers proposed by humans than proposed by computers.

The results of the present study corroborate and extend earlier research that demonstrated that feelings of anger were a better predictor of rejecting unfair offers than the unfairness of the offer itself (Pillutla and Murnighan, 1996). The importance of emotions in decision-making that includes aspects of uncertainty, has been recognized previously. For instance, patients with damage to important brain regions involved in emotion, the ventromedial prefrontal cortex and amygdala, showed impairments in decision-making (Bechara et al., 1999). Furthermore, skin conductance responses have been shown to be predictive of deciding advantageously on a gambling task (Bechara et al., 1997). This was taken to support the view that nonconscious somatic markers can guide advantageous behavior, consistent with the somatic marker hypothesis (Damasio, 1994), although it has been recently argued that subjects performing the gambling task might have more conscious knowledge than was previously presumed, potentially accounting for the advantageous decisions (Maia and McClelland, 2004). And it is important to note that the results from the Ultimatum Game in the present study do not concern nonconscious somatic markers in the absence of consciously accessible knowledge. In contrast, the Ultimatum Game has no uncertainty, and outcomes of the decision are perfectly predictable even before the decision has been made. Then again, Bechara et al. (2005) have made clear that the somatic marker hypothesis does not address the question of conscious knowledge of the situation, but rather that emotion-related signals guide decision-making. Taking this into account, somatic markers are based on the affective and emotional system and are able to guide actions such as decision-making, independently of conscious knowledge of the decision situation (Bechara et al., 2005), suggesting that the observed relationship between increased skin conductance responses to human offers specifically could be interpreted as a somatic marker. Thus, our findings suggest that emotional state plays a crucial role in such strategic decision-making.

By employing an autonomic measure of emotional arousal we were able to test the hypothesis that affective state influences decision-making in the Ultimatum Game. Our finding of higher skin conductance responses to unfair human offers, which were correlated with subsequent rejections, provides direct empirical support for economic models that acknowledge the role of emotional factors in decision-making behavior (Camerer, 2003; Sanfey et al., 2003). Indeed, the role of emotions in decision-making has been previously acknowledged from studies that demonstrated that patients with ventromedial prefrontal cortex damage not only show deficient decision-making behavior but also deficits in the ability to express and experience emotions, resulting in the somatic marker hypothesis (see Bechara and Damasio, 2005). In addition, the relationship between elevated skin conductance activity and rejections of unfair offers mirrors and extends the relationship between anterior insula activation and rejections of unfair offers reported by Sanfey et al. (2003), using brain imaging. This is consistent with findings reporting that insula activity is related to awareness of bodily processes and affective feeling states (Critchley et al., 2004). On the other hand, the amygdala and ventromedial prefrontal cortex have also been implied to be important structures for emotion (including the physiological component) as well as decision-making (Bechara et al., 1999). We conclude that taking emotions and its neural basis into account will ultimately yield more powerful economic models of strategic decision-making.

Acknowledgements

We would like to thank T. Rietkerk for help with data collection. M. van 't Wout and A. Aleman were supported by a VernieuwingsImpuls grant (no 016.026.027) from the Netherlands Organization for Scientific Research (NWO).

Chapter 11

rTMS over the right dorsolateral prefrontal cortex affects strategic decision making

Mascha van 't Wout, René S. Kahn, Alan G. Sanfey, André Aleman.rTMS over the right dorsolateral prefrontal cortex affects strategic decision making.

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Abstract

Although decision-making is typically seen as a rational process, emotions play a role in tasks that include unfairness. Recently, activation in right dorsolateral prefrontal cortex during offers experienced as unfair in the Ultimatum Game was suggested to subserve goal-maintenance in this task. However, this is restricted to correlational evidence and it remains unclear whether the dorsolateral prefrontal cortex is crucial for strategic decision-making. The present study used repetitive transcranial magnetic stimulation in order to investigate the causal role of the dorsolateral prefrontal cortex in strategic decision-making in the Ultimatum Game. The results showed that repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex resulted in an altered decision-making strategy compared to sham stimulation. We conclude that the dorsolateral prefrontal cortex is causally implicated in strategic decision-making in healthy human study participants.

Introduction

Human economic decision-making is typically seen as a rational, cognitive process. Recent research, however, demonstrates that in strategic decision-making tasks, which include fairness and unfairness, emotional experiences of unfairness may play an important role (Camerer, 2003). One of the games often used to measure strategic decision-making in humans is the Ultimatum Game (Guth et al., 1982). In the Ultimatum Game, a proposer offers a fair or unfair division of a sum of money to a responder. The responder decides to accept or reject this offer, ending the game. If the responder accepts the offer, the amount of money is split as agreed. If the responder rejects it, however, neither player receives anything. As the offers by the proposer are fixed, participants in the role of the responder would be expected to go for the maximum utility (i.e. accepting all offers). This is typically not the case, however, and responders tend to reject unfair offers (Nowak et al., 2000).

The neural basis of performance in the Ultimatum Game was recently studied using functional magnetic resonance imaging (Sanfey et al., 2003). An important brain area activated during unfair offers in the Ultimatum Game was the right dorsolateral prefrontal cortex (DLPFC), which was suggested to subserve cognitive control or goal maintenance in the task (Sanfey et al., 2003). Goal-directed behavior requires information as to whether actions were successful in obtaining outcomes, such as rewards. People with damage to the prefrontal cortex, for instance, are characterized by problems in goaldirected behavior and in decision-making (Bechara et al., 2000). Furthermore, animal studies reported that the DLPFC couples the information of rewards to actions and controls behavior (Wallis and Miller, 2003). Indeed, the DLPFC has been associated with optimizing decision-making in monkeys; that is, the DLPFC may guide behavior on the basis of prior choices and outcomes (Barraclough et al., 2004). Thereby, the DLPFC seems to be a convergence zone for a broad range of information and, consequently, is able to guide behavior.

In the present study, we investigate the previous suggestion that the right DLPFC is involved in goal maintenance in the Ultimatum Game (Sanfey et al., 2003). To investigate a possible causal role of the DLPFC in this regard, we used repetitive transcranial magnetic stimulation (rTMS). rTMS delivers short magnetic pulses that penetrate the skull and disrupt neural processing in a noninvasive, reversible way (Walsh and Pascual-Leone, 2003). We hypothesized that the right DLPFC is crucial for determining the strategy of rejecting unfair offers, and therefore rTMS of the DLPFC will interfere with the chosen strategy, or even shift this strategy towards more acceptance. More specifically, as the normal pattern in the Ultimatum Game is to reject unfair offers, the decision to reject an unfair offer would normally be made faster than the decision to accept the unfair offer. Our hypothesis is that after rTMS of the right DLPFC this normal

pattern is changed. That is, it would take more time to reject an unfair offer and might even result in more acceptances of unfair offers after rTMS.

Methods

Participants

Seven college students (two men, five women) participated in the study (age range: 19–31 years, mean age: 24 years, SD: 4.3 years) and were paid for their participation. All participants were right-handed, except for one who was ambidextrous. Participants were screened for contraindications to TMS, neurological and medical problems. The local ethics committee approved the study (Declaration of Helsinki) and all participants provided written, informed consent after the procedure had been fully explained.

Transcranial magnetic stimulation protocol

Two conditions were contrasted, rTMS versus sham stimulation over the right DLPFC, each followed by one of two parallel versions of the Ultimatum Game. For both the rTMS and sham condition we used a MagStim Rapid magnetic stimulator (MagStim Co., Whitland, Wales) with a figure-of-eight magnetic coil with a diameter of 70 mm for each loop. Sham stimulation was accomplished using a Magstim placebo coil, which has an appearance identical to that of the real coil, and also delivers the characteristic 'click' sound. The order of the conditions, real TMS or sham, and the two Ultimatum Games was alternated over participants. Minimum time interval between TMS and sham was 30 minutes, to prevent carry-over effects (Kosslyn et al., 1999; Oliveri et al., 2004). The right DLPFC site of stimulation was targeted at F4 using the electroencephalogram 10–20 coordination system according to the guidelines of previous studies (Pascual-Leone and Hallett, 1994; Mottaghy et al., 2000; Koch et al., 2005). Participants wore a head-cap during the whole experiment. The coil was placed tangential to the surface of the skull. In the TMS condition, participants were stimulated with 1Hz TMS during 12 min over the DLPFC, marked at the head-cap, at 45% intensity of the apparatus. This slow frequency rTMS block was preceded with a priming block of 5 min with 6Hz at 25% intensity of the apparatus, to prolong and intensify the depressant effect (Iyer et al., 2003). The above-mentioned parameters have been applied in earlier studies of cognitive TMS (Robertson et al., 2003) and have been shown to affect brain metabolism (Mottaghy et al., 2003). All stimulation parameters were in accordance with safety guidelines for rTMS (Wassermann, 1998).

Ultimatum Game

Both parallel versions of the Ultimatum Game consisted of 32 trials, in which participants were subsequently presented with 16 male and 16 female proposers. Participants always played the role of the responder. In both versions of the Ultimatum Game, the money was split eight times according to the ratio 5:5 (fair) and 7:3, 8:2 and 9:1 (unfair). Participants were presented with a picture of their proposer, after which the proposal was presented and participants could respond by button press to accept or reject the offer (see Figure 1). Participants were asked to respond as fast as possible to the offer. The different offers were assigned in a random order. Participants were paid 10% of the total amount that was earned (i.e. accepted offers) in the Ultimatum Game.

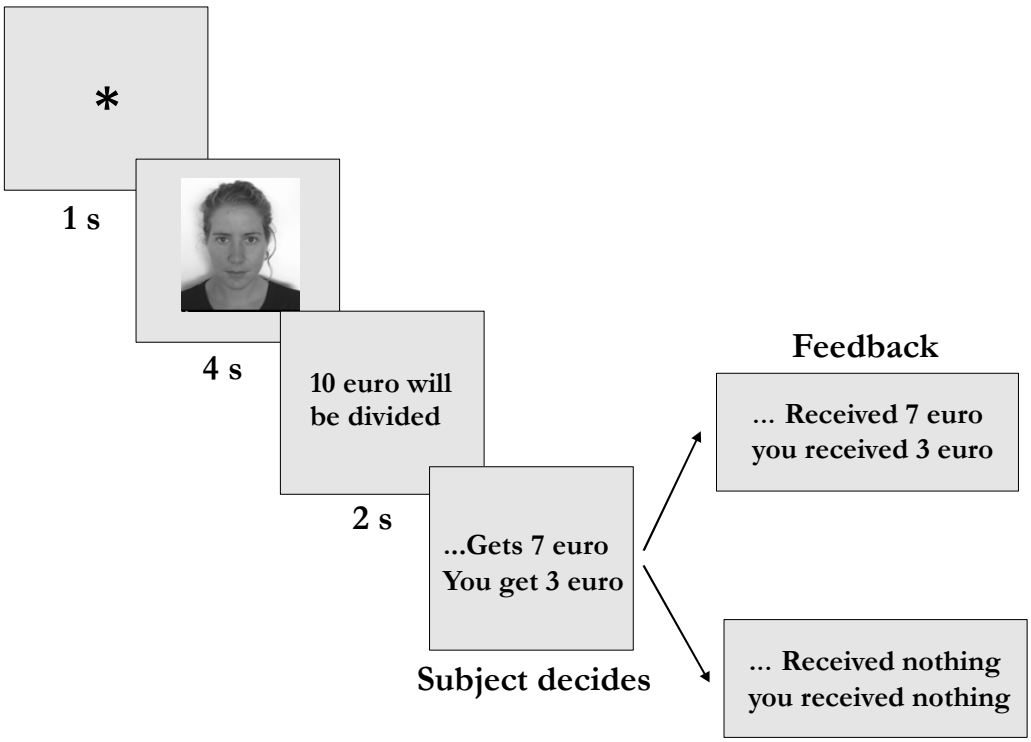

Figure 1. A single round in the Ultimatum Game.

Statistical analyses

Reaction times (ms) and acceptance rates (%) were analyzed across individual trials using multilevel analysis of variance (which takes nonindependence within participants into account), as implemented in SPSS (version 11.5, SPSS Inc., Chicago, Illinois, USA). TMS condition (rTMS or Sham) was included as a fixed effect, whereas participants were

regarded as correlated random effects. Behavioral responses were included as dependent variables. Alpha level was set at 0.05, two tailed.

Results

In the analyses, we focused on the unfair offers, which is where we predicted effects of rTMS over the right DLPFC. With regard to reaction times, there was a significant effect of decision (accept or reject), t=-2.26, P¼=0.03 and of TMS (rTMS versus sham), t=-4.20, P=0.00003. Furthermore, there was a significant interaction between decision and TMS, t=3.28, P=0.001 (see Figure 2). When we included only accepted trials in the analysis, there was no significant effect of rTMS (t=0.62, P=0.54), whereas when only rejected trials were selected, there was a significant effect of rTMS on reaction times (t=-5.61, P<0.0001). Furthermore, there was a trend to accept more offers after rTMS than after sham, t=-1.89, P=0.059.

The behavioral results replicated the characteristic pattern that has been documented for responders in the Ultimatum Game: that is, all fair offers were accepted, whereas half of the unfair offers were rejected. The mean reaction time of decision-making in fair offers was 983.9 ms (SD 553 ms) for TMS and 933.4 ms (SD 352 ms) in the sham condition. The acceptance rates of unfair offers decreased as these offers became less fair. After rTMS 48.2% of unfair offers were accepted and after sham 42.3% of unfair offers were accepted. The mean reaction time of decision-making was 1141.5 ms (SD 535 ms) for TMS and 1036.5 ms (SD 442 ms) in the sham condition.

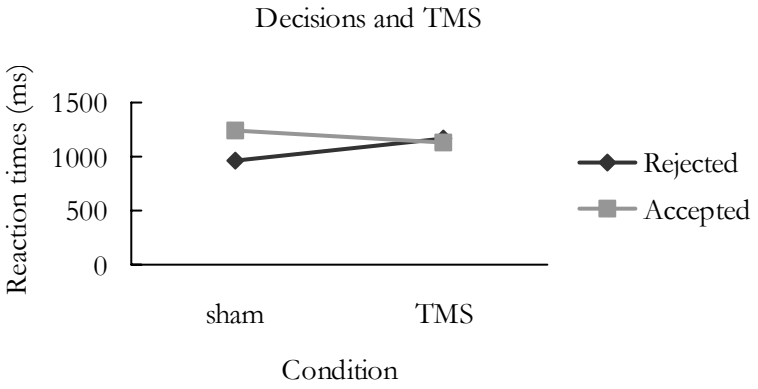

Figure 2. Reaction times for subsequently accepted and rejected unfair offers computed for TMS and Sham condition separately.

Discussion

Using rTMS, we observed a critical involvement of the right DLPFC in strategic decision-making. In the Ultimatum Game, people are confronted with fair and unfair divisions of money and individuals typically adopt a strategy of rejecting very unfair offers even though this reduces their financial earnings. Indeed, our behavioral results showed that all fair offers were accepted, but acceptance rates decreased as offers became less fair, replicating the well documented patterns of acceptance in the Ultimatum Game (Guth, 1982; Bolton and Zwick, 1995; Roth, 1995; Guth et al., 2001; Sanfey et al., 2003). After rTMS over the right DLPFC, however, this pattern was changed, with longer reaction times for rejecting unfair offers, and a trend towards more acceptances of unfair offers.

Given the shorter reaction times and the observation that rejection of very unfair offers is more common than acceptance, rejecting unfair offers might be considered as the 'default' reaction. If the DLPFC guides goal-directed behavior by optimizing decision strategy on the basis of prior choices, neural interference by rTMS must cause behavioral interference with the default strategy; that is, choosing the rejection of unfair offers. This is exactly what we observed, as reaction times for rejection of unfair offers were prolonged after rTMS of the DLPFC. This strongly suggests a causal role for the right DLPFC in strategic decision-making. These findings are an extension of Barraclough et al. (2004), who reported a role of the DLPFC in optimizing decision-making in monkeys. Moreover, Hadland et al. (2001) demonstrated with rTMS that the DLPFC is important in deciding on different responses. In addition, an interference of rTMS over the DLPFC has been observed during decision-making in a spatial working memory task (Koch et al., 2005). Future research should further elaborate on our findings by studying the causal role of the left and right DLPFC in different decision-making paradigms with TMS.

The rejection of such a great proportion of unfair offers (more than 50%) in the Ultimatum Game suggests that motives other than maximizing financial gain play a prominent role. Notably, from a social utility viewpoint, it has been suggested that the rejection of unfair offers might be more optimal than accepting these offers, as rejecting unfair offers may bolster one's position in the social hierarchy. Not receiving a small amount of money may be worth the sacrifice, to punish the persons who proposed the offer (Fehr and Gachter, 2000). This effect also holds in single-shot encounters such as our version of the Ultimatum Game, which suggests that this is a rather intuitive mechanism that is not based on elaborate conscious reflection alone. Indeed, input from emotional systems may be of major importance, as shown by the correlation of insula activation with subsequent rejections in the Ultimatum Game (Sanfey et al., 2003).

Although this study supports the causal role of the right DLPFC in strategic decision-making, a limitation is that TMS was applied to the right hemisphere only. Future studies should incorporate a more complex experimental design including TMS over the right and left hemispheres and the inclusion of different cognitive measures. This design would allow conclusions regarding specificity of the right DLPFC in decision-making and the influence of other functions that are associated with the DLPFC. For instance, the DLPFC is also associated with attention and perception–action integration. We cannot rule out that these processes were affected by rTMS as well. If these processes were affected by rTMS, however, we would expect to find an overall reduction of attention or perception–action integration. In contrast, we observed a specific effect of TMS on decision-making; that is, a slowing of decision-making in reaction to unfair offers but not to fair offers.

A related issue concerns the precision of rTMS and its influence on other brain regions. Although we did not confirm the position of the DLPFC for each participant using magnetic resonance imaging scans and a neuronavigator, our procedure of targeting the F4 position of the 10–20 electroencephalogram coordination system has been frequently used in previous research and has been shown to correspond to the right DLPFC (Pascual-Leone and Hallett, 1994; Mottaghy et al., 2000; Koch et al., 2005). Moreover, the DLPFC is a relatively large area, and as TMS affects approximately 1–2cm in diameter (Walsh and Cowey, 2000) it is safe to assume that the DLPFC was successfully targeted.

A second point refers to the influence of TMS on other brain areas connected to the DLPFC. rTMS over the DLPFC might affect other, connected regions as well, which has also been suggested with regard to the beneficial effects of rTMS over the right DLPFC on depression (Zangen and Hyodo, 2002). Future research should focus on the possible effects of rTMS over the DLPFC on a more widespread network subserving decision-making.

Conclusion

The present findings extend neuroimaging studies of the role of the DLPFC in decision-making. Whereas these studies are based on correlational rather than causal evidence, the present findings of an altered decision-making strategy after rTMS suggest a causal role of the right DLPFC in strategic decision-making.

Acknowledgements

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Chapter 12

Vulnerability for schizophrenia and goal-directed behavior: the Ultimatum Game in relatives of patients with schizophrenia

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Vulnerability for schizophrenia and goal-directed behavior: the Ultimatum Game in relatives of patients with schizophrenia.

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Abstract

Recent theories propose that patients with schizophrenia show an abnormal influence of emotional arousal on cognition due to lesions of the amygdala. Here, we investigate the influence of this dysregulation of emotion on goal-directed behavior, i.e. strategic decision-making in persons with a genetic liability to schizophrenia. 37 Siblings of patients with schizophrenia were compared with 25 matched control participants on the Ultimatum Game, which is a measure of decision-making including emotional aspects such as unfairness. Results showed that siblings of patients with schizophrenia rejected unfair offers more often compared to control participants. We suggest that persons with a genetic liability to schizophrenia are more influenced by their emotions compared to people without this genetic liability and that this heightened influence of emotional arousal is central to schizophrenia.

Introduction

Since the early days of describing and classifying the symptoms of schizophrenia, emotional disturbances, like affective flattening, are regarded as cardinal symptoms (Bleuler, 1911). Indeed, in recent years a growing body of research demonstrated deficits in the processing of emotions (Mandal et al., 1998; Edwards et al., 2002). Although some researchers have argued that these deficits might be secondary consequences of the illness, others suggested that emotional disturbances are central to schizophrenia (Weniger et al., 2004). This latter suggestion is supported by research showing behavioral and functional emotion-processing deficits equivalent to schizophrenia in relatives of patients with schizophrenia, albeit to a lesser extent with respect to severity (Toomey et al., 1999; Staal et al., 2000). Although schizophrenia can be associated with deficits in the perception and expression of emotions, there appears to be a disjunction with normal experience of emotions (Kring and Neale, 1996; Aghevli et al., 2003). The experience of negative emotions might even be higher in patients with schizophrenia (Myin-Germeys et al., 2000), especially before the onset of symptoms, such as hallucinations (Delespaul et al., 2002). This heightened emotional experience has also been demonstrated in psychosis-prone individuals (van 't Wout et al., 2004).

This co-occurrence of deficits in emotion processing and expression in combination with normal or higher emotional experience may sound contradictory. However, a recent neurobiological model of emotional abnormalities in schizophrenia suggests that this pattern can be explained by an anatomical lesion of the basolateral nucleus of the amygdala, resulting in suppressed projections to the prefrontal cortex, giving rise to deficient active processing and expression of emotions. In addition, an imbalance in dopamine systems due to this amygdala lesion will lead to abnormal input to the central nucleus, resulting in aberrant emotional reactivity, arousal (Aleman and Kahn, 2005). On the basis of this model it may be expected that an increase of emotional arousal will override normal goal-directed behavior mediated through the prefrontal cortex. However, investigating this model in schizophrenia patients is difficult due to confounding variables, such as medication use and active symptoms. Hence, investigating healthy first-degree relatives that share a genetic background and do not show severe symptoms or use medication, but appear to demonstrate emotion-processing abnormalities equivalent to schizophrenia is appealing.

A paradigm in which the influence of emotions and goal-directed behavior results in different outcomes is strategic decision-making that includes aspects of unfairness. A well-studied task to measure strategic decision-making is the Ultimatum Game (Guth et al., 1982). In the Ultimatum Game, a sum of money is split between two people, a proposer and a responder. The proposer decides how this money should be split between

the two. The responder decides if he or she will either accept or reject this offer. If the responder accepts the offer, the amount of money is split as agreed. However, if the responder rejects it, neither player receives anything. In either event, the game is over. Thus, accepting all unfair offers by the responder reflects goal-directed behavior, as one will gain as much money as possible. However, emotions appear to have an overriding influence on decision-making in the Ultimatum Game as most unfair offers are rejected (Nowak et al., 2000). Indeed, in a recent study, we showed that emotional arousal, i.e. skin conductance to unfair offers is predictive of rejection these unfair financial offers made by other people (van 't Wout et al., 2006). This is in agreement with an fMRI study demonstrating that activation of the anterior insula, a brain area implicated in aversive emotions such as disgust (Phillips et al., 1997), was related to the rejection of unfair offers proposed by humans (Sanfey et al., 2003). Subsequently accepted unfair offers were associated with higher dorsolateral prefrontal cortex activity, probably reflecting goal-directed behavior, i.e. more cognitive ealuation (Sanfey et al., 2003).

The aim of the present study was to test the hypothesis of the impact of emotions on decision-making in people with a genetic liability to schizophrenia. We investigated siblings of patients with schizophrenia to reduce possible confounding factors like medication and severe symptomatology. We hypothesize that siblings of patients with schizophrenia would show more emotionally driven behavior at the cost of cognitive evaluation in decision-making that includes aspects of unfairness compared to people without the liability for schizophrenia. More specifically, we expected that siblings of patients with schizophrenia reject unfair offers more often than control participants.

Methods

Participants

37 Siblings of patients with schizophrenia and 25 non-psychiatric controls participated in the experiment. Demographic data of the participants are shown in Table 1. Siblings of patients were recruited through advertisements at the Ypsilon website, which is a website dedicated to relatives of patients with schizophrenia and through patients seeking treatment at the University Medical Center Utrecht. The diagnosis of schizophrenia for the affected sibling was confirmed with a CASH interview (Andreasen et al., 1992). However, for ethical reasons we were unable to verify the diagnosis for 12 affected siblings with the CASH interview. Control participants were drawn from the general population via advertisements in local newspapers. Inclusion criteria for all participants were age between 18 and 65 years and good physical health. Exclusion criteria were neurological conditions, history of head injury with loss of consciousness, recent history

of alcohol and substance abuse, or mental retardation. None of the control participants and siblings had a history of psychiatric illness or use of psychiatric medication confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998). The local ethics committee approved the study and all subjects provided written informed consent after the procedure had been fully explained, according to the Declaration of Helsinki.

Table 1. Age, education level (mean and SD) and sex distribution of siblings of patients with schizophrenia and control participants.

	Siblings (N=37)	Controls (N=25)	P
Age (in years)	29.0 (9.1)	31.8 (8.2)	0.31
Sex (male:female)	21:16	20:5	0.06
Education	15.7 (2.3)	14.6 (2.6)	0.08

Ultimatum Game

Participants were instructed as to the nature and rules of the Ultimatum Game. Participants only acted in the role of responder. In the task instructions it was emphasized that the participant's partners in the game played the game independently of each other, with no collusion. Participants were also told that they would be paid according to their choices in the game. Participants played 40 rounds, 20 times with another person and 20 times with the computer, each time dividing 5 euro ($6.50). Of these 40 rounds, the money was fairly split 20 times (2.50 euro to each player) and in another 20 rounds the offer was unfair (in euros: four times 4.50 versus 0.50; four times: 4.00 versus 1.00 and twice 3.50 versus 1.50). In such a way that the 20 offers from human partners were identical to the 20 offers from the computer. The different offers (fair, unfair and human, computer) of partners were assigned in a random order. Participants were presented with a picture of their proposer, after which the proposal was presented and participants could respond by button press to accept or reject the offer. Participants were paid an additional 10% of the total amount of money that was earned (i.e. accepted offers) in the Ultimatum Game.

Results

Fair offers were mostly accepted in both groups (97%), but this was not the case for unfair offers and acceptance rate decreased as the offers became less fair, see Table 2 for acceptance rates of the different unfair offers. There was no difference in acceptance rate between unfair offers proposed by humans and unfair offers generated by computers in

siblings (Wilcoxon signed rank test: Z=-0.69, p=0.49) and control participants (Wilcoxon signed rank test: Z=-1.06, p=0.29). Hence, offers from human proposers and computer proposers are combined in subsequent analyses.

A Mann-Whitney U test with the different offers as variables demonstrated that siblings accepted a comparable amount of fair offers as control participants, offers proposed by humans: Z=-0.21, p=0.84. However, siblings rejected the two most unfair offers more often than control participants, Z=-2.20, p=0.028 for 4:1 offers and Z=-2.24, p=0.025 for 4.50:0.50 offers.

Table 2. Mean acceptance rate (%) and SD in parentheses for the different offers in the sibling group and control group.

Offer	Siblings (N=37)	Control participants (N=25)
Human		
3.50:1.50	28.4 (41.7)	50.0 (45.6)
4:1	20.9 (31.5)	39.0 (40.9)
4.50:0.50	10.1 (20.8)	29.0 (41.3)
Computer		
3.50:1.50	36.5 (43.5)	52.0 (46.7)
4:1	22.9 (33.0)	46.0 (37.9)
4.50:0.50	11.5 (22.5)	33.0 (37.3)

Discussion

This study investigated the influence of emotions in decision-making in persons with a genetic liability to schizophrenia, i.e. siblings of patients with schizophrenia. Our results revealed that siblings rejected unfair offers more often compared to people with no familial history of schizophrenia. This suggests that individuals with genetic vulnerability for schizophrenia rely more on emotional aspects of unfairness associated with these unfair offers in their decisions rather than the cognitive evaluation of the amount of money to gain. The role of emotions in decision-making might be explained by social utility theories that predict the rejection of low ultimatum offers of responders to reduce envy and expect a fair share as most frequent outcome to repay trust and reduce guilt (Camerer, 2003). In addition, other theories focused on the observation that people have the tendency to reciprocate, i.e. to punish other people for unfair offers by rejecting these offers and in that way to keep up social status and reputation (Nowak et al., 2000). From these theories it could be hypothesized that siblings of patients with schizophrenia experience (consciously or not) more emotions or arousal associated with the presentation

of unfair offers and punish selfish proposers more often. At least, these results suggest that siblings of patients are more influenced by emotional arousal on cognitive functioning. This is in agreement with findings from autism, a disorder that is characterized by social deficits reminiscent of those observed in schizophrenia, and decision-making in the Ultimatum Game. More specifically, autistic individuals appeared to use two approaches in the Ultimatum Game: cut the total in half, or keep it all (Sally and Hill, 2006).

The second important conclusion that can be drawn from this study is that the increased influence of emotional aspects on cognitive functioning in schizophrenia cannot be solely attributed to confounding variables, such as active symptomatology, medication use or hospitalization, but probably reflects a core feature of schizophrenia. This suggestion is in line with previous research that showed that emotional, in particular negative information interferes with spatial memory in schizophrenia (van 't Wout et al., in press). In addition, patients with schizophrenia have a tendency to recognize ambiguous stimuli as being harmful or threatening (Phillips et al., 2000) and show greater affective reactivity of speech, which refers to an exacerbation of communication disturbances by stress (Docherty et al., 1998; (Cohen and Docherty, 2004). This increased affective reactivity of speech has also been described in relatives of patient with schizophrenia (Docherty et al., 1998).

This increased influence of emotions on cognitive functions, such as goal-directed behavior, might be due to dysfunction of neural structures that process emotive information, such as the amygdala, the medial prefrontal cortex, the orbitofrontal cortex, the anterior cingulate and the insula (LeDoux, 1996; Davidson and Irwin, 1999; Phan et al., 2002). That these emotion structures play a role in the Ultimatum Game is demonstrated by Sanfey et al. (2003), who showed that activation of the anterior insula was associated with rejecting unfair offers from other people, probably reflecting emotional arousal. In addition, in a previous study we reported that emotional arousal, i.e. skin conductance responses that is mediated through the amygdala (Bouscein, 1992), was in fact related to rejecting unfair offers from human proposers (van 't Wout et al., 2006). There is a growing body of research that demonstrate abnormalities in brain structures important for emotion processing in schizophrenia, especially the amygdala (Phillips et al., 2003b). Specifically, anterior cingulate dysfunction during choice anticipation has been demonstrated in schizophrenia and might explain the myopia for the future in schizophrenia (Quintana et al., 2004), which could result in abnormal decision-making. These brain abnormalities are also observed in biological first-degree relatives of patients with schizophrenia and other high-risk groups for schizophrenia (Seidman et al., 1997; Seidman et al., 1999; Seidman et al., 2002; Seidman et al., 2003; van Rijn et al., 2005).

Future research should elucidate the influence of emotional arousal on decision-making in patients with schizophrenia and relatives of patients or other high-risk groups for schizophrenia using skin conductance or neuroimaging techniques.

This study is a behavioral test of the theoretical models put forward by Grace (2000) and Aleman and Kahn (2005) suggesting that due to a dysfunction of the basolateral amygdala and an imbalance in dopamine systems, aberrant emotional reactivity or arousal will override normal goal-directed behavior in schizophrenia. Normally the nucleus accumbens selects the most effective plan on the basis of past experiences or current context, which is mediated through the hippocampus and amygdala. When confronted with threatening information, the brain has to signal whether this potentially threatening object requires action resulting in an overriding influence of the amygdala on the nucleus accumbens in order to trigger flight behavior. In schizophrenia, hyperactivity of the amygdala might result in excessive priority of processing the affective connotation of a stimulus (amygdala) at the cost of goal-directed behavior (prefrontal cortex) (Grace, 2000; 2003; Aleman and Kahn, 2005), and this might also be rpesent in siblings of patients albeit probably to a lesser extent than in patients.

Taken together, this study clearly demonstrates that siblings of patients with schizophrenia appear to rely more on emotional aspects of unfairness associated with unfair offers in decision-making. This may be explained due to an overriding influence of emotional brain centers (amygdala) over structures important for goal-directed behavior (dorsolateral prefrontal cortex). Moreover, these findings suggest that the increased influence of emotional aspects that influence behavior is present in individuals at risk for schizophrenia and could be interpreted as a cardinal feature of schizophrenia.

Acknowledgements

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Conclusions

Chapter 13

Summary and discussion

This thesis is focused on describing the nature of emotional abnormalities in schizophrenia. Central to this thesis is that not all emotion processes are deficient in schizophrenia, but that specific aspects of emotion processing are disturbed, while other processes are intact. This is contrary to prevalent assumptions that emotion processing in general is diminished in schizophrenia (Leentjens et al., 1998; Grossberg, 2000; Edwards et al., 2001; Kohler et al., 2003; Shayegan and Stahl, 2005), but consistent with other studies that suggest that schizophrenia is associated with a reduced ability to perceive and express emotions, with at the same time intact or even heightened emotional experience (Kring et al., 1993; Kring and Neale, 1996; Myin-Germeys et al., 2000; Aleman and Kahn, 2005). This disjunction between emotional processes in schizophrenia was investigated in more detail in this thesis. Second, this thesis dealt with investigating the presence of emotional abnormalities in individuals high on the schizophrenia spectrum continuum. Emotional abnormalities in people at high-risk for schizophrenia are hypothesized, because emotional abnormalities appear to be a core feature of schizophrenia and would therefore be expected to be present to a certain degree in high-risk individuals. Finally, we investigated the influence of social-emotional aspects on other cognitive functions in patients with schizophrenia and individuals at high-risk for schizophrenia.

The nature of emotion deficits in schizophrenia

On the basis of the findings reported in *chapter 2* we concluded that the automatic allocation of attention towards facial affect appears to be intact in patients with schizophrenia. More specifically, patients with schizophrenia showed normal threat-related interference, which was comparable to the interference in control subjects. In contrast, the controlled processing of facial affect, i.e. the labeling of faces with an emotional expression, was disturbed in schizophrenia compared to control subjects. This deficit in labeling facial affect was most pronounced for the labeling of fearful faces and was related to negative symptoms. This findings confirms that not all emotion processing is impaired in schizophrenia, and supports previous findings that acknowledge spared automatic affect processing in schizophrenia (Rossell, 2004).

The relationship between patient characteristics, such as negative symptoms and facial affect perception as observed in *chapter 2*, was further investigated in *chapter 3*. Here, we replicated our finding that patients with more negative symptoms made more errors in the recognition of fearful faces in a larger sample, which also included chronic patients. Furthermore, we showed that male patients made more errors in recognizing fearful faces. Moreover, we found associations between errors in recognizing neutral faces and subtype of schizophrenia, in that paranoid patients outperformed non-paranoid patients. In addition, patients that were diagnosed at a later age with schizophrenia made more errors

in recognizing neutral faces. It should be noted however, that neutral faces often appear cold (Ekman and Rosenberg, 1997) and thus might have a negative connotation or that neutral faces may be used as a rest category. Interestingly, no other patient characteristics were predictive of facial affect perception, suggesting that positive symptoms are not related to facial affect perception in schizophrenia. Indeed, positive symptoms include hallucinations and delusions, which might be related to abnormalities in the experience of emotions instead of deficits in the perception and expression of emotions. For instance, an increase in the subjective experience of emotions, especially anxiety, seems to precede the onset of hallucinations (Delespaul et al., 2002). The relationship between positive symptoms and increased emotional awareness is further investigated in *chapter 7*. In contrast, negative symptoms refer to problems in the expression of emotions, such as blunted affect and social-emotional withdrawal. Because both aspects require an active emotional response, problems in the expression of emotions could be related to problems in the labeling of emotions. Moreover, these findings may point to a shared neurobiological basis of negative symptoms and social-emotional dysfunction for which males are more vulnerable than females, possibly in prefrontal-limbic circuits (Gur et al., 2004).

In *chapter 4* we investigated the influence of automatic processing of threat-related information on object-location memory in schizophrenia. Results showed that patients with schizophrenia performed worse in relocating objects, independent of overall intellectual ability. This is consistent with evidence showing hippocampal volume reductions in schizophrenia (Lawrie and Abukmeil, 1998; Shenton et al., 2001), as integrity of the hippocampus is crucial for intact object-location memory (Kessels et al., 2001). In addition, patients were particularly worse in the relocation of objects with a symbolic threatening content. Thus, a threatening semantic emotional content of schematic stimuli interferes with spatial memory in schizophrenia, which was absent in control participants. These results suggest that with regard to the interaction between emotion and cognition, schizophrenia can be associated with an increased influence of threatening content on spatial cognition, such as object-location memory. This is in line with studies that demonstrated an increased emotional interference on cognition, such as speech in particular when discussing negative items (Docherty et al., 1998) and attention. We hypothesized that a disproportional influence of the amygdala, which is thought to process threatening information in particular (Morris et al., 1996), on other brain areas might underlie this increased emotional interference.

Emotion processing not only includes the perception and expression or experience of emotions, but also the psychophysiological responses of the body to emotion eliciting stimuli, i.e. emotional arousal (Lang, 1984). In *chapter 5*, emotional

arousal was measured with skin conductance activity in response to affective faces in schizophrenia and control subjects. Results showed attenuated autonomic responses in patients to faces that convey an immediate threat towards the observer, i.e. angry faces and fearful faces, whereas these faces were normally evaluated on subjective valence and arousal. In contrast, autonomic arousal was at normal levels for happy faces and non-emotional, physical stimuli (handclap and sigh). However, happy faces were rated as less positive and more arousing by patients than by control participants. Furthermore, especially patients with more negative symptoms rated happy faces as less positive. Although almost all patients used atypical antipsychotic medication, which is anticholinergic (Mueck-Weymann et al., 2001) the present findings are probably not due to medication effects as we did not find an overall reduction of skin conductance activity but a specific inability to respond to threatening faces. The finding of a specific affective hyporesponsivity to threatening faces does not support previous research that demonstrated higher baseline levels and increased reactivity to affective pictures or faces (Kring and Neale, 1996; Williams et al., 2004). However, recent studies refined these results by demonstrating that increased autonomic reactivity is specifically present in patients with high levels of symptoms (Schell et al., 2005; Zahn and Pickar, 2005). As the amygdala has been implied in the regulation of autonomic emotional reactivity (Bouscein, 1992), our findings are consistent with studies that imply reduced amygdala reactivity in schizophrenia (Gur et al., 2002b; Phillips et al., 2003b; Aleman and Kahn, 2005).

Emotion processing in individuals at high risk for schizophrenia

The investigation of aspects that are characteristic of schizophrenia in individuals at high-risk for schizophrenia (i.e. first degree relatives) is a valuable strategy for two reasons. First, high-risk individuals are not clinically psychotic and have not been treated with antipsychotic medication. In this regard, the investigation of emotion processing in high-risk individuals enables the study of deficits related to the liability for schizophrenia without confounding influences. In that way, results can validate the observed results in patients. Second, if emotion-processing deficits are observed in high-risk individuals it may be inferred that these disturbances may form part of the vulnerability to schizophrenia. On the other hand, one must keep in mind that interpretation of findings in siblings of patients might be difficult as non-psychotic relatives manifest neurocognitive, symptomatic, behavioral and structural brain abnormalities usually to a lesser degree than patients, i.e. somewhere intermediate between patients and control participants (Toomey et al., 1999; Staal et al., 2000).

In *chapter 6* abnormal expression and experience of emotions measured with the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001) were

investigated in patients with schizophrenia, siblings of patients and control subjects. Since the incidence and severity of alexithymia have been observed to be higher in men than in women (Lane et al., 1998; Salminen et al., 1999; Vorst and Bermond, 2001) sex differences were taken into account. Results showed that male patients and male siblings reported difficulties in the verbalizing of feelings compared to control males. Furthermore, male patients had difficulties identifying feelings. However, male patients reported to be more aware of their emotions than control males. In contrast, the female patients, female siblings and female controls did not differ significantly from each other. The pattern of difficulties in verbalizing and identifying emotions, together with *increased* subjective emotional arousal, as observed in male patients has been termed "type II alexithymia" (type I alexithymia would be a general reduction of all aspects of emotion regulation (Bermond, 1995; 1997)) and is highly problematic. On the one hand, one experiences high levels of emotional arousal or distress, but on the other hand one is faced with an inability to verbalize and identify these emotions. It follows hence that one will not know the origin of one's own feelings and will therefore not be able to reduce or regulate those feelings. In addition, patients with more negative symptoms were especially worse in the identification of emotions. The finding of deficits in aspects underlying emotion regulation in siblings could indicate that these deficits observed in schizophrenia are a core deficit in schizophrenia and might reflect vulnerability for schizophrenia for which especially males seem vulnerable. A previous study has shown that male patients are also worse off in facial emotion recognition than female patients (Scholten et al., 2005). Together, these data suggest that male patients with schizophrenia are especially vulnerable to emotional abnormalities, which may explain the worse social functioning and functional outcome in male patients as compared to female patients (Leung and Chue, 2000).

Chapter 7 discussed the question whether abnormalities in emotion processing, including facial affect perception, expression and the experience of emotions are present in individuals at the high end on the psychosis spectrum, in particular persons with a tendency to experience hallucinations. To this end, 20 individuals from the normal student population that scored high on the Launay-Slade Hallucination Scale, LSHS (Launay and Slade, 1981) and 20 individuals that scored low on the LSHS were compared on recognition of facial affect and the ability to expression and experience emotions as measured with the BVAQ (Vorst and Bermond, 2001). Results revealed that psychosis-prone people reported to be more easily aroused by emotion inducing events, which is consistent with findings in patients with schizophrenia reported in *chapter 6*. However, no other emotional abnormalities in emotional expression and emotion perception were observed. This is not in line with findings of emotional abnormalities in other high-risk

groups, such as siblings of patients with schizophrenia who appear to have difficulties in the expression of emotions (*chapter 6*). However, the difference between these two groups is that in *chapter 7* we investigated university students that perform on a high level and generally have higher intellectual abilities than the general population (*chapter 6*). Psychosis-prone individuals with high intellectual capacities might be able to cope better with the problems associated with schizotypal traits. In addition, the psychosis-prone group differs from the investigated sibling sample in that the psychosis-prone group was selected on their high scores on the presence of hallucinations, whereas the siblings were only screened for having a schizophrenia sibling. It may be that the sibling sample also experienced latent negative symptoms, which were apparently not present in the psychosis-prone student sample (see *chapter 6*). Previous studies demonstrated that especially negative symptoms are associated with abnormal emotion processing (see *chapter 2, 3, 8* and Gaebel and Wölwer, 1992; Schneider et al., 1995; Kohler et al., 2000a). However, the difference between siblings and psychosis-prone students might also be a qualitative difference. For instance, Torgerson et al. (2002) suggested that there is a difference of schizotypal traits observed in individuals inside the genetic spectrum of schizophrenia, i.e. relatives of patients, compared to individuals outside the genetic schizophrenia spectrum, i.e. high scoring persons on schizotypy. More specifically, schizotypal persons outside the genetic schizophrenia spectrum show more ideas of reference, suspiciousness, paranoia, social anxiety, self-damaging act, chronic anger, free-floating anxiety and sensitivity to rejection. Individuals within the genetic schizophrenia spectrum in contrast are characterized by inadequate rapport, odd communication, social isolation, delusions and hallucinations.

Finally, the processing of social cues in patients with schizophrenia and individuals high on the schizophrenia spectrum was investigated (*chapter 8* and *9*). More specifically, *chapter 8* describes a study in which the processing of biological-relevant social features, i.e. explicit trustworthiness evaluation of neutral faces, was investigated. Results showed that patients with schizophrenia rated faces as more trustworthy compared to healthy control participants. In addition, there was a trend for siblings of patients to rate faces as more trustworthy than controls, i.e. siblings rated faces intermediate between patients and controls. This evaluation of faces as more trustworthy was most pronounced in faces that were rated as least trustworthy by controls. These data suggest that abnormal evaluation of trustworthiness is not entirely due to confounding variables, such as medication, hospitalization or severe psychopathology. Moreover, these findings suggest that abnormal trustworthiness evaluation at least in part is related to vulnerability for schizophrenia. The observed pattern of higher trustworthiness evaluation in patients with schizophrenia and siblings of patients is consistent with observations using the same task

in patients with amygdala lesions and in autistic persons, a group that is also characterized by social dysfunction.

Underlying the ability to recognize social cues lies the ability to effortlessly process a number of basic, social cues, such as other's gaze direction, head orientation and body postures (Jellema and Perrett, 2005). Usually, these basic social cues are automatically processed, which is necessary to continuously infer the meaning of the rapidly changing social signals. In *chapter 9* the automatic, effortless processing of non-emotional social cues, i.e. gaze direction and implied biological motion was investigated in different groups on the schizophrenia spectrum. This was accomplished by using a novel illusion (Jellema et al., 2004), in which judgment of the distance between two objects is influenced by the fact that these objects are two human figures looking at each other and running towards each other, or, on the contrary, two figures looking away and running away from each other. Normal subjects rate the distance as smaller when the figures look at each other and run towards each other. Results showed that in patients with schizophrenia, siblings of patients with schizophrenia and Klinefelter men (47, XXY chromosomal pattern) this bias was not present. This was especially the case in patients with more severe negative symptoms, i.e. patients that are characterized by additional social emotional disturbances. Thus, not only can schizophrenia be associated with social-emotional processing, but also aspects underlying social cognition (i.e. effortless processing of social cues) seem disturbed in schizophrenia and people high on the schizophrenia spectrum. Moreover, basic social cue processing deficits seem related to the vulnerability for schizophrenia, instead of illness in general and with a potential involvement of genes on the X-chomosome. Because it is suggested that the ability to process these social cues automatically is a prerequisite for establishing successful social relationships (Frith and Frith, 1999), the observed basic social cue processing deficits might underly impairments in other aspects of social cognition and social functioning

Ratio versus emotion in decision-making and the risk for schizophrenia

An important question is whether emotional abnormalities in schizophrenia might have a consequence for other cognitive functions, such as goal-directed behavior. Goal-directed behavior can be assessed using decision-making paradigms. Although decision-making is traditionally seen as a rational and cognitive process, there is growing awareness that emotions play a crucial role. For instance, a decision-making paradigm in which emotions versus mere economical rational thinking have dramatically different results is the Ultimatum Game (Guth et al., 1982). Previous research using functional MRI investigated the neural basis of the Ultimatum Game and demonstrated insula activation relating to

rejection of unfair offers proposed by humans, which probably reflect emotional arousal rather than rational evaluation (Sanfey et al., 2003).

In *chapter 10* we provide evidence for the relationship between emotional arousal as measured with skin conductance activity and the rejection of unfair offers proposed by other humans in the Ultimatum Game. In contrast, there was no relationship between skin conductance activity and rejection of unfair offers proposed by computers ("non-human"). The emotional responses to unfair offers proposed by humans has been explained with reference to social utility theory, that focuses on guilt from getting more than others, and envy from getting less, which predicts rejections of low ultimatum offers to reduce envy, and repayment of trust in order to reduce guilt (Camerer, 2003). Alternative explanations have focused on the human instinct to reciprocate, and the idea that adaptive human behavior emerged from playing repeated games in close-knit groups. Hence, "punishing" others for unfair offers in order to keep up social status will persist in one-shot games (Nowak et al., 2000). Both aspects might play a far greater role in unfair offers proposed by humans than proposed by computers. Overall, this study confirms Sanfey et al.'s (2003) interpretation that negative emotional state might play a major role in rejecting unfair offers, and supports research that acknowledges the role of emotions in decision-making.

In *chapter 11* we investigated the role of the dorsolateral prefrontal cortex in decision-making in the Ultimatum Game using repetitive Transcranial Magnetic Stimulation (rTMS). Activation of the dorsolateral prefrontal cortex was previously observed during the decision to reject or accept unfair offers in the Ultimatum Game, which was suggested to reflect cognitive control or goal maintenance (Sanfey et al., 2003). If the dorsolateral prefrontal cortex guides goal-directed behavior by optimizing decision strategy on the basis of prior choices (Barraclough et al., 2004), we predicted neural interference by rTMS to cause behavioral interference with the present strategy. Results showed that after rTMS over the right dorsolateral prefrontal cortex the "default" strategy of fast (i.e. the normal pattern of shorter reaction times for rejected unfair offers relative to accepted offers) rejection of very unfair offers was changed. That is, reaction times for rejecting unfair offers was longer after rTMS compared to sham and we observed a trend towards more acceptances of these unfair offers. Hence, these findings of an altered decision-making strategy after rTMS suggest a causal role of the right dorsolateral prefrontal cortex in strategic decision-making.

Finally, in *chapter 12* we investigated abnormal strategic decision-making that included emotional aspects as measured with the Ultimatum Game. On the basis of previous studies (see *chapter 4, 6, 7* and Docherty et al., 1998; Cohen and Docherty, 2004) patients with schizophrenia and individuals at risk for schizophrenia might be

characterized by increased affective reactivity, i.e. increased emotional awareness and increased interference of emotive information of cognition. In this study siblings of patients with schizophrenia were compared with individuals without a familial history of schizophrenia on strategic decision-making. Results showed that siblings of patients with schizophrenia rejected more unfair offers compared to individuals without a family history of schizophrenia. This suggests that siblings of patients with schizophrenia may rely more on emotional aspects of unfairness associated with unfair offers in decision-making. This could be hypothesized to be due to an overriding influence of emotional brain centers, such as amygdala or insula over structures important for goal-directed behavior (Grace, 2000; Aleman and Kahn, 2005). Moreover, these findings suggest that the increased influence of emotional aspects that influence behavior is present in individuals at risk for schizophrenia and may be interpreted as an important feature of schizophrenia.

Integrating research and theory regarding emotional abnormalities in schizophrenia

Taken together, emotional abnormalities appear to be central to schizophrenia and are also present in individuals with a liability for schizophrenia-like traits or an increased genetic risk. This suggests that emotional abnormalities can be regarded as a vulnerability marker for schizophrenia. Clearly, these emotional abnormalities do not reflect an overall reduction in all aspect of emotion processing, i.e. perception, expression, experience and psychophysiology. Instead, schizophrenia patients and individuals at high risk report normal or higher levels of emotional experience, whereas the expression of emotions appears deficient. With respect to the perception of emotion, results depend on the type of processing that occurs, i.e. automatic, incidental processing or controlled, elaborative processing of affective information. These findings suggest a disjunction between deficits in elaborative processing of emotions on the one hand, and normal or increased emotional reactivity on the other hand. Moreover, deficits in the perception and expression of emotions appear to be consistently related to negative symptoms (*chapters 2, 3, 5, 6* and *9*), such as blunted affect and social emotional withdrawal. In addition, positive symptoms might be related to an increased subjective emotional arousal (*chapter 7*).

Hence schizophrenia could be regarded as an affective disorder, a classification that is now preserved for depression and related disorders. The cancellation of strong boundaries between different psychiatric disorders promotes the investigation of similarities, such as symptoms, between clinical pictures instead of only looking within one syndrome. For instance, whereas schizophrenia is regarded as a non-affective psychotic disorder, patients with bipolar disorder, a typical affective disorder, often report psychotic symptoms. Moreover, the neurocognitive profile of schizophrenia and bipolar disorder

does not seem to be qualitatively different, but rather quantitative: the same pattern but more severe in schizophrenia (Krabbendam et al., 2005). On the other hand, patients with schizophrenia often report depressive symptoms. The overlap between symptoms of these illnesses suggests a common neural basis of these symptoms. Research investigating parallels between bipolar disorder and schizophrenia found that schizophrenia and bipolar disorder share in part a genetic susceptibility (Craddock et al., 2006). This calls for a broad, dimensional approach to schizophrenia and psychosis research (Meehl, 1990; Weiser et al., 2005).

Recently, a model of emotional abnormalities has been forwarded to address the seemingly contradictive observations of deficits in the perception of emotions in combination with an intact or increased subjective experience and reactivity to emotive information in schizophrenia (Aleman and Kahn, 2005). This model of emotional abnormalities extends and integrates previous theoretical neural models of Grace (2000), specifying a neural basis for the presence of positive emotional symptoms, which includes the increased emotional reactivity, and Grossberg (2000), who proposed an amygdala "lesion" to be responsible for negative emotional symptoms, i.e. reduced expression and perception of emotions. Aleman and Kahn (2005) propose that a selective lesion of the basolateral nucleus of the amygdala combined with reduced prefrontal connectivity leads to reduced active emotional processing, accounting for deficits in the expression and perception of emotions. In addition, the central nucleus of the amygdala receives abnormal input of the basolateral nucleus and together with an imbalance in dopamine levels this will result in aberrant regulation of the central nucleus accounting for higher emotional reactivity (Aleman and Kahn, 2005). Indeed, there is a growing body of research that demonstrate hypofunction of brain structures important for emotion processing in schizophrenia, especially the amygdala (Schneider et al., 1998; Gur et al., 2002b; Hempel et al., 2003; Phillips et al., 2003b; Takahashi et al., 2004). This model does not address differences between controlled (or strategic) and automatic emotional information processing, nor does it account for the specific pattern of alexithymia observed in the research reported in the present thesis. It should therefore be complemented by including abnormalities in cingulate cortex, that has been implied in alexithymia (Houtveen et al., 1997; Parker et al., 1999; Aleman, 2005), in addition to medial prefrontal and orbitofrontal cortex, which are also important for emotion regulation (Dolan, 2002; Phillips et al., 2003a). Indeed, abnormalities in anterior cingulate, medial prefrontal cortex and superior temporal gyrus have been demonstrated in schizophrenia and biological first-degree relatives of patients with schizophrenia and other high-risk groups for schizophrenia (Fletcher et al., 1999; Ashton et al., 2000; Rajarethinam et al., 2000; Shenton et al., 2001; Seidman et al., 2003; Quintana et al., 2004; Takahashi et

al., 2004; Mitelman et al., 2005; van Rijn et al., 2005). Future research should also investigate other structures of the social brain, such as the insula, in schizophrenia patients and individuals at high-risk. Moreover, connections between structures in the social brain can also further elucidate the neural basis of specific emotion processing abnormalities in schizophrenia.

In an attempt to integrate the findings described in this thesis some apparently contradictory findings need to be addressed. First, we found that the automatic, incidental processing of facial affect appeared to be intact in patients with schizophrenia, resulting in normal interference from fearful faces in a gender decision task (*chapter 2*). In contrast, patients and siblings, albeit to a lesser extent, were not influenced by automatic, effortless processing of social cues in their distance judgments (*chapter 9*). Furthermore, in *chapter 4* the automatic, incidental processing of threatening objects resulted in increased interference on object-location memory in schizophrenia. Apparently, one cannot conclude that all forms of automatic processing of stimuli with an emotional connotation remains unaffected. However, important methodological differences should be kept in mind when comparing the results of these studies. In *chapter 2* we used a task that measures automatic allocation of attention to facial affect, where we expected emotional interference in the non-schizophrenia control group, which was indeed observed. On this emotional interference task with biological relevant emotive stimuli (faces), patients did not differ from control participants. In contrast, the stimuli in *chapter 4* were highly symbolic schematic stimuli that lacked any direct biological relevance, and for which we did not expect (nor did we observe) emotional interference in the control group. Thus, the finding of a threat-related interference in schizophrenia for these symbolic emotive stimuli suggests an aberrant influence of negative emotional information on other cognitive functions. With respect to the findings of a lack of automatic, effortless processing of social cues in schizophrenia (*chapter 9*), it is important to note that these are non-emotive stimuli, but consist of cartoon drawings that differ in gaze direction and implied biological motion. Notably, a differential neural basis for the processing of biological relevant emotional cues, such as facial affect, and non-emotional social cues, such as gaze direction or body postures, has been proposed. Whereas, the automatic, incidental processing of emotional faces is mediated by the amygdala (LeDoux, 1996; Gläscher and Adolphs, 2003), the processing of non-emotional social cues, such as gaze direction and biological motion is though to be subserved by the superior temporal gyrus (Jellema and Perrett, 2005).

Second, the results of measures of arousal measured with skin conductance responses (*chapter 5*) and behavioral measures of subjective emotional arousal (*chapter 6*) did not converge in yielding similar results. However, skin conductance reflects autonomic

arousal and this may differ from the subjective report of emotional arousal. Whereas the first has been linked to function of the right amygdala (Gläscher and Adolphs, 2003), the latter may rely more on insula and anterior cingulate (Phillips et al., 2003a; Critchley et al., 2004). In addition, the difference between normal subjective ratings of arousal for angry and fearful faces (*chapter 5*) and the heightened subjective experience of emotional arousal (*chapter 6*) might be explained by the fact that faces (*chapter 5*) are generally not very arousing compared to (personal) affective events that were discussed in *chapter 6* (Lang et al., 1999).

Methodological considerations and future directions

In the research described in this thesis we chose to investigate a relatively highly educated, stable patient sample with low levels of symptomatology to eliminate confounding effects of clinical variables, such as acute phase of psychosis or severe symptoms, as much as possible. However, as a consequence, the foregoing results might not generalize to other, more typical groups of schizophrenia with more severe symptomatology and a more chronic stage of the illness. Nevertheless, we were able to define specific emotion processing abnormalities in these groups of patients. Since schizophrenia is a highly heterogeneous disease, differences in symptomatology and other patient characteristics may account for the diversity of findings observed in emotion research in schizophrenia. For instance, with respect to skin conductance recent studies demonstrated that an increased autonomic reactivity is specifically present in patients with high levels of symptoms (Schell et al., 2005; Zahn and Pickar, 2005). Furthermore, we consistently report more severe deficits in the perception and expression of emotions in patients that are characterized by predominantly negative symptoms. Thus, the investigation of clinical homogeneous subgroups of patients characterized by specific symptoms might be an essential approach in the future. Moreover, it would be interesting to include other psychiatric groups in the future to investigate whether abnormalities are specifically related to schizophrenia spectrum pathology or whether comparable disturbances are also observed in other groups that may share a common neurobiological background.

With respect to the stimuli used in the described studies there are a number of methodological points to address. First, in *chapter 2* and *3* we used static pictures of posed facial expressions of affect. The use of these stimuli might lack ecological validity as the processing of facial affect is generally in a dynamic situation and genuine facial expressions might be easier to recognize. For instance, it has been suggested that patients with schizophrenia are in particular poor in the recognition of posed facial affect whereas deficits were less pronounced for the recognition genuine facial affect recognition (LaRusso, 1978; Davis and Gibson, 2000). However, there is presently insufficient

evidence to allow strong conclusions regarding this issue. It should also be noted that impaired perception of static pictures of posed facial emotional expressions correlate with social dysfunction to a larger extent than other neuropsychological deficits (Hooker and Park, 2002), which strongly supports the concurrent validity of these facial affect recognition tasks. In addition, in other research using ecologically more appealing stimuli, such as vignettes of everyday situations, patients with schizophrenia were still poorer in processing interpersonal cues relative to comparison subjects (Corrigan and Green, 1993).

Apart from the specific abnormalities described in this thesis it could additionally be concluded that patients with schizophrenia have specific deficits in the processing of negative emotive information (*chapter 2,3,4* and *5*). However, this is a difficult issue as emotion-specific deficits might be due to the psychometric property of negative affective stimuli, i.e. fearful faces being more difficult to recognize than happy faces (Johnston et al., 2001; Edwards et al., 2002). Notably, this does not apply to the threat-related interferences on object-location memory (*chapter 4*), because we assume that all objects are equally difficult to remember. Nevertheless, caution is needed in concluding that schizophrenia is characterized by an emotion specific deficit in processing threatening information. Further research should include different psychiatric groups or other types of emotional material, such as affective prosody (Scherer, 1981; Edwards et al., 2002) dynamic facial stimuli, emotional semantics and real life emotional scenes, to draw firm conclusion about this issue.

Clinical implications

The finding of a particular pattern of emotion abnormalities in patients with schizophrenia and individuals at high risk for schizophrenia could inform research into the underlying brain pathology and ultimately the development of treatment strategies that selectively target those brain systems. The specific pattern of emotional abnormalities, with impaired expression and categorization of emotions in combination with intact automatic perception of emotional facial expressions and an increased subjective emotional reactivity, suggests problems in the regulation of their feelings. Furthermore, it appears that in particular male patients and patients that are characterized by severe negative symptoms are prone for emotional disturbances. These groups should therefore receive special clinical attention with regard to social-emotional problems and skills.

From a clinical perspective, the results of the research described in this thesis can be used for the development of cognitive social-emotion training and affect regulating training. Ultimately one hopes that such interventions may result in better social functioning in patients with schizophrenia. Cognitive training (regarding attention, memory, executive function) has been shown to improve cognitive functioning in

schizophrenia (Krabbendam and Aleman, 2003). The next step is to target *social* cognition, including emotional processing. There is evidence of a relationship between social cognition and social functioning (Ihnen et al., 1998; Hooker and Park, 2002; Roncone et al., 2002; Brune, 2005). Cognitive emotional training (along with social skills training) might result in patients experiencing less social isolation, which can have positive consequences for career opportunities, the initiation of meaningful interpersonal relationships and reduce maybe even other schizophrenia symptoms like depression. In particular, emotion training in which verbal labels are explicitly associated with emotional cues could have beneficial effects. Given that patients show normal or even increased attention towards emotional information, a selective impairment of identifying and describing affective information might be trainable. Indeed, preliminary studies have been carried out in recent years and have yielded encouraging results. For instance, Frommann et al. (2003) and Silver et al. (2004) reported improvements in the identification, recognition, discrimination and verbalizing of facial emotional signs in patients schizophrenia after training.

Furthermore, training or therapy focused on the regulation of emotions might also be a valuable approach in schizophrenia. One such approach is the "emotion-focused therapy" proposed by Greenberg (2002). Although it is not specifically tailored to the needs of patients with schizophrenia, it can be applied to psychiatric patients in general, and adjusted to each individual. In this approach, patients are taught how to become aware of their emotions, to understand their bodily reactions, and to express emotion in ways that are appropriate to the context. This includes coaching patients in learning to describe their feelings in words, which will help them develop problem-solving skills. The process of describing emotions, accepting emotions and changing maladaptive emotions into productive emotions can thus help people to understand and better regulate their feelings (Greenberg and Bolger, 2001). The approach has been shown to be efficacious in treating depression (Pos et al., 2003). A controlled investigation of the efficacy of emotion-focused therapy in schizophrenia would thus seem in place. Ultimately, treatment strategies that enable patients with schizophrenia to better understand and regulate their emotions will significantly improve the quality of life of people suffering from this devastating disorder.

Samenvatting in het Nederlands

Emotionele stoornissen bij schizofrenie, zoals een vervlakking of vermindering van affect zijn al sinds het begin van het beschrijven en classificeren van de ziekte schizofrenie belangrijke symptomen. Deze emotionele problemen zijn vaak al aanwezig in de prodromale fase, dat is de fase die vooraf gaat aan een (eerste) psychotische fase, maar waarin mensen zich regelmatig al wel sociaal-emotioneel terugtrekken. Deze emotionele stoornissen spelen waarschijnlijk een grotere rol in problemen met het aangaan van betekenisvolle relaties bij mensen met schizofrenie dan bijvoorbeeld psychotische klachten. Psychotische klachten kunnen dikwijls goed onderdrukt worden door antipsychotische medicatie, echter emotionele stoornissen zijn moeilijker onder controle te krijgen door bestaande medicatie en problemen in sociaal en emotioneel functioneren zijn dan ook één van de belangrijkste aspecten waar mensen met schizofrenie tegenaan blijven lopen.

Hoewel het onderzoek naar de aard van de emotionele stoornissen bij schizofrenie relatief achterloopt op het onderzoek naar andere cognitieve stoornissen, zoals geheugen en aandacht, staan emotiestoornissen bij schizofrenie de laatste jaren meer in de belangstelling. Recente studies laten zien dat patiënten met schizofrenie het vaak slechter doen op emotionele informatieverwerkingstaken vergeleken met controle proefpersonen. Een belangrijke conclusie van de meeste studies is dan ook dat emotie in het algemeen verminderd is bij mensen met schizofrenie. Echter enkele studies suggereren dat mogelijk niet alle emotieverwerking gestoord is bij schizofrenie. Zo kan er een onderscheid gemaakt worden tussen emotieperceptie, de expressie van emoties en de ervaring van emoties. Met name voor de laatste is er enige evidentie dat patiënten met schizofrenie een intacte of zelfs een verhoogde emotie-ervaring hebben. Het doel van de in dit proefschrift beschreven studies is om meer inzicht te krijgen in de aard van de emotionele stoornissen bij schizofrenie en in personen die een verhoogd risico hebben om schizofrenie te ontwikkelen en hoe emotionele informatie andere cognitieve processen, zoals geheugen of het nemen van beslissingen, beïnvloedt in schizofrenie en hoog risico groepen voor schizofrenie.

De belangrijkste hypothesen die onderzocht werden zijn dat (1) niet alle emotie verwerking gestoord is bij schizofrenie en dat sommige aspecten van emotieverwerking intact of zelfs verhoogd zijn, met name de ervaring van emoties. (2) Dat emotionele stoornissen kenmerkend zijn voor schizofrenie en dat deze voor schizofrenie kenmerkende symptomen ook voorkomen in hoog risicogroepen voor schizofrenie.

De aard van emotie stoornissen bij schizofrenie

In het eerste deel van dit proefschrift werd onderzocht welke aspecten van emotieperceptie in schizofrenie gestoord zijn en hoe stoornissen in emotieperceptie samenhangen met karakteristieken van patiënten met schizofrenie. In *hoofdstuk 2* werd de automatische en gecontroleerde verwerking van emotionele gezichtsexpressies onderzocht in schizofrenie. Hieruit bleek dat automatische, incidentele verwerking van informatie met een emotionele lading vergelijkbaar was met die van controle proefpersonen. Echter patiënten met schizofrenie waren slechter in het herkennen van gezichten met een angstige gezichtsexpressie en dit was met name het geval bij patiënten met negatieve symptomen, zoals een vervlakking van affect. Dit suggereert dat emotionele gezichtsexpressies wel verwerkt worden op een automatisch niveau, maar dat vervolgens het toekennen van een emotionele betekenis aan die gezichten problemen oplevert bij patiënten met schizofrenie. Ten tweede kan op basis van deze resultaten geconcludeerd worden dat niet alle emotieverwerkingsprocessen bij schizofrenie gestoord zijn.

De relatie tussen patiënteigenschappen, zoals het hebben van negatieve symptomen en emotionele gezichtsherkenning gevonden in *hoofdstuk 2*, werd verder onderzocht in *hoofdstuk drie*. Hier repliceerden we de relatie tussen het ervaren van negatieve symptomen en moeite met het herkennen van angstige gezichten in een grotere en ziekere groep patiënten en bleken met name mannelijke patiënten meer moeite te hebben met het herkennen van angstige gezichten. Tevens bleken paranoïde patiënten beter dan niet-paranoïde patiënten in het herkennen van neutrale gezichtsexpressies en zijn patiënten die later gediagnosticeerd zijn met schizofrenie slechter in het herkennen van neutrale gezichten. Interessant is verder de afwezigheid van andere correlaties tussen patiënteigenschappen, zoals positieve symptomen en emotionele gezichtsherkenning. Positieve symptomen van schizofrenie, zoals wanen en hallucinaties, zijn wellicht gerelateerd aan een abnormale *ervaring* van emoties (zie ook *hoofdstuk 7*) in tegenstelling tot problemen in de perceptie en expressie van emoties wat meer met negatieve symptomen lijkt samen te hangen. Al met al passen deze resultaten in het idee dat stoornissen in de perceptie en expressie van emoties een gezamenlijke neurale basis hebben.

In *hoofdstuk 4* werd de invloed van automatische verwerking van abstracte dreigende stimuli op object-locatiegeheugen onderzocht. De resultaten lieten zien dat patiënten met schizofrenie in het algemeen slechter zijn in het onthouden waar een object stond in de ruimte. Dit is consistent met studies die hippocampus beschadigingen hebben aangetoond in schizofrenie, aangezien de hippocampus belangrijk is voor object-locatiegeheugen. Tevens waren patiënten specifiek slechter in het terugplaatsen van objecten met een dreigende emotionele betekenis wat suggereert dat een dreigende emotionele lading interfereert met het object-locatiegeheugen in schizofrenie. Deze

resultaten zijn consistent met eerder onderzoek waarin schizofrenie geassocieerd wordt met een verhoogde interferentie van negatieve emoties op cognitie. Tevens passen deze resultaten in bestaande modellen van schizofrenie gebaseerd op het idee dat hersenstructuren belangrijk voor de verwerking van bedreigende stimuli, zoals de amygdala, overactief zijn en zorgen voor een verhoogde emotionele interferentie op andere cognitieve processen.

Een ander belangrijk aspect van emotieverwerking zijn de bijbehorende fysiologische reacties op emotionele stimuli, zoals een verhoogde zweetproductie (huidgeleiding), hartslag en ademhaling. In *hoofdstuk 5* werd de huidgeleiding in reactie op emotionele gezichtsexpressies onderzocht bij patiënten met schizofrenie en vergeleken met controle proefpersonen. Uit dit onderzoek bleek dat patiënten met schizofrenie minder huidgeleiding hadden na het zien van boze en angstige gezichten vergeleken bij controle proefpersonen. Niettemin was de subjectieve evaluatie van boze en angstige gezichten op valentie (positief-negatief) en spanning vergelijkbaar met die van controles. Daarentegen lieten patiënten wel een met controles vergelijkbare huidgeleiding zien na het bekijken van blije gezichten of na een niet emotionele, fysieke stimulus (zucht of handklap). Echter patiënten gaven aan de blije gezichten als minder positief te ervaren en er onrustiger van te worden dan controles. De verminderde huidgeleiding na het zien van boze en bange gezichten bij patiënten met schizofrenie kan niet worden toegeschreven aan medicatie-effecten, maar passen eerder in het beeld van amygdala-afwijkingen bij patiënten met schizofrenie.

Emotiestoornissen bij mensen met een verhoogd risico voor schizofrenie

Aangezien emotieperceptiestoornissen kenmerkend zijn voor schizofrenie, werd in het tweede deel van dit proefschrift ingegaan op de hypothese dat voor schizofrenie kenmerkende symptomen ook voorkomen in hoog-risicogroepen voor schizofrenie. Verschillende hoog-risicogroepen zijn onderzocht, maar de meeste nadruk lag op broers en zussen van patiënten met schizofrenie. Het onderzoeken van hoog-risicogroepen voor schizofrenie is een waardevolle strategie om twee redenen. Ten eerste, deze mensen zijn niet ziek en gebruiken geen medicatie waardoor het mogelijk is afwijkingen kenmerkend voor schizofrenie te onderzoeken zonder verstorende factoren zoals medicatie en ernstige psychopathologie. Ten tweede, als er stoornissen in de emotieverwerking gevonden worden in hoog-risicogroepen kan daar uit afgeleid worden dat deze afwijkingen een onderdeel zijn van de gevoeligheid voor schizofrenie.

In *hoofdstuk 6* werd de subjectieve expressie en ervaring van emoties, gemeten met de Bermond Vorst Alexithymie Questionnaire (BVAQ) onderzocht bij patiënten met schizofrenie, broers en zussen van patiënten en controle-proefpersonen. Vooral

mannelijke patiënten en broers van patiënten met schizofrenie bleken moeite te hebben met het onder woorden brengen van hun gevoelens vergeleken met controles. Tevens hadden mannelijke patiënten moeite met het identificeren van hun gevoelens vergeleken met controles. Tegelijkertijd bleken patiënten met schizofrenie zich meer bewust te zijn van hun gevoelens vergeleken met controles. Een dergelijk patroon was afwezig bij vrouwen, en vrouwen met schizofrenie en zussen van patiënten verschilden niet van vrouwelijke controles. Dit patroon van moeite hebben met het verbaliseren en identificeren van emoties tegelijk met een verhoogde subjectieve emotionele ervaring van emoties wordt ook wel type 2 alexithymie genoemd (in tegenstelling tot type 1 alexithymie waarbij alle emotie aspecten verminderd zijn). De problemen in het verwoorden en identificeren van emoties is in eerder onderzoek gerelateerd aan neuroticisme. Dit is begrijpelijk aangezien een verhoogde ervaring van emoties vraagt om reflectie op die emoties. Echter door problemen met het onder woorden brengen en identificeren van emoties, zal men deze emoties niet goed kunnen duiden wat de basis vormt voor problemen in affectregulatie en mogelijk kunnen leiden tot sociale disfunctie. Tevens bleken met name patiënten met negatieve symptomen problemen te hebben met het identificeren van hun emoties. Deze bevindingen van problemen in aspecten belangrijk voor emotieregulatie in mannelijke patiënten en broers van patiënten suggereren dat deze problemen gerelateerd zijn aan een gevoeligheid voor schizofrenie, met name voor mannen.

In *hoofdstuk 7* werd de perceptie, expressie en ervaring van emoties onderzocht in 20 personen die hoog op het psychosecontinuüm scoorden gemeten met de Launay Slade Hallucinatie Schaal (LSHS) vergeleken met 20 personen laag op het psychosecontinuüm. De resultaten lieten verbanden zien tussen positieve schizofreniespectrum-symptomen en een verhoogd bewustzijn van de ervaring van emoties wat consistent is met de bevindingen uit *hoofdstuk 6* en met andere studies die lieten zien dat positieve symptomen, zoals hallucinaties in verband gebracht zijn met een verhoogde emotionele reactiviteit. Personen hoog op het psychosespectrum hadden echter geen problemen met de perceptie en expressie van emoties. Dit komt wellicht omdat deze mensen niet ziek zijn en waarschijnlijk ook nooit ziek worden. Het ervaren van hallucinaties blijkt namelijk bij 10 tot 15 % van de normale bevolking voor te komen.

Zowel in *hoofdstuk 8* als in *hoofdstuk 9* werd de verwerking van sociale cues bij patiënten met schizofrenie, personen hoog op het schizofreniespectrum en controle proefpersonen onderzocht. *Hoofdstuk 8* beschrijft een studie waarin werd gekeken naar de betrouwbaarheidsevaluatie van gezichten in patiënten, broers en zussen van patiënten en controles. Resultaten lieten zien dat patiënten met schizofrenie gezichten betrouwbaarder vinden dan controles. Broers en zussen van patiënten hebben de neiging om net zoals

patiënten gezichten betrouwbaarder te vinden dan controles, echter boers en zussen scoren tussen patiënten en controles in op betrouwbaarheidsevaluatie. Het als meer betrouwbaar inschatten van gezichten door patiënten was het meest duidelijk in gezichten die door controles het meest onbetrouwbaar gevonden werden. Deze resultaten zijn consistent met eerdere bevindingen van abnormale betrouwbaarheidsevaluatie bij mensen met autisme, een stoornis die ook wordt gekarakteriseerd door sociale disfuncties.

In *hoofdstuk 9* werd de automatische, moeiteloze verwerking van niet-emotionele sociale cues, wat belangrijk wordt geacht in het snel kunnen begrijpen van sociale cues, onderzocht in verschillende groepen hoog op het schizofreniespectrum. Dit werd gedaan met behulp van een visuele illusie die gebaseerd is op het automatisch verwerken van sociale cues, in dit geval kijkrichting en geïmpliceerde biologische beweging in schematische tekeningen van mensen. Normaal gesproken schatten mensen de afstand kleiner in tussen mensen als men naar elkaar kijkt en rent, vergeleken met als mensen van elkaar weg kijken en rennen. Patiënten met schizofrenie doen dat echter niet en laten geen invloed van deze sociale cues op het inschatten van de afstand tussen de mannetjes zien. Een zelfde gebrek aan invloed van deze sociale cues op het schatten van de afstand werd ook gezien in broers en zussen van patiënten en mannen met Klinefelter syndroom (mannen met een 47, XXY chromosomaal patroon), waarvan bekend is dat zij hoog op het schizofreniecontinuüm scoren. Het niet automatisch verwerken van sociale cues was gerelateerd aan het ervaren van negatieve symptomen bij patiënten. Deze resultaten suggereren dat problemen in het automatisch verwerken van sociale cues gerelateerd is aan een gevoeligheid voor schizofrenie en suggereert een mogelijke betrokkenheid van het X chromosoom. Aangezien het automatisch verwerken van sociale cues als voorwaarde wordt gezien voor het kunnen aangaan van sociale relaties, kunnen de stoornissen in het automatisch verwerken van sociale cues bijdragen aan problemen in sociale cognitie en sociaal functioneren in schizofrenie.

Emoties, doelgericht gedrag en een verhoogd risico op het ontwikkelen van schizofrenie

Het derde deel van dit proefschrift ging verder in op de invloed van emoties op cognitie, met name doelgericht gedrag. In voorgaande hoofdstukken is op diverse manieren aangetoond dat patiënten met schizofrenie en mensen met een verhoogde kans op het ontwikkelen van schizofrenie emoties en emotionele informatie abnormaal verwerken. Deze emotiestoornissen kunnen een grote invloed hebben op andere aspecten van cognitie, zoals doelgericht gedrag. Doelgericht gedrag is met name in het maken van beslissingen een belangrijk component. Vanuit traditionele economische modellen wordt het nemen van beslissingen beschouwd als een rationeel proces, echter de rol van emoties

wordt steeds meer erkend. Een taak waarin ratio (doelgericht gedrag) en emoties een andere uitkomst geeft is het Ultimatum Spel.

In *hoofdstuk 10* werd onderzocht in hoeverre emoties een rol spelen op het nemen van beslissingen. Dit werd onderzocht met behulp van een beslissingsparadigma waarin oneerlijkheid een belangrijke rol speelt, het Ultimatum Spel waarin iemand een, eerlijk of oneerlijk, aanbod doet bij een verdeling van geld. De mate van emotionele 'arousal' werd gemeten met huidgeleidingsresponse en deze bleek voorspellend te zijn voor het afwijzen van een oneerlijke verdeling van geld aangeboden door een andere persoon, maar niet wanneer het geld verdeeld was door een computer. Deze bevindingen kunnen zó verklaard worden dat bij een oneerlijk bod van mensen men afgunst ervaart wanneer men minder krijgt. Daarbij kan het straffen van iemand die het geld oneerlijk verdeelt, een belangrijke rol spelen in het afwijzen van een oneerlijk bod. Beide aspecten spelen een grotere rol als het gaat om een oneerlijk bod van andere mensen dan van computers. Tevens bevestigt deze studie de eerdere aanwijzingen dat emoties een cruciale rol spelen bij het nemen van economische beslissingen.

In *hoofdstuk 11* hebben we met behulp van repetitieve transcraniale magnetische stimulatie (rTMS) onderzocht of de dorsolaterale prefrontale cortex cruciaal is bij het nemen van een beslissing. Bij TMS wordt er met behulp van een spoel op de schedel door middel van korte magnetische pulsen de activiteit in een bepaald hersengebeid kortdurend beïnvloed. Eerder onderzoek naar de neurale basis van beslissingen in het Ultimatum Spel suggereert dat de dorsolaterale prefrontale cortex belangrijk is bij het bepalen van de beslisstrategie. Een verstoring van de dorsolaterale prefrontale cortex door middel van TMS zou dan moeten zorgen voor een verandering van de normale beslisstrategie. Dat is precies wat gebeurde, na stimulatie van de rechter dorsolaterale prefrontale cortex veranderde het 'normale' patroon van een oneerlijk bod sneller afwijzen dan accepteren in langzamer afwijzen van een oneerlijk bod. Tevens was er een neiging tot vaker accepteren van een oneerlijk bod. Het veranderen van beslisstrategie na TMS van de rechter dorsolaterale prefrontale cortex suggereert dat de rechter dorsolaterale prefrontale cortex een causale rol speelt bij het nemen van beslissingen.

In *hoofdstuk 12* hebben we gekeken naar de vraag of afwijkingen in emotionele informatieverwerking zoals we die eerder aantoonden in broers en zussen van patiënten met schizofrenie een rol spelen in het nemen van beslissing op basis van emoties in het Ultimatum Spel. De resultaten lieten zien dat broers en zussen van patiënten vaker een oneerlijk bod afwijzen dan mensen zonder genetische gevoeligheid voor schizofrenie. Dit suggereert dat broers en zussen van patiënten met schizofrenie hun beslissingen meer laten leiden door emoties. Dit is consistent met modellen van schizofrenie die ervan uitgaan dat hersengebieden belangrijk voor de verwerking van emoties, zoals insula en

amygdala een overdreven invloed hebben op hersenstructuren belangrijk voor doelgericht gedrag. Tevens kan de door de aanwezigheid van een verhoogde invloed van emoties op cognitie bij familieleden van patiënten beschouwd worden als een cruciaal kenmerk van schizofrenie.

Conclusie

In *hoofdstuk 13* werden de resultaten van voorgaande hoofdstukken samengevat en implicaties voor toekomstig onderzoek en de klinische praktijk besproken. De belangrijkste bevindingen zijn dat we ondersteuning vonden voor de notie dat emotiestoornissen horen bij de karakteristieke problemen van schizofrenie en dat die ook aanwezig zijn bij familieleden en andere hoog-risicogroepen voor schizofrenie. Echter niet alle emotieverwerkingsprocessen blijken gestoord te zijn. In plaats daarvan lijkt er een onderscheid te zijn tussen een gestoorde perceptie en expressie van emoties, en een intacte of zelfs verhoogde emotionele ervaring. Wat betreft emotieperceptie in schizofrenie blijkt met name de gecontroleerde emotieperceptie gestoord te zijn, terwijl de automatische verwerking van emotionele informatie intact of zelfs een versterkte invloed heeft op andere cognitieve aspecten. Tevens vonden we consistent een relatie tussen het hebben van negatieve symptomen en problemen in de perceptie en expressie van emoties. Aan de andere kant lijken positieve symptomen gerelateerd te zijn aan een verhoogde subjectieve emotionele ervaring.

Op basis van deze bevindingen zou men kunnen suggereren dat schizofrenie een affectieve stoornis is, net zoals depressie. Door het bekijken van symptomen over aandoeningen heen in plaats van binnen een ziekte te kijken is het mogelijk om een gezamenlijke neurale basis voor deze stoornissen te onderzoeken. Tot slot zijn er een aantal implicaties voor de klinische praktijk. Zo kan het opzetten van emotietrainingen voor patiënten uiteindelijk bijdragen aan een beter sociaal functioneren van patiënten met schizofrenie. Een voorbeeld is het leren labelen van emoties op gezichten of een emotieregulatie training die erop gericht is mensen emoties te leren duiden en ermee om te gaan.

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Bedankt!

Veel liefs, Mascha

April 2006

Curriculum Vitae

Mascha van 't Wout werd geboren op 28 januari 1978 te Ede. In 1996 behaalde zij het VWO diploma aan Het Wagenings Lyceum te Wageningen. In datzelfde jaar is zij gestart met de opleiding Psychologie aan de Universiteit Utrecht. Zij vervolgde haar psychologiestudie in de richting neuropsychologie en cursussen klinische psychologie en revalidatiepsychologie. In 2000 voltooide zij haar klinische stage in het algemeen psychiatrisch ziekenhuis GGZ Meerkanten te Ermelo en werkte zij vervolgens als neuropsycholoog onder supervisie in het kader van het aldaar lopende Alzheimeronderzoek. In 2001 studeerde zij af in de richting neuropsychologie. In 2002 werd zij als onderzoeksassistent aangesteld bij de capaciteitsgroep Psychologische Functieleer (Psychonomie) van de Universiteit Utrecht (in samenwerking met de afdeling Psychiatrie van het Universitair Medisch Centrum). Vanaf 2003 is zij bij dezelfde capaciteitsgroep aangesteld als junior onderzoek, waar zij sinds die tijd promoveert.

Mascha van 't Wout was born on January 28, 1978 in Ede. In 1996 she completed her secondary school education at the Wagenings Lyceum in Wageningen. In the same year, she commenced her psychology education at the Utrecht University. In 2000 she finished her clinical internship at the GGZ Meerkanten in Ermelo. She obtained her psychology degree in 2001. In 2002 she was appointed as a PhD student at the department of experimental psychology of the Utrecht University in cooperation with the University Medical Center Utrecht.

Notes / Aantekeningen

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