Affect Regulation in Schizophrenia

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CHAPTER 1

General Introduction

Schizophrenia

Schizophrenia is a serious mental disease, characterised by psychosis (delusions and hallucinations), apathy (a lack of motivation), social withdrawal, and cognitive impairment, which result in impaired functioning in different areas, such as work, school, independent living, and interpersonal relationships (Mueser and McGurk, 2004). Apart from the above-mentioned deficits, these patients also experience emotional disturbances, which have received increasing attention over two past decades (Edwards et al., 2001; Pinkham et al., 2007). For example, schizophrenic patients are impaired in their ability to recognize emotional facial expressions (Loughland et al., 2002). The abnormalities in emotion identification and emotional behaviour have been found to be associated with the poor social functioning observed in patients with schizophrenia (Borod and Madigan, 2000). It is still unclear whether the impairment in affect perception is a specific emotional deficit or whether it is related to a more generalized impairment in perception and attention (Bozikas et al., 2004).

Emotional information processing

The ability to recognize emotional cues from the environment is an important component of survival: signalling potential danger or reward and preparing for an appropriate response increases the chances of survival (Phillips et al., 2003a). According to Phillips et al. (2003a), the generation of an affective state following an emotion-eliciting stimulus consists of several processes. First, the appraisal and identification of the emotional significance of the stimulus. Second, the production of an affective state, including autonomic, neuroendocrine and somatomotor responses, as well as a conscious emotional feeling. Finally, the regulation of the affective state and its behavioural responses. The first and second processes may be inhibited in such a way that the affective state and behaviour are contextually appropriate. Phillips et al. (2003a) suggested that the above described processes are dependent on two neural systems: a ventral and a dorsal system. The ventral system consists of the amygdala, insula, ventral striatum and ventral regions of the anterior cingulate gyrus and prefrontal cortex. This system plays a role in the identification of the emotional significance of environmental stimuli and the production of the emotional state. Furthermore, it is also important for automatic regulation and mediation of the autonomic responses accompanying the emotional states. The dorsal system consists of the hippocampus, and dorsal regions of the anterior cingulate gyrus and prefrontal cortex. These regions are important for the integration of cognitive and emotional processes and can be influenced by emotional input. This system is also involved in the performance of executive functions, such as selective attention, planning and effortful rather than automatic regulation of emotional states. The dorsal and ventral systems are reciprocally

connected, and specific abnormalities in one of these systems or in both systems may result in abnormal emotional information processing. In a review on abnormal brain functioning during emotional stimulation, Philips et al. (2003b) concluded that schizophrenic patients showed impaired responses of the amygdala, anterior insula, and ventral striatum, regions that are part of the ventral system, which is involved in the identification of the emotional significance of a stimulus, overt displays of emotions, and autonomic responses to emotion-eliciting stimuli, i.e. the more basic responses to these stimuli.

Figure 1. Examples of threat, nature, and erotic pictures, respectively (IAPS; Center for the Study of Emotion and Attention, 1999).

Emotional responding: subjective, psychophysiological, and motor reactions

As stated above, schizophrenic patients appear to be impaired in their basic responding to emotion-eliciting stimuli. Emotional responding can be induced and investigated using different methods, for example with questionnaires, by asking a subject to imagine a certain emotion-eliciting event, or by reading a story of watching a video tape. An often used paradigm to investigate emotions consists of presenting emotion-eliciting pictures to subjects and measuring the accompanying subjective, psychophysiological and motor responses. For this purpose, a standardized set of over 600 emotional pictures has been developed: the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999; see for examples Figure 1). Typically, these pictures are presented during 6 seconds each, and subjects are asked to view these pictures the entire time they appear on the screen and subsequently rate them on two rating scales, representing the degree of pleasantness and the degree of arousal they evoked in the subject during the viewing of a specific picture. Using emotion-eliciting pictures, several types of responses can be analysed to investigate emotional information processing: subjective evaluations, psychophysiological responses, and motor reflexes.

Subjective evaluations

Although schizophrenic patients seem impaired in their ability to recognize and express emotional facial expressions, they do appear to experience emotions in a way similar to healthy controls. Several studies have found that patients and controls did not differ in their subjective ratings of pleasantness and arousal when presented with emotion-eliciting pictures (Quirk and Strauss, 2001; Schlenker et al., 1995; Takahashi et al., 2004; Volz et al., 2003). In two other studies, schizophrenic patients reported that they experienced the same amount of pleasant emotions as healthy controls, but greater amounts of unpleasant emotions in response to emotion-eliciting stimuli (Kring, 1999; Kring and Neale, 1996). It has also been found that schizophrenic patients experience less positive emotions and more negative emotions in response to daily stressors (Myin-Germeys et al., 2001) and emotion-eliciting pictures (Curtis et al., 1995), compared with healthy control subjects.

This apparent paradox between the impaired ability of schizophrenic patients to recognize and express emotional facial expressions and yet the intact ability to experience emotions, needs further investigation. If schizophrenic patients experience emotions in a way similar to healthy control subjects, they perceive the emotion-eliciting stimuli in a similar way as well. This could imply that the disturbances in emotion recognition in schizophrenic patients are restricted to facial stimuli, as opposed to more general emotion-eliciting stimuli. In this thesis, the subjective responses of schizophrenic patients to a variety of emotion-eliciting pictures are compared to the subjective evaluations of healthy control subjects. Furthermore, by combining the subjective evaluations of these pictures with the psychophysiological responses during picture viewing, we aimed to investigate the emotional experiences of these patients more thoroughly. A difference between the patients and healthy control subjects would suggest a different basic emotional information processing mechanism in schizophrenic patients.

Psychophysiological responses

The psychophysiological responses that accompany emotional reactions are mostly generated by the autonomic nervous system. To understand and interpret these psychophysiological reactions, a basic understanding of the autonomic nervous system is needed.

The autonomic nervous system (autonomic means ‘self-governing’) is subdivided into the parasympathetic and the sympathetic nervous system (see Figure 2). The sympathetic nervous system is most involved during activities that require stored energy from the body, such as excitement or exercise. During sympathetic activation, the heart rate increases, sweat activity increases, blood flow to the skeletal muscles increases, and the digestive system is inhibited. The

parasympathetic system, on the other hand, is involved in increasing the supply of stored energy in the body that occurs during relaxation: the heart rate decreases and the digestive system is activated (Carlson, 2001). The activity of these two systems can be reciprocal, meaning that the increase of one system is accompanied by the decrease of the second system, but the two systems can also be coactivated or coinhibited (Berntson et al., 1991). The autonomic nervous system is mainly activated by the spinal cord, brain stem and hypothalamus, but it also receives input from the cerebral cortex, especially the limbic cortex (Guyton, 1991). The limbic cortex is involved in both cognitive as well as emotional processes, through its connections with various regions in the brain, among which the hypothalamic visceromotorcenters, and prefrontal and orbitofrontal cortices (Barbas, 2000).

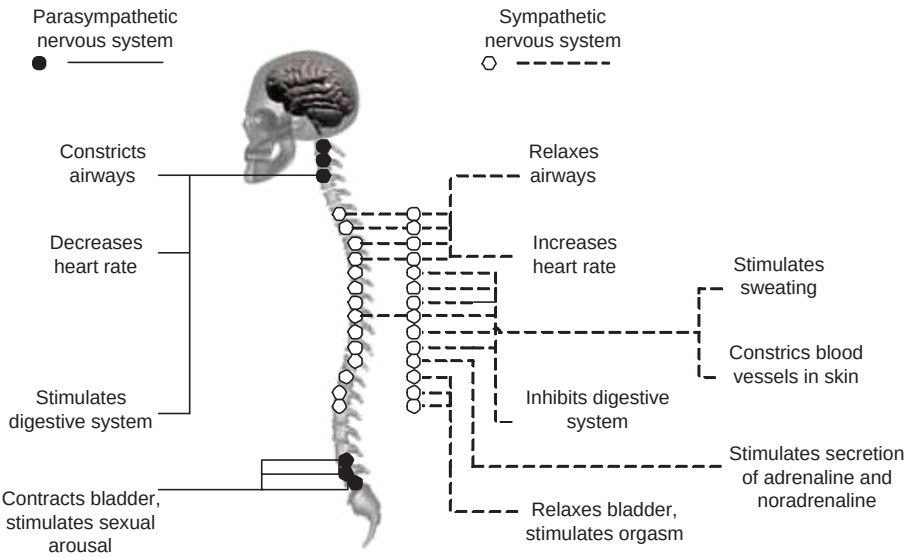

Figure 2. The autonomic nervous system: parasympathetic and sympathetic divisions.

To investigate the underlying emotional processes during picture viewing more objectively, psychophysiological responses can be used. The emotion-eliciting pictures used in this thesis are capable of eliciting characteristic patterns of physiological responses in healthy individuals. For example, the skin conductance response is most pronounced for more arousing pictures (i.e., the highly pleasant and highly unpleasant pictures) than for neutral pictures, as is the blood pressure

response (Globisch et al., 1999). Changes in breathing rate are more likely to accompany changes in arousal than they are to accompany pleasantness (Gomez et al., 2004).

The cardiac response to different types of stimuli (emotion-eliciting pictures, neutral or aversive tones) can be used to investigate both attentional as well as emotional information processing. The classic cardiac response pattern to emotional pictures consists of an initial deceleration, an acceleration and a second deceleration. The initial deceleration is termed the orienting response, and represents the intake of stimulus material, which is part of an attentional processing mechanism. However, this initial orienting phase is also influened by emotional processing: the initial deceleration tends to be largest for unpleasant pictures. The subsequent heart rate acceleration tends to be largest for pleasant pictures (Bradley and Lang, 2000; Levenston et al., 2000). The cardiac response is also used in studies in which acoustic stimuli (tones) are presented to subjects: the cardiac response to loud, aversive noises is termed the cardiac startle response. The first acceleration and deceleration of this response reflect an attentional process: a disengagement from ongoing activity that leads to the detection of potential danger (Ramírez et al., 2005).

Since psychophysiological responses can be linked to underlying emotional information processing mechanisms (Bradley, 2000), we investigated the psychophysiological responses of schizophrenic patients during the viewing of emotion-eliciting pictures to investigate whether schizophrenic patients experience these pictures in a way similar or different to healthy control subjects, suggesting a similar or different underlying emotional processing mechanism. Little research has been conducted in this area with schizophrenic patients. One study found that heart rate deceleration and skin conductance responses were largest when patients and controls viewed emotionally arousing pictures, but no differences between schizophrenic patients and controls were found (Volz et al., 2003). However, in that study only skin conductance and heart rate responses were measured. In this thesis, apart from heart rate and skin conductance, blood pressure and respiration will also be investigated. Because scenes of threat, violent death and erotica generally cause the strongest emotional and psychophysiological responses (Bradley et al., 2001a), we focused on the responses of schizophrenic patients and healthy control subjects during the viewing of nature scenes, erotica, and mutilations.

Another issue regarding emotional disturbances in schizophrenia is the debate on whether the impairment in affect perception is a specific emotional deficit or whether it is related to a more generalized impairment in perception and attention (Bozikas et al., 2004). Therefore, we aimed to investigate whether the cardiac orienting responses to pictures and the cardiac startle responses to acoustic stimuli differed between patients and controls, since these two responses are influenced by

attention. In a second experiment, we presented both emotion-eliciting pictures as well as acoustic startle stimuli. A difference in one of these two cardiac responses (orienting or startle), or both, between patients and controls could provide further information on the attentional and emotional processing mechanisms in schizophrenic patients.

Motor reflexes: the eyeblink reflex

Apart from psychophysiological responses, behavioural reflexes can also be investigated during the viewing of pictures to provide further information on emotional processing mechanisms. An extension of the above described method involving emotion-eliciting pictures is the so-called emotional startle modulation paradigm (Lang et al., 1990; Vrana et al., 1988). This paradigm has been developed to investigate the ongoing emotional state of a subject while viewing emotion-eliciting pictures. During the presentation of several pictures, loud noises are presented through headphones to provoke a startle reflex in the subject. A startle reflex is an automatic response to a sudden and intense stimulus, such as a loud noise. The startle reflex is usually measured by recording the electromyographic activity of the m. orbicularis oculi, which contracts during the startle eyeblink response, the most reliable component of the whole body startle reflex (Blumenthal et al., 2005). The orbicularis oculi muscle is directed by the nucleus of the seventh cranial nerve, the facial motor nucleus, which makes it possible to monitor activity of the sensory-somatic nervous system by measuring blink reflexes (Blumenthal, 1998). Figure 3 presents a schematic eyeblink response after presentation of a startle stimulus.

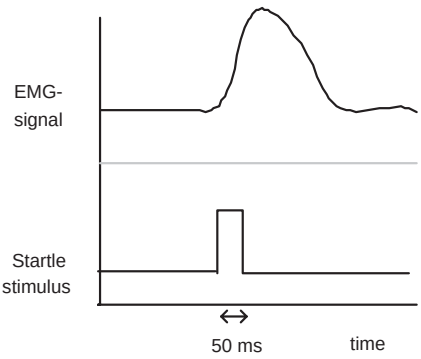

Figure 3. Schematic eyeblink response after startle stimulus presentation

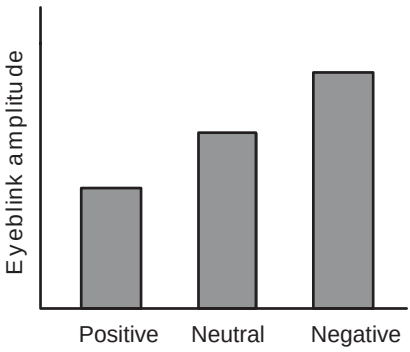

Figure 4. Schematic presentation of the expected startle modulation pattern.

The underlying theory of this paradigm defines emotions as action dispositions, which organize behavior along a valence dimension ranging from appetitive to aversive emotions (Lang et al., 1990). According to this theory, two motivational systems exist in the brain: the appetitive (positive emotions) and defensive (negative emotions) system, that each can vary in terms of activation or arousal. When the appetitive system is activated, behaviours such as approach, attachment and consummation are prepared, whereas avoidance, escape and defense behaviours are prepared when the aversive motivational system is activated. The term 'arousal' represents the intensity of activation of either the appetitive or the aversive system or the coactivation of both systems. Behavioural reflexes can also be organized along the valence dimension, such as the salivary response (appetitive) and the startle reflex (aversive). If the emotional state and the reflex match in valence (i.e. both appetitive or both aversive), the reflex will be enhanced. Conversely, if there is a mismatch between the emotional state and the reflex, the reflex will be attenuated (Lang et al., 1990). Several studies have shown that the startle reflex is reduced when viewing arousing pleasant slides, and enhanced when viewing arousing unpleasant slides (Bradley et al., 2001a, 2006; Grillon and Baas, 2003); see Figure 4 for a schematic presentation.

The moment at which the startle stimulus is presented during the viewing of a picture is important for the interpretation of the response. The magnitude of the startle response is modulated both by attention as well as emotion; it depends on the duration between picture onset and startle onset whether the eyeblink response is influenced more by attentional processes or more by emotional processes. If the startle stimulus is presented early during the viewing of emotional pictures (300/500 ms; Bradley et al., 1993; Vrana et al., 1988), the startle response is influenced by attentional information processing: both pleasant and unpleasant pictures elicit smaller eyeblink responses compared with neutral pictures. At longer latency intervals (1300 ms – slide offset), the effects of stimulus content are more pronounced: negative pictures elicit larger eyeblink responses, and positive pictures elicit smaller responses compared with neutral pictures (Bradley et al., 1993).

Only three studies have been published previously that investigated the eyeblink startle responses of schizophrenic patients during the viewing of emotion-eliciting pictures. One study did not find any differences in the startle responses between schizophrenic patients, their first-degree relatives and healthy control subjects (Curtis et al., 1999). Another study, however, found that schizophrenic patients did not show the expected startle potentiation to negative pictures, whereas their responses to positive and neutral pictures were similar to those of healthy control subjects (Schlenker et al., 1995). Finally, a study that investigated the startle responses elicited at different time points during the viewing of pictures, found that schizophrenic patients failed to show the expected startle potentiation only when the

stimulus was presented early during the viewing interval (Volz et al., 2003). These authors concluded that schizophrenic patients need more time than healthy control subjects to process the aversive information from unpleasant pictures, leading to a delay in the activation of the defense system in these patients.

The research conducted thus far regarding emotional startle eyeblink modulation in schizophrenia is scarce, and with mixed results. Only one study (Volz et al., 2003) presented the startle stimulus at different time points during picture viewing to investigate the contribution of both attentional as well as emotional influences. Since it is still unclear whether the impairment in affect perception in schizophrenia is a specific emotional deficit or whether it is related to a more generalized impairment in perception and attention, we aimed to investigate this using the emotional startle modulation paradigm with startle stimuli presented at different moments during picture viewing. This paradigm can provide further information on the ongoing emotional states schizophrenic patients experience during the viewing of different types of pictures.

Cardiovascular health

Thus far, several methods to investigate emotional information processing have been described, such as subjective evaluations, psychophysiological responses, and motor eyeblink reflexes. Three of the psychophysiological responses that are investigated in this thesis are heart rate, blood pressure, and respiration, which play important roles in the cardiovascular system. Apart from the specific cardiovascular responses to emotional stimuli, it is also important to evaluate the general cardiovascular health of these patients. The relative risk of patients with schizophrenia to suffer from cardiovascular disease is reported to be two-fold higher than in the general population (Henneskens et al., 2005), and using antipsychotic medication increases the risk for cardiovascular disease and sudden cardiac death three-fold (Strauss et al., 2004). Therefore, we also investigated the functioning of the cardiovascular control system of schizophrenic patients during a neutral rest period as opposed to an emotional picture paradigm.

A widely used method to assess the functioning and stability of the autonomic nervous system is by measuring heart rate variability (HRV) and blood pressure variability (BPV). A higher cardiovascular variability is indicative of a more healthy cardiovascular control mechanism (Bär et al., 2005). HRV and BPV can be derived from the beat to beat series of the electrocardiogram by means of R-top detection, and from the blood pressure time series, respectively. With this noninvasive method, the variations in the R-R interval time lengths and the sytolic and diastolic blood pressure levels that accompany the R-R interval can be identified. Short-term beat to beat fluctuations in heart rate and blood pressure

primarily reflect the functioning of the sympathetic and the parasympathetic cardiovascular control systems (Akselrod et al., 1981).

Spontaneous variations in heart rate and blood pressure are caused by many different factors, such as respiration, blood pressure regulation, thermoregulation, circadian rythms, and other unidentified factors (Stein et al., 1994). Each of these factors causes a rhythmic change in the HR fluctuations. By transforming the time event series of the heart rate into the frequency domain, specific frequencies of the oscillating physiological rhythms can be identified. This method is known as power spectral analysis (Kamath and Fallen, 1993). Figure 5a shows an example of an interbeat interval time series, and Figure 5b shows the HR powerspectrum of this time series. Within the frequency domains of the heart rate and blood pressure (ranging from 0.003 to 0.40 Hz), the most often used frequency domains for assessing short-term cardiovascular functioning are the high frequency (HF) and the low-frequency (LF) domains. The fluctuations in the HF domain (0.15 – 0.40 Hz) of the heart rate are almost completely determined by the respiratory rhythm, which is a marker for vagal (parasympathetic) input (Burggraaf et al., 2001; Malliani, et al, 1991; Parati et al., 1995). The fluctuations in the LF domain (0.04-0.14 Hz) of blood pressure can be seen as a marker of sympathetic vasomotor tone (Parati et al., 1995).

Apart from measuring HRV and BPV, it is also possible to asses the baroreflex receptor sensitivity (BRS) by combining the time series from the heart rate and blood pressure. The baroreflex loop is important for the fast regulation of both heart rate and blood pressure, and BRS can be used as a measure for both sympathetic and parasympathetic cardiovascular regulation (Rüdiger et al., 2001). Diminished baroreflex modulation has been found in pathological conditions such as acute myocardial infarction, diabetes mellitus, and congestive heart failure (La Rovere et al., 1998; Frattola et al., 1997; Mortara et al., 1997), but also in smoking (Mancia et al., 1996).

Studies investigating cardiovascular functioning in unmedicated schizophrenic patients found higher heart rates, lower HF power, and less BRS in these patients compared with healthy control subjects, indicating decreased vagal control over the heart (Bär et al., 2005, 2007; Boettger et al., 2006; Valkonen-Korhonen et al., 2003). Since decreased HRV indices have been found to predict mortality in various clinical populations, the lower HF power in unmedicated schizophrenic patients suggests a higher risk for cardiovascular disease and even an increased risk for cardiac mortality in these patients (Boettger et al., 2006; Stein et al., 1994). The use of antipsychotic medication may further increase this risk for cardiovascular diseases (Agelink et al., 1998, 2001; Cohen et al., 2001; Kim et al., 2004; Mueck-Weymann et al., 2002; Oyewumi et al., 2004; Rechlin et al., 1994, 1998; Zahn and Pickar, 1993).

Most of the above described studies only investigated the effects of the antipsychotic medication on the cardiovascular variability in these patients. However, multiple factors can influence the HRV and BPV. In our study, we investigated the effects of antipsychotic medication on cardiovascular variability while controlling for smoking habits, gender, the use of benzodiazepines, the severity of the psychotic symptoms, and the duration of the use of antipsychotic medication. Furthermore, most studies on HRV in schizophrenic patients investigated chronic patients (aged 30-40 years), who have been ill for several years. However, duration of illness may be another important factor for the functioning of the cardiovascular control system. The patients in our subject sample were relatively young (aged 18-30 years), and some of them were experiencing a psychotic episode for the first time. Thus, our patient sample allowed us to investigate whether the disease itself, antipsychotic medication, or other factors contributed to cardiovascular disease in young, recent-onset schizophrenic patients, without the confounding factor of chronicity.

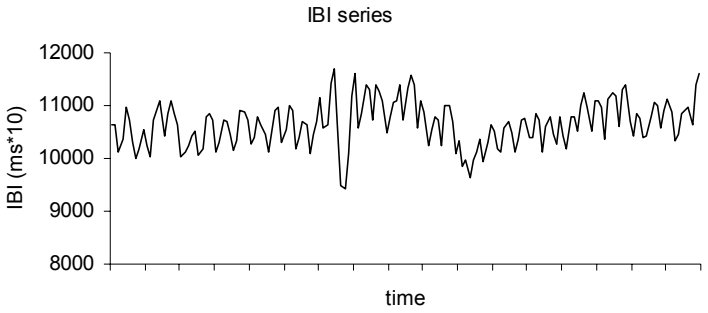

Figure 5a: example of an interbeat interval (IBI) time series

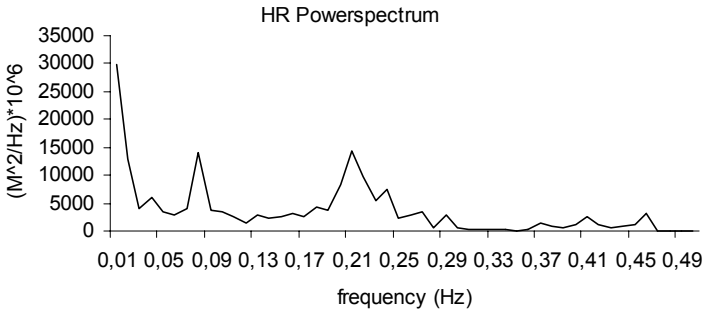

Figure 5b: example of a heart rate (HR) powerspectrum

Aims of the thesis

Since schizophrenic patients appear to be impaired in their basic responses to emotion-eliciting stimuli (Philips et al., 2003b), the present thesis aimed to investigate the basic subjective, physiological and motor responses of schizophrenic patients to emotion-eliciting pictures. More specifically, we aimed to investigate:

- the ongoing emotional states of schizophrenic patients and healthy controls during the viewing of emotion-eliciting pictures using psychophysiological and startle eyeblink responses;
- the subjective responses of schizophrenic patients and healthy controls during the viewing of emotion-eliciting pictures;
- the attentional processes during the viewing of emotion-eliciting pictures in schizophrenic patients and healthy controls using startle eyeblink and cardiac responses;
- the cardiovascular functioning of unmedicated and medicated schizophrenic patients during a neutral rest period using cardiovascular variability measures.

Outline of the thesis

To investigate psychophysiological and subjective responses to emotion-eliciting pictures, we presented a variety of these pictures to schizophrenic patients and healthy control subjects while measuring heart rate, skin conductance, blood pressure and respiration. In *Chapter 2*, the time course of these physiological responses (heart rate, blood pressure, skin conductance and respiration) during the viewing of emotion-eliciting pictures is investigated.

Schizophrenic patients show impairments in emotion recognition, yet they often report the same emotional experiences as healthy control subjects (Kring, 1999; Kring and Neale, 1996). In *Chapter 3* we investigated whether the psychophysiological responses that accompanied the subjective responses to emotion-eliciting pictures differed between schizophrenic patients and healthy control subjects.

To investigate the ongoing emotional states of the subjects, we presented acoustic startle noises while subjects viewed emotion-eliciting pictures. During this experiment, we measured several psychophysiological responses, such as heart rate, but we also measured the electromyographic (EMG) activity of the orbicularis oculi, the muscle that surrounds the eye and contracts during an intense stimulation, such as a loud noise. However, this signals needs to be processed and conditioned before any eyeblink responses can be calculated. *Chapter 4* describes the signal conditioning method that was developed for the quantification of the eyeblink responses: the envelope method.

Because there is still some debate about the underlying mechanism of the emotional disturbances in schizophrenia, being either a specific emotional deficit or

a more general attentional deficit (Bozikas et al., 2004), we aimed to investigate both attentional as well as emotional processes during picture viewing using the emotional startle paradigm. In *Chapter 5* we investigated the eyeblink responses of schizophrenic patients and healthy controls subjects. The emotional startle paradigm described above has been developed to investigate the ongoing positive and negative emotions of subjects during the viewing of emotion-eliciting scenes, and this enabled us to investigate the underlying emotions of schizophrenic patients during picture viewing without depending on their subjective responses to the pictures.

To further investigate the attentional and emotional functioning of schizophrenic patients, we investigated the cardiac responses of patients and controls during the emotional startle paradigm in *Chapter 6*. In chapter 6, we investigated whether the orienting response to pictures and the cardiac startle response to acoustic stimuli differed between patients and controls.

In *Chapter 7,* we investigated whether the cardiovascular functioning of medication-free patients differed from healthy control subjects during a neutral rest period. Because antipsychotic medication could influence cardiovascular functioning, we also investigated the effects of several antipsychotics on heart rate variability, blood pressure variability and baroreflex receptor sensitivity in patients taking antipsychotic medication.

Finally, a summary of the results and the conclusions and interpretations of the above-described studies are presented in *Chapter 8*.

CHAPTER 2

Physiological responsivity to emotional pictures in schizophrenia

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Abstract
Schizophrenic patients are known to experience difficulties in emotional information processing, yet knowledge of their physiological responsivity to emotional stimuli is limited. The purpose of this study was to investigate the physiological reactions of schizophrenic patients to emotional stimuli. We presented pictures selected from the International Affective Picture System (IAPS) to patients and controls, while assessing their subjective evaluations in terms of valence and arousal scores and measuring their responses of heart rate (HR), breathing rate (BR), skin conductance level (SCL) and diastolic (DBP) and systolic blood pressure (SBP). For the analysis of the physiological data, three emotional picture categories were formed: positive (erotic content), negative (physical injuries) and neutral (landscapes). Patients and controls did not differ in their subjective evaluations of the pictures. Also, for both patients and controls, the SCL and DBP responses to positive emotional pictures were larger as compared to negative and neutral pictures. However, the patients did show significantly increased HR responses to the positive emotional pictures as compared to controls, possibly as a result of a decreased parasympathetic activity. Only for the BR response to the positive emotional pictures did we observe significant positive correlations with the PANSS scores. These first data suggest that altered physiological responsivity to emotional pictures in schizophrenia is limited to those with positive emotional content. Further studies will need to refine the dynamics of this stimulus category in relation to clinical state and medication effects.

Introduction

Schizophrenia is a psychiatric illness which causes both emotional as well as cognitive disturbances (Bleuler, 1911; Kraepelin, 1919). Bleuler (1911) defined schizophrenia essentially as a splitting of thoughts from feelings. Blunted affect and anhedonia have been recognised as core features of the disorder since this first description (Philips et al., 2003). Abnormalities in emotion identification and emotional behaviour have also been found to be associated with the poor social functioning observed in patients with schizophrenia (Borod and Madigan, 2000).

Over the past decade the emotional disturbances schizophrenic patients experience have received increasing attention (Edwards et al., 2001). Schizophrenic patients appear to have an impairment in recognising faces and emotional facial expressions (Addington and Addington, 1998; Kohler et al., 2003), as well as an impairment in identifying affective prosody (Edwards et al., 2001). Baudouin et al. (2002) found that the emotion processing deficit schizophrenic patients experience was related to negative symptoms and that the inability to selectively attend to emotion was correlated with the severity of the negative symptoms, although Kohler et al. (2000) found a positive correlation between emotion recognition and both negative and positive symptomatology.

Although individuals with schizophrenia exhibit significantly diminished facial expressions of emotion, patients report an emotional experience that is equal to or possibly greater than that of non-psychiatric controls (Aghevli et al., 2003; Earnst and Kring, 1999). These findings of Aghevli et al. (2003) support the existence of a discrepancy between the expression and experience of emotion in schizophrenia which is consistent with the inhibition model of blunted affect as suggested by Bleuler (1911), in which patients with schizophrenia are assumed to experience a normal range of emotions but do not reflect this in their emotional expression. However, an emotional experience comprises not only its subjective expression in terms of language or expressed feelings, but also its underlying physiological concomitants. These last processes are less well studied in schizophrenia.

Lang et al. (1998) have postulated the existence of two motivational systems in the brain, i.e., appetitive (positive emotions) and defensive (negative emotions), that each can vary in terms of activation or arousal. Arousal here is not viewed as having a separate substrate, but rather as representing the intensity of activation of either the appetitive or the aversive system or the coactivation of both systems, which may be reflected in physiological processes. Although research investigating the emotional disturbances in schizophrenic patients has thusfar mainly focused on the recognition of faces and facial expressions, it is also relevant to investigate the emotional disturbances that schizophrenic patients experience daily in their environment in relation to their physiological

responsivity. For this purpose, pictures of affective events and objects can be used. Emotional pictures are ecologically valid stimuli in the sense that they involve processing of the kinds of visual material that people encounter frequently in their daily lives (Bradley and Lang, 1999). Furthermore, the validity of emotional pictures in investigating emotional processing and brain activity has been demonstrated by several neuroimaging studies in which pictures with emotional content, selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1997), were presented to subjects (Hariri et al., 2002, 2003; Moratti et al., 2004; Müller et al., 2003; Phan et al., 2004).

Lang et al. (1997) have developed the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1997), a set of over 600 pictures, which includes normative ratings of the levels of pleasure and arousal associated with each picture. In healthy subjects, pictures with scenes of threat, violent death and erotica cause the strongest subjective emotional arousal and the largest physiological responses such as reflected in skin conductance level (SCL), whereas, unrelated to subjective arousal, unpleasant-evaluated pictures induce a greater heart rate (HR) deceleration and pleasant pictures a relatively greater peak acceleration (Bradley & Lang, 2000). At present, there are no such data available from patients with schizophrenia.

Apart from subjective evaluations, physiological responses to emotional stimuli in schizophrenia may be influenced by pathophysiological factors associated with distinct symptom domains (Buchanan and Carpenter, 1994). For instance, physiological variables have been associated with the presence of both positive and negative symptoms. There has been a tendency for positive symptoms to be associated with an increased skin conductance orienting response (SCOR), but these findings have been very mixed (Dawson et al, 1989; Green et al., 1989; Gruzelier and Raine, 1994; Zahn et al., 1991). With respect to HR, only a few studies have attempted to link tonic and phasic HR to schizophrenic symptomatology (Brekke et al., 1995). Toichi et al. (1999) found that the presence of a psychotic state suppresses HR variability, whereas schizophrenic patients with negative symptoms and ventricular enlargement have been found to show reduced resting HR (Cannon et al., 1992). Brekke et al. (1995) showed that negative symptoms were related to deficits in visuomotor processing, lower resting HR and increased HR reactivity to stress. They also observed that disorganised symptoms were related to increased SCOR and lower skin conductance stress reactivity. Overall, these data underline the relevance to study physiological responsivity to emotional stimuli in relation to the clinical symptoms of the schizophrenic patients.

The purpose of this study was to investigate the physiological reactions of schizophrenic patients to pictures with emotional content. During the

presentation of pictures selected from the IAPS (Center for the Study of Emotion and Attention, 1997), HR, SCL, breathing rate (BR), and diastolic and systolic blood pressure (DBP, SBP) were measured in order to identify alterations in responsivity to emotional stimuli of schizophrenic patients as compared to normal controls. Additionally, we assessed their subjective evaluations of the pictures in terms of valence and arousal ratings. Because scenes of threat, violent death and erotica cause the strongest emotional arousal and the largest physiological responses (Bradley et al., 2001a), we focused on pictures depicting erotica (positive emotions), mutilations and burns (negative emotions), and landscapes (neutral). Furthermore, we investigated the relationship between clinical symptom severity and physiological responsivity in schizophrenic patients, using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). By combining physiology with subjective evaluations and clinical symptoms, we hoped to increase our understanding of emotional disturbances in schizophrenic patients.

Methods

Subjects

Subjects were 28 inpatients (26 males, 2 females) selected from the Psychosis ward of the department of Psychiatry of the Erasmus University Medical Center in Rotterdam, and 30 age-matched controls (21 males, 9 females). The mean age of the patients was 24 (± 5) years and the mean age of the control subjects was 26 (± 6) years. The psychiatric diagnoses were performed by a senior psychiatrist; patients were eligible if they had the diagnosis schizophrenic or schizophreniform disorder according to the criteria of the DSM-IV (APA, 1994). Patients suffered from the paranoid (n=16), disorganised (n=7), undifferentiated (n=2) and residual (n=1) types of schizophrenia, and two patients were diagnosed as having a schizophreniform disorder. All patients experienced a psychotic episode at the time of the study. Twenty patients received medication: 6 risperidone, (mean dose 2.4 mg ± 0.9), 10 haloperidol (mean dose 2.7 mg ± 1.1), 4 olanzapine (mean dose 10.0 mg ± 4.1), and 8 patients were medication free at the time of testing. In order to assess symptom severity, the Dutch translation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used. The mean score on the PANSS was 72 (± 21) for the whole patient group.

Controls were recruited by means of advertisements. All controls were healthy and drug-free at the time of testing as assessed by means of an interview and a questionnaire. None of the controls had experienced past or current psychiatric illnesses.

Exclusion criteria for both patients and controls were colour blindness, respiratory diseases, cardiovascular diseases, and any other physical condition that could lead to a distraction from task performance.

After the subjects were given a complete description of the study, written informed consent was obtained. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center Rotterdam.

Procedure

All experimental sessions took place between 09.00 and 11.00 hrs in the morning. The subject sat in a comfortable chair in a small, sound-attenuated dimly lit room. Electrodes for recordings of HR, SCL, respiration and BP were applied according to standard procedures. Subjects performed the following three tasks, with five minutes of resting in between: an emotional priming task, the emotional picture task, and an emotional interference task. During the rest periods the subjects were asked to relax, to breathe regularly and not to speak. Saliva samples for cortisol assessments were obtained from the subjects after the first resting period and after the last task. Both patients and controls were asked not to use any coffee or cigarettes before and during testing. Only data of the emotional picture task will be presented in this paper.

In order to assess the clinical severity of the psychiatric symptoms for the schizophrenic patients, the PANSS interview was performed by a senior psychiatrist before the experimental measurement of the schizophrenic patient. The three subscales of the PANSS (Positive symptoms, Negative symptoms and General psychopathology) as well as the Total score of the PANSS were used for the analyses of potential relationships between clinical symptom severity and physiological responsivity to emotional stimuli.

The emotional picture task

The physiological responsivity to emotional stimuli of schizophrenic patients and control subjects were investigated by continuous measurement of the physiological signals (HR, SCL, respiration, and BP) before and during presentation of the emotional pictures. The pictures were selected from the IAPS (The Center for the Study of Emotion and Attention, 1997). The selected pictures were used by Bradley and Lang (1999) in a previous study. The stimuli were divided into four different categories: (1) pleasant, high arousal; (2) pleasant, low arousal; (3) unpleasant, high arousal; and (4) unpleasant, low arousal. From each of these four categories ten pictures were selected, which were used for the experimental condition. Three additional pictures were used as practice stimuli. Subsequently, 3 categories were formed for analysis of the physiological responses to the pictures. This selection was made based on the findings of Bradley et al (2001a), who found that pictures with erotic content and physical

injuries resulted in the most pronounced physiological responses. Our own data of healthy controls showed a similar pattern, and therefore a selection was made, resulting in three stimulus categories, each containing four pictures. The first category was *neutral*, including pictures of landscapes (IAPS picture numbers 5600, 5870, 5250, and 5830). The second category was *positive,* including pictures with erotic content (IAPS picture numbers 4220, 4210, 4490, and 4660). The third category was *negative*, including pictures of mutilations and burns (IAPS picture numbers 3100, 3170, 3000, and 8480).

Both patients and control subjects were asked to rate the emotional pictures on their degree of valence and arousal in order to obtain subjective evaluations of the pictures. Before the start of the emotional picture task, the subjects were familiarised with the SAM (Self-Assessment Manikin; Bradley and Lang, 1994) rating procedure. The SAM consisted of two sequential presentations on the computer screen, each containing five figures. In the first presentation, the figures represented the degree of pleasantness of the picture on a scale from one to five, and in the second presentation the figures represented the degree of arousal associated with each picture, also on a scale from one to five. During each of the sequential 43 trials, a fixation cross was presented for 20 seconds on the computer screen, followed by a 6-second presentation of a picture. Directly after the presentation of the picture, the subject was asked to rate the picture on both SAM dimensions of pleasure and arousal and then to relax again during the next 20 seconds.

During the task, pictures were presented on the computer screen, while the subjects sat at approximately 75 cm from the screen. Subjects responded with their dominant hand using a response box with five buttons.

The task was designed using E-prime (Psychology Software Tools, Inc., 2002), a software program for the generation and data collection of computerised psychological experiments.

Physiological measures

Continuous measurements were made of the HR, BP, SCL and respiratory signals. HR was determined from the consecutive R-R intervals of the ECG (precordial lead). Non-invasive BP was measured using a 2300 Finapres^{TM} Blood Pressure Monitor (Ohmeda, Englewood CO, USA; Penàz, 1976). With this method, a finger cuff containing photoelectronic components for measuring a blood plethysmograph and a bladder for applying pressure to the finger, is wrapped around the subject's finger of the non-dominant hand, and continuous arterial pressure is measured non-invasively. It was made sure that the non-dominant hand was located at the heart level in order to obtain reliable BP data. Respiration was measured using an inductive plethysmography method (belts containing a magnetic coil, Respitrace^{TM}). SCL was assessed using two active

Ag/AgCl electrodes attached to the medial phalanx of the index and ring fingers of the non-dominant hand.

All data were sampled and stored on a flashcard by means of a portable digital recorder (Vitaport™ System; TEMEC Instruments B.V., Kerkrade, The Netherlands); after completion of the recording, all physiological data were imported and processed on a Personal Computer using a Vitagraph™ software module (TEMEC Instruments BV, Kerkrade, The Netherlands).

Analysis of physiological data

The ECG was sampled at 128 Hz. A custom made computer program calculated the interbeat intervals of the ECG using R-top detection, resulting in a HR series consisting of beats per minute. These values were visually inspected for detection and removal of artefacts. Respiration was sampled at 8 Hz. With the plethysmography method, the excursions of the thorax associated with breathing were registered; from this oscillatory signal, the respiration or breathing rate (BR) of the subject was derived by means of instantaneous frequency analysis (Martens, 1992). The data were quantified in BR per minute and inspected visually for detection and removal of artefacts. SCL was sampled at 8 Hz and stored in μSiemens. BP was sampled at 128 Hz. The data were quantified using a custom made computer program, which calculated diastolic and systolic arterial pressure (DBP, SBP) values in mmHg for each consecutive R-R interval of the ECG.

For each picture we presented during the task, the values of the five physiological signals (i.e., HR, BR, SCL, DBP and SBP) were calculated every half second, starting from one second before stimulus onset until 6 seconds after stimulus onset. Thus, fifteen data points were calculated for each picture, resulting in a time series of the physiological response for each of the five signals. The baseline for each of the signals was calculated as the mean of the two data points before stimulus onset. In order to compute responses per picture, for each signal the baseline was subtracted from every half-second value after stimulus onset, resulting in a time series consisting of difference scores. Subsequently, for each of the three categories of pictures (positive, negative and neutral), mean response time series were calculated using the time series of the individual pictures belonging to that category, resulting in three time series per group (controls and patients) for each of the five physiological signals. Overall baselines per signal were computed by calculating the mean of all the baselines of the 43 individual pictures.

In order to quantify the relationships between the physiological responses to the emotional pictures and symptom severity, characteristic picture response values were defined for each of the five signals: the HR response was defined as the fastest half second value after the initial deceleration (based on Lang et al.,

1993), the SCL response as the largest value (in μSiemens) between 4 and 6 seconds after picture onset, whereas for BR, DBP and SBP the response values of the 6th second after picture onset were chosen, because this time-point appeared to differentiate best between the 3 emotional picture categories.

Statistical analysis

All patients and controls participated successfully in the experiment, although the HR and SCL data were lost for one patient due to technical problems.

In order to quantify differences in baseline values of the five physiological signals between patients and controls, independent samples t-tests were performed.

A Time (t_1-t_{13}) by Picture (positive, negative and neutral) by Group (patient and control) mixed model analysis of variance (ANOVA for repeated measures) was used for each of the five physiological signals to examine the effects of Time, Picture type and Group. We defined Group as the between subjects factor, and Time and Picture as the within subjects factors. Because of the non-linear responses that were found for the physiological signals, the relationship with Time was modelled as a third order function by including in the model time, time squared and cubic time. The within-subject serial correlation of the responses was assumed to have a first order autoregressive structure. Within the model, the interaction effects were tested for significance.

Within both groups, differences in the SAM ratings for pleasure and arousal between the three picture categories were analysed using the nonparametric Friedman's chi-square test. To test the differences in pleasure and arousal ratings between the patient and the control group, nonparametric Mann-Whitney U-tests were performed.

For each picture category, the five physiological response values were correlated with each of the three subscales of the PANSS (positive and negative symptoms and general psychopathology) and with the total PANSS score, in order to explore the relationships between severity of clinical symptoms and physiological responsiveness.

All statistical analyses were two-tailed, and the alpha was defined as 0.05. We used the Statistical Packages for the Social Sciences (SPSS) version 10.1 (SPSS Inc., 2000) and SAS 6.12 (SAS Institute, Inc., 1996) to analyse our data.

Results

Baselines

In Table 1, the results are shown for the baselines of each of the five physiological signals. The patients showed a significantly higher mean HR ($t = -3.73$, $p < 0.01$) and a significantly higher mean BR ($t = -2.71$, $p < 0.01$) than controls.

Table 1. Mean baseline values (sd) of the physiological parameters for the control group and patient group.

	Controls (n=30)		Patients (n=28)	
	Mean	(SD)	Mean	(SD)
SCL (μS)	9.03	(4.9)	7.59	(4.8)
HR (bpm)*	66.9	(8.5)	77.2	(11.9)
BR (breaths/m)*	13.9	(2.8)	16.0	(3.2)
DBP (mmHg)	85.6	(13.4)	82.5	(19.3)
SBP (mmHg)	140.4	(23.1)	137.0	(16.8)

* = significant difference between groups, $p < 0.01$
SCL: skin conductance level; HR: heart rate; BR: breathing rate;
DBP: diastolic blood pressure; SBP: systolic blood pressure

Emotional stimuli and physiological responses
Figures 1-5 present the mean responses in time of the physiological signals to each picture type (positive, negative and neutral) for both the control and the patient group.

Skin conductance level: a significant Time effect was found ($F = 6.80$, $p< 0.05$), indicating that the SCL responses of the subjects changed significantly in time from picture onset to the end of the picture presentation (Figure 1). Furthermore, a significant interaction effect was found for Time by Picture ($F = 3.83$, $p< 0.05$): in both the patient and the control group, the different emotional categories of pictures resulted in different response curves. Both groups showed a largest response to the positive pictures as compared to the neutral and negative pictures (Figure 1).

Heart rate: a significant Time effect was found ($F = 4.46$, $p< 0.05$), indicating that the HR responses of the subjects changed significantly during the 6-second picture presentation. Also, significant interaction effects were found for Time by Group ($F = 4.79$, $p< 0.05$) and for Picture by Group ($F = 5.12$, $p < 0.05$), indicating that the patient group showed a significantly different HR response in time as compared to the control group, regardless of picture valence, and that the patients also showed significantly different HR levels to the emotional pictures as compared to the control group. While viewing the positive pictures, the patients showed a gradual increase followed by a decrease in HR response, whereas the control subjects showed a biphasic response: an initial decrease, followed by a slight increase in HR (Figure 2). Furthermore, the controls showed a more pronounced decrease in HR while viewing negative pictures, in comparison with the patients.

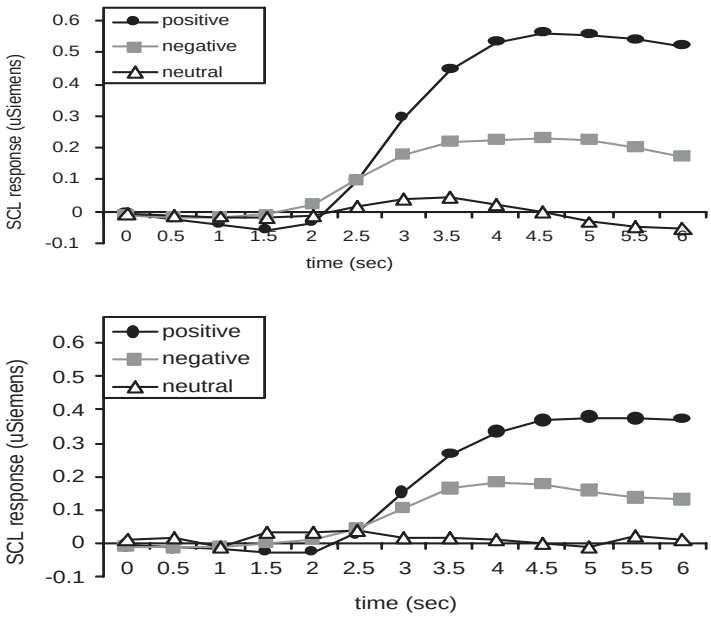

Figure 1. Mean SCL response (μSiemens) to positive, negative and neutral pictures during a 6-second picture presentation period; upper panel controls, lower panel patients.

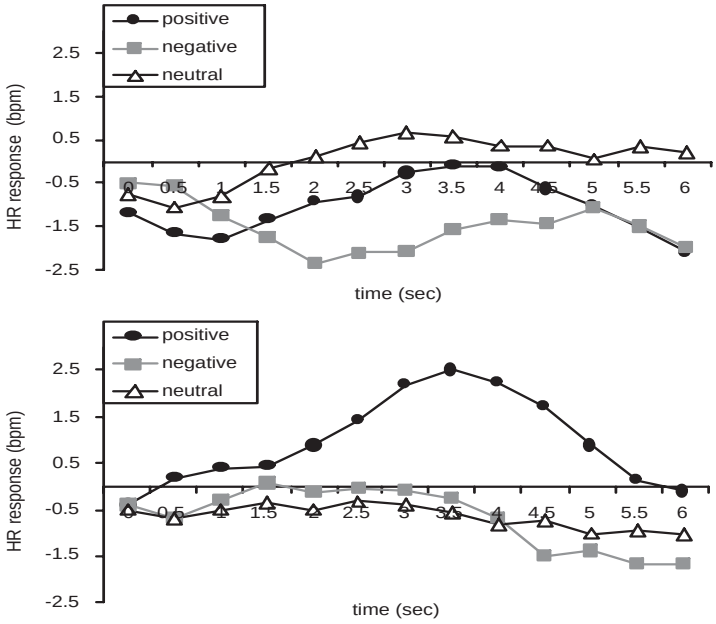

Figure 2. Mean HR response (bpm) to positive, negative and neutral pictures during a 6-second picture presentation period; upper panel controls, lower panel patients.

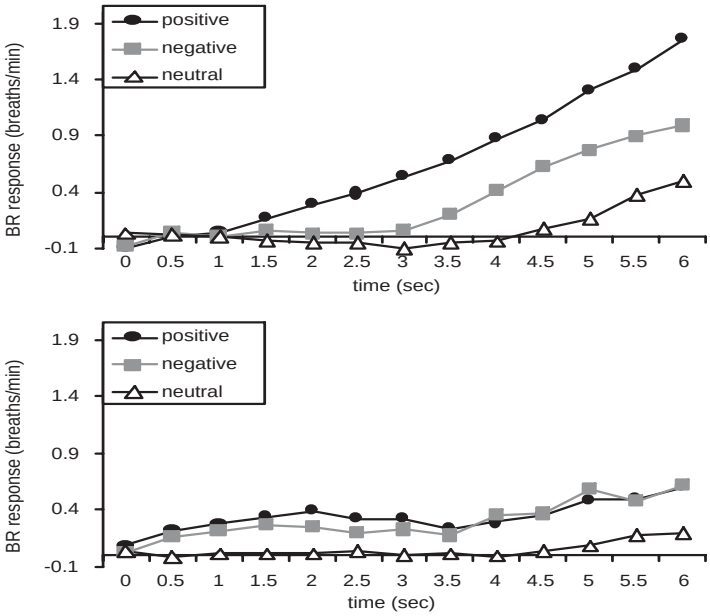

Figure 3. Mean BR response (breaths/min) to positive, negative and neutral pictures during a 6-second picture presentation period; upper panel controls, lower panel patients.

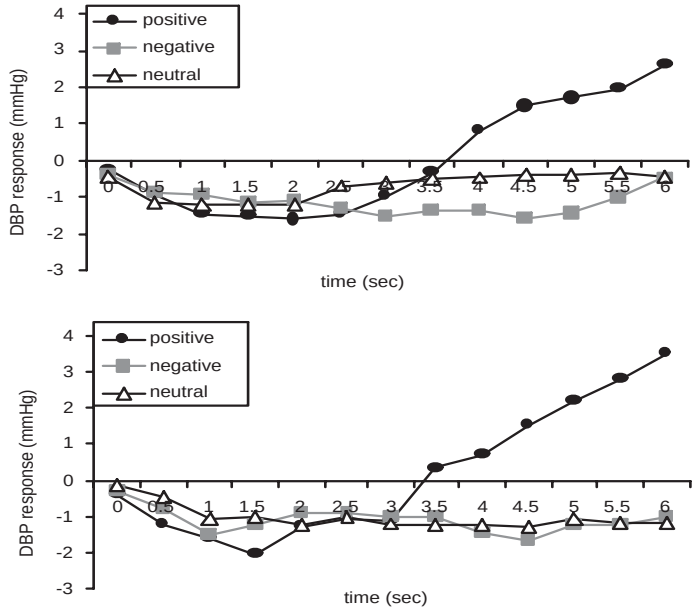

Figure 4. Mean DBP response (mmHg) to positive, negative and neutral pictures during a 6-second picture presentation period; upper panel controls, lower panel patients.

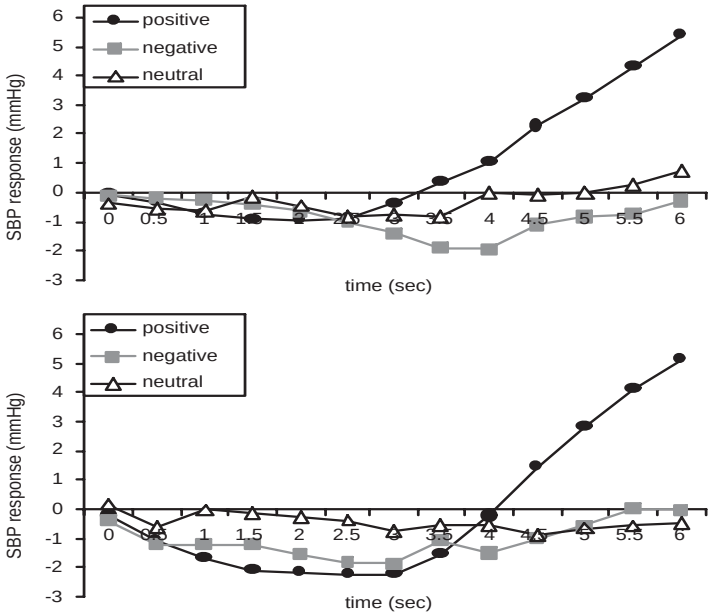

Figure 5. Mean SBP response (mmHg) to positive, negative and neutral pictures during a 6-second picture presentation period; upper panel controls, lower panel patients.

Breathing rate: for BR, no significant differences were found in response patterns either between or within the subject groups (Figure 3).

Systolic and diastolic blood pressure: a significant Time effect was found for both SBP and DBP ($F= 10.21$, $p< 0.00$; $F = 23.70$, $p< 0.00$, respectively), but only DBP showed a significant interaction effect for Time by Picture ($F = 4.33$, $p< 0.05$). Both groups showed a gradual increase in DBP response to the positive pictures as compared to the neutral and negative pictures (Figures 4, 5).

Emotional stimuli and subjective ratings

Within groups: Within the control group, the SAM-ratings of pleasure to the emotional picture categories differed significantly ($\chi^2(2) = 6$, $p < 0.05$; Table 2), with the negative pictures showing the lowest ratings, and the neutral pictures showing the highest ratings. The arousal ratings also differed significantly within the control group ($\chi^2(2) = 6$, $p < 0.05$), with the neutral pictures showing the lowest arousal ratings, and the positive and negative pictures both showing higher arousal ratings as compared to the neutral pictures. Within the patient group similar patterns were observed: the SAM-ratings of pleasure differed significantly ($\chi^2(2) = 6.5$, $p < 0.05$; Table 2), with the negative pictures showing

the lowest ratings, and the neutral pictures showing the highest ratings. For the patients, the arousal ratings also differed significantly for the different emotional picture categories ($\chi^2(2) = 6.5$, $p < 0.05$), with the neutral pictures showing lower ratings than the positive or negative picture categories.
Between groups: The patients and the controls did not differ in their subjective evaluations of the pictures, based on the pleasure and the arousal ratings. For the neutral pictures, however, a trend was found for the arousal ratings ($U = 1.5$, $p = 0.057$): the patients tended to rate the neutral pictures as more arousing as compared to the control group.

Table 2. Mean (sd) SAM-ratings for pleasure and arousal for the three picture categories Positive, Negative and Neutral, for the control group and the patient group.

Category	Controls		Patients	
	Pleasure*	Arousal*	Pleasure*	Arousal*
Positive	3.64 (0.8)	2.95 (0.4)	3.57 (0.8)	2.82 (0.5)
Negative	1.62 (0.4)	3.09 (0.2)	1.72 (0.7)	2.79 (0.1)
Neutral	4.14 (0.4)	1.76 (0.3)	4.14 (0.4)	2.23 (0.3)

* = significant difference between the emotion categories within groups, $p < 0.05$

Symptom severity and physiological responsivity
The mean scores of the patient group for the different subscales of the PANSS are listed in Table 3. Only the BR response to positive emotional pictures showed a significant positive correlation with the PANSS-subscales *Positive* ($R = .55$, $p< 0.01$), *General* ($R = .48$, $p< 0.05$), and with the *Total PANSS* score ($R = .47$, $p < 0.05$).

Table 3. The mean (sd) PANSS scores of the schizophrenic patients.

PANSS subscales	Mean (sd) n =28
Positive	16.7 (5.8)
Negative	20.0 (7.7)
General	35.6 (10.7)
Total PANSS score	72.2 (21.5)

Discussion
The purpose of this study was to investigate the physiological reactions of schizophrenic patients to pictures with emotional content. The schizophrenic patients showed higher HR and BR levels at baseline as compared to controls. Patients and controls did not differ in their subjective evaluations regarding valence and arousal of the pictures. Regarding physiological responses to the emotional pictures, for both patients and controls, the SCL and DBP responses to positive emotional pictures were larger as compared to negative and neutral

pictures. However, patients did show different HR responses to the emotional pictures. When evaluating physiological responsivity to emotional pictures in relation to clinical symptoms, none of the parameters, except for BR response, showed significant correlations with the PANSS scores.

To our knowledge, this is the first study to evaluate physiological reactions to emotional pictures in schizophrenic patients. We found that the control group and the patient group showed significantly different HR responses to the emotional pictures. Although we did not find a significant Time x Group x Picture interaction, we did find a significant Time x Group interaction. As can be seen in Figure 2, the responses to the positive emotional pictures are likely to contribute the most to this interaction effect. The control group showed an overall modest decrease in HR, first a deceleration, followed by only a slight acceleration. This pattern is similar to the findings of Bradley and Lang (2000) in healthy subjects. The patient group, however, showed a different type of response in time, as reflected by an initial gradual increase in HR, which was followed by a gradual decline after 3 seconds. According to Laceys' model of information processing, stimulus intake (outward directed attention) produces heart rate deceleration, while stimulus rejection (inwards directed processing) is associated with heart rate acceleration (Lacey and Lacey, 1970). Thus, according to this model, healthy subjects first direct their attention to the emotional stimulus (initial deceleration in heart rate) followed by an evaluation of the stimulus (the acceleration in heart rate). This theory is supported by the findings of several studies (Bradley and Lang, 2000; Hubert and De Jong-Meyer, 1990, 1991): while viewing emotional pictures or film clips, a classic triphasic pattern of HR is usually obtained, with an initial deceleration, followed by an acceleratory component, and a second deceleration.

The schizophrenic patients showed an initial acceleration when viewing the emotional pictures, which could imply a deficit in their ability to direct their attention to the emotional stimulus (deficit in orienting). However, Palomba et al. (1997) offer another possible explanation for the initial acceleration: according to Laceys' model, mild emotional stimulations are likely to produce an orienting response, while intense emotional states should be associated with inhibited information processing for protective purposes, resulting in an acceleration of the heart rate. It is possible that the schizophrenic patients experienced the erotic pictures as highly emotional, resulting in a heart rate acceleration. However, the patients did not differ in their subjective ratings of valence and arousal of the erotic pictures as compared to controls. Thus, from our results it is not clear whether the patients had difficulty in orienting to the erotic pictures, or whether the erotic stimuli were experienced as highly emotional by the schizophrenic patients.

The heart is doubly innervated by both the sympathetic and the parasympathetic nervous systems (Palomba et al., 1997). The increased HR responsivity which patients exhibited during the presentation of positive pictures as well as the higher mean HR level during baseline could be a result of either a sympathetic activation or a parasympathetic inhibition of the autonomic nervous system (Berntson et al., 1991; Guyton, 1991). However, since we did not find any significant differences in SCL and BP between patients and controls, there is reason to believe that a reduced parasympathetic nervous system activity alone may explain the HR differences that were found between the patients and controls in this study. Other studies (i.e. Malaspina et al., 1997; Toichi et al., 1997, 1999) have also found results to support the suggestion of a reduced parasympathetic activity in schizophrenic patients.

However, different studies investigating resting HR in schizophrenic patients have led to different results. Most studies found that schizophrenic patients exhibit higher resting HR levels as compared to controls (Zahn, 1975; Zahn et al., 1981; Volz et al., 1994; Zahn et al ., 1997), but not all studies have observed this: some studies report lower or normal resting HR (Dykman et al., 1968; Nielsen et al., 1988). In order to investigate whether the differences in baseline level for HR and BR we found in our study were due to the medication that the patients were taking, we performed a post-hoc analysis comparing the baseline levels of patients with (n=20) and patients without medication (n=8). We found that the mean baseline HR levels for both groups of patients were similar. Therefore, the increased mean HR levels of the patients could presently not be related to the combined effects of risperidone, haloperidol and olanzapine. The higher BR observed in patients, however, may be related to these drug effects, since we observed a significantly higher mean baseline BR for patients on medication. Due to the fact that different types of medications were used, it is presently not clear how to explain this finding.

We found similar ratings of valence and arousal for the emotional pictures between the control and the patient group, whereas the patients did show a different physiological response to the emotional pictures. This finding provides further support for the notion of a discrepancy between the subjective experience and the expression of emotions in schizophrenic patients, as suggested by Bleuler (1911). Kring and Neale (1996) also found support for the inhibition hypothesis: although schizophrenic patients differed in their amount of outwardly expressed emotions during the presentation of emotional film clips, they did not differ in the amount of subjective experienced emotion.

We found that only the positive pictures differentiated between the control and the patient group for the physiological responses. In this study, we presented erotic pictures as positive stimuli. It is possible that the specific nature of these erotic pictures led to the different physiological response pattern of the patient

group. For example, the physiological reactions of the control and the patient group may be the result of feelings other than 'pleasure', such as shame or discomfort when watching the erotic pictures, resulting in a greater arousal as compared to the pictures showing mutilations and landscapes. However, the subjective ratings of pleasure and arousal for the positive emotional pictures of the patient and the control groups were similar, although both patients and controls rated the neutral pictures as more positive than the 'positive'(erotic) pictures. For future research other types of picture categories should be studied, for instance non-erotic positive pictures, in order to investigate the difference in physiological and subjective responses between erotic and non-erotic positive pictures.

In this study, we did not differentiate between different subtypes of patients. For future research in this area, it may be useful to divide the schizophrenic group in different subgroups according to their symptomatology. In doing so, the relationship between different subtypes of schizophrenia and physiological responsivity can be investigated in more detail (Buchanan and Carpenter, 1994; Gruzelier and Davis, 1995). A further limitation of the study was, that we presented the physiological responses to different emotional catergories, which each contained only four pictures. The reliability of the physiological responses to each stimulus category found in the present study may therefore be questionable. However, our data do resemble the results of a previous study conducted by Lang et al (1993). In a subsequent study, each stimulus category should contain more stimuli in order to increase the reliability of the type of physiological response to each picture category.

Pictures of affective events and objects provide ecologically valid stimuli that people encounter daily in their lives. Furthermore, physiological changes, mediated by the somatic and autonomic systems are indices of the emotional environment of a person (Lang et al., 1998). As suggested by Bleuler (1911), schizophrenic patients may experience the same emotions as do 'normal' people, only schizophrenic patients have difficulties expressing their emotions. It would be a great advantage if one could investigate the emotional experiences of schizophrenic patients using more objective measures such as physiological parameters and relate these to the subjective feelings that the schizophrenic patients experience. In this first study, we observed that differences between patients and controls do exist regarding physiological responsivity to emotional stimuli, but that they are nuanced, stimulus specific and for most part unrelated to symptom severity. Further investigations will need to clarify the dynamics of the stimulus characteristics and the effects of specific pharmacological treatments on the physiological responses in order to come to a fuller understanding of emotional disturbances in schizophrenic patients.

CHAPTER 3

Subjective and physiological responses to emotion-eliciting pictures in male schizophrenic patients

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Abstract
Several studies have shown that schizophrenic patients have difficulties in their ability to recognize emotional facial expressions, whereas other research indicated that they subjectively report the same emotional experience as healthy controls. The purpose of this study was to investigate whether the physiological responses that accompany emotions differ between schizophrenic patients and controls, which would suggest a different basic emotional processing mechanism in these patients. We presented 40 emotion-eliciting pictures to male patients (n=26) and controls (n=21), while measuring heart rate (HR), breathing rate (BR), skin conductance response (SCR) and systolic blood pressure (SBP). Each subject rated each picture for its degree of valence and arousal. Mixed-effects regression models were used to investigate the relationships between the subjective ratings and the physiological responses. In both groups, BR and SCR increased with increasing arousal ratings, suggesting sympathetic activation. The SBP of both groups increased with increases in both the valence and the arousal ratings. However, whereas the patients' HR first decreased with decreasing pleasure ratings and subsequently increased with higher arousal and valence ratings, the HR in the control group was influenced by a complex interaction between valence and arousal ratings. Thus, the schizophrenic patients showed similar relationships between subjective ratings and SCR, BR, and SBP, but a different relationship between subjective ratings and HR compared with the healthy controls.

Introduction

Schizophrenic patients experience difficulties in emotional functioning (Bleuler, 1911/1950). They seem impaired in their ability to recognize emotional facial expressions, which is an important component of effective social functioning (Gur et al., 2002; Loughland et al., 2002). The patients themselves also display fewer facial expressions of emotions, which can have far-reaching social implications (Kring, 1999).

Although schizophrenic patients display the above described emotional disturbances, they do appear to experience emotions in a way similar to healthy controls. In two studies schizophrenic patients reported that they experienced the same amount of pleasant emotions as healthy controls, and greater amounts of unpleasant emotions in response to emotion-eliciting stimuli (Kring, 1999; Kring and Neale, 1996). It has also been found that schizophrenic patients experience less positive emotions and more negative emotions in response to daily stressors, compared with healthy control subjects (Myin-Germeys et al., 2001). Furthermore, several studies have found that patients and controls did not differ in their subjective ratings of pleasantness and arousal by different emotion-eliciting pictures (Quirk and Strauss, 2001; Takahashi et al., 2004; Volz et al., 2003). This paradox between the inability of schizophrenic patients to recognize and express emotional facial expressions and yet the ability to experience emotions in a way similar to healthy controls, has previously been explained by the suggestion that schizophrenic patients do not have a specific deficit in facial emotion recognition, but rather a more broader perceptual deficit (Kerr and Neale, 1993; Salem et al., 1996).

Apart from the ability to recognize emotional facial expressions, another important component of social functioning is the accurate identification and interpretation of emotional events in the environment, which increases the organism's chances of survival. The idea that emotions serve as survival mechanisms is supported by the fact that emotions are always accompanied by physiological reactions, such as changes in the somatic muscles and the viscera. These changes support the behavioural responses to the environmental stimuli (Bradley and Lang, 2000; Kring, 1999).

To investigate the subjective and physiological responses of individuals to emotional stimuli, a standardized set of over 600 emotional pictures has been developed: the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999). These stimuli are capable of eliciting characteristic patterns of physiological responses in healthy individuals. The deceleration of the heart rate (HR) –the basic cardiac response to perceptual stimuli– tends to be greatest for unpleasant pictures; the peak HR acceleration tends to be greatest for pleasant pictures (Bradley and Lang, 2000; Levenston et

al., 2000). Furthermore, Lang et al. (1993) found a significant linear relationship between HR acceleration and arousal ratings, albeit modest. Similarly, skin conductance responses (SCRs) are more pronounced for more arousing pictures (i.e., the highly pleasant and highly unpleasant pictures) than for neutral pictures, as is the blood pressure (BP) response (Globisch et al., 1999). Finally, changes in breathing rate (BR) are more likely to accompany changes in arousal than they are to accompany pleasantness: total breath duration and inspiratory time shortened when arousal ratings increased (Gomez et al., 2004). However, Gomez et al. (2004) also found that inspiratory time lengthened when the pictures were rated as more pleasant, suggesting that the degree of pleasantness is also capable of eliciting changes in respiration.

Only a few studies have investigated the autonomic responses of schizophrenic patients to emotion-eliciting pictures. Volz et al. (2003) have found that HR deceleration and SCR were largest when patients and controls viewed emotionally arousing pictures, but no differences between schizophrenic patients and controls were found. In a previous study conducted by our group (Hempel et al., 2005), we presented pictures selected from three distinct categories (positive: erotica, negative: mutilations, and neutral: landscapes) to schizophrenic patients while measuring their physiological responses. We found that both schizophrenic patients and healthy control subjects showed larger SCRs and larger responses in diastolic blood pressure (DBP) to pleasant, arousing pictures compared with unpleasant pictures. Nonetheless, schizophrenic patients showed a different HR response than the control subjects: the patients' HR did not decrease during the first seconds of viewing. In other words, the patients failed to show an orienting response to the pictures.

In the above described studies, the autonomic responses of the subjects were related to a priori defined picture categories, which were based on the normative ratings that accompany the IAPS pictures. In the present study, the subjective and physiological responses to emotion-eliciting pictures were investigated without defining picture categories in advance, in order to account for the differences in subjective ratings of individuals.

The aim of this study was to investigate whether the subjective responses to a broad range of emotion-eliciting pictures were related to the same physiological responses in schizophrenic patients and healthy controls. In doing so, we tried to elucidate whether the basic emotional motivations to emotion-eliciting pictures of schizophrenic patients were similar to those of healthy controls, since physiological responses can be linked to underlying emotional information processing mechanisms (Bradley, 2000). In the present study, a variety of pictures with different emotional contents selected from the IAPS were presented to both groups. During these presentations, HR, skin conductance level (SCL), BR and

systolic blood pressure (SBP) were measured continuously and subjects were asked to rate each picture on two subjective rating scales for valence and arousal using the Self-Assessment Manikin (Bradley and Lang, 1994).

In general, we hypothesized that the relationships between physiological responses and subjective ratings would differ between patients and controls only for HR, based on our previous study. More specifically, we expected that the HR of the controls would decrease most while viewing unpleasant pictures, whereas the schizophrenic patients would not show this decrease in HR response (Hempel et al., 2005). We expected the SBP, BR, and SCR to increase when the arousal ratings increased in both groups (Globisch et al., 1999; Gomez et al., 2004; Lang et al., 1993). Finally,we hypothesized that patients and controls would not differ in their subjective ratings of the emotion-eliciting pictures (Quirk and Strauss, 2001).

Methods

Subjects

Only males were included in this study, because differences have been found between men and women in their physiological responses to emotional pictures (Bradley, 2000; Sarlo et al., 2005). Twenty-six male inpatients (mean age 24 ± 5 years) selected from the Unit for Psychotic Disorders of the department of Psychiatry at Erasmus MC (Medical Center) in Rotterdam, and 21 age-matched male controls (mean age 25 ± 5 years) participated in this study. The psychiatric diagnoses were established by a senior psychiatrist. Patients were eligible if they met the criteria for schizophrenia according to the DSM-IV (APA, 1994). Patients suffered from the paranoid (n=14), disorganised (n=7), undifferentiated (n=2) and residual (n=1) types of schizophrenia, and two patients were diagnosed as having a schizophreniform disorder. All patients were very recently diagnosed with schizophrenia, and were experiencing a psychotic episode at the time of the study. Eight patients were previously hospitalized, all within one year before the present study; the remaining 18 patients had never been hospitalized before, and were experiencing their first (known) psychotic episode.

At the time of the testing, 19 patients were receiving medication: 5 risperidone (mean dose 2.6 mg ± 0.9), 10 haloperidol (mean dose 2.7 mg ± 1.1), and 4 olanzapine (mean dose 10.0 mg ± 4.1); 7 patients were drug-free. In order to assess symptom severity, a Dutch translation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used. The mean score on the PANSS was 72 (± 22; range 43-112) for the whole patient group.

Controls were recruited by means of advertisements. As assessed by an interview and a questionnaire, all controls were healthy and drug-free at the time of testing. None had experienced past or current psychiatric illnesses.

Exclusion criteria for both patients and controls were colour blindness, respiratory diseases, cardiovascular diseases, and any other physical condition that could lead to a distraction from task performance.

The study was approved by the Medical Ethical Committee of Erasmus MC Rotterdam. The study was carried out in accordance with the Declaration of Helsinki.

Affective stimuli

Forty pictures were selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999). The stimuli were chosen on the basis of their normative ratings and could be divided in four different categories: (1) pleasant, high arousal; (2) pleasant, low arousal; (3) unpleasant, high arousal; and (4) unpleasant, low arousal[1]. From each of these four categories ten pictures were selected, which were randomized and used for the experimental condition. The pictures were previously used in a study by Bradley and Lang (1999). All subjects viewed the pictures in a fixed random order. Three additional pictures were used as practice stimuli.

Procedure

One or more days before the start of the experiment, subjects were given a complete description of the study, both orally and in writing. When subjects fully understood the information given to them, their written informed consent was obtained.

All experimental sessions took place between 09.00 and 11.00 hrs. All participants were asked to refrain from coffee drinking and smoking before and during testing. The whole experimental procedure lasted 1.5 to 2 hrs. The subjects sat in a comfortable chair in a sound-attenuated, dimly lit room. Electrodes for the recordings of HR, SCL, SBP and BR were applied according to standard procedures.

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[1] The slide numbers of the IAPS pictures were as follows. Practice pictures: 7010, 4220, 3100. Pleasant, high arousal: 4210, 4490, 4660, 5600, 5830, 7230, 7270, 8080, 8490, 8510; the mean normative rating for valence was 7.21 and for arousal 5.84. Pleasant, low arousal: 1750, 1920, 2070, 2370, 2510, 4100, 5250, 5870, 7280, 7320; the mean normative rating for valence was 7.11 and for arousal 3.98. Unpleasant, high arousal: 1930, 2800, 3000, 3150, 3170, 6940, 8480, 9040, 9050, 9410; the mean normative rating for valence was 2.36 and for arousal 6.38. Unpleasant, low arousal: 1270, 2200, 2205, 2520, 2700, 2715, 2720, 9000, 9010, 9110; the mean normative rating for valence was 3.67 and for arousal 4.14.

Subjects performed three different tasks, the second of which was the emotion-inducing picture task discussed in the present article. Before and after each task, subjects were asked to relax, to breathe regularly and not to speak for five minutes. The first task that subjects performed was a brief reaction time task in which masked emotional faces were presented (Ekman and Friesen, 1976), and subjects had to indicate whether they saw a positive or a negative emotional face. This task lasted for 3 minutes, after which a resting period of 5 minutes was introduced. Then the emotion-inducing picture task was presented which is described in this study, followed by a 5-minute resting period. The third and final task was a reaction time task, again presenting emotional faces (Ekman and Friesen, 1976). The minimum period of 5 minutes between the first and second task was believed to be sufficient to rule out any effects of the previous task, which was not stressful or cognitively demanding, nor did it involve any IAPS-pictures. The investigator was present in the room during the entire session. Before the start of the task, subjects were familiarised with the computerised version of the SAM (Self-Assessment Manikin; Bradley and Lang, 1994) using three practice stimuli.

Measurements

Subjective ratings

Valence and arousal ratings were registered using an adapted version of the SAM rating-procedure (Bradley and Lang, 1994). The SAM consisted of two subsequent screens, each containing five figures. On the first screen, the figures represented the degree of pleasantness of the pictures -ranging from very unpleasant to very pleasant- on a scale from one to five. On the second screen, each figure represented the degree of arousal associated with each picture -ranging from very calm to very arousing- also on a scale from one to five.

During each trial, a fixation cross was presented for 20 seconds on a 19-inch computer screen, followed by a 6-second presentation of a picture. After picture offset, the subjects were asked to rate the picture on both SAM dimensions of pleasure and arousal. After their response, the fixation cross appeared again for 20 seconds, in order to give the physiological signals the opportunity to return to baseline levels.

The subjects were seated approximately 75 cm from the computer screen and responded with their dominant hand using a response box with five buttons.

The task was designed using E-prime (Psychology Software Tools, Inc., 2002), a software program for the generation and data collection of computerised psychological experiments.

Physiological measurements

During the experiment, continuous measurements were made of HR, SBP, SCL and BR. HR was recorded using a precordial lead, and was sampled at 128 Hz. BP was measured non-invasively using a 2300 Finapres™ Blood Pressure Monitor (Ohmeda, Englewood CO, USA; Penàz, 1973), and was sampled at 128 Hz. BR was obtained using an inductive plethysmography method (belts containing a magnetic coil, Respitrace™), and was sampled at 8 Hz. SCL was measured using two adhesive disposable active Ag/AgCl electrodes attached to the volar surfaces of the medial phalanges of the index and ring fingers of the non-dominant hand. SCL was sampled at 8 Hz, and stored in μSiemens.

All data were sampled and stored on a flashcard by means of a portable digital recorder (Vitaport™ System; TEMEC Instruments B.V., Kerkrade, the Netherlands). Upon completion of the recording, all physiological data were imported and processed on a Personal Computer using a Vitagraph™ software module (TEMEC Instruments BV, Kerkrade, the Netherlands).

Data analysis and reduction

For the analyses of our data, custom-made computer programs were used.

General baselines of the physiological signals were calculated from the five minutes resting period before the onset of the experiment.

For each picture, the values of the 4 physiological signals (HR, SCL, BR, and SBP) were calculated every half second, starting from 1 second before stimulus onset until 6 seconds after stimulus onset. All response values were first visually inspected for detection and removal of artefacts. Baselines for each of the signals were calculated from the mean of the two data points (1 second) before each stimulus onset. The baseline was subtracted from the signal for every half-second after stimulus onset, resulting in a time series consisting of difference scores (Bradley et al., 2001a).

For HR, the interbeat intervals were calculated using R-top detection. The HR series was derived from the inverse of the interbeat interval for each half second datapoint, resulting in a HR series consisting of beats per minute. The deceleration of the HR was defined as the largest decrease between 0 and 3 seconds after stimulus onset. The HR acceleration response was defined as the peak HR response between 3 and 6 seconds after stimulus onset (Gatchel and Lang, 1973; Lang et al., 1993).

SCR amplitude (μSiemens) was scored as the largest change relative to baseline within 1 to 4 seconds after picture onset (Bradley et al., 2001a). SCR responses were included in the analysis only if the SCR was at least 0.01 μSiemens. All SCR responses were log-transformed in order to reduce the skewness of the distribution.

For BP, the data were quantified using a computer program which calculated SBP for each R-R interval of the ECG. The SBP response was defined as the largest response between 0 and 6 seconds after picture onset.

The plethysmography method for BR registered the excursions of the thorax associated with breathing as an oscillatory signal, from which the BR of the subject was erived by means of instantaneous frequency analysis (Martens, 1992). With this type of analysis, small changes in the oscillatory signal can be detected immediately using the phase angle and instantaneous amplitude per sample to calculate the instantaneous frequency, and subsequently transform it into BR per minute. The BR response was defined as the largest increase between 0 and 6 seconds after picture onset.

Statistical analysis

In order to detect differences in basic physiology between patients and controls, the general baselines of the physiological signals during the 5 minute resting period were compared between groups using Student t-tests. Levene's test was used to test whether variances among the groups were homogeneous. If Levene's test indicated heterogeneous variances, the groups were compared by a t-test for unequal variances.

To investigate whether the groups differed in their subjective ratings of the a priori defined subgroups of emotional pictures (1= pleasant, high arousal; 2 = pleasant, low arousal; 3 = unpleasant, high arousal; and 4 = unpleasant, low arousal), we seperately analysed the subjective ratings for pleasure and arousal, using factorial ANOVA's (Analysis of Variance). Valence (pleasant vs. unpleasant) and Arousal (high vs. low) were defined as the within-subjects factors, and Group (patient vs. control) was defined as the between-subjects factor.

To assess the covariation between individual subjects' reports of valence and arousal and their psychophysiological responses (HR, BR, SCR, SBP), we used the mixed-effects regression model similar to Gomez and Danuser (2004). One of the major strenghts of this statistical approach is that all original data are used and analysed in the same statistical model. Thus, each combination of the subject's responses of valence, arousal and physiological response to each separate picture are used in the model, accounting for differences in the distributions of responses between individuals and groups. This leads to a minor loss of information of the original data. This statistical approach assumes linearity of the model and normality of the residuals and random effects, which is not always possible when collecting psychophysiological data. However, inspection of the data indicated a conformity to these assumptions.

Each model included random effects for Subjects and Pictures, and fixed effects for Valence, Arousal, Group, and the interaction terms Valence x Arousal,

Valence x Group, Arousal x Group, and the 3-way interaction term Valence x Arousal x Group. In order to find the best fit for the data, the models were tested with and without the interaction terms, using likelihood ratio tests and F-tests.

The Statistical Packages for the Social Sciences (SPSS) version 10.1 (SPSS Inc., 2000) and SAS 8.2 (SAS Institute Inc., 1999-2001) were used to analyse our data. The significance level for all analyses was set at 0.05.

Results

All patients and controls completed the experiment. For the general baseline analysis, SCR data was lost for 1 control subject and 2 patients, and SBP data was lost for 1 control subject and 3 patients. Furthermore, for the mixed effects regression analysis, HR data was completely lost for one patient and SCR data for another patient. All data was lost due to equipment failure. The actual number of subjects included will be mentioned for each analysis.

Subjective ratings

Valence ratings

Significant main effects were found for both Valence ($F(1,45)=239.15$, $p< 0.001$) and Arousal ($F(1,45)=16.85$, $p < 0.001$), indicating that, overall, both groups rated the pleasant pictures as more pleasant than the unpleasant pictures, and the less arousing pictures as more pleasant than the highly arousing pictures. A significant interaction effect was found for Valence x Arousal ($F(1, 45) = 69.68$, $p < 0.001$). The interaction effect we found was due to the higher valence ratings for the 'unpleasant, low arousal' pictures as compared with the 'unpleasant, high arousal' pictures. No significant Group main effects nor interactions were found, indicating that the groups did not differ in their Valence ratings. Mean Valence ratings for both groups are presented in Table 1.

Arousal ratings

A significant main effect was found for Arousal ($F(1,45)= 111.98$, $p < 0.001$), indicating that both groups rated the highly arousing pictures as more arousing than the less arousing pictures. Furthermore, a significant interaction effect was found for Valence x Arousal ($F(1,45) = 6.22$, $p < 0.05$), due to the larger arousal ratings for 'high arousal, unpleasant' pictures compared with the 'high arousal, pleasant' pictures. No significant Group main effects nor interactions were found. Mean Arousal ratings are presented in Table 1.

Table 1. Mean (SD) Valence and Arousal ratings for controls and schizophrenic patients.

		Controls (n=21)		Patients (n=26)	
		Valence	Arousal	Valence	Arousal
Picture Type		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Pleasant	High arousal	3.90 (0.38)	2.42 (0.72)	3.83 (0.64)	2.56 (0.87)
	Low arousal	3.74 (0.32)	1.67 (0.64)	3.74 (0.71)	1.94 (0.81)
Unpleasant	High arousal	1.83 (0.51)	2.85 (1.09)	2.00 (0.75)	2.72 (1.00)
	Low arousal	2.53 (0.30)	2.54 (0.65)	1.79 (0.68)	1.85 (0.62)

Valence ratings : 1=very unpleasant; 2= unpleasant; 3=neutral; 4= pleasant; 5=very pleasant. Arousal ratings: 1=very calm; 2= calm; 3=slightly arousing; 4= arousing; 5=highly arousing

Baselines

In Table 2, the results are shown for the general baselines of each of the five physiological signals. The SCL of the patients was significantly lower than the SCL of controls ($t(42)=2.98$, $p<0.01$). The patients' HR was significantly higher during baseline compared with the control group ($t(45) = -2.61$, $p < 0.05$). Patients also breathed significantly more rapidly during baseline compared with the control subjects ($t(45) = -2.64$, $p < 0.05$).

Table 2. Mean (SD) baselines of the physiological signals during the 5 minute resting period prior to the experimental procedure, presented for each group.

	Controls		Patients	
Skin conductamce level (μSiemens)**	9.9 (6.8)	n=20	5.2 (3.7)	n=24
Heart rate (bpm)*	69 (10)	n=21	79 (15)	n=26
Breathing rate (breaths/min)*	14 (3)	n=21	16 (3)	n=26
Systolic blood pressure (mmHg)	132 (19)	n=20	132 (15)	n=23

* = significant difference between groups, $p < 0.05$;
** = significant difference between groups, $p < 0.01$

Relationships between physiological responses and subjective ratings

Each model consisted of the fixed effects, represented by the β-coefficients, and the residual variance, consisting of a between-subjects component, $\alpha_{subjects,}$ a within-subjects and between pictures component, $\alpha_{pictures,}$ and a within-subjects pure error component, ε.

Heart rate responses

For HR deceleration a significant Valence x Group interaction effect was found ($F(1,1823)=3.96$, $p<0.05$). This interaction effect indicated that the effect of Valence ratings on HR was different between the patients and the controls. In the control group, the HR decreased with 0.43 beats per minute (bpm) per unit

increase in Valence rating, corrected for Arousal ratings, whereas the HR of the patient group was hardly affected by varying Valence ratings (Table 3 and Figure 1), only increasing with 0.01 bpm per unit increase of Valence.

For HR acceleration, a significant three-way interaction was found, Valence x Arousal x Group ($F(1,1826)=3.78$, $p<0.05$), indicating that the interaction effect of Valence x Arousal was different for controls and patients (Table 4). In the patient group, the effect of Valence ratings on HR increased with increasing Arousal ratings, with [0.08 x Arousal] bpm. The effect of the Arousal ratings increased with increasing Valence ratings, with [0.20 + 0.08 x Valence] bpm. In other words, the more pleasant and arousing the picture was, the more the HR of the patients increased. In the control group, however, the effect of subjective ratings on the HR varied. For every increase in Valence rating, the HR either increased or decreased, depending on the Arousal rating, with [0.87 - 0.35 x Arousal] bpm. The net effect of an increase in Valence ratings on HR was, that HR increased with Arousal ratings 1 to 2 (very calm and calm), but subsequently decreased with Arousal ratings 3 to 5 (normal to very arousing). For every increase in Arousal rating the HR either increased or decreased, depending on the Valence rating, with [0.65 - 0.35 x Valence] bpm. The net effect of an increase in Arousal ratings on HR was, that HR increased when the Valence rating was 1 (very unpleasant), but decreased when the Valence rating ranged from 2 to 5 (unpleasant to very pleasant). In Figure 2 a three-dimensional plot is presented in order to clarify the complex interaction effects of

Skin conductance responses

For the SCR, a significant main effect for Arousal was found ($F(1,872) = 5.84$, $p < 0.05$), indicating that, in both groups, the SCR increased with 0.09 unit LnSCR per unit increase in Arousal rating, corrected for Valence ratings (see Table 5 and Figure 3).

Breathing rate responses

For BR, a significant main effect for Arousal was found ($F(1,1787) = 7.33$, $p < 0.01$). In both groups, the BR increased with 0.13 breaths per minute per unit increase in Arousal rating, corrected for Valence ratings (see Table 6 and Figure 4).

Systolic blood pressure responses

For SBP, a significant interaction effect was found for Valence x Arousal ($F(1,1751) = 4.64$, $p < 0.05$). In both groups, for every increase in Valence rating, the slope of SBP on Arousal ratings increased with 0.18 mmHg, and vice versa (see Table 7 and Figure 5).

Table 3. Beta coefficients of the model fitted for HR deceleration

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	-2.08	1.06	-1.95	0.05	-4.17	0.01
V	-0.43	0.27	-1.58	0.11	-0.96	0.10
A	-0.37	0.30	-1.22	0.22	-0.96	0.22
Group	-1.80	1.10	-1.63	0.10	-3.96	0.37
V x A	0.06	0.08	0.83	0.40	-0.08	0.21
V x Group	0.44	0.22	1.99	0.05	0.01	0.88
A x Group	0.24	0.26	0.92	0.36	-0.27	0.75

Significant effects ($p<0.05$) are presented in bold. V=Valence; A=Arousal; CI=confidence interval. NB. The control group was the reference group in the model.

Table 4. Beta coeffiecients of the model fitted for HR acceleration

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	1.76	1.93	0.91	0.36	-2.03	5.55
V	0.87	0.55	1.58	0.11	-0.21	1.96
A	0.65	0.60	1.07	0.28	-0.54	1.83
Group	0.41	2.31	-0.18	0.86	-4.13	4.94
V x A	-0.35	0.18	-1.90	0.06	-0.71	0.02
V x Group	-0.87	0.65	-1.35	0.18	-2.14	0.40
A x Group	-0.45	0.74	-0.62	0.54	-1.90	0.99
V x A x Group	0.43	0.22	1.95	0.05	0.01	0.86

Significant effects ($p<0.05$) are presented in bold ; V=Valence; A=Arousal; CI=confidence interval. NB. The control group was the reference group in the model.

Table 5. Beta coeffiecients of the model fitted for SCR

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	-1.72	0.28	-6.21	<0.01	-2.28	-1.17
V	-0.02	0.03	-0.48	0.63	-0.08	0.05
A	0.09	0.04	2.42	0.02	0.02	0.17
Group	-0.46	0.33	-1.37	0.18	-1.13	0.22

Significant effects ($p<0.05$) are presented in bold. V=Valence; A=Arousal; CI=confidence interval. NB. The control group was the reference group in the model.

Table 6. Beta coeffiecients of the model fitted for BR

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	2.04	0.27	7.67	<0.01	1.52	2.57
V	-0.06	0.04	-1.35	0.18	-0.14	0.03
A	0.13	0.05	2.71	0.01	0.04	0.23
Group	-0.30	0.28	-1.08	0.29	-0.87	0.26

Significant effects (p<0.05) are presented in bold. V=Valence; A=Arousal; CI=confidence interval. NB. The control group was the reference group in the model.

Table 7. Beta coeffiecients of the model fitted for SBP

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	4.19	0.94	4.45	<0.01	2.34	6.05
V	-0.06	0.24	-0.23	0.82	-0.54	0.42
A	-0.09	0.29	-0.30	0.76	-0.66	0.49
Group	-0.03	0.65	-0.05	0.96	-1.35	1.28
V x A	0.18	0.09	2.15	0.03	0.02	0.35

Significant effects (p<0.05) are presented in bold. V=Valence; A=Arousal; CI=confidence interval. NB. The control group was the reference group in the model.

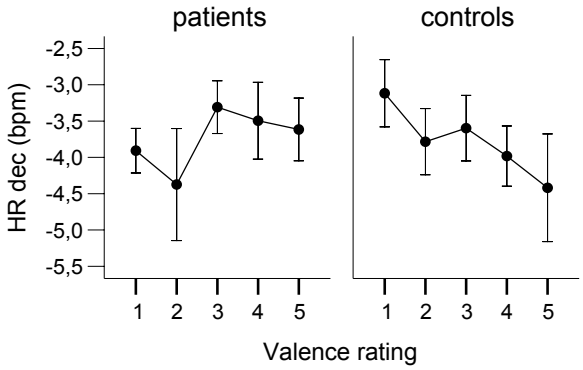

Figure 1. Mean heart rate deceleration (HR dec; bpm ±SE) by valence ratings (1= very unpleasant; 5=very pleasant). The left panel represents the HR response of the patients; the right panel represents the response of the control subjects.

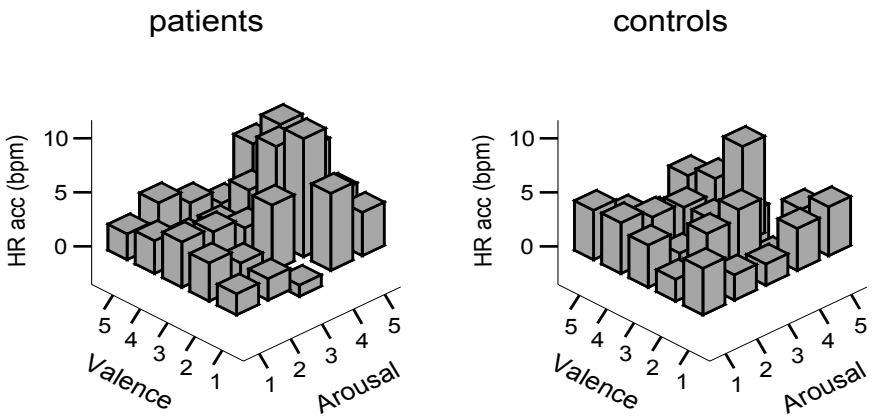

Figure 2. Three-dimensional representation of the mean heart rate acceleration (HR acc; bpm) by valence and by arousal ratings. The left panel represents the HR response of the patients, and the right panel represents the response of the control subjects.

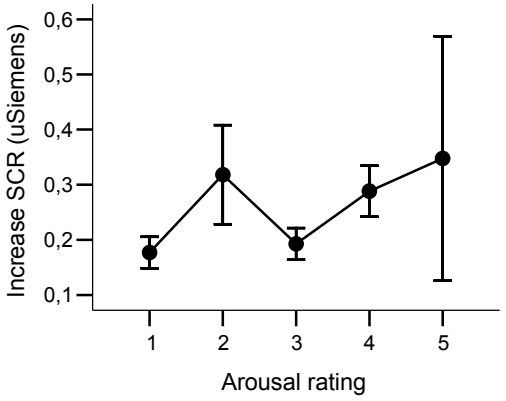

Figure 3. Mean increase in skin conductance response (SCR;µSiemens ± SE) by arousal ratings (1= very calming; 5= very arousing) for all subjects.

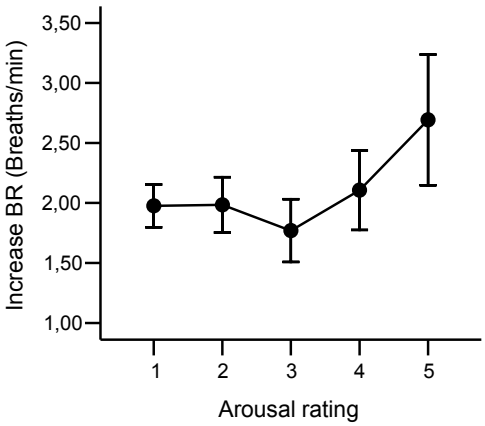

Figure 4. Mean increase in breathing rate (BR; breaths/min ± SE) by arousal ratings (1= very calming; 5= very arousing) for all subjects.

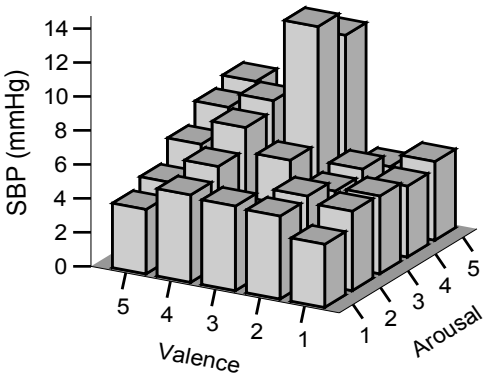

Figure 5. Three-dimensional representation of the mean increase in systolic blood pressure (SBP; mmHg) by valence and by arousal ratings for all subjects.

Discussion

The aim of this study was to investigate if the physiological responses to emotion-eliciting pictures related to the subjective responses differently for schizophrenic patients and healthy control subjects. In summary, we found that the only difference between patients and controls lay in the HR responses in relation to the subjective ratings. For SCR, BR, and SBP no differences between the two groups were found: SCR and BR increased with increasing arousal ratings, and SBP increased with increasing arousal and valence ratings. Furthermore, no differences between the groups were found when we investigated the subjective ratings of the a priori defined picture categories. Both groups responded as expected: the interaction effects indicated that the unpleasant, highly arousing pictures were rated as more unpleasant than the unpleasant, less arousing pictures, and the unpleasant, highly arousing pictures were rated as more arousing than the pleasant, highly arousing pictures.

HR responses in relation to subjective ratings

For HR deceleration, we found a difference between the patients and the controls, which indicated that the controls showed larger orienting responses (i.e. larger HR decelerations) with increasing valence ratings, i.e. when they rated the pictures as pleasant. On the basis of previous research, we hypothesized that the HR deceleration of the control group would become larger as ratings of unpleasantness increased (Bradley and Lang, 2000). A greater initial deceleration in HR is indicative of a more profound orienting response during passive picture viewing (intake of the stimulus material), and this orienting response is greater when viewing negative pictures (Bradley and Lang, 2000). It is unclear why the controls in this study showed the opposite pattern of what is generally reported in the literature. Thus, contrary to our expectations, our findings suggest that the controls had a large orienting response to the positively rated pictures, whereas the patients did not show a clear linear relationship between subjective ratings and HR deceleration. This latter finding is in line with our previous study (Hempel et al., 2005), in which the patient's HR did not seem to decelerate during the first three seconds of picture viewing, whereas the HR of the controls did. This absence of HR deceleration in the patient group indicates an absence of the orienting response, suggesting a lack of stimulus intake during the first three seconds of picture viewing. However, since the subjective ratings of the patients did not differ from the controls, the patients were able to process the stimulus material in a similar way to controls, possibly needing more time to do so.

The other difference we found between patients and controls was that, in the control group, the impact of the Valence ratings on the HR response depended on the Arousal ratings. In other words, the HR of the control group was more

influenced by the interaction between these two rating scales than the HR of the patient group. If the picture was rated as pleasant by the control group, it depended on the arousal rating whether the HR would increase or decrease. With calm, pleasant pictures the HR increased, whereas with arousing, pleasant pictures the HR decreased. This would suggest a sustained orienting response towards arousing, pleasant pictures such as erotic scenes. Very arousing, unpleasant pictures such as mutilations resulted in HR accelerations in the control group. The results we found are inconsistent with the literature on healthy control subjects (Bradley and Lang, 2000; Lang et al., 1993). The HR of the controls decreased with increasing arousal ratings. This result seems contradictory to the results described by Lang et al. (1993), who found a modest linear relationship between Arousal ratings and HR acceleration in healthy subjects. The difference in results between the present study and the study by Lang et al. (1993) is possibly due to methodological differences, in particular the statistical methods that were applied.

The HR of the patient group was less influenced by the interaction of the Valence and Arousal ratings. Instead, the HR of the patient group increased with increasing valence and arousal ratings, consistent with the literature on healthy control subjects (Bradley and Lang, 2000; Lang et al., 1993).

SCR, BR and SBP responses in relation to subjective ratings

For SCR and BR we found similar relationships between the subjective ratings and the physiological responses in both groups: both the SCR and the BR responses increased with increasing arousal ratings. These findings are consistent with previous research conducted with healthy subjects (Gomez et al., 2004; Lang et al., 1993; Van Diest et al., 2001), and indicate that patients did not differ from controls in their SCR and BR responses to arousing pictures.

The SBP responses increased when both the arousal and the valence ratings increased in both groups. This result replicates the findings of two other studies (Globisch et al., 1999; Sarlo et al., 2005), in which it was also found that highly arousing pleasant pictures prompt a significant increase in blood pressure relative to neutral pictures. Sarlo et al. (2005) related this increase in blood pressure to a peripheral activation as a result of sexual arousal. In the present study, we included only 3 pictures with erotic content. It seems unlikely that this small number of erotic pictures alone caused this relationship, indicating that an increase in peripheral blood pressure can also be induced by pleasant, arousing pictures without erotic content.

Parasympathetic versus sympathetic activity

The finding that patients did not differ from control subjects for SCR might indicate that these patients do not differ in their sympathetic responses to emotion-

eliciting pictures. This idea is further supported by the finding that patients and control subjects did not differ in their SBP response, which is also mainly influenced by the sympathetic nervous system (Sakaguchi et al., 1983; Watanuki and Kim, 2005). The patients and controls also had similar baseline levels of SBP. The patients did show a lower baseline value of SCL compared with the control group, but this lower baseline did not seem to affect the responses of the patients to the emotion-eliciting pictures.

HR is controlled by the parasympathetic and sympathetic nervous systems. Since the patients and controls did not differ in their sympathetic responding to the emotion-eliciting pictures, the differences between patients and controls in HR responses may be due to differences in parasympathetic activation of the autonomic nervous system. During the baseline period, HR was significantly higher in the patient group than in the control group. Bär et al. (2005) have related the increased HR of schizophrenic patients to a parasympathetic hypofunction in the acute stage of the disease. However, since we found that the controls did not show the expected relationships between HR responses and subjective ratings, it is difficult to interpret the differences between patients and controls. A parasympathetic hypofunction seems unlikely however, considering the presence of the HR responses of the patients in relation to the arousal ratings.

Limitations

Our control group did not respond as we had expected on the basis of the existing literature on physiological responses to emotion-eliciting pictures. We should, therefore, be cautious, both in interpreting the results and in comparing the patient group with the control group. On the other hand, our approach to investigating the relationships between emotion-eliciting pictures and psychophysiological responding was different to that of other research in this area. To our knowledge, this is the first study to investigate the relationship between subjective ratings of these pictures and physiological responses in schizophrenic patients. It is quite possible that relating physiological responses to a priori defined picture categories leads to different results than relating physiological responses to subjective ratings of a variety of pictures, regardless of the exact picture contents. The effects of the application of different statistical methods on the relationship between physiological and subjective responses should be investigated more thoroughly in future studies.

Another limitation of this study was the small sample size, particularly of the control group, which could account for the possible lack of power for the analyses. Only males were included in this study, because of the differences that have been found between men and women in their physiological responses to emotion-eliciting pictures (Bradley, 2000; Sarlo et al., 2005). Unfortunately, these

small sample sizes may have influenced our results: the regression models that we used in the present paper tested multiple variables and interactions, and we cannot rule out the possibility that some of the significant interaction effects we found were in fact due to chance (type I errors). On the other hand, it is possible that we have not detected possible effects as a result of the relatively large confidence intervals of some of the regression estimates (see Tables 3 to 7), introducing type II errors.

The patient and control groups were matched for age and gender. However, they were not matched for educational level or socioeconomic status. Although the subjective rating task the subjects had to perform was not designed to be cognitively demanding, and the subjects were told in advance that there were no'wrong answers', the possible differences between the groups in educational level or socioeconomic status may have influenced their responses to the pictures. The lack of differences between the subjective ratings of the two groups, however, suggests that these possible influences on the results were minimal.

The differences between patients and controls we found for the HR responses and the baseline values of HR, BR and SCL could be the result of the medication most patients were using. When we performed post-hoc analyses, in which we tested for differences in the baseline values between patients who used medication at the time of testing and patients that did not, no differences were found. We also performed post-hoc analyses for the physiological responses in relation to the subjective ratings when we found significant group main or interaction effects. We did not find any differences between patients with and without medication. However, a medication effect cannot be completely ruled out, since a lack of statistical power due to the small drug-free group (n=7) could possibly account for the absence of significant effects.

Conclusion

The purpose of this study was to investigate whether schizophrenic patients and healthy controls differed in their relationships between physiological responses and subjective ratings, which would suggest a different underlying emotional processessing mechanism in schizophrenic patients during the viewing of emotion-eliciting pictures.

We found that the schizophrenic patients showed the relationships between physiological responses and subjective ratings consistent with the existing literature on healthy control subjects. Based on these findings, we suggest that the basic emotional processing mechanisms that can be inferred from psychophysiological responses are comparable between schizophrenic patients and healthy control subjects. However, since we did not find the expected relationships

between HR responses and subjective ratings in the control group, the only physiological response in which the two groups differed, these results should be interpreted with caution.

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CHAPTER 4

Cardiac responses to emotion-eliciting pictures and startle stimuli in male schizophrenic patients: attention and emotion

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Abstract
Schizophrenic patients suffer from both cognitive as well as emotional disturbances. However, there is still some debate whether the emotional disturbances are specific to emotional functioning, or rather reflect a more generalized impairment in attentional functioning. This study aimed to investigate whether different physiological responses to emotion-eliciting pictures result from impairments in attentional or emotional functioning, or both. We measured cardiac responses of 34 patients and 40 healthy control subjects while acoustic startle stimuli and emotion-eliciting pictures were presented. Patients and controls did not differ in their cardiac responses to the startle stimuli, but the cardiac responses of the patients during picture viewing did differ from those of controls. The patients showed a significantly decreased initial orienting response (0-3 seconds), regardless of the contents of the pictures. Furthermore, the heart rate response of the patients increased significantly with increasing arousal ratings during the second phase of picture viewing (3-6 seconds), whereas the opposite was found in controls. These results indicated that schizophrenic patients initially directed less attention to the pictures, and subsequently responded in a defensive manner to both pleasant and unpleasant pictures. We conclude that the differences in emotional processing between patients and controls are the result of disturbances in both attentional and emotional processes. Furthermore, schizophrenic patients have a lower threshold for physiological defensive responding, which may result in the misinterpretation of emotion-eliciting stimuli, with possible consequences for the social functioning of these patients.

Introduction

In the last 20 years, an extensive amount of papers has been published on the impaired emotional functioning of schizophrenic patients. Most of this research has focused on the impaired ability of these patients to recognize emotions from facial expressions (Pinkham et al., 2007), which is an important component of effective social functioning (Loughland et al., 2002). It is still unclear whether the impairment in affect perception is a specific emotional deficit or whether it is related to a more generalized impairment in perception (Bozikas et al., 2004). Apart from the ability to recognize emotional expressions, the ability to recognize emotional cues from the environment is another important component for survival: signalling potential danger or reward and preparing for an appropriate response increases the chances of survival (Phillips et al., 2003a). Emotions are accompanied by physiological reactions, such as changes in the somatic muscles and the viscera. These changes support the behavioral responses to the environmental stimuli and prepare the organism for action, such as fight, flight or approach behaviour (Bradley and Lang, 2000; Kring, 1999). The cardiac response is an important component of this behavior, and the response varies with the contents of emotion-eliciting pictures. In healthy subjects, the heart rate response during picture viewing shows a triphasic pattern: first an initial deceleration, followed by an acceleration and a subsequent deceleration (Bradley and Lang, 2000). The initial deceleration of the heart rate (HR) is considered to be the basic cardiac response to perceptual stimuli, also referred to as the orienting response (OR), and tends to be greatest for unpleasant pictures. The cardiac OR is thought to reflect the intake of stimulus information (Graham & Clifton, 1966; Turpin, 1986, Turpin et al.,1999). The peak HR acceleration (AR), on the other hand, tends to be greatest for pleasant pictures (Bradley and Lang, 2000; Levenston et al., 2000).

Cardiac responses to emotion-eliciting pictures have not been investigated extensively in schizophrenic patients. Two studies measured cardiac responses to emotion-eliciting pictures as part of a larger investigation, but they did not find any clear differences between schizophrenic patients and healthy control subjects (Schlenker et al., 1995; Volz et al., 2003). However, both studies calculated the averaged heart rate response during slide viewing relative to a 1- or 2-second baseline before picture onset, without taking into account the triphasic pattern of the cardiac response. In a study previously conducted by our group, the time series of the heart rate responses to emotion-eliciting pictures were investigated (Hempel et al., 2005). Schizophrenic patients showed only minor orienting responses to neutral and negative pictures, and no orienting response to positive (erotic) pictures. The substantial increase in heart rate, that was evoked by the erotic pictures in schizophrenic patients, suggested stimulus rejection (Lacey and Lacey,

1970). However, the patients and controls did not differ in their subjective ratings of the pictures: both groups equally rated the erotic pictures as more pleasant and arousing than the neutral pictures.

A more simple and objective paradigm to investigate cardiac responses, is by presenting acoustic stimuli (tones) to subjects while measuring their heart rate responses. Cardiac responses to acoustic stimuli can be used to distinguish three types of responses: orienting (OR), defense (DR), and startle responses (SR), depending on the stimulus characteristics (Gautier and Cook, 1997; Turpin, 1986). In this paper we will focus on the SR to acoustic stimuli. The SR is the cardiac response to a loud and unexpected noise, and is considered to be a defensive reaction, thought to be mediated vagally (Fernández and Vila, 1989). The SR reflects a disengagement from ongoing activity that leads to the detection of potential danger, thereby rejecting the intake of the current stimulus information (Lacey and Lacey, 1970; Ramírez et al., 2005). By presenting a loud acoustic stimulus to patients it can be investigated whether schizophrenic patients show a different classical defensive response to acoustic stimuli compared with healthy control subjects.

The presentation of emotion-eliciting pictures is an often used paradigm to bring about an emotional state in the subject. At present it is unclear whether the absence of a clear orienting response to emotion-eliciting pictures in schizophrenic patients (Hempel et al., 2005) is the result of a general attention deficit, the result of rejection of the stimulus material based on the contents of the stimulus, or both. Therefore, the aim of this study was to investigate cardiac responses to both emotion-eliciting picture stimuli as well as acoustic startle stimuli. We presented a variety of pictures selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999). Twelve acoustic startle stimuli were also presented in between picture presentations, to investigate the cardiac SR to acoustic stimuli. Based on previous research (Hempel et al., 2005), we hypothesized that the schizophrenic patients would show diminished OR responses and increased AR responses to the emotion-eliciting pictures, in particular to the positive pictures. Furthermore, we investigated the SR's to acoustic stimuli of these patients, to investigate whether they differed regarding their defensive responses to non-emotional stimuli. Finally, we also investigated the relationship between the OR, AR and SR, to establish whether cardiac responses to emotional visual stimuli were related to cardiac responses to acoustic startle stimuli.

Methods

Subjects

In this study, 34 male schizophrenic patients (mean age 22 ± 5 years) and 40 male control subjects (mean age 23 ± 4 years) participated. The patients were recruited from the early psychosis unit at the department of Psychiatry of Erasmus MC, University Medical Center Rotterdam. All patients were screened by a clinical psychiatrist (NvB, CH) and included in the study when they were diagnosed as suffering from schizophrenia or a schizophreniform disorder according to the criteria of the DSM-IV (APA, 1994). In order to assess symptom severity, the Dutch translation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used.

All patients experienced a psychotic episode at the time of the study. Antipsychotic treatment was administered according to the clinical treatment protocol of the Erasmus MC clinic for psychotic disorders, which is congruent with both the schizophrenia treatment guidelines of the Dutch Psychiatric Association and the American Psychiatric Association.

Controls were recruited by means of advertisements. All controls were healthy and unmedicated at the time of testing as assessed by means of an interview and a questionnaire. None of the controls or their first-degree relatives had experienced past or current psychiatric illnesses. Exclusion criteria for both patients and controls were respiratory diseases, cardiovascular diseases, the use of medication that could influence the autonomic nervous system, and any other physical condition that could lead to a distraction from task performance.

After the subjects were given a complete description of the study, written informed consent was obtained. The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, and was carried out in accordance with the Declaration of Helsinki.

General procedure

All experimental sessions took place between 09.00 and 11.00 hrs in the morning. The subject sat in a comfortable chair in a small, sound-attenuated dimly lit room. Both patients and controls were asked not to use any coffee or cigarettes before and during testing. Electrodes for the recordings of the EMG (electromyographic) signal, heart rate, skin conductance level, respiration and blood pressure were applied according to standard laboratory procedures. After the application of the electrodes, the experimental session began with a rest period of five minutes in which subjects were asked to relax and not to speak. After this first rest period the headphones were put on, and the startle task was explained. The duration of the startle task was approximately 25 minutes. After completion of the task, all electrodes were removed from the subjects and they were asked to perform the

subjective rating task, which lasted approximately 15 minutes. All tasks were designed using E-prime (Psychology Software Tools, Inc., 2002).

Startle task

Subjects were seated approximately 75 cm from the computer screen. All subjects were asked to relax, to breathe regularly and not to speak during the task. They were informed that they first would be hearing five loud noises through the headphones, but that they did not have to respond. These first five startle stimuli were presented to the subjects to let them accustom to these sounds and to decrease the impact of habituation effects during the experiment. After the first 5 startles, they were told that they were about to view a series of different pictures, and that loud noises were occasionally presented through the headphones. They were asked to look at the pictures the entire time they were presented on the screen, but that they did not have to respond.

Each picture was presented during 6 seconds, with an intertrial interval (ITI) ranging from 12-25 seconds. A total of 48 pictures were presented; during 12 of these pictures (4 positive, 4 neutral and 4 negative) no startle stimulus was presented. During the remaining 36 pictures, startle stimuli were presented either 300, 800, 1300 or 3800 ms after picture onset in such a way that each of these latency conditions occurred 3 times during the viewing of positive, neutral and negative pictures. In addition, 12 startle stimuli were randomly presented during the ITI's. Thus, a total of 48 pictures and 48 startle stimuli were presented.

Subjective rating task

The 48 pictures that were presented during the startle task, were presented again in the subjective rating task, in a randomized order different from that of the startle task. The subjects were seated approximately 75 cm from the computer screen and responded with their dominant hand using the numbers on the keyboard. A fixation cross was presented for 3 seconds on a 17-inch computer screen, followed by a 6-second presentation of a picture. After picture offset, the subjects were asked to rate each picture using the SAM (Self-Assessment Manikin; Bradley and Lang, 1994), on the two dimensions of pleasure and arousal. After their response, the fixation cross appeared again for 3 seconds, followed by the next picture.

Stimulus Material

Forty-eight pictures were selected from the IAPS (Center for the Study of Emotion and Attention, 1999). The stimuli were chosen on the basis of their normative ratings provided with the IAPS, and could be divided into six different categories, based on their contents. The positive pictures contained pictures with erotic contents and with adventure contents, the neutral pictures contained pictures with

nature contents and household objects, and the negative pictures contained pictures with mutilation and threat contents[1]. Trials presenting same-sex pictures were excluded from further analysis to avoid gender differences in response to sexually arousing pictures[2]. The pictures were presented using a Dell Dimension M200a Personal Computer with a Pentium processor and a 17-inch Samsung SyncMaster monitor.

The startle stimulus was a discrete white noise burst of 100 dB during 50 ms, with an instantaneous rise and fall time, presented binaurally through headphones. The startle stimuli were presented through Sennheiser HD 265 linear headphones. The sound intensity of the startle stimulus was checked every week using a sound level meter to make sure that the startle stimulus was 100 dB for every participant.

Measurements

Subjective ratings

Valence and arousal ratings were registered using the SAM rating-procedure. The SAM consisted of two subsequent screens, each containing five figures. On the first screen, the figures represented the degree of pleasantness of the pictures -ranging from very unpleasant to very pleasant- on a scale from 1 to 9. On the second screen, each figure represented the degree of arousal associated with each picture -ranging from very calm to very arousing- also on a scale from 1 to 9.

Cardiac responses

During the experiment, continuous measurements were made of the heart rate (HR). HR was recorded using a precordial lead, and was sampled at 512 Hz. All data were sampled and stored on a flashcard by means of a portable digital recorder (Vitaport^{TM} System; TEMEC Instruments B.V., Kerkrade, the Netherlands). Upon completion of the recording, all physiological data were imported and processed on a Personal Computer using a Vitascore^{TM} software module (TEMEC Instruments BV, Kerkrade, the Netherlands). Subsequently, the interbeat intervals were calculated using R-top detection. A low pass filtered cardiac event series (LPFCES; Hyndman and Mohn, 1973) was calculated, using a low pass filter of 0.5 Hz. This method is based on the IPFM-model: the Integral Pulse Frequency Modulation model (Hyndman and Mohn, 1973). Subsequently,

[1] Positive IAPS pictures: 4220, 4290, 4490, 4520, 4608, 4660, 4670, 4680, 5260, 5470, 5621, 5910, 8030, 8170, 8490, 8501. Neutral IAPS pictures: 5120, 5260, 5510, 5530, 5535, 5711, 5731, 5740, 5900, 7000, 7002, 7004, 7006, 7009, 7010, 7020, 7025. Negative IAPS pictures: 3000, 3010, 3060, 3069, 3080, 3102, 3120, 3170, 6200, 6212, 6230, 6260, 6300, 6313, 6350, 6550.

[2] Removed pictures for men: 4490, 4520. Removed pictures for women: 4220, 4290.

data series for each individual stimulus were extracted from the data, both the pictures and the acoustic startles, starting 2 seconds before stimulus onset and ending 7 seconds after stimulus onset. Cardiac responses for each stimulus were calculated by subtracting the 6 seconds after stimulus onset from the 2-second baseline period before each stimulus. This resulted in data series consisting of difference scores for each separate stimulus.

The responses to the 12 pictures that were presented without a startle stimulus were used for the analyses of the OR and the subjective ratings. The responses to the 12 acoustic startle stimuli were used for the analyses of the acoustic SR.

For the cardiac responses to emotional pictures, we defined the greatest deceleration, the orientation response (OR), as the largest decrease between 0 and 3 seconds after stimulus onset, and the greatest acceleration response (AR) was defined as the peak HR response between 3 and 6 seconds after stimulus onset (Gatchel and Lang, 1973; Lang et al., 1993). For the cardiac responses to the acoustic startle stimuli, the startle responses (SRs) were defined as the largest acceleration between 1-6 seconds after stimulus onset; this peak was expected to occur around 4 seconds after startle stimulus onset (Turpin et al., 1999). The mean of the 12 SRs of each individual subject to the acoustic startle stimuli was used for further analyses.

Statistical Analyses

To analyze whether the SRs to acoustic stimuli differed between the patients and the control group, an independent samples T-test was performed, with Group as the between subjects factor.

To investigate whether the patients and controls differed in their cardiac responses to the different pictures in relation to their subjective ratings, two repeated measures ANOVAs were conducted, with OR and AR as the dependent variables, Pleasure and Arousal as the within subjects factors, and Group as the between subjects factor. Using the maximum likelihood method, the best fit for each model was found (from a saturated model, including all main and interaction effects, to the smallest possible model that explained the same amount of variance as the saturated model). We used the individual SAM-ratings that accompanied each picture instead of the predefined picture categories, because the pictures were presented in a random order during the experiment. Thus, although the picture types were equally represented in the picture-only condition, the exact contents of the 12 pictures varied per subject.

We were also interested whether the cardiac SR elicited by acoustic startle stimuli was related to the cardiac OR and/or AR elicited by the picture stimuli.

Within each group, the mean cardiac ORs and ARs (regardless of picture type) were correlated with the mean cardiac SRs using Pearson correlations.

Finally, to investigate whether the different picture types were rated differently between groups, the subjective ratings of these picture types were analysed using Wilcoxon Signed Rank tests.

All analyses were two-tailed, and the alpha was set at 0.05. The Statistical Packages for the Social Sciences (SPSS) version 13.0 (SPSS Inc., 2004) and SAS 8.2 (SAS Institute Inc., 1999-2001) were used to analyse our data.

Results

Subject characteristics

In Table 1 the characteristics of the subject sample are presented.

Table 1. Subject characteristics

		Patients (n=34)	Controls (n=40)
Age		22 ± 5 years	23 ± 4 years
PANSS scores	Total	70 ± 18	
	Positive symptoms	18 ± 7	
	Negative symptoms	17 ± 6	
	General symptoms	36 ± 11	
Medication (n of patients)	No Antipsychotic	9	
	Haloperidol	4	
	Clozapine	4	
	Olanzapine	8	
	Risperidone	7	
	Quetiapine	2	

Acoustic startle response (SR)

The patients and controls did not differ significantly in their cardiac SRs to acoustic startle stimuli. The mean heart rate increase of the patients after the presentation of the startle stimulus was 5.1 (± 3.0) beats per minute (bpm), and of the controls 6.0 (± 3.4) bpm (t[73]=-1.13, p=0.26).

Cardiac responses and subjective ratings

The Orienting Response (OR)

When we investigated the relationship between the subjective arousal and pleasure ratings and the cardiac OR, we found that the subjective ratings did not explain sufficient variance to be retained in the models. Only a significant main effect of Group was found ($F[1,72] = 11.75$, $p = 0.001$). The patients showed an overall smaller cardiac OR, regardless of the subjective ratings (see Figure 1).

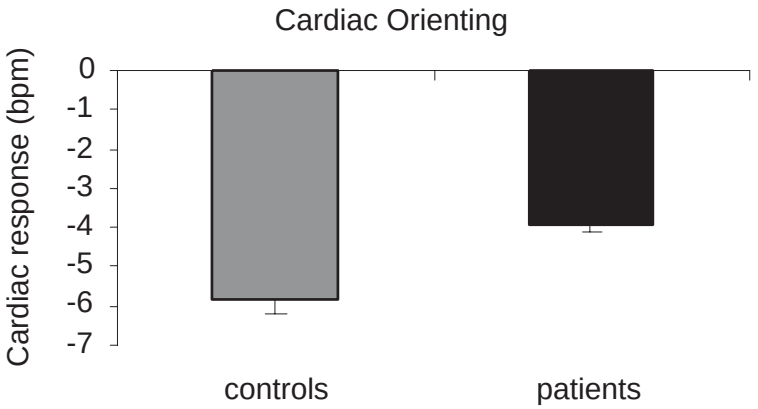

Figure 1. Cardiac orienting response to emotion-eliciting pictures (beats per minute; SE) for the control subjects (grey bar) and the schizophrenic patients (black bar).

The acceleration response (AR)

When we investigated the relationship between the subjective ratings and the AR in patients and controls, we found that only the arousal ratings were related to the cardiac responses. The best fit for the model was AR = Group + Arousal + Group*Arousal. The main effect of group was significant ($F[1,72] = 7.53$, $p < 0.01$), the main effect of Arousal was significant ($F[1,72] = 4.92$, $p < 0.05$), and the interaction effect of Group*Arousal was most significant ($F[1,72] = 18.20$, $p < 0.001$). This interaction effect indicated that the cardiac AR of the patients increased with 0.2 bpm with each point of increase in SAM arousal rating, whereas the AR of the controls decreased with 0.6 bpm with each point of increase in SAM arousal rating (see Table 2 and Figure 2).

Table 2. Beta coeffiecients of the model fitted for the cardiac AR

Effect	β	SE	t value	p-value	95% CI	
					lower	upper
Intercept	1.0	0.7	1.53	0.13	-0.3	2.4
Group	2.5	0.9	2.74	<0.01	0.7	4.4
Arousal	0.2	0.1	1.52	0.13	-0.1	0.4
Arousal * Group	-0.80	0.2	-4.27	<0.001	-1.2	-0.4

Significant effects ($p < 0.01$) are presented in bold; CI=confidence interval. NB. The patient group was the reference group in the model.

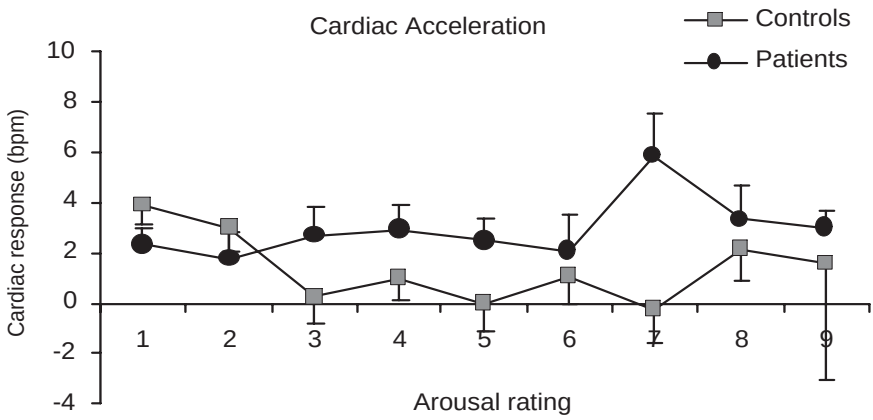

Figure 2. Cardiac acceleration responses (beats per minute; SE) to emotion-eliciting pictures in relation to the arousal ratings of schizophrenic patients (black dots) and healthy control subjects (grey squares).

Relationships between cardiac SR, OR and AR

Only within the control group the cardiac SR to acoustic stimuli showed a significant positive correlation with the cardiac AR to pictures (see Table 3).

Table 3. Pearson correlations between the startle response (SR), the orienting response (OR), and the acceleration response (AR) for patients (n=34) and controls (n=40)

	Patients	Controls
SR & OR	r = 0.10	r = -0.21
SR & AR	r = -0.01	r = 0.49**
OR & AR	r = 0.27	r = 0.16

** p = 0.001

Subjective ratings

The mean pleasure and arousal ratings of the patients and controls are presented in Figures 3a and 3b. With regard to the pleasure ratings, the patients rated the erotic pictures significantly less pleasant than the control group, $Z=-2.92$, $p < 0.01$. With regard to the arousal ratings, the patients rated the adventure, household and nature pictures as more arousing than the control group, $Z=-2.99$, -3.39, and -2.52 respectively, all $p < 0.05$.

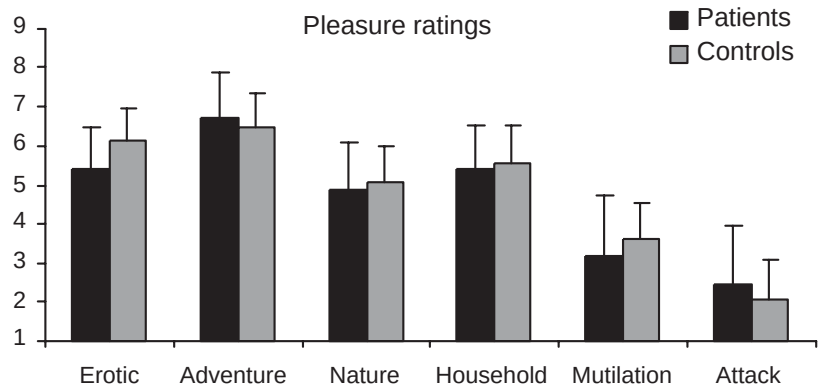

Figure 3a. Pleasure ratings (± SD) of patients and controls for each picture category.

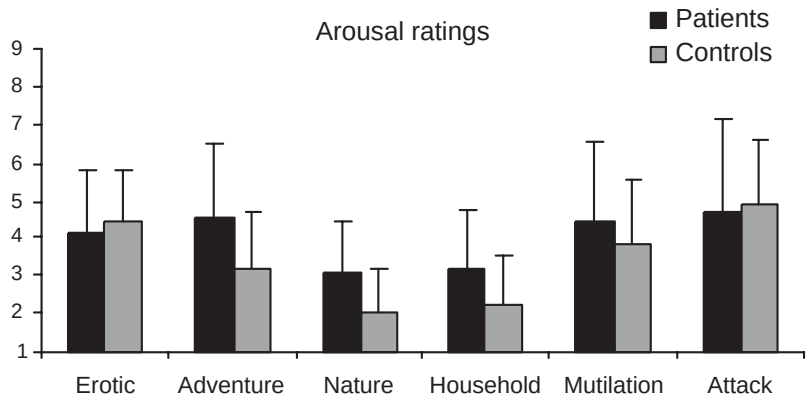

Figure 3b. Arousal ratings (± SD) of patients and controls for each picture category.

Discussion

This study aimed to investigate whether schizophrenic patients and control subjects differed in their cardiac responding to emotion-eliciting pictures, and whether this was the result of a different emotional responding, a different attentional responding, or both. From our results it appears that the differences in cardiac responding between patients and controls results from differences in both attentional as well as emotional processing of pictures.

The patients showed a similar cardiac SR to acoustic startle stimuli when compared with control subjects. Since the functional significance of the cardiac SR is thought to be a disengagement from ongoing activity that leads to the detection of potential danger (Ramirèz et al., 2005; Turpin et al., 1999), our results suggest that the patients' ability to detect potential danger was similar to that of healthy controls.

However, the cardiac response patterns during picture viewing did differ significantly between patients and healthy control subjects. The patients showed less orienting responses to the pictures in general, regardless of arousal or pleasure ratings. This result indicates that the schizophrenic patients were less able to attend to visual stimuli during the initial stage of picture viewing (0-3 seconds). Thus, initially, patients differ from healthy control subjects in their *attentional* resources during the processing of pictures.

When we investigated the differences in cardiac responses during the second stage of picture processing (i.e. the acceleration response) between both groups, we found a significant interaction effect of arousal by group. The acceleration response (AR) of the patients increased, whereas the AR of the controls decreased with increasing arousal ratings. The precise interpretation of the acceleratory component of the cardiac response during passive picture viewing is, however, not clear. Bradley and Lang (2000) reported that the acceleration is larger while viewing pleasant pictures as opposed to unpleasant pictures, linking its' significance to hedonic valence. However, increased heart rate acceleration has also been associated with stimulus intensity. When a stimulus is experienced as very intense and/or noxious, this results in a defense reaction, leading to heart rate acceleration (Palomba et al., 1997; Lacey and Lacey, 1970). Our results showed that the AR is mostly related to the intensity of the emotion-eliciting picture (i.e. the arousal ratings), favoring the theory by Lacey and Lacey: cardiac acceleration during the second stage of picture processing is an indication of a defense response, leading to stimulus rejection. Our results on the correlations between the different types of cardiac responses further underline this suggestion on the defensive nature of the AR during picture viewing, since this AR was significantly positively correlated with the SR after acoustic stimulation, known to be a defensive response (Ramírez et al., 2005). However, this positive correlation was only found within the control group, and not in the patient group, further indicating that the processing of emotional pictures in patients differs from that of control subjects.

The results of the control group were straightforward: the ARs decreased with increasing arousal ratings, indicating that more attention was directed towards more arousing stimuli. We did not investigate the cardiac responses to the specific picture contents, but we did find that the controls subjectively rated the

attack pictures as most arousing, followed by the erotic, mutilation, adventure, household and nature pictures. This result replicates previous studies, in which negative pictures showing attack and threat scenes, but also positive pictures showing erotic scenes, induced the largest cardiac decelerations (Bradley et al., 2001a; Sánchez-Navarro et al., 2006).

In contrast, the cardiac ARs of the patient group increased with increasing arousal ratings. Thus, the more arousing a picture was experienced by the patients, the larger the cardiac defense response, as reflected by the AR. The patients subjectively rated the nature and household pictures as least arousing, and the erotic, adventure, mutilation and attack pictures as most arousing; they did not show any differentiation between these last four picture types in arousal ratings. These results suggest that schizophrenic patients do not attend to these pictures as much as healthy control subjects, and even react in a more defensive manner to both unpleasant as well as pleasant pictures, possibly rejecting the stimulus information.

If patients rejected the stimulus information during picture viewing, it would be expected that they experienced the pictures as unpleasant. However, the patients rated the pictures in a similar manner as healthy control subjects, with the exception of the erotic pictures, which were significantly rated as less pleasant compared with the ratings of the controls. Since the patients rated the adventure pictures as most pleasant, followed by the erotic, nature and household pictures, it does not seem likely that they really experienced the pleasant pictures as unpleasant. On the other hand, it is possible that social desirability played a role during these self-reported ratings: patients rated the erotic pictures as pleasant, whereas they did not experience them as such. Another explanation would be, that the pictures presented during the experiment were experienced as more arousing and emotional by the patients than by the controls. Only the adventure, nature and household picture were rated significantly more arousing by the patient group compared with the control group, so this explanation does not seem valid either. Instead, it seems that the threshold for (cardiac) defensive responses to arousing pictures is lower in schizophrenic patients than in healthy control subjects. Increased arousal responding, as measured by skin conductance responses to both neutral and fearful faces, has been found in schizophrenic patients. In a study by Williams et al. (2004), the impairments in schizophrenia were due primarily to a dysfunctional visceral network, and the impairments were most pronounced in paranoid patients. Furthermore, the schizophrenic patients showed reduced activity in the medial prefrontal cortex, which is thought to be involved in the cognitive appraisal of visceral input and subsequent decision making. This reduced medial prefrontal activity suggests a dysfunction in the regulation of the amygdala-autonomic function, leading to perseveration and exacerbation of arousal

responses, resulting in hypervigilance and misattributions that may reinforce the paranoid thoughts of the patients (Phillips et al., 2003b; Williams et al., 2004).

The above described study (Williams et al., 2004) offers an explanation for our findings regarding the negative, arousing pictures, but not directly for our findings regarding the positive, arousing pictures. Research in this area is scarce. In a previous study conducted by our group (Hempel et al., 2005), we also found that schizophrenic patients showed an increase in heart rate response during the viewing of erotic pictures, and that the patients showed less heart rate deceleration during picture viewing in general. The present study, in which a different subject sample and a different picture set were used, confirms these previous results.

Limitations

In the present study, we did not account for medication effects due to the small sample sizes, whereas this may have affected our results. For example, one of the side effects of antipsychotic medication is the loss of sexual interest. Olfson et al. (2005) found that 45.3% of the investigated 139 medicated male schizophrenic patients, receiving either haloperidol, olanzapine, risperidone or quetiapine, experienced sexual dysfunction. On the other hand, the schizophrenic patients also responded in a defensive manner when viewing adventure pictures, a result that is not very likely to be caused by a loss of sexual interest.

Another confounding factor may have been smoking. Smoking influences cardiovascular health, increasing sympathetic modulation and decreasing baroreflex gain and vagal modulation on the cardiovascular system during rest (Lucini et al., 1996). It is not clear what the effect of smoking was on the cardiac responses to visual stimuli. Because of our relatively small sample sizes we did not investigate this effect, since most of the patients (28 out of 34 patients) and only some of the controls (8 out of 40) were smokers. In future studies on cardiac responses, however, smoking should be taken into account.

We did not differentiate between paranoid and nonparanoid patients in our analyses. Rather, we chose to investigate a more heterogenous patient sample, to be able to generalize our results to a patient population that suffered from recent-onset schizophrenia, regardless of specific symptoms.

Another possible limitation concerns our data reduction method. This paper presents results of the cardiac data obtained from the pictures that were presented in the absence of acoustic startle stimuli, causing each specific picture category to contain only 2 pictures. However, since our results are convincing even with such a limited number of individual stimuli, this limitation underlines the strengths of our results at the same time.

Conclusion

Our results suggest that the decreased ability to allocate attention was specific to the viewing of pictures, regardless of their valence. In other words, the differences in emotional processing between patients and controls are not the result of either attention or emotion difficulties, but rather of a combination of these two processes, that seem to interact with each other. Our results further suggest that schizophrenic patients physiologically respond in a defensive manner to arousing emotion-eliciting stimuli, initially showing less orienting and subsequently showing more defensive acceleration during picture viewing. This manner of responding may have several consequences.

First of all, prolonged defensive reactivity is a serious risk for both mental as well as physical health (Vila et al., in press). In fact, Nuechterlein et al. (1994) considered autonomic hyperreactivity as one of the vulnerability factors for developing schizophrenia. Furthermore, exaggerated psychological and physiological reactivity may lead to cardiovascular disease (Lovallo and Gerin, 2003). The relative risk of patients with schizophrenia to suffer from cardiovascular disease is reported to be two-fold higher than that of the general population (Henneskens et al., 2005). This higher relative risk is caused by several different factors, and exaggerated physiological responding may be one of these risk factors.

Secondly, abnormalities in the identification of emotionally salient information may lead to misinterpretations of the intentions of others, which may result in dysfunctions in social behavior (Phillip et al., 2003b). Indeed, Kapur et al. (2005) postulated that the increased activity of the dopamine system during psychosis renders the patients in a state of hypervigilance, experiencing aberrant novelty and salience. Whereas hallucinations and delusions are the most well-known factors of the disease, the social impairments of these patients are the most debilitating (Mueser and McGurk, 2004), resulting in impaired functioning in several areas, thereby reducing the quality of life of these patients.

A recommendation for future research would be to investigate whether the defensive response style is either a trait or a state marker, and whether this response style is also present in the first degree relatives of schizophrenic patients, to establish whether it is a potential vulnerability marker.

CHAPTER 5

Cardiovascular variability during treatment with haloperidol, olanzapine or risperidone in recent-onset schizophrenia

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Abstract

This study aimed to investigate the effects of treatment with haloperidol, olanzapine and risperidone on cardiovascular variability in patients with recent-onset schizophrenia by means of spectral analysis. Unmedicated patients (n=18) had a higher mean heart rate and a tendency for a lower high frequency power of heart rate variability than healthy control subjects (n=57), indicating a decreased cardiac vagal control in unmedicated schizophrenic patients. Patients treated with haloperidol (n=10) showed significantly less low frequency power of heart rate and sytolic blood pressure variability compared with olanzapine-treated patients, suggesting that haloperidol attenuated sympathetic functioning. In contrast, olanzapine-treated (n=10) patients showed the highest power in the low frequency range of heart rate and systolic blood pressure variability, suggesting an increased sympathetic cardiac functioning. No significant effects of risperidone (n=13) were found. None of the antipsychotic agents differed in their parasympathetic cardiovascular effects. We conclude that young, unmedicated schizophrenic patients differed from controls in their parasympathetic functioning, but that the antipsychotic agents haloperidol, risperidone and olanzapine induced only minor cardiovascular side effects.

Introduction

In a review conducted by Newman and Bland (1991), the life expectancy of schizophrenic patients was reported to be 20% shorter than that of the general population. Besides factors such as suicide, this lower life expectancy is primarily caused by coronary heart disease (CHD) in these patients. The relative risk of patients with schizophrenia to suffer from cardiovascular disease is reported to be two-fold higher (Henneskens et al., 2005), and for patients between the ages of 25 to 44 years even five-fold higher than that of the general population (Casey and Hansen, 2003). This higher relative risk is caused by several different factors, such as antipsychotic medication, cigarette smoking, hypertension, blood cholesterol, obesity, diabetes mellitus, and a more harmful lifestyle in general (Henneskens et al., 2005).

Antipsychotic medication use in schizophrenia: risk of cardiovascular disease

Currently, the most widely used atypical antipsychotics in six European countries and in the United States are risperidone, olanzapine, and clozapine (Broekema et al., 2007; Hermann et al., 2002), but haloperidol is still one of the most often prescribed conventional antipsychotics. Using antipsychotic medication increases the risk for cardiovascular disease and sudden cardiac death three-fold, and the risk increases significantly with higher doses of antipsychotic medication (Strauss et al., 2004). Since the heart is innervated by both sympathetic and parasympathetic branches of the autonomic nervous system, it is important to investigate the effects of antipsychotic agents on these branches.

Besides the anti-dopaminergic properties of haloperidol, haloperidol also has anti-adrenergic properties, affecting the sympathetic nervous system. Olanzapine, clozapine and risperidone block dopamine as well as serotonine receptors, and they all block adrenergic receptors, but only olanzapine and clozapine also block muscarinic receptors. Thus, all antipsychotic agents may affect cardiac functioning, but haloperidol and risperidone may affect the sympathetic nervous system only, whereas olanzapine and clozapine may affect both the sympathetic as well as the parasympathetic nervous system (Stahl, 2000).

Assessing cardiac functioning and stability: spectral analysis

A widely used method to assess the functioning and stability of the autonomic nervous system is by measuring heart rate variability (HRV) and blood pressure variability (BPV). HRV and BPV can be derived non-invasively from the beat to beat series of the electrocardiogram and from the blood pressure time series, respectively. Short-term beat to beat fluctuations in heart rate (HR) and blood pressure (BP) reflect the functioning of the sympathetic and parasympathetic

cardiovascular control systems (Akselrod et al., 1985). A higher HRV is indicative of a more healthy cardiovascular control mechanism, whereas a significantly decreased HRV is observed in various clinical populations, and predicts bad prognosis (Stein et al., 1994).

Within the frequency domains of HR and BP fluctuations (ranging from 0.003 to 0.50 Hz), two dominant peaks are usually identified. Fluctuations in the high frequency (HF) domain range from 0.15-0.50 Hz. The power (i.e. variance) of R-R interval time series in this domain is almost completely determined by the respiratory rhythm, which is a marker for vagal (parasympathetic) tone, but only at frequencies above 0.15 Hz (Burggraaf et al., 2001; Malliani, et al, 1991; Parati et al., 1995). The fluctuations in the low frequency (LF) domain typically oscillate from 0.04 Hz to 0.14 Hz. The fluctuations in HR within this domain are caused by mixed vagal-sympathetic inputs, whereas the variability of BP in this frequency range can be seen as a marker of sympathetic vasomotor tone (Parati et al., 1995).

By combining the time series from the HR and BP, it is also possible to assess the baroreflex receptor sensitivity (BRS). The baroreflex loop is important for the fast regulation of both HR and BP, and BRS can be used as a measure for both sympathetic and parasympathetic cardiovascular regulation (Rüdiger and Bald, 2001). Diminished baroreflex modulation has been found in pathological conditions such as acute myocardial infarction, diabetes mellitus, and congestive heart failure (La Rovere et al., 1998; Frattola et al., 1997; Mortara et al., 1997), but also during smoking (Mancia et al., 1997).

Cardiovascular functioning in schizophrenia

Studies investigating the HRV in unmedicated schizophrenic patients found higher heart rates and lower HF power in these patients compared with healthy control subjects, indicating decreased vagal control over the heart, whereas no differences were found in the LF range (Bär et al., 2005; Boettger et al., 2006; Valkonen-Korhonen et al., 2003). Since decreased HRV indices have been found to predict mortality in various clinical populations, the lower HF power in unmedicated schizophrenic patients suggests a higher risk for cardiovascular disease and even an increased risk for cardiac mortality in these patients (Boettger et al., 2006; Stein et al., 1994).

Most studies on cardiovascular functioning in schizophrenic patients treated with antipsychotic medication have focused on the antipsychotic agents clozapine and olanzapine. Clozapine increases mean heart rate and reduces HRV and LF and HF values, indicators of a reduced vagal control over the heart (Agelink et al., 1998; Agelink et al., 2001; Cohen et al., 2001; Kim et al., 2004; Mueck-Weymann et al., 2002; Oyewumi et al., 2004; Rechlin et al., 1994; Rechlin et al., 1998; Zahn and Pickar, 1993). The effects of olanzapine on cardiovascular indices is unclear,

with some studies reporting decreased vagal control (Agelink et al., 2001; Mueck-Weymann et al., 2002), and others reporting increased vagal control (Silke et al., 2002). Haloperidol did not seem to affect HRV values (Malaspina et al., 2002), but it did increase mean heart rate in medicated patients compared with healthy control subjects in one study (Agelink et al., 1998). No effects of risperidone on HRV were found in healthy control subjects (Silke et al., 2002).

Aim of the study

The present study aimed to investigate the cardiovascular side effects of three widely used antipsychotic agents (haloperidol, risperidone and olanzapine) in young schizophrenic patients in a naturalistic setting. The cardiovascular functioning of medicated patients, unmedicated patients and healthy control subjects was investigated during a five minute resting period by means of spectral analysis.

Several factors need to be considered when investigating cardiovascular functioning in schizophrenic patients. Cigarette smoking is an important risk factor for CHD in schizophrenia (Henneskens et al., 2005). Several studies found that about 70% of the schizophrenic patients smoked cigarettes, which is twice as high as in the general population (Goff et al., 2005; McCreadie, 2003). Another important factor for CHD is gender: the risk of CHD for schizophrenic males was 9.4% compared with 7% in the control population, wheres the risk of CHD for schizophrenic females was 6.3% compared with 4.2% in the control population (Goff et al., 2005). Indirect adverse effects of atypical antipychotics, such as weight gain and metabolic abnormalities, are also considered risk factors for cardiovascular disease. Particularly clozapine and olanzapine can cause large increases in weight gain (Henneskens et al., 2005; Wirshing, 2004). Furthermore, the clinical symptom severity or duration of the illness may have effects on HRV functioning. The duration of the illness and the presence of a psychotic state have both been found to be negatively related to vagal functioning (Bär et al., 2005; Toichi et al., 1999). Finally, the use of co-medication such as benzodiazepines may influence HRV functioning. Contrasting results have been found regarding benzodiazepines: some studies report a decrease in vagal control after benzodiazepine administration (Agelink et al., 2002; Vogel et al., 1996), while others found a stimulating effect of lorazepam on parasympathetic activity (Tulen et al., 1994).

In the present study, heart rate, systolic blood pressure, HRV, BPV and BRS were investigated, while controlling for the effects of benzodiazepines, duration of antipsychotic treatment, the severity of the clinical symptoms (PANSS), gender, and smoking habits.

Methods

Subjects

In this study 59 (52 male; mean age 24 ± 5 years) schizophrenic patients and 75 control subjects (57 male; mean age 23 ± 4 years) participated. The patients were recruited from the Psychosis ward of the department of Psychiatry of Erasmus MC, University Medical Center Rotterdam. We sought to include all consecutively admitted patients who fulfilled the inclusion criteria as soon as the patients were able to perform the test procedures. The patients either did not use antipsychotic medication or used antipsychotic medication for at least one week, and the antipsychotic medication had to be either haloperidol, risperidone or olanzapine. All patients were screened by a clinical psychiatrist (NvB, CH) and included in the study when they were diagnosed as suffering from schizophrenia or a schizophreniform disorder according to the criteria of the DSM-IV (APA, 1994). All diagnoses were confirmed by a second senior psychiarist (NvB, CH). In order to assess symptom severity, the Dutch translation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used.

All patients experienced a psychotic episode at the time of the study. Thirty-nine patients received medication (11 haloperidol; 15 risperidone; 13 olanzapine) and 20 patients were medication-free at the time of testing. Antipsychotic treatment was administered according to the clinical treatment protocol of the Erasmus MC clinic for psychotic disorders, which is congruent with both the schizophrenia treatment guidelines of the Dutch Psychiatric Association and the American Psychiatric Association.

Controls were recruited by means of advertisements. All controls were healthy and drug-free at the time of testing as assessed by means of an interview and a questionnaire. None of the controls had experienced past or current psychiatric illnesses. Exclusion criteria for both patients and controls were respiratory diseases, cardiovascular diseases, the use of medication that could influence the autonomic nervous system, and any physical condition that could lead to a distraction from task performance.

After the subjects were given a complete description of the study, written informed consent was obtained. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam.

Procedure

All experimental sessions took place between 09.00 and 11.00 hrs in the morning. The subject sat in a comfortable chair in a small, sound-attenuated dimly lit room. Electrodes for the recordings of HR, skin conductance level (SCL), respiration and BP were applied according to standard procedures. Each experimental session began with a rest period of five minutes, after a stabilization period of 15 minutes,

during which the subjects were asked to relax, to breathe regularly and not to speak. After the rest period, subjects were asked to perform three simple computer tasks, which will not be described here, since the HRV measures were based on the rest periods only. Both patients and controls were asked not to use any coffee or cigarettes before and during testing on the morning of the assessments.

The PANSS rating scale was assessed within one week after the HRV assessment, and was scored by a senior psychiatrist.

Physiological measures

Continuous measurements were made of the HR, BP, SCL and respiration. HR was determined from the consecutive R-R intervals of the ECG (precordial lead), and sampled at 512 Hz. Non-invasive BP was measured using a 2300 Finapres™ Blood Pressure Monitor (Ohmeda, Englewood CO, USA; Penàz, 1973), and was sampled at 128 Hz. It was made sure that the non-dominant hand was located at the heart level in order to obtain reliable BP data. Respiration was measured using an inductive plethysmography method (belts containing a magnetic coil, Respitrace™), and was sampled at 8 Hz. With the plethysmography method, the excursions of the thorax associated with breathing were registered.

All data were sampled and stored on a flashcard by means of a portable digital recorder (Vitaport™ System; TEMEC Instruments B.V., Kerkrade, The Netherlands). After completion of the recording, all physiological data were imported and processed on a Personal Computer using a Vitascore™ software module (TEMEC Instruments BV, Kerkrade, The Netherlands).

Analysis of physiological data

A customized software program calculated the interbeat intervals (IBI) of the ECG using R-top detection, resulting in IBI time series. This time series was inspected for detection and removal of artifacts. If isolated supraventricular extra beats occurred within a time segment, a linear interpolation correction procedure was applied. However, an effort was made to avoid corrected time segments. If more than 5% of a IBI time segment needed correction, the segment was discarded from analysis. Subsequently, diastolic and systolic arterial pressure (DBP, SBP) values in mmHg for each consecutive R-R interval of the ECG were calculated. If more than 10% of a BP time segment needed correction, it was discarded from analysis. For data reduction purposes, only SBP data will be presented in the present article.

The time series of IBI and SBP during the 5 minutes rest period were scrutinized for stationarity. Consecutive 3 minute periods of HR, respiration, and SBP time series were subjected to a discrete Fourier transform, based on non-equidistant sampling of the R-wave incidences (CARSPAN program, Groningen, The Netherlands; Mulder et al., 1988; Van Steenis et al., 1994), to yield power

spectra of the rhythmic oscillations over a frequency range of 0.02-0.50 Hz, with a resolution of 0.01 Hz. For each time segment, the power was calculated for the low frequency band (LF: 0.05-0.14 Hz) and the high frequency band (HF: 0.15-0.5 Hz), in addition to mean HR, SBP, and respiratory rate. Spectral power for each selected frequency band was expressed in relative terms, i.e., as a fraction of the mean value of the considered signal (squared modulation index). As an index of baroreflex sensitivity (BRS), the gain (or modulus) in the low frequency band between the systolic pressure values and R-R interval times was computed per time segment, based on those frequency points within the 0.05-0.14 Hz range with a coherence between the two signals of ≥ 0.35. Mean SBP and SBP power data of 4 controls and 4 patients were excluded from further analyses because unreliable high SBPs were found, which were not consistent with the manually measured SBPs.

For each time segment, samples of the respiratory signal were obtained at each incidence of the R-wave. Subsequently, these respiratory time series were subjected to spectral analysis, and the dominant peak in the spectrum was assessed. Power spectra of the respiratory time series were evaluated primarily to assess if changes in HR variability between patients and controls were related to changes in respiratory frequency. Subjects with a breathing frequency of 0.14 Hz or lower were removed from the dataset because this influenced the interpretation of the LF band. This resulted in the removal of 18 control subjects and 8 patients: the data of 57 control subjects and 51 patients were used for further analyses.

Statistical analyses

In order to investigate possible differences between the patient (medicated and unmedicated) and control groups concerning their demographic characteristics, we performed chi-square tests on the distributions of gender and smoking status. The possible differences in age and BMI between the control group and the medicated and unmedicated patients groups were investigated by means of univariate analyses of variance. To investigate whether the unmedicated and medicated patient groups differed in their duration of illness and PANSS scores, we performed independent samples t-tests.

The spectral power data of HRV LF, HRV HF, BRS and SBPV were transformed to natural logarithmic values (ln) because of skewness of the distributions. The data of the mean HR and mean SBP were not transformed.

First, to investigate whether the unmedicated patients and controls differed in HR, SBP, HRV LF, HRV HF, SBPV and BRS values an ANCOVA was performed, with Group (patients versus controls) as between subjects variable and Gender (male/female) and Smoking (yes/no) as covariates. The respiration rates between groups were investigated by means of an Independent Samples T-test.

To investigate whether the antipsychotics influenced the cardiovascular parameters within the patient group, the effect of antipsychotic agents on mean HR and SBP, HRV LF and HRV HF, SBPV LF and BRS indices was examined by means of ANCOVAs, in which Medication (medication free, haloperidol, olanzapine, risperdal) was the independent variable, and Benzodiazepine use (yes/no), Gender (male/female), Smoking (yes/no), Duration of present medication use (in weeks), and the PANSS total score and the PANSS score for positive symptoms were entered as possible covariates. The covariate that least contributed to the model was removed, and a new model was specified using the remaining covariates. This process repeated itself until the best fit for the model was found. If a significant difference between groups was found, pair wise comparisons tested which groups differed significantly from each other. These multiple comparisons were adjusted using the Sidak correction.

All statistical analyses were two-tailed, and the alpha was defined as 0.05. We used the Statistical Packages for the Social Sciences (SPSS) version 13.0 (SPSS Inc., 2004) to analyze our data.

Results

Demographic data

Table 1 presents the demographic details of the patient and control samples, and Table 2 presents the medication distribution in the patient group. The dosages of the different antipsychotics were converted to chlorpromazine equivalents (based on Cahn et al., 2002). The patient groups consisted of significantly less females than males compared with the control group ($\chi^2 = 6.96$, $p < 0.05$), and the patient groups consisted of significantly more smokers than non-smokers compared with the control group ($\chi^2 = 27.74$, $p < 0.01$). No differences in age or BMI were found between the three groups ($F[2,105] = 0.34$ and $F[2,88] = 1.09$, respectively). However, we did find that the unmedicated patients showed higher scores for the positive symptoms scale of the PANSS ($t[46] = 2.16$, $p < 0.05$).

Table 1. Demographic data of the medicated and unmedicated schizophrenic patients and the control subjects

Clinical and demographic data		Medicated patients	Unmedicated patients	Controls
Number of participants (male/female)*		33 (29/4)	18 (17/1)	57 (40/17)
Age (mean ± sd)		23 ± 4	24 ± 6	23 ± 4
Smoker/Non-smoker*		24/7 (2 unknown)	12/6	13/44
Body Mass Index (mean ± sd)		23 ± 5	22 ± 3	23 ± 2
Duration of illness[+] (months; mean ± sd)		13 ± 16	9 ± 15	
PANSS-scores (mean ± sd)	Total	67 ± 19	78 ± 20	
	Positive symptoms*	16 ± 6	20 ± 5	
	Negative symptoms	17 ± 7	19 ± 7	
	General psychopathology	34 ± 10	40 ± 12	

* significant difference between groups in gender distribution ($\chi^2 = 6.96$), smoker/non-smoker distribution ($\chi^2 = 27.74$), and PANSS positive scores ($t = 2.16$), all $p < 0.05$

[+] duration of illness was defined as the moment at which the first psychotic symptoms were mentioned

Table 2. Medication use and mean dosage per day (presented in chlorpromazine equivalents)

Medication	N	Mean daily dosage (mean mg ± sd)	Duration (weeks) of antipsychotic use (mean ± sd)	Benzodiazepine use (lorazepam/oxazepam)
Medication Free	N=18			N=4 (4/0)
Haloperidol	N=10	130 ± 60	9 ± 14	N=5 (5/0)
Risperidone	N=13	145 ± 50	8 ± 9	N=4 (3/1)
Olanzapine	N=10	200 ± 82	6 ± 4	N=4 (3/1)

Unmedicated patients versus controls

Table 3 presents the results of the ANCOVAs of the outcome variables with Group (unmedicated patients versus control subjects) as the between subjects factor and Gender and Smoking as the covariates for each of the dependent variables.

When corrected for Gender and Smoking, mean HR was significantly higher in the unmedicated patient group compared with the control group ($F[1;71] = 8.68$, $p<0.01$). Furthermore, the difference in HRV HF power between patients and controls almost reached statistical significance: the HRV HF power was less in the patient group than in the control group after correcting for Gender and Smoking ($F[1;71] = 3.37$, $p = 0.07$). None of the other dependent variables differed between groups.

The Gender covariate was significant for the mean SBP data only, with females having a lower SBP compared with males ($B = -10.77$, $t = -2.57$, $p = 0.01$). The Smoking covariate was a significant factor for HRV LF, HRV HF and BRS. Smokers had a signifcantly higher HRV LF power ($B = 0.41$, $t = 2.05$, $p < 0.05$), a significantly higher HRV HF power ($B = 0.62$, $t = 2.15$, $p < 0.05$), and a significantly higher BRS ($B = 0.28$, $t = 2.17$, $p < 0.05$) compared to non-smokers.

Finally, the difference in respiration rate between patients and controls almost reached significance, $t[22.99] = -2.00$, $p = 0.06$. The mean respiration rate of the unmedicated patients was 0.28 ± 0.06 Hz, and of the control subjects 0.25 ± 0.04 Hz.

Medication effects within patient group

In Table 4, the Corrected Models for Medication within the patient group are presented. Only for the LF domains of HRV and SBPV significant effects of Medication were found within the patient groups. When corrected for Gender and Smoking, HRV LF differed significantly between medication groups, $F[5;43] = 3.62$, $p < 0.05$. The pair wise comparisons revealed that patients using olanzapine had a significantly higher HRV power in the LF range compared with patients using haloperidol (mean difference 0.85, $p < 0.05$). The significant Gender covariate indicated that females had a lower HRV LF power compared to males ($B = -0.60$, $t = -2.15$, $p < 0.05$).

When corrected for Benzodiazapine use and Smoking, SBPV LF also differed significantly between medication groups, $F[5;40] = 3.22$, $p < 0.05$. Again, pair wise comparisons revealed that patients using olanzapine had a significantly higher SBPV power in the LF range compared with patients using haloperidol (mean difference 1.15, $p < 0.05$).

No significant medication effects were found for the other cardiovascular parameters. However, Gender and Benzodiazepine use significantly influenced the

mean HR of the patients. The parameter estimates indicated that females had significantly higher HRs compared with males (B = 14.25, t = 2.41, p < 0.05), and that using benzodiazepines also significantly increased HR (B = 8.89, t = 2.40, p < 0.05). Smoking tended to decrease mean HR (B = -7.00, t = 4.06, p = 0.09), and increasing the duration of medication use tended to increase mean HR (B = 0.42, t = 1.78, p=0.08).

The mean SBP was not influenced by the use of different antipsychotics, but the model did indicate that females had a lower mean SBP compared with males (B = -24.79, t = -4.12, p<0.01) when corrected for the other variables in the model. HRV HF power was not significantly different between medication groups, but increasing the duration of medication use decreased HRV HF power (B = 0.06, t = -2.34, p < 0.05). The model for BRS indicated that an increase in the total PANSS score significantly decreased BRS (B = -0.06, t = -2.22, p < 0.05).

Table 3. Results of ANCOVA's of the outcome variables, tested between unmedicated patients (n=18) and controls (n=57), corrected for gender and smoking.

	Covariate	F	p	partial η^2 of the model	Estimates per group (mean ± sem)
Mean HR	Gender	1.35	0.25	0.116	Patient: 79.97 ± 3.01
	Smoker	2.42	0.12		Control: 69.53 ± 1.60
	Group*	**8.68**	**0.04**		
Mean SBP	**Gender***	**6.61**	**0.01**	0.142	Patient: 129.60 ± 4.03
	Smoker	1.40	0.24		Control: 122.92 ± 2.07
	Group	2.00	0.16		
Ln (HRV LF)	Gender	0.01	0.91	0.056	Patient: 7.21 ± 0.19
	Smoker*	**4.21**	**0.04**		Control: 7.38 ± 0.10
	Group	0.56	0.46		
Ln (HRV HF)	Gender	1.54	0.26	0.101	Patient: 6.75 ± 0.28
	Smoker*	**4.64**	**0.04**		Control: 7.34 ± 0.15
	*Group**	*3.37*	*0.07*		
Ln (BRS)	Gender	0.01	0.93	0.064	Patient: 2.01± 0.12
	Smoker*	**4.69**	**0.03**		Control: 2.18 ± 0.07
	Group	1.40	0.24		
Ln (SBPV LF)	Gender	0.07	0.79	0.038	Patient: 6.33 ± 0.18
	Smoker	1.20	0.28		Control: 6.63 ± 0.09
	Group	2.00	0.16		

HR = heart rate; SBP = systolic blood pressure; Ln (HRV LF) = natural logaritmic of power in the low frequency band of heart rate; Ln (HRV HF) = natural logaritmic of power in the high frequency band of heart rate; Ln (BRS) = natural logaritmic of baroreflex sensitivity; Ln (SPBV LF) = natural logaritmic of systolic blood pressure variability low frequency band.

* p<0.05, presented in bold; p<0.10, presented in italics

Table 4. Uncorrected and Corrected models for the ANCOVAs comparing patients (n=53) using different types of medication, corrected for several covariates.

	Covariates	F	p	Partial η^2 of the model	Estimates per group (mean ± sem)
Mean HR	**Corrected Model***	**3.45**	**0.01**	0.37	F: 81.03 ± 3.07
	Medication	1.27	0.30		H: 70.16 ± 4.41
	Benzodiazepine use*	**5.76**	**0.02**		R: 76.92 ± 3.50
	Gender*	**5.80**	**0.02**		O: 75.36 ± 3.82
	*Smoking**	*2.97*	*0.09*		
	*Duration medication**	*3.16*	*0.08*		
Mean SBP	**Corrected Model***	**3.59**	**0.01**	0.37	F: 126.97 ± 3.40
	Medication	0.29	0.83		H: 126.34 ± 4.92
	Gender*	**16.99**	**0.00**		R: 122.97 ± 3.54
	Smoking	2.31	0.14		O: 127.01 ± 4.21
	PANSS total score	0.64	0.43		
Ln (HRV LF)	**Corrected Model***	**2.87**	**0.03**	0.25	F: 7.33 ± 0.14
	Medication*	**3.62**	**0.02**		H: 6.73 ± 0.20
	Gender*	**4.63**	**0.04**		R: 7.06 ± 0.17
	Smoking	1.33	0.26		O: 7.58 ± 0.18
Ln (HRV HF)	Corrected Model	1.65	0.16	0.19	F: 6.55 ± 0.32
	Medication	0.98	0.41		H: 7.49 ± 0.45
	Duration medication*	**5.49**	**0.02**		R: 6.77 ± 0.36
	Benzodiazepine use	2.44	0.13		O: 6.61 ± 0.39
	Smoking	0.63	0.43		
Ln (BRS)	Corrected Model	1.66	0.17	0.17	F: 8.58 ± 0.88
	Medication	0.24	0.87		H: 8.14 ± 1.11
	PANSS total score*	**4.91**	**0.03**		R: 7.51 ± 0.96
	Gender	2.54	0.12		O: 7.79 ± 1.18
Ln (SBPV LF)	**Corrected Model***	**2.50**	**0.05**	0.24	F: 6.47 ± 0.19
	Medication*	**3.22**	**0.03**		H: 5.80 ± 0.28
	Benzodiazepine use	2.91	0.10		R: 6.58 ± 0.22
	Smoking	2.26	0.12		O: 6.95 ± 0.24

HR = heart rate; SBP = systolic blood pressure; Ln (HRV LF) = natural logaritmic of power in the low frequency band of heart rate; Ln (HRV HF) = natural logaritmic of power in the high frequency band of heart rate; Ln (BRS) = natural logaritmic of baroreflex sensitivity; Ln (SPBV LF) = natural logaritmic of systolic blood pressure variability low frequency band. F=medication free; H=haloperidol; R=risperidone; O=olanzapine

* $p<0.05$, presented in bold; $p<0.10$, presented in italics

Discussion

The aim of this study was to investigate the effects of the antipsychotic agents haloperidol, risperidone and olanzapine on the cardiovascular parameters of HR, SBP, HRV, SBPV and BRS in young schizophrenic patients in a naturalistic setting, while controlling for the effects of gender, smoking habits, duration of treatment, benzodiazepines, and the severity of clinical symptoms (PANSS).

Decreased vagal control in unmedicated schizophrenic patients

As expected, we found that the unmedicated schizophrenic patients had a significantly higher mean HR and a tendency for a lower power in the HF range of HRV. The lower power in the HF range of HRV in the unmedicated patients group can partially be explained by a higher BR in these patients, although this difference in breathing rate was not statistically significant. Furthermore, the lack of a statistically significant finding may be explained by our finding that smoking increased HRV HF power: 66% of the unmedicated patients were smokers, whereas only 23% of the control subjects were smokers. Thus, despite the larger amount of smokers in the unmedicated patient group, we still found a decreased HF power for HRV. The higher HR and lower power in the HF domain of unmedicated schizophrenic patients indicates a decreased vagal control over the heart in these patients, consistent with previous research (Bär et al., 2005; Boettger et al., 2006; Valkonen-Korhonen et al., 2003; Toichi et al., 1999). Since decreased HRV indices have been found to predict mortality in various clinical populations (Stein et al., 1994), the decreased parasympathetic cardiac functioning in unmedicated schizophrenic patients suggests an increased risk of mortality from cardiovascular diseases in schizophrenia. The relatively young ages of our schizophrenic patients underline the importance of cardiovascular research in this patient group. This decreased vagal control over the heart may be caused by the mental stress evoked by the disease, resulting in a state of hyperarousal, as previously suggested by Bär et al. (2007). We did not find any evidence for a different sympathetic cardiac control mechanism, as reflected by the lack of differences between groups in mean SBP, SBPV LF, or HRV LF.

Unlike Bär et al. (2007), we did not find a significantly decreased BRS in the unmedicated schizophrenic patients compared with the healthy controls. Besides the study of Bär et al. (2007), the BRS has not previously been investigated in schizophrenic patients. The lack of a significant finding in the present study may be due to the lack of statistical power, since we compared 18 unmedicated patients with 57 healthy control subjects. The difference in techniques to calculate BRS between the studies could also have contributed to the difference in results. Bär et al. (2007) used the sequence method (time domain) to calculate the BRS, whereas we used the weighed coherence function, a technique

in which the amount of linear coupling between the two signals in the frequency domain was calculated. On the other hand, Parati et al. (2000) concluded that the quantification of BRS based on both methods is quite similar.

Effects of antipsychotic agents haloperidol, olanzapine and risperidone on cardiovascular functioning

We investigated the effects of relatively low doses of antipsychotic medication, since young first-episode schizophrenic patients respond to lower doses than chronic patients (Lieberman et al., 2003; Schooler et al., 2005). When the effects of the antipsychotics on the cardiovascular parameters were investigated, we found significantly lower powers in the LF ranges of HRV and SBPV for the patients using haloperidol compared with olanzapine.

The anti-cholinergic properties of haloperidol are negligible, making parasympathetic effects unlikely, but haloperidol does have anti-adrenergic properties, influencing the peripheral sympathetic nervous system. Thus, the anti-adrenergic properties of haloperidol seemed to cause a small decrease in sympathetic nervous system activity, leading to a possible improvement in cardiac functioning (Cody, 1997), at least when low doses of haloperidol (3 mg/day) are administered. Alpha1-adrenergic blockade further causes cardiovascular side effects such as orthostatic hypotension and drowsiness (Stahl, 2000). However, we did not find a significant reduction in SBP in haloperidol-treated patients compared with medication-free patients, making it impossible to draw any firm conclusions from those results.

Olanzapine-treated patients showed significantly higher HRV LF and SBPV LF values compared to patients treated with haloperidol. Although the differences with the other antipsychotics were nonsignificant, the olanzapine-treated patients showed the highest power in the LF ranges compared with all other patients, including the medication-free patients. This finding contrasts with the results of Mueck-Weymann et al. (2002), who found decreases in both LF and HF power in olanzapine-treated patients compared with healthy controls, but confirms the results of two other studies, that found a tendency of LF power to increase and HF power to decrease during treatment with olanzapine compared with a medication-free baseline period (Mann et al., 2004), and compared with healthy control subjects (Cohen et al., 2001), suggesting a shift in sympathetic-parasympathetic balance in favour of sympathetic tone. Another study comparing olanzapine-treated patients with drug-free patients found an increase in HF power, and a decrease in HR, suggesting an increase in vagal control over the heart after treatment with olanzapine (Silke et al., 2002).

Olanzapine has both anti-cholinergic as well as anti-adrenergic properties, having the capacity to affect both the sympathetic as well as the parasympathetic

nervous system (Stahl, 2000). As described above, contrasting results have been found in olanzapine-treated patients, with some studies indicating an increase in vagal control, and other studies indicating an increase in sympathetic control over the heart. The results of the present study are in favour of the latter suggestion: we found the highest HRV LF and SBPV LF powers in patients treated with olanzapine compared with the other patient groups, indicating a slight increase in sympathetic control over the heart. Since chronic activation of the sympathetic nervous system during rest has adverse effects on the myocardium and the peripheral circulation (Cody, 1997), the higher sympathetic nervous system activation in olanzapine-treated patients could add to the already increased risk for cardiovascular diseases found in unmedicated patients, although the effects found in the present study were small.

The cardiovascular parameters of the patients treated with risperidone did not seem to be affected much by this antipsychotic. Compared with medication-free patients, we found small and nonsignificant decreases in mean HR, mean SBP, HRV LF power, and BRS. Risperidone has anti-adrenergic properties, primarily exerting effects on the sympathetic nervous system, although these effects appear to be very small. Thus, confirming the conclusion of Silke et al. (2002), at least when administered in low doses (3-4 mg/day), risperidone has no effect on cardiovascular functioning.

Methodological considerations and limitations

Smoking appeared to be an important covariate in many of the models. When we compared the unmedicated patients with the control subjects, smoking significantly explained a portion of the variation in the models of HRV LF and HF, and BRS, with smokers showing higher powers in all three parameters than non-smokers. This was an unexpected finding, since smoking generally reduces the HF power of HRV, although the higher LF power of HRV we found in the present study is congruent with previous research (Lucini et al., 1996). The increased BRS we found in smokers compared to non-smokers is also inconsistent with previous research (Mancia et al., 1997), so these results should be interpreted with caution.

Several other covariates appeared to explain a portion of the variation in the models as well, and should be considered in future research. When we investigated the medicated patients, the use of benzodiazepines was significantly related to a higher HR, and also explained variability in the models of HRV HF and SBPV LF. Gender was significantly related to mean SBP, mean HR and HRV LF, with females having a lower SBP, a higher HR and a lower HRV LF power compared with males. Smoking tended to decrease mean HR, but was not significantly related to any of the other cardiovascular parameters, although it did explain

enough variability in all the models except for BRS to be retained in these models. The duration of medication use explained variance in the models of mean HR and HRV HF. When the duration of medication use increased, the HR increased and the HF power of HRV decreased. This indicates that prolonged medication use has a negative effect on vagal functioning of the heart, irrespective of the type of antipsychotic medication that is being used. Bär et al. (2005) previously found that increase in disease duration is related to decreased vagal functioning. As they also noted, an increase in duration of medication use is related to an increase in disease duration, and with the present results it is not clear which of these two factors is responsible for the decrease in vagal functioning. The total PANSS score explained some variance in the model for mean SBP, and a higher total PANSS score was significantly related to a decrease in BRS. However, we did not find a relationship between positive symptoms and parasympathetic functioning, as suggested by other researchers (Bär et al., 2005; Toichi et al., 1999).

The present study used a between subjects design to investigate medication effects on cardiovascular functioning, in which patients using different types of medication were compared to a group of medication-free patients. A more elegant research design would be a within subjects design in which the cardiovascular functioning of all subjects is measured before treatment, and again after a reasonable treatment period, using a double-blind design. Furthermore, the present study only investigated the side effects of antipsychotic treatment during a rest period, not during physical exercise or mental stress, which could increase our knowledge about side effects of antipsychotic treatment on cardiovascular indices in schizophrenic patients. Unfortunately, in the present study it was not possible to measure HRV in these patients both before and during treatment.

The relatively small patient samples could have obscured possible significant effects of the antipsychotic medication on HRV parameters. The patient subgroups consisted of 10 to18 patients. Although it is not uncommon in this type of research to investigate samples as small as 15 subjects, larger sample sizes are preferable.

We mentioned in the introduction that weight gain may negatively affect cardiovascular functioning, but we did not investigate BMI in the models. We did not include BMI as a covariate because most patients were experiencing their first psychotic episode and had not been exposed to weight-inducing antipsychotics for a substantial amount of time, causing little variation in BMI. Furthermore, the patients and controls did not differ in their BMI (see Table 1).

Another possible limitation was the wide range of the duration of medication use, varying between 1 week and 44 weeks. It should be noted, however, that we did not investigate the clinical effects of the antipsychotics, but their cardiovascular side effects instead. We only corrected for the period of time

that the patients were using their present medication. Information about previously used antipsychotics should be used in future studies.

Two final limitations of the study regarding the control group should also be mentioned. First, the drug-free status of healthy control subjects was based on self-report measures in stead of urine toxicology tests. Second, we did not include data on the menstrual cycle of the female participants, which may have influenced the HRV measures for the female participants.

Conclusion

Young, unmedicated schizophrenic patients suffer from an autonomic dysfunction, in which the vagal control over the heart during periods of rest is decreased, leading to an imbalance between sympathetic and parasympathetic control over the heart. When antipsychotic medication is administered to these young patients, only minor effects on the balance between sympathetic control and parasympathetic control were found. Olanzapine slightly increased sympathetic control, whereas haloperidol slightly reduced sympathetic control. In the present study, none of the antipsychotic agents influenced the parasympathetic control over the heart.

Our results suggest that even young, unmedicated schizophrenic patients suffer from an increased risk of cardiovascular disease, possibly caused by the mental stress evoked by the disease.

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CHAPTER 6

The envelope method: a new signal conditioning method to obtain electromyographic startle eyeblink responses

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Abstract
In this paper, we introduce a new EMG-signal conditioning method, the 'envelope method', with the purpose of improving signal conditioning methods for startle blink research. The envelope method, based on the Hilbert transform, does not change the properties of the original signal, in contrast to the commonly used smoothing method. Comparison of the two methods, envelope and smoothing, on their discriminating abilities and response probability (proportion of detectable startle responses) revealed that the envelope and the smoothing methods had similar qualities in terms of the ability and probability to detect responses. No differences were found in startle reactivity in the presence of unpleasant compared to neutral pictures using either method. However, the envelope method proved to be superior to the smoothing method in discriminating between startle blink responses elicited during pleasant versus unpleasant and neutral foregrounds. This characteristic may be advantageous for psychophysiological research, particularly in a clinical setting.

Introduction

The electromyographic (EMG)-signal is commonly used in psychophysiological research to investigate the human startle eyeblink response (Blumenthal et al., 2005). The startle eyeblink response is part of the larger whole body startle reflex, which is caused by a sudden and intense stimulus with a rapid risetime, such as a loud and sudden noise. The startle blink response is studied in different research paradigms, such as prepulse inhibition and emotional startle modulation. With prepulse inhibition, a non-startling acoustic stimulus inhibits blink magnitude to a startle probe if it is presented within a short time interval before the startle probe (e.g., Graham, 1975). This inhibitory effect has been assumed to reflect low-level sensory gating as well as attentional processes (e.g., Hackley & Boelhouwer, 1997; Filion, Dawson, & Schell, 1993). The magnitude of the startle blink response can, however, also be modulated by an emotional foreground stimulus, such as an emotion-eliciting picture. The subject is primed into a positive or a negative emotional state, facilitating either approach or withdrawal behavior (Lang et al., 1990). Since the startle reflex can be classified as withdrawal behavior, priming a subject into a negative emotional state will increase the intensity of the response to the startle-eliciting stimulus. A positive emotional foreground stimulus, on the other hand, will attenuate the intensity of the startle reflex. Studies investigating startle modulation by means of prepulse inhibition or affective modulation can provide relevant information on determinants of specific sensory, attentional and emotional processes in healthy and clinical populations.

The most common way to measure the intensity of the startle response in humans is by measuring the EMG activity of the orbicularis oculi muscle below the eye. This EMG-signal is a small biosignal, which needs to be amplified and conditioned before response parameters can be calculated from it. Several studies have investigated and described different signal conditioning methods that are used in this type of research, such as smoothing and integrating, and the effects of filter settings and time constants on the resultant EMG-signal (Blumenthal, Elden, & Flaten, 2004; Blumenthal et al., 2005; Fridlund & Cacioppo, 1986; Van Boxtel, Boelhouwer, & Bos, 1998). Overall, these researchers concluded that similar results can be obtained using these different signal conditioning methods. However, a common problem in this research area is the loss of data due to undetectable responses. Furthermore, it is important to know which method has the most discriminating abilities, particularly for clinical research.

The aim of this study was twofold. First, we introduce a new signal conditioning method, here referred to as the ‘envelope method’, with the purpose of improving signal conditioning methods for startle eyeblink measurements. The envelope method does not change the properties of the original signal, in contrast to the smoothing or integrating techniques, and eyeblink responses are therefore

expected to be measured more accurately using this method. In this paper, the envelope method is intended to be an eyeblink quantification aid and is not intended to be an electrophysiological measure of muscular action. However, we do not exclude that the envelope method can be used for this purpose. Second, we compared two different signal conditioning methods, smoothing and the envelope method, on their discriminating abilities and response probability (proportion of detectable startle responses). We presented a number of acoustic startle-eliciting stimuli to healthy subjects while they viewed a variety of emotion-eliciting pictures. The startle eyeblink was measured by means of the EMG-signal, which was subsequently subjected to the two different signal conditioning methods.

Signal conditioning methods

The two signal conditioning methods used in this study are the envelope method and the smoothing method (see Figure 1). The EMG-signal was sampled at 1024 Hz. The time constant of the high-pass hardware filter of the analog-digital converter was 0.015 sec., and the anti-aliasing hardware filter was 500 Hz.

The envelope method

The envelope method is based on the assumption that most biological signals contain a rapidly oscillating component in combination with slower varying amplitude. The EMG-signal with startle-induced eyeblink responses is such a signal (see signal s(t) in Figure 2). For the envelope method, the signal was not rectified after the initial bandpass filter described above. The Hilbert transform as described below was applied to the bandpass filtered signal, and subsequently a (optional) lowpass filter was applied (40 Hz) in order to increase the comparability with the smoothing method, which was also lowpass filtered at 40 Hz, and to make the detection of the eyeblinks easier.

The Hilbert transform: A complex number $z = x + jy$ has a phase and amplitude. Visualizing this complex number as a vector in the complex plane (Figure 3), the phase is the angle φ between the vector and the positive x-axis and the amplitude of the complex number is the length $A = \sqrt{x^2 + y^2}$ of the vector. A complex signal $z(t) = x(t) + jy(t)$ has a moving or rotating vector in the complex plane (Figure 4), i.e., the phase is a time-varying function $\varphi(t)$. Furthermore, the amplitude is also a time-varying function: $A(t) = \sqrt{x(t)^2 + y(t)^2}$.

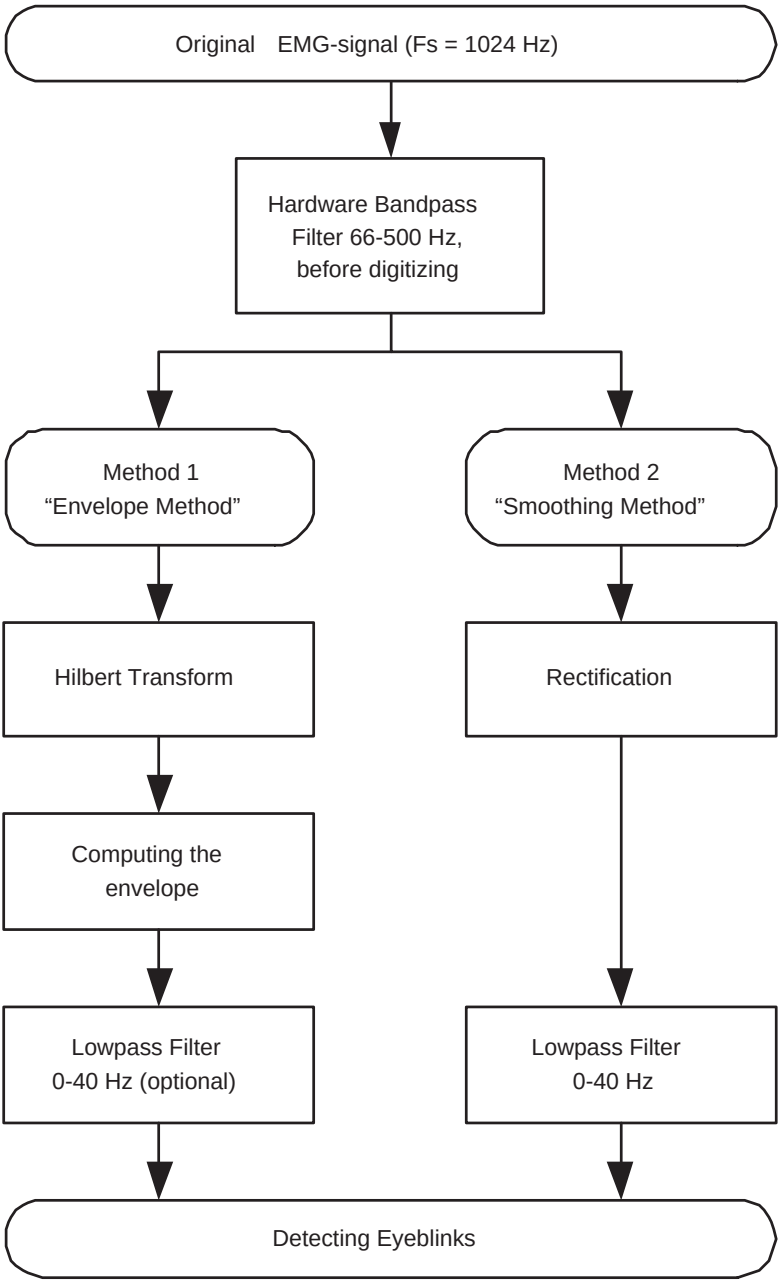

Figure 1. Outline of the two methods: envelope and smoothing.

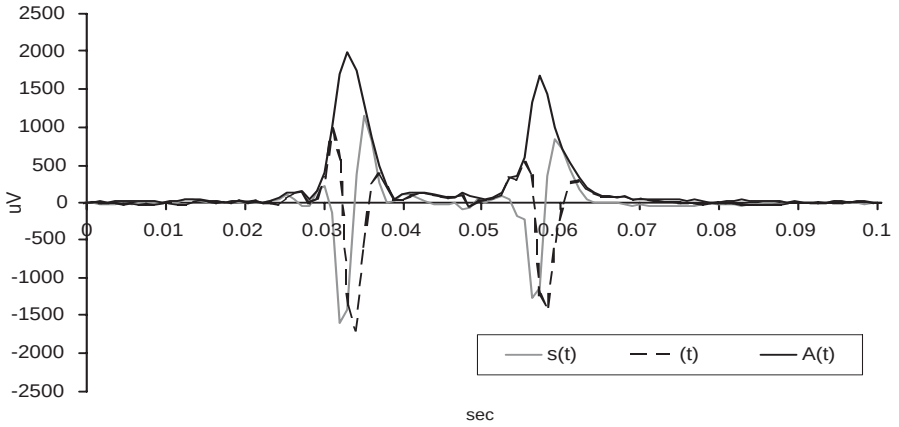

Figure 2. Example of Hilbert transformed EMG-signal. s(t)=original signal, σ(t)=imaginary signal, A(t)=amplitude signal.

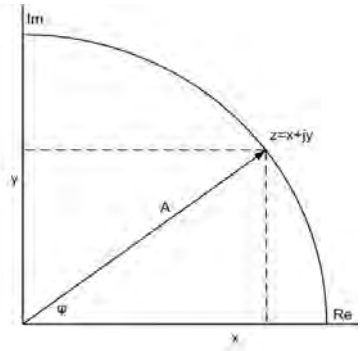

Figure 3. Graphical representation of a complex number.

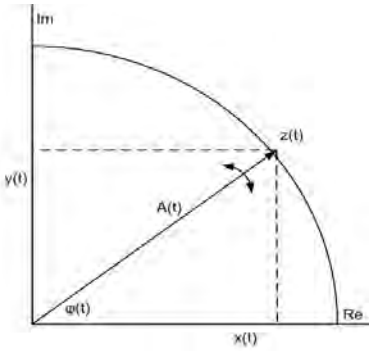

Figure 4. Graphical representation of a complex signal.

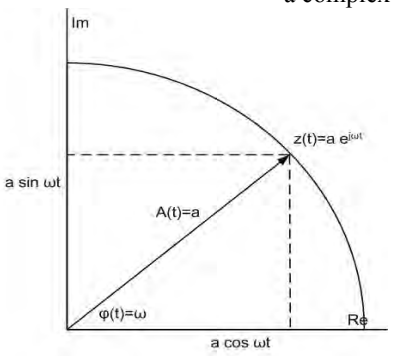

Figure 5. Graphical representation of a simple harmonic function.

On the other hand, a real number does not have a phase, because it is not a vector. Also, a real signal $x(t)$ does not have a time-varying phase, it only has a time-varying amplitude $a(t) = x(t)$. However, it is important to have a definition of the time-varying phase $\varphi(t)$ and a time-varying amplitude $A(t)$ of a real signal at hand. This is because a) the rate of change $d\varphi/dt$ of the phase, i.e., the number of oscillations of the vector per unit time, measures locally, at time t, the frequency of the signal, this it is called the instantaneous frequency; and b) $A(t)$ measures at time t the energy of the signal (in contrast to $a(t)$); this is called the instantaneous amplitude or envelope (Figure 2).

Can we represent a real signal $x(t)$ in a 'natural way' as a complex signal $z(t) = x(t) + jy(t)$, as suggested above? The 'natural way' to represent a real signal as a complex signal is possible when the phase and the instantaneous amplitude are meaningful. The 'natural way' to represent a simple harmonic $x(t) = a\cos\omega t$ is to define $y(t) = a\sin\omega t$, i.e., $z(t) = ae^{j\omega t}$, because then $A(t) = a$ and $\varphi(t) = \omega$ (Figure 5, Gabor, 1946). In analogy, the complex representation of $x(t) = a(t)\cos\varphi(t)$ is $z(t) = a(t)e^{j\varphi(t)}$, thus $y(t) = a(t)\sin\varphi(t)$, in which case $A(t) = a(t)$ and the phase is $\varphi(t)$. In general, the 'natural' imaginary component $y(t)$ is a signal that is +90° out of phase with respect to $x(t)$, because then the oscillations of the real signal are transformed into a rotating vector in a 'natural way' (Gabor, 1946). This procedure is called the quadrature method, $y(t)$ is called the quadrature signal of $x(t)$, and $z(t) = x(t) + jy(t)$ is called the quadrature method signal.

In general, the real signal $x(t)$ is not a simple harmonic function and cannot be written in the form $x(t) = a(t)\cos\varphi(t)$. In that case $x(t)$, Gabor advocated the following method: we compute the Fourier transform of $x(t)$ and replace each component $a\cos\omega t$ by $ae^{j\omega t}$ and each component $b\sin\omega t$ by $-jbe^{j\omega t}$. The inverse Fourier transform of this result is the imaginary component $y(t)$. It is equivalent to suppressing the negative frequency components in the Fourier transform of $x(t)$ and to multiply the positive frequency components by two before computing the inverse transform. Gabor showed that the imaginary signal $y(t)$ is given by the integral: $y(t) = p.v.\int_{-\infty}^{\infty} \frac{x(\tau)}{\tau - t} d\tau$, in which p.v. means

that Cauchy's principal value has to be taken of this improper integral. In this case, the complex signal $z(t) = x(t) + jy(t)$ is called the analytic signal, and $y(t)$ is called the Hilbert transform of $x(t)$ (Gabor, 1946).

The analytical signal is meaningful if it is equal to, or an approximation of, the quadrature method signal because then the instantaneous amplitude and phase are meaningful, as explained above. However, the analytical signal is not always equal to the quadrature method signal (Boashash, 1992). It has been shown that, if the analytical signal $z(t) = A(t)e^{j\varphi(t)}$ of a real signal $x(t)$ satisfies these two constraints:

1. the spectrum of $A(t)$ is contained in a frequency region $-\omega_1 < \omega < \omega_1$; and
2. the spectrum of $e^{j\varphi(t)}$ is zero for $-\omega_1 \le \omega \le \omega_1$,

the analytical signal approximates the quadrature method signal and the phase, the instantaneous frequency, and instantaneous amplitude are meaningful. Under these same conditions, reflecting a rapidly oscillating component in combination with a slower varying amplitude, the instantaneous amplitude $A(t)$ and the instantaneous phase $\varphi(t)$ can be treated as independent signals, where $A(t)$ describes the slowly varying amplitude and the phase signal $\varphi(t)$ describes the rapidly oscillating component of the original signal (Boashash, 1992). We use the envelope $A(t)$ to quantify eyeblink parameters such as amplitude, area, onset point, peak time and duration.

A great advantage of the Hilbert transform is, that it can be designed as a zero-phase FIR (finite impulse response) filter. The Fourier transform of a lengthy signal may be troublesome; therefore it is easier to filter a long signal with a Hilbert filter in order to obtain the Hilbert transform and the analytical signal. Another advantage of this method is, that the original signal is not modified by this method, i.e., the envelope method does not change the properties of the signal.

A practical design of the Hilbert filter in the frequency domain is given in Figure 6. A description of a practical implementation is beyond the scope of this article, but can be requested from the author.

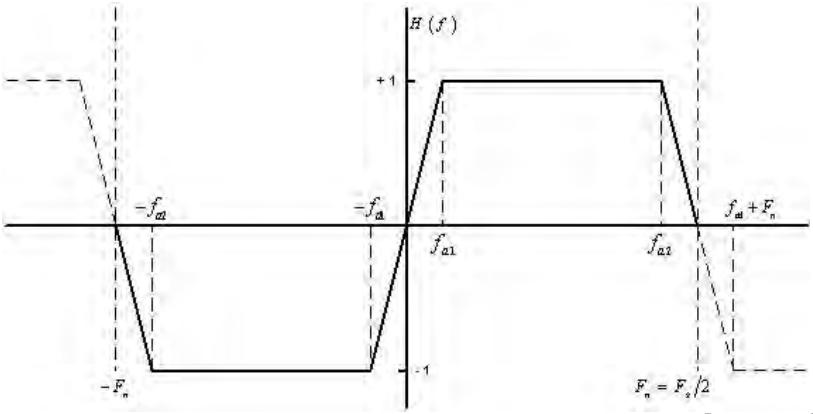

Figure 6. Design of a Hilbert transform FIR-filter. The transition bands $[-f_{a1}, f_{a1}]$ and $[f_{a2}, f_{a1}+F_n]$ at $f=0$ and $f=\pm F_n=\pm F_s/2$, respectively, are 'squared cosine shaped' slopes (after periodical extension of the frequency response). (F_n is the so called Nyquist-frequency and equals to half of the sample frequency.)

The smoothing method

The bandpass filtered signal was rectified, conversing all data points into absolute values (Blumenthal et al., 2005). The rectified signal was filtered by applying a lowpass filter. The -6dB cutoff frequency of the passband was defined at 40 Hz. Like the passband filter, this filter was a zero-phase FIR filter with a $\cos^2$-slope. The steepness of the slope was better than –20dB per octave.

Application

Subjects

Participants were 57 healthy volunteers (15 female; mean age 22 ± 4 years). These subjects were recruited by means of advertisements in and around Erasmus University and Erasmus MC (Medical Center), Rotterdam. As assessed by means of an interview and a questionnaire, all subjects were healthy and drug-free at the time of testing. None had experienced past or current psychiatric illnesses. The subjects received either course credits or a monetary reward, and all participants provided written informed consent before the onset of the experiment. The study was approved by the Medical Ethics Committee of the Erasmus MC, and has been performed in accordance with the Declaration of Helsinki.

Experimental procedure

The experiment was always performed between 09.00 and 11.00 hrs in the morning. Subjects were seated in a comfortable chair, in a dimly lit, sound-attenuated room. Apart from the EMG cup electrodes, electrodes for the measurement of the electrocardiogram, skin conductance, blood pressure and respiration were attached to the subject according to standard laboratory procedures.

After a baseline period of five minutes, participants were first familiarized with the acoustic startle noises: five acoustic startle stimuli were presented through headphones at irregular time intervals. Subsequently, the subject was informed that he or she would be viewing pictures with different contents, ranging from very pleasant to very unpleasant, and that the previously heard startle noises would be presented during the viewing of the pictures at irregular time intervals, but that these noises could be ignored. The subjects were instructed to relax and view the pictures quietly. The duration of the task was approximately 20 minutes.

Stimulus material

Forty-eight startle stimuli were presented during the experiment. The startle stimulus was a discrete white noise burst of 100 dB, with a duration of 50 ms and an instantaneous rise and fall time. The startle probe was presented binaurally through Sennheiser HD 265 linear headphones.

Forty-eight emotion-eliciting pictures were selected from the International Affective Picture System (IAPS; Lang et al., 2005)[1]. The pictures were 16 positive, 16 neutral and 16 negative pictures, selected on the basis of the normative ratings provided with the IAPS. Positive pictures consisted of erotic scenes and thrilling sports and objects; neutral pictures included nature scenes and household objects; negative pictures showed mutilations and threat scenes.

The pictures were presented in a random order, which was determined by the computer. Each picture was presented during 6 s, with an intertrial interval (ITI) ranging from 10-25 s. During 12 of the 16 pictures within each picture category (positive, neutral or negative) startle stimuli were presented 300, 800, 1300 or 3800 ms after picture onset (Bradley et al., 1993). Each of these interstimulus intervals (ISIs) was presented 3 times within each picture category. The four remaining pictures in each category were presented without the startle stimulus, and 12 startle stimuli were presented during the ITIs at random intervals.

[1] Positive pictures: 4220, 4290, 4490, 4520, 4608, 4660, 4670, 4680, 5260, 5470, 5621, 5910, 8030, 8170, 8490, 8501. Neutral pictures: 5120, 5510, 5530, 5535, 5711, 5731, 5740, 5900, 7000, 7002, 7004, 7006, 7009, 7010, 7020, 7025. Negative pictures: 3000, 3010, 3060, 3069, 3080, 3102, 3120, 3170, 6200, 6212, 6230, 6260, 6300, 6313, 6350, 6550.

EMG measurement

The EMG was measured using two cup electrodes (Ag/AgCl) placed below the left eye of the subject, over the orbicularis oculi muscle. One electrode was placed below the eye, in line with the pupil when the subject was looking straightforward, and the second electrode was placed 10 mm lateral to the first. The electrodes were filled with electrolyte paste (Spectra® 360; Parker Laboratories, Inc.). A third electrode served as isolated ground electrode, which was placed on the forehead of the subject.

Data reduction and analysis

The EMG-signal was sampled with a frequency of 1024 Hz and stored in A/D units on a portable digital recorder (Vitaport^{TM} System; TEMEC Instruments BV, Kerkrade, The Netherlands). The physiological data were subsequently imported and processed on a Personal Computer using Vitascore^{TM} software (TEMEC Instruments BV, Kerkrade, The Netherlands). Customized software routines, written in Microsoft Visual C++ V6, within the Vitascore^{TM} software were applied to further analyze the EMG-signal according to the two methods described above.

In order to investigate the differences in response probability between the two signal conditioning methods and between the different ISIs (300, 800, 1300 or 3800 ms or ITI-stimuli), the number of detectable trials (responses) within the ISI-condition was divided by the total number of presented trials within that ISI-condition for each method (Blumenthal et al., 2005). Thus, the response probability was calculated for the total amount of presented startle stimuli, but also separately for the startle stimuli occurring at either 300, 800, 1300, 3800 ms after slide onset and for the startles presented during the ITIs.

The EMG data were visually inspected for baseline contamination, such as movement artifacts and spontaneous eyeblinks (Blumenthal et al., 2005). The baseline was defined as the mean EMG value during 50 ms before startle stimulus onset. If the baseline of a particular startle response was contaminated, this trial was rejected from the data sets of both methods, and was excluded from further analyses.

Response onset was defined as the first point where the EMG value exceeded two standard deviations above baseline (Blumenthal et al., 2005), searched for in decreasing time starting from the peak of the response in the direction of the onset of the startle stimulus. The onset latency was defined as the time interval between the onset of the startle stimulus and the onset of the response. The allowed time window for onset latency was 20-100 ms after startle onset. The relative amplitude was defined as the difference between the peak amplitude and the mean baseline value. The allowed time window for the peak

amplitude was 20-150 ms after startle onset. In this interval, the first derivative of the conditioned EMG-signal was computed. The time points where the first derivative was zero were marked as peaks. If multiple peaks occurred within this time window, the peak with the largest value was used for further analyses (Blumenthal et al., 2005).

If the startle response did not satisfy the above-defined requirements, or if the peak amplitude did not exceed two standard deviations above baseline, it was scored as 'non-response' (missing). Non-responses were calculated separately for each method. Subjects were excluded from further analysis if the number of rejected trials exceeded 33% of all trials in one or both methods (Graham & Murray, 1977).

Statistical analyses

The difference in response probability of the four ISI-conditions in relation to the two methods was investigated using a related factorial ANOVA with the factors Time (300, 800, 1300 or 3800 ms) and Method (envelope versus smoothing) as within subjects factors, and Response Probability as the dependent variable. Where appropriate, the Greenhouse-Geisser correction method was used. We also investigated whether the response probability of the startle stimuli presented during the ITI differed between the two methods, using a paired samples t-test.

In order to investigate the discriminating ability of the two methods in emotional startle modulation, separate factorial ANOVA's for Onset Latency and Relative Amplitude being the dependent variables were performed, with Method (envelope vs. smoothing), Picture Type (negative vs. neutral vs. positive), and Time (300 vs 800 vs 1300 vs 3800 ms) as the within subjects factors.

Since eyeblink responses are often standardized due to the large interindividual variation in eyeblink magnitude, we also investigated whether the standardized data (z-scores) of the two methods differed in their discriminating ability. Therefore, we performed two factorial ANOVA's, one for each method, with Picture Type (negative vs. neutral vs. positive), and Time (300 vs 800 vs 1300 vs 3800 ms) as the within subjects factors, and the standardized eyeblink response amplitudes as the dependent factor. We performed the ANOVA's separately for each method because of the nature of standardization: the results could not be compared directly between methods because the z-scores of the methods were highly comparable.

All statistical analyses were two-tailed, and the alpha was set at 0.05. We used the Statistical Packages for the Social Sciences (SPSS) version 13.0 (SPSS Inc., 2004) to analyse our data.

Results

The data of 3 subjects were not included in the analyses on both response probability as well as discriminating ability due to more than 33% missing values in the data. Therefore, the analysis on response probability was performed using n=54. For the analysis on the discriminating abilities of the two methods, n=50 (11 female; age 22 ± 4 years) was used. Four subjects were excluded by SPSS due to incomplete data: 2 subjects were excluded due to incomplete data in both methods, and another 2 subjects were excluded due to incomplete data when using the smoothing method but not the envelope method.

Response probability

When we analysed the response probability of eyeblink responses at different time points during picture viewing, or during the intertrial intervals, the proportions of detectable responses between the two methods did not differ significantly (see Table 1).

Table 1. Proportions of detectable responses using the envelope and smoothing methods at different timepoints during the emotional startle modulation paradigm.

	Envelope Method	Smoothing Method
ITI-stimuli	0.914	0.915
300 ms	0.927	0.928
800 ms	0.921	0.918
1300 ms	0.913	0.920
3800 ms	0.886	0.886

ITI=intertrial interval

Discriminating ability in an emotional modulation paradigm

Onset Latency

For Onset Latency, a significant main effect of Picture Type was found, $F(2, 98)=4.19$, $p < 0.05$, partial $\eta^2=0.08$. The simple contrasts showed that negative pictures resulted in earlier eyeblink onsets than positive pictures, $F(1, 49)=8.64$, $p < 0.01$, $\eta^2=0.15$. No significant difference between methods was found.

Relative Amplitude

When we investigated the raw data of the relative amplitudes, several significant main and interaction effects were found. The main effect of Method indicated that the relative amplitudes obtained with the envelope method were larger than the amplitudes obtained using the smoothing method, $F(1,49) = 79.52$, $p<0.001$, partial $\eta^2=0.62$. The significant main effect of Time indicated that the relative

amplitude increased with increasing time, $F(3, 147)=2.87$, $p < 0.05$, $\eta^2=0.06$. The significant main effect of Picture Type indicated that the relative amplitude was smallest for positive pictures compared with both neutral and negative pictures, $F(2,98) = 9.90$, $p<0.01$, partial $\eta^2=0.17$.

The significant interaction effect of Method x Time indicated that the increase in relative amplitude with increasing time differed between the methods, $F(3,147)=3.82$, $p < 0.05$, partial $\eta^2=0.07$. More specifically, the increases in amplitude from 300 ms to 1300 ms and from 800 ms to 1300 ms are larger when the results were obtained using the envelope method compared with the smoothing method, $F(1,49)=9.60$ and 8.02, respectively, both $p < 0.01$.

The most relevant effect, however, is the significant interaction effect of Method x Picture Type, since this effect indicated that the differences between the startle responses elicited during the viewing of the various picture types differed between methods, $F(2,98) = 9.83$, $p< 0.001$, partial $\eta^2=0.17$. The differences in response amplitudes between positive and neutral, and between positive and negative pictures were significantly larger when the data were obtained using the envelope method compared with the smoothing method, $F(1,49)=24.12$ and 8.77 respectively, both $p< 0.01$ (see Figure 7).

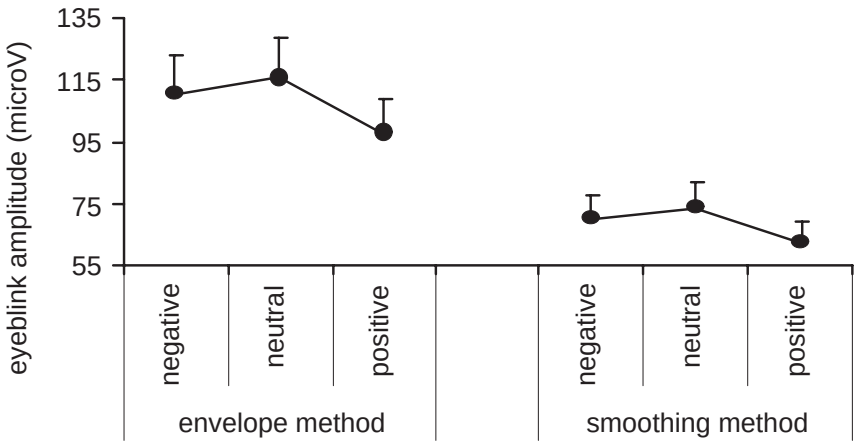

Figure 7. Estimated marginal means of the eyeblink amplitudes (μV) obtained with the envelope and smoothing method when viewing negative, neutral and positive pictures.

We also performed two separate ANOVA's, one for each method, using the z-transformed scores of the relative amplitude. As with the raw scores, main effects of Time and Picture Type were found with both methods (see Table 2). The main effect of Time indicated that the responses increased with increasing time, and the main effect of Picture Type indicated that the postive pictures elicited significantly smaller eyeblinks compared to both the neutral and the negative pictures. When the envelope method was used, the F-values were larger compared with the F-values when the smoothing method was used, indicating that stronger effects are obtained using the envelope method.

Table 2. Results of the ANOVA's for the envelope and smoothing methods using the z-transformed scores.

		Envelope Method		Smoothing Method	
Effect		F-value	p-value	F-value	p-value
Within subjects effects	Time	**4.81**	**0.003**	**4.38**	**0.006**
Within subjects contrasts	Linear	**8.80**	**0.005**	**8.71**	**0.005**
	Quadratic	0.96	0.332	0.561	0.457
	Cubic	3.49	0.068	2.22	0.143
Within subjects effects	Picture Type	**21.77**	**0.000**	**20.08**	**0.000**
Within subjects contrasts	Negative vs Positive	**22.33**	**0.000**	**20.90**	**0.000**
	Negative vs Neutral	1.02	0.316	1.03	0.316
	Positive vs Neutral	**59.89**	**0.000**	**53.83**	**0.000**

Significant differences are presented in bold, $p < 0.01$

Discussion

In the present paper a new method for the conditioning of the raw EMG-signal, the envelope method, was presented and evaluated in relation to a commonly used method, the smoothing method. When applied to an EMG-signal with startle-induced eyeblink responses, the envelope method outlines the rapid oscillations in an eyeblink. Compared with the non-linear rectifying 'smoothing' method (which adds high frequency components), the Hilbert transform does not change the properties of the signal. Furthermore, the Hilbert transform itself does not reduce the amplitude due to lowpass filtering or smoothing, resulting in a more accurate quantification of eyeblink parameters. In addition, the method may also distinguish the different phasic components of an eyeblink. However, in this study we applied a moderate lowpass filter to the envelope of the signal, in order to make the peak detection easier and to increase the comparability with the smoothing method. In case no lowpass filter would be applied to the envelope of the signal, this would further increase the ease of peak detection.

Application

When examining the differences in the response probability between the two methods, no significant differences were found. However, two subjects were excluded due to incomplete data when the results were obtained after the smoothing method, and not after the envelope method. This paradox, i.e. no significant differences in response probability between the two methods yet the exclusion of two persons in one method and not the other when investigating discriminant ability, is due to the different types of analyses. The data used for the response probability were based on individual responses per picture presentation, whereas the data that were used for the discriminant ability analyses were based on averaged scores per picture type. When the responses were averaged per picture type, some of the cells remained empty (i.e. not all picture types were represented in the data), resulting in incomplete data for the discriminant analyses in some cases.

The smoothing and envelope methods did differ in their ability to discriminate between various emotional stimuli based on startle blink responses. Although the differences that were found between startle responses when viewing positive as opposed to either neutral or negative pictures were present when using both methods, the differences between the responses elicited when viewing the various emotional stimuli were largest when using the envelope method. This was found both with the raw amplitude data, as well as the standardized z-scores of the data. This property of the envelope method can be very advantageous, particularly in applied clinical research or when using more complex research designs: with

this new method the possibility increases to detect subtle differences between patients and control subjects.

Limitations

We presented the data obtained after applying the Hilbert transform, followed by a 40 Hz lowpass filter in order to increase the comparability with the smoothing method. However, the envelope method can also be used without low pass filtering, which will result in more accurate peak detections, leading to an increased discriminating ability when using different stimulus conditions. The present results are limited due to the lack of the unfiltered data, and future research should investigate these data more thoroughly.

A second limitation was the finding that the negative pictures did not evoke startle potention compared with the neutral pictures. It is possible that the negative pictures did not evoke a true defensive emotional state in the subjects, resulting in an absence of startle potentiation. Bradley et al. (2001a; 2006) previously found that negative pictures rated low in arousal did not elicit startle potentiation reliably. We did not present the data on the subjective ratings of the subjects in the present paper, but the SAM (Bradley & Lang, 1994) used in the present study had a rating scale ranging from 1 to 9, while the overall mean ratings from our subject sample did not exceed 5, which is considered 'moderately arousing'. These low arousal scores may explain why our subjects did not show startle potentiation during the viewing of negative pictures.

Conclusion

Summarizing the findings of the present article, the envelope and the smoothing methods have similar qualities in terms of the ability and probability to detect eyeblink responses. However, the envelope method is superior to the smoothing method in discriminating between startle eyeblink responses elicited during different emotional foregrounds. The discriminating abilities of the envelope method should be investigated in more detail, in particular in clinical settings, to establish whether the envelope method is indeed more valuable than the smoothing method in startle eyeblink research, and possibly other research domains.

Acknowledgements

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CHAPTER 7

Emotional startle modulation in male patients with recent-onset schizophrenia: decreased positive motivation during erotic stimuli?

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Abstract
Schizophrenic patients suffer from both cognitive as well as emotional disturbances. This study investigated the ongoing emotional states of patients and healthy controls during the viewing of emotion-eliciting pictures. Aversive startle stimuli were presented at 4 different latencies (300, 800, 1300 and 3800 ms) from picture onset. Positive pictures elicited significantly smaller eyeblinks compared with the neutral and negative pictures, and patients and controls responded in a similar fashion. When we analyzed specific picture contents (erotic, nature or threat), we found a nonsignificant trend effect for the erotic pictures, which indicated that the eyeblink responses of patients during the viewing of erotic pictures increased with increasing viewing time, suggesting a decrease in positive motivation. The lower subjective pleasure ratings of erotic pictures by the patients compared with the controls underlined this suggestion. The present results indicate the need to further investigate sexual needs and expectations of schizophrenic patients, to eventually improve the quality of life in these patients.

Introduction

Schizophrenia is a severe psychiatric illness, which causes both emotional as well as cognitive disturbances (Bleuler, 1911; Kraepelin, 1919). Over the past decade, the emotional disturbances that schizophrenic patients experience, have received increasing attention (Edwards et al., 2001). For example, schizophrenic patients are impaired in their ability to recognize emotional facial expressions, which is an important component of effective social functioning (Gur et al., 2002; Loughland et al., 2002). Abnormalities in emotion identification and emotional behavior have also been found to be associated with the poor social functioning observed in patients with schizophrenia (Borod and Madigan, 2000).

Besides the ability to perceive emotions in others, it is also important to accurately identify and interpret emotional meanings from situations in the environment. The idea that emotions serve as survival mechanisms is supported by the fact that emotions are accompanied by physiological reactions, such as changes in the somatic muscles and the viscera. These changes support the behavioral responses to the environmental stimuli (Bradley and Lang, 2000; Kring, 1999).

An experimental paradigm has been developed to investigate the ongoing positive and negative emotions of subjects during the viewing of emotion-eliciting scenes: the emotional startle modulation paradigm (Vrana et al., 1988; Lang et al.,1990). In this paradigm, different emotion-eliciting pictures are presented to subjects on a screen, and occasionally loud startle noises are presented through headphones, to provoke a startle reflex in the subjects. The startle reflex is usually measured by recording the electromyographic activity of the m. orbicularis oculi, which contracts during the startle eyeblink response, the most reliable component of the whole body startle reflex (Blumenthal et al., 2005).

The underlying theory of this paradigm defines emotions as action dispositions, which organize behavior along a valence dimension ranging from appetitive to aversive emotions (Lang et al., 1990). The appetitive (positive) emotions can lead to approach and consummatory behavior, whereas the aversive (negative) emotions can lead to avoidance and defensive behavior. Behavior also includes several reflexes, which can be organized along the valence dimension, such as the salivary response and the startle reflex. If the emotional state and the reflex match in valence (i.e. both appetitive or both aversive), the reflex will be enhanced. Conversely, if there is a mismatch between the emotional state and the reflex, the reflex will be attenuated (Lang et al., 1990). In the past two decades, this theory has received substantial support from numerous studies that investigated the effects of emotional picture viewing on the intensity of the startle eyeblink response: the startle reflex is reduced while viewing arousing pleasant slides, and enhanced while viewing arousing unpleasant slides (Grillon and Baas,

2003). Besides the valence dimension, the arousal dimension is also an important factor for emotional startle modulation to occur. For example, startle potentiation occurs most reliably when unpleasant pictures are highly arousing (Bradley et al., 2001a; 2006).

The magnitude of the startle response is modulated both by attention as well as emotion, depending on the duration between picture onset and startle onset. If the startle stimulus is presented early during the viewing of emotional pictures (300/500 ms; Bradley et al., 1993; Vrana et al., 1988), the startle response is influenced by attentional information processing: both pleasant and unpleasant pictures elicit smaller eyeblink responses compared with neutral pictures. This effect is explained by the attentional interpretation of prepulse inhibition: highly arousing pictures are more interesting and more complex than neutral pictures, resulting in longer periods of processing protection compared with less interesting pictures. Reflexes elicited around 800 ms were generally inhibited compared with neutral pictures, but they were sensitive to the affective contents of the pictures since differences in startle magnitude were found between pleasant and unpleasant pictures. At longer latency intervals (1300 ms – slide offset), the effects of stimulus content were more pronounced: negative pictures elicited larger eyeblink responses, and positive pictures elicited smaller responses compared with neutral pictures (Bradley et al., 1993).

Bradley et al. (2001a) investigated whether specific picture contents elicited different startle response magnitudes. They found that negative pictures with animal attack, human attack, and contamination elicited the largest eyeblink responses. For the pleasant pictures, erotica (couples and opposite sex nudes) elicited the smallest blink reflexes. Thus, from a survival perspective, the two most relevant picture contents elicited the most pronounced responses: pictures signaling threat elicit the largest eyeblink responses, and pictures with erotic scenes elicit the smallest responses.

Attentional modulation of the startle reflex, or prepulse inhibition (PPI), has been investigated extensively in schizophrenic patients and their relatives (for example Cadenhead et al., 2000; Dawson et al., 1993; Ludewig et al., 2002; Ludewig et al., 2003; Meincke et al., 2003). Braff et al. (2001) reviewed the literature on PPI in human subjects and concluded that schizophrenic patients exhibit reduced PPI, independent of stimulus characteristics. Since PPI is considered a sensorimotor gating mechanism, this finding suggests that schizophrenic patients are impaired in their ability to filter out irrelevant stimulus information from awareness.

A considerably smaller amount of research has been conducted on the emotional modulation of the startle response in schizophrenic patients. Only three studies have been published previously investigating emotional startle modulation

in these patients, with varying results. In the first study (Schlenker et al., 1995), schizophrenic patients did not differ from healthy controls in their eyeblink responses to positive and neutral pictures, but compared to neutral pictures, their responses to negative pictures were not potentiated, in contrast to healthy controls, who did show startle potentiation. Curtis et al (1999), however, did not find any differences between schizophrenic patients, their first-degree relatives and healthy control subjects with regard to eyeblink responses. All participants showed the expected startle modulation pattern, with positive slides eliciting the smallest eyeblinks, and negative slides the largest. Volz et al. (2003) investigated the temporal course of emotional startle modulation in these patients. Following the study of Bradley et al. (1993), startle stimuli were presented at varying intervals (150, 300, 800, 1300, and 3800 ms) during the viewing of emotional pictures. Schizophrenic patients and healthy controls did not differ in their startle responses when the startle stimulus was presented 3800 ms after picture onset. However, when the startle stimulus was presented earlier during picture viewing, patients did not show startle potentiation to unpleasant pictures, whereas the controls did show startle potentiation as early as 300 ms. For the pleasant and neutral pictures no differences between groups were found. Volz et al. (2003) concluded that schizophrenic patients need more time than healthy control subjects to process the aversive information from unpleasant pictures, leading to a delay in the activation of the defense system.

The present study aimed to further investigate the effects of different startle latencies on the emotional startle modulation in schizophrenic patients and healthy control subjects. A variety of emotion-eliciting pictures, selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999), were presented to participants. During the viewing of these pictures, startle stimuli were presented at varying latencies from picture onset (300, 800, 1300 and 3800 ms), while EMG eyeblink responses were measured. First, we examined the influence of the general picture categories of positive, neutral and negative pictures on startle eyeblink responses in schizophrenic patients. Second, we investigated whether the specific picture contents of erotica, nature and threat yielded more information about emotional information processing in these patients. We selected these three specific contents based on the results of previous studies mentioned above (e.g. Bradley et al., 2001a), which indicated that highly arousing pictures yielded the strongest results, due to their biological relevance.

Methods

Subjects

In this study 41 male schizophrenic patients (mean age 22 ± 5 years) and 40 male control subjects (mean age 23 ± 4 years) participated. The patients were recruited from the Psychosis ward of the department of Psychiatry of Erasmus MC, University Medical Center Rotterdam. We sought to include all consecutively admitted patients who fulfilled the inclusion criteria as soon as the patients were able to perform the test procedures. All patients were screened by a clinical psychiatrist (NvB, CH) and included in the study when they were diagnosed as suffering from schizophrenia or a schizophreniform disorder according to the criteria of the DSM-IV (APA, 1994). All diagnoses were confirmed by a second senior psychiatrist (NvB, CH). In order to assess symptom severity, the Dutch translation of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used.

All patients experienced a psychotic episode at the time of the study. Twenty-nine patients received medication; 12 patients were medication-free at the time of testing. Antipsychotic treatment was administered according to the clinical treatment protocol of the Erasmus MC clinic for psychotic disorders, which is congruent with both the schizophrenia treatment guidelines of the Dutch Psychiatric Association and the American Psychiatric Association.

Controls were recruited by means of advertisements. All controls were healthy and drug-free at the time of testing as assessed by means of an interview and a questionnaire. None of the controls or their first-degree relatives had experienced past or current psychiatric illnesses. Exclusion criteria for both patients and controls were respiratory diseases, cardiovascular diseases, the use of medication that could influence the autonomic nervous system, and any other physical condition that could lead to a distraction from task performance.

After the subjects were given a complete description of the study, written informed consent was obtained. The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam.

General procedure

All experimental sessions took place between 09.00 and 11.00 hrs in the morning. The subject sat in a comfortable chair in a small, sound-attenuated dimly lit room. Both patients and controls were asked not to use any coffee or cigarettes before and during testing. Electrodes for the recordings of the EMG (electromyographic) signal, heart rate, skin conductance level, respiration and blood pressure were applied according to standard laboratory procedures. After the application of the electrodes, the experimental session began with a rest period of five minutes in which subjects were asked to relax and not to speak. After this first rest period the

headphones were put on, and the startle task was explained. The duration of the startle task was approximately 25 minutes. After completion of the startle task, a second rest period of 5 minutes was introduced, followed by an emotional probe detection task in which emotional faces were presented other than the IAPS pictures used for the startle task. This second task lasted 3 minutes, again followed by a 5-minute rest period. After this final rest period, all electrodes were removed from the subjects and they were asked to perform the final task: the subjective rating task, which lasted approximately 15 minutes.

Startle task

Subjects were seated approximately 75 cm from the computer screen. All subjects were asked to relax, to breathe regularly and not to speak during the task. They were informed that they first would be hearing five loud noises through the headphones, but that they did not have to respond. These first five startle stimuli were presented to the subjects to let them accustom to these sounds and to decrease the impact of habituation effects during the experiment. After the first 5 startles, they were told that they were about to be view a series of different pictures, and that loud noises were occasionally presented through the headphones. They were asked to look at the pictures the entire time they were presented on the screen, but that they did not have to respond.

Each picture was presented during 6 seconds, with an intertrial interval (ITI) ranging from 12-25 seconds. A total of 48 pictures were presented; during 12 of these pictures (4 positive, 4 neutral and 4 negative) no startle stimulus was presented. During the remaining 36 pictures, startle stimuli were presented either 300, 800, 1300 or 3800 ms after picture onset in such a way that each of these latency conditions occurred 3 times during the viewing of positive, neutral and negative pictures. In addition, 12 startle stimuli were randomly presented during the ITI's. Thus, a total of 48 pictures and 48 startle stimuli were presented.

Subjective rating task

The 48 pictures that were presented during the startle task, were presented again in the subjective rating task, in a randomized order different from that of the startle task. During each trial, a fixation cross was presented for 3 seconds on a 17-inch computer screen, followed by a 6-second presentation of a picture. After picture offset, the subjects were asked to rate the picture on both SAM dimensions of pleasure and arousal. After their response, the fixation cross appeared again for 3 seconds. The subjects were seated approximately 75 cm from the computer screen and responded with their dominant hand using the numbers on the keyboard. The task was designed using E-prime (Psychology Software Tools, Inc., 2002).

Stimulus Material

Forty-eight pictures were selected from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 1999)[1]. The stimuli were chosen on the basis of their normative ratings provided with the IAPS, and could be divided into three different categories: positive, neutral and negative pictures. The positive pictures contained pictures with erotic contents and with thrilling sports and money contents, the neutral pictures contained pictures with nature contents and household objects, and the negative pictures contained pictures with mutilation and threat contents. Trials presenting same-sex pictures were excluded from further analysis to avoid gender differences in response to sexually arousing pictures[2]. The pictures were presented using a Dell Dimension M200a Personal Computer with a Pentium processor and a 17-inch Samsung SyncMaster monitor.

The startle stimulus was a discrete white noise burst of 100 dB during 50 ms, with an instantaneous rise and fall time, presented binaurally through headphones. The startle stimuli were presented through Sennheiser HD 265 linear headphones. The sound intensity of the startle stimulus was checked every week using a sound level meter to make sure that the startle stimulus was 100 dB for every participant.

Measurements

Subjective ratings

Valence and arousal ratings were registered using the SAM rating-procedure (Self-Assessment Manikin; Bradley and Lang, 1994). The SAM consisted of two subsequent screens, each containing five figures. On the first screen, the figures represented the degree of pleasantness of the pictures -ranging from very unpleasant to very pleasant- on a scale from 1 to 9. On the second screen, each figure represented the degree of arousal associated with each picture -ranging from very calm to very arousing- also on a scale from 1 to 9.

Physiological responses

The EMG activity of the m. orbicularis oculi was measured using two Ag/AgCl cup electrodes filled with electrolyte paste (Spectra® 360; Parker Laboratories, Inc.) placed below the left eye. One electrode was placed in line with the pupil

[1] Positive IAPS pictures: 4220, 4290, 4490, 4520, 4608, 4660, 4670, 4680, 5260, 5470, 5621, 5910, 8030, 8170, 8490, 8501. Neutral IAPS pictures: 5120, 5260, 5510, 5530, 5535, 5711, 5731, 5740, 5900, 7000, 7002, 7004, 7006, 7009, 7010, 7020, 7025. Negative IAPS pictures: 3000, 3010, 3060, 3069, 3080, 3102, 3120, 3170, 6200, 6212, 6230, 6260, 6300, 6313, 6350, 6550.

[2] Removed pictures for men: 4490, 4520. Removed pictures for women: 4220, 4290.

over the skin above the m. orbicularis oculi when the subject was looking straight ahead, and the second electrode was placed 1 cm lateral to the first. A third electrode was attached to the forehead, serving as an isolated ground electrode.

The EMG-signal was sampled at 1024 Hz and stored in A/D units on a flashcard using a portable digital recorder (Vitaport^{TM} System; TEMEC Instruments B.V., Kerkrade, the Netherlands). Upon completion of the recording, all physiological data were imported and processed on a Personal Computer using a Vitagraph^{TM} software module (TEMEC Instruments BV, Kerkrade, the Netherlands).

First, a zero-phase bandpass finite impulse response (FIR-) filter with cos^2-slopes was applied to the EMG-signal. The -6dB cutoff frequencies of the passband were defined at 28Hz and 500Hz (Van Boxtel et al., 1998), with a steepness at both slopes better than -20dB per octave. Subsequently, a Hilbert transform was applied to the signal, in order to calculate the envelope of the original signal. This signal conditioning technique does not affect the original values of the signal (Gabor, 1946). Finally, a lowpass filter of 40 Hz was applied.

Data analysis and reduction

The EMG-recording of each participant was examined visually for possible baseline contaminations (e.g., noise, movement artifacts) and spontaneous or voluntary blinks before the onset of the startle stimulus. In the case of artifacts, the blink response could not be accurately quantified for that particular trial, resulting in trial-rejection.

The baseline value of each individual eyeblink response was calculated as the mean voltage of the signal 50 ms before startle stimulus onset. Response onset was defined as the time point within 20-100 ms after startle onset at which the EMG signal exceeded two standard deviations above baseline value (Blumenthal et al., 2005), searched from right to left in time, i.e. from peak back to startle onset, to avoid 'accidental/premature onsets'. Relative amplitude was computed as the difference between the peak and the baseline value of each response. Peaks had to exceed an amount of two standard deviations above baseline value to be further analyzed as a blink response. In case no peak within the 20-150 ms scoring window satisfied this requirement, the response was scored as missing (or 'nonresponse'). In case of multiple peaks within the 20-150 ms scoring window, the peak with the highest value was determined as response peak. Subjects who did not show valid eyeblinks in more than 33% of the trials were excluded from further analysis (Graham and Murray, 1977; Volz et al., 2003).

To reduce the large interindividual variation in the eyeblink responses, we transformed the data into z-scores within each subject. The z-scores were increased with 5, in order to make the data unidirectional. For data reduction

purposes, only relative amplitude was used as the dependent variable in the analyses.

Statistical analyses

Subjective ratings

To compare the subjective ratings of schizophrenic patients and healthy control subjects, non-parametric Mann-Whitney U-tests were performed on both the pleasure and arousal ratings for positive, neutral and negative pictures with Group as between subjects factor. This same analysis was performed on both the pleasure and arousal ratings for pictures with the specific erotic, nature and attack contents.

To investigate whether the different picture types were rated differently within groups, we performed a Friedman's chi-square test on the ratings for the positive, neutral and negative pictures for the patients and controls separately to evaluate whether there was an overall difference between the categories in the pleasure and the arousal ratings. If the test indicated that the pictures were rated differently within each group, we performed Wilcoxon Signed Rank Tests, comparing the ratings for the picture types pair-wise, to analyze which picture types were rated significantly different from each other within each group. This analysis was repeated using the pleasure and arousal ratings for pictures with the specific erotic, nature and attack contents.

Eyeblink responses

To investigate the effects of different startle latencies on the emotional startle modulation, we performed a 2x3x4 Repeated measures ANOVA, with Group (patients vs. controls) as the between subjects factor, and PictureType (positive vs. neutral vs. negative) and StartleLatency (300 vs. 800 vs. 1300 vs. 3800 ms) as the within subjects factors. Subsequently, we investigated whether specific contents of the pictures led to different responses: we performed a 2x3x4 Repeated measures ANOVA, with Group (patients vs. controls) as the between subjects factor, and PictureContent (erotic vs. nature vs. attack) and StartleLatency (300 vs. 800 vs. 1300 vs. 3800 ms) as the within subjects factors.

The statistical analyses were performed using SAS 8.2 (SAS Institute Inc., 1999-2001). The significance level for all analyses was set at 0.05. In the ANOVA for specific picture contents, 85 cells were empty due to missing data (10.3 % of 828 observations). SAS is able to perform a reliable linear mixed model under the assumption that the data is missing at random (MAR), in contrast to missing completely at random (MCAR). The experiment was designed in such a way that each startle latency occurred 3 times within each picture category. By dividing the categories into subcategories with specific contents, a problem arises when data is missing due to factors such as undetectable eyeblinks or baseline contaminations,

in which case the individual response was removed before further analyses. In this case, the cell for a specific picture type and startle latency may contain only 1 or no observation. Fortunately, SAS considers this latter case as MAR and is able to proceed with the analyses. The consequence of this type of analysis is, that SAS increases the standard error of the estimates, making the analyses more conservative.

Results

Subjects

Six patients were unable to complete the experiment due to restlessness. Four patients and two control subjects did not show eyeblinks in 33% of the trials, and data of these participants was excluded from further analyses. Table 1 presents the demographic data of the remaining 31 patients and 38 control subjects and Table 2 presents the medication use of the remaining patients.

Table 1. Demographic data of the schizophrenic patients and control subjects

Clinical and demographic data		Patients (N=31)	Controls (N=38)
Age (mean ± sd)		22 ± 5	23 ± 4
Duration of illness (months; mean ± sd)		11 ± 17	
PANSS-scores	Total	70 ± 18	
(mean ± sd)	Positive symptoms	18 ± 7	
	Negative symptoms	16 ± 5	
	General psychopathology	36 ± 11	

Table 2. Medication use and mean dosage per day of the patient sample

Medication	N	Mean daily dosage (mg ± sd)	Number of weeks medication (mean ± sd)	Benzodiazepine use (lorazepam/oxazepam)
Medication Free	8			2 (2/0)
Haloperidol	5	3.0 ± 1.4	2 ± 1	3 (3/0)
Risperidone	4	2.9 ± 0.7	4 ± 3	2 (1/1)
Olanzapine	9	15.6 ± 6.8	5 ± 7	4 (3/1)
Clozapine	4	300 ± 81.6	4 ± 3	3 (3/0)
Quetiapine	1	300	1	0

Emotional startle modulation

General picture categories

First, we investigated the effects of general picture type (positive, neutral, negative) and startle latency (300, 800, 1300, and 3800 ms) between groups (patients versus controls; see Figures 1a and 1b). We found a significant main effect for Picture Type, $F(2;67)=21.66$, $p< 0.001$, which indicated that the positive pictures evoked smaller eyeblinks compared with either the neutral and the negative pictures, $t(67)= 3.48$ and 3.44 respectively, $p<0.001$. The negative and neutral pictures did not evoke different responses. We also found a significant main effect for Startle Latency, $F(3;67)=12.06$, $p< 0.001$, which indicated that the responses evoked at 300 and 800 ms were significantly smaller than the responses evoked at 1300 and 3800 ms (300 ms versus 1300 and 3800 ms: $t(67)=3.36$ and 2.26 respectively, $p< 0.05$; 800 ms versus 1300 and 3800 ms: $t(67)=3.36$ and 2.10 respectively, $p<0.05$). The schizophrenic patients and healthy controls did not significantly differ in their responses to the emotional pictures, given the lack of significant group or interaction effects.

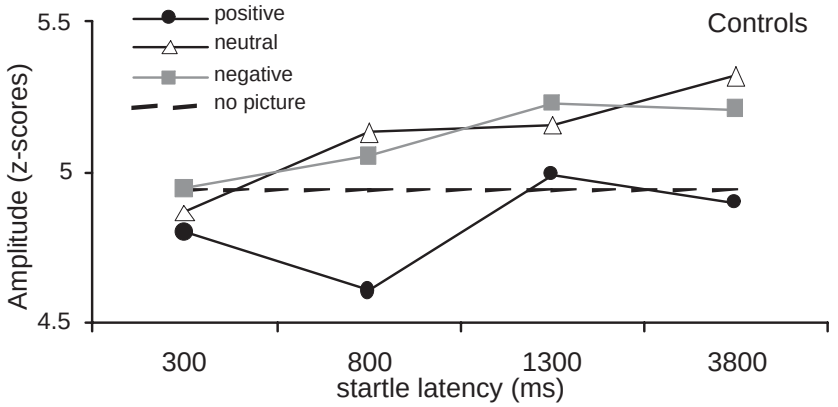

Figure 1a. Startle responses of the controls during the viewing of positive, neutral and negative pictures at different startle latencies.

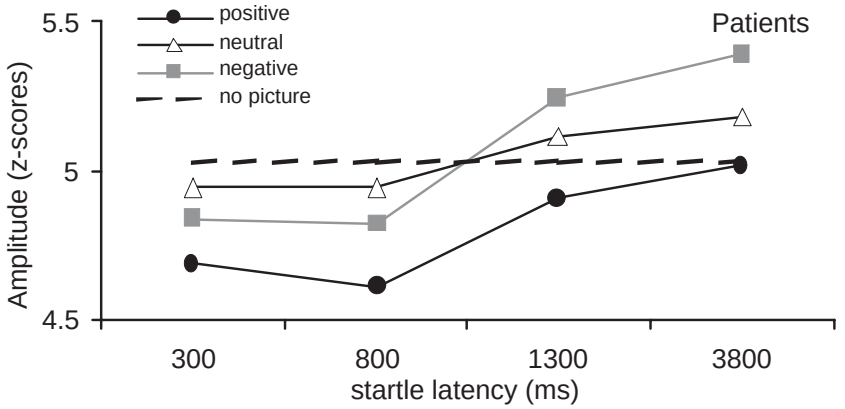

Figure 1b. Startle responses of the patients during the viewing of positive, neutral and negative pictures at different startle latencies.

Specific picture contents

Second, we investigated the effects of specific picture contents (erotic, nature, threat) and startle latency (300, 800, 1300, and 3800 ms) between groups (patients versus controls; see Figures 2a and 2b). We found a significant main effect of Picture Type ($F(2;67)=45.64$, $p<0.001$), indicating that the responses to the erotic pictures were significantly smaller than to the nature and threat pictures, $t(67)=7.79$ and 7.54 respectively, $p<0.001$. The responses to nature and threat pictures did not differ from each other. We also found a significant main effect of Startle Latency ($F(3;67)=9.45$, $p<0.001$), indicating that the eyeblink responses increased with increasing startle latency. The interaction effect of Group x Latency x Picture Type was not significant, although it did show a nonsignificant trend, $F(6;67)=1.82$, $p=0.107$.

Although the 3-way interaction was not significant and only showed a slight trend, we decided to further investigate this effect because of its potential importance (see Table 3). The difference between the responses to erotic and threat pictures was equal between groups, except for a slightly decreasing difference between these two picture categories in the patient group from 1300 to 3800 ms, whereas in the control group the difference in responses to erotic and threat pictures increased from 1300 to 3800 ms.

The difference in responses to nature and threat pictures was also similar between groups, except for a slight difference in responses to these pictures when the 300 ms and 3800 ms latencies were compared: the patients showed smaller responses to nature pictures compared with threat pictures at 300 ms but not at 3800 ms, whereas the controls did not differ between their responses to nature and threat pictures at 300 ms and 3800 ms.

The largest difference between patients and control subjects was found when we compared the responses to the nature and erotic pictures. In the patient group, the difference in responses between erotic and nature pictures decreased from 300, 800 or 1300 to 3800 ms, whereas in the control group this difference increased from 300, 800 or 1300 to 3800 ms. Thus, in contrast to healthy control subjects, schizophrenic patients seemed to be less positively motivated by erotic pictures with increasing viewing time.

The decrease in startle response from 300 to 800 ms was only found in the control group, not in the patient group. This difference between groups was due to a lack of differentiation between picture types in the control group. In the control group, the responses to the erotic and nature pictures did not differ at 300 ms but they did differ at 800 ms, whereas in the patient group the responses to the erotic pictures were smaller than to the nature pictures, and this pattern was also found at 800 ms.

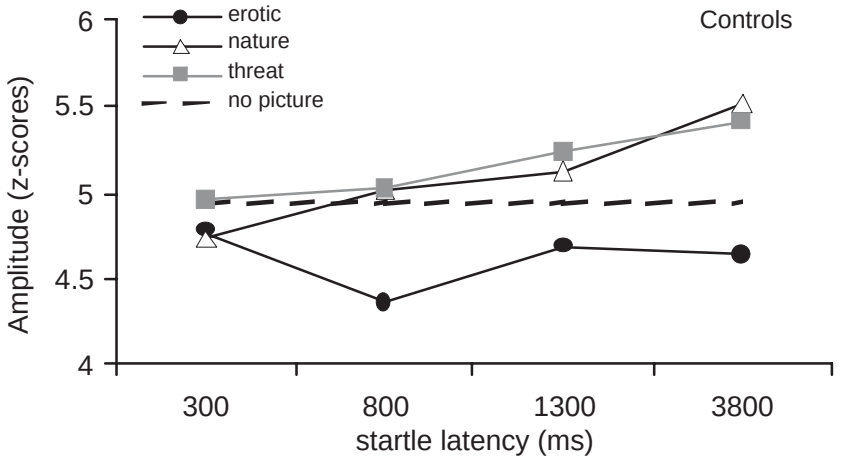

Figure 2a. Startle responses of the controls during the viewing of erotic, nature and threat pictures at different startle latencies.

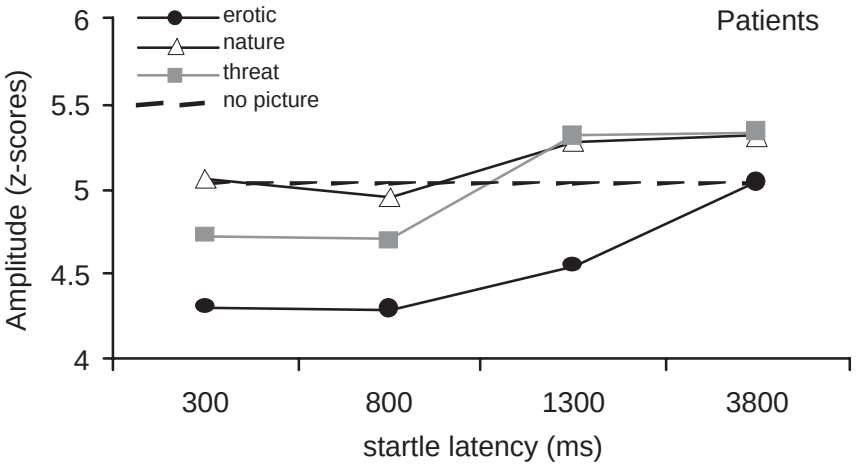

Figure 2b. Startle responses of the patients during the viewing of erotic, nature and threat pictures at different startle latencies.

Table 3. Estimates of the regression model for the significant Group x Picture Type x Startle Latency interaction effect for specific picture contents (erotic, nature and threat)

			Estimate	Standard error	t-value	p-value
Controls vs. Patients	Erotic vs. threat	300 vs. 800	-0.47	0.50	-0.93	0.35
		300 vs. 1300	-0.03	0.49	-0.07	0.94
		300 vs. 3800	-0.70	0.51	-1.39	0.17
		800 vs. 1300	0.43	0.42	1.04	0.30
		800 vs. 3800	-0.24	0.42	-0.57	0.57
		1300 vs. 3800	*-0.67*	*0.40*	*-1.67*	*0.10*
	Erotic vs. nature	**300 vs. 800**	**-0.85**	**0.44**	**-1.96**	**0.05**
		300 vs. 1300	-0.53	0.48	-1.11	0.27
		300 vs. 3800	**-1.45**	**0.52**	**-2.78**	**0.01**
		800 vs. 1300	0.33	0.35	0.92	0.36
		800 vs. 3800	*-0.60*	*0.35*	*-1.73*	*0.09*
		1300 vs. 3800	**-0.92**	**0.38**	**-2.44**	**0.02**
	Threat vs. nature	300 vs. 800	-0.39	0.44	-0.89	0.38
		300 vs. 1300	0.49	0.39	-1.25	0.21
		300 vs. 3800	*-0.75*	*0.45*	*-1.65*	*0.10*
		800 vs. 1300	0.11	0.42	-0.25	0.80
		800 vs. 3800	-0.36	0.45	-0.79	0.43
		1300 vs. 3800	0.25	0.42	-0.59	0.55

Significant effects ($p \leq 0.05$) are presented in **bold**
Trend effects ($p \leq 0.10$) are presented in *italics*

Subjective ratings

One patient did not complete the subjective rating task, reducing the number of patients for this analysis to 30. The valence and arousal ratings of both groups are presented in Table 4.

Subjective ratings between groups

When we compared the subjective ratings of both groups for the general categories of positive, neutral and negative pictures, the patients and controls did not differ in their pleasure ratings. The patients rated the neutral pictures as more arousing than the control subjects ($U=319$, $p < 0.01$), but they rated the positive and negative pictures equally arousing as the control subjects.

When we compared subjective ratings of both groups for the more specific categories of erotic, nature and threat pictures, the patients rated the erotic pictures less pleasant than the control group ($U=344.5$, $p < 0.01$), and the patients tended to rate the threat pictures as slightly more unpleasant than the control subjects ($U=435$, $p = 0.095$). The patients rated the nature pictures as more arousing than the control group ($U=356$, $p < 0.01$), but no differences were found for the arousal ratings of the other two categories.

Table 4. Valence and Arousal ratings of the patients and controls

	Patients (n=30)		*Controls (n=38)*	
	Valence	Arousal	Valence	Arousal
Picture Type	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Positive	6.0 (0.9)	4.3 (1.8)	6.3 (0.7)	3.8 (1.3)
Erotic*	5.4 (1.1)	4.0 (1.6)	6.1 (0.8)	4.4 (1.4)
Neutral+	5.2 (0.9)	3.2 (1.4)	5.3 (0.9)	2.0 (1.2)
Nature+	5.5 (1.1)	3.3 (1.6)	5.5 (1.0)	2.2 (1.3)
Negative	2.9 (1.4)	4.4 (2.2)	2.9 (0.9)	4.3 (1.5)
Threat	3.2 (1.5)	4.3 (2.1)	3.6 (1.0)	3.7 (1.7)

* = significant difference between groups in pleasure ratings, $p < 0.01$
+ = significant difference between groups in arousal ratings, $p < 0.01$

Subjective ratings within groups

In all cases, the Friedman's chi square tests were highly significant ($\chi^2 > 10$, df =2), so we proceeded with the pair-wise testing using the Wilcoxon Signed Rank test. The results of these comparisons are summarized in Table 5.

Within both groups, positive pictures were rated significantly more pleasant than neutral and negative pictures, and the negative pictures were rated significantly more unpleasant than neutral and positive pictures. Within both

groups, the positive and negative pictures were rated significantly more arousing than the neutral pictures. The patients did not rate the positive and negative pictures differently, but the controls rated the negative pictures as significantly more arousing than the positive pictures.

The patients rated the pictures with erotic and nature contents as equally pleasant, but they rated the threat pictures as significantly more unpleasant than the erotic and nature pictures. The controls rated the erotic pictures as significantly more pleasant than both the nature and threat pictures, and they rated the threat pictures as significantly more unpleasant than both the erotic and nature pictures. Both groups rated the erotic and threat pictures significantly more arousing than the nature pictures, but only the control group rated the erotic pictures as more arousing than the threat pictures; the patients rated the erotic and threat pictures as equally arousing.

Table 5. Summary of pair-wise comparisons (Wilcoxon Signed Rank Test, Z-statistic) for the subjective valence and arousal ratings within groups

	Patients (n=30)		*Controls (n=38)*	
Pair wise comparisons	Valence	Arousal	Valence	Arousal
Positive – Neutral	3.88**	4.39**	4.98**	5.51**
Positive – Negative	4.96**	0.20	5.51**	2.47*
Neutral – Negative	4.84**	3.65**	5.51**	5.44**
Erotic – Nature	0.03	3.98**	3.41**	5.52**
Erotic – Threat	4.67**	0.91	5.51**	2.47*
Nature – Threat	4.48**	3.28**	5.50**	5.19**

** $p < 0.001$; * $p \leq 0.01$

Discussion

The aim of the present study was to investigate the effects of different startle latencies on the emotional startle modulation in schizophrenic patients. Overall, we found only a minor difference between schizophrenic patients and healthy control subjects with regard to their eyeblink responses to erotic pictures, which is discussed below.

Emotional startle modulation

When the responses to the general picture categories of positive, neutral and negative pictures were investigated, no differences between schizophrenic patients and controls were found, consistent with the results of Curtis et al. (1999). In both groups, positive pictures elicited smaller eyeblinks than either neutral or negative pictures, but the responses to the negative pictures did not differ from the

responses to the neutral pictures. The main effect of startle latency indicated that the startle responses increased with increasing viewing time, consistent with previous studies (Bradley et al., 1993; 2006).

When we analyzed the effects of specific picture categories on eyeblink responses, we found similar results: erotic pictures elicited smaller responses than either the nature or threat pictures, which did not differ from each other. Again, the main effect of startle latency indicated that the startle responses increased with increasing viewing time. Although the interaction effect of Group x Picture Type x Startle Latency was not significant, visual inspection of the data indicated that the startle responses of schizophrenic patients to erotic pictures increased from 300 ms to 3800 ms. This finding suggests that the positive priming effect of erotic pictures decreased with increasing viewing time in schizophrenic patients, whereas the opposite was found for healthy control subjects: erotic pictures seemed to induce positive emotional states, and this effect increased with increasing viewing time. This finding was in agreement with our findings of subjective ratings: the schizophrenic patients rated the erotic pictures less pleasant compared with the control subjects, and they rated the erotic and nature pictures equally pleasant.

We also found that, at 300 ms, the responses to the erotic pictures were smaller than to the nature pictures in the patient group, but not in the control group. Our findings in control subjects contrast the results of 3 previous studies (Bradley et al., 1993, 2006; Volz et al., 2003), in which the eyeblink responses of healthy participants were smaller to positive pictures compared with neutral pictures as early as 300 ms, suggesting prepulse inhibition. Also, our finding that the responses of the patients differentiated as early as 300 ms does not match the results of Volz et al. (2003), who found no differentiation between eyeblink responses of schizophrenic patients to different types of pictures at 300 ms. The exact nature of the differences between our findings and those of others remains to be elucidated, but a possible explanation for our results in the patient group may be the impaired attentional gating found in these patients (Braff et al., 2001): schizophrenic patients are unable to protect the processing of a first stimulus (picture) from a second stimulus (startle stimulus). Although the erotic pictures were rated and experienced as less pleasant when viewed during 6 seconds, it is possible that the erotic contents of the pictures did evoke positive priming in the schizophrenic patients after only 300 ms of viewing time.

To our knowledge, no previous studies have investigated the effects of specific picture contents, such as erotica, on startle responses in schizophrenic patients. The patients in our study were all young male adults. We did not ask our patients about their sexual functioning or sexual needs, but previous studies have found that the social function needs of schizophrenic patients are similar to those of healthy individuals, including social relationships, intimacy and sexual function

(Bengtsson-Tops and Hansson, 1999; McDonald and Badger, 2002). Unfortunately, Bengtsson-Tops and Hansson (1999) found that, although having social relations is one of the five most important needs of schizophrenic patients, it is also one of the most often unmet needs, as was having intimate relationships. The increase in startle eyeblink response to erotic pictures with increasing viewing time may reflect a feeling of unmet sexual needs or expectations, eliciting a response suggestive of a more neutral or even negative feeling. An alternative explanation may be the loss of sexual interest due to the use of antipsychotic medication. Olfson et al. (2005) found that 45.3 % of the investigated 139 medicated male schizophrenic patients, receiving either haloperidol, olanzapine, risperidone or quetiapine, experienced sexual dysfunction. This group reported significantly lower ratings of quality of life and level of enjoyment of their life. However, in a post-hoc analysis we did not find any differences between medicated (n=23) and non-medicated (n=8) patients: both groups showed an increase in startle eyeblinks to erotic pictures with increasing viewing times, $F(1,29)=0.71$, $p=0.41$. This finding suggests that medication status alone does not explain the increase in startle response to the erotic pictures. The quality of life of psychiatric patients is an important issue, and further research on the social and sexual needs and expectations of these patients may aid in the improvement of the quality of life of these patients.

In contrast to the findings of Volz et al. (2003), we did not find a significant difference between patients and controls regarding their responses to negative pictures in general or to threat pictures specifically. In the present study, neither the patients nor the controls showed any significant startle potentiation during the viewing of negative slides compared with neutral slides. It is possible that the negative and threat pictures did not evoke a defensive emotional state in the subjects, resulting in an absence of startle potentiation. Since arousal has been found to be an important factor in the emotional modulation of eyeblink reflexes, this may explain why our subjects did not show startle potentiation during the viewing of negative pictures. Bradley et al. (2001a; 2006) previously found that negative pictures rated low in arousal did not elicit startle potentiation reliably. The SAM (Bradley & Lang, 1994) used in the present study had a rating scale ranging from 1 to 9, while the overall mean ratings from our subject samples did not exceed 5, which is considered ‘moderately arousing’. It is possible that the pictures viewed passively in our experiment did not provoke the expected emotional priming necessary to modulate the startle response emotionally. On the other hand, the positive pictures in general and the erotic pictures specifically did elicit the expected startle inhibition, at least in the control subjects, despite the relatively low arousal scores. An alternative explanation may be that the neutral pictures were unable to bring the person back to a baseline motivational state, in

which no particular negative or positive emotions are experienced. The startle experiment as a whole was experienced as very unpleasant by the participants, partly because of the negative pictures, partly because of the aversive startle stimulus. It is possible that the subjects were primed negatively by the experimental procedure, and only the positive pictures were able to bring the subjects in a positive motivational state.

In summary, schizophrenic patients and controls appeared to respond in a similar manner to neutral and negative pictures during emotional startle modulation. However, more research is needed to clarify the tendency of erotic pictures to elicit increasing startle responses with increasing viewing time in the schizophrenic patient group.

Subjective ratings

The patients and controls did not differ in their pleasure ratings of the positive, neutral and negative pictures, consistent with three previous studies (Hempel et al., 2007; Schlenker et al., 1995; Volz et al., 2003), but inconsistent with the study of Curtis et al. (1995), who found that schizophrenic patients rated positive pictures less pleasant, and negative pictures less unpleasant than healthy control subjects. In the present study, both groups rated the positive pictures as more pleasant than the neutral and negative pictures, and the negative pictures were rated as more unpleasant than the positive and neutral pictures. The only difference we found between groups concerned the arousal ratings: the schizophrenic patients rated the neutral pictures as more arousing compared with the controls. The positive and negative pictures were rated equally arousing by both groups, consistent with previous research (Hempel et al., 2007; Schlenker et al., 1995; Volz et al., 2003). As expected, the positive and negative pictures were rated as more arousing than the neutral pictures within each group, but only the control group rated negative pictures more arousing than the positive pictures, whereas the patients rated them as equally arousing.

With regard to the specific emotional contents, we found that schizophrenic patients rated the erotic pictures less pleasant, and they tended to rate the threat pictures as more unpleasant than the controls. The patients rated the erotic and nature pictures equally pleasant, whereas the controls rated the erotic pictures more pleasant than both the nature and threat pictures. Both groups rated the threat pictures as more unpleasant than both the erotic and nature pictures. The patients rated the nature pictures as more arousing than the control subjects, but no differences in arousal ratings between groups were found for erotic or threat pictures. Within each group, the erotic and threat pictures were rated more arousing than the nature pictures, but the controls rated the erotic pictures as more

arousing than the threat pictures, whereas the schizophrenic patients did not differ in their arousal ratings of these two picture contents.

Limitations

In our study we did not control for possible medication effects, due to the rather small sample sizes. Medication could be a possible confounding factor, since atypical antipsychotics have been found to normalize or improve PPI in schizophrenic patients (Kumari et al., 2000). However, Curtis et al. (1999) found that medication status was unrelated to emotional startle amplitude modulation when they measured the acoustic startle reflex in schizophrenic patients.

Another limitation of this study was the fact that eyeblink responses to the specific picture contents per startle latency condition were based on only one or two individual response(s). In some cases, baseline contamination or absence of an eyeblink response led to empty cells during the analyses. Fortunately, the SAS program is able to perform a reliable analysis despite missing values, but the disadvantage of this type of analysis is, that SAS increases the standard errors, making the statistical test more conservative. The lack of statistically significant interaction effects between groups, picture types and startle latencies may have been a consequence of this conservative testing method.

Conclusion

Overall, schizophrenic patients and healthy control subjects showed similar eyeblink responses during an emotional startle modulation paradigm: the eyeblink responses were smaller during the viewing of positive pictures compared with neutral and negative pictures. This finding suggests that emotion-eliciting pictures evoke similar motivational states in schizophrenic patients and controls. However, the increasing startle responses to erotic pictures during longer viewing periods in schizophrenic patients needs further investigation. More extensive subjective evaluations of the pictures could also clarify some of the findings. Although the Self-Assessment Manikin is very useful for the rapid evaluation of pictures and increases the comparability of subjective ratings, more extensive subjective evaluations could provide further information about the experiences of these patients while viewing emotion-eliciting pictures. Moreover, more research should be focused on the sexual needs and expectations in general of these young male patients, since this is an important factor for the quality of life in this patient group.

CHAPTER 8

Conclusions and General Discussion

Conclusions and general discussion

In the last 20 years, an extensive amount of papers has been published on the impaired emotional functioning of schizophrenic patients. Most of this research has focused on the impaired ability of these patients to recognize emotions from facial expressions (Pinkham et al., 2007). However, emotional processing consists of more components than facial affect recognition alone. According to Trémeau (2006), these components include antecedent events, appraisal, emotional experience, physiological changes, changes in motivational states, expression and behavior, changes in cognitive functioning and beliefs, and regulatory processes. Of these components, the best studied are emotion expression, emotion recognition and emotional experience. Schizophrenic patients show fewer overt emotional expressions, are more impaired in the ability to recognize emotions in others, and report similar degrees of pleasant emotions and similar or higher degrees of negative emotions (Trémeau, 2006). Less well studied, however, are the physiological responses and motivational states of these patients during emotional processing.

This thesis aimed to investigate these components more thoroughly. The main question of this thesis was: do schizophrenic patients respond differently to emotion-eliciting pictures regarding their physiological, motoric and subjective responses? Since these responses are mainly governed by the autonomic nervous system, we also investigated the functioning of the cardiovascular control system during rest. Below, the main results and conclusions of the specific aims that were formulated in Chapter 1 will be discussed, followed by an interpretation and integration of the studies, recommendations for future research, and, finally, the conclusions of the thesis are presented.

Ongoing emotional states: psychophysiological and motoric responses

The first aim of this thesis was to investigate whether the ongoing emotional states of schizophrenic patients and healthy controls differed during the viewing of emotion-eliciting pictures using psychophysiological and startle eyeblink responses. We used three different approaches to investigate this:

1) the time series of the physiological signals during the viewing of specific picture contents (Chapter 2);
2) predefined physiological response measures in relation to the subjective ratings during picture viewing (Chapters 3 and 4); and
3) motoric eyeblink responses to startle stimuli during the viewing of specific picture contents (Chapter 7).

Except for the cardiac responses, patients did not differ significantly from controls regarding their psychophysiological responses during picture viewing. The skin conductance, blood pressure and breathing rate responses were similarly related to

arousal ratings in both patients and controls. However, the cardiac responses during picture viewing did differ between patients and controls. The largest difference between the cardiac responses of patients and controls during the second phase of picture viewing (3-6 seconds) concerned the arousing pleasant pictures, such as erotic scenes. The patients showed increased heart rate accelerations to arousing pleasant pictures, indicating a defensive response, whereas the controls showed the opposite pattern: decreased heart rate acceleration to arousing pleasant pictures, indicating sustained attention towards these pictures (Chapters 3 and 4).

Regarding the negative pictures, the differences between patients and controls were less clear. For the patient group, in Chapter 2 no clear differences between responses to negative and neutral pictures were found, whereas in Chapters 3 and 4 the heart rate of the patients increased with increasing arousal ratings, for both pleasant and unpleasant pictures, suggesting a defensive response towards negative, arousing stimuli. For the control group, contradicting results were found. In the study described in Chapter 3, the heart rate of the controls increased while viewing negative, arousing pictures, whereas in the studies described in Chapters 2 and 4 the heart rate of the controls decreased while viewing these pictures. Overall, schizophrenic patients showed defensive responses, and healthy control subjects showed sustained attention towards unpleasant, arousing pictures. The latter finding, sustained attention towards negative pictures, is in line with previous research on healthy control subjects (Bradley et al., 2001a; Sánchez-Navarro et al., 2006).

The motoric eyeblink responses seemed to underline the above-described findings, although the results were not significant. The eyeblink responses during the viewing of erotic pictures tended to increase with increasing viewing time, again suggesting a more defensive response towards these pictures when the patients were exposed to it for more than 3 seconds. The controls, on the other hand, did not show this increase in startle eyeblink response during the presentation of erotic pictures. Contrary to other studies (see for a review Grillon and Baas, 2003), the responses to negative pictures did not differ from those to neutral pictures in either group, suggesting that the negative pictures did not elicit an aversive motivational state in our subjects.

Summarizing the above results, both the cardiac and the startle eyeblink responses indicate that schizophrenic patients show a defensive response towards pleasant stimuli, such as erotic pictures. The responses of schizophrenic patients to negative stimuli were less clear, but they also suggest a defensive response towards negative pictures. Since the patients did not subjectively rate the negative pictures differently from healthy control subjects, we suggest that schizophrenic patients have a lower threshold for defensive responses compared with healthy

subjects. However, having a lower threshold for defensive responses does not necessarily implicate that they consciously experienced the pictures in a more negative way than healthy control subjects. In a study conducted by Sánchez-Navarro et al. (2006), a subgroup of healthy subjects was found to show cardiac defensive responses to mutilation pictures, whereas they did not subjectively rate these pictures differently than the subgroup of persons who did not show this defensive response. Thus, a dissociation between subjective and physiological responses in our sample of schizophrenic patients seems a plausible explanation.

On the other hand, we cannot rule out the possibility of a truly different emotional experience during the pictures, especially regarding the erotic pictures. The schizophrenic patients rated the erotic pictures as less pleasant than the control group, they showed cardiac defensive responses, and their startle eyeblink response tended to increase with increasing viewing time during the presentation of these pictures. All these results taken together, schizophrenic patients appear to experience erotic pictures as less pleasant than healthy subjects.

Subjective responses to emotion-eliciting pictures

The second aim of this thesis was to investigate whether the subjective responses to emotion-eliciting pictures differed between schizophrenic patients and healthy controls. In general, schizophrenic patients rated the pleasantness of emotion-eliciting pictures in a way similar to healthy controls, suggesting that they understood the meanings of the pictures (Chapters 2, 3, and 7). The only exception occurred when pictures with erotic contents were presented; these were rated as less pleasant by the schizophrenic patients compared with the healthy controls. A consistent finding regarding the subjective responses to neutral pictures was that patients rated these pictures (household and nature contents) as more arousing than the healthy control subjects. This finding may be a further clue towards a theory of lowered threshold responses, although we did not find any differences when the physiological or motoric responses to neutral pictures were analysed.

Attentional differences in picture processing

Since schizophrenic patients suffer from both cognitive as well as emotional disturbances, our third aim was to investigate whether the attentional processes during the viewing of emotion-eliciting pictures differed between schizophrenic patients and healthy controls using startle eyeblink and cardiac responses.

The pattern of startle eyeblink responses to acoustic stimuli presented at different time points during picture viewing was similar between patients and healthy controls: the need for attentional resources decreased with increasing viewing time, allowing emotional information processing of the pictures (Chapter 7). We also used cardiac responses to acoustic stimuli and pictures to investigate

the attentional processes of schizophrenic patients (Chapter 4). The patients did not show a significantly different heart rate response to the acoustic stimuli, but they did show a different cardiac response during the first 3 seconds of picture viewing. The patients showed less heart rate deceleration, indicative of a decreased orienting response. In other words, the ability of the patients to attend to the pictures was decreased compared with the healthy control group. Healthy subjects, on the other hand, showed sustained attention while viewing arousing pictures. In Chapter 3 we found that the orienting responses of the controls were related to their valence ratings, showing larger increases with higher pleasure ratings, whereas the heart rate of the patients was barely affected by any of the subjective ratings.

The above described results show that schizophrenic patients allocate less attentional resources during the initial phase of picture viewing, yet they are able to process the picture in a similar way as healthy control subjects, as shown by the eyeblink startle responses. Since we did not find any differences in cardiac responses between patients and controls after the presentation of the isolated acoustic stimuli, and the orienting response to emotion eliciting pictures was not related to subjective ratings in patients whereas it was in controls, our results suggest that this decreased ability to allocate attention was specific to the viewing of pictures, regardless of their valence. In other words, the differences in emotional processing between patients and controls are not the result of either attention or emotion difficulties, but rather of a combination of these two processes, that seem to interact with each other.

Cardiovascular functioning during rest

Our fourth aim was to investigate the cardiovascular functioning of unmedicated and medicated schizophrenic patients during a baseline rest period using cardiovascular variability measures (Chapter 5). It was found that unmedicated schizophrenic patients had a higher heart rate and lower power in the high-frequency range of heart rate, indicating a decreased vagal control over the heart in these patients. The effects of antipsychotic agents on the cardiovascular control system were restricted to minor effects on the sympathetic functioning, and no effects on the parasympathetic functioning of the autonomic nervous system. Thus, we conclude that schizophrenic patients suffer from a decreased functioning of the parasympathetic nervous system during rest, regardless of the use of antipsychotic medication.

Clinical implications

Lowered threshold for defensive responding

The idea of a lowered threshold for a defensive responding style has clinical implications, since a prolonged defensive reactivity has been identified as a serious risk for both mental as well as physical health (Vila et al., in press).

With regard to the mental health, Nuechterlein et al. (1994) considered autonomic hyperreactivity as one of the vulnerability factors for developing schizophrenia. On the other hand, autonomic reactivity may also result from certain characteristics of the disease. One underlying cause of the lowered threshold for defensive responses may be the paranoid nature of schizophrenia, rendering these patients into a state of increased alertness towards suspicious stimuli. A recent study by Moritz and Laudan (2007) showed that both paranoid and nonparanoid patients responded faster to target stimuli following pictures containing paranoia-relevant items, such as guns. Green and Phillips (2004) suggested that schizophrenic patients with persecutory delusions show an initial attentional bias towards threat stimuli, followed by active avoidance of the threat during a later stage of information processing. Although their suggestion of an initial attentional bias towards threat stimuli does not match with our finding of a decreased orienting response, the active avoidance strategy they suggest does match our findings of increased defensive responses to arousing pictures. The decreased orienting response we found in our schizophrenic patients is in line with the evidence that schizophrenia patients gather little information before responding on certain tasks, a response style termed 'jumping to conclusions' (Moritz and Laudan, 2007; Moritz et al., 2007). The response style of jumping to conclusions and actively avoiding stimulus information results in biased data selection, leading to the incorrect processing and appraisal of stimuli. Abnormalities in the identification of emotionally salient information can lead to misinterpretations of the intentions of others, possibly reinforcing paranoid thoughts, which may result in an impairment in social behavior, a deficit often found in schizophrenic patients (Phillips et al., 2003b).

Decreased parasympathetic activity

Another possible implication of this thesis stems from the finding that exaggerated psychological and physiological reactivity may lead to cardiovascular disease (Lovallo and Gerin, 2003). The relative risk of patients with schizophrenia to suffer from cardiovascular disease is reported to be two-fold higher than that of the general population (Henneskens et al., 2005). The increased heart rate level and decreased heart rate variablity in the high frequency domain we found in schizophrenic patients have been related to a decreased functioning of the parasympathetic nervous system in schizophrenic patients (Bär et al., 2005;

Boettger et al., 2006; Valkonen-Korhonen et al., 2003; Toichi et al., 1999). The increases in the heart rates of the patients during the viewing of arousing pictures also seem to result from a reduction in parasympathetic activity, since it has previously been found that the cardiac defense response was negatively correlated with a measure for vagal activity (respiratory sinus arrhythmia) after intense stimulation (Reyes del Paso et al., 1993). Thus, our results suggest that schizophrenic patients suffer from a decreased parasympathetic functioning, known to be a risk factor for cardiovascular disease, and consequently for mortality (Stein et al., 1994). The importance of our findings is underlined by the fact that we included relatively young schizophrenic patients, thereby reducing the impact of chronicity of the disease and longterm medication use. Furthermore, we did not find any relationship between parasympathetic functioning and the severity of the disease, nor with the subscales for positive, negative or general psychopathology, suggesting that our findings were not limited to a subgroup of schizophrenic patients, but rather to schizophrenia in general.

Perhaps the defensive cardiac responses were not caused by a different emotional processing mechanism, but rather by an overall decreased functioning of the parasympathetic nervous system in schizophrenic patients. In the future, it should be investigated whether the differences in cardiac responding during emotions is caused by a dysfunction of the parasympathetic nervous system alone, by a dysfunction in emotional processing, or by a combination of these factors. However, even if it would be the case that the defensive cardiac responses are caused solely by a decreased vagal function, the resulting defensive responses may still influence the perception of the schizophrenic patients through somatic markers (Damasio, 1994). These somatic markers, i.e. the feelings of the body, may influence the internal representations of stimuli, leading to misinterpretations or biased feeling towards situational stimuli.

Defensive reactions to erotic stimuli

The results of this thesis indicate that schizophrenic patients experience erotic stimuli in a different manner than healthy subjects: all three types of responses we investigated, the subjective, psychophysiological and motoric eyeblink responses, indicated that they experienced these erotic stimuli as less pleasant compared to healthy control subjects. Previous studies have found that the social needs of schizophrenic patients are similar to those of healthy persons, including social relationships, intimacy, and sexual functioning (Bengtsson-Tops and Hansson, 1999; McDonald and Badger, 2002). However, Fan et al. (2007) found that both male and female schizophrenic patients experienced difficulties in the area of sexual functioning, such as desire, arousal and orgasm. Unfortunately, they did not investigate the underlying causes of this decreased sexual functioning.

One possible explanation for the decreased pleasure ratings to erotic stimuli could have been the loss of sexual function or interest due to antipsychotic medication. Olfson et al. (2005) found that 45.3% of the 139 medicated patients experienced sexual dysfunction. This group reported significantly lower ratings of quality of life and level of enjoyment of their life. Another factor could have been the denied access to intimacy and sexual behavior of our inpatients on the psychiatric ward. Bengtsson-Tops and Hansson (1999) found that, although having intimate relationships is one of the five most important needs of schizophrenic patients, it is also one of the most often unmet needs. It is also possible that the expectations about the future influenced their reactions to erotic stimuli. Possibly, the erotic pictures did not only represent sexual behaviors, but also social and intimate relationships in a much broader sense. Having a serious mental illness can have severe consequences for the kind of lives the patients were used to before the onset of the illness. Indeed, several studies have found that persons with schizophrenia often experience feelings of hopelessness, and they may expect failure in the future and feel that they no longer can affect the course of their lives (Lysaker et al., 2004).

The quality of life of psychiatric patients, and schizophrenic patients in particular, is an important issue and has received increasingly more attention in the last decades (Bobes et al., 2007), and further research on the social and sexual needs and expectations of these patients may aid in the improvement of the quality of life of these patients.

Limitations

In this thesis, we only included male participants when we investigated the relationship between physiological and subjective responses (Chapters 3 and 4) and the eyeblink startle responses to emotion-eliciting pictures (Chapter 7), whereas when we investigated the time series of the physiological responses (Chapter 2), the heart rate variability (Chapter 5), and the effectiveness of the envelope method (Chapter 6), we included both male and female participants. We controlled for the possible effects of gender on cardiovascular parameters during rest when we investigated the heart rate variability (Chapter 5), and found that gender affected heart rate, systolic blood pressure and the low frequency domain of heart rate variability. Furthermore, men and women differ in their psychophysiological responses to emotion-eliciting pictures: females tend to respond more to unpleasant stimuli, whereas men show stronger responses towards pleasant stimuli (Bradley et al., 2001b). Thus, some of our findings may have been the result of our sample selection. For example, the lack of startle potentiation during the viewing of negative pictures may be explained by the fact that we only included male subjects for this analysis, who are less responsive to

negative stimuli than females. In future studies, both male as well as female patients should be investigated regarding their psychophysiological responding during picture viewing, and the gender factor should be taken into account during statistical analyses.

Another possible limitation in this thesis is the finding that the heart rate levels of patients during a baseline rest period were significantly higher than the heart rate levels of controls. Differences at baseline may have influenced the subsequent responses during picture viewing. However, the law of initial values (Wilder, 1967) states that an elevation in baseline generally results in smaller increases and larger decreases during responding, a pattern opposite to that found in our schizophrenic sample. Therefore, a confounding effect on the cardiac responses of schizophrenic patients caused by the higher heart rate levels during rest does not seem likely.

The smoking behavior of the patients was very different from that of the healthy control subjects: most schizophrenic patients were smokers, whereas most healthy controls were not. In the normal population, smoking increases heart rate and decreases heart rate variability and baroreflex gain, indicators of an increased risk for cardiovascular diseases (Mancia et al., 1997; Lucini et al., 1996). In our study on heart rate variability (Chapter 5), we controlled for the smoking behavior of the subjects, but in the other chapters investigating cardiac responses to emotion-eliciting pictures, we did not. Smoking generally decreases heart rate variability, suggesting that cardiac responding to stimuli would also be decreased. However, we did not find a decreased cardiac responsivity during picture viewing in schizophrenic patients, suggesting that smoking did not affect the cardiac responses in our studies.

Schizophrenia is a very heterogeneous disease, with different patients expressing different symptoms. We did not differentiate between different types of schizophrenic patients, such as paranoid versus nonparanoid, deficit versus nondeficit, or anhedonic versus nonanhedonic patients. Instead, our subject samples existed of young patients, suffering from recent-onset schizophrenia, regardless of the specific symptoms each patient expressed. Thus, our samples were homogeneous with regard to the duration of the illness, but heterogeneous with regard to the symptom expressions of the patients.

Recommendations for future research

This thesis was an effort to elucidate a small part of the complex emotional processing mechanisms in schizophrenic patients. Obviously, more research is needed to fully understand the underlying causes, the mechanisms and the consequences of a different emotional response system in schizophrenic patients.

Our studies have been performed in a laboratory setting, using visual stimuli that were selected from a large and standardized picture database (International Affective Picture System; Center for the Study of Emotion and Attention, 1999). By presenting these pictures, we hoped to induce emotional states in our subjects. However, these pictures may not have been experienced as real life situations, thereby decreasing the impact of the pictures on the emotional experiences during picture viewing. Future investigators should make an effort to resemble emotional situations as close as possible, so that the results can be used to generalize more to real life. One possible technique to this end is computerized virtual reality: by presenting three-dimensional images the situations may resemble real life more than the two-dimensional pictures currently used in many studies.

We found that schizophrenic patients responded less positively to erotic stimuli compared to healthy control subjects. We were not able to investigate the underlying causes of this finding, but future research should focus on this issue. Social and sexual functioning are important components of the quality of life in psychiatric patients, and by investigating and subsequently improving these specific needs, the quality of life of these patients may increase.

Furthermore, it should be investigated whether the increased defensive cardiac responding of patients to arousing stimuli influences the subjective experiences during picture viewing. If so, this could partly explain misinterpretations and biased thoughts towards situational stimuli in schizophrenic patients. To investigate this, a more extensive subjective rating scale or method should be used than the presently used Self-Assessment Manikin (SAM; Bradley and Lang, 1994), which only covers the general dimensions of valence and arousal.

Conclusions

Four main conclusions can be formulated on the basis of this thesis.

- First of all, the schizophrenic patients did not differ substantially from healthy control subjects regarding their psychophysiological and motoric responses during the viewing of emotion-elicting pictures. However, the patients did show increased cardiac responses to arousing pictures, both pleasant and unpleasant, indicating an overall defensive response style. Especially, the defensive responses to erotic stimuli were persistent across studies, suggesting that schizophrenic patients experienced these pictures as less pleasant compared with the healthy control subjects.
- The only differences in subjective ratings between patients and controls concerned the erotic pictures, which were rated significantly less pleasant by the patients, and the neutral pictures, which were rated significantly more arousing

by the patients than by the control group. The latter finding on neutral pictures may be a further clue towards a lowered threshold for defensive responses in schizophrenic patients.

- Schizophrenic patients showed decreased cardiac orienting responses and increased cardiac defensive responses towards emotionally arousing stimuli, both pleasant and unpleasant. These results may indicate a response style termed 'jumping to conclusions', often found in schizophrenic patients, which results in impaired information gathering, possibly leading to misinterpretations of situational stimuli, and reinforcing paranoid thoughts.
- Finally, schizophrenic patients showed a decreased functioning of the parasympathetic nervous system during a baseline rest period, indicating an increased risk for cardiovascular diseases and mortality. The use of antipsychotic medication had only a minor effect on the activity of the sympathetic nervous sytem, and no effect on the activity of the parasympathetic nervous system.

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SUMMARY
&
SAMENVATTING

Summary

Schizophrenia is a serious mental illness, characterised by delusions and hallucinations, but also by cognitive and emotional disturbances. The emotional disturbances these patients suffer from have been extensively investigated during the past twenty years, and have been associated with the impaired social functioning in schizophrenia. For example, it has been found that schizophrenic patients have difficulty with the expression and recognition of emotional facial expressions. It has also been found that these patients have trouble recognising the emotional significance of a stimulus, and that they show different autonomic responses during emotions. Emotional information processing can be investigated using several methods. One of these methods is by presenting emotion-eliciting pictures while measuring the psychophysiological responses of the subjects. By investigating physiological reactions to emotion-eliciting stimuli, it is possible to objectively investigate whether schizophrenic patients experience these emotion-eliciting pictures in a similar or in a different way compared with healthy subjects.

Previous research has focused on the ability of schizophrenic patients to recognize emotional facial expressions. However, it is also important to be able to recognize the emotional significance of a certain situation, for example its' potential danger. The aim of this thesis was to investigate whether schizophrenic patients experienced emotion-eliciting pictures in a similar or different manner as healthy control subjects, by investigating their subjective and psychophysiological responses to these pictures. A difference in psychophysiological responsivity during picture viewing could indicate that the mechanism for affect regulation in these patients is different from that of healthy persons.

In *Chapter 1,* we briefly described what is known about emotional disturbances in schizophrenia. Subsequently, an overview is presented of the different methods to investigate emotional information processing: subjective, psychophysiological and reflex behavior. Also, the specific aims of the thesis were presented:

- to investigate the ongoing emotional states of schizophrenic patients and healthy controls during the viewing of emotion-eliciting pictures using psychophysiological and startle eyeblink responses;
- to investigate the subjective responses of schizophrenic patients and healthy controls during the viewing of emotion-eliciting pictures;
- to investigate the attentional processes during the viewing of emotion-eliciting pictures in schizophrenic patients and healthy controls using startle eyeblink and cardiac responses;
- to investigate the cardiovascular functioning of unmedicated and medicated schizophrenic patients during a neutral rest period using cardiovascular variability measures.

In *Chapter 2,* we investigated the time series of the psychophysiological responses of schizophrenic patients and healthy control subjects while they viewed emotion-eliciting pictures with nature, mutilations and erotic contents. Both groups showed increases in skin conductance and diastolic blood pressure while viewing erotic pictures compared with pictures of nature and mutilations. The cardiac response to the pictures differed between patients and controls. The heart rate of the controls initially decreased, indicating that the controls were directing their attention to the pictures (orienting response), followed by either an increase (positive pictures) or a decrease (negative pictures) in heart rate. The patients, on the other hand, barely showed an initial decrease, and when viewing erotic pictures they even showed an increase in heart rate. The absence of an orienting response indicates that schizophrenic patients are less able than healthy subjects to direct their attention to the pictures. The immediate increase in heart rate when viewing erotic pictures could indicate that the patients experienced these pictures as highly emotional, and that these pictures elicited a defensive reaction: the increase in heart rate is associated with the rejection of information. Because the patients subjectively rated the pictures equally pleasant and arousing as healthy subjects, it is hard to say whether the differences between patients and controls were the result of the absence of the orienting response, the result of the rejection of erotic pictures, or both. Based on these results we concluded that a different psychophysiological responsivity in schizophrenia is limited to the viewing of erotic pictures, and that only the heart rate response is able to demonstrate this difference.

In *Chapter 3,* we investigated whether the relationships between subjective and physiological responses differed between patients and controls. The skin conductance and breathing rate responses in both groups increased when the arousal ratings increased. The systolic blood pressure increased in patients and controls when both the pleasure and arousal ratings increased. However, the patients showed a different relationship between their subjective ratings and heart rate responses compared with the control subjects. The controls showed increased orienting responses when the degree of pleasantness increased, whereas the patients did not show a clear relationship between heart rate responses and degree of pleasantness. The heart rate acceleration of the patients increased when the subjective degree of arousal increased, which indicated that the patients showed defensive responses. The relationship between the heart rate acceleration and the subjective ratings of the control groups was more complex: the effect of the degree of pleasantness on the heart rate depended on the degree of arousal, and vice versa. Based on these results, we concluded that the only difference we found between both groups concerned the heart rate responses. However, since the heart rate

responses of the controls did not match the pattern of responding previously found in other studies, these results should be interpreted with caution.
In *Chapter 4*, we investigated whether schizophrenic patients differed from control subjects in their cardiac responses to emotion-eliciting pictures and loud startle stimuli. We found that schizophrenic patients did not differ from healthy control subjects in their cardiac responses to loud startle stimuli, which indicated that these patients were able to detect potential danger, similar to control subjects. However, schizophrenic patients did show a decreased orienting response to the pictures, regardless of the specific contents of the pictures. Furthermore, they showed increased cardiac responses during the viewing of arousing pictures, both pleasant as well as unpleasant, whereas the control subjects showed more heart rate *deceleration* during these pictures. We concluded that patients showed a defensive response during arousing pictures, thereby rejecting the information of the pictures, while healthy control subjects showed sustained attention to these pictures, thereby increasing information processing. Because the patients did not differ from the control subjects regarding their subjective responses to the pictures, our results seem to indicate that schizophrenic patients have a lowered threshold for defensive responding.

In *Chapter 5,* we investigated whether the cardiovascular system functioned similarly or differently in schizophrenic patients and healthy controls during a period of rest. Using spectral analysis, we investigated the cardiovascular variability in both groups. When corrected for the differences in gender and smoking habits, we found that the mean heart rate of schizophrenic patients was significantly higher than in controls. We also found a trend effect for the power in the high frequency domain of heart rate, which was lower in schizophrenic patients compared with controls. Because the use of antipsychotic medication may also influence the functioning of the cardiovascular system, we investigated the effect of several antipsychotic medications (olanzapine, haloperidol, and risperidone) on the cardiovascular variability in schizophrenic patients. When corrected for the effects of smoking and gender, we found that the power in the low frequency domain of heart rate was significantly higher when patients used olanzapine compared with haloperidol. We also found that the power in the low frequency domain of systolic blood pressure was significantly higher when patients used olanzapine compared with haloperidol, corrected for the use of benzodiazepines and smoking. We concluded that the higher mean heart rate and the lower power in the high frequency domain of heart rate variability in unmedicated patients suggested a decrease in the parasympathetic influence on the heart, which is an indicator for an increased risk for cardiovascular diseases and mortality. Furthermore, we concluded that the effect of antipsychotic medication

on the cardiovascular variability was limited: olanzapine increased the sympathetic control over the heart, whereas haloperidol decreased this activity. However, these effects were not clinically relevant. None of the antipsychotic medications influenced the activity of the parasympathetic control over the heart.

Besides psychophysiological responses, we also investigated the magnitude of the eyeblink reflex in response to a loud startle stimulus. In *Chapter 6*, we presented a technique that has not previously been applied to the analysis of eyeblink responses: the envelope method. This technique was compared to an often used technique, called smoothing. In this study we found that the ability to discriminate between different responses was better using the envelop method compared with the smoothing method. This quality of the envelop method can be very advantageous when clinical samples are studied, in which subtle differences need to be detected.

In *Chapter 7*, it was investigated whether schizophrenic patients and healthy control subjects differed in their magnitudes of the eyeblink responses when loud startle stimuli were presented during the viewing of emotion-eliciting pictures. These startle stimuli were presented at different time points during the viewing of the pictures (300, 800, 1300 and 3800 ms after picture onset). When we analysed the eyeblink reflexes of patients and controls during the viewing of positive, neutral and negative pictures, we did not find any differences between the two groups. Viewing positive pictures resulted in significantly smaller eyeblinks compared with neutral and negative pictures, and the magnitude of the eyeblink reflex increased when the startle stimuli were presented with increasing viewing time, regardless of the contents of the pictures. We also investigated the eyeblink responses when subjects were viewing pictures of erotica, nature and mutilations. In general, we found similar results as described above for the more general picture categories. However, we also found a trend effect, indicating that the eyeblink magnitude of the patients when viewing erotic pictures increased with increasing viewing time. This finding suggested that the positive effect of the erotic pictures on the emotional state decreased when patients were exposed to them for longer time periods, whereas the opposite was found for healthy control subjects. The subjective ratings confirmed these results: schizophrenic patients rated the erotic pictures as less pleasant compared with the healthy controls, and they rated the erotic pictures as equally pleasant as the pictures with nature scenes. From these results we concluded that emotion-eliciting pictures generally lead to similar emotional states in schizophrenic patients and controls, but that more research should focus on the effects of erotic pictures on the emotional states of the patients.

In *Chapter 8*, the most important results and conclusions were presented. In relation to the aims of this thesis, the following findings were discussed:

- both the cardiac as well as the eyeblink responses indicated that schizophrenic patients show defensive responses to arousing pictures, with both positive as well as negative contents;
- schizophrenic patients rated erotic pictures as less pleasant, and neutral pictures as more arousing compared with healthy control subjects;
- schizophrenic patients seemed less able to direct their attention to emotion-eliciting pictures initially, although they did seem to process the pictures in a way similar to control subjects, based on their eyeblink responses;
- the activity of the parasympathetic nervous system during rest is decreased in unmedicated schizophrenic patients, and the use of antipsychotic medication has only a limited effect on the activity of the sympathetic nervous system, and no effect on the parasympathetic nervous system.

The clinical implications of these results are associated with both mental and physiological functioning of schizophrenic patients. The patients showed decreased orienting and increased defensive responses during the viewing of emotion-eliciting pictures. This suggests that they gather less information during the viewing of pictures, possibly leading to misinterpretations of situational stimuli, and thereby reinforcing paranoid thoughts. The decreased activity of the parasympathetic nervous system during rest is an indicator of an increased risk for cardiovascular diseases, a finding that is consistent with the increased occurrence of these types of diseases in schizophrenia. We also found that schizophrenic patients seemed to experience the erotic stimuli as less pleasant compared with healthy controls, a finding that is important for further research on improving the quality of life of these patients.

Samenvatting

Schizofrenie is een ernstige psychiatrische stoornis, die vooral gekenmerkt wordt door wanen en hallucinaties, maar ook door cognitieve en emotionele stoornissen. De emotionele stoornissen die deze patiënten ervaren zijn de laatste twintig jaar veel onderzocht en worden in verband gebracht met het slechte sociale functioneren van deze patiëntengroep. Zo is onder andere gevonden dat schizofrene patiënten moeite hebben met het uiten en herkennen van emotionele gezichtsuitdrukkingen. Daarnaast is gevonden dat schizofrene patiënten vooral moeite hebben met het herkennen van het emotionele belang van een stimulus en dat zij andere autonome responsen vertonen tijdens emoties. Emotionele informatieverwerking kan op verschillende manieren worden onderzocht. Een veel gebruikte manier om emoties bij personen op te roepen, is door het aanbieden van emotie-opwekkende plaatjes terwijl de psychofysiologische responsen van personen gemeten worden. Door lichamelijke reacties te onderzoeken tijdens het bekijken van emotie-opwekkende plaatjes, kunnen we op een relatief objectieve manier onderzoeken of schizofrene patiënten deze plaatjes op dezelfde of juist op een andere manier ervaren dan gezonde mensen.

In het verleden is vooral onderzoek gedaan naar het vermogen van schizofrene patiënten om emotionele gelaatsuitdrukkingen te herkennen. Het is echter ook belangrijk om emotionele betekenissen te kunnen herkennen in verschillende *situaties*, zoals wanneer er gevaar dreigt of juist wanneer er iets plezierigs gebeurt. Het doel van dit proefschrift was om te onderzoeken of schizofrene patiënten emotionele situaties op dezelfde wijze ervaren als gezonde mensen, door middel van het bestuderen van hun subjectieve en psychofysiologische responsen die door deze plaatjes worden opgewekt. Een verschil in psychofysiologische responsiviteit tussen deze twee groepen zou een aanwijzing kunnen zijn voor een afwijkend mechanisme betreffende affectregulatie bij schizofrene patiënten.

In *Hoofdstuk 1* werd kort beschreven wat bekend is over de emotionele stoornissen die schizofrene patiënten ervaren. Daarna werd een overzicht gegeven van de manieren waarop emotie-herkenning kan worden onderzocht: subjectief, psychofysiologisch, en reflexmatig. Ook werden de doelstellingen van dit proefschrift gepresenteerd:

- het onderzoeken van de emotionele toestand van schizofrene patiënten en gezonde controles tijdens het bekijken van emotie-opwekkende plaatjes door middel van psychofysiologische responsen en de oogknipreflex in reactie op een luide toon;

- het onderzoeken van de subjectieve responsen van schizofrene patiënten en gezonde controles tijdens het bekijken van emotie-opwekkende plaatjes;
- het onderzoeken van de aandachtsprocessen van schizofrene patiënten en gezonde controles tijdens het bekijken van emotie-opwekkende plaatjes met behulp van de oogknipreflex en hartslagresponsen;
- het onderzoeken van het cardiovasculaire functioneren van schizofrene patiënten met en zonder antipsychotische medicatie tijdens een periode van rust, door het meten van de cardiovasculaire variabiliteit.

In *Hoofdstuk 2* werden de psychofysiologische responsen van schizofrene patiënten en gezonde controles tijdens het bekijken van afbeeldingen van erotiek, de natuur en verminkingen onderzocht. Beide groepen vertoonden toenames in zweetactiviteit en diastolische bloeddruk tijdens het bekijken van erotische plaatjes vergeleken met afbeeldingen van de natuur en verminkingen. De hartslagrespons verschilde echter tussen patiënten en controles. De gezonde controles vertoonden eerst een daling van de hartslag, hetgeen aangeeft dat de persoon zijn/haar aandacht richt op de stimulus (oriëntatierespons), gevolgd door of een stijging (bij positieve plaatjes), of een verdere daling (bij negatieve plaatjes). De patiënten vertoonden echter nauwelijks een eerste daling, en bij de positieve plaatjes vertoonden zij meteen een stijging van de hartslag, die sterker werd naarmate het plaatje langer in beeld was. Het uitblijven van een duidelijke oriëntatierespons geeft aan dat de patiënten niet goed in staat waren hun aandacht op de plaatjes te richten. De directe toename in hartslag tijdens de erotische plaatjes kan betekenen dat de patiënten de plaatjes als zeer emotioneel ervaarden, en dat de erotische plaatjes een defensieve reactie opriepen: de toename in hartslag wordt dan geassocieerd met het onderdrukken van informatieverwerking omdat deze als te emotioneel wordt ervaren. Omdat de patiënten de plaatjes subjectief net zo plezierig en opwindend beoordeelden als de controles, is het moeilijk te zeggen of de verschillen in hartslagrespons werden veroorzaakt door het uitblijven van een oriëntatierespons, door het verdringen van de erotische plaatjes, of beide. Op basis van deze resultaten concludeerden we dat een afwijkende psychofysiologische responsiviteit van schizofrene patiënten zich beperkt tot plaatjes met een positieve emotionele inhoud (erotische plaatjes), en dat alleen de hartslagrespons in staat is dit verschil aan te tonen.

In *Hoofdstuk 3* werd onderzocht of de relaties tussen subjectieve responsen en psychofyiologische responsen op plaatjes verschilden tussen patiënten en controles. De zweetactiviteit en de ademhalingsfrequentie van zowel de patiënten als de controles namen toe als de subjectieve mate van opwinding (*arousal*) van het plaatje toenam. De systolische bloeddruk nam in beide groepen toe wanneer

zowel de mate van plezierigheid als de mate van opwinding toenamen. De patiënten vertoonden echter een andere relatie tussen hun hartslagresponsen en subjectieve beoordelingen dan de controles. De controles vertoonden een grotere oriëntatierespons wanneer de mate van plezierigheid toenam, terwijl de patiënten geen duidelijke relatie tussen mate van plezierigheid en de oriëntatierespons vertoonden. De hartslagversnelling van de patiënten nam toe wanneer de mate van opwinding en de mate van plezierigheid toenamen, hetgeen wijst op een defensieve respons. De relatie tussen de subjectieve beoordelingen en de hartslagversnelling bij de controles was complexer: de invloed van de mate van plezierigheid was afhankelijk van de mate van opwinding, en andersom. Op basis van bovenstaande resultaten concludeerden we dat het enige verschil dat tussen de twee groepen werd gevonden, de hartslagresponsen betrof. Echter, omdat de hartslagresponsen van de controles in deze studie afweken van wat er over het algemeen in de literatuur gevonden wordt, moeten deze resultaten voorzichtig geïnterpreteerd worden.

In *Hoofdstuk 4* werd onderzocht of schizofrene patiënten verschilden van gezonde controles betreffende hun hartslagresponsen op emotie-opwekkende plaatjes en luide tonen (startlestimuli). Patiënten en controles verschilden niet in hun hartslagrespons na aanbieding van een luide startlestimulus, hetgeen aangeeft dat patiënten net zo goed in staat zijn potentieel gevaar te detecteren als gezonde controles. Schizofrene patiënten vertoonden echter wel een verminderde oriëntatierespons op de plaatjes, waaruit blijkt dat zij minder goed in staat waren hun aandacht op deze plaatjes te richten, ongeacht de specifieke inhoud van de plaatjes. Daarnaast vertoonden zij toegenomen hartslagresponsen tijdens het bekijken van zowel positieve als negatieve opwindende plaatjes, terwijl gezonde controles een grotere hartslag*daling* vertoonden tijdens deze plaatjes. Wij concludeerden hieruit dat patiënten een defensieve respons vertoonden tijdens opwindende plaatjes, waarbij de informatieverwerking van deze plaatjes wordt onderdrukt, terwijl gezonde controlepersonen hun aandacht juist meer richten op deze plaatjes, zodat deze beter verwerkt kunnen worden. Omdat de patiënten over het algemeen niet veel verschilden van controles wat betreft hun subjectieve responsen op de plaatjes, lijken de resultaten erop te wijzen dat zij een verlaagde drempel hebben voor het vertonen van defensieve responsen.

In *Hoofdstuk 5* werd onderzocht of het cardiovasculaire systeem van schizofrene patiënten op dezelfde wijze functioneert als dat van gezonde controles tijdens een rustperiode. Met behulp van spectraalanalyse werd de cardiovasculaire variabiliteit van beide groepen onderzocht. Wanneer gecorrigeerd werd voor de verschillen in geslacht en rookgewoonten, was de gemiddelde hartslag van medicatievrije

patiënten significant hoger. Daarnaast vonden wij een trendeffect, dat aangaf dat de power in de hoge frequentieband van de hartslagvariabiliteit bij patiënten lager was dan bij controles. Omdat antipsychotische medicatie ook van invloed kan zijn op het cardiovasculaire systeem, werd de invloed van verschillende antipsychotica (olanzapine, haloperidol en risperidon) op de cardiovasculaire variabiliteit onderzocht. Wanneer er voor de effecten van geslacht en roken werd gecorrigeerd, was de power in het lage frequentiedomein van de hartslagvariabiliteit significant hoger wanneer patiënten olanzapine gebruikten dan wanneer ze haloperidol gebruikten. Daarnaast was de power in het lage frequentiedomein van de bloeddrukvariabiliteit significant hoger wanneer patiënten olanzapine gebruikten dan wanneer ze haloperidol gebruikten, gecorrigeerd voor het gebruik van benzodiazepines en roken. Wij concludeerden dat de hogere hartslagfrequentie en lagere power in het hoge frequentiedomein van de hartslagvariabiliteit bij medicatievrije schizofrene patiënten wijzen op een verminderde parasympathische controle over het hart bij deze patiënten, hetgeen een aanwijzing is voor een verhoogde kans op cardiovasculaire aandoeningen. Daarnaast concludeerden we dat de invloed van het gebruik van medicatie op de cardiovasculaire variabiliteit beperkt was: olanzapine verhoogde de sympathische invloed op het hart, terwijl haloperidol deze verlaagde; dit waren echter geen klinisch relevante effecten. Geen van de antipsychotica beïnvloedde de parasympathische controle over het hart.

Naast psychofysiologische responsen hebben wij ook de grootte van de oogknipreflex in reactie op een luide startlestimulus onderzocht. In *Hoofdstuk 6* werd een techniek gepresenteerd die nog niet eerder is toegepast voor oogknipperanalyses: de envelopmethode. Deze techniek werd vergeleken met een veel gebruikte techniek, genaamd *smoothing*. Uit dit onderzoek kwam naar voren dat men met behulp van de envelopmethode beter in staat is verschillen tussen responsen aan te tonen dan met de smoothingmethode. Deze eigenschap van de envelop-techniek kan heel voordelig zijn wanneer men klinische groepen onderzoekt, waarbij het gaat om subtiele, maar werkelijke verschillen.

In *Hoofdstuk 7* werd onderzocht of schizofrene patiënten en gezonde controles verschilden in de grootte van hun oogknipresponsen wanneer luide startlestimuli werden aangeboden tijdens het bekijken van verschillende emotie-opwekkende plaatjes. Deze startlestimuli werden op verschillende momenten tijdens het kijken aangeboden (300, 800, 1300 of 3800 ms na aanvang van het plaatje). Wanneer we de oogknipreflexen van patiënten en controles tijdens het bekijken van positieve, negatieve en neutrale plaatjes vergeleken, vonden wij geen verschillen tussen de twee groepen. Positieve plaatjes leidden tot kleinere oogknipperresponsen

vergeleken met neutrale en negatieve plaatjes, en hoe later de startlestimulus tijdens het bekijken van de plaatjes werd aangeboden, hoe groter de oogknipreflex was, ongeacht het type plaatje. We hebben ook de oogknipreflexen onderzocht wanneer de proefpersonen naar specifieke afbeeldingen van erotica, de natuur, of bedreigingen keken. Over het algemeen werden dezelfde resultaten gevonden als hierboven, voor de algemene plaatjes-categorieën. Er werd echter ook een trendeffect gevonden, dat aangaf dat de grootte van de oogknippers van de patiënten tijdens het bekijken van erotische plaatjes toenam naarmate ze langer naar het plaatje keken. Dit suggereert dat het positieve effect van erotische plaatjes afnam bij patiënten naarmate ze langer naar het plaatje keken, terwijl het omgekeerde werd gevonden bij de controles. De subjectieve beoordelingen van de plaatjes door de patiënten ondersteunden deze bevinding: de schizofrene patiënten beoordeelden de erotische plaatjes minder plezierig dan de controles, en bovendien beoordeelden ze de erotische plaatjes net zo plezierig als de natuurplaatjes. Hieruit concludeerden wij dat emotie-opwekkende plaatjes over het algemeen dezelfde emotionele stemmingen in schizofrene patiënten opwekken als in gezonde mensen, maar dat er meer onderzoek moet worden gedaan naar de effecten van erotische plaatjes op de stemming van deze patiënten.

In *Hoofdstuk 8* werden de belangrijkste bevindingen en conclusies gepresenteerd. In relatie tot de doelstellingen van het proefschrift werden de volgende bevindingen besproken:

- zowel de hartslagresponsen als de oogknipreflexen wijzen erop dat schizofrene patiënten een defensieve reactie vertonen op opwindende plaatjes, met zowel positieve als negatieve inhoud;
- schizofrene patiënten beoordelen erotische plaatjes als minder plezierig, en neutrale plaatjes als meer opwindend ten opzichte van gezonde controlepersonen;
- patiënten lijken minder goed in staat hun aandacht te richten op emotie-opwekkende plaatjes tijdens de eerste fase van het bekijken ervan, hoewel zij uiteindelijk wel in staat zijn de plaatjes op vergelijkbare manier te verwerken als gezonde controles, zoals blijkt uit hun oogknipreflexen;
- de activiteit van het parasympathische zenuwstelsel tijdens rust is verminderd bij medicatievrije schizofrene patiënten. Het gebruik van antipsychotica heeft slechts een beperkte invloed op de activiteit van het sympathische zenuwstelsel, en geen effect op het parasympathische zenuwstelsel.

De klinische implicaties van deze bevindingen hebben betrekking op zowel het psychische als het lichamelijke functioneren van deze patiënten. De patiënten vertoonden verminderde oriëntatie- en verhoogde defensieve hartslagresponsen tijdens het bekijken van emotie-opwekkende plaatjes. Dit suggereert dat zij minder

informatie vergaren tijdens het bekijken van situationele stimuli. Deze manier van reageren kan leiden tot het verkeerd interpreteren van stimuli uit de omgeving, waardoor paranoïde gedachten versterkt kunnen worden. De verminderde activiteit van het parasympathische zenuwstelsel tijdens rust is een indicatie voor een verhoogd risico op cardiovasculaire aandoeningen, een bevinding die overeenkomt met de verhoogde kans op dit soort aandoeningen bij schizofrene patiënten. Ook werd gevonden dat de patiënten de erotische stimuli als minder positief ervaarden dan gezonde controles, een bevinding die van belang kan zijn voor verder onderzoek naar het verbeteren van de kwaliteit van leven van deze patiënten.

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Dankwoord

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PUBLICATIONS AND PUBLISHED ABSTRACTS

Curriculum Vitae

Roelie Janneke Hempel werd op 27 april 1981 geboren in Oud-Beijerland. In 1999 haalde zij haar VWO-diploma aan de Willem van Oranje in Oud-Beijerland. In september van datzelfde jaar is ze begonnen met de studie Psychologie aan de Universiteit van Amsterdam. Na het behalen van de propedeuse in 2000 vervolgde zij haar studie bij de vakgroep Psychonomie. Haar afstudeeronderzoek getiteld "Emotional priming, emotional interference and physiology in schizophrenia" voerde ze uit op de afdeling Psychiatrie van het Erasmus MC, onder begeleiding van Dr. Joke H.M. Tulen (Erasmus MC) en Dr. Winni F. Hofman (Universiteit van Amsterdam). In september 2003 behaalde zij haar doctoraalexamen. Van oktober 2003 tot april 2004 bleef ze als junior onderzoeker betrokken bij het onderzoek op de afdeling Psychiatrie. In april 2004 is zij begonnen met haar promotie-onderzoek, waarvan u nu het resultaat in handen heeft: "Affect regulation in schizophrenia" (Affectregulatie bij schizofrenie). Dit proefschrift werd geschreven onder begeleiding van Dr. Joke H.M. Tulen (co-promotor) en Prof.dr. Michiel W. Hengeveld (promotor), beiden verbonden aan de afdeling Psychiatrie van het Erasmus MC. Momenteel is Roelie werkzaam op deze afdeling als wetenschappelijk onderzoeker.

Publications and published abstracts

Publications

Hempel, R. J., Tulen, J. H. M., Van Beveren, N. J. M., & Hengeveld, M. W. (2005). Emotionele informatieverwerking bij schizofrene patiënten: herkenning van gelaatsuitdrukkingen. *Tijdschrift voor Psychiatrie, 47,* 83-92.

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