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Emotional startle modulation in male patients with recent-onset schizophrenia

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Abstract

Patients with schizophrenia suffer from both cognitive as well as emotional disturbances, leading to reduced social functioning and quality of life. This study investigated the ongoing emotional states of medicated and antipsychotic-free patients and healthy controls using an emotional startle paradigm. During positive, neutral and negative emotional pictures, aversive acoustic startle stimuli were presented at 4 different probe latencies (300, 800, 1300 and 3800 ms) from picture onset. In both patients and controls, positive pictures, and more specifically erotic pictures, elicited significantly smaller eye blinks compared with startle stimuli presented during neutral and negative pictures. With regard to the subjective ratings, medicated patients rated erotic pictures significantly less pleasant and the adventure, nature, and household pictures as significantly more arousing than healthy control subjects. The present results indicate the need to further investigate emotional responding to specific picture contents, with specific focus on the sexual needs and expectations of schizophrenic patients, so as to eventually improve the quality of life in these patients.

Introduction

Thus far, an extensive amount of research papers has been published on the impaired emotional functioning in patients with schizophrenia. Most of this research has focused on the impaired ability of these patients to recognize emotions from facial expressions [1], which is crucial for forming and maintaining interpersonal relationships [2, 3], and patients with schizophrenia are known to experience difficulties with social functioning [4-6].

Although patients with schizophrenia 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 valence when presented with emotion-eliciting pictures [7-13], although their experienced emotions have been found to differ from non-affected individuals. For example, 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 [14, 15]. It has also been found that schizophrenic patients experience less positive emotions and more negative emotions in response to daily stressors [16] and emotion-eliciting pictures [17], compared with healthy control subjects. In their review, Kring and Moran [18] summarized that individuals with schizophrenia have a deficit in the expressive component but do not appear to be strongly deficient in the experiential and physiological components of emotion. Thus, previous studies indicate that individuals suffering from schizophrenia are able to correctly identify and classify stimuli, suggesting that previously reported emotional disturbances in patients with schizophrenia are limited to facial stimuli rather than more general emotion-eliciting stimuli.

It is 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 [14, 19]. An experimental paradigm has been developed to investigate the ongoing positive and negative emotions of participants during the viewing of emotion-eliciting scenes: the emotional startle modulation paradigm [20, 21]. In this paradigm, different emotion-eliciting pictures are presented to participants on a screen, and occasionally loud startle noises are presented through headphones, to provoke a startle reflex in the participants. The startle reflex is measured by recording the electromyographic

activity of the m. orbicularis oculi, the most reliable component of the whole body startle reflex [22].

The underlying theory of this paradigm defines emotions as action dispositions, which organize behavior along a valence dimension ranging from appetitive to aversive emotions [20]. 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 [20]. 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 [23]. Besides the valence dimension, the arousal dimension is also an important factor for emotional startle modulation to occur: startle potentiation occurs most reliably when unpleasant pictures are highly arousing [24, 25].

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 to 500 ms; [21, 26], 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 (from 1300 ms till 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 [26]. Bradley et al. [24] investigated whether specific picture contents elicited different startle response magnitudes. They found that negative pictures with animal threat, human threat, and contamination elicited the largest eyeblink responses. For the pleasant pictures, erotica (couples and opposite sex nudes) elicited the smallest blink reflexes.

Finally, household objects were found to elicit neither inhibited nor potentiated startle, and thus can be considered most neutral. 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.

Five previous studies have been conducted thus far that have investigated the emotional startle responses in patients with schizophrenia. In the first study [8], the eyeblink responses of patients with schizophrenia to negative pictures were not potentiated, whereas healthy control subjects did show startle potentiation, and this difference was significant. Curtis et al. [17] did not find any differences between patients with schizophrenia, their first-degree relatives and healthy control subjects with regard to eyeblink responses during the viewing of emotion-eliciting pictures. Volz et al. [10] investigated the temporal course of emotional startle modulation in these patients. Following the study of Bradley et al. [26], startle stimuli were presented at varying intervals (150, 300, 800, 1300, and 3800 ms) during the viewing of emotion-eliciting pictures. Patients with schizophrenia 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 showed startle potentiation as early as 300 ms. For the pleasant and neutral pictures no differences between groups were found. The authors [10] concluded that patients with schizophrenia 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. Yee et al. [13] did not find any differences in eyeblink responding to emotion-eliciting pictures between healthy controls and prodromal, first-episode, or chronic patients with schizophrenia. Finally, Kring et al. [12]found that patients with schizophrenia showed a similar startle pattern to emotion-eliciting stimuli as healthy control subjects during picture presentation. Controls also demonstrated this pattern shortly after pictures were removed from view, whereas patients did not. So, while the motivational system stayed engaged in the control group, possibly to help guide future behavioral responses, this was not the case in the patient group.

Summarizing, previous studies have demonstrated that individuals with schizophrenia report similar subjective responses and show similar eyeblink responses to emotion-eliciting pictures as healthy control subjects, indicating that their underlying motivational systems appear to be intact, at least when directly confronted with an emotional stimulus. However, except for Yee et al. [13], these studies only investigated the emotional

responses of these patients to general picture types of positive, neutral, and negative pictures, whereas specific picture contents might be able to inform us about more specific underlying motivations to certain themes shown in these pictures. In addition, except for the study by Curtis et al. [17], none of these studies have compared the responses of patients with and without antipsychotic medication, while it has previously been shown that antipsychotics can modify physiological and subjective responding to emotion-eliciting stimuli in patients with schizophrenia [27].

The aim of the present study was to broaden our knowledge about the underlying motivations of patients with schizophrenia while viewing topic-specific emotion-eliciting pictures using startle eyeblink responses, whilst taking medication use into account. During the viewing of emotion-eliciting pictures, startle stimuli were presented at varying startle latencies from picture onset (300, 800, 1300 and 3800 ms) while eyeblink responses were measured, to allow us to investigate the temporal time course of emotional responding in this patient group. Based on previous research, we expected that individuals with schizophrenia and healthy control subjects would exhibit comparable reports of experienced subjective ratings and startle eyeblink responses when we would analyse the responses using general picture types, while the responses to topic-specific picture contents would be able to inform us more precisely about the underlying motivations of patients with schizophrenia. Because of the potential importance of antipsychotic medication use on psychophysiological responses, we analyzed our data separately for medicated and antipsychotic-free patients.

Methods

Subjects

In this study, 33 male patients with schizophrenia (9 antipsychotic-free, 24 medicated) and 40 male control subjects 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 senior clinical psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) [28], and included in the study if they were diagnosed as suffering from schizophrenia according to the criteria of the DSM-IV [29]. All patients experienced a psychotic episode at the time of the study. All patients were inpatients and most of them were experiencing their first psychotic episode or were receiving treatment for the first time. In order to assess symptom severity, the Dutch translation of the Positive and Negative Syndrome Scale (PANSS) [30] was used. 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 a short phone interview and a structured 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 and cardiovascular diseases, and we also excluded controls who indicated that they were using any type of medication that could influence the autonomic nervous system

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.

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 the day of the experimental session. Before the application of the electrodes participants were asked to complete a shortened version of the Dutch Profile of Mood States (POMS) [31]. Electrodes

for the recordings of the startle eyeblink 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 do the subjective rating task, which lasted approximately 15 minutes. All tasks were designed using E-prime (Psychology Software Tools, Inc., 2002).

Experimental tasks

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 allow them to get accustomed to these sounds and to decrease the impact of habituation effects during the experiment. The startle stimulus was a discrete white noise burst of 100 dB during 50 ms, with an instantaneous rise and fall time. The startle stimuli were presented binaurally 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.

After the first 5 startles, they were told that they were about to view a series of 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. Forty-eight pictures were selected from the IAPS [32]. 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[1]. The positive pictures had erotic and adventure contents, the neutral pictures showed nature scenes and household objects, and

[1] Positive IAPS pictures: 4220, 4290, 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.

the negative pictures contained pictures with mutilation and threat contents. The pictures were presented using a Dell Dimension M200a Personal Computer with a Pentium processor and a 17-inch Samsung SyncMaster monitor.

Each picture was presented for 6 seconds, with an inter-trial 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. All pictures and startle stimuli were presented completely at random so that each subject was presented with a different order of stimuli.

Subjective rating task

The 48 pictures that were presented during the startle task were again presented in the subjective rating task, using a randomized order different from that of the startle task. The participants were asked to rate how they felt during the viewing of the pictures. They 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; [33]. 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- again on a scale from 1 to 9. After their response, the fixation cross appeared again for 3 seconds, followed by the next picture.

Psychophysiological measurements

During the experiment, continuous measurements were made of electromyographic (EMG) activity. 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™ software module (TEMEC Instruments BV, Kerkrade, the Netherlands).

Startle eyeblink 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.). One electrode was placed in line with the pupil of the left eye 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 data was sampled at 1024 Hz. 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 [34], 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 require rectification of the signal and therefore does not affect the original values of the signal [35]. Finally, a lowpass filter of 40 Hz was applied.

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 [22], 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. If a peak did not exceed an amount of two standard deviations above baseline, the response was scored as zero. If the peak was detected outside the 20-150 ms scoring window, the response was scored as missing and excluded from further analyses. In case of multiple peaks within the 20-150 ms scoring window, the peak with the highest value was determined as response peak. Participants who did not show valid eyeblinks in more than 33% of the trials were excluded from further analysis [10, 36].

Statistical analyses

All analyses were conducted using SPSS version 13.0 and MlWin 2.10 [37]. All alpha's were set at 0.05 unless otherwise specified.

Participant Demographics

We investigated whether the groups differed in age, smoking, symptom scores, and duration of illness by using Analyses of Variance (ANOVA), chi-square test, t-test, or non-parametric Mann-Whitney Test where appropriate. In case of unequal variances we used the corrected degrees of freedom to determine the level of significance.

Profile of Mood States (POMS)

To assess whether there were any differences in mood scores between the three groups (medicated, antipsychotic-free and controls), we used separate ANOVAs per subscale and for the total scale, which were followed up by Bonferroni-corrected post-hoc tests. The maximum scores for each of the scales were as follows: depression 32; fatigue 24; tension 24; anger 28; vigour 20. The total score was calculated by subtracting the vigour score from the sum of all the other scores (i.e. depression + fatigue + tension + anger – vigour = total), so that a higher score represented a more negative mood state.

Startle eyeblink responses

Because the Kolmogorov-Smirnov tests indicated that the data was not normally distributed, we normalized the EMG data using the natural logarithm. Two hierarchical linear models (HLM) were developed: one to examine the eyeblink responses to general picture types (Picture Type: positive, neutral, negative) and one to examine the eyeblink responses to specific picture contents (Picture Content: erotic, adventure, household, nature, mutilation, attack).

We entered Subject, Time, and Picture Type (for the 3 types) or Picture Content (for the 6 types) as repeated variables in the two HLM models. The following fixed variables were entered: Group (antipsychotic-free, medicated, and control), Time (300, 800, 1300 and 3800 msec) as a linear polynomial, Picture Type or Picture Content, Group x Time, Group x Picture Type/Content, Time x Picture Type/Content, and Group x Time x Picture Type/Content. The following covariates were entered: smoking (yes/no), age, illness duration (months), antipsychotic medication duration (weeks), and the total score on the Profile of

Mood States (POMS; where a higher score indicates a more negative mood state). We started with a fully saturated model containing all factors and covariates, after which the best fit for the model was sought using the log likelihood method.

Subjective ratings

Since the Kolmogorov-Smirnov tests indicated that the distributions of the SAM rating of pleasure and arousal were normally distributed within the groups (p-values ranged from 0.13 to 1.00), we performed two repeated measures ANOVA's with Pleasure or Arousal rating as the dependent variable, Group (medicated, antipsychotic-free and controls) as the between subjects factor, and Picture Type (for 3 types) or Picture Content (for 6 types) as the within subjects factor. In case of a significant interaction effect, we followed this up with separate ANOVAs.

Results

Participant demographics

Five patients and one control subject did not show eyeblinks in 33% of the trials, and data from these participants was excluded from further analyses. The five patients that were excluded did not differ in age, PANSS scores, POMS scores or medication use from the patients that were included in the present analysis. Table 1 presents the demographic data of the remaining 28 patients (8 antipsychotic-free, 20 medicated) and 39 control subjects while Table 2 presents the medication use of the remaining patients.

As can be seen in Table 1, there were significantly more smokers in both patient groups than in the control group (χ^2=29.71, $p < 0.001$). With regard to symptom severity, antipsychotic-free patients had higher scores for all subscales and the total score of the PANSS than medicated patients (positive: $F[1,25] = 4.43$, $p < 0.05$; negative $F[1,25] = 6.35$, $p < 0.05$; general psychopathology $F[1,25] = 5.53$, $p < 0.05$; total score $F[1,25] = 10.35$, $p < 0.01$). The duration of illness seemed shorter in medicated versus antipsychotic-free patients, but due to the large standard deviations this was not a significant difference (Mann-Whitney $U = 47$, $p = 0.09$).

Table 1. Demographic characteristics of the patient and control groups

		Medicated patients (n=20)	***Antipsychotic-free patients (n=8)***	***Controls (n=39)***
Age (mean ± sd)		22 ± 7	21 ± 4	23 ± 4
Smokers (Yes/No)[a]		17/3	6/2	8/31
Duration of illness (months ± sd)		15 ± 19	3 ± 3	
Duration of current medication use (weeks ± sd)		4 ± 5		
PANSS[b] (mean ± sd)	Positive symptoms	17 ± 6	23 ± 7	
	Negative symptoms	15 ± 5	20 ± 5	
	General psychopathology	33 ± 9	44 ± 13	
	Total	64 ± 17	87 ± 15	

PANSS = Positive and Negative Syndrome Scale; sd = standard deviation

[a] There were significantly more smokers in both patient groups than in the control group ($\chi^2_{(2)} = 25.31$, $p < 0.001$)

[b] Antipsychotic-free patients had higher PANSS scores for all subscales than medicated patients (positive: $F[1,25] = 4.43$, $p < 0.05$; negative $F[1,25] = 6.35$, $p < 0.05$; general psychopathology $F[1,25] = 5.53$, $p < 0.05$; total score $F[1,25] = 10.35$, $p < 0.01$).

Table 2. Mean dosages and duration of current antipsychotic and benzodiazepine treatment

Antipsychotic	***n***	***Mean dosage (mg) ± sd***	***Co-medication***
No Antipsychotic	8		Lorazepam (n=2)
Olanzapine	8	16.3 ± 6.9	Lorazepam (n=2)
			Oxazepam (n=1)
Risperidone	4	3.0 ± 0.7	Lorazepam (n=1)
			Oxazepam (n=1)
Haloperidol	4	2.8 ± 1.5	Lorazepam (n=2)
Clozapine	3	300.0 ± 100.0	Lorazepam (n=2)
Quetiapine	1	600.0	n/a

sd = standard deviation

Profile of Mood States (POMS)

The POMS-scores of the three groups are reported in Table 3. The medicated and antipsychotic-free patients did not differ significantly in their mood scores for any of the subscales or the total score. However, the patients did significantly differ from the controls with regard to their mood scores (Depression $F[2,64] = 12.51$; Fatigue $F[2,64] = 6.70$; Tension $F[2,64] = 13.85$; Anger $F[2,64] = 1.59$; Vigor $F[2,64] = 3.83$; Total score $F[2,64] = 14.63$; all *p*s smaller than 0.05). Post-hoc tests indicated that the antipsychotic-free patients showed significantly decreased mood on all subscales and the total score, while the medicated patients had significantly decreased mood scores on all scales except the vigor subscale.

Table 3. Profile of Mood scores for medicated and antipsychotic-free patients and control subjects

		Medicated Patients (n=20)	***Antipschotic-free Patients (n=8)***	***Controls (n=39)***
POMS	Depression[a]	7.2 ± 7.4	7.6 ± 9.5	0.8 ± 1.6
mean ± sd	Fatigue[a]	6.3 ± 6.0	7.9 ± 5.5	2.9 ± 2.8
	Tension[a]	6.2 ± 4.7	5.8 ± 3.8	1.7 ± 2.2
	Anger[a]	4.5 ± 4.5	6.6 ± 5.6	1.3 ± 2.2
	Vigor[b]	10.6 ± 4.5	7.8 ± 4.9	11.8 ± 3.3
	Total[a]	11.7 ± 20.8	20.1 ± 23.0	-5.0 ± 7.2

sd = standard deviation;

[a] Significant difference between control subjects and both patient groups, $p < 0.05$

[b] Significant difference between control subjects and antipsychotic-free patients, $p < 0.05$

General picture types

Eyeblink responses

The following factors did not contribute significantly to the model and were therefore removed: the three-way interaction between Group x Time x Picture Type, the two-way interactions of Group x Picture Type, Group x Time, and Picture Type x Time, and the covariates Age, and Smoking.

As can be seen in Table 4 and Figures 1a-c, the main effect of Group (joint $\chi^2_{(1)}=45.05$, $p<0.001$) indicated that antipsychotic-free patients showed overall smaller eyeblink responses compared to medicated patients and healthy controls. The main effect for Time was also significant, indicating that eyeblink responses increased with increasing startle latency ($Z=2.65$, $p < 0.01$). Finally, the main effect for Picture Type was also significant (joint $\chi^2_{(1)}=7.61$, $p<0.01$), indicating that the eyeblink responses to positive pictures were smaller than to neutral and negative pictures. With regard to the covariates, the significant effect for Duration of Medication use indicated that the longer a person received antipsychotic medication, the smaller their eyeblink responses, while the significant effect for Duration of Illness indicated that the longer a person was suffering from schizophrenia, the

larger their startle eyeblink responses. Current mood also had a significant effect on eyeblink responses: higher POMS (i.e. more negative mood) scores were related to smaller eyeblinks.

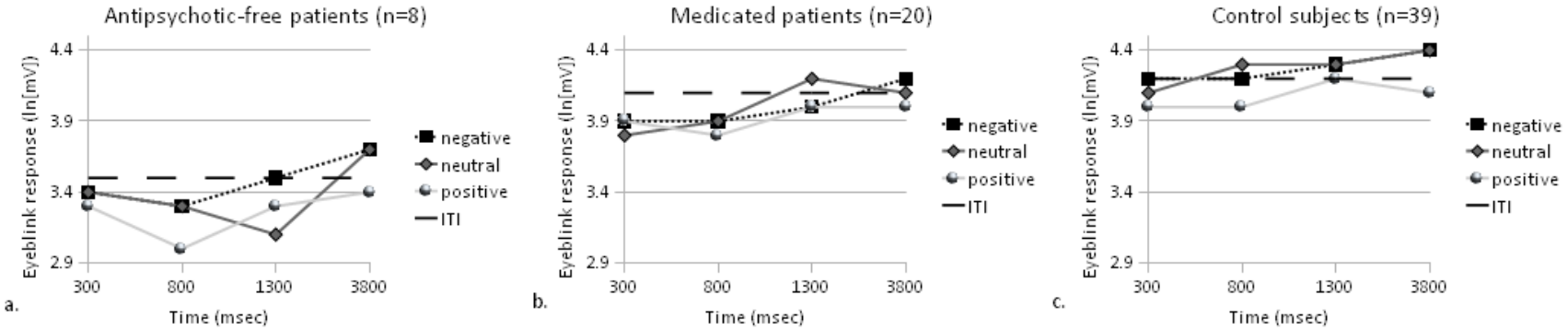
Table 4. Beta coefficients of the HLM for eyeblink responses (ln[mV]) to positive, neutral, and negative pictures in antipsychotic-free patients, medicated patients, and healthy control subjects.

Factor	*Comparison*	*Beta coeffi-cient*	*Standard error*	***Z-score****
Constant		4.23	0.07	**65.12**
Group	AF vs C	-0.78	0.12	**-6.40**
	M vs C	-0.04	0.11	-0.36
	M vs AF	0.74	0.13	**5.76**
Picture Type	Neg vs Neu	0.01	0.08	0.16
	Pos vs Neu	-0.15	0.08	-1.81
	Pos vs Neg	-0.16	0.08	**-1.98**
Time[1]		0.18	0.07	**2.65**
Duration of illness (months)		0.01	0.004	**2.25**
Duration of medication use (weeks)		-0.06	0.02	**-4.00**
POMS total score		-0.004	0.002	**-2.00**

* Numbers expressed in **bold** indicate significant effects at the 0.05 level.

AF = Antipsychotic-free patients (n=8); C = Control (n=39); M = Medicated patients (n=20).

Neg = negative pictures; Neu = neutral pictures; Pos = positive pictures

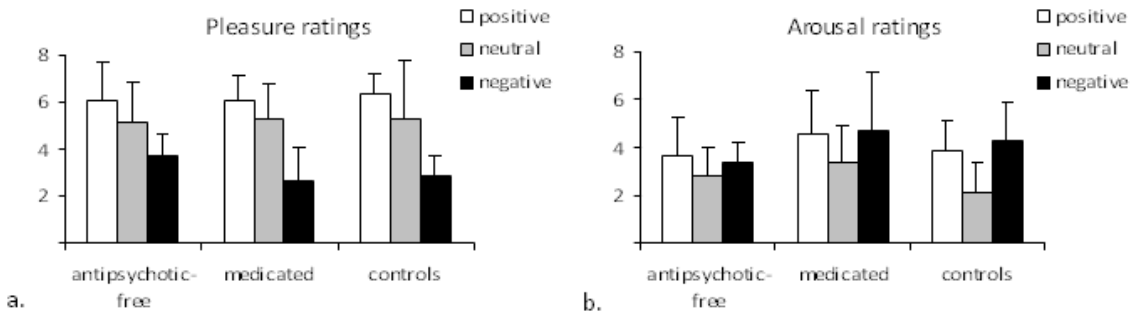


Figures 1 (a-c). Time series of the eyeblink responses to negative, neutral and positive picture stimuli in (a) antipychotic-free patients; (b) medicated patients; and (c) healthy control participants at 4 different startle latencies during picture presentation. Please note: 'ITI' refers to Inter-Trial Interval, i.e. the eyeblink responses to startle stimuli presented in between pictures.

Subjective ratings

The mean SAM ratings for pleasure and arousal are presented in Figures 2a and b. For the pleasure ratings, we found a significant main effect for Picture Type ($F[1.7;111.0] = 32.85$, $p < 0.001$, partial $\eta^2 = 0.34$). Post-hoc comparisons showed that the positive pictures were rated as most pleasant, followed by the neutral pictures, while the negative pictures were rated as least pleasant (all *p*s < 0.001). No significant main or interaction effects for Group were found.

For the arousal ratings only the interaction effect between Picture Type and Group was significant ($F[1.6; 102.7] = 6.41$, $p < 0,01$, partial $\eta^2 = 0.09$). Follow-up ANOVAs showed that groups differed in their arousal ratings of neutral scenes ($F[2,64] = 6.25$, $p < 0.01$), and post-hoc comparisons showed that the medicated patients rated these scenes as more arousing than the control subjects.



Figures 2 (a-b). Pleasure (a) and arousal (b) ratings of positive, neutral, and negative pictures for antipsychotic-free patients, medicated patients, and healthy control subjects.

Specific Picture types

Eyeblink Responses

The following factors did not contribute significantly to the model and were therefore removed: the three-way interaction between Group x Time x Picture Type, the two-way interactions of Group x Picture Type, Group x Time, and Picture Type x Time, and the covariate Age.

As can be seen in Table 5 and Figures 3a-f, the main effect of Group ($\chi^2_{(2)}=54.35$, $p<0.001$) indicated that antipsychotic-free patients showed overall smaller eyeblink responses compared to medicated patients and healthy controls. Similar to the previous analysis, the main effect for Time was significant, indicating that eyeblink responses increased with increasing startle latency ($Z=3.15$, $p < 0.01$).

There was also a main effect for Picture Type (($\chi^2_{(2)}$=19.41, p < 0.001) indicating that the eyeblink responses to the erotic pictures were significantly smaller than to any of the other picture types.

With regard to the covariates, the significant effect for Smoking indicated that people who smoked had generally smaller eyeblink responses. The significant effect for Duration of Medication use indicated that the longer a person received antipsychotic medication, the smaller their eyeblink responses, while the significant effect for Duration of Illness indicated that the longer a person was suffering from schizophrenia, the larger their startle eyeblink responses. Current mood also had a significant effect on eyeblink responses: higher POMS (i.e. more negative mood) scores were related to smaller eyeblinks.

Table 5. Beta coefficients of the HLM for eyeblink responses (ln[mV]) to emotion-eliciting pictures with specific contents in antipsychotic-free patients, medicated patients, and healthy control subjects.

Factor	*Comparison*	*Beta coeff-cient*	*Standard error*	***Z-score****
Constant		4.19	0.07	**59.90**
Group	AF vs C	-0.63	0.10	**-6.08**
	M vs C	0.10	0.09	1.09
	M vs AF	0.73	0.10	**7.13**
Time[1]		0.17	0.05	**3.15**
Picture Type	Mutilation vs Attack	0.06	0.09	0.60
	Household vs Attack	0.03	0.09	0.32
	Nature vs Attack	0.01	0.09	0.08
	Adventure vs Attack	-0.01	0.09	-0.09
	Erotica vs Attack	-0.32	0.10	**-3.33**
	Household vs Mutilation	-0.03	0.09	-0.30
	Nature vs Mutilation	-0.05	0.09	-0.54
	Adventure vs Mutilation	-0.06	0.09	-0.69
	Erotica vs Mutilation	-0.38	0.10	**-3.91**
	Nature vs Household	-0.02	0.09	-0.24
	Adventure vs Household	-0.04	0.09	-0.40
	Erotica vs Household	-0.35	0.10	**-3.66**
	Adventure vs Nature	-0.01	0.09	-0.15
	Erotica vs Nature	-0.33	0.10	**-3.40**

Erotica vs Adventure	-0.31	0.10	**-3.28**
Smoking	-0.20	0.07	**-2.88**
Duration of illness (months)	0.01	0.00	**3.67**
Duration of medication use (weeks)	-0.07	0.01	**-5.42**
POMS total score	-0.004	0.002	**-2.00**

* Numbers expressed in **bold** indicate significant effects at the 0.05 level.

AF = Antipsychotic-free patients (n=8); C = Control (n=39); M = Medicated patients (n=20).

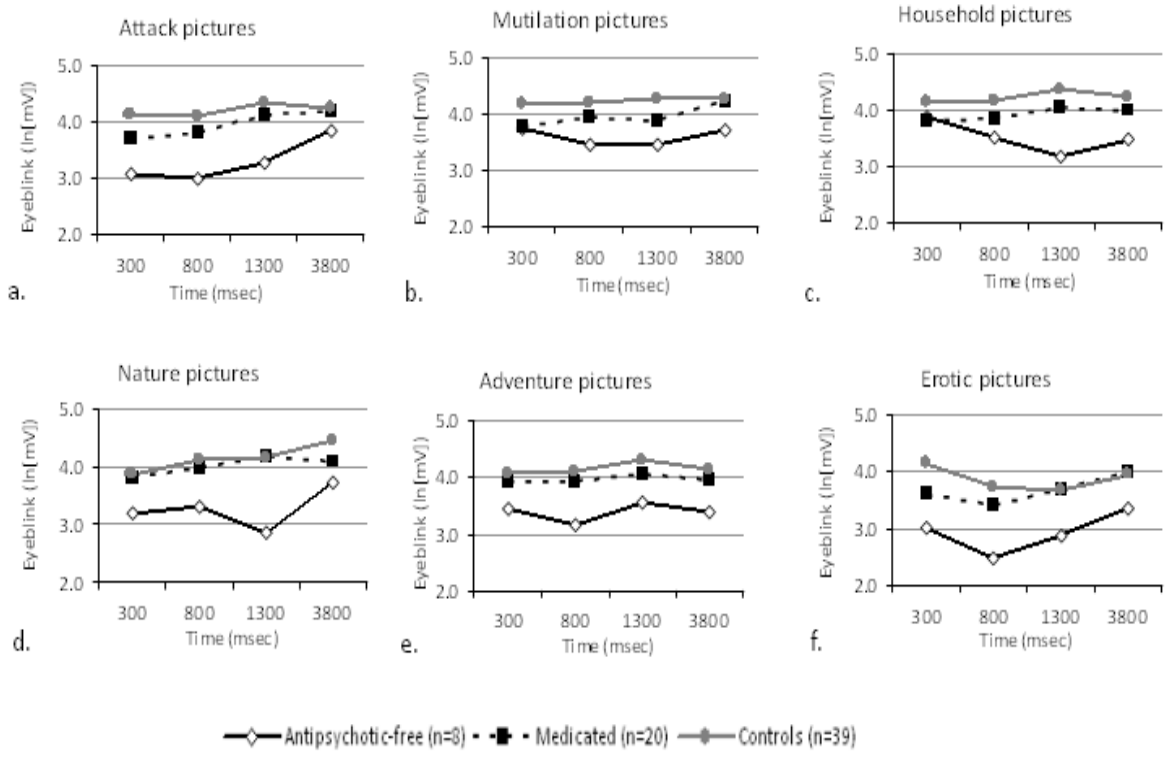
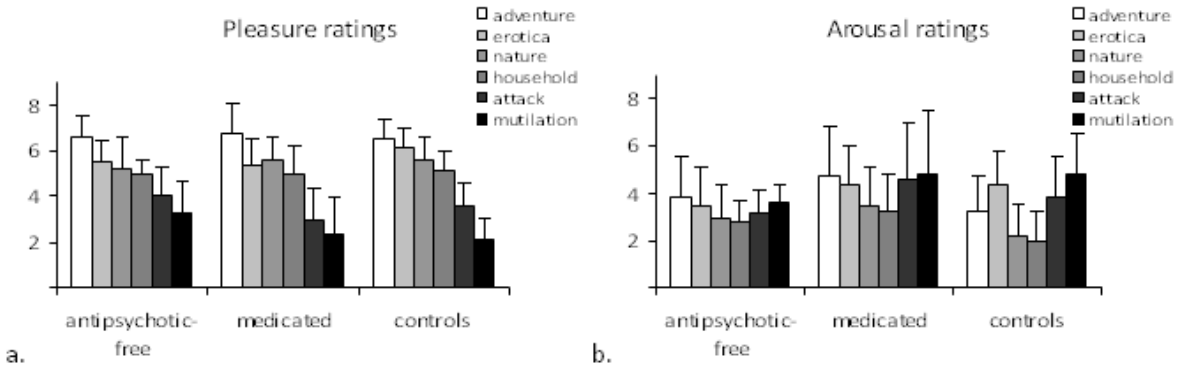


Figure 3 (a-f). Mean eyeblink responses of antipsychotic-free patients, medicated patients, healthy control participants at 4 different startle latencies (300, 800, 1300, and 3800 ms) during the presentation of (a) attack, (b), mutilation, (c) household, (d) nature, (e) adventure, and (f) erotic pictures.

Subjective ratings

The mean SAM ratings for pleasure and arousal are presented in Figures 4a and 4b. For the pleasure ratings, we found a significant main effect for Picture Content ($F[3.0;194.7] = 25.90$, $p < 0.001$, partial $\eta^2 = 0.29$). Post-hoc comparisons showed that all picture contents received different pleasure ratings, except for the erotic and nature pictures, which were not rated differently from each other. The interaction effect between Picture Content and Group was also significant ($F[3.0;194.7] = 3.75$, $p < 0.05$, partial $\eta^2 = 0.06$), indicating that the groups rated the pictures slightly different. Follow-up ANOVAs showed that the groups differed in their ratings of pictures displaying erotica ($F[2,64) = 5.51$, $p < 0.01$), attack ($F[2,64) = 3.70$, $p < 0.05$), and mutilation scenes ($F[2,64) = 3.19$, $p < 0.05$). Post-hoc comparisons further revealed that medicated patients rated erotic pictures as significantly less pleasant than the controls, while antipsychotic-free patients rated the mutilation pictures significantly less unpleasant than the controls. Finally, there was a trend for medicated patients to rate attack pictures as less pleasant compared to the controls and antipsychotic-free patients.

For the arousal ratings only the interaction effect between Picture Content and Group was significant ($F[2.8; 182.5] = 7.90$, $p < 0.001$, partial $\eta^2 = 0.11$). Follow-up ANOVAs showed that the groups differed in their ratings of pictures displaying adventure ($F[2,64) = 5.27$, $p < 0.01$), household ($F[2,64) = 6.83$, $p < 0.01$), and nature scenes ($F[2,64) = 5.37$, $p < 0.01$). Post-hoc comparisons indicated that the medicated patients rated these scenes significantly more arousing than control subjects.



Figures 4 (a-b). Pleasure (a) and arousal (b) ratings of stimuli with specific picture contents for antipsychotic-free patients, medicated patients, and healthy control subjects.

Discussion

The aim of this study was to investigate whether male patients with schizophrenia differed from healthy control subjects in their startle eyeblink responses to emotion-eliciting pictures. A distinction was made between patients who were taking antipsychotic medication and patients who were not, because the demographic information indicated that these two groups differed significantly in terms of symptom severity and illness duration, and because antipsychotic medication is known for its ability to alter emotional responding [27].

We found that the antipsychotic-free patient group generally showed significantly smaller eyeblink responses than the control group. The overall decreased startle responses are most likely due to a generally decreased amount of attentional resources, in line with the existing literature on attentional deficits in these patients [38-40]. It should be noted, however, that there were no significant differences between patients with and without antipsychotic medication in terms of emotional startle modulation, a finding that is in line with Curtis et al. [17].

Across groups and analyses, we found that the eyeblink responses increased with increasing startle latency, in line with the attentional component of this paradigm [26]. We also found that the positive pictures, and more specifically the erotic pictures, elicited smaller eyeblink responses than neutral or negative pictures.

Eyeblink responses

When the eyeblink responses to both the general and specific picture categories were analyzed, no differences between patients with schizophrenia, either on or off antipsychotic medication, and controls, were found. This finding is consistent with previous studies conducted in this field, which have generally shown comparable startle patterns in patients with schizophrenia compared with healthy control subjects [8, 10, 12, 13, 17]. Across all groups, positive pictures elicited smaller eyeblink responses than neutral and negative pictures. However, in contrast to previous studies, the negative pictures did not elicit startle potentiation, despite subjective ratings indicating that the negative pictures were experienced as unpleasant and more arousing than neutral pictures. Arousal has been found to be an important factor in the emotional modulation of eyeblink reflexes: Bradley et al. [24, 25] previously found that negative pictures rated low in arousal did not elicit startle potentiation reliably. The Self-Assessment Manikin [33] 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’. Thus, it is possible that the pictures viewed passively in our experiment did not provoke the level of arousal necessary to modulate the startle response effectively. The arousal ratings found in our study were lower than what we would have expected based on

the IAPS manual, from which the stimuli were selected. This finding is in line with a study by Libkuman et al. [41], who have also found lower arousal ratings to IAPS stimuli in their sample compared to the reported arousal ratings in the IAPS manual. One explanation they offer for this finding is that by now individuals have been exposed to this type of material in the media so frequently that people have habituated to shocking images of threat and mutilations. On the other hand, the positive pictures, and in particular the erotic stimuli, did elicit the expected startle inhibition despite the relatively low arousal scores. An alternative explanation may be that the subjects were already in a more negative state caused by the experimental procedures (i.e. loud noises and aversive pictures), and only the positive pictures were able to bring the subjects into a positive motivational state.

Subjective ratings

With regard to the general picture types, there were no differences in valence ratings between the three groups, a finding that was consistent with previous studies [8, 10-13, 42, 43]. However, compared with healthy controls, the medicated patients rated the neutral pictures as more arousing. When we investigated valence ratings to the specific picture contents, we found that medicated patients rated the erotic pictures as significantly less pleasant than controls, while antipsychotic-free patients rated the mutilation pictures as significantly less unpleasant than controls. When analyzing the arousal ratings, we found that medicated patients rated nature, household, and adventure pictures more arousing than healthy control subjects. Previous studies investigating arousal ratings have found mixed results. While at least 3 previous studies [8, 10, 13] did not find any differences in arousal ratings, Kring et al.[12] found that patients with schizophrenia reported generally decreased arousal ratings, while Aminoff et al. [11] reported decreased arousal ratings in patients while viewing aversive pictures. However, none of these studies have focused on specific picture contents; a method that could be used to explore the nature of emotional responding in these patients in more depth. Below we offer some possible explanations about our findings.

Erotic pictures

The present study found that medicated patients with schizophrenia rated erotic pictures as less pleasant than healthy control subjects. 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 patients with schizophrenia are similar to those of healthy individuals, including social relationships, intimacy and sexual function [44-46]. Bengtsson-Tops and Hansson [44]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. Thus, the decreased pleasure ratings in

response to erotic pictures with may reflect a feeling of unmet sexual needs or expectations, eliciting a response suggestive of a more neutral or even negative feeling. 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 [47]. This explanation would also be in line with their reported deficit in 'anticipatory pleasure' [48, 49], i.e., the inability to anticipate that future events will be pleasurable as well as the ability to experience pleasure in anticipation of things to come.

An alternative and more straightforward explanation may be the loss of sexual interest due to the use of antipsychotic medication. Olfson et al. [50] 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, the responses of the medicated patients did not differ significantly from those of the antipsychotic-free patients, suggesting that medication status alone does not explain the decreased pleasure ratings in response to 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.

Increased arousal ratings

Medicated patients rated adventure, nature, and household scenes as more arousing than healthy control subjects. This finding is in line with one of our previous studies, in which we found a trend for increased arousal ratings in response to neutral stimuli, which consisted of landscape pictures [43]. Other studies have not found increased arousal ratings [8, 10, 13], or have even found decreased arousal ratings [11, 12]. These other studies have mainly used a mixture of household objects and nature scenes as their neutral pictures. One possible explanation for increased arousal ratings may be that these pictures seemed slightly ambiguous to these patients. For example, a landscape can seem harmless, threatening, or lonely, and a single empty mug or a chair could represent loneliness too. Previous studies have shown that patients with schizophrenia respond differently to ambiguous stimuli compared with healthy control participants [51, 52], and Horan et al. [53] have shown that these patients have difficulty attributing the correct meaning to ambiguous stimuli in a social context. However, none of these studies directly explains our findings of increased arousal ratings to seemingly neutral stimuli. Future studies should aim to investigate the nature of emotional responses to specific stimuli in more detail, to inform us about the underlying motivations of patients with schizophrenia.

Limitations

With regard to our sample, there were several limitations. First, the sample size for the antipsychotic-free patients was very small, so any lack of a significant difference between antipsychotic-free patients and healthy control subjects could be due to a lack of statistical power. Second, we only included male participants in this study, which reduces the generalizability of our results. Third, due to the small sample sizes, we did not differentiate the patient group based on their symptom scores. This approach could have identified two sub-groups of patients, as in the study of Strauss en Herbener [54]. They found that 60% of their patient group reported subjective responses similar to healthy control subjects, while 40% rated negative stimuli as more unpleasant and more arousing than controls, and this same group rated a larger proportion of positive pictures as unpleasant. This 'atypical cluster' of patients displayed more severe symptoms on the PANSS Negative Symptom Scale and the Chapman Anhedonia Scale, as well as more functional impairment on the Heinrichs-Carpenter Quality of Life Scale than the patients in the normative group

With regard to our findings, neither the patients nor the controls showed any significant startle potentiation during the viewing of negative slides compared with neutral slides, suggesting that our manipulation of bringing subjects into a negative emotional state may have failed. The subjective ratings did show the expected pattern for negative pictures, but it is possible that the negative pictures did not evoke a sufficient defensive emotional state in the subjects to elicit startle potentiation.

Conclusion

Generally, schizophrenic patients and healthy control subjects showed similar eyeblink response patterns 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 decreased pleasure ratings of schizophrenic patients to erotic pictures and the increased arousal ratings to adventure, nature, and household pictures need further investigation.

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. Finally, more research should focus 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.

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